Michael S. Ritsner *Editor*

Handbook of Schizophrenia Spectrum Disorders

Volume II

Phenotypic and Endophenotypic Presentations

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Foreword

Schizophrenia Spectrum Disorders: Insights from Views Across 100 years

Schizophrenia spectrum and related disorders such as schizoaffective and mood disorders, schizophreniform disorders, brief psychotic disorders, delusional and shared psychotic disorders, and personality (i.e., schizotypal, paranoid, and schizoid personality) disorders are the most debilitating forms of mental illness, worldwide. There are 89,377 citations (including 10,760 reviews) related to "schizophrenia" and 2,118 (including 296 reviews) related to "schizophrenia spectrum" in PubMed (accessed on August 12, 2010).

The classification of these disorders, in particular, of schizophrenia, schizoaffective and mood disorders (referred to as functional psychoses), has been debated for decades, and its validity remains controversial. The limited success of genetic studies of functional psyhoses has raised questions concerning the definition of genetically relevant phenotypes.

Many researchers around the world have investigated schizophrenia spectrum, and related disorders from the perspectives of diagnostics, early detection of psychotic disorders, genetics, neuroscience, prognosis, and treatment. Therefore, these

fields have considerably expanded with new findings that were obtained through clinical and longitudinal observations and neuropsychological, neurophysiological, neuroimaging, neuroanatomical, neurochemical, molecular genetic, genomic and proteomic analyses, which have generated a necessity for syntheses across the functional psychoses.

The present three-volume handbook is a collection that continues to achieve my goal of providing a comprehensive up-to-date state of the art overview of the literature that addresses the challenges facing clinical and biological psychiatry. This series follows four recently published books:

- *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment.* Ritsner, Michael S.; Awad, A. George (Eds.), Springer, 2007, 388p.
- *Neuroactive Steroids in Brain Functions, and Mental Health. Novel Strategies for Research and Treatment.* Ritsner, Michael S.; Weizman A. (Eds.), Springer Science+Business Media, B.V., 2008. 559p.
- *The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes. Volumes I–IV.* Ritsner, Michael S. (Ed.), Springer Science+Business Media, B.V., 2009.

  Volume I: Neuropsychological Endophenotypes and Biomarkers. 231 pp.
  Volume II: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers. 244 pp.
  Volume III: Metabolic and Peripheral Biomarkers. 231 pp.
  Volume IV: Molecular Genetic and Genomic Markers. 232 pp.

- *Brain Protection in Schizophrenia, Mood and Cognitive Disorders.* Ritsner, Michael S. (Ed.), Springer Science+Business Media, B.V., 2010. 663p.

This handbook offers a broad synthesis of current knowledge about schizophrenia spectrum and related disorders. It is based on methodological pluralism regarding psychiatric nosology and raises many controversial issues, and limitations of categorical nosology of functional psychoses covering the ongoing debate on key conceptual issues that may be relevant for the development of DSM-V and ICD-11.

Reflecting the copious amount of new information provided, the handbook has been divided *into three volumes*. *Volume I* contains 20 chapters and serves as an introduction and *overview of theoretical issue, and neurobiological advances*. The chapters in this volume review the schizophrenia construct, diagnosis and classification of the schizophrenia spectrum disorders, and schizotypy concept; present proof-of-concept Multidimensional Continuum Model of functional psychoses and evolutionary models of autism; new findings regarding neurodevelopmental, neurodegenerative, and neurochemical abnormalities; genetic and environmental influences; changes in gene expression; neurotransmitter activity; brain imaging and morphological abnormalities in subjects with schizophrenia and other psychotic disorders, methamphetamine psychosis as a model for biomarker discovery in schizophrenia and advances in proteomics. Our knowledge

of the genetics of schizophrenia and its borderlands is heavily indebted to the research and writings of *Professor Irving Gottesman*. The chapter that summarizes his contributions in that historical context is an invaluable contribution to the handbook.

Volume II contains 19 chapters focusing on *phenotypic and endophenotypic presentations* of schizophrenia spectrum and related disorders. The authors discuss psychopathology, stress, social anxiety, neuropsychological, neurocognitive and neurophysiological findings, endophenotype and neuroethological approaches, quality of life deficits, and risk for cancer morbidity and mortality. The authors also review advances and *challenges* in mapping the prodromal phases of psychosis, in the prediction and early detection of first-episode psychosis, early- and late-onset schizophrenia, the longitudinal course of these disorders, as well as the interface of acute transient psychoses, the association of metacognition with neurocognition and function in schizophrenia, neurophysiology of cognitive dysfunction in schizophrenia, schizo-obsessive states, and risk for cancer morbidity and mortality in schizophrenia spectrum disorders.

Volume III includes 18 chapters that provide a wealth of information regarding treatment approaches, comorbidity, recovery, and outcomes of schizophrenia and spectrum disorders; in particular, recovery-based treatment approaches, antipsychotic and neuroprotective-based treatment; prevention and early intervention in at-risk states for developing psychosis, psychotherapy, cognitive remediation, cognitive behavior therapy; and interventions targeting social and vocational dysfunction in schizophrenic spectrum disorders. Furthermore, therapeutic approaches to schizophrenia with medical illness, comorbid substance abuse, suicidality, implications for treatment and community support, the relationship between religiosity/spirituality and schizophrenia, and the ethical ramifications of biomarker use for mood disorders are also reviewed and discussed.

Since many of the contributors to this handbook are internationally known experts, they not only provide up-to-date state of the art overviews, but also clarify some of the ongoing controversies and future challenges and propose new insights for future research. The contents of these volumes have been carefully planned, organized, and edited. Of course, despite all the assistance provided by contributors, I alone remain responsible for the content of this handbook including any errors or omissions which may remain. Similar to other publications contributed to by diverse scholars from diverse orientations and academic backgrounds, differences in approaches and opinions, as well as some overlap, are unavoidable.

This handbook is designed for use by a broad spectrum of readers including psychiatrists, neurologists, neuroscientists, endocrinologists, pharmacologists, psychologists, general practitioners, geriatricians, graduate students, and health care providers in the fields of mental health. It is hoped that this book will also be a useful resource for the teaching of psychiatry, neurology, psychology and policy makers in the fields of mental health.

I would like to gratefully acknowledge all contributors from 16 countries (Australia, Brazil, Canada, China, Czech Republic, Denmark, Germany, Ireland, Italy, Israel, Japan, Spain, Switzerland, Ukraine, United Kingdom, and USA)

for their excellent cooperation. I wish to thank *Professor William T. Carpenter*, distinguished psychiatrist, who was willing to write the afterword for this handbook. I also wish to take this opportunity to thank the wonderful staff in my clinical department as well as in other departments in Shaar-Menashe Mental Health Center (Director – Dr. Alexander Grinshpoon) for their commitment, support, and cooperation. I would like to thank my wonderful and generous friends, particularly Boris Altshuler, Anatoly Polischuck, and Stella Lulinsky. They always took the time to listen, even when I was just complaining. The support they have given me over the years is the greatest gift anyone has ever given me. Finally, I thank Springer Science Business Media B.V. for the goodwill and publication of this book, particularly Mr. Peter Butler, and Dr. Martijn Roelandse, publishing editors, who did their utmost to promote this project and provided valuable assistance that made the book possible.

I sincerely hope that this handbook will further knowledge in the complex field of psychiatric disorders.

Haifa, Israel
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Michael S. Ritsner

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Chapter 1
Negative Symptoms Across the Schizophrenia Spectrum: Phenomenological and Neurobiological Perspectives

George Foussias, Ofer Agid, and Gary Remington

Abstract Recognition of the negative symptoms of schizophrenia dates back to the earliest descriptions of Kraepelin and Bleuler. Since, there has been increasing interest in this domain of psychopathology, in large part driven by the recognition of its importance in determining functional outcomes. This is highlighted by the recent formation of a National Institute of Mental Health (NIMH) initiative focused on negative symptoms. In the present chapter we explore the historical and current conceptualization of the negative symptoms of schizophrenia, including the recent formulation of two core subdomains of negative symptoms: (1) Diminished expression; and (2) Amotivation. We then expand this current conceptualization through an exploration of these negative symptoms across the schizophrenia spectrum, including schizoaffective disorder, high-risk and prodromal non-affective psychosis populations, as well as the schizophrenia spectrum personality disorders. The phenomenology of negative symptoms in schizophrenia and schizoaffective disorder, derived from studies examining one or both of these illnesses, are compared and contrasted. We then explore the prominence of such negative symptoms in the clinical presentation of high-risk and prodromal populations. Moreover, with the expanding genetic boundaries of the schizophrenia spectrum that now includes schizotypal, schizoid, paranoid, and avoidant personality disorders, we discuss the presence of negative symptoms in these populations. A growing body of evidence for the neurobiological underpinnings of these symptoms from across the schizophrenia spectrum is explored. We subsequently conclude with a synthesis of the negative symptom construct across the schizophrenia spectrum, based on available scientific evidence, and highlight fundamental questions that remain to be addressed as we move towards a more comprehensive understanding of negative symptoms and ultimately strive to improve functional outcomes for individuals with schizophrenia.

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Abbreviations

AES	Apathy evaluation scale
BPRS	Brief psychiatric rating scale
CT	Computed tomography
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
fMRI	functional magnetic resonance imaging
GABA	Gamma amino butyric acid
MRI	Magnetic resonance imaging
NAA	N-acetylaspartate
NIMH	National institute of mental health
NOS	Not otherwise specified
OFC	Orbitofrontal cortex
PANSS	Positive and negative syndrome scale
PAS	Physical anhedonia scale
PET	Positron emission tomography
PFC	Prefrontal cortex
rCBF	regional cerebral blood flow
SANS	Scale for the assessment of negative symptoms
SAPS	Scale for the assessment of positive symptoms
SAS	Social anhedonia scale
SDS	Schedule for the deficit syndrome
SPD	Schizotypal personality disorder
SPECT	Single photon emission computed tomography
VTA	Ventral tegmental area

Introduction

The recognition of negative symptoms as a central feature of schizophrenia dates back to the earliest systematic descriptions by Kraepelin and Bleuler [1, 2]. Both of these pioneers highlighted the central role of avolition in the phenomenology and course of schizophrenia, as well as the characteristic diminishment of affective expression that coexisted in this illness. The subsequent assimilation of these symptoms into the construct of "negative" symptoms arose from a tradition in neurology, with Hughlings Jackson building upon Spencer's work on dissolution and evolution of the nervous system [3]. Hughlings Jackson proposed that negative symptoms reflected the loss of normal function and dissolution of "neural arrangements",

whereas positive symptoms (i.e., psychotic symptoms) were seen to represent the loss of higher inhibitory control and resultant excitation or release of lower systems [4].

The introduction of modern psychopharmacology in the 1950s drove interest over the next decades in the characterization and treatment of the positive symptoms of schizophrenia, and offered the hope of functional recovery and deinstitutionalization. However, this initial enthusiasm gave way to the realization that schizophrenia was more than the sum of its positive symptoms, and the growing realization that other symptom domains were critical in determining functional outcomes in schizophrenia.

The mid-1970s and early 1980s saw attention turn once again to the role of negative symptoms. The earlier distinction of positive and negative symptoms was embraced by psychiatry, and led to seminal work into subtypes of schizophrenia, good- and poor-outcome trajectories, and positive and negative schizophrenia [5–7]. There also emerged a broader understanding of the negative symptom construct, which included symptoms of affective flattening, alogia, avolition/apathy, anhedonia and asociality, and inattention [8]. In addition, there arose the distinction between primary, or idiopathic, and secondary negative symptoms, the latter of which were seen to result from iatrogenic, disease-related, and environmental causes (e.g., extrapyramidal symptoms, depression, suspicious withdrawal, etc.). A subgroup of individuals with schizophrenia was identified that exhibited primary enduring negative symptoms, even during times of clinical stability, and was classified as the "deficit syndrome" [9]. This classification was found to be stable over several years [10], and prevalent in both first-episode and chronic populations (15 and 25–30%, respectively) [11].

In the ensuing chapter, we explore current advances in the understanding of the phenomenology of negative symptoms in schizophrenia, their relationship with cognitive functioning, and their impact on functional outcomes. In addition, accumulating evidence for the existence of two key underlying subdomains of negative symptoms is discussed. The negative symptom construct in related illnesses within the schizophrenia spectrum, including schizoaffective disorder and the early prodromal stages of schizophrenia spectrum illnesses is also reviewed. Related symptoms observed in the schizophrenia-spectrum personality disorders are then examined and, finally, we review the current understanding of the neurobiological underpinnings of negative symptoms and discuss directions for future investigations in the field.

The Negative Symptoms of Schizophrenia

Definition and Assessment

The formation of a NIMH initiative to understand and treat the negative symptoms of schizophrenia highlights the growing recognition of the importance of these symptoms in determining the course and outcome of schizophrenia. A consensus

statement developed at the initial stages of this initiative identified negative symptoms as consisting of blunted affect, alogia, asociality, anhedonia, and avolition [12]. This definition echoes quite closely the long-standing definition by Andreasen and colleagues [8].

The NIMH consensus statement also identifies the Scale for the Assessment of Negative Symptoms (SANS) as the most important rating instrument to date for assessing these symptoms in schizophrenia, having the most extensive coverage of all the negative symptoms [8, 12]. Other commonly used rating instruments, including the Positive and Negative Syndrome Scale (PANSS) [13] and the Brief Psychiatric Rating Scale (BPRS) [14], among others, show varying degrees of overlap with the SANS, and although exhibiting good overall inter-correlation also exclude important negative symptoms [15, 16]. Another well established and valuable instrument, although designed primarily for the diagnosis of the deficit syndrome rather than symptom severity ratings, is the Schedule for the Deficit Syndrome (SDS) [17], which also shows varying overlap with negative symptoms as defined in the SANS [15, 16]. Importantly, a novel negative symptom scale is emerging as a result of the recent NIMH initiative, with hopes that it will offer improved assessment of negative symptoms [18].

While there is considerable overlap between traditional and contemporary definitions of negative symptoms, there are also some notable differences. Attentional impairment, as described by the SANS, had long been considered a negative symptom. However, subsequent factor analyses have consistently shown that impaired attention overlaps more closely with a separate domain of schizophrenic symptomatology, the disorganization symptom domain [19, 20]. Similar findings have emerged for the inappropriate affect and poverty of content of speech items of the SANS [19–22]. As a result, these items have frequently been excluded from investigations of the negative symptoms of schizophrenia, as well as from the recent NIMH consensus definition of negative symptoms [12, 23–25].

Negative Symptoms and Cognitive Dysfunction in Schizophrenia

In concert with the growing recognition of the importance of negative symptoms in the phenomenology of schizophrenia, there also emerged a greater appreciation for the existence of cognitive dysfunction as a key feature of this illness [26]. Both cognitive and negative symptoms have been implicated in playing a substantial role in functional recovery in schizophrenia [24, 27, 28]. In addition, cross-sectional studies have repeatedly found that the negative symptoms of schizophrenia correlate with various measures of cognitive performance (reviewed in [29, 30]). This has raised questions regarding the nature of their relationship, as well as their distinct roles in determining functional outcomes in schizophrenia.

In an extensive review of the available scientific literature on the nature of the relationship between cognition and negative symptoms in schizophrenia, Addington [29] noted that several domains of cognitive function exhibit a low-to-moderate inverse correlation with negative symptom severity, but that negative symptoms

account for only a small proportion of the variance in cognitive functioning (approximately 10%). The overall conclusion was that a relationship exists, although there does not appear to be a clear link between negative symptoms and specific cognitive deficits. An evaluation of change in cognitive function and negative symptoms in individuals with schizophrenia failed to find a longitudinal relationship between these two symptom domains, leading to the suggestion that they represent semiautonomous disease processes [31]. An additional critical evaluation of the relationship between cognition and negative symptoms by Harvey et al. [30] came to a similar conclusion, suggesting that these symptom domains appear to arise from related but separate etiologies with the added possibility that their interrelationship is influenced by "third variable" relationships with other features of schizophrenia, such as distal outcome measures. An additional examination of the role of social cognition in schizophrenia (i.e., "the mental operations that underlie social interactions" [32]) and its relationship with other cognitive functions and negative symptoms has served to reinforce previous conclusions, finding that negative symptoms appear to be weakly related yet distinct from social cognition and traditional cognitive functions (the latter of which were also noted to be distinct yet related constructs) [25].

Despite these overall broad conclusions, some recent work has served to highlight the complexity of the interrelationship between cognitive and negative symptoms in schizophrenia. In an evaluation of reward- and punishment-driven learning, individuals with schizophrenia, compared to healthy controls, were found to have a selective deficit in the ability to learn from positive outcomes; further, this deficit was significantly correlated with the severity of negative symptoms but not standard cognitive functions [33]. In addition, concerns have been raised about the impact of motivational deficits (i.e., apathy) on measures of cognitive performance, with the possibility that cognitive dysfunction in schizophrenia may in part be secondary to a lack of motivation [34]. In keeping with these concerns, an examination of the relationship between effort and cognitive function in schizophrenia revealed that insufficient effort accounted for one-third of the variance in cognitive test performance, and that lack of effort was significantly correlated with negative symptom severity [35].

Negative Symptoms in Schizophrenia – Two Distinct Subdomains

Traditionally, the negative symptoms have been described as either a unitary construct or, alternatively, in terms of the discrete symptoms of blunted affect, alogia, asociality, anhedonia, and avolition. However, there has been accumulating evidence over the last few decades to suggest that the negative symptoms cohere into two separate, though interrelated, subdomains (reviewed in [36]). Studies that have explored this underlying subdomain structure have relied on factor and component analyses using the SANS, largely due to its more extensive coverage of negative symptoms, in individuals with schizophrenia.

An investigation by Mueser et al. [37] that evaluated negative symptoms using the SANS in a sample of schizophrenia patients identified 3 underlying factors: (1) affective flattening, (2) avolition/apathy and anhedonia/asociality; and (3) alogia and inattention. Importantly, the poverty of speech item from the alogia subscale of the SANS loaded on the affective flattening factor, whereas the remainder of the subscale, including poverty of content of speech, aligned more closely with inattention. Subsequent work by Sayers et al. [22] also examined the underlying factor structure of negative symptoms in patients with schizophrenia-spectrum illnesses, using a modified version of the SANS that excluded inappropriate affect and poverty of content of speech items. In individuals with schizophrenia, they found a factor structure, in keeping with the previous work of Mueser et al. [37], consisting of: (1) diminished expression (affective flattening); (2) social amotivation (avolition/apathy and anhedonia/asociality); and (3) inattention/alogia. Additional work in this area by Peralta and Cuesta [20] explored the factor structure of negative symptoms in the context of a comprehensive evaluation of the subdomains of symptomatology in schizophrenia using both the SANS and the Scale for the Assessment of Positive Symptoms (SAPS). They identified two central subdomains of negative symptoms: (1) poverty of affect and speech; and (2) social dysfunction. The poverty of affect and speech factor consisted of the affective flattening subscale, except the inappropriate affect item (which loaded on a separate disorganization factor) and poverty of speech and poverty of content of speech items. The social dysfunction factor consisted of the avolition/apathy and anhedonia/asociality subscales of the SANS. A third factor, attention, was found to be related to both negative and disorganization symptoms of schizophrenia.

As discussed earlier, an important distinction that has been highlighted in the field of negative symptom research has been the identification and differentiation of negative symptoms that are primary to the illness versus those that are secondary to other factors including psychotic symptoms, medication side effects, institutionalization, and depression, among others. With the emerging evidence suggesting the existence of two key underlying subdomains of negative symptoms, one important question is whether the presence of secondary negative symptoms influences the structure of these underlying subdomains. In an effort to address this question, Kelley et al. [38] evaluated individuals with schizophrenia and schizoaffective disorder both on and off antipsychotic medication. They found that the underlying factor structure of negative symptoms identified by other groups, consisting of poverty of affect and speech, and avolition/apathy and anhedonia/asociality, remained stable regardless of patient medication status. A similar examination by Kimhy et al. [39] of the subdomain structure of primary negative symptoms, as assessed with the SDS, in individuals diagnosed with the deficit syndrome revealed findings in keeping with previous evidence for schizophrenia more generally defined. The 2 distinct factors identified were: (1) avolition (consisting of curbing of interests, diminished sense of purpose, and diminished social drive); and (2) emotional expression (consisting of restricted affect, diminished emotional range, and poverty of speech).

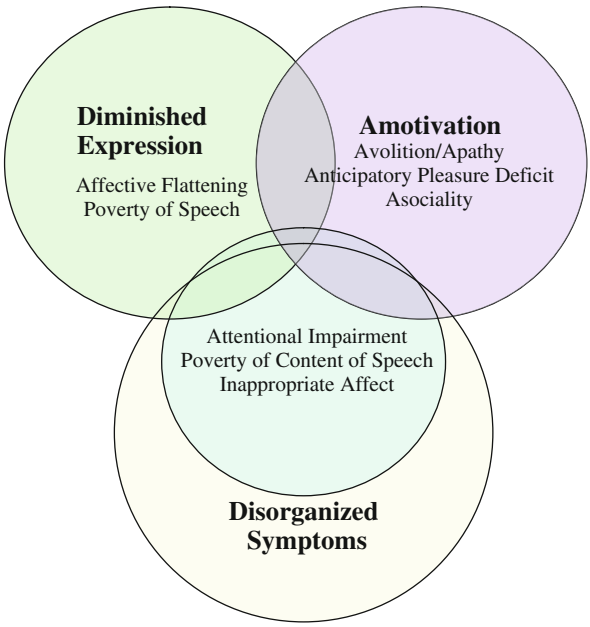

Fig. 1.1 The current conceptualization of the negative symptoms of schizophrenia, involving two key interrelated yet separable subdomains – diminished expression and amotivation. Other symptoms historically considered to be negative symptoms that have been demonstrated to align more closely with the disorganized symptoms of schizophrenia are also highlighted

In summary, the contemporary conceptualization of negative symptoms in schizophrenia has mirrored quite closely historical notions of these symptoms dating back to the earliest descriptions by Kraepelin and Bleuler, though with some important clarifications. Symptoms of attentional impairment, inappropriate affect, and poverty of content of speech appear to be more closely related to the separate domain of disorganization symptoms that also commonly occurs in schizophrenia, rather than with the remaining negative symptoms. Further, the other negative symptoms appear to segregate into two underlying factors; diminished expression (i.e., affective flattening and poverty of speech), and amotivation (i.e., avolition/apathy and anhedonia/asociality) (Fig. 1.1).

Further Refinements of the Negative Symptom Construct

With the growing recognition of the importance of negative symptoms, and an increased understanding of the constituent negative symptoms and their organization into separate subdomains, there has also emerged a growing interest in the role of each of these symptoms in schizophrenia. This has been particularly prominent for the symptoms of anhedonia and amotivation, which we will explore in turn. Of note, we view the terms amotivation, motivational deficits, avolition, and apathy as being interchangeable, and from here forward will opt for the terms amotivation or motivational deficits in discussing this negative symptom.

There have been long-standing notions that anhedonia, the diminished capacity to experience pleasant emotions, is a core feature of schizophrenia, based largely on findings of increased levels of self-reported anhedonia using the Chapman Physical Anhedonia Scale (PAS) and Social Anhedonia Scale (SAS) [40]. However, concerns around the construct and discriminant validity of these scales [41–44], as well as conflicting results using other rating instruments of anhedonia, have called into question the nature and presence of a hedonic deficit in schizophrenia [40, 45]. In addition, a recent evaluation of two discrete components of hedonic experience, anticipatory pleasure (i.e., pleasure derived from anticipating that an activity will be enjoyable) and consummatory pleasure (i.e., pleasure derived from engaging in an enjoyable activity), by Gard et al. [46] has provided valuable insights. They have demonstrated that individuals with schizophrenia report intact consummatory pleasure, though exhibit deficits in anticipatory pleasure compared to healthy individuals.

An expanding literature base has also developed around the systematic evaluation of hedonic experiences using experimental paradigms employing a variety of emotion-eliciting stimuli including films, pictures, sounds, and tastes. Findings have been rather consistent in supporting the position that individuals with schizophrenia experience both pleasant and unpleasant emotions in the moment with approximately equal intensity compared to healthy controls [47–50]. This has been found to be independent of both their diminished capacity for outward expression of emotions and medication status. A similarly intact in-the-moment hedonic experience has also been found in a comparable investigation in deficit and non-deficit schizophrenia and healthy controls [51]. Moreover, the study by Burbridge and Barch [48] failed to find a relationship between patients' self-reported anhedonia using the PAS and SAS and their ratings of emotional experiences to various emotional stimuli including pictures, faces, films, sounds, and words. An examination of physiological responsiveness to pleasant and unpleasant images, in both first-episode and chronic schizophrenia populations, also demonstrated intact objective experience of emotions in both groups compared to healthy controls [52]. Two recent systematic reviews of emotional experiences in individuals with schizophrenia conclude that, despite some contradictory findings in the literature, the vast majority of evidence suggests that individuals with schizophrenia exhibit a preserved or intact hedonic capacity [53, 54].

In addition to the enhanced understanding of emotional experiences in schizophrenia, there has also been accumulating knowledge about the motivational deficits seen in this illness. Several groups have documented the presence of motivational deficits, measured by the Apathy Evaluation Scale (AES) [55], in both first-episode and chronic schizophrenia populations [56, 57]. Further, Murray et al. [58] examined incentive motivation, as measured by the Cued Reinforcement Reaction Time Task, and demonstrated that first-episode psychosis patients exhibit incentive motivational deficits compared to healthy controls. However, they used a mixed sample of individuals that were later diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, and psychosis NOS, making firm conclusions about this specific process in schizophrenia difficult.

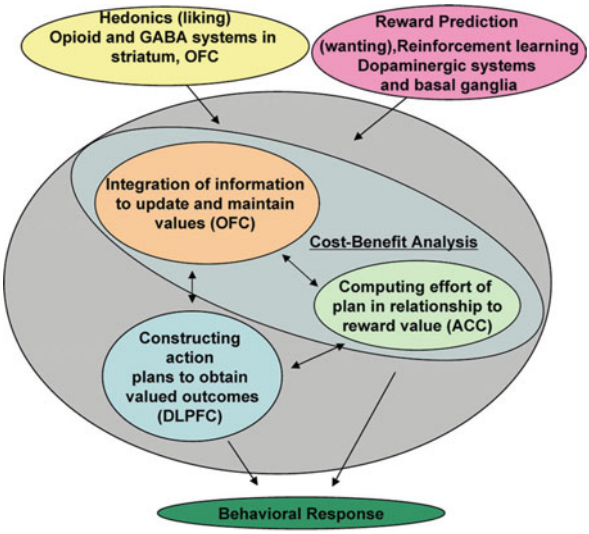

Fig. 1.2 Schematic representation of the multiple components of motivation involved in the initiation and execution of goal-directed behavior. (After [59])

Advances in affective and cognitive neuroscience have suggested that motivational processes, that is the translation of appetitive or reward information into behavioral responses, involve four discrete components: (1) hedonics or "liking" (reviewed above); (2) reward prediction and "wanting"; (3) cost-benefit analysis/effort computation; and (4) generation and execution of goal-directed action plans necessary to achieve the valued outcome (Fig. 1.2) (reviewed in [59]). Phenomenological investigations of reward prediction and "wanting" suggest that individuals with schizophrenia have deficits in their ability to learn about the rewarding properties of stimuli, particularly on difficult tasks. Deficits in the ability to couple behavior to the motivational properties of a stimulus have also been demonstrated in schizophrenia, despite equivalent subjective arousal and pleasure ratings for the stimulus [49]. Further, studies have also demonstrated that individuals with schizophrenia exhibit difficulties integrating information about rewards and punishments, maintaining and updating internal value representations on tasks appropriately, and using this information to guide future goal-directed behaviour, deficits which appear to be related to working memory impairment and negative symptoms in this population [58–60]. In addition, there exists a large body of evidence for impairments in the cognitive functions involved in goal maintenance and planning in schizophrenia, with the suggestion that these impairments impact the generation and execution of goal-directed action plans in individuals (reviewed in [59]).

Overall, investigations of hedonic experience in schizophrenia based on self-report and laboratory paradigms have indicated an intact capacity to experience pleasant and unpleasant emotions in the moment, with emerging evidence suggesting that deficits exist in the ability to anticipate pleasure or enjoyment from future activities. Furthermore, motivational deficits in schizophrenia have been repeatedly identified in investigations over the past century, with more recent

findings suggesting that amotivation results from a complex interplay between deficits in reward prediction and learning, maintaining and updating value and cost information about goals, and in generating and executing goal-directed behavior.

Negative Symptoms and Functional Outcomes in Schizophrenia

Negative symptoms have been consistently linked to functional outcomes in schizophrenia, with several studies demonstrating worse functional outcomes in individuals with more severe negative symptoms [24, 61–63]. These studies have shown that negative symptoms are significantly related to impairments in occupational functioning, household integration, relationships, and recreational activities. There have also been similar associations demonstrated in relation to the enduring primary negative symptoms seen in the deficit syndrome [11]. Further, investigations of the associations between the discrete subdomains of negative symptoms of schizophrenia and functional outcomes have served to highlight some of the fundamental symptoms that may drive these overall relationships. Sayers et al. [22] found that the amotivation subdomain of negative symptoms was significantly correlated with social dysfunction in schizophrenia, including instrumental role performance, household adjustment, extended family functioning, social/leisure functioning, and general adjustment. In keeping with this, others have demonstrated that motivational deficits are significantly correlated with functioning in first-episode and chronic schizophrenia populations both cross-sectionally [56, 57, 64, 65], and longitudinally [66, 67]. In contrast, the diminished expression subdomain of negative symptoms has not been found to be significantly related to functional outcomes in schizophrenia [22], especially after accounting for the impact of amotivation in this regard [64]. In addition, an evaluation of affective flattening and its impact on social skills did not find a relationship between the two [68]. There has been one study, however, suggesting that affective flattening was associated with functional outcomes both cross-sectionally and longitudinally, although this was confounded by the same group with more severe affective flattening also having more pronounced negative symptoms overall [69].

The role of anhedonia and its impact on functional outcomes in schizophrenia has also received considerable attention over the last several decades, although with inconsistent results. Significant relationships have been demonstrated between anhedonia and functional outcomes both in some short-term and long-term follow-up studies [70, 71], but not consistently [72]. However, these studies have relied on the PAS and SAS for their assessment of hedonic capacity, and the existing concerns about the validity of these scales, as well as mounting evidence of intact hedonic capacity in schizophrenia, suggest interpreting these associations with caution. Further, evaluation of anticipatory and consummatory pleasure deficits in schizophrenia indicate that deficits in anticipatory, but not consummatory, pleasure are correlated with worse community functioning [46].

There has also been a substantial body of literature that has documented a significant role for cognitive dysfunction in determining functional outcomes in schizophrenia [28], raising questions about the relationship between cognitive dysfunction and negative symptoms and their interaction in this regard. A recent meta-analysis by Ventura et al. [73] established that a significant relationship exists for both cognitive dysfunction and negative symptoms with functional outcomes in schizophrenia; further, negative symptoms appear to play an additional role in explaining some of the relationship between cognition and functioning. Other studies as well have confirmed that motivational deficits in particular play a significant role in explaining the relationship between cognitive dysfunction and functional outcomes in schizophrenia [65, 74].

Summarizing, a review of the literature suggests that negative symptoms are critically related to functional outcomes in schizophrenia, and also play a role in explaining the association between cognitive dysfunction and functioning. Further, accumulating evidence indicates that it is the motivational deficits that lie at the core of the negative symptoms, serving a central role in determining functional outcomes.

Negative Symptoms in Schizoaffective Disorder

Studies have not only evaluated the presence and factor structure of negative symptoms in individuals with schizophrenia, but also examined other diagnostic groups including schizoaffective disorder. This offers an opportunity to compare and contrast the expression and underlying structure of negative symptoms between these two diagnostic categories. Some studies have reported that, with the exception of poverty of speech and affective flattening which were more severe in schizophrenia versus schizoaffective disorder, negative symptoms were of equivalent severity between the groups [75, 76]. In contrast, several others have shown that individuals with schizophrenia exhibit more severe negative symptoms overall compared to those with schizoaffective disorder. Importantly, this has included studies that have examined the severity of these symptoms both cross-sectionally [20, 77–79], and longitudinally [80–82] across diagnostic groups.

In addition to studies that have evaluated overall levels of negative symptoms and individual symptom severity across diagnostic groups, there have also been comparisons between schizophrenia and schizoaffective disorder with regard to the underlying subdomain structure of negative symptoms. As described above, there has been emerging evidence in schizophrenia that negative symptoms exist in two key subdomains – diminished expression and amotivation. In keeping with the findings in schizophrenia, factor analyses by Peralta and Cuesta [20] and Sayers et al. [22] identified essentially identical underlying subdomains in samples that included individuals with schizoaffective disorder. Although the authors suggest that the identical subdomain structure of negative symptoms in these more heterogeneous samples supports a lack of difference between schizophrenia and schizoaffective disorder, further investigation comparing these two diagnostic categories is warranted.

Overall, comparisons of the severity of negative symptoms between individuals with schizophrenia and schizoaffective disorder suggest that negative symptoms are generally more severe in schizophrenia. With regard to the underlying subdomain structure of negative symptoms, investigations to date have suggested that the negative symptoms cohere into the subdomains of diminished expression and amotivation in both schizophrenia and schizoaffective disorder. Unfortunately, more extensive investigations of the differential expression of particular negative symptoms, including anhedonia and amotivation, between schizophrenia and schizoaffective disorder have yet to be conducted.

Negative Symptoms in the Schizophrenia Prodrome

Attention has also focused on the prodromal phase of schizophrenia, with the hope of intervening early and preventing the substantial functional impairment that characterizes this illness. The prodrome is characterized by a variety of attenuated symptoms of schizophrenia as well as functional decline, and occurs from weeks to years prior to the onset of frank psychotic symptoms [83]. However, the identification of the prodrome typically occurs retrospectively, following the onset of psychosis and the individual's presentation for treatment. Evaluation of the early stages of schizophrenia prospectively have relied on the identification of individuals who are at high risk of developing schizophrenia, often referred to as having an at-risk mental state. Established criteria for this at-risk mental state typically identify three different at-risk syndromes: (1) those with a history of attenuated psychotic symptoms; (2) those that experience brief intermittent psychotic symptoms; and (3) those with a family history of psychosis and a recent history of functional decline [84].

Investigations of the symptomatology of individuals in this at-risk mental state have identified the existence of a discrete negative symptom domain, including symptoms of avolition, diminished emotional expression and experience, decreased ideational richness, and social isolation and withdrawal, akin to that seen in schizophrenia [85, 86]. They represent some of the most frequently reported symptoms, emerging early in the course of the prodrome, before the onset of attenuated or frank psychotic symptoms [84, 87, 88]. Consistent with findings in first-episode and chronic schizophrenia, the severity of negative symptoms in the at-risk mental state has also been associated with functional impairment in this population [85, 89–91].

There have also been some limited investigations of emotional expression and experience in the prodrome. A retrospective evaluation of symptoms prior to the onset of psychosis suggested that affective flattening was present in this prodromal phase prior to the development of frank psychosis [92]. Further, an evaluation of home movies of children who later developed schizophrenia found that female children exhibited a reduction in affective expression, in particular joyful expressions, relative to their siblings who did not develop schizophrenia [93].

Investigations of emotional experience in this population have centered primarily on evaluations using questionnaires and clinical interviews, which have suggested increased emotionality in the form of depression and anxiety symptoms (reviewed in [94]). However, one recent study evaluating subjective experiences to pleasant and unpleasant pictures, in conjunction with physiological responsiveness and arousal measures, suggests that individuals in the at-risk mental state have overall patterns of emotional experience similar to those of healthy control and schizophrenia populations [52]. Some modest differences were noted in subjective ratings of visual stimuli, as well as some inconsistent patterns of physiological responsiveness, thought to be related to the small sample size as well as the inherent diagnostic heterogeneity in this population (i.e, where only some individuals will go on to develop schizophrenia). There have also been some phenomenological investigations that have identified the presence of amotivation as a common feature in the prodrome of schizophrenia [84, 88]; however, more detailed or specific evaluations of motivational deficits in at-risk mental state populations have yet to be conducted.

Overall, negative symptoms consistent with those characteristic of schizophrenia have been identified in at-risk mental state or prodromal populations. These symptoms appear as a distinct domain of psychopathology and exhibit similar associations with functional impairment as seen in schizophrenia. Some limited investigations into specific negative symptoms suggest similar deficits in emotional expression and motivation, along with intact hedonic experience, in keeping with findings in schizophrenia. However, there continues to be a need for more extensive evaluations of these symptoms in this population, including prospective longitudinal evaluations in efforts to eliminate issues around sample heterogeneity that are common in cross-sectional investigations in this area.

Negative Symptoms in Schizophrenia-Spectrum Personality Disorders

Investigations of the genetics of schizophrenia through large scale family studies have identified several personality disorders deemed to be genetically related to schizophrenia (i.e., schizophrenia spectrum disorders, including schizotypal, schizoid, paranoid, and in some studies avoidant personality disorders) [95–98]. However, research interest in this area has focused primarily on schizotypal personality disorder (SPD) for several reasons: (1) SPD has been found to exhibit the closest and most consistent genetic relationship with schizophrenia [98, 99]; and (2) Schizotypy has long been considered to represent an intermediate phenotype with a high risk for conversion to schizophrenia [100]. Interest in these related disorders, and in particular schizotypy, has been driven by the prospect of investigating pathophysiological mechanisms implicated in schizophrenia without the confounds of antipsychotic treatment, institutionalization, chronic illness, or other environmental effects.

Phenomenological investigations of schizotypy have relied on both categorical approaches, with formal diagnostic criteria for SPD, and dimensional approaches measuring schizotypal trait severity using the scales developed by Chapman and colleagues (e.g., perceptual aberration, magical ideation, and anhedonia), and others (reviewed in [101]). Factor analytic studies evaluating the dimensions of schizotypy, both from categorical and dimensional perspectives, have consistently identified the existence of two primary domains of schizotypal symptoms, positive schizotypy and negative schizotypy [101–104]. The negative schizotypy dimension consists of symptoms of social withdrawal, anhedonia, poverty of speech, and blunted affect, and bears striking resemblance to the negative symptom domain in schizophrenia. Further, an examination of the genetic relationship between symptoms of schizophrenia and schizotypal symptoms in non-psychotic relatives revealed a significant correlation between the negative symptoms in probands with schizophrenia and negative schizotypy in their relatives [105]. These findings suggest that there is a genetic, in addition to a phenomenological, relationship between the negative symptoms of schizophrenia and schizotypy.

Exploration of the discrete negative symptoms observed in schizotypy have focused primarily on hedonic deficits, particularly due to the central role anhedonia has had in defining schizotypy as a schizophrenia risk phenotype. Investigations of anhedonia have relied primarily on self-report assessments and have suggested that individuals with SPD, and especially those with negative schizotypy, report elevated levels of anhedonia, and in particular social anhedonia, compared to healthy controls.(reviewed in [94, 106]) Limited work using laboratory-based emotional stimuli has, however, produced mixed results. A study of individuals with SPD found that these individuals report equivalent experiences of emotions compared to healthy controls [107], whereas studies evaluating physiological reactivity to emotional stimuli among individuals with negative schizotypal symptoms, particularly anhedonia, found both reduced [108] and intact responsiveness [109]. In addition to the studies of hedonic experience in schizotypy, Berenbaum et al. [107] also evaluated affective expression in the context of laboratory-based viewing of emotional stimuli, and did not find a difference in affective expression between schizotypal and healthy control populations.

While there has been extensive examination of similarities between schizotypy or SPD and schizophrenia, particularly with regard to cognitive functioning and neuroimaging, investigation of negative symptoms in this population has been quite limited. There is consistent evidence for phenomenological overlap, as well as a finding of a genetic relationship, in negative symptom dimensions in schizophrenia and schizotypy, although further investigation of the specific negative symptoms in schizotypy has been quite limited. Evidence from self-report measures suggests elevated levels of anhedonia in this population, especially in those with negative schizotypy, although laboratory-based objective assessments have provided inconsistent results. Further, the one objective evaluation of affective flattening in this population did not find a difference compared to healthy controls, in contrast to what is characteristically seen in schizophrenia. Evaluations of other important negative symptoms, including motivational deficits, are to our knowledge non-existent

in this population, as are similar examinations in the other schizophrenia spectrum personality disorders. One major limitation of this work that deserves highlighting is the inconsistent definitions of schizotypy in this field, which undoubtedly increases sample heterogeneity and may have a significant impact on overall conclusions that can be drawn from the work in schizotypy at this stage.

Negative Symptoms in the Schizophrenia Spectrum – Neurobiological Underpinnings

Along with their phenomenological descriptions of schizophrenia and their emphasis on the centrality of negative symptoms, Kraepelin and Bleuler, building on emerging evidence by Alzheimer of neuronal loss in the frontal cortex of the brains of individuals with schizophrenia, also speculated that these symptoms arose from structural and functional abnormalities in the frontal lobes of the brain [1, 2, 110]. However, early interest in these symptoms and their neurobiological underpinnings faded due to multiple factors, including the lack of available investigative techniques and the shifting focus in the field towards positive symptoms, their neurobiology, and treatment. With growing recognition of the importance of negative symptoms in the course and outcome of schizophrenia, as well as advances in neuroimaging techniques, there has been a growing body of literature exploring the structural and functional brain correlates of negative symptoms as well as brain regions that may be critical in the development of specific negative symptoms. Below we review this expanding field of research in schizophrenia, as well as investigations pertaining to the other schizophrenia spectrum illnesses where available. Of note, the majority of neurobiological investigations have included samples consisting primarily of individuals with schizophrenia, although often individuals with schizoaffective disorder have also been included. To date, we are not aware of studies that have examined differential structural and functional brain correlates of negative symptoms between schizophrenia and schizoaffective disorder. In the sections that follow we refer to findings in schizophrenia, although acknowledge that they are often results from mixed samples.

Structural and Functional Imaging Studies

Investigations of the structural brain correlates of negative symptoms, involving computed tomography (CT) and magnetic resonance imaging (MRI) studies, have offered mixed results. Early work in this field by Andreasen et al. [111] demonstrated reductions in frontal lobe volumes in schizophrenia, but failed to demonstrate a relationship with negative symptom severity. A subsequent study by the same group found that patients with prominent negative symptoms had significantly enlarged cerebral ventricles compared to patients with mixed or prominent positive symptomatology [112]. Other structural imaging studies examining frontal lobe

volume changes have collectively shown only modest differences in frontal lobe volumes between patients with schizophrenia and healthy controls [113], and most investigations have failed to demonstrate a specific relationship between total frontal lobe volume and negative symptoms [114].

More detailed examinations of specific brain regions, rather than total regional volumes, have documented some important associations with negative symptoms. Several studies have revealed significant associations between negative symptom severity and reduction in prefrontal cortical (PFC) volumes, including orbitofrontal (OFC), medial and lateral prefrontal cortices [114–118]. In addition, volumetric studies have also revealed associations between negative symptoms and volume reductions in temporal cortex [115, 116], bilateral caudate [119], limbic [116], right parietal cortex [120], left fusiform gyrus [121], and corpus callosum [122]. However, there have also been contradictory findings, including associations between negative symptom severity and increased volume including cortical and frontal gray matter [123], OFC [124], right posterior superior temporal gyrus [125], and hippocampus [126].

Advances in MRI resolution and processing techniques have also enabled investigators to evaluate the integrity of white matter tracts in the brain, a modality entitled diffusion tensor imaging (DTI). Studies using this imaging modality have demonstrated an association between negative symptom severity and abnormalities in orbitofrontal white matter tract integrity [127], internal capsule and superior longitudinal fasciculus, corpus callosum, anterior thalamic radiations, fronto-occipital fasciculus, left temporal lobe white matter tracts [128], and bilateral uncinate fasciculi [129]. However, these findings have not been consistent between studies [129, 130].

Longitudinal investigations examining progressive structural brain changes and their associations with symptomatology have also offered valuable insights. A recent systematic review of the longitudinal structural imaging literature in schizophrenia revealed that there is consistent evidence for progressive reductions in overall brain tissue volume and enlargement in lateral ventricle volumes, with changes being most pronounced in frontal and temporal cortices [131]. In addition, several groups have demonstrated associations between negative symptom severity and progressive volume reductions in frontal lobe [132], prefrontal and posterior temporal lobe [133], and left insular cortex [134]. However, there have also been studies that have found inverse associations (i.e., an association between improvement in negative symptoms over time and progressive brain volume decreases), as well as other studies failing to find an association (reviewed in [131]).

Additional investigations aimed at evaluating structural pathology in schizophrenia have utilized proton magnetic resonance spectroscopy to evaluate concentrations of the intraneuronal chemical N-acetylaspartate (NAA), with reduced NAA concentrations being indicative of a higher degree of neuronal pathology. Some of these studies have demonstrated a significant relationship between reduced prefrontal NAA concentration and more severe negative symptoms [135, 136], although others have failed to replicate this association [137].

In keeping with the large number of structural imaging studies that have been conducted over the past several decades, there has been an accumulation of imaging studies that have examined the functional brain correlates of negative symptoms in schizophrenia using a variety of techniques including single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI). Examinations of cerebral metabolism in individuals with schizophrenia have demonstrated a relationship between negative symptom severity and reduced frontal metabolism [138, 139], particularly in the dorsolateral prefrontal cortex (DLPFC) [140] and ventral prefrontal and temporal cortices [141]. Others, though, have failed to find a significant association between negative symptom severity and hypometabolism [142]. In addition, evaluations of regional cerebral blood flow (rCBF) have demonstrated an association between more severe negative symptoms and reduced rCBF in frontal, DLPFC, cingulate, temporal, basal ganglia, and thalamic regions [143–145].

With the enhanced resolution of MRI scanners, fMRI studies have afforded the field further opportunities to evaluate the functional correlates of negative symptoms. A recent and systematic review of the vast schizophrenia fMRI literature reported significant relationships between task-dependent activation of the ventrolateral prefrontal cortex and ventral striatum and negative symptom severity; that is, more severe negative symptoms were associated with reduced activation in both areas [146]. Interestingly, this review did not find support for the long-standing notion of DLPFC hypoactivity and its relationship with negative symptoms (as demonstrated by the rCBF and cerebral metabolism studies discussed above). A subsequent study, however, found a significant relationship between diminished novelty-induced activation of the ventral striatum, premotor area, and DLPFC and higher negative symptom severity in individuals with schizophrenia [147]. Further, a study by Honey et al. [148] demonstrated impaired functional connectivity between the anterior cingulate cortex and the supplementary motor area in individuals with schizophrenia with prominent negative symptoms.

In summary, numerous structural and functional imaging studies have been carried out in efforts to uncover the neurobiological substrates of the negative symptoms of schizophrenia. Although findings are not entirely consistent, these investigations collectively offer valuable insights into the potential neurobiological underpinnings of negative symptoms. The collective evidence suggests that negative symptoms are related to a hypoactive frontal lobe, and in particular to dysfunction within the OFC, ventrolateral prefrontal cortex, ventral striatum, DLPFC and some areas of the temporal lobe.

Investigations of the Deficit Syndrome

Neurobiological investigations of the deficit syndrome have also been undertaken, with research into both the structural and functional correlates of this subgroup of patients with schizophrenia. The few structural imaging studies that have been

conducted have found contradictory results: one study comparing deficit and non-deficit schizophrenia demonstrated significant reductions in prefrontal white matter volumes in the non-deficit group, while the deficit group was similar to healthy controls; a second study found that patients with deficit schizophrenia had smaller total prefrontal lobe volumes, although they considered both gray and white matter volumes together and did not use the SDS for diagnostic categorization of the deficit group (reviewed in [11]). A more recent study comparing deficit and non-deficit schizophrenia (as diagnosed by the SDS), and healthy controls did not demonstrate a significant difference in DLPFC volumes between deficit and non-deficit groups, although both groups had significantly smaller DLPFC volumes compared to healthy controls [149]. Further, a DTI study investigating the integrity of the white matter tract connecting the frontal and parietal lobes in deficit and non-deficit schizophrenia, compared to healthy controls, found a significant reduction in white matter tract integrity in the deficit group compared to healthy controls, and a trend towards a reduction in tract integrity in the deficit compared to the non-deficit group [150]. In addition, functional imaging studies using PET have also demonstrated that individuals with deficit schizophrenia have reduced blood flow and glucose metabolism in the DLPFC compared to those with non-deficit schizophrenia and healthy controls (reviewed in [11]).

Neurobiological Correlates of Specific Negative Symptoms in Schizophrenia

With the accumulating evidence of associations between structural and functional brain abnormalities and the negative symptoms in schizophrenia, investigations have also been undertaken in efforts to delineate the neurobiology of specific negative symptoms. While there have not been any studies examining the diminished expression subdomain of negative symptoms, there has been limited exploration of the structural brain correlates of its component symptoms. Recent work has revealed associations between severity of alogia and reductions in cingulate cortex volumes [151], as well as abnormalities in the bilateral uncinate fasciculi as determined by DTI [129]. Further, severity of affective flattening in individuals with schizophrenia has been associated with morphological abnormalities of the right anterior putamen surface [152], and with increased right hippocampal volume [126].

From a phenomenological perspective, the hedonic experience of individuals with schizophrenia has been demonstrated to be intact (as reviewed above). Functional neuroimaging, however, has presented a somewhat more complicated picture. Several groups have shown that individuals with schizophrenia, despite reporting equivalent hedonic experiences in laboratory settings to pleasant and unpleasant stimuli, exhibit mixed abnormalities in neural responses to these stimuli compared to healthy controls. These abnormalities have included: reduced activation of limbic and paralimbic regions (including the insula and nucleus accumbens), though with increased activation of extensive frontal cortical areas [153]; reduced activation of orbitofrontal, medial, and dorsolateral prefrontal cortices, and

amygdala [154]; reduced activation in OFC and insula [155]; and, reduced ventral striatum and putamen activation although with no difference in other brain regions [156]. Further, a study investigating the neural responses to receipt of a reward did not show any differences between individuals with schizophrenia and healthy controls, including similar ventral striatal and OFC activation [157]. A recent study also examined the functional neural correlates of self-reported physical anhedonia in individuals with schizophrenia, and found physical anhedonia severity to be related to reduced activation in medial prefrontal and orbitofrontal cortices, ventral striatum, and putamen activation [158]. However, concerns about the validity of the PAS highlighted earlier suggest cautious interpretation of these correlations.

Investigations into the neurobiological underpinnings of motivational deficits in schizophrenia have also provided valuable insights. From a structural neuroimaging perspective only one study has been carried out, which demonstrated that individuals with higher amotivation (i.e., a high apathy group as evaluated by the AES) exhibit significant reduction of bilateral frontal lobe volumes compared to a low amotivation group [159]. With regard to functional neural correlates of motivational deficits, several investigations have evaluated activation of the reward system, reward prediction, and the concept of "wanting" in individuals with schizophrenia. These studies have pointed towards the ventral striatum as playing a central role in reward prediction and reward anticipation; for example, individuals with schizophrenia exhibit blunted activation of the ventral striatum in response to reward-indicating cues, both when unmedicated and when treated with typical, but not atypical, antipsychotics [160–162], as well as abnormal striatal responses to reward-prediction errors (i.e., situations in which the reward obtained differs from that which was expected) [163]. Further, both of these abnormalities in striatal response were correlated with negative symptom severity, and in the later case with amotivation severity specifically. In addition, the recent study by Simon et al. [157] found that the degree of ventral striatal activation in subjects with schizophrenia during reward anticipation was inversely correlated with the severity of amotivation (as measured by the AES), although they did not corroborate others' findings of differential striatal responses in schizophrenia and healthy control subjects.

Insights into the neurobiology of other domains deemed important for motivation and goal-directed behavior, including value and effort computations (i.e., cost-benefit analysis), and the process of generating and executing an action plan to pursue and achieve goals, have drawn upon examining these processes in normal controls. For example, investigations in the area of cognitive neuroscience have implicated a role for the OFC in the computation and representation of the value of particular goals, and the anterior cingulate along with its connections to the nucleus accumbens and forebrain in the determination of the effort or cost of pursuing a particular goal. Further, the generation and execution of action plans in pursuit of goals has been suggested to be carried out by the DLPFC (reviewed in [59]). Findings of structural and functional abnormalities in these same brain regions in schizophrenia, as well as associations between some of these areas with negative symptoms, have fueled speculation that these areas are critically related to the severity of

motivational deficits in schizophrenia. However, the lack of studies following this line of investigation makes specific conclusions in this area quite tentative.

Overall, there has been a growing interest in the exploration of the neurobiological correlates of specific negative symptoms. Limited work into the etiology of diminished expression has suggested a role for the anterior cingulate in poverty of speech, as well as putamen and hippocampal involvement in affective flattening. A larger body of literature has examined the neurobiology of anhedonia, with paradoxical findings. Despite having intact subject hedonic experiences, individuals with schizophrenia appear to exhibit reductions in the activation of several prefrontal cortical regions and the ventral striatum in the context of receiving a reward. Similar examinations into the motivational deficits characteristic of schizophrenia have revealed relationships with reduced frontal lobe volumes, as well as with deficient activation of the ventral striatum in the context of amotivation and during reward prediction. Other important facets of motivational processes, including neurobiological correlates of cost-benefit computations and generation and execution of a goal-directed action plan, have yet to be investigated in schizophrenia.

The Role of Dopamine Dysregulation in the Negative Symptoms of Schizophrenia

Dopamine has figured prominently in conceptualizations of the neurochemical dysfunction that underlies the symptoms of schizophrenia. This was driven initially by the recognition of dopamine's role in the development of psychotic symptoms, and the integral role of dopamine antagonism, specifically dopamine D_2 receptors (localized primarily in subcortical brain structures), that characterizes all known antipsychotic medications (reviewed in [164]). However, recognition that D_2 antagonism offered little benefit in alleviating the cognitive and negative symptoms of schizophrenia, accumulating evidence of hypofrontality and its relationship with cognitive/negative symptoms, and the postulated role of dopamine D_1 receptors in PFC functioning contributed to a reconceptualization of dopamine's role in schizophrenia. The revised model suggests that symptoms of schizophrenia result from a cortical/subcortical dopaminergic imbalance, with positive symptoms arising as a consequence of a subcortical hyperdopaminergic state, while negative symptoms represent the phenotypic expression of an underlying hypodopaminergic state [165].

Dopamine's role in the pathophysiology of negative symptoms was historically driven by the structural and functional imaging findings of associations between negative symptoms and abnormal findings in brain regions richly innervated by dopaminergic projections from the ventral tegmental area (VTA), in particular the PFC which forms the terminus of the mesocortical dopamine pathway. However, neurochemical studies of PFC function and D_1 receptor binding (prominent in this region) have faced technological challenges limiting work in this area. To date,

results have been inconsistent in linking PFC D_1 activity and negative symptoms (reviewed in [164, 166]) whereas other studies have identified associations between negative symptoms and subcortical dopamine function, with blockade or reductions in density of striatal D_2 receptors being correlated with severity of negative symptoms, particularly affective flattening and amotivation [167, 168]. Once again, though, results have been inconsistent [169].

It remains, however, that advances in our understanding of dopamine's role in motivational processes have offered valuable insights into the neurochemical basis of motivational deficits in schizophrenia. A wealth of recent evidence has established that dopamine is integral in motivation and "wanting", in contrast to previously held notions of dopamine as a signal for the experience of pleasure or "liking", which has since been linked to activation of opioid and gamma amino butyric acid (GABA) systems [170]. Further refinements in our understanding of motivation have revealed that dopamine plays a central role in reward prediction, mediated by dopaminergic projections from the VTA to ventral and dorsal striatal regions, that appears essential for learning and updating reward associations and the predictability of rewards [171]. Further, striatal dopamine has been found to play a role in determining the effort required to achieve a goal or reward as part of a cost-benefit analysis process. Specifically, dopamine depletion in the nucleus accumbens results in animals choosing low effort/low reward over high effort/high reward options.(reviewed in [59]) Extension of this work to schizophrenia has focused primarily on reward prediction through examination of neural responses to reward-predicting cues. In addition to reduced ventral striatal activation in response to reward cues (discussed above), there is evidence that D_2 antagonism is directly related to this reduction in ventral striatal activation, with implications regarding the origins of both primary and secondary amotivation [162, 172]. These conclusions arise from comparisons between patients treated with typical and atypical antipsychotics, with the assumption that D_2 receptor binding is higher with typical antipsychotics; however, no direct measurement of D_2 receptor occupancy was undertaken.

Summarizing, investigations of the neurochemical basis of negative symptoms in schizophrenia have focused primarily on the role of dopamine, in large part due to the prominence of the dopamine hypothesis of schizophrenia, as well as evidence suggestive of a hypodopaminergic state in frontal cortical regions and its possible link with negative symptoms. Despite initial speculation, the role of the D_1 receptor in negative symptoms has produced inconsistent findings. Other studies, though, have endorsed a role for subcortical dopamine in negative symptoms, especially dopamine signaling in the striatum and its impact on reward prediction and deficits therein. Dopamine has also been implicated in other facets of motivation, although investigations in schizophrenia are lacking. There has also been emerging evidence for the role of other neurotransmitter systems, and in particular glutamate, in the pathophysiology of schizophrenia [173], although their specific role in the etiology of negative symptoms is yet to be determined.

Neurobiological Correlates of Negative Symptoms in Schizophrenia Spectrum Illnesses

Substantially less research has been conducted examining the neurobiological correlates of negative symptoms in these populations. Structural imaging studies of individuals classified as being at ultra-high risk of conversion to psychosis have demonstrated an association between more severe negative symptoms in the prodrome and reduced insular cortex volume [174], as well as thinning of the anterior cingulate cortex in individuals that go on to develop psychosis [175]. Emerging multimodal imaging studies have demonstrated dopaminergic dysfunction in individuals at high risk of developing psychosis that may be linked to cognitive dysfunction observed in this population, although specific relationships with negative symptoms have not been reported to date [176, 177].

In schizotypy, structural imaging studies have report reductions in frontal and temporal lobe volumes in SPD that are intermediate between those found in schizophrenia and healthy controls [115]. Such reductions, although significantly associated with negative symptom severity in schizophrenia, are not associated with negative symptoms in schizotypy. In contrast, reduction in cingulate [115] and frontal lobe volume [103, 178] have been correlated with negative symptoms in schizotypy. A further report noted a significant relationship between reduced caudate volume and severity of negative symptoms in female subjects with SPD [179]. Studies in SPD have also reported abnormal frontal lobe activation similar to schizophrenia although links with discrete negative symptoms have not been identified (reviewed in [94]). There is emerging evidence of dopaminergic dysfunction in SPD, with the suggestion that reduced dopaminergic activity may also be associated with negative symptoms in SPD [103].

Conclusions and Future Directions

A central role for negative symptoms in the phenomenology and course of schizophrenia dates back over a century now, to the earliest descriptions of this illness. A resurgence of interest in this area has served to reinforce some of the traditional notions of negative symptoms, while highlighting the existence of two key symptom subdomains – diminished expression and amotivation. A growing body of evidence has consistently demonstrated intact subjective hedonic experiences in schizophrenia, in addition to a prominent and complex role for amotivation in determining functional outcomes, both through direct effects on functioning and indirectly through its impact on cognition. Investigations of the negative symptoms across disorders related to schizophrenia, including schizoaffective disorder and schizotypal personality disorder, as well as in the prodromal phase of schizophrenia, have highlighted the existence of a similar negative symptom domain, although often of lower severity, as well as limited evidence of intact hedonic experiences and concurrent motivational deficits.

More recent advances in investigative neuroimaging have advanced the field considerably in terms of underlying neurobiological correlates. Structural and functional imaging studies have pursued the notion of hypofrontality in schizophrenia and its relationship with negative symptoms, with evidence that abnormalities in prefrontal cortical and ventral striatal regions provide the most consistent links with negative symptoms. Dopamine has figured prominently in hypotheses around the pathophysiology of schizophrenia, with the suggestion that negative symptoms are related to a cortical hypodopaminergic state; however, neurochemical data supporting this and a link with negative symptoms has not been forthcoming. In contrast, a growing body of evidence has underscored the importance of reward prediction and the role of dopaminergic signaling in the ventral striatum as one component of a complex motivation system. Across the schizophrenia spectrum there have been very few neurobiological investigations of negative symptoms, although those that have been conducted suggest involvement of similar brain regions to those implicated in schizophrenia.

We have witnessed significant advances in our understanding of negative symptoms in schizophrenia over the last several decades, a shift that has highlighted their critical role in functional outcomes. This work is in its earliest stages though; for example, our understanding regarding the respective roles of cortical and subcortical neurobiological abnormalities in negative symptoms is, at best, rudimentary. The value of multimodal imaging studies in this regard cannot be overstated, with opportunities to concurrently evaluate structural and functional correlates of negative symptoms on multiple levels, from regional metabolic and blood flow changes to specific neurochemical involvement in the processes under investigation. At the same time, we await further advances in these technologies that currently limit the questions we ask, as is currently the case regarding the PFC and D_1 activity. A focused exploration of the multiple facets of goal-directed behaviour, including clear delineation of systems that are critical in neural cost-benefit computations and the execution of goal-directed action plans, is also essential. Of course, only in understanding these processes within the context of normal behaviour can we begin to delineate the pathophysiologic mechanisms that characterize the deficits seen in schizophrenia. Finally, future work must also address issues around sample heterogeneity, medication effects, and expand the work on motivational deficits to prodromal, neuroleptic-naïve first episode patients, and the schizophrenia spectrum personality disorders. The search for effective treatments of the negative symptoms in schizophrenia, and the prospect of improved functional outcomes in this illness, are critically dependent on the results of this important work.

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Chapter 2
Neurocognitive Deficits, Negative Symptoms, and Insight in Schizophrenia

Adrian Preda, Robert Bota, and Philip Harvey

Abstract The symptom domains of primary negative symptoms, insight and cognitive deficits in schizophrenia appear to overlap on a number of aspects. These domains are: (1) relatively independent of the psychotic, affective and secondary negative symptoms domains; (2) relatively persistent; (3) show only marginal improvement with the available antipsychotic treatments; (4) are strongly correlated in cross sectional measures, and (5) associated with outcome measures. Despite such similarities the relationship between insight, negative and cognitive symptoms is yet to be clarified. Are we looking at independent categories of symptoms, at a primary versus secondary symptoms type of correlation – e.g. insight deficits secondary to cognitive deficits – or maybe at a common neuropathological "lesion" or endophenotype with multiple manifestations? Is the functional deficit an effect, a cause or just another category that correlates with insight, negative and cognitive symptoms? In this chapter we will selectively review cross-sectional and longitudinal data to clarify the relationship between these schizophrenia domains. We conclude that the evidence to date suggests that we are in fact looking at independent symptoms domains. This conclusion has important applications. At a theoretical level the implication is that, similarly to its clinical presentation, the underlying neurocircuitry and pathophysiology of schizophrenia is diffuse and heterogeneous rather than localized and homogeneous. At a more pragmatic level the relative independence of the cognitive and negative symptoms suggests that effective interventions might need to selectively target each of the domains.

Keywords Cognitive deficits · Negative symptoms · Deficit · Insight · Schizophrenia

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Abbreviations

AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
BDNF	Brain-derived neurotrophic factor
BP-I	Bipolar disorder type I
COGS	The consortium on genetics of schizophrenia
COMT	Catechol-O-methyl transferase
CPT	Continuous performance tests
DTI	Diffusion tensor imaging
DSM	Diagnostic and statistic manual
FA	Fractional anisotropy
FE	First episode
FGA	First generation antipsychotic
GABA	γ-amino-butyric acid
GAF	Global assessment of function
ICD	International classification of disease
IP	Identical pairs
MRI	Magnetic resonance imaging
NMDA	N-methyl D-aspartate
PANSS	Positive and negative syndrome scale
PD	Personality disorder
PSP	Personal and social performance
QOL	Quality of life
rTMS	repetitive transcranial magnetic stimulation
SATCI	The schedule for assessing the three components of insight
SCID	Structured clinical interview for DSM disorders
SGA	Second generation antipsychotic
STG	Superior temporal gyri
VBM	Voxel-based morphometry
WCST	Wisconsin card sorting test

Definitions and Conceptual History

Dementia praecox, the name that Kraepelin [1] used to first describe schizophrenia, is translated as early dementia. The name clearly implies the presence earlier in life of cognitive deficits similar to those typically observed in much older patients diagnosed with dementia. In addition to different types of delusions and hallucinations, Kraeplin's *dementia praecox* definition included cognitive impairment (e.g. attention, memory, orientation, language, and thought deficits) as well as negative symptoms. Specifically, avolition/amotivation was seen as a core feature of the syndrome. In fact, Kraeplin's description of the "amotivational syndrome" as a "weakening of those emotional activities which permanently form the mainsprings of volition", followed by "emotional dullness, failure of mental activities, loss of

mastery over volition, of endeavor, and of ability for independent action", remains to this day one of the best descriptions of negative symptoms. Kraepelin also described his patients' lack of insight; referring to the patients' inability to recognize they are suffering from a mental illness and are in need of care; however he did not see this as a characteristic trait of schizophrenia. Of note, Kraeplin's original description simply stated what the clinical symptoms of *dementia praecox* were, without an implication of what might be primary versus secondary.

Following Kraeplin, Bleuler [2] differentiated between schizophrenia core or fundamental symptoms, the "Grundsymptome", and the "Akzessorische Symptome" (accessory symptoms) of schizophrenia. In his "Grundsymptome" Bleuler included a number of negative symptoms, specifically abnormalities in association, affect, ambivalence, relationship to reality (autism), and volition. What we now label as catatonic features and positive symptoms, including delusions and hallucinations, in addition to disorders of attention, orientation, memory, consciousness and motility, Bleuler saw as the "Akzessorische Symptome" (accessory or secondary symptoms).

In the development of psychiatry as a science the Kraepelinian/Bleulerian fondness for description was followed by the Freudian determination to explain it all. Not surprisingly within a subjective hierarchy informed mostly by symbolism and metaphor the unanalyzable cognitive deficits and unalluring negative symptoms fell out of favor. In this context, the re-classification of cognitive and negative symptoms as "secondary" might have been an unintended consequence of increased emphasis on the much more colorful and fun to interpret Schneiderian first rank symptoms [3] including symptoms such as paranoia and abnormal perceptions. Noteworthy is also the fact that the 1950s witnessed chlorpromazine's victory over the positive symptoms of schizophrenia (i.e. delusions and hallucinations). This important event, in addition to marking the birth of modern psychopharmacology, further reified the positive symptoms as a biological cornerstone of psychosis. It is this combination of historical circumstances that set the research cards against studying cognitive impairment and negative symptoms in schizophrenia.

Only following the advent of diagnostic systems heavily invested in reliability such as the PSE, the RDC and DSM III has the field been able to overcome its prejudices and deem cognition and negative symptoms in schizophrenia as subjects worthy of interest in their own right [4–6].

To illustrate, the Schneiderian belief that the first rank symptoms were pathognomic to schizophrenia and have prognostic value, while not supported by empirical evidence and at odds with both Kraepelin's and Bleuler's views, has carried on through all the DSM and ICD editions. The present ICD 10 and DSM IV formulations of schizophrenia require the presence of only one first rank symptom for a diagnosis of schizophrenia [7, 8]. At the same time DSM IV lists lack of insight under "Associate Features of Schizophrenia" while curiously acknowledging that altered insight is "one of the most common symptoms" and "may be one of the best predictors of poor outcome" in schizophrenia. DSM IV also emphasizes that negative symptoms and cognitive dysfunction are indicative of a poor prognosis (under "Course"), that cognitive dysfunction is "often present" and introduces a negative

(deficit) dimension under "Alternate Dimensional Descriptors of Schizophrenia". Yet, despite all the above, negative symptoms alone are not deemed sufficient for fulfilling the Criterion A DSM requirement for a diagnosis of schizophrenia and cognitive deficits are discussed only briefly under "Associated Features" [8].

Cognitive Deficits: What we have learnt is that the story of cognition in schizophrenia might be the very opposite of what we imagined it to be. While positive psychotic symptoms may fluctuate during the course of the illness, the fact that cognitive deficits are relatively constant raised important question about what constitutes core or primary, versus secondary deficits [9]. We used to think of schizophrenia as a building where the ungluing of meta-cognition and other higher processes cracks its cognitive "bricks" and eventually results in the collapse of the whole edifice. Based on multiple lines of evidence we now think just the opposite: already cracked cognitive bricks, further damaged by wear and tear, eventually crack for good and eventually result in the ruin of the whole edifice. Patients with schizophrenia consistently perform 1–1.5 to 1.5–2 standard deviations lower than normal controls on a variety of neuropsychological tasks targeting attention, working memory, processing speed, problem solving and social cognition, among others [10, 11]. In their meta-analysis of 43 separate samples of 2,204 first episode (FE) patients Mesholam-Gately and colleagues [12] conclude that cognitive deficits in FE schizophrenia are similar to those reported in chronic schizophrenia. Furthermore, the study reports an increase in FE deficits compared to earlier premorbid IQ levels and stability of course afterwards. While the significant heterogeneity of effect sizes across studies limits the validity of the conclusions, such data suggests that cognitive deficits appear *before* other clinical symptoms and tend to remain stable overtime. Rather than an effect, cognitive deficits might be a *cause* (or even the cause – but the evidence supporting this hypothesis is less convincing at this time) of schizophrenia. In other words, dysfunction at the level of basic cognitive processes such as attention, processing speed, working memory, among others, might just be the reason for the ungluing and collapse of the higher functions.

Negative Syndrome: The negative symptoms are defined as reduction or even absence of a normal psychological function. A number of negative symptoms have been described over time but the current use typically refers to poverty of speech (alogia), avolition-apathy, amotivation, physical anergia and anhedonia-asociality [13, 14]. The history of the concept can be traced back to a paper published in 1861 by Sir John Russell Reynolds (1828–1896) who described positive and negative symptoms as an "excess or negation of vital properties" (for a review, see Perce 2004 [15]). "Superimposed" behaviors such as abnormal movements but also paranoid delusions and hallucinations were labeled as positive symptoms; "losses" of sensation, feeling, motor abilities (culminating with coma) were labeled as negative symptoms. Around the same time Herbert Spencer's evolutionary theory, and specifically his ideas about the evolution and dissolution of the nervous system, were gaining preeminence. Hughlings Jackson integrated Spencer's theories and Reynolds' observations and concluded that positive symptoms represented an excessive expression of normally inhibited neural processes, while negative symptoms were due to a more diffuse Spencerian dissolution of neural function:

> Anatomically, the negative elements are losses of adjustment of the organism, as a whole, to the environment in the order, according to the "depth" of the dissolution, from the most special and complex of them towards the most general and simple. [16]

Interestingly, Jackson's positive/negative classification, while speculative, implied that negative symptoms would have a poorer course, response to treatment and prognosis, which has now been confirmed by empirical evidence.

The demise of psychoanalysis marked a change in the philosophy underlying the diagnostic research process in psychiatry: from a pre-DSM III etiological, analytically informed approach to a post-DSM III, atheoretical, descriptive nosology. Strauss et al. [17] work discussing of 3 different schizophrenia domains (i.e. positive symptoms, negative symptoms and a disorder of relation) can be understood in the context. Even if it revamped interest in negative symptoms Strauss et al. [17] contribution did not generate enough momentum (or data) to result in a separate negative symptom core for the DSM III [6] diagnosis of schizophrenia. However, "the one disorder, multiple core domains" theory of schizophrenia, resulted in a number of theoretical models, parsing a presumably unitary concept (i.e. schizophrenia) in different subtypes: type I and II, positive and negative symptoms type, and deficit and non-deficit schizophrenia [13, 14, 18–20]. All these models share the assumption that negative symptoms are a core deficit and should be separated in a distinct subtype due to its different course, prognosis and response to treatment.

The negative symptoms of schizophrenia are further classified as primary (persistent, intrinsic to schizophrenia) and secondary (temporary, associated with and presumably due to other factors such as depression, medication adverse effects, or positive symptoms [21]. While secondary negative symptoms may be reduced by treating the causative agent, primary negative symptoms are viewed as enduring and persisting between psychotic episodes [22–25].

Insight: The origin of insight can be traced back to the psychoanalytic literature. However, while psychoanalysis conceptualizes insight as a state of sudden "illumination" of a previously unconscious process, insight in schizophrenia is a multidimensional concept referring to awareness of illness, its specific symptoms and their consequences, as well as need for treatment [26, 27]. Insight is enduring rather than temporary and it refers to the patient's ability to understand that some of his non-reality based experiences (usually hallucinatory experiences and delusional representations) are secondary to having schizophrenia rather than "real". Awareness and attribution of both current and past symptoms represent specific aspects of insight. Additional dimensions of insight include a more global understanding of the diagnosis and need from treatment [28]. Insight has been variously discussed as an independent symptom domain, as secondary symptom (correlated with affective symptoms), or as a dependent symptom that is part of a broader domain including: (1) positive symptoms (where insight is a type of delusion); (2) negative symptoms (where insight, as other negative symptoms, is a decrease of a normal function, i.e. awareness); and (3) neurocognitive dysfunction (where insight deficits are thought to be similar to the better understood syndrome of

anosognosia described in some neurological syndromes). Our rationale for including it in this chapter is based on proposed theories about its shared characteristics with the negative and cognitive symptoms domains: correlates with premorbid functioning, negative prognostic value when present at the onset of illness and baseline, course, and association with functional outcomes, and more specifically social dysfunction.

Epidemiology

Demographic Variables

Cognitive Impairment: Cognitive functioning is associated with a number of demographic variables, including educational attainment, ethnicity, and sex [29]. These demographic variables are also associated with cognitive performance in people with schizophrenia as well [30]. The influence of education and ethnicity is roughly the same level of association with cognitive variables in people with schizophrenia as in healthy individuals. However, since people with schizophrenia are commonly found to have lowered levels of educational attainment compared to others from similar socioeconomic backgrounds, the influence of education on cognition may be somewhat more salient. Further, people with schizophrenia routinely manifest reduced levels of educational attainment than their parents and siblings [31]. As described below, reduced cognitive performance is present prior to the occurrence of any other symptoms of schizophrenia, possibly being a contributory factor to reduced educational attainment and suggesting a direction of relationship wherein early cognitive impairments increase the challenge associated with school

Negative Syndrome: Primary negative symptoms have been associated with poor premorbid function, male gender and low Intelligence Quotient [14]. Male gender not only increases the risk for negative symptoms but male schizophrenia patients have also been reported to have more severe negative symptoms [32, 33]. Men also present more frequently with flat affect than women patients with schizophrenia [34–38].

Insight: Lack of insight appears to be a culturally independent symptom of schizophrenia. Amador et al. [28] reported that acute schizophrenia was associated with poor insight in all the countries and cultures surveyed in the World Health Organization International Pilot Study of Schizophrenia. The evidence about demographics association with overall insight or insight specific domains is mixed. The preferred demographic distribution for negative and cognitive symptoms does not seem to apply for insight deficits n schizophrenia. In their study of 42 patients with schizophrenia and 22 patients with bipolar disorder with psychotic features Arduini et al. [39] reported no difference between male and female in insight scores. Schwartz et al. [40] studied 66 patients with chronic schizophrenia and found no association between insight and demographic variables. However, in a recent large scale multi-site clinical trial of 303 subjects with schizophrenia baseline insight correlated positively with premorbid functioning and level of education [41].

Breadth of Impairments: Genetics, Family Histories and First Degree Relatives

Cognitive Impairment: Cognitive impairments have been recognized in the relatives of people with schizophrenia for decades [42]. Studies of cognitive impairments on the part of relatives have had some of the same results as studies of schizotypal personality disorder (PD). Profiles of impairment appear similar and the level of impairment is somewhat reduced compared to schizophrenia. These impairments have long been characterized as "markers of vulnerability" in that these impairments may well identify individuals at extra high risk as noted above. However, until recently a definitive single-sample study was lacking and that study is now partially completed.

Concurrent with the development of the MATRICS initiative, the Consortium on Genetics of Schizophrenia (COGS) study sought to identify genetically-linked variation in cognitive performance [43]. This research study followed up years of less systematic research on genetic influences on cognition in schizophrenia and the general population. The previous work had implicated multiple different potential susceptibility genes for cognitive changes, including COMT, BDNF, and multiple other candidates. These studies have consistently shown that multiple aspects of cognitive functioning are related to gene expression variants [44].

It has been known for years that cognitive impairments tend to have a genetic component, and that estimates of the heritability of neuropsychological performance is quite high, with average heritability quotients over 0.40 [34]. Many of the more functionally relevant aspects of cognitive impairment are known to be consistently heritable, including episodic memory (heritability range = 0.3–0.6), attention/vigilance (mean = 0.54), working memory (range = 0.3–0.6), and executive functioning (range = 0.3–0.6). Thus, cognition is a heritable trait in families of patients with schizophrenia, and determining the relative importance of the heritable components of cognition for functional disability in schizophrenia is important. As these measures were selected for use in multi-site trials, they are ideal for use in large scale treatment studies.

Negative Syndrome: In the Roscommon Family Study negative symptoms in all probands diagnosed with nonaffective psychoses predicted corresponding dimensions of schizotypy in the patients' nonaffected first degree relatives as well as odd speech, suspicious behavior, and social dysfunction [45]. While the associated social dysfunction was expected, the authors commented that the association with odd speech and suspicious behavior was surprising. As a possible explanation they noted the overlap between suspiciousness (a positive factor) and the negative factors asociability and poor rapport. These findings remained significant when probands with a nonschiophrenics psychosis were included, which suggest a negative symptoms dimension on the spectrum of schizophrenia disorders, starting with schizotypal personality traits and ending with schizophrenia psychosis. Furthermore, positive symptoms in patients predicted positive schizotypal traits and negative symptoms predicted negative schizotypal traits in relatives. These findings suggest that in addition to a continuum of risk for both positive and negative symptoms these are two etiologically distinct domains of schizophrenia [45].

A family history of schizophrenia has been reported to correlate with a more severe course of schizophrenia, including an increased risk for negative symptoms. The presence of pervasive negative symptoms is considered a marker of relatively high genetic loading for schizophrenia [46]. In their recently published meta-analysis of 12 negative symptoms studies Esterberg et al. [47] reported that a family history has a small but significant effect on negative symptoms. Cardno et al. [46] found that the risk of schizophrenia in relatives was predicted by the presence of pervasive negative symptoms (OR: 9.44, 95% CI = 1.98–45.01) and the absence of pervasive positive symptoms (OR = 0.09, 95% CI = 0.01–0.78) in probands, where pervasive negative symptoms were defined by the presence of *all* of the symptoms: social withdrawal, autistic behavior, poverty of thought/speech, and flat affect.

Insight: Is family history relevant for insight deficits? As discussed above there is a familial transmission of cognitive deficits and negative symptoms; also both cognitive deficits and negative symptoms appear to co-aggregate with insight deficits [48]. Therefore it can be assumed that secondary (to cognitive impairment) insight deficits can be seen in families with schizophrenia. However, this does not clarify if there is a familial transmission or familial risk diathesis for primary insight deficits in schizophrenia. To address this question Danki et al. [49] studied the relationships between a family history of schizophrenia and insight deficits in a Turkish sample of 66 stable patients with a SCID based diagnosis of schizophrenia. The Schedule for Assessing the Three Components of Insight (SATCI) overall score and the scores of 5/8 SATCI subscales (i.e. awareness of illness, awareness of a mental illness, explanation of the illness, belief in the delusion, explanation of experiences, and reaction to not believing – optional eighth question), were all significantly lower in patients with a family history of schizophrenia [49, 50]. While interesting, these findings are based on a single site cross sectional study with a relatively small sample size; thus, they remain preliminary until future replication. At the same time, while Danki et al. [49] results appear to indicate there is a family effect of schizophrenia on insight, they do not answer the more direct question about the familial transmission of insight deficits in schizophrenia.

Breadth of Impairments: Schizophrenia Spectrum and Other Disorders

Cognitive Impairment: There are other conditions that are related to schizophrenia and several of these conditions have similar cognitive impairments. Most similar from a phenomenological perspective is schizotypal personality disorder. This condition manifests variants of positive and negative symptoms of schizophrenia, at slightly reduced levels of severity, and there is clear evidence of cognitive impairments as well. These impairments have similar signatures compared to schizophrenia, with slightly reduced levels of severity. For instance, in a series of studies of a large sample of people with schizotypal PD, we found that the profile of

impairments was similar to that seen in schizophrenia, greater in severity than people with other personality disorders, and approximately one half as severe as those seen in schizophrenia [51, 52]. These findings are widely replicated and it is believed that it is likely that cognitive impairments similar to those seen in schizophrenia may be a common feature, but that alterations in the subcortical dopaminergic functioning that are associated with schizophrenia are generally lacking in people with schizotypal personality disorder.

Bipolar Illnesses: The majority of studies in the medical literature tend to focus on schizophrenia and demonstrate somewhat greater impairment in schizophrenia compared with BP-I [53, 54]. Although neuropsychological functioning in BP-I has been less extensively studied than in schizophrenia, evidence does suggest that mood disorder patients frequently manifest neuropsychological deficits in attention, executive, and memory functions [53–60]. Symptomatic BP-I patients have been shown to have widespread cognitive abnormalities [61]. Evidence from studies supports the hypothesis that there are persistent residual neuropsychological impairments in patients in euthymic phases of illness [59, 62, 63]. Neuropsychological studies directly comparing patients with schizophrenia and BP showed relatively equivalent dysfunction on the Wisconsin Card Sorting Test [64], visual backward masking [65, 66], and overall neuropsychological function [57, 67].

In a recent study of first episode patients who were clinically stabilized from a first episode that included psychotic symptoms, we [68] found that the profile of clinically stable patients with bipolar and unipolar affective disorders was essentially identical to that seen in schizophrenia patients. Similar to the results for relatives of people with schizophrenia and individuals with schizotypal PD, the severity of impairment in people with schizophrenia was about twice as great compared to normative standards as the patients with affective disorders who did not differ substantially.

Although many BP-I subjects can have periods of syndromal remission (and do not typically have the same prevalence of disability or long-term deterioration as those with schiophrenia), these periods of "recovery" are not accompanied by normalization of social, familial, and occupational role function for a substantial proportion of cases [69]. A meta-analysis of 17 studies examining psychosocial outcome in patients with BP-I found that 30–60% of them fail to regain full functioning in social and occupational domains [70]. Mixed affective states [71], psychotic symptoms [72, 73], and more previous episodes [74–77] are among the variables that have found to be associated with poor outcome. A recent report from a longitudinal first episode study of bipolar disorder with manic episodes found that experiencing symptomatic relapse and remission was a relatively common occurrence compared to functional recovery [78]. Although 43% of first episode bipolar patients appeared to experience functional recovery (compared to only 18% of first episode patients with schizophrenia), the criteria for functional recovery was only return to premorbid functioning, with no requirement for successful ongoing everyday outcome (and this finding is still a very low rate of normal functional outcome).

Negative Syndrome: In a multicenter retrospective study of 1,452 patients diagnosed with schizophrenia spectrum disorders (schizophrenia, schizophreniform, and schizoaffective disorder) the majority of the patients (57.6%) had at least one or more negative symptoms, while primary negative symptoms were reported in 12.9% of patients [79]. The patients with schizophrenia had more frequent and more severe negative symptoms than patients with a diagnosis of schizophreniform or schizoaffective disorder [79]. Persistent negative symptoms are more prevalent in schizophrenia than in depressed patients, where negative symptoms also seem to correlate with depressive symptoms [80]. In a long term prospective study of schizophrenia, schizoaffective and affective disorder patients, the prevalence of negative symptom was found to be high at the 15 year follow up: 75% of the schizophrenia patients, 68% of the schizoaffective patients, and 44% of the patients with affective disorders where found to have at least one negative symptom [81]. However, schizophrenia patients had much more severe negative symptoms at the 15 year follow up compared to both the schizoaffective and affective disorder controls [81, 82].

Insight: Converging evidence suggests that there is a type of insight deficits that appears to be specific to schizophrenia. Insight deficits in schizophrenia appear to have a different course that of insight deficits seen in affective disorders. There is less variation in the course of insight deficits course in schizophrenia (trait like) *vs*. a state dependent course in affective disorders. Also, schizophrenia patients have more severe of insight deficits than patients with any other major psychiatric diagnosis, including schizoaffective disorder. In a multisite, cross-sectional study of 412 patients with schizophrenia, schizoaffective and mood disorders (with and without psychotic features) poor insight was more prevalent and more severe in patients with schizophrenia [83]. Wifffen et al. [41] also found lower insight in their cross-sectional measurement of insight in schizophrenia patients ($N = 213$) compared with schizoaffective patients ($N = 90$).

In people with schizophrenia there is a positive correlation between insight and symptoms of depression, paranoia and anxiety [84, 85]. Insight preservation in these domains is important because it predicts quicker resolution of symptoms, with less hospitalization in the period of time leading to relapse [86]. At the same time, in a 2 year longitudinal study, patients with schizophrenia with other Axis I comorbidities had less improvement in their awareness of illness at 12, 18 and 24 months follow up points and less insight into the consequence of illness at 18 and 24 months follow up [87].

Neurobiological Considerations

When it comes to insight, the neurobiological literature is remarkable for its dearth of reports. The situation is quite the opposite for cognitive deficits and, to some extent, negative symptoms where, with the accessibility of sophisticated brain imaging and neurophysiology tools and following the mandate set out by the MATRICS

guidelines, the pace of publishing of new reports has had a fairly steep slope. Reviewing the wealth of interesting reports is beyond the scope of this limited review. Thus for practical reasons we will review only a few selected studies and focus on a summary of findings with special relevance to cognition and negative symptoms.

Brain Structural Abnormalities

Ventricular and Whole Brain Volumes: Since the advent of the first neuroimaging technologies, there have been findings of reductions in cortical volume and increased ventricular size in people with schizophrenia. There was a previous belief that volumetric reductions and increased ventricular size were associated with specific profiles of symptoms specifically cognitive impairments and deficit syndrome [23], but the bulk of the evidence has suggested that small increases in ventricular size, not great enough on average to be viewed as clinically abnormal, are present in many people with schizophrenia. That said, there is some evidence of correlation between medial temporal lobe volume and memory impairment. These cortical changes are present at the time of the first episode or even during prodromal periods prior to formal diagnosis and have been reported quite consistently to progress, in terms of gray matter loss, over follow-up periods starting at that time. Evidence does suggest that these changes are slightly greater in individuals with poor lifetime functional outcomes who, consistent with the evidence presented above, are at the highest risk for experiencing cognitive and functional declines in later life [88]. Further, some studies have shown that ventricular enlargement is correlated with global cognitive impairments. Findings of decreasing cortical volume or increasing ventricular size in longitudinal studies have lead to the suggestion that these changes are reflective of active illness processes [89].

Gray Matter Changes: Advances in neuroimaging technology have led to the ability to separately examine gray and white matter. Consistent findings suggest that gray matter volumes are reduced in schizophrenia across the lifetime course of the illness. Recent studies have suggested that these changes in cortical volume are associated with an increased frequency of psychotic relapses, starting at the time of the first episode. These findings are consistent with the late-life findings reviewed above suggesting that more severe and unremitting psychotic symptoms are associated with cognitive decline over follow-up periods ranging from 3 to 6 years in older patients. Thus, progressive loss of cortical gray matter, correlated with frequency of psychotic episodes, is a potential determinant of cognitive impairments and negative symptoms in schizophrenia.

A number of brain regions have been studied in relation to negative symptoms. Kim et al. [90] reported that superior temporal gyri abnormalities are present at baseline and correlate with negative symptoms severity even in neuroleptic naïve patients. A prospective 3-year volumetric MRI study found that volume changes in the left anterior amygdala-hippocampal complex significantly correlated with PANSS negative symptoms change over the study period [91]. A bilateral decrease

in gray matter volume in the superior temporal gyri and anterior amygdala – hippocampal complex has also been shown in a small cross-sectional region of interest MRI study comparing male chronic schizophrenia patients with predominant negative symptoms *vs.* healthy controls [92]. Such longitudinal findings, while interesting, are limited by the confounding effect of concomitant medications (mainly first generation antipsychotics – FGAs in the cited studies). Interestingly, Meisenzahl et al. [93] failed to replicate these findings; however, their sample appears unique in terms of clinical stability and a higher proportion of patients stabilized on second generation antipsychotics (SGAs) at the time of the study. Lui et al. [94] using an voxel-based morphometry (VBM) approach found negative correlations between temporo-precuneus connectivity and total PANSS scores as well as scores for negative symptoms and anergia.

White Matter Abnormalities: Many theories of cognition and negative symptoms in schizophrenia have focused on impairments in connectivity as their central feature. In addition, there are several neuropathological abnormalities that implicate white matter changes. Most central is the finding that neuronal density is increased in certain brain regions in schizophrenia, in the absence of increases in cell number [95]. This finding combines with findings of decreased cellular arborization and fewer synaptic contacts (i.e. fewer dendritic spines) to suggest that findings of global reductions in cortical volumes could be due to abnormalities in white matter. These indirect suggestions have been confirmed by a series of neuroimaging studies that suggest abnormalities in the organization and integrity or cortical white matter. Central among these findings have been studies using diffusion tensor imaging (DTI) [96]. Through measuring water diffusion in myelin sheaths, it is possible to visualize the orientation of these axons. Axons organized in parallel will have higher anisotropy values and be organized more coherently. Multiple studies have reported reductions in fractional anisotropy (FA) in people with schizophrenia compared to healthy controls, suggesting reduced coherence of white matter tracts. In a very recent study, we reported that the age of the patient (ranging in age of 18–80), was associated with tract specific reductions in fractional anisotropy in the corpus callosum in comparison with healthy controls who were similar in age [97]. Thus, these findings do provide an initial suggestion of progressive deterioration of white matter in people with schizophrenia.

Pyramidal Cells: Approximately 75% of cortical neurons are pyramidal cells, so designated because of their triangular shape. These neurons utilize glutamate as a transmitter and are regulated by interneurons, which utilize the inhibitory transmitter γ-amino-butyric acid (GABA). The suggestion has been made that the reason for increased density in the absence of loss of neurons is due to reduced number of axons and dendritic spines attached the pyramidal cells. An implication of this is loss of afferent inputs from the thalamus, which would lead to reduced cortical activation [98]. A possible mechanism of this particular structural abnormality could be an excessive degree of normal pruning processes which reduces the total number of dendrites during adolescence. A further, and more speculative possibility, is that of triggered apoptosis, possibly induced by altered dopamine and glutamatergic functioning. In either case, increased neuronal density is one of the more consistently

detected neuropathological findings in schizophrenia post-mortem tissue and one that suggests a direct connection between abnormal cortical structure and functional activity of critical brain regions in schizophrenia.

Brain Neurotransmission Abnormalities

The section above gives a sense of the relationships between neuronal factors and patterns of distribution of cortical activation in people with schizophrenia. Schizophrenia has been extensively studied as a disease of impaired neural transmission due to the discovery of the antipsychotic effects of chlorpromazine in the 1950s. Recent increases in the understanding of the interactions between different CNS neurotransmitters have lead to a more sophisticated understanding of the processes of cellular activation and communication in the pathophysiology of cognitive impairments in schizophrenia.

Dopamine: The primary effect of antipsychotic medications is to block dopamine D2 receptors in the corpus striatum. All effective antipsychotic medications have this properties and all medications that have been tried as antipsychotic medications that lack this effect have failed in clinical trials. Several influential theories of cognitive impairment in schizophrenia have focused on cortical/striatal dopamine balance. In healthy individuals, increased activation of cortical dopamine neurons is associated with reductions in striatal activity and vice versa, reflecting a regulatory relationship between these regions. In contrast, there is apparently a disjunction in these regulatory processes in people with schizophrenia and blockade of striatal dopamine receptors does not lead to a corresponding increase in cortical dopamine tone.

Reduced cortical dopamine activity has been a prominent idea regarding the origin of cognitive impairments and negative symptoms of the illness [99]. Many cognitive functions are related to dopaminergic activity and compounds that increase dopamine transmission, such as amphetamine, lead to improvements in these functions. For example, attention, working memory, and related executive functions as well as some negative symptoms are improved with amphetamine treatment and reduced regional cortical activation, detected with fMRI techniques as described above, is associated with impaired performance on these types of tasks or increased severity of negative symptoms. Direct stimulation of cortical dopamine receptors with dopamine D1 agonists can reverse the adverse of effects of aging and chronic antipsychotic treatment on working memory performance in monkeys, again suggesting the dopamine-relevance of many of the common cognitive impairments in people with schizophrenia.

Other evidence implicating dopamine in the cognitive impairments seen in schizophrenia comes from studies of the genetic variants associated catehol-O-methyl-transferese (COMT) [100]. There are two polymorphisms associated with this gene, valine/VAL and methionine/MET, with the VAL allele associated with greater catabolic potential in the DA receptor region and hence

reduced levels of available dopamine. VAL–VAL homozygotes have been shown to have reduced levels of cognitive functions that are relevant to schizophrenia, including working memory and executive functioning, Although the evidence for COMT as a susceptibility gene for schizophrenia is limited, the fact that this dopamine-relevant genetic variation is broadly associated with cognitive functioning, including in individuals with schizophrenia spectrum personality disorders, again indicates the role of dopamine in the cognitive abnormalities in schizophrenia.

Glutamate: Glutamate is an excitatory transmitter that is widely distributed in the CNS, but one of the potentially important locations for these receptors is on dendritic spines. There are at least two receptor subunits for glutamate: N-methyl D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), both of which are also widely distributed. NMDA antagonists such as ketamine and phencylclidine (PCP) trigger syndromes in healthy individuals that are a close analogue to schizophrenia, including positive and negative symptoms, impairments in communication, and cognitive deficits [101]. People with schizophrenia are even more sensitive to these effects than healthy individuals.

There are two domains where glutamatergic abnormalities might cause brain changes and cognitive impairments. One is the suggestion that glutatmergic hypoactivity, as would be induced by chronic hyperdominergic activity, similar to the effects of PCP and ketamine, can trigger apoptosis. These programmed cell death processes would be difficult to detect at post-mortem because they do not necessarily cause gliosis at the time of occurrence. At the same time, this is a difficult idea to test because post-mortem tissue would have to be obtained during a period of active apoptosis and these occurrences may be sporadic in nature. A second area where glutamatergic abnormalities could be related to cortical changes is through their potential direct effect on white matter. Chronic glutamatergic hyperactivity, which could be a consequence of impaired DA-glutamate interactions, has been proven to be toxic to oligodendrocytes. This process may be due to induction of dysregulation in calcium homeostasis and increased intracellular calcium. As oligodendrocytes are damaged, demylination can occur, which further reduces the ability of neurons to modulate glutamate activity. Thus, alterations in cortical white matter previously detected in DTI studies could possibly arise from glutamatergic processes, suggesting a mechanism through which psychosis, cognitive impairment, negative symptoms and disorganized behavior may be directly linked to each other.

A final mechanism through which glutamatergic dysregulation could impact on cognitive functioning is through disruption of dopamine input to pre-frontal sites where critical cognitive operations are performed. Impaired excitatory input to cortical DA receptors could lead to chronic changes in their functioning, on both functional and morphological levels. One potential consequence of this process, suggested by Lewis and Sweet [102], is that chronic reductions in excitatory input to cortical D1 receptors could lead to compensatory, but ineffective, upregulation of these neurons. This upregulation could then cause a consequential down regulation

in the synthesis of GABA. As GABA itself regulates the level of glutatmatergic functioning, such a process could contribute to further dysregulation in the balance of these transmitters

GABA: Post-mortem data has found reduced levels of GABA signaling in a critical interneuronal subsystem: chandelier cells [103]. About 33% of interneurons that contain GABA were found to express essentially undetectable levels of a critical regulator of GABA synthesis: glutamic acid decarboxylase -67 (GAD-67). GAD-67 is an enzyme that regulates production of GABA and it is highly responsive to excitatory input directed towards GABA-containing interneurons. Thus reduced excitatory signaling into GABA neurons would lead to reductions in synthesis of GABA. Interestingly, levels of signaling of the primary transporter of GABA, GABA transporter 1 (GAT-1), are also undetectable in these same interneurons. As GABA regulates levels of glutamatergic activity, decreased GABA functioning has the potential to contribute to the cascade of reduced cortical input, compensatory upregulation of D1 receptors, and maintenance of multi-system dysregulation of neuro transmitters. It has been suggested that GABAergic dysfunction is at the root of synaptic plasticity deficits in schizophrenia (for a review, see Costa et al. [104]). Several lines of evidence support the hypothesis that GABAergic downregulation, associated with reduced reelin secretion from GABAergic neuron axon terminals on dendrites, somata and the axon initial segment of pyramidal neurons, might be responsible for the decreased PFC neuropil of schizophrenia patients. While neuropil findings have been reported in post-mortem studies, a number of in vivo studies reported that PFC changes in schizophrenia associated with both cognitive deficits and negative symptoms,

Acetylcholine: Acetylcholine is another transmitter potentially associated with cognitive changes in schizophrenia. In specific the nicotinic receptor subsystems of the cholinergic system appear to be altered in people with schizophrenia. There are several lines of evidence in this regard. Expression of the nicotinic alpha-7 receptor in the prefrontal cortex is altered in both people with schizophrenia and their relatives. Individuals with schizophrenia are more likely to smoke than the general population, starting prior to the onset of their illness, as well as smoking more heavily and extracting more nicotine from cigarettes than nonschizophrenic fellow smokers [105]. There have been postmortem reports of altered nicotinic receptor density in people with schizophrenia as well, but it is challenging to rule out the effects of smoking in that regard.

There has been limited evidence of alterations in muscarinic receptor systems in schizophrenia. Post-mortem studies have not found reductions in indices of muscarinic activation or in levels of acetylcholine. However, one study reported reduced levels of cholinergic neurons in the ventral striatum in schizophrenia, in the absence of any evidence of other neurodegenerative changes. One possible confound throughout this research is the use of antimuscarinic medications to treat extrapyramidal side effects of antipsychotic medications. The long-term effects of these medications are unknown and whether their use in early and middle life could influence the postmortem detection of illness-related alterations in muscarinic activity is uncertain.

Functional Changes in Brain Activity

The original conceptualization of brain dysfunction during cognitive processing on the part of people with schizophrenia was “hypofrontality”. At the same time, negative symptoms of schizophrenia are thought of as reflecting a frontal lobe dysfunction (for a review, see Semkovska et al. [106]). Studies of high-load executive functioning, attentional, and working memory paradigms consistently revealed reduced relative activity in the regions roughly corresponding to the dorso-lateral prefrontal cortex when compared to the brain activation of healthy individuals performing similar tasks. Recently, it has been found that such tasks are not associated with a specific localized reduction in regional brain activation, leading to small total level of brain activity, but rather with similar overall levels of brain activation in healthy and schizophrenia populations and a differential regional pattern of distribution. In specific, it has been reported consistently that reductions in anterior frontal lobe activity are associated with increases in activation in other regions, typically the anterior cingulated, more posterior frontal regions, and the occipital cortex, when compared to healthy individuals.

Hypofrontality and/or a fronto-temporal disconnection have been proposed an underlying neurocircuitry abnormalities resulting or contributing to the formation and maintenance of negative symptoms.

The hypothesis put forward to explain these apparently contradictory findings is the idea the schizophrenia patients may have a different memory-load activation response curve in the dorsolateral prefrontal cortex than controls. A typical observation is that dorsolateral activity increases as task load increases, until capacity is exceeded, at which point dorsolateral activity decreases on the part of people with schizophrenia [107]. Callicott et al. [107] suggested that the relationship between task load and dorsolateral activity may not be different in schizophrenia and healthy individuals; the load-activity curve may be the same, but patients may have lower capacity leading to a decline in activity at loads processing loads lower than in controls. Glahn et al. [108] performed a meta-analysis of brain activation studies in schizophrenia using the N-back task, finding clear support for hypoactivation in the dorslateral prefrontal cortex in schizophrenia patients. At the same time, they also documented consistently increased activation in the anterior cingulate and left frontal pole relative to controls. This pattern of findings suggests that dorsolateral disturbances in schizophrenia during executive tasks do not represent focal abnormalities of a specific neuroanatomical region, but probably an impairment in the ability to engage functional networks subserving executive functions [109]. Many of the functional imaging studies that have investigated cortical brain activation during performance of episodic memory tasks in schizophrenia have also demonstrated abnormalities in a range of prefrontal regions, including both decreased activity and increased activity. Studies of prefrontal activation during episodic memory encoding have been more likely to find decreased than increased activation. These studies have shown reduced activation in ventrolateral prefrontal regions, including BA47 and BA45, regions associated with semantic elaboration or encoding of information in memory (for a review see Barch [110]). It has been suggested

that reduced activation in these regions reflects a failure to generate and/or apply effective encoding strategies among individuals with schizophrenia.

The anatomic components of the hypothetical neural network underlying cognitive dysfunction and the primary negative symptoms and are not completely understood but, on the basis of converging lines of evidence from nonhuman primates and from neuroimaging studies of humans, the prefrontal cortex, specifically the dorsolateral prefrontal (DLPFC), parietal, temporal and anterior cingulated are thought to play critical roles. Reminding of the Jacksonian diffuse neural dissolution theory type II schizophrenia patients have smaller brains with bigger cerebral ventricles [18]. Several studies have suggested that primary negative symptoms are functionally localized to the frontal and parietal cortices [111].

Rossell et al. [112] evaluated 78 male patients diagnosed with DSM-IV schizophrenia and 36 male control matched for age and IQ. All the patients underwent psychological testing and structural MRI. There were no significant correlates between the level of insight and the whole brain, white and grey matter volumes. However, Laroi et al. [113] in a study looking at the relation between insight and frontal function in 21 medicated patients with schizophrenia and 21 controls reported a possible association between poor insight and frontal lobe deficit, but no anatomical correlation with good insight. Out of the 21 patients with schizophrenia 5 had slight and 2 moderate frontal atrophy, while the other did not show any signs of frontal lobe atrophy [113]. The divergences between the two studies could be understood as differences in patient selection, tools used and differences in number of patients evaluated.

Clinical Considerations and Diagnosis

Cognitive Impairment and Cognitive Domains: Starting with Kraepelin and Bleuler, schizophrenia has been traditionally differentiated from affective psychoses. This categorically informed perspective was later reinforced with a combination of Schneiderian first ranks symptoms and a lack of concomitant affective symptoms that were thought to be specific of schizophrenia. Standing on such giants's shoulders it was easy to *not* see that cognitive deficits, more studied in schizophrenia, might not in fact be a schizophrenia-only type of problem. While there is evidence supporting the current psychiatric classification systems (i.e. DSM IVTR and ICD-10) decision to maintain a categorical approach for schizophrenia versus affective psychoses converging lines of evidence suggests that cognitive deficits, rather than being pathognomic of schizophrenia, and a "point of rarity" between different diagnoses, are a *shared* deficit between schizophrenia and affective psychoses [54, 114, 115]. Furthermore it appears that within schizophrenia itself cognitive deficits are present on a continuum rather as a constant, fixed factor [115].

Following an increase in the research community interest in cognition in schizophrenia The National Institute of Mental Health initiated the MATIRCS project. By evaluating available factor analytic studies MATRICS aimed to define a

consensus battery to examine cognitive outcomes in treatment studies of schizophrenia [11]. A goal of this process was to identify the most relevant cognitive domains of impairment in schizophrenia and identify the best existing tests to evaluate these domains. Examining previous studies of the psychometric characteristics of individual tests and the factor structure of cognitive performance in schizophrenia, 6 functional domains were selected and several candidate tests identified. The functional domains identified by MATRICS were Verbal Memory, Visual Memory, Processing Speed, Working Memory, Attention-Vigilance, and Reasoning and Problem Solving. Also MATRICS included a test of social cognition, but many studies have found that social cognition may not be as strongly related to other cognitive measures, which are often referred to as "neurocognitive" tests.

These cognitive domains do reflect the current thinking about which aspects of neuropsychological functioning are impaired in people with schizophrenia. It is more controversial as to whether cognitive impairments in people with schizophrenia reflect a distributed set of focal impairments as would be seen with regionally specific lesions, such as temporal or frontal lobe impairments, or whether they are elements of a broad impairment that affects nearly all measurable cognitive domains. We will first describe the domains and then evaluate the possibility that there are regionally-specific, focal impairments in schizophrenia or global deficits.

Processing Speed and Psychomotor Slowing: Processing speed refers to performance on tasks which require sustained high level effort and rapid responses. This is likely related to the concept of psychomotor slowing, but there are multiple possible contributors to impairments in processing speed. The most common test for assessing processing speed are the Symbol Digit Substitution Test and the Trailmaking Test, but often verbal fluency tests such as Animal Naming are considered to be processing speed tests as well. Meta analyses suggest that processing speed deficits may be the largest impairments in people with schizophrenia [116]. There are several on-going discussions regarding processing speed, including about the extent to which the speed of processing reflects a common function with both mental and motor aspects or two different processes: a cognitive deficit i.e. decreased speed of processing information and a motor deficit, specifically slowness in initiation and execution of a movement (psychomotor slowing) and whether processing speed actually underlies other impairments on the part of people with schizophrenia [117].

Attention and Vigilance: Impairments in both sustained and selective attention are well known to be present in schizophrenia. Sustained attention is commonly referred to as "vigilance", although it has been known for 30 years that the impairments are actually deficits in the ability to discriminate target and non-target information and not in declining performance over time. Attention deficits e also promising markers of vulnerability to the illness and are stable over time across changes in clinical state in people with the illness. The most common tests to measure vigilance are continuous performance tests (CPT) and these tests are used in several versions, including tests that require detection of predetermined target sequences (e.g., 3–7) or detection of the same target occurring twice in sequence (e.g., Identical Pairs "IP").

Verbal Learning and Memory: Impairments in verbal memory are among the most significant seen in schizophrenia, with deficits occurring in the ability to learning information presented either once, such as a story learning tests, or multiple times such as in list learning tests. There are several features of impairments seen in these tests, which include lower performance on the first learning trial of list learning tests, reduced learning curves, and failure to spontaneously employ semantic strategies to aid recall. Interestingly, recognition memory performance does not appear to be notably impaired and prompts and cues (such as reminding the individual of the semantic categories) aids recall. These findings suggest that the impairments are not like an amnestic condition such as Alzheimer's disease where rapid forgetting is common and performance at delayed recall is almost entirely determined by the amount of information acquired during the learning trials. Verbal memory can be measured with list learning, story learning, and other similar tasks.

Visual Memory: Visual memory impairments in schizophrenia appear to be quite similar in their characteristics compared to verbal memory deficits. This area of impairment has been studied considerably less than verbal memory functioning. However, the MATRICS validation study, the level of impairment seen in visual memory was similar to that seen in verbal learning and memory. Visual memory tests also have single presentation and multitrial learning formats.

Working Memory: Working memory has been a long-time target for study in schizophrenia, at least partially because of the findings of regional specificity of certain types of working memory. Working memory refers to the abilities required to maintain information on line and perform manipulations of the information. Working memory can include both spatial and verbal working memory and there are suggestions that slightly different neural networks are involved in spatial, verbal, and object working memory. As working memory functions in primates show evidence of localization to the frontal lobes, some have referred to working memory as an executive function. While there are clearly similarities to executive functions in some of the cognitive tests used to measure working memory, these cognitive processes have a number of distinctions. Typical tasks used to measure working memory include various forms of span tests (digit and spatial), n-back tests, and sequencing tests.

Reasoning and Problem Solving: There is a long history of description and study of impairments in reasoning and problem solving in people with schizophrenia. Originating with classic descriptions of the "loss of abstraction" seen in schizophrenia, this domain has been the center of a considerable amount of research. Several of the classic tests used in schizophrenia research, such as the Wisconsin Card sorting test (WCST) examine reasoning and problem solving. Further, these tests have been central to the conception of impaired functioning in the frontal lobes, based on the results of studies that used the WCST as a tool in neuroimaging studies. There are multiple impairments seen in this domain, including deficits in performance on tests of abstraction such as proverbs, problem solving tests such as the WCST, and maze learning tests.

Are these cognitive domains truly separable? Although the MATRICS initiative characterized the cognitive domains presented above as separable, there is no claim

that they are independent. In fact, the results of several recent factor analytic studies have suggested that the cognitive impairments may best be characterized by a single dimension. For example, in the large-scale CATIE study where over 1,300 patients received a cognitive assessment, the best fitting factor model was unidimensional [118]. Other studies have also found that the best way to discriminate healthy individuals and people with schizophrenia is by conceptualizing cognitive impairment as a single dimension [119].

As noted above, processing speed is the single greatest deficit in people with schizophrenia. When abbreviated assessments are developed empirically, processing speed indices routinely are the single largest correlate of overall neuropsychological performance, as well as other important outcomes such as real-world residential functioning or performance-based indices of functional capacity. In the CATIE baseline study, four tests: digit symbol, verbal learning, grooved pegboard, and letter-number sequencing, accounted for 87% of the variance in the composite score based on 22 different tests. These tests required an average of 19 min to complete, suggesting that quite robust estimates of overall performance on NP tests can be obtained with abbreviated assessments. This finding is consistent with the results of studies aimed at developing abbreviated assessment batteries, which have routinely found that abbreviated assessments, either derived from longer batteries or developed de novo, are highly correlated with scores on longer assessments [120, 121].

In summary, there are multiple domains of cognitive impairment in schizophrenia, but whether define a profile of impairment or a generalized pattern of impairment is not fully clear. Also, it is clear that global indices of performance are predictable with quite abbreviated batteries and this may mean that there are fewer truly critical domains than has been believed in the past.

Negative Syndrome: The negative symptoms, specifically affective flattening, alogia, and avolition, is one of the five schizophrenia symptoms clusters (criterion A) in DSM IV-TR [8]. Asociability overlaps conceptually with DSM IV-TR criterion B of social/occupational dysfunction. Other negative symptoms (e.g. anhedonia) are discussed in the "Associated Features" section of the DSM chapter on schizophrenia.

The lack of affective reactivity is a typical example of a negative symptom. Under normal circumstances most people have "full" affect, appropriately displaying a range of context dependent emotions. Patients with schizophrenia may present with either decreased affective reactivity, in clinical parlor "reduced" or "limited range" of affect, or in extreme cases no affective reactivity, described clinically as blunted or flat affect. Of note, the "negative symptom" label for affect refers to the range of affect and not to its content. In other words, affective content such as anger, disappointment etc., even if "negative" from a subjective perspective, cannot be labeled as a negative symptom.

Alogia (Greek *α- a-* "without" + *λόγος logos* "speech") refers to decreased verbal output. With the exception of neurological deficits that would impede the translation of thought in language, it is assumed that language is a fair representation of thought processes. Thus, alogia has been historically used to label

interchangeable (to some extent) manifestations, i.e. "poverty of (content of) speech" and "poverty of thought", a global reduction in the quantity of thought. As such alogia was considered as a hallmark of the "negative formal thought disorder" characteristic of schizophrenia. However, following DSM III emphasis on reliability and precise definitions, the preferred use for alogia is as a label for a language deficit [122]. One can further differentiate between "poverty of speech", where the patient tends to answer briefly, with monosyllabic answers that frequently prompt further questioning for clarification purposes, and "poverty of content of speech", where the patient's answers, while long enough, are too vague, repetitive, over-abstract or over-concrete to be informative [122]. Clinically, alogia needs to be differentiated from other manifestation of schizophrenia, including distractibility (either due to poor attention or attending to internal stimuli), thought blocking, anxiety or a paranoid state. While it can also be a sign of depression (where alogia can be secondary to severe apathy and anhedonia), severe mental retardation or dementia, a combination of primary alogia and other negative symptoms is most times characteristic of schizophrenia. Other explanations for decreased speech (secondary alogia) include social anxiety, certain personality disorders, secondary gain, states of acute intoxication, or, at times, the examiner's inability to build rapport with the patient.

Avolition (a "without" + volition/will) refers to the patient's inability to initiate and maintain a goal directed activity or, in a more general sense, pursue any meaningful, life enriching activities. The term is in fact imprecise as it is difficult to clinically differentiate avolition from amotivation, apathy and anhedonia. From a phenomenological standpoint these dysfunctions are more similar than different, even though theoretically they represent deficits of different neuropsychological functions.

Negative symptoms occur on continuum with normality, i.e. they are not qualitatively but quantitatively different from normal states. They may also be secondary to positive symptoms (e.g. patient gives up making day to day plans due to his oppressive auditory hallucinations), depressive symptoms (depressed mood with anhedonia), chronicity, or medication adverse effects (e.g. anticholinergic effects of low potency FGAs or anticholinergic add ons to prevent/treat EPS interpreted as anergia; EPS interpreted as flat affect). Furthermore, positive symptoms may mimic negative symptoms (e.g. guarded, paranoid affect interpreted as flat; social isolation secondary to paranoid delusions interpreted as asociality) [8, 14].

Thus, a careful clinical differential is necessary to diagnose primary negative symptoms. The course of symptoms (persistent), a chronological, and a cause and effect relationship can help illuminate the diagnosis. When in doubt, a case of $N = 1$ experiment, where the patient's symptoms are measured during an on/off double blind sequential intervention of interest trial should be considered.

Insight: For research and clinical purposes, insight could be defined along five dimensions. These are: one's awareness of mental disorder and social consequences of illness, awareness of the need for treatment, awareness of symptoms in particular and relatedness of symptoms to the disorder [123]. However, reflective capacity in one domain does not predict reflective capacity in other domains [124]. Overall,

patients have more insight in the negative than the positive symptoms of the illness [125]. Insight in the neurocognitive deficits has been shown to be extremely limited even for patients who otherwise have a fair degree of insight [126, 127]. Vos et al. [128] found a decrease in predictive ability in patients with schizophrenia when compared with control. Decreased emotional awareness [129] and autonoetic awareness [130] has been reported patients with schizophrenia. Poor insight can also result in decreased awareness of side effects of medications, such as tardive dyskinesia [131].

Course

Short term: Likely Secondary: Differentiating between phenomenologicaly similar primary and secondary symptoms is essential in order to understand their short versus long term course [20]. While primary symptoms are persistent, secondary symptoms will improve once their cause is addressed. For example, if a negative symptom is secondary to depressive symptoms, a relief in the negative symptom will follow an improvement in the depressive symptomatology. Similarly, medication adverse effects might mimic negative symptoms or result in cognitive deficits. When this is the case, discontinuing or changing the offending agent to a better tolerated alternative [e.g. a first generation antipsychotic (FGA) to a second generation antipsychotic (SGA)] will result in a decrease or disappearance of the observed secondary symptom. A cause and effect relationship can be established if the reintroduction of the suspected agent is followed by a re-appearance of the suspected symptom.

The short term course of insight has been studied in a prospective 6 weeks study of 29 patients acutely hospitalized with DSM-III schizophrenia [132]. Insight into the past symptoms but not into the current illness improved considerably during the observed period. Of note, insight was inversely correlated with the presence of negative symptoms at the follow up evaluations [132].

Premorbid and First Episode (FE)

Cognitive Impairment: Individuals who are destined to develop schizophrenia show detectable cognitive differences compared to their peers as early as age 7. These findings have been replicated in large samples of studies of individuals who are being conscripted into the military service in Israel and in Sweden [133]. These changes are smaller than the impairments seen at the time of the first episode, roughly 0.5 SD worse than normative expectations, with this finding being quite consistent across studies. However, such a level of mean performance is not outside the normal range and in fact, 35% of general population performs at this level of lower. As a result, cognitive impairments are not useful as potential predictors of risk for the development of schizophrenia.

The domains of impairment appear to be relatively general during the premorbid period, but some research has focused in on what may be a specific profile of risk. In children who manifested increased risk for schizophrenia as a function of having a parent with the illness, global attentional deficits across multiple measures were associated with increased risk for the development of a psychotic disorder [134].

Some individuals who develop schizophrenia manifest a prodromal period that is detectable between the premorbid and first episode stages of the illness. During this prodromal period, there are a number of behavioral changes that are detectable. Cognitive changes during this period have been somewhat difficult to detect. For instance, it has been reported that at the time of onset of the prodrome, certain cognitive abilities such as episodic memory have already deteriorated to a level consistent with that seen during an active phase of illness. In a recent study, based on a large-scale follow-up of clinical high risk [118] individuals who were manifesting prodromal symptoms, the individuals in the CHR group with the lowest cognitive performance scores on an 8-test cognitive battery were most likely to convert to a psychosis diagnosis. Further, within the cognitive battery, low scores on measures of processing speed and verbal memory were the best predictors. These data suggest that cognitive changes occur very early in prodromal periods and the largest changes occur in individuals most likely to develop a psychotic condition.

Cognitive impairments appear to be fully developed at the time of the first episode of illness in those individuals who develop schizophrenia. Comparisons with more chronic patients reveal similar profiles and severities of impairment, suggesting that progression may not be common during the early course of illness. A 10 year longitudinal study demonstrated the stability of baseline cognitive deficits in FE patients compared with a group of healthy controls [135]. A recently published comprehensive metanalysis reports significant deficits in FE patients compared to their prior premorbid levels but a stable, chronic course after as well as no significant differences when comparing deficits in FE and chronic schizophrenia patients [12]. In another very recent and methodologically sophisticated study, high risk, first-episode, and healthy individuals were followed up over a 6-month follow-up. After adjustment for practice effects and regression to the mean, it was found that a higher than expected proportion of first episode patients improved on their verbal memory performance and a higher proportion than expected worsened in processing speed and working memory. Further, the at-risk subjects who converted to psychosis were also found to worsen in these same two variables [136]. Thus, the issue of whether there is deterioration in cognitive functioning is still an open question. It is quite clear that during this same time period, the first 10 years of illness, there are progressive changes in brain volume, often found to be associated with more psychotic exacerbations. It has been suggested that standard clinical neuropsychological tests are less sensitive to functional decline than experimental tests with greater cognitive demands.

Negative Syndrome: Andreasen's negative symptoms, Crow's type II, and Carpenter's deficit schizophrenia are all characterized by an insidious onset [9, 13, 14, 19, 20, 23]. Negative symptoms are fairly prevalent in first episode patients with schizophrenia, with estimated rates of 35–70% during relatively short (less than

2 years) longitudinal studies [80, 137, 138]. Studies of first-episode schizophrenia patients reported that flat affect is present at the onset of illness [34]. The age of onset appears to play a role in the course of negative symptoms. In a population of chronically institutionalized schizophrenia patients an earlier onset was associated with greater numbers of negative symptoms throughout life [139]. In a sample of patients who did not meet criteria for schizophrenia but were diagnosed as vulnerable to psychosis negative symptoms were significantly correlated with quality of life (QOL) and with global function as measured by the global assessment of function (GAF) scale [8, 140]. Premorbid social competence scores and premorbid schizoid traits significantly predicted the presence of negative symptoms 10 years later is schizophrenia/schizoaffective sample [141].

Insight: Insight impairment is also common in early schizophrenia and has been associated with cognitive and executive declines in multiple domains [142, 143]. During the prodrome of schizophrenia, the level of insight inversely correlates with the need of acute services [144]. This finding is possibly associated with the several factors: better support systems, treatment seeking behavior earlier in the course of relapse, and better compliance with treatment recommendations [85, 145]. For FE schizophrenia, lack of insight was a strong predictor of involuntary hospitalization [146].

Long Term Course

Cognitive Impairment: Regardless of the course of cognition in schizophrenia in early and mid life, there is quite consistent evidence that a least some people with schizophrenia show deterioration in their functioning in their later years. Patients with a history of long-term institutional stay and extremely severe and refractory positive symptoms have been shown to have subtle worsening in their cognitive functioning over a variety of follow-up periods [147]. While the presence of degenerative conditions such as Alzheimer's disease or vascular dementia does not explain these changes, some recent evidence suggests that normal-range presence of aging related changes may actually relate to risk for cognitive decline. We recently reported on a postmortem study of 110 patients with schizophrenia and found that the number of hippocampal neurofibribrillary tangles and cortical neurotic plaques were correlated with the severity of cognitive impairments [148]. Further ApoE4 carrier status was also associated with severity of cognitive impairment and the interaction of carrier status and the interaction of carrier status and plaque count was also a significant contributor.

Finally, we have also recently shown that the current presence of institutionalization is not driver of cognitive changes in older people with schizophrenia [149]. Examining a large sample of community dwelling older people with schizophrenia who varied widely in the longest institutional stay (from 1 week to 30 years), we found a correlation between longest hospitalization and risk for decline in scores on a performance-based measure of everyday living skills. We found that all of the

older people with schizophrenia, across institutional stay, showed evidence of cognitive worsening when compared to healthy controls, who manifested a practice effect. As previously reported, older patients with schizophrenia failed to manifest normal practice effects on neuropsychological tests, which is itself evidence of impaired performance. In the Granholm et al. [150] study, the older the patients with schizophrenia, the smaller their practice effects were after reassessment.

Negative Syndrome: The different types of schizophrenia with predominant negative symptoms, starting with Kraepelin *Dementia Praecox* and including modern day typologies, i.e. Andreasen's negative symptoms type, Crow Type II, as well as the deficit syndrome of schizophrenia, share a chronic course [1, 9, 13, 14, 18–20, 23]. While a poor response to D2 antagonists, the cornerstone of schizophrenia therapy at the time of Crow's and Andreasen's modern classifications, might have added to the impression of a chronic course, long term prospective studies have since confirmed this symptoms cluster persistence and stability over time. Negative symptoms appear to be not only persistent but also increasing with age [36]. In a cross sectional study of 272 patients with schizophrenia divided in 4 age groups aging was associated with increased symptom severity [37]. In a retrospective study of 99 chronically institutionalized patients the lifelong course of schizophrenia was characterized by a decrease in positive symptoms and an increase in negative symptoms [139]. Prospective studies also confirmed Kraepelin' observation about the chronic course of deficit symptoms. The longitudinal Munich study, one of the longer and the largest prospective study of schizophrenia to date, found that first-hospitalized patients had significantly more negative symptoms 15 years later [81, 82]. Putnam et al., in a prospective 1 year-long study of geriatric inpatients with schizophrenia, reported a significant increase in negative symptom severity over the study period [151]. Of note, both Putnam et al. [151] and Mancevski et al. [139] conclusions are limited by an implicit selection bias. Putnam et al. [151] only included inpatient geriatric schizophrenia patients, while Mancevski et al. [139] included records for patients who remained in state hospitals as inpatiens through the deinstitutionalization of the 1950s and 1960s and eventually died in a psychiatric hospital. A prospective 1 year long outpatient study comparing 63 patients with flat affect with 99 patients without (non flat affect) reported that flat affect was correlated with poorer premorbid adjustment, worse current quality of life, and worse outcome at 1-year follow-up [34].

Insight: In a cross sectional study of 111 patients diagnosed with schizophrenia using DSM-III criteria Cernovsky et al. [152] reported that 97.3% showed poor insight at same point during their illness and 58.6% at the time of assessment. In this study, patients with poor insight were more likely to display poor judgment, less reliable reports, were more preoccupied with delusions, less educated and socially withdrawn. While the level of insight was not correlated with outcome, the presence of insight at the first assessment predicted less need of psychiatric hospitalization and better compliance with treatment, independent of environment. In another study, schizophrenia patients with involuntary admissions showed diminished awareness of illness when compared with voluntary admitted schizophrenia patients [153]. Furthermore, poor insight was correlated with higher need of hospitalization at

2 ½ and 3 ½ follow up. The level of insight into the presence of illness and need for treatment increased significantly only in patients with voluntary hospitalization, compared with the ones with involuntary hospitalizations for the follow up period. Poor insight also correlates with negative symptoms, delusion of grandeur and sexual delusions, thought broadcasting and poor premorbid adjustment at onset of illness [154]. Medalia and Thysen [126, 127] report that patients with schizophrenia had significantly less insight into their neuro-cognitive symptoms than their clinical symptoms.

Treatment Considerations

Biological Interventions

Antipsychotics

First Generation Antipsychotics (FGAs): Traditional antipsychotic medications have no efficacy in the treatment of primary negative symptoms or cognitive impairment, beyond occasional improvement in attention [155–157].

Droulout et al. [158] found a strong correlation between low level of insight and poor medication adherence. Furthermore, insight was correlated with medication adherence independently of patients demographic and other clinical characteristics. In another study, low insight at the onset of schizophrenia predicted poor medication adherence at 6 months follow up [159]. Subjective response to antipsychotic medication was correlated with insight and paranoid ideation [160]. Sajatovic et al. [161] report that in a sample of 47 patients with schizophrenia ($N = 33$) and schizoaffective disorder ($N = 12$) treated with first and second generation antipsychotic medications or mixed treatment, only the patients treated with first generation antipsychotics showed significant improvement in their attitude toward medications. However, the change was not large enough to differentiate between groups.

Second Generation Antipsychotics (SGAs)

Cognitive Impairment: The evidence supporting the cognitive benefits or superiority for negative symptoms of SGAs versus FGAs is mixed. Two large, publicly funded, pragmatic trials comparing SGAs versus FGAs, CATIE [162] and CUtLASS [163] did not support prior claims of SGAs superiority in terms of global effectiveness, quality of life or specific domain improvement [163, 164]. CATIE did report a modest improvement over a 12 months period in a combined measure for psychosocial functioning (Quality of Life Scale) that includes a number of negative symptoms [165]. However, there were no significant differences between the different SGA agents and perphenazine. The interpretation of these results is further limited by the fact that negative symptoms change was not directly assessed. Also, due to a high dropout rate the QLS outcome could be assessed only in one-third of the patients who started the trial, which further limits the interpretation of the study

results. Furthermore in their meta-analysis of 150 RCTs including 21,533 patients comparing 9 SGAs with FGAs, Leucht et al. [162] did not find that SGAs were more efficacious for negative symptoms or quality of life (as a proxy for cognitive effects; of note, overall cognition or specific cognitive domains were not specifically assessed). However, in a meta-analysis focused on cognitive outcomes, including 18 RCTs with 1,837 patients, Guilera et al. [166] found that SGAs produced a slight improvement in the global cognitive index and in several cognitive domains (3 out 11 domains tested), compared with typical antipsychotics [166]. Due to a small effect size and as the potential for publication bias could not be excluded, due to a restricted search, Guilera et al. [166] conclusions should be treated with caution.

Negative Syndrome: In a randomized, placebo controlled study of 61 patients with refractory schizophrenia and partial response to clozapine, adding aripiprazole 5–30 mg to clozapine reduced negative symptoms over an 8 weeks period [167].

Insight: In a 52 weeks double-blind trial of 323 patients with schizophrenia or schizoaffective disorder receiving risperidone long-acting injectable, Gharabawi et al. [168] reported that insight scores correlated significantly with CGI-S, PANSS subscales, Strauss-Carpenter Levels of Functioning, and Personal and Social Performance (PSP). Overall, insight scores improved significantly at end-point observation period [169]. Aguglia et al. [170] reported improvement in insight in patients diagnosed with schizophrenia who were switched from conventional to atypical antipsychotic medication. However, in another study, only patients on first generation antipsychotics had significant improvement in the insight domain and was no differences between the groups of patients treated with first, second and mixed first and second generation antipsychotics in terms of insight [161]. This observation of no differences in insight in patients treated with first or second generation antipsychotics, was also supported by Buckley et al. [171] Less awareness into the symptoms predicted a poor drug attitude, however, there were no differences in attitude between first and second generation antipsychotics.

Antidepressants: In a metaanalysis of 11 studies (393 patients with schizophrenia spectrum disorders) selective serotonin re-uptake inhibitor augmentation did not improve the negative symptoms of schizophrenia [172].

Other Medications: Even though theoretically justified based on the underlying etiophysiology no gabaergic, glutaminergic, acethylcholinergic or other compounds have been established as efficacious for the treatment of negative symptoms or cognitive deficits in schizophrenia. Multiple studies have been conducted without notable success. As we noted elsewhere [173], methodological issues are not responsible for these failures.

Other Biological Interventions

Negative Syndrome: A meta-analysis of 9 trials ($N = 213$ patients) found a small to moderate effect size for repetitive transcranial magnetic stimulation (rTMS) for negative symptoms in schizophrenia. The effect size increased with changes in the rTMS dose and duration, with larger effect size found for stimulation above 10 Hz and duration of treatment longer than 3 weeks [174].

Psychological Interventions

Negative Syndrome and Insight Deficits: The number of CBT trials for negative symptoms and insight in schizophrenia is relatively small; however based on the available results CBT appear as a promising intervention for these clinical domains of schizophrenia. Nieznanski et al. [175] reported improved insight scores in patients who received 12 sessions of cognitive skills training versus psychoeducation. In a large (N = 422) multisite randomized controlled trial comparing nurse-led cognitive behavior therapy (6 sessions over 2–3 months) with treatment as usual, CBT improved insight, reduced negative symptoms and increased time to relapse and reduced number of inpatient days [176]. The gains were shown at 1 year in the CBT group. No improvement was found for overall symptoms, and positive symptoms, which is consistent with the view that insight and negative symptoms are independent clinical domains. Of note, at 1 year the groups did not separate in terms of return to work/ school, which suggest that the insight/negative symptoms effect might need more than 1 year to result in functional outcome improvement. Cognitive deficits were not assessed in this study.

In a review, Lewis [177] suggested that suicidal risk in schizophrenia can be reduced by working through the grief associated with facing the developing illness and attaining an usable insight that integrate both affective and cognitive components.

Cognitive Remediation in Schizophrenia

Behavioral cognitive remediation has been shown recently to produce cognitive changes and lead to relevant real-world functional improvements. Several of these approaches have shown positive effects that are durable even months after the behavioral intervention is terminated (e.g., McGurk et al. [178]). While previous results were often less positive, there have been several independent findings of cognitive enhancement leading to functional improvements. For instance, Vinogradov et al. [179] found that cognitive enhancement therapy lead to an improvement in levels of BDNF, a change not detected in a sample of people with schizophrenia who were exposed to video games during the same time period. Further, using strategies that focus on executive functioning and multiple components of cognitive abilities at the same time have led to the largest successes. McGurk and colleagues found that cognitive training (involving computerized training and planning skills) in combination with a supportive employment program yielded not just improved cognition, but higher retention rates in the program, fewer depressive symptoms, more time working, and higher wages than those in supported employment alone. Similarly, the work of Wexler and Bell [180] supports the use of cognitive remediation as a method for improving outcomes work outcomes, with a 2-year follow-up of their patients showing similar positive long-term outcomes [181].

Functional Relevance of Cognition, Negative Symptoms and Insight in Schizophrenia

A discussion about function needs to first define function and then clarify, within the parameters of the specific function definition, what constitutes ideal functioning which is no easy task considering there is no consensus on what might represent ideal functioning. It is understood that "good function" is relative and depends both on the subject's own agenda as well social and cultural, time and place specific factors. A systematic way of accounting for these variables can be organized along 3 main dimensions: (1) subjective wellbeing/satisfaction (2) functioning in daily life, and [114] external resources and social support. This is the basis of the Quality of Life (QOL) concept, a complex construct that is generally agreed as a good enough functional outcome [182].

Cognitive Impairment: One of the major reasons for the increased interest in cognition in schizophrenia is functional relevance. Cognitive impairments are strong predictors of the impairments in real-world functioning that affect many people with schizophrenia [183]. Previous speculation was aimed at whether there were specific relationships between domains of cognitive functioning and specific real-world outcomes such as social and vocational milestones. At this time, the research findings are inconsistent in terms of specific relationships between cognitive functions and aspects of functional outcomes. As noted above, processing speed is a major contributor to the prediction of real-world outcomes much like it contributes to the prediction of overall cognitive performance.

One recent development in the study of cognition and functioning in schizophrenia is that of performance-based assessment of everyday functional skills, often referred to as assessment of "functional capacity" [184]. These assessment instruments are similar to neuropsychological tests in that they are designed to measure performance, not self-report, and to have suitable psychometric characteristics in domains of test retest reliability, sensitivity to change with treatments. These measure tap a number of aspects of functioning, including social, vocational, and residential skills. Further, the latest stages of the MATRICS process also include these indices as co-primary measures of treatment outcomes.

Several studies have suggested that the "true" causal influence between cognitive impairments and real-world functional deficits is through the impact of cognitive deficits on functional capacity. These studies have shown that cognitive performance measures add relatively little incremental prediction of real world functioning after functional capacity measures are considered [185]. In addition, these measures have shown excellent validity across different psychiatric diagnoses and appear to predict real-world outcomes quite similarly in bipolar and schizophrenia patients and in schizophrenia patients across different Western Cultures.

Negative Syndrome: The deficit or negative syndrome of schizophrenia has generally been considered too have a poor a poor prognosis due to its chronic course, and generally poor response to medications [9, 14, 18].

The predictive value of negative symptoms has been analyzed in a prospective 10-year follow up study of patients with schizophrenia/schizoaffective disorder, non-psychotic disorders and other psychotic disorders [141]. Negative symptoms were predictive of work functioning and cognitive deficits at later follow-up for the full study sample; in addition, a divided by group analysis showed significant results for the schizophrenia/schizoaffective group only, which might indicate more secondary negative symptoms in the other groups [141].

Converging line of evidence including cross sectional studies, retrospective and prospective studies consistently show that negative symptoms have been associated with a poor overall outcome. In a prospective 1-year study comparing 63 flat affect patients and 99 non flat affect patients flat affect correlated with worse quality of life (cross sectional measure) and worse outcome at the final 1 year follow up [34]. A longitudinal FE study with a 7-year follow-up reported that negative symptoms at intake, in addition to verbal memory, processing speed and attention, predicted global psychosocial functioning [186]. In a prospective 10-year study negative symptoms correlated with concurrent and prospective impairments in social functioning at all three study visits (i.e. 4.5-, 7.5- and 10-year follow-ups) with deficits in work functioning and higher rehospitalization rates at two of the three follow-up visits [141]. Finally, the prospective large sample Munich study of first hospitalized patients found that a negative syndrome at discharge indicated a poor outcome (as measured by Global Assessment Scale) 15 years later [81, 187].

Insight: It has been estimated that between 30 and 50% of patients with schizophrenia have poor insight (for a review, see Baier [188]). Hwang et al. suggests that better insight is predicted by the presence of affective symptoms such as depression and anxiety [189]. Sevy et al. [190] proposed that lack of insight into the symptoms correlates with severity of illness in schizophrenia. However, patients with schizophrenia with better insight can have more affective symptoms and suicidal ideation, which in turn could affect quality of life [191].

Interestingly, when it comes to insight an early onset of schizophrenia appears to carry a better prognosis: Heinrichs et al. [86] found that in 63% of the early schizophrenia patients have preserved insight, which in turn correlated with significantly lower hospitalization rate when compared to patients with poor insight. Early improvement of insight in FE schizophrenia appear to also predict a better outcome at 1 year follow up [192]. According to the report from family members of patients with schizophrenia, as the illness progresses, the number of patients with good insight can decrease to 27% [193]. Yen et al. [194] in a study of 74 Chinese outpatients with schizophrenia in remission reported that from all the insight dimensions only insight into treatment was associated with less hospitalization and better social adjustment. Llorca [195] reports that a lack of insight correlates with poor or partial compliance and that in turn, is associated with poor outcome. Overall, insight predicts relapse and remission in patients with schizophrenia [196].

Cross Relationships

The relationship between cognitive and negative symptom: Both the primary negative symptoms and cognitive dysfunction domains appear to share a number of characteristics: 1. They are relatively independent of the psychotic, affective and secondary negative symptoms domains, which tend to vary together in correlation with the course of illness and response to medications; 2. They have long term stability; 3. They respond poorly to available antipsychotic treatments; 4. They are both correlated with prognosis; 5. They are correlated with outcome, specifically with social and functional outcomes.

T*he relationship between cognitive deficits and insight*: Sevy et al. [190] suggested that poor insight into consequence of illness correlates with positive symptoms and poor insight into the need for treatment correlates with poor cognition. Lack of awareness in various aspects of the illness specifically correlates with degree of impairment in cognitive, affective and psychotic symptoms [197]. Interestingly, patients with a fair degree of overall insight can show severe insight deficits into their cognitive impairments [198].

The relationship between insight and negative symptoms: A number of studies showed that lack of insight correlates with prognosis and functional/social outcomes; similarly, prognosis and social isolation correlate with negative symptoms [199]. While these correlations suggest that these might be somewhat interconnected domains, the nature and strength of the insight – negative symptoms relationship is far from clear. In their metanalysis of 20 studies ($N = 1{,}487$ subjects) Mintz et al. [123] reported a significant inverse correlation with a mean effect size of –0.23 (CI = –0.48–0.02), indicating that as negative symptoms increased, overall insight decreased. Four out of the five tested insight dimensions were inversely correlated and significant: awareness of mental disorder –0.20; attribution of symptoms to disorder –0.33; understanding of the social consequences of disorder –0.40; and awareness of the need for treatment –0.40). The relatively modest effect sizes for awareness of mental disorder (–0.20) and attribution of symptoms to disorder (–0.33) are harder to interpret. The moderate effect sizes for awareness of the social consequences of disorder (–0.40) and need for treatment (–0.40) might be yet another indication of the fact that negative symptoms correlate with social dysfunction. Mintz et al. [123] also reported an older age of onset effect on the relationship between negative symptoms and insight: the older the patient was at the onset of illness the stronger the negative correlation. Of note, this finding is at odds with preexistent literature suggesting that the younger the patient the higher the risk of negative and cognitive symptoms [35]. The modest to moderate at best effect sizes of this study have been interpreted as an indication that insight might represent a separate symptom domain [41]. Further supporting this hypothesis, in a prospective 6-months, multi-site, open-label, risperidone long-acting injection phase IV trial of 303 subjects with recent onset ($\leq$2 years) schizophrenia injection Wiffen et al. [41] reported that changes in insight did not correlate with changes in total symptoms

or negative symptoms which further suggests that this might possibly be independent symptom domains. More studies are needed for a conclusive resolution of these questions.

Discussion

In this review we presented in parallel characteristic aspect of 3 symptoms domains of schizophrenia that have been traditionally linked to one another: neurocognitive deficits, negative symptoms and insight deficits. Differentiating between primary and secondary symptoms (for all the discussed domains) is paramount. Primary symptoms show a number of common characteristics across domains: a correlation with premorbid level of functioning, a chronic course, and a relative independence of other symptom domains (i.e. positive symptoms). Insight appears to inversely correlate with low mood and anxiety, which is not the case for the other domains. However, this finding might also be an artifact of a poor separation between primary and secondary insight deficits. In terms of neurobiological correlates there is a partial overlap between cognitive and negative symptoms; however specific neurobiological correlates have also been reported. The neurobiology of insight is even less clear.

While all three domains are associated with poor prognosis and poor functional outcomes, negative symptoms and cognitive deficits share a positive association (i.e. higher severity results in poorer prognosis and outcomes), while insight correlates negatively (i.e. better insight correlates with poorer prognosis and outcome. Furthermore, negative symptoms and cognitive deficits appear to have an independent effect on prognosis and outcome.

Available interventions are generally ineffective for negative symptoms and cognitive deficits and have shown mixed results for insight.

We conclude that despite apparent similarities and partial overlaps insight deficits, negative symptoms and cognitive deficits are separate symptom domains of schizophrenia. There is a stronger relationship between cognitive deficits and negative symptoms than between insight and negative symptoms or cognitive deficits.

This conclusion has important applications. At a theoretical level the implication is that, similarly to its clinical presentation, the underlying neurocircuitry and pathophysiology of schizophrenia is diffuse and heterogeneous rather than localized and homogeneous. At a more pragmatic level the relative independence of the insight, cognitive and negative symptoms suggests that effective interventions might need to selectively target each of the domains.

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Chapter 3
Stress, Dissociation and Schizophrenia

Petr Bob

Abstract Recent findings indicate that binding and synchronization of distributed activities are crucial for the mechanism of consciousness and there is increased evidence that disrupted feature binding produces disintegration of consciousness in schizophrenia. These data suggest that the disrupted binding and disintegration of consciousness could be related to dissociation, which is historically linked to Bleuler's concept of splitting in schizophrenia. Main topic of this chapter is influence of stress on brain structures, dissociation of consciousness and increased sensitivity to stressors. Stress induced sensitization likely may influence limbic irritability and epileptic-like activity through changes in brain synchronization and complexity that affect binding and other mechanisms of consciousness. These changes in brain dynamics may manifest in the form of cognitive, affective and memory symptoms that are similar to psychopathological symptoms, which occur in temporal lobe seizures but in non-epileptic conditions. These findings have also practical implications for pharmacological treatment because several patients with schizophrenia and also other patients who experienced extreme stress could be identified for anticonvulsant treatment.

Keywords Consciousness · Binding problem · Dissociation · Schizophrenia · Traumatic stress

Consciousness and Schizophrenia

More than three centuries ago, Rene Descartes in his theoretical concept anticipated the "binding problem" of consciousness and thought that "... although the soul is joined to the whole body there is a certain part where it exercises its functions more than all the others" [1, 2]. This process of cognitive "binding"

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presents a process that integrates neural activities of functionally distinct cognitive modules [3]. In this context, the hypothetical center for information convergency was termed by Daniel Dennett "Cartesian theatre" [4, 5], although in recent neuroscience such place in which distributed information in the brain comes together has not been found [6]. With respect to these findings Dennett [5] proposed "a multiple drafts" theory of consciousness that defines consciousness as a distributed process where instead of a single and central "Cartesian theatre," there is a content-fixation that occurs in various places at various times in the brain (see Dennett [5, p. 365]). In agreement with these findings, further evidence indicates mechanisms of multiregional functional interaction related to binding of distributed information [7–9] and there is evidence that neocortical processing is distributed during all sensory and motor functions [9].

Acumulating evidence from experimental studies also shows that this process of dynamic binding can be related to transient and precise synchronization of neuronal activities that is significantly disturbed in certain pathological conditions, such as in schizophrenia [10, 11]. These disturbed interactions produce patterns of temporal disorganization with decreased functional connectivity that may underlie specific perceptual and cognitive states and cause disintegration of information across specialized brain areas [12, 13]. For example, functional disconnections between certain parts of the brain could likely play a role in dissociative disorders and may occur during dreaming or hypnosis [14–16]. This disintegration of consciousness probably produces defective self-monitoring and self-experiencing [17–19] and this lack of interaction and disintegration likely reflects the process of functional segregation of sets of neurons localized in different cortical areas.

Together these findings suggest that mental dissociation that is likely related to disturbed neural integration may represent a significant factor in the development of schizophrenia [10, 11, 16, 20]. The disturbed neural integration may cause heightened number of independent neural assemblies (i.e. heightened brain complexity) and in principle it is possible that the heightened complexity is on level of mental representations linked to a number of independent clusters in associative chains or ideas which leads to disorganization in cognition and mental associations. These neuropsychological deficits may result in dissociative symptoms in schizophrenia and increased complexity in verbal associations. Increased neural complexity in the case of schizophrenia therefore might represent a neural process that determines random-like and disorganized cognition, although in fact it may be characterized by complex law- mediated behavior [21]. These processes consequently might lead to information overload, deficits in attentional filtering and frontal lobe executive dysfunction [22–24]. Supportive data for this concept linking dysfuncional integration on the level of brain and mental connectivity also present word recall studies which indicate some disturbances in connectivity linked to associative strength. For example, several studies have shown the influence of NMDA receptor antagonists on recurrent inhibition that produces a schizophrenia-like disturbances in association patterns and dysregulation in suppression of associations [25–27]. The dysregulation could be closely related to defective attentional filtering and a failure to inhibit activity of irrelevant neural assemblies [28, 29] and pathologically increased

neural complexity [30]. The increased complexity could be linked to competing associations caused by the presence of a conflict among them that determines defective attentional filtering.

Together these findings suggest that current research on disturbances of binding and connectivity in schizophrenia may provide new conceptual understanding which may enable to connect neurobiological studies of schizophrenia with several recent psychological concepts that historically follow ideas proposed by Bleuler and concept of dissociation described by Janet.

Bleuler, Janet and the Concept of Schizophrenia

In the 1880s, Eugen Bleuler after completion of his medical studies in Zürich in 1881, started to develop a new concept that the core problem in chronically psychotic patients is determined by disruptions of thought linkages and deficits in coordination of different psychological functions leading to "loosening of associations" that preceded his redefinition of Kraepelin's term dementia praecox. Later in 1911 Bleuler in his work Dementia praecox or the group of the schizophrenias, introduced the term schizophrenia to describe this serious illness that replaced dementia praecox [31–33]. In his Text-book of psychiatry he wrote [34]: "It is not alone in hysteria that one finds an arrangement of different personalities one succeeding the other. Through similar mechanism schizophrenia produces different personalities existing side by side." (p. 138). The process of splitting in schizophrenia is according to Bleuler [34–37] the same as splitting of psychic connections in hysteria and in an extreme version it can lead to the emergence of alter personalities and typical amnesia. These important Bleuler's ideas regarding the notion of schizophrenia are historically related to the concept of dissociation developed by Pierre Janet [31, 38–42]. Etiology of schizophrenia is thus traditionally explained by Bleuler along the lines of Pierre Janet as being a consequence of dissociative reaction, analogous to somnambulism, fugue states, hypnosis or psychogenic amnesia [31, 41]. Dissociative reaction is most often a consequence of abuse or traumatic experiences leading to a loss of the inhibitory control of certain mental contents that may lead to the production of split fragments of the psyche due to abnormal intensive negative affect. Pierre Janet, in his work about psychological automatisms, defines the process of loosening associations using word "désagrégation" that was later synonymously used with the term "dissociation" and became known mainly through the works of William James and Morton Prince [31]. According to this Janet's description, dissociation means defect of the associated system that creates the secondary consciousness, which he called the subconscious fixed idea [31, 38, 39]. Following hypnotic experiments with his teacher Charcot, Janet found that people under hypnosis experienced exceptional states of divided consciousness which manifested as "different personalities" [31, 38]. This line of investigation later appeared also in psychoanalytical works of Sigmund Freud and Joseph Breuer who considered secondary consciousness in "Studies in hysteria" [43].

These historical data suggest that basic ideas underlying concept of schizophrenia and dissociation are very close. Main arguments for this historical connection

are very similar terminological definitions that were proposed by Bleuler and Janet for description of mental disintegration in schizophrenia and dissociative states. In this similar context, Janet used the term dissociation to denote a splitting of the psyche and on the contrary Bleuler and Jung used the term dissociation as a synonym for splitting, which suggest that historical roots for the same meaning of splitting and dissociation seem to be evident [31, 33, 44]. Similar relationship is also between structural descriptions of the subconscious fixed idea defined by Janet and the psychic complex comprehensively described by Jung [31, 44]. Jung in his research on complexes confirmed Janet's findings of the dissociability of consciousness and the potentiality of a personality disintegration into fragments [45]. Similarly Bleuler in his "Consciousness and Associations" described complexes analogically to Janet's description of fixed ideas and wrote that there is "no difference in principle between unconscious complexes and these several personalities endowed with consciousness" because of increasing number of disturbed associations with the ego as a whole (Bleuler [32, p. 291]). Similarly in the recent literature the fixed idea is described as a formation of new spheres of consciousness around memories of intensely arousing experiences with a high emotional charge, which organize cognitive, affective and visceral elements of the traumatic experience while simultaneously keeping them out of conscious awareness [39]. It is analogical to the definition of the complex as an organized collection of ideas, emotions, impulses and memories that share a common emotional tone, and have been excluded partly or entirely from consciousness but continue to influence a person's thoughts, emotions and behavior [46].

The term complex was introduced by Theodor Ziehen, who used this term in the late 1890s for explanation of prolonged reaction time in the word association test as a reaction to something unpleasant for the subject [31]. Jung elaborated the theory of psychic complexes in his experiments in Burghölzl and described them in his studies of word associations [47–49]. He for the first time proposed that when a deficit occurs in free associations it is caused by a complex [47, 49]. According to Jung's findings the complex always has its own autonomy and behaves as a split part of the psyche. When a complex is evoked into the consciousness, its physiological or pathological influence depends on a degree of its autonomy or, contrary to that, compatibility with other complexes respective to the ego-complex. In the case of pathological influence the complex leads to a lowered mental level (abaissement du niveau mental) [31, 38–40].

The fundamental causes of the etiology of pathological dissociated fixed ideas or complexes, as Janet suggested, are mainly traumatic events, which produce traumatic memories. Complexes thus generate alternate fields of the psyche, and it is possible, by means of these complexes, to explain also extreme cases which occur in multiple personality disorder or schizophrenia [41]. In the The Psychology of the Dementia Praecox, Jung experimentally demonstrated a dynamic concept of schizophrenia based on the theory of dissociated complexes [31, 44]. He applied the associative experiment to schizophrenic subjects and compared these results to experiments performed in normal persons. These experiments led him to define a condition of inner distraction determined by a complex. The condition is

analogical to Weygandt's term "apperceptive deterioration" and is closely related to the concept of "abaissement du niveau mental" proposed by Janet as the cause of dissociation [31, 40, 44, 50, 51]. Jung's experimental findings in neurotic and psychotic patients as well as in normal persons have documented material supporting Bleuler's clinical hypothesis regarding the common mechanisms underlying the formation of symptoms in hysteria and the symptoms of dementia praecox [31, 44]. According to Jung, during schizophrenia the psyche is split-off into a plurality of autonomous complexes and the whole personality is pathologically disintegrated. Jung also provides detailed analysis that certain changes in consciousness found in dementia praecox are very similar to them found in dissociative states or in hypnosis [44]. Typical changes present signs of a narrowing of consciousness and abnormal increase in the indistinctness of all subsidiary associations, which may explain tendency to accept an idea without inhibition and correction. This phenomenon may occur in schizophrenia or trauma related dissociative states and presents a phenomenon analogous to hypnotic suggestion characterized by increased sensitivity and suggestibility [44]. This process likely may be explained by dis-association of the complex that tends to paralyse other psychic activities from other mental processes that usually enable inhibitory control. This conceptual understanding of schizophrenia is according to Jung also in agreement with clinical data reported by Riklin [44 Riklin, 1904- Zur Psychologie hysterischer Dammerzustande und des Ganser'schen Symptoms], who found that patients may manifest delusional orientation or hallucinatory experience according to a manner of questioning related to psychological events linked with complex. For example, Riklin also reported a case study ("Cases Illustrating the Phenomena of Association"), where a critical stimulus word presented to the patient induced a twilight state which is typically presented as a state of consciousness related to an experience of visual or auditory hallucinations and other psychotic symptoms [44]. These historical data also suggest that association and dis-association of various mental contents may present basic model that connect Janet's and Bleuler's conceptual understanding of the mind and its changes during psychopathological states.

Following these findings also later studies of word associations reported that schizophrenic responses to a stimulus word are often bizarre, idiosyncratic and without expected context [24, 44, 52–54] and that patients with schizophrenia have impaired verbal fluency which is likely caused by dysfunction in access and/or retrieval of lexical information [55–57]. Recent data also indicate that schizophrenic patients manifest a deficit in the organization of semantic memory in schizophrenia which is more disorganized and less definable than those of controls, with more semantic links and more bizarre and atypical associations [57–59]. In agreement with the concept proposed by Bleuler and Jung also several studies of textual analyses of the semantic processing have found that schizophrenic speech is less predictable, more repetitious, and often violates the rules of normal discourse [24, 60–62].

This historical conceptual framework for dissociation and "splitting" in schizophrenia is also in agreement with recent findings indicating significant influence of stress-related events and dissociation in the pathogenesis of schizophrenia

[16, 63–67]. These findings on dissociation in schizophrenia are also in agreement with recent models of schizophrenia suggesting a specific role of stress in pathogenesis of schizophrenia. For example, Walker and Diforio [68] proposed "a neural diathesis-stress model" of schizophrenia that integrates the psychosocial and biological research on stress in schizophrenia. The model is based on evidence that stress worsens symptoms and that the diathesis is associated with a heightened response to stressors. The authors suggest that a neural mechanism for these phenomena presents mainly the augmenting effect of the HPA axis on dopamine synthesis and receptors that may lead to abnormalities in dopamine receptors, which together with hippocampal damage significantly influence hypersensitivity to stress in schizophrenic patients. In context of this model Read et al [63] developed "a traumagenic neurodevelopmental model". The model is based on basic principles of the diathesis-stress model of schizophrenia and proposes that genetic deficit creates a predisposing vulnerability in the form of oversenstivity to stress related to adversive life events of child abuse which according recent evidence present basic contributors to development of schizophrenia [69–76]. Main mechanisms of this process present influences of traumatic events on the developing brain and neurobiological abnormalities that frequently occur in patients with schizophrenia, which mainly include overactivation of the HPA axis, structural changes to the brain such as hippocampal damage, cerebral atrophy, reversed cerebral asymmetry, ventricular enlargement and also dopamine, norepinephrine, and serotonin abnormalities [63].

In agreement with findings that dissociation is closely related to stress and traumatic events these data suggest that dissociation in schizophrenia may play an important role in its development. For example, Lysaker and Larocco [77] studied the prevalence of significant traumas in schizophrenia patients and reported that two thirds of their chronic schizophrenia patients exhibited clinically significant trauma symptoms including intrusive experiences, defensive avoidance and dissociative symptoms. Current data also indicate that hallucinating schizophrenia patients had higher percentages of dissociative experiences in comparison to other schizophrenia patients [78]. In agreement with these findings, Ross [42] – in his new theory of the existence of a dissociative subtype of schizophrenia – proposed that the subtype may occur in some patients, who have a history of traumatic experiences and manifest significant level of dissociative symptoms.

Dissociation, Stress Sensitization and Schizophrenia

Recent research findings provide increasing evidence that stress experiences and especially traumatic stress are related to psychological and neurobiological processes that may have lasting consequences and significantly influence brain functions, and play an important role in various psychiatric diseases including dissociative disorders and schizophrenia [79–81]. Among specific influences of stress on brain functions belong influences on memory consolidation which significantly affect fixating of new information in long-term memory [82, 83] and may also disturb mental integrity, and lead to dissociation of memory and mental experience

[84, 85]. These findings also suggest that dissociation could be explained by atypical memory consolidation caused by inescapable stress, which may block the induction of long-term potentiation in the medial prefrontal cortex and hippocampus [82, 86–88]. The dissociated memories related to a traumatic event are often accompanied to increased sensitivity, aversive feelings and also to physical sensations representing somatoform components of dissociation [85, 89, 90]. Recent findings suggest that repeated stressful events leading to an increase in responsiveness to stress stimuli and increased vulnerability to stressors may determine sensitization process that may have lasting consequences with kindling-like progression [91, 92]. This state of increased sensitivity may be related to an imbalance in interactions between dopaminergic and glutamatergic systems, altered dopamine neurotransmission and consequent alterations in cognitive biases that present important and critical conditions in pathogenesis of schizophrenia [93, 94]. According to recent findings this increased sensitivity and imbalance of neural systems could be explained by sensitization that leads to an increased response to certain stimulus, which at the beginning of this process was subthreshold and caused no or low responses [95, 96].

A specific form of sensitization that could play a role in pathogenesis of schizophrenia is progressively increasing response of groups of neurons due to repetitive subthreshold stimulation that may later lead to epileptic or epileptiform activity [91, 97, 98]. This phenomenon known as "kindling" was firstly reported by Sevillano in 1961 and later elaborated by Goddard who comprehensively described this process using stereotactically implanted electrodes [91]. Recent findings suggest that the kindling related to focal after-discharges within the amygdala and other brain structures may cause local changes in synchronization and seizure-like activity which could be important in pathogenesis of schizophrenia [97–99]. These findings potentially may explain treatment resistance to usual antipsychotic medication in several schizophrenia patients and also clinical importance of an appropriate anticonvulsant medication, even in patients who do not display seizures or epileptiform abnormalities on scalp EEG [100, 101]. Several findings also show that epileptiform activity may occur as symptoms similar to temporal lobe epilepsy such as somatic, sensory, behavioral and memory symptoms that may occur also in nonepileptic conditions [80, 102]. These symptoms have been found to play a role also in schizophrenia and significant presence of these symptoms in treatment resistant patients might indicate good response to anticonvulsant drugs [103].

Within this context also dopaminergic hypothesis of schizophrenia provides results that show positive schizophrenic symptoms as consequences of hyperdopaminergic kindling in mesolimbic dopaminergic system [98, 99, 104]. The concept of kindling as a model for psychopathology in several schizophrenia patients is in agreement with recent findings that schizophrenia is often related to a loss of physiological balance between excitation and inhibition [99]. Typical for this disbalance is that the normal equilibrium between excitation and inhibition permanently alters by repeated focal excitation or kindling, resulting in a permanent state of excessive focal excitability and spontaneous seizures [99, 105]. Several recent findings suggest that similar "kindling" or sensitization may originate in inhibitory systems in response to focal physiological pulsed discharges of limbic and

hypothalamic neurons and this excess of inhibitory factors may then manifest as a psychosis [99]. This excessive focal inhibition may be induced by increased release or increased receptor density of several inhibitory transmitters [106]. According to these findings discharges related to increased excitatory neural activity may also be modulated by a regionally-specific compensatory upregulation of GABA-A receptors in response to decreased GABAergic input in hippocampal pyramidal cells [107, 108]. In general, GABA neurons provide both inhibitory and disinhibitory modulation of cortical and hippocampal circuits, contribute to the generation of oscillatory rhythms and participate in discriminative information processing such as gating of sensory information, and attentional filtering within the corticolimbic system that are typically affected in schizophrenia [97, 109, 110]. In agreement with this role of GABA neurons in cognitive functions several findings also suggest that disturbances in GABA system might be related to stressful conditions and alterations in the dopamine system [80, 81, 94, 109]. Furthermore influence on disturbances in GABA system may also exert increased flow of excitatory activity from the basolateral nucleus of the amygdala [109].

In more general context these above reviewed data are in agreement with recent findings suggesting an importance of sensitization or "kindling-like" phenomena in pathogenesis of mental disorders that have received a great deal of attention in efforts to conceptualize the pathophysiology of seemingly diverse psychiatric disorders such as schizophrenia, mood disorders, drug addiction, or posttraumatic stress disorder [91, 93, 111, 112].

Conclusions and Future Directions

Recent findings indicate that binding and synchronization of distributed neural activities that enable information integration are crucial for the mechanism of consciousness and there is increased evidence that disrupted feature binding and information integration produce disintegration of consciousness in schizophrenia [10]. These disturbed interactions produce patterns of temporal disorganization with decreased functional connectivity that may underlie specific perceptual and cognitive states, and several data indicate that this disintegration of consciousness in schizophrenia could be related to dissociation, which is historically linked to Bleuler's concept of splitting. Within this context dissociative processes in schizophrenia were reported in various studies and a new framework for understanding schizophrenia was recently suggested by Ross [42] in his theory of the existence of a dissociative subtype of schizophrenia that may occur in some patients who have symptoms closely related to dissociative identity disorder and have a history of traumatic experiences. Several findings also suggest that the lack of brain connectivity related to conscious disintegration in schizophrenia could be specifically related to a level of dissociation [16], which suggests a direction for further research that could examine relationships of brain connectivity to dissociation mainly in patients with dissociative disorders but also in other patients and healthy

controls. Other important aspect for further research is stress sensitivity related to dissociative states. In this context, various data indicate that stress induced sensitization likely may influence limbic irritability and epileptic-like activity through changes in brain synchronization and complexity that affect binding and other mechanisms of consciousness. These changes in brain dynamics may manifest in the form of cognitive, affective and memory symptoms that are similar to psychopathological symptoms, which occur in temporal lobe seizures but in non-epileptic conditions. These findings also suggest a direction for future research that potentially may have important practical implications for pharmacological treatment of several patients with schizophrenia and other patients who experienced extreme stress and could benefit from anticonvulsant treatment.

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Chapter 4
Understanding the Role of Emotion in Psychosis: Social Anxiety Disorder in First-Episode Psychosis

Maria Michail and Max Birchwood

Abstract Affective disturbances are highly prevalent in non-affective psychosis and exert significant impact upon its course and outcome. Low mood and associated suicidality, anxiety symptoms, withdrawal and isolation have been consistently observed throughout the course of psychosis, during the prodromal phase and following symptomatic recovery. Social anxiety disorder in particular is among the most prevailing disturbances manifest in people with psychosis. Prevalence rates range between 17 and 36% in people with psychosis. The nature and phenomenology of social anxiety in psychosis are not well understood and the need to identify the developmental and psychological origins is of fundamental importance. In this chapter we will thoroughly examine the phenomenology of social anxiety in first-episode psychosis and we will also investigate its relationship with positive symptoms and particularly paranoia Understanding the pathways and psychological processes that lead to the development of affective dysfunction in psychosis will have important implications for psychological interventions and treatments.

Keywords Affect · Social anxiety · Paranoia · Psychosis

Abbreviations

CBT	Cognitive behavioural therapy
DSM	Diagnostic and statistical manual of mental disorder
FEP	First-episode psychosis
PPD	Post-psychotic depression
SaD	Social anxiety disorder

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Introduction

Eugene Bleuler was one of the first to emphasize the importance of affect and its pronounced impact upon the course and outcome of psychosis. The famous "*Krapelian dichtocomy*" which supported the clear distinction between mood and psychotic illnesses on the basis of etiological origins, symptomatology, course and outcome was first challenged by Bleuler. Bleuler recognized the disorders of affect as one of the four primary symptoms (blunted *"Affect"*, loosening of *"Associations"*, *"Ambivalence"*, and *"Autism"*) of schizophrenia, as opposed to delusions and hallucinations which were perceived as secondary. Specifically, Bleuler postulated the incongruity between emotions and thought content in people with schizophrenia as well as their diminished or even complete lack of emotional responsiveness. Bleuler's recognition of the importance of affective disturbances in schizophrenia has influenced current diagnostic definitions and criteria of schizophrenia.

Affect and Psychosis: Evidence Towards a Link

The sharp distinction between affect and psychosis which has dominated both research and clinical practice during the nineteenth and twentieth century has gradually been abandoned. New evidence from epidemiological, familial and molecular genetic studies [1–3] have come to light demonstrating the endemic nature of affective disturbances in psychosis.

Molecular genetic studies. In a twin study by Cardno et al. [1], the authors aimed to identify whether the schizophrenic, schizoaffective and manic syndromes shared common genetic and environmental risk factors. Findings showed a great degree of overlap in risk factors between the three syndromes. Specifically, significant genetic correlations were reported between the schizophrenic and manic syndromes. This finding is in accordance with a review of genetic linkage studies of schizophrenia and affective disorders [4] which supports the genetic overlap of the two syndromes. Cardno et al. [1] further reported that environmental risk factors contributing to schizophrenia were also shared by the manic syndrome. The authors reported similar findings with regards to the schizoaffective syndrome which also shared genetic, although not environmental, components with schizophrenia and mania. Craddock and Owen [3] in their review also make reference to findings from family and gene studies showing how mania and schizophrenia share certain susceptibility genes and chromosomal regions, challenging thus the "*Kraepelian dichotomy*".

*Studies in high risk group*s. Studies examining developmental risk factors and premorbid variables predicting transition to psychosis have been instrumental in depicting the important role of affective disturbances even prior to the onset of psychosis. Tien and Eaton [5], in a prospective study examining the psychopathological precursors for schizophrenia, reported the relationship between anxiety, specifically social phobia, social withdrawal and panic attacks with an increased risk for the development of DSM-III schizophrenia. Similar findings were later reported by Hollis [6] in a study examining the developmental precursors in children and

adolescents with schizophrenia. Increased rates of premorbid dysfunction and particularly emotional disturbances such as social anxiety, withdrawal and isolation were documented in those individuals who developed schizophrenia. Findings from the Edinburgh High Risk Study [7, 8] confirm how the presence of social withdrawal and socio-emotional dysfunction in people identified as being at risk for developing psychosis are among those factors predicting transition to psychosis. Specifically, introversion, social anxiety and isolation were the most prominent and prevalent during the prodrome and distinguished individuals at high-risk who became ill from those who stayed well.

Studies in the acute phase of psychosis. A substantial bulk of evidence has consistently shown the high prevalence of affective disorders (depression, suicidality, post-traumatic stress disorder, social anxiety and associated distress) during the course of psychosis. Upthergrove et al. [9] reported a 50% prevalence of depression in people with first-episode psychosis. Similar findings have been reported in studies of enduring schizophrenia (Leff, cited in DeLisi, 1990) [10]. The presence of depressive symptoms in the course of psychosis has been among the predictive factors for actual suicide and suicide attempts particularly among people with first-episode psychosis [11]. Barrett et al. [12] have reported increased rates of suicide attempts in people with early psychosis and their association with higher number of depressive episodes. Elevated levels of social anxiety symptoms and avoidance have also been reported during the course of psychosis [13–15] along with symptoms of post-traumatic stress disorder and associated distress [16, 17].

Studies in the post-psychotic phase. The presence of affective disturbances following symptomatic recovery has been thoroughly documented in literature. Upthergrove et al. [9] reported a 32% prevalence of post-psychotic depression (PPD) in young people with first-episode psychosis accompanied by high rates of suicidal thinking. Previously reported findings [18] confirm the high prevalence of PPD in psychosis and also show that this develops independently to positive and negative symptoms. Symptoms of PTSD have also been reported in the year after discharge in patients with a psychotic disorder of recent onset [16] and also in patients in treatment of recent onset psychosis [19]. Findings suggest that potentially stigmatizing beliefs and the trauma of psychosis itself (e.g. admission, police involvement) may be implicated in the development of PTSD following a psychotic episode [19, 20]. Social anxiety disorder has also been observed in about 30% of individuals in the year following a first-episode of psychosis [21, 22]. This was accompanied by elevated levels of depression and the presence of other comorbid anxiety disorders [21].

Social Anxiety Disorder

What Is Social Anxiety?

According to the DSM-IV [23], social anxiety disorder (social phobia) is defined as *"a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by*

others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing". People with social anxiety desire to make a favourable impression during social encounters but at the same time doubt their ability to do so; they fear that they will be scrutinized and negatively evaluated due to perceived failed social performance [24]. These fears lead people with social anxiety to avoid all or some social situations and in extreme cases they could lead to complete social isolation [25]. Exposure to the feared situation is almost always accompanied by physical symptoms, for example, sweating, trembling, heart racing, which could develop (although not necessarily) to panic attacks.

Evidence regarding the distinction of social phobia into two subtypes, the non-generalized and generalized social phobia, is ambiguous; although the DSM-IV does acknowledge the presence of the latter. This encompasses a wider range of fears linked to interaction situations and therefore is not restricted to particular environmental circumstances (i.e. it is "free-floating"). It may include talking to others, asking questions, meeting new people, manifest in fear and avoidance of everyday situations [26]. These kinds of social fears have been exclusively reported in approximately two-third of people with lifetime social phobia indicating that the generalized subtype might be more prevalent compared to the non-generalized one [27]. This, sometimes also called "specific" or "discrete", is mainly characterized by performance-type fears, the most common being that of speaking in public or performing in front of an audience [28, 29]. It seems therefore that the generalized subtype reflects a more pervasive and debilitating form of the illness which is supported by evidence showing higher rates of comorbidity with mood and other anxiety disorders [26] and lower recovery rates, compared to the non-generalized, specific subtype [27].

Questions about whether these subtypes form two distinct clinical entities or whether they represent variants of the same disorder [30] have given rise to two different conceptualizations; the "*quantitative distinction*" which holds that social phobia should be perceived dimensionally on a continuum of severity with mild levels of social anxiety or subsyndromal social anxiety on one end, moving to specific social phobia followed by generalized social phobia without avoidant personality disorder as a more severe form and ending to the opposite pole, with the most severe form of social phobia that of generalized subtype with avoidant personality disorder [30–34]; and the "*qualitative distinction*" which represents the subtypes as two different clinical entities based primarily on the type of feared situations. While generalized social phobia is characterized by anxiety and fear of any situations that might involve interaction with others, specific social phobia seems to be limited to performance situations, particularly that of speaking in public. Additionally, the non-continuous nature of the two subtypes seems to be further validated by differences in age of onset, heritability, physiological reactions when exposed to the feared situations and developmental history [30].

Epidemiology

One of the most well known epidemiological investigations carried out in the United States, the National Comorbidity Survey [35], reported prevalence estimates of 12-month and lifetime social anxiety disorder as 7.1 and 12.1%, respectively. The lifetime prevalence of social anxiety in other western countries seems to range between 3.1 and 15.6% [36, 37]. The variation in prevalence rates among different epidemiological studies could be attributed to the application of different diagnostic criteria and instruments for the identification and assessment of social anxiety disorder.

Studies investigating the course of social anxiety have established the long-term morbidity of the illness [38, 39]. Social anxiety develops at an early age, usually during childhood or adolescence and once established, follows a stable, chronic course if treatment is not initiated [38, 39]. Recent findings show that social anxiety is also very prevalent in later life [40]. Findings regarding the sociodemographic characteristics of social anxiety disorder support that this is more prominent among the female population [26, 28–42]; although there have been studies [31] which have failed to confirm such gender differences. Moreover, higher incident rates have been consistently observed among unmarried individuals usually coming from a lower socioeconomic background, with poorer educational attainment and higher unemployment rates [28–42]. The average duration of illness is approximately 29 years [38, 43] and the likelihood of a full remission or recovery is significantly lower compared to that of other anxiety disorders [43]. In an 8 year longitudinal study of 163 patients with social phobia, Yonkers et al. [39] found that only 38 and 32% of female and men respectively experienced a complete remission indicating the unremitting and persisting nature of the disorder. Additionally, such lower rates of recovery were found to be associated, particularly in women, with a history of suicide attempts, the presence of co-morbid disorders, the most prominent that of agoraphobia, avoidant personality disorder and alcohol abuse, and also with poor baseline functioning [39, 43].

The highly impairing nature of the disorder is reflected in the marked disabilities affecting the majority of life domains. Deterioration of social functioning manifest in avoidance and withdrawal from social interactions, decrease in work productivity and interpersonal relations produce a significant decrease in quality of life [44]. Despite the highly impairing nature of social anxiety only up to a half of patients seek and receive treatment during the course of the illness [44, 45] and this is primarily in the form of pharmacological interventions.

Co-morbidity

One of the characteristic features of social anxiety disorder that could possibly contribute to its highly impairing nature, is its co-occurrence with other

psychiatric disturbances and most importantly with mood disorders [46–48], eating disorders [26, 49] as well as substance use problems [28, 50]. Co-morbidity has been consistently reported in people with social phobia triggering further serious psychopathological implications during the course of the illness [51].

Depression has been the most commonly reported disorder appearing during the course of social anxiety [26, 46, 51, 52]. Reports from epidemiological and clinical studies estimate that prevalence rates range from 19 to 91% depending on the population used, the application of different diagnostic instruments and problems with defining clear diagnostic thresholds [47]. Furthermore, when comorbidity occurs, social anxiety usually precedes the onset of depression raising the possibility of operating as a predictor of the subsequent onset, severity and course of mood disturbances [51]. A prospective community study of young people aiming at examining the relationship between social anxiety and depression longitudinally showed significantly higher rates of a depressive disorder during the follow-up period in those adolescents who, at baseline, where diagnosed with social anxiety compared to those with no mental disorder [51]. Additionally, the co-occurrence of social anxiety and depression in adolescence increased even more the risk for the later development of depression which course seemed to be more malignant characterized by persistent and prolonged depressive symptomatology, suicidal ideation and even suicidal attempts. These findings seem to be consistent with those derived from the National Comorbidity Study [46] showing an association between a primary diagnosis of social phobia and following onset, severity and course of depressive disorders. A substantial bulk of evidence shows a consistent pattern of co-occurrence of social phobia with depressive disorders. Social phobia usually precedes the onset of depression raising, therefore, the possibility of being an important predictor or risk factor for the later development of affective disorders. Aiming to identify the mechanisms by which social phobia could increase the risk for depression, Stein et al. [51, 52] suggested that the latter could develop as a direct consequence of demoralization, social withdrawal and isolation triggered by the constraints imposed to those suffering from social anxiety. However, a causal relationship is yet to be established and empirically proven.

Anxiety symptoms have been frequently reported in people suffering from eating disorders [26, 49]. Among the anxiety disorders most commonly associated with anorexia and bulimia nervosa is social phobia with prevalence rates ranging between 20 and 55% [49, 53] and 13–75% [49, 54], respectively. In a similar vein with depressive disorders, when such comorbidity occurs, social phobia seems to consistently predate the onset of eating disorders [49], however, evidence of a possible causality has not been established and the temporal relationship between the two disorders still remains unclear.

Other disorders that social anxiety has been consistently associated with are alcohol and substance use [50], other anxiety disturbances, particularly agoraphobia and panic disorder [28, 48] while a heightened risk for suicide attempts has also been reported among those who exhibit such patterns of comorbidity [55].

Developmental Psychopathology of Social Anxiety

The understanding of the pathways that lead to the development and maintenance of social anxiety require the examination of the contribution and interrelationship of a variety of risk factors including genetic, familial, temperamental and cognitive. According to the basic tenets of developmental theory and developmental psychopathology, multiple pathways may lead to the acquisition of such a diverse disorder *(principle of equifinality)* whereas, at the same time, any predisposing factors to social anxiety could account for the development of other disorders *(principle of multifinality)* [56]. This raises the need to consider an integrative framework of genetic, environmental and psychological vulnerability factors when attempting to provide a comprehensive account of the pathogenesis of social anxiety.

Genetic factors. A substantial bulk of evidence has stressed the modest but significant role of heritability of anxiety disorders and more specifically of social anxiety. Source of such evidence include (a) *gene studies* [57, 58]. Gelernter et al. [58] in the first genetic linkage analysis for social anxiety disorder, found evidence for linkage for chromosome 16 in an area where norepinephrine transporter, the most obvious candidate gene, is located (b) *twin studies* [59, 60] which report heritability estimates ranging between 30 and 50%. It is important to mention, however, that attempts to provide evidence for the specificity of genetic factors in the etiology of social anxiety [59] have failed. Instead, the same factors predisposing to the development of social anxiety could account for the acquisition of a range of anxiety disorders (i.e. agoraphobia, simple phobia etc), leading thus to the conclusion that what is inherited is a general vulnerability towards anxiousness [61] possibly mitigated by familial and environmental component, (c) *family studies* [62, 63] where the role of genetics interacts with that of environmental factors. In a direct-interview family study of patients with generalized social phobia, Stein et al. [62] reported higher rates of this subtype of social phobia compared to the specific – nongeneralized- one (26.4% vs 2.7%) among first-degree relatives of probands with generalized social phobia. This finding seems to confirm earlier evidence [64] of an association between parental and proband social phobia and moreover indicates a subtype distinction on a familial basis. However, although the familial contribution to social phobia seems to be substantial, Stein et al. [62] stress the importance of delineating the extent to which this contribution is heritable in nature or arises due to other family environmental factors (e.g. parenting style). A recent prospective-longitudinal study [63] aimed at addressing this exact issue; examining the familial transmission of social phobia, the possibility of a subtype distinction and most importantly the role of parental rearing styles and family functioning characteristics as risk factors for the development of social phobia in adolescents. Findings were based on baseline and follow-up data of adolescents and their parents from the Early Developmental Stages of Psychopathology Study (EDSP). The Munich-Composite International Diagnostic Interview (M-CIDI) was used for diagnostic assessments of adolescents and also to derive a separate family-history in order to

evaluate psychopathology in their parents. Extending previous findings [62, 64], Lieb et al. [63] argued in favour of the impact of multiple familial factors in the etiology of social phobia. Parental social phobia was only one of them with children of affected parents being more likely to develop social phobia compared to those of non-affected parents. There was some indication that this association might be stronger for the generalized subtype, however, this could only be suggestive due to the small sample size of adolescents with generalized social phobia. Parental rearing styles and specifically overprotection and rejection were also reported among those family risk factors linked to the emergence of social anxiety in offspring.

Temperamental factors. Temperament refers to the intrinsic behavioural characteristics of a child that can be modified through interaction with the environment [61]. The possibility that certain early temperamental traits may provide a diathesis for social anxiety through shared common causal mechanisms has attracted considerable interest. "*Behavioural inhibition*" (BI) is one of these early traits which could potentially act as precursor to the later development of social phobia. Introduced by Kagan and collegues (cited in Mick and Telch [65] and Ollendick and Hirshfeld-Becker [56]), behavioural inhibition reflects a tendency to react with fear, withdrawal and avoidance to unfamiliar people, situations or objects and is estimated to be present in 10–15% of 2–3 year old children. Although there is a certain overlap with shyness in that both constructs represent a heightened autonomic arousal in social situations which leads to avoidance and isolation, behavioural inhibition is broader since it can be observable both in social and nonsocial situations [56]. Research findings have also pointed towards a relative degree of stability of this temperamental trait across age [56], although it is rarely the case that increased severity of inhibition remains constant throughout the lifespan [66].

The possibility of an association between behavioural inhibition in childhood and the development of social anxiety in adulthood has been thoroughly investigated [67–70]. In a recent study by Schofield et al. [70], the authors aimed at examining the relationship between behavioural inhibition and internalizing disorders, specifically social anxiety, depression and anxious arousal. Furthermore, they aimed at differentiating between the social vs. non social aspect of behavioural inhibition and determine their relationship with social anxiety and depression. Findings of the study showed that the presence of behavioural inhibition during childhood was related to social anxiety symptoms in young adults. A moderate relationship between behavioural inhibition and depression and anxious arousal was also reported. According to the authors, this could suggest that temperamental factors do not pose a specific risk for social anxiety, rather for internalizing disorders in general. However, what was important is the fact that the social component of behavioural inhibition shared a strong relationship with social anxiety as opposed to the nonsocial component which was found to be related to symptoms of depression and anxious arousal. The authors stressed the importance of distinguishing between the two aspects (social vs. nonsocial) of behavioural inhibition when attempting to determine risk factors specifically for social anxiety.

These findings are consistent with previous accounts suggesting a differential link between the components of behavioural inhibition and social anxiety. Neal

et al. [61] introduced the concept of two dimensions of behavioural inhibition; one referring to physically threatening situations and another observed in socially threatening situations. Based on previous findings [65] that point towards a link between social anxiety in adulthood and manifestation of childhood BI specifically under social circumstances, Neal et al. [68] suggested that it is the social component of behavioural inhibition that appears to lie on a continuum with social anxiety rather than the physical one. Moreover, this proposition could provide some explanation of why some behavioural inhibited children do not develop social anxiety later on.

Family environment. The role of genetic and temperamental factors in the etiology of social anxiety is indisputable. However, an integrative model of the developmental course and pathogenesis of the illness would be incomplete if it failed to consider the psychosocial contribution and specifically the impact of the familial environment among those factors predisposing to social anxiety. Parenting style, restricted exposure to social situations, attachment problems are some of the variables that could potentially determine the course of an individual's emotional development [71–75]. Moreover, familial antecedents like the above could determine whether and how a genetic predisposition towards social anxiety becomes actualized in adulthood.

Parenting Style

Parental behaviour and childrearing practises are among those family factors whose importance in the development of anxiety has been consistently stressed in the literature [71, 76, 77]. Retrospective reports of adults with social anxiety disorder and observational studies of parent/child interaction are the main sources of information that indicate a significant link between parenting style and the development of social anxiety in adulthood [78]. The majority of studies based on adults' retrospective reports of parenting styles indicate a rather consistent pattern of parental overprotection and control, lack of emotional warmth [71, 76, 77] and the use of shame as a method of discipline [72] during childhood. Lieb et al. [63] examining the associations between social phobia and specific family environmental factors, including parenting style, reported that increased levels of parental overprotection and rejection were related to increased levels of social phobia in adolescents. This association became more pronounced for those adolescents whose parents suffered from a psychopathological condition. Similar findings were reported in a recent study by Knapee et al. [77] examining the association between parental psychopathology and adverse family environment as risk factors for the development and maintenance of social phobia. The authors reported that lack of emotional warmth and dysfunctional family functioning characteristics were linked to higher levels of persistence of social phobia (alone and in interaction with parental psychopathology). Observational studies investigating the actual rather than the perceived parenting styles have also been used. Hudson and Rapee [61] aimed at detecting signs of parental overinvolvement in a sample of clinically anxious children during a puzzle task with their mothers. Maternal intrusiveness was evident throughout the task; however, this factor was not specific for socially

anxious children rather it applied to anxiety disorders in general. In a similar vein, Dadds, Barrett, Rapee, Ryan [79] reported a pattern of overprotective parenting during discussions about ambiguous situations between parents and clinically anxious children.

Attachment

A further way of accounting for the development of anxiety problems and specifically social anxiety is looking at psychopathology within the context of attachment theory and specifically early attachment relations with the primary caregiver. According to Bowlby [80], an active, reciprocal and stable relationship with the attachment figure-usually the mother- lays the foundation for a healthy social and emotional development whereas disruption of this bond could entail serious consequences in the developmental trajectory of the individual. Dysfunctional patterns of attachment behaviour and more specifically pathogenic parenting, including lack of emotional responsiveness and affection, uncertainty about caregiver's availability can all potentially trigger the development of an insecure attachment to the caregiver [80]. Within this context of insecure attachment the risk for the development of anxiety symptoms is significantly elevated. A substantial bulk of evidence has supported the role of insecure attachment as a risk factor for the development of anxiety disorders in adulthood. In a longitudinal study, Warren et al. [74] aimed at establishing a specific link between anxious/resistant attachment in infancy and anxiety symptomatology in adolescence. Infants at 12 months of age participated in the Strange Situation procedure [81] and at follow-up at 17 years of age were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children. It was found that 15% of the 172 adolescents who participated in the study were diagnosed with at least one anxiety disorder the most common being that of social phobia. Anxious attachment with the caregiver during infancy predicted the development of anxiety disorders in adolescence. Muris et al. [75] examined the relationship between insecure attachment and symptoms of anxiety and depression in young adolescents. Results showed that ambivalently attached adolescents based on their responses on the Attachment Questionnaire for Children (AQC) – an adaptation of Hazan and Shaver's [82] instrument for measuring attachment patterns in adults-reported higher levels of anxiety and depression accompanied by lower levels of trust and higher levels of alienation compared to those who were classified as securely attached. It seems therefore that not only attachment style but also quality of attachment could be a risk factor for psychopathology. Muris and Meesters [83], using the AQC, extended these findings in order to investigate the contribution of both behavioural inhibition and insecure attachment in the etiology of anxiety disorders. Their findings pointed towards an interrelationship between attachment style and behavioural inhibition in that levels of secure attachment seemed to decline as behavioural inhibition increased. Moreover, both variables were related to a range of anxiety disorders with social phobia the most commonly occurring among those classified as behaviourally inhibited and insecurely attached. Apart from the combined effect of attachment and behavioural inhibition, Muris and Meesters [83]

also found evidence supporting the unique contribution of each factor since both attachment style and behavioural inhibition accounted for independent proportions of the variance of anxiety symptoms. The findings of this study were also confirmed by Shamir-Essakow et al. [84] who also examining the association between insecure attachment, behavioural inhibition and anxiety in an "at risk" sample of preschool children. Children classified as insecurely attached to their caregivers reported higher levels of behavioural inhibition compared to those securely attached. Behaviourally inhibited children displayed higher levels of anxiety compared to the non-inhibited ones. Similarly, insecure children reported greater anxiety –even when maternal anxiety was controlled for- compared to their secure counterparts confirming previous findings of the role of maladaptive attachment styles as risk factors for the development of anxiety disorders [74]. A recent study by Brumariu and Kerns [85] extends previous findings by reporting links between specific attachment patterns (ambivalent, anxious, avoidant) and different aspects of social anxiety in a longitudinal study. The presence of ambivalent attachment was consistently related (both at baseline and at 2 year follow up) to social anxiety symptoms and more specifically to fear of negative evaluation in young children. The authors stress the importance of looking at specific aspects and clusters of social anxiety when examining its relationship to attachment dimensions.

An influential attempt to provide an integrative model of social anxiety is reflected in F. Vertue's proposed model [86] in which aspects from the self-presentation and evolutionary theory are incorporated within the framework of attachment focusing particularly on internal working models of self and others. Vertue argued that these accounts of social anxiety should be considered complementary as both self-presentation and evolutionary theory perceive social anxiety as an adaptive emotion aiming at warning individuals in situations where the danger of social exclusion and loss of survival and reproduction resources is imminent. Attachment theory is congruent with evolutionary theory in that they both propose that under threatening conditions individuals tend to maintain proximity or seek help from their caregiver or their powerful social allies so as to achieve and ensure survival. Moreover, the underlying mechanisms of social anxiety proposed by attachment and self-presentation theory, namely fear of separation and fear of exclusion, could be considered as parallel since they reflect the individual's need for dependence on members of their network (caregivers, group members etc) for survival and reproductive success [86].

The foundation of Vertue's integrated model lies in the concept of internal working models. These represent a set of beliefs about the self and others and are developed through a continued and consistent interaction with the caregiver [87]. Vertue [86] used this concept of internal working models as a pathway to Leary's proposed conditions for the occurrence of social anxiety: (a) motivation to make a good impression to others, (b) fear that such an attempt will fail and (c) fear that such failure could possibly lead to rejection, devaluation and loss of access to desired resources. According to Vertue, the motivation to make a good impression has been linked with a need for approval which is thought to be evident in those children who grew up with rather overprotective and overcontrolling parents. The

combination of negative, unresponsive parental behaviour and adverse childhood experiences provides the pathway for the development of negative internal working models where the self is seen as unworthy, incompetent and others as unavailable and unresponsive. People who hold such perceptions are likely to be dependent on others' approval hence they will be highly motivated to make a good impression which is characteristic of people with social anxiety. Furthermore, individuals who hold maladaptive beliefs about themselves and others will be more inclined to perceive social encounters as potentially threatening to their social status. This fear of devaluation and rejection is the main concern of people with social anxiety. Consequently, the desire to create a good image of oneself and at the same time uncertainty about the ability to do so and the possibility of social exclusion that such a failure might entail may well affect individuals' interpersonal skills; namely their ability to successfully engage in social interactions. Thus, the development of social anxiety is seen in relation to dysfunctional internal working models and their impact upon the way individuals perceive themselves, their social environment and their repertoire of social skills.

The Role of Childhood Trauma

Adverse experiences in the developmental trajectory of individuals have been consistently associated with the subsequent onset and persistence of a number of psychiatric disorders including social anxiety [88–90]. A substantial bulk of findings both from epidemiological [88] and clinical studies [91] seem to propose the role of childhood adversity as a potential risk factor for the development of anxiety disorders, specifically social phobia. Data from the National Comorbidity Survey [88] demonstrates an overall positive pattern of association between previous exposure to traumatic experiences and subsequent onset of mental disorders. Among those adversities, social phobia was most strongly related to the occurrence of a loss event (death of father, divorce), the history of sexual and/or physical abuse as well as aggression within the family. It is worth mentioning, however, that similar associations were also reported for other types of psychiatric disorders for which childhood adversities operate as a strong predictor. Data from an epidemiological study in Canada [90] seems to support the above findings identifying at the same time more specific associations between social phobia and childhood risk factors. Marital conflict in family, history of physical and sexual abuse and running away from home were among those factors consistently reported by people suffering from social phobia, although in some cases gender differences were also noted. For example, sexual abuse was found to be related to the development of social phobia particularly in women whereas involvement with the juvenile justice system was more frequently reported by men. These findings were confirmed by previous studies showing a link between early sexual and physical abuse and the subsequent development of social phobia, particularly in women [89, 92]. Chartier et al. [90] also suggested the possibility of differences in the prevalence of traumatic experiences among subtypes of social phobia as their findings showed significantly stronger associations between

certain childhood adversities – marital conflict, physical and sexual abuse- and the severe type of social phobia.

When examining the impact of environmental risk factors on the development and maintenance of later dysfunction, it is also important to consider the role of protective factors which could help restore dysfunctional developmental trajectories. In a recent review of environmental risk factors for social anxiety, Brook and Schmidt [93] emphasize the contribution of resilience factors in restoring the developmental outcome of being exposure to life adversities. Manassis and Bradley [94] in a study examining the interaction between temperamental factors and attachment for the understanding of the pathogenesis of social anxiety, supported the importance of factors which could deflect the development of psychopathology. The involvement of other family members, for example the father, could counterbalance the negative effects of a dysfunctional attachment by encouraging the engagement of the child in interpersonal situations which could provide the opportunity for the development and promotion of their coping strategies and social skills.

The Presence of Social Anxiety in Psychosis

Prevalence and Phenomenology

Social anxiety is among the most prevalent and debilitating affective disturbances manifest in people with psychosis [18, 21, 22, 95]. In a recent study by Michail and Birchwood [21], social anxiety was diagnosed in 25% of people with first-episode psychosis (FEP). In addition to the 25% with formal SaD, there was also a further 11.6% who reported clear social interaction difficulties and/or signs of avoidance not sufficient though to reach formal diagnostic criteria (ICD-10). These "*borderline*" cases, though not satisfying formal criteria, were nevertheless reporting interpersonal difficulty that may well warrant intervention at a clinical level. In addition, cases with subsydromal levels of social anxiety and social interaction difficulties were also present. Similar incidence rates of social anxiety have been reported in other studies of FEP [22, 95] and also in studies with enduring schizophrenia, where rates range between 17 and 36% [14, 96, 97]. The highly impairing nature of social anxiety in psychosis has been consistently reported in literature. In a study of outpatients with schizophrenia, Pallanti et al. [97] reported that those diagnosed with comorbid social anxiety disorder had a higher rate of suicide attempts, lower social adjustment and overall quality of life compared to those without social anxiety. Previous findings by Penn et al. [98] also support the significant impact of social anxiety on social disability.

The phenomenology of social anxiety in psychosis has been thoroughly investigated by Michail and Birchwood [21]. In their study comparing the severity and phenomenology of social anxiety in psychosis with that in non psychosis, the

authors revealed a very similar clinical profile with regards to levels of social anxiety and social avoidance; the number and severity of autonomic anxiety symptoms and social evaluative concerns. What is more, social anxiety both in people with psychosis and non psychosis occurred in the context of an equally high level of other anxiety disorders underlying the similarity of the two groups. The presence of social anxiety in people with psychosis was also accompanied by marked levels of depression; approximately 31% of FEP people exhibited moderate to severe levels of post-psychotic depression.

Social Anxiety and Relationship with Paranoia

The relationship between social anxiety and positive psychotic symptoms, particularly paranoia, has attracted considerable attention; however, the processes that underlie this relationship are yet to be clarified. On the contrary, empirical evidence has thoroughly established the interaction between general anxiety symptoms and paranoid ideation. In a series of studies [99, 100] examining the role of anxiety in the development and maintenance of persecutory ideation, Freeman and his colleagues have shown how people with anxiety disorders and those with persecutory delusions share a selective bias to threat-related information. The engagement in safety-seeking behaviours was a common theme among the two groups particularly in those situations perceived as potentially threatening or dangerous. Freeman et al. [100] also reported that the increased use of safety behaviours by individuals with persecutory delusions was associated with higher levels of anxiety. Based on these findings, Freeman et al. [100] have proposed that similar processes underlie anxiety and paranoia. Anxiety involves the anticipation of threat and danger which can be physical, social, psychological as well as intense worry about the consequences such a threat will entail. Analogous themes underlie persecutory delusions referring to perceived danger or harm intended to be inflicted upon the individual by the persecutor. Freeman et al. [99] suggested therefore that anxiety is likely to play a fundamental role in the formation and maintenance of persecutory delusions via these common processes/mechanisms.

The relationship between anxiety and paranoia is rather straightforward and has been empirically established. However, social anxiety has a somewhat different quality and its relationship to paranoia and persecutory ideation is complicated. One of the most recent attempts to delineate this relationship was by Michail and Birchwood [21]. In a study of young people with first-episode psychosis, the authors compared levels of positive symptoms, including suspiciousness and persecution, as measured by the PANSS (Positive and Negative Symptom Scale) between people with psychosis and social anxiety (FEP/SaD) and those with psychosis only (FEP/no SaD). Findings revealed no differences in PANSS positive symptoms between psychotic individuals with vs. without social anxiety; including no relationship between PANSS suspiciousness/persecution and social anxiety in the whole FEP (with and without SaD) sample. Furthermore, the level of PANSS suspiciousness/persecution did not affect the severity of social anxiety within the FEP/SaD group itself. The

results also revealed that the majority of psychotic people with social anxiety did not report any premorbid social anxiety, which suggests that social anxiety in this group developed as a new phenomenon following the onset of psychosis or built upon sub-threshold levels of anxiety and interpersonal sensitivity. This is consistent with previous findings [22].

These findings confirm previous studies reporting no link between positive symptoms and social anxiety [95, 97] which suggests that the presence of social anxiety in psychosis is not simply driven by clinical paranoia and persecutory threat. It is important to mention though findings in the Michail and Birchwood [21] study also revealed a subgroup of socially anxious psychotic people (45%) which reported significantly more persecutory threat and anticipated harm as measured by the Details of Threat Questionnaire [99] compared to psychotic people without social anxiety. When investigating further the inter-relationship between social anxiety and persecutory threat within this sub-group no link between level of social anxiety and persecutory threat was revealed. This is of particular interest as it suggests that even among those individuals with psychosis and social anxiety, social anxiety is not necessarily contaminated by ongoing persecutory beliefs.

Based on these findings therefore it is suggested that social anxiety cannot simply be perceived as "co-morbidity" and does not arise as a by-product of paranoia and persecutory beliefs. The need to understand the processes that underpin the development and maintenance of social anxiety in psychosis is fundamental as this will entail significant implications for psychological interventions and treatments of affective disturbances in psychosis.

Social Anxiety in Psychosis: a Psychological Reaction?

In providing a framework for the understanding of affective dysfunction in psychosis, Birchwood [101] suggested that emotional difficulties, like social anxiety, trauma, depression and distress, could develop in response to psychological circumstances. Such circumstances could include for example life events that the individual feels he/she has no control, the illness itself or traumatizing experiences. The occurrence of depression in schizophrenia has been associated with patients' perceptions of controllability of the illness and acceptance of the entrenched cultural stereotypes [102]. With regards to post-psychotic depression, findings show that this is related to appraisals of psychosis as a major life event which entails loss, shame, humiliation and enforced entrapment [103].

The above theoretical framework could also be applied for the understanding of the emergence of social anxiety in psychosis. It is suggested that social anxiety develops as a psychological reaction to psychosis, and particularly as a reaction to the stigma and shame attached to mental illness. Psychosis is considered as a highly stigmatized condition [104]; aside from the long-term psychiatric disabilities and the subsequent distress entailed in receiving a diagnosis of mental illness, people also have to endure the adverse effects of the stigma attached to their illness [105, 106]. Acquiring such a stigmatized attribute can overshadow the individual's identity. In

a study examining people's appraisals about their mental illness, the self and status in the social environment, Birchwood et al. [102] showed how psychotic individuals have come to appraise their selves as a function of their illness-the self *is* the illness. It is suggested therefore that shame about mental illness and fear of being devalued and rejected by others once the diagnosis is revealed underlies the development and maintenance of social anxiety and avoidance in psychosis. Social anxiety and avoidance could be viewed as a form of safety behaviour aiming at "*saving*" the individual from the perceived social threat of being down-ranked and humiliated. Birchwood et al. [22] have demonstrated how a group of socially anxious psychotic people reported elevated levels of shame proneness and shamefulness arising from their illness accompanied by feelings of rejection and loss of social status, compared to a group of non-socially anxious psychotic people. This was confirmed by Gumley et al. [107] who found that people with psychosis and social anxiety held negative appraisals about their illness, including shame and feelings of inferiority, more so compared to those without social anxiety.

Understanding how these processes operate and specifically how shame appraisals might impede social interaction in people with psychosis warrants further investigation.

Clinical Implications and Future Directions

Social anxiety is evidently one of the most commonly diagnosed affective disorders in psychosis and one that exerts a significant impact on social disability. Its relationship to psychotic symptoms and particularly paranoia is rather complex and attempts to delineate any potential links between the two concepts have yielded contradictory findings. Recent evidence [21, 22] however seem to dispute the notion that social anxiety and avoidance are simply a by-product of paranoia and persecutory ideation and point towards a new understanding of the illness and its pathogenesis. Shame cognitions arising from mental illness accompanied by feelings of entrapment and loss of social status are suggested to operate in psychosis. Fear of disclosure of the illness and the consequences such a disclosure will bear in terms of stigmatization and social exclusion is suggested to contaminate social interactions by promoting patterns of avoidance, withdrawal and isolation.

Understanding how these processes operate exactly will have significant clinical implications and will offer a novel conceptual framework for psychological interventions and treatments for social anxiety in psychosis. Cognitive-behavioural therapy (CBT) is an indispensable treatment option for people with psychosis, according to the UK National Institute for Clinical Excellence [108]. The aim of CBT is "*to reduce psychotic symptoms, increase insight and promote medication adherence"* [108]. A recent review by Tarrier and Wykes [109] of the evidence for the effectiveness of CBT has focused on 20 randomised controlled trials with the majority focusing predominantly on alleviating medication resistant symptoms and preventing relapse. Affective problems such as depression, social anxiety

and distress have been treated as part and parcel of the psychotic experience and not as independent dimensions affecting the course and outcome of the illness. Furthermore, psychological interventions such as CBT for the treatment of affective disorders in non-psychotic people are also applied for the management of affective dysfunction when this is comorbid in psychosis with the same criteria for success i.e. reduction of symptoms and general psychopathology, increase in quality of life [110, 111]. However, what this approach fails to take into consideration is the idiosyncratic relationship between affect and psychosis and the appraisals that might underlie this relationship. Birchwood and Trower [112] have questioned whether a shift in the current focus of CBT is necessary, given that affect is so clearly implicated in the ontogeny of psychosis. They suggest that the new focus of CBT should be the interplay between affect and psychosis and the appraisals linked to the psychotic experience. Hence, the new generation of CBT trials should aim at targeting distress, behavioural anomaly in psychosis and associated core appraisals as their primary outcome leaving as secondary the psychotic phenomena themselves. In the case of social anxiety, we propose that the focus of CBT should be to target the idiosyncratic core cognitions that may underpin the development of social anxiety in psychosis: appraisals of shame arising from the illness accompanied by feelings of social defeat and anticipation of a catastrophic loss of social status; also, the distress that may result from such maladaptive cognitions. A similar suggestion has also been proposed by Gumley et al. [107] who support that CBT should incorporate strategies aiming to identify the negative appraisals about the self and the illness as a way of helping individuals with psychosis understand how social anxiety and emotional distress develops.

Conclusions

This chapter focuses on providing a new understanding of affective dysfunction in psychosis. Given the endemic nature and impact of affective symptoms like depression, distress and social anxiety in people with psychosis, it is of primary importance to revise and reconstruct the current conceptual framework for their management and treatment. Such a framework should focus on targeting the dysfunctional appraisals and core cognitions which lie at the heart of affective disorders and understanding that such symptoms might not necessarily be a "side-effect" of psychotic symptomatology per se.

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Chapter 5
Face Perception in Schizophrenia Spectrum Disorders: Interface Between Cognitive and Social Cognitive Functioning

Yue Chen

Abstract Perceiving facial features, both affective and non-affective, plays a vital role in everyday life. While it is known that the processing of facial emotion expressions is compromised in schizophrenia, the mechanisms underlying face perception and their connection with cognitive and social cognitive functioning are somewhat elusive. Two important and unresolved issues have been whether visual and cognitive processing of face information is implicated in schizophrenia spectrum disorders, and how non-affective information processing relates to deficient affective processing. Recent investigations have demonstrated that not only affective but also non-affective visual and cognitive facial features are processed abnormally in these mental disorders. The cascade of face perception processes implicated includes detection, identity discrimination, emotion discrimination and working memory. Furthermore, the abnormal processing of face information in patients is associated with the processing of basic visual signals as well as the information portrayed in social functioning. These new research advances highlight the broad network of brain systems involved in abnormal face perception in schizophrenia spectrum disorders, spanning cognitive and social cognitive domains.

Keywords Schizophrenia · Schizoaffective · Visual processing · Cognition · Emotion perception · Theory of mind

Abbreviations

BOLD	Blood-oxygen-level dependence
FG	Fusiform gyrus
fMRI	functional magnetic resonance imaging
EEG	Electroencephalographiy

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Introduction

Face perception refers to the perceptual ability to comprehend information embedded in faces. This information includes face as a special type of object, as an identity, as a gender, as an expression of emotion and as other events in the mind. Given the paramount importance of this information in the social world, a specialized brain system is evolved for face perception [1–4]. Compared with other types of information, the processing of face information is efficient and sophisticated [5]. According to the information processing model of face perception [6], the processing of facial signals comprises multiple functional components; namely, visual detection, discrimination of individuality, analysis of emotion expression and working memory, which can be conducted serially and in parallel (Fig. 5.1).

Impaired performance on perceiving various facial features, especially those in the affective domain, has been widely reported in schizophrenia [7–12]. The mechanisms responsible for these impairments, however, have not been completely determined. Face perception relies upon both visual inputs from a bottom-up process and cognitive and social cognitive information from a top-down process. As both the bottom-up and top-down processes are implicated in this mental disorder [13–16], a key standing issue is whether the face perception impairments represent a manifestation of social cognitive problems, or stem from more basic visual processing problems. Recent studies address this issue by investigating the processing of both affective and non-affective facial information, either separately or collectively, in patients with schizophrenia spectrum disorders and by searching for the link between the two processing domains.

Recent studies address this issue by investigating the processing of both affective and non-affective facial information, either separately or collectively, in patients with schizophrenia spectrum disorders and by searching for the link between the two processing domains. This chapter selectively highlights these advances in the understanding of visual and cognitive processing of face information associated with

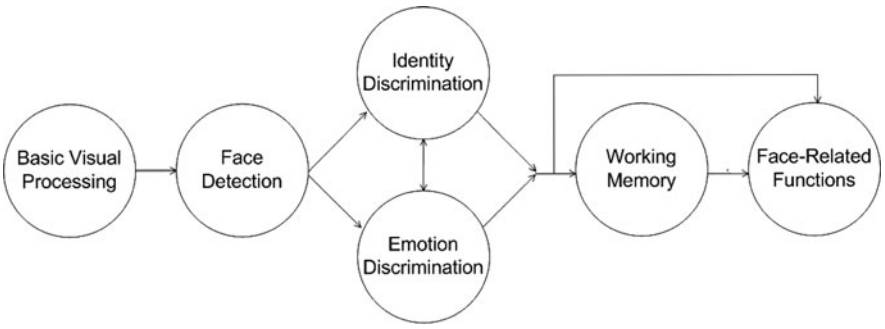

Fig. 5.1 Schematic illustration of a hierarchical model of facial processing components. The basic model is adapted from the functional processing model of face recognition [6], with emphasis on vision-related components

this mental disorder. A vast literature exists on the affective aspect of face perception; this chapter, however, emphasizes the non-affective aspect and the relationship between the two. This complementary and synthesized approach to face perception attempts to provide an interface for studying face-related cognitive and social cognitive functioning in schizophrenia.

Peceptual Processing of Non-affective Facial Information

Despite the known impairment of facial emotion recognition in schizophrenia, the problem in perceiving non-affective aspects of facial information has been considered as a contributing factor to face-related cognitive and social cognitive functions in patients suffering from this mental disorder.

A number of early studies assessed the perception of facial images with neutral expression while examining facial emotion recognition, and found deficient performance in both aspects of face perception in patients [17, 18]. Such studies suggest that impairments in processing facial information are not constrained to the affective domains. In terms of understanding the functional components of face perception (visual detection, identity discrimination, etc), these early studies have limitations in that the study design did not differentiate either the basic perceptual components involved or face versus non-face visual object perception.

The recent study of patients' ability to detect the presence of a face, the putative first stage of face perception, has advanced the research on the facial processing components involved in schizophrenia. As an index for the highly efficient face perception, the stimulus inversion effect refers to the phenomenon that the relatively superior performance in perceiving upright vs. inverted images is disproportionately greater for faces than for non-face visual objects. Using images containing only primary facial configurations with no emotive information, Chen and colleagues found reduced stimulus inversion effect in patients during face detection, suggesting inefficient processing of basic facial information [19]. However, in tree detection, a control task administered in the same study, no reduction of stimulus inversion effect was found in patients. Butler and colleagues found poor performance in perceiving facial images of neutral expression but not reduced stimulus inversion effect in patients [20]. One methodological difference between the two studies is the use of short stimulus duration (100 ms or less) in the former and relatively long stimulus duration (300+ ms) in the latter. It is likely for patients to perform poorly on the face detection task under more challenging conditions (i.e. shorter stimulus duration), but further studies are needed to determine whether the methodological difference plays a significant role in the discrepant results. Along the same line, Zivotofsky and colleagues found that schizophrenia patients are specifically deficient in detection of human face images, as compared to animal face images, embedded within an array of other irrelevant images [21]. These results provide tentative evidence that face detection, relative to detection of non-face visual objects, is compromised in schizophrenia.

One other component of face perception which recent research has gained important insights on is identity discrimination, in which different individuals are identified according to their facial images. Several studies have found deficient face identification performance in patients while studying emotion recognition [22–24]. For example, Martin and colleagues showed that patients performed poorly in reporting whether two face images belong to the same person or have the same emotion [25]. One critical issue arising from these results is whether the perceptual problem is specific to the domain of face identity, as other factors such as the ability to recognize general visual objects could play a role here. By a systematic manipulation of the difference between two facial identities via morphing, Chen and colleagues measured the perceptual thresholds for identity discrimination and found only a modest decrement in patients' performance [26]. Patients' degraded performance in face identity discrimination was not correlated with their performance in car identity discrimination. Using self-face as identity, Lee and colleagues found that patients are faster in searching their own face images than famous face images [27] whereas Kircher and colleagues found poor self-face recognition in patients only when the face images were presented on the right visual field [28]. These results together suggest that face identity discrimination is moderately affected in schizophrenia.

Poor performance on working memory of face in schizophrenia appears to be a common finding according to several studies [26, 29–31]. While these studies agree on the existence of a face memory problem, however, the nature of the impairment in this mental disorder is not completely clear. Deficient working memory itself is a cognitive dysfunction associated with schizophrenia [32–34], which could lead to the impaired performance in face working memory tasks. Beyond this, the question as to whether there exists a working memory deficit specific to faces has not been examined in this mental disorder.

Like other cognitive dysfunctions, the problems in detection, identity discrimination and working memory of faces are possibly related to the clinical symptoms of schizophrenia. Philips and David suggest that deficient facial processing may be a factor for delusional misidentification in patients [9]. The cumulative evidence from the studies reviewed thus far, however, remains equivocal. Some studies showed an association between performance in face perception tasks and clinical statuses [19, 23, 25, 26] yet others did not show such an association [22, 24, 31]. A different way to address this issue is to separate patients into subgroups based on clinical classification and compare face perception performance between them. In doing so, Chen and colleagues found that between schizophrenia and schizoaffective patients there is a modest group difference in face detection (Fig. 5.2). This result suggests that the problem in this facial processing component is not unique to a subtype of schizophrenia spectrum disorders. On the other hand, schizophrenia patients showed significantly worse performance in face identity discrimination than schizoaffective patients, suggesting that the problem in face identity discrimination is not associated with the prominent mood symptoms in the latter group.

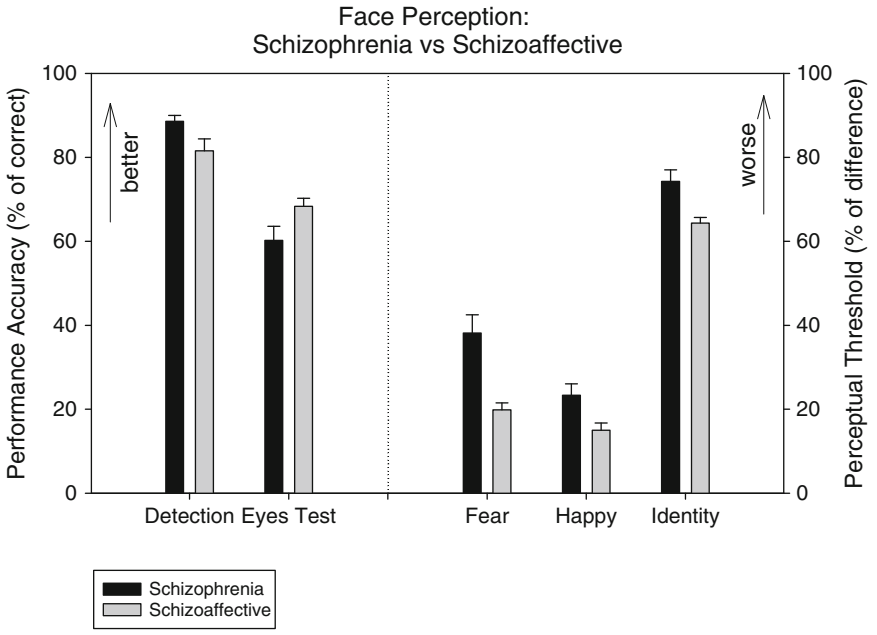

Fig. 5.2 Comparison of face perception performance between schizophrenia (SZ) and schizoaffective (SA) patients. Included are face detection (Detection; n=22 for SZ and n=21 for SA), the theory of mind (Eyes test; n=16 for SZ and n=15 for SA), fear discrimination (Fear; n=17 for SZ and n=13 for SA), happiness discrimination (Happiness; n=17 for SZ and n=13 for SA), and identity discrimination (Identity; n=22 for SZ and n=17 for SA). The two groups were significantly different in Detection (p<0.05), Eyes test (p<0.05), Fear (p<0.01), Happiness (p<0.05), and Identity (p<0.01). Error bars indicate ±1 standard error

Cortical Processing of Non-affective Facial Information

The FG is a primary cortical area subserving the processing of basic face information [2]. Schizophrenia patients have reduced volume in the FG [35, 36]. This volume reduction extends bilaterally to anterior and posterior fusiform areas and is found in both first-episode and chronic patients. This anatomical abnormality may be a neural substrate for the functional abnormalities in face perception shown in patients.

Cortical responses to face images appear to be altered in schizophrenia. Electrophysiological studies have shown that in responses to face images, patients' EEG amplitudes are decreased [37], particularly those components that underlie the encoding of facial features [38]. FMRI studies have found a spectrum of abnormal cortical responses to face-related stimuli. Yoon and colleagues found comparable FG BOLD signals between patients and controls [39]. In contrast, Yoo and colleagues found reduced FG BOLD signals in patients [40]. Silverstein and colleagues

showed increased left FG BOLD signals in patients [41] whereas Quintana and colleagues showed decreased right FG BOLD signals in patients [42]. Considering the very different natures of face perception tasks or stimulations from face images used in these studies, the altered and heterogeneous cortical responses in patients suggest that the neurophysiology of face perception engages complex processes in the FG and other face-related cortical areas, and that the cortical processing of non-affective face information is selectively, rather than universally, implicated in schizophrenia. Such a process can be holistic or pertinent to perceptual organization, as suggested in two recent studies [19, 41].

Associations of Affective and Non-affective Face Perception

Processing of affective facial information in schizophrenia has been extensively reported and reviewed in literature [11, 38, 43–47]. Until recently, however, the study on the relationship between affective and non-affective face perception has been largely lacking.

Several studies provide consistent evidence for an association between the processing of affective facial information and the processing of non-affective facial information including basic visual signals. When measuring EEG response to emotive facial images, Turesky and colleagues found a reduced early response component that putatively corresponds to sensory processing [38]. This result, while indirect, prompted them to suggest that deficient early visual processing may play a role in patients' abnormal response to emotion signals. Norton and colleagues used psychophysical methods to directly measure contrast sensitivity, an index for basic visual processing, and emotion discrimination in the same patients [48]. They found that the two performance measurements are significantly correlated in patients. In the same study, Norton and colleagues also measured facial identity discrimination using images of neutral expression, and found that patients' performance in the face identity discrimination task is significantly correlated with that in the emotion discrimination task. Together, this set of results suggests an association between the processing of affective and non-affective face information in schizophrenia.

Although the correlation measures demonstrated an association between basic visual and affective processing of face information, the earlier study left open the directionality of the association: that is, whether visual processing has a causal effect on affective processing [49], or vice versa [50, 51]. Two recent studies address this issue by directly manipulating visual signals (spatial frequency) of face images and measuring the visual modulation effect on emotion discrimination in patients. Lee and colleagues found that patients adopt an "atypical strategy" to make use of various types of visual features (such as requiring more exposure of facial areas) when perceiving emotional faces [52]. McBain and colleagues found greater effects on emotion perception in patients when the spatial frequency contents of facial images are modulated [53]. The results from both studies thus support the notion that basic visual processing plays a significant role in deficient emotion processing in schizophrenia.

Conclusions and Future Directions

Recent studies indicate that visual and cognitive processing of face information is impaired in schizophrenia. One critical question is whether there is a face-specific impairment pertinent to this mental disorder, as the poor face perception performance demonstrated in patients could well be another reflection of general visual and cognitive dysfunction. Despite having been raised and addressed to some extent in previous studies, this question has not been convincingly answered. Evaluation of the effects of modulating visual and cognitive signals embedded in facial images on face perception, as implemented in recent studies, represents a promising approach. Further, this evaluation should be extended to the clinically unaffected relatives of patients since the latter group shares the predisposition to schizophrenia, but without the symptom-related generalized deficits associated with the disorder.

While disassociating the face-specific deficit from overall cognitive deficits is critical, it remains perhaps a viable possibility that both types of deficits exist concurrently and influence the poor face perception performance in patients. Special and sophisticated assessment designs are needed in order to tease out specific visual and cognitive mechanisms underlying the perceptual ability in schizophrenia.

Recent studies also indicate an association between patients' face perception deficits in affective and in non-affective domains. Such an association suggests a new approach to the understanding and remedying of impaired emotion processing in patients. Going upstream of the information processing, it would be interesting to characterize how the basic face perception deficits contribute to other social cognitive dysfunctions such as the Theory of Mind in schizophrenia patients. Going downstream, given that basic visual processing provides inputs for face perception, the role of the bottom-up process should be emphasized in future research in order to design and select effective intervention strategies for improving social functioning in patients.

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Chapter 6
Toward a Neuroethology of Schizophrenia: Findings from the Crimean Project

Victor P. Samokhvalov and Oxana E. Samokhvalova

Abstract Many authors emphasise the importance of the inclusion of ethological data in diagnostics and differential diagnostics of schizophrenia, depression and phobias, estimates of therapy efficiency and evolutionary interpretations. It is important to reformulate the clinical phenomenology of mental disorders in ethological terms to considerably increase the validity of clinical supervision and diagnostics of mental disorders. However, actual studies of mental disorders by ethological methods have met with significant difficulties. This chapter based on findings from the Crimean Neuroethology Project. In the framework of this project the behaviour of patients with schizophrenia was described using ethological methods, including non-experimental observation of elements of facial expression, posture, gesture, manipulation, behaviour patterns and communication with doctors and relatives. Comparative evolutionary research on primate and human behaviour is discussed. Studies have shown that schizophrenia is associated with the relative independence of evolutionarily archaic brain structures and newer ones. Our preliminary data indicate that the patterns and ethological structure of behaviour, as part of the schizophrenia phenotype, can include elements of the endophenotype and are an essential element in describing schizophrenia.

Keywords Schizophrenia · Neuroethology · Endophenotype

Abbreviations

AES	Acute emotional stress
CD	Coefficient of dogmatisms
CFAP	Complex fixed action pattern
CPG	Central pattern generator
DLPFC	Dorsolateral prefrontal cortex

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EBF	Eye-brow flash
EEG	Electroencephalography
FI	Finger index
fMRI	functional magnetic resonance imaging
FSM	Finite-state machine
LTPR	Limbic psychotic trigger reaction
MA	Manipulation activity
PPI	Prepulse inhibition
SPEMD	Smooth pursuit eye movement dysfunction
VAQ	Verb-adjective quotient
VD	Vocabulary diversity
VLPFC	Ventrolateral prefrontal cortex
VNQ	Verb-adjective quotient

Introduction

Since the times of classical ethology, pioneered by the 1973 Nobel Prize winners, K. Lorenz [1], N. Tinbergen [2], and M. von Frisch [3], it has been believed that all basic principles of animal ethology are also applicable in humans for the purpose of evolutionary comparisons. However, in contrast to behaviourism, the specific goal of ethology was to describe innate, instinctive behaviour. Thus, it was considered necessary to describe the typology and structure of naturally occurring behaviour, or in the words of N. Tinbergen [4], the "morphology of behaviour". In subsequent work it becomes necessary to establish the mechanisms of a behaviour, including neuronal and biochemical, as well as its dependence on environmental factors, and then to describe its evolution. Thus, already at the classical ethology stage, the main task was considered identification of the connection between behaviour's evolution and the brain's evolution.

Historically, ethological and evolutionary research developed in parallel with classical neurobiology and neurophysiology beginning in the mid-twentieth century [5]. Although neurobiology and neuroethology used experimental research methods [6–11], classical ethologists insisted on non-experimental observation in natural conditions and minimal experimental intervention [1–3]. Research on the physiology of animal behaviour and human ethology has been concentrated in Europe, as well as similar work on the neurobiology of behaviour has been concentrated in the USA. Nevertheless, by the beginning of the twenty-first century, the field of neurobiology of behaviour had absorbed ethology as the ultimate goal of neurobiology – studying the brain structures involved in behaviour – seems more pragmatic than the study of the evolution of behaviour [11].

Human ethology [12], as a theoretical substantiation of ethological psychiatry [13], the study of the pathophysiology of behaviour in mental disorders and the first comparative primate research [14] was closely connected to work in the field

of evolutionary neurobiology by MacLean, whose "triune brain" hypothesis considered the brain stem as the source of reflexes and unconscious thought (reptilian brain), the limbic system (paleo-mammalian brain) as the source of emotions and species-specific social behaviour, and the neocortex (neomammalian brain) as the source of cognition [15, 16].

Actual studies of mental disorders by ethological methods, however, have met with significant difficulties in the definition of behavioural attributes. The problem is that natural human behaviour is polyphonic, like a musical score [12], in which the full repertoire of nonverbal behaviour (e.g., facial expression, posture, gesture, manipulations) is imposed on the components of speech. In addition, the behaviour varies depending on the stimulus and dialogue system because the existence of an inductor and a recipient is always assumed. Essentially, it is possible to investigate behaviour by considering separate channels of communication: olfactory, visual, auditory, tactile, and social [17]. Using this approach, behaviour can be compared through evolutionary history and related to concrete brain structures, the more primitive of which are rather well understood. However, it is also possible to assume that visually observable behaviour, including facial expression, posture, gesture, and manipulations, is analogous to a text consisting of elements and complexes (patterns) that are organised in the compound form of natural behaviours. However, if the number of elements reaches hundreds of thousands, the number of patterns will be in the tens of thousands, and the number of complex forms of species-specific behaviour can approach tens. In particular, the behaviours of sleeping, locomotion, comfort seeking, parental behaviour, aggression, sexual behaviour, possession and exchange, migration and territorial behaviour, information seeking behaviour, and eating behaviour [12] are relevant. The majority of patterns comprising a complex form of behaviour are considered complex fixed action patterns (CFAPs), which, from the neuroethological point of view, are related: the systems of inductor – recipient; the peripheral apparatus that generates and recognises species-specific signals; the brain, which analyses patterns within signals; sensory systems, which receive a signal; and a cerebral decoding device, which transforms a signal to a message that may or may not lead to modification of behaviour [18]. Cerebral patterns are constructed by a CPG (central pattern generator), many of which are interconnected; the activity of the system is apparent in the rhythms of any behaviour, including locomotion. In particular, eye contact and social gaze are generated in a circuit comprising the superior temporal sulcus, amygdala, and orbitofrontal cortex [19].

Research on the structure and typology of concrete behaviour has yielded insights into the design of robots and computer systems, which in turn can act as models of concrete forms of behaviour. In particular, the creation of a visuomotor coordination frog model (Rana computatrix) and a model of brain functioning mechanisms based on a mirror-system hypothesis have led to an improved understanding of the importance of computational neuroethology [20, 21].

Comparative evolutionary studies of behaviour date back to Charles Darwin [22]. In classical human ethology, there are numerous data on the similarity of a number of elements, patterns and forms of behaviour, as well as systems of communication, between higher primates and humans [8–10, 14, 17].

In schizophrenia research, experimental biological models of catatonia have been developed in monkeys, Caviidae, mice and rats [23–25]. These models have enabled the localisation in certain brain structures of withdrawal, stereotypies, dissociation, catatonia and unmotivated aggression. Nevertheless, the best animal model of schizophrenia is the behaviour of monkeys raised in isolation or with an ineffective mother [26, 27]. Comparative primate models also have important meanings for the anthropological study and of speech because, from the neurobiological point of view, elements of manipulation activity (MA) and gesture are closely connected to the centres of speech in postfrontal parts of the dominant hemisphere [14].

The structures of primate and human behaviour are very similar, as can be observed in parallels in facial expression, posture, gesture, manipulation, olfactory communication and vocalisation. Besides, the contexts of primate and human behaviour are very similar, in particular the general contexts of aggressive and friendly behaviour, sexual behaviour, sleeping, grooming and parental behaviour [28]. The first discussion of intuitive diagnostics of schizophrenia on the basis of complete impressions about a patient, and most of all about his behaviour, was H.C. Rumke's description of "praecox gefuhl" (feeling). This sensation arises in a clinician within the first few minutes of contact with a patient [29]. Intuitive diagnostics may even be more exact than psychometric estimation of a mental state [30]. Many authors further emphasise the importance of the inclusion of ethological data in diagnostics and differential diagnostics of schizophrenia, depression and phobias, estimates of therapy efficiency and evolutionary interpretations [31–41]. It is important to reformulate the clinical phenomenology of mental disorders in ethological terms to considerably increase the validity of clinical supervision and diagnostics of mental disorders. This system can also be applied to research on animal models of mental disorders and experimental psychopharmacology [42]. The most widely used and validated system for ethological research on schizophrenia is the Ethological Coding System for Interviews (ECSI) by A. Troisi. The ECSI glossary consists of 37 elements [42], mostly facial expressions and gestures, recoded in contexts of affiliation, submission, prosociality, flight, assertion, displacement and relaxation. Research has shown that the ethological structure of schizophrenia differs from that of healthy individuals in reduced expression of prosocial behaviour, gesture and displacement behaviour; however, correlations between nonverbal behaviour and symptoms were weak, except that schizophrenia patients with a high level of an anxiety more frequently established eye contact with interviewer. Thus, it was concluded that social behaviour is rather independent of schizophrenia diagnosis [42]. Further, it has been reported that the negative symptoms of schizophrenia are accompanied by decreased facial expression, and patients with schizophrenia as a whole use less of the behavioural repertoire in comparison with mentally healthy persons. These findings were not influenced by gender or cultural differences between the patient and interviewer [43]. Observation of the variation of 16 facial expression elements among paranoid and nonparanoid schizophrenics during an interview have more often shown avoidance of eye contact among nonparanoid schizophrenics [44]. These results were supported via ECSI, which has shown that the facial expression feature of schizophrenia is a predictor of social distancing [45]. Via observation in a psychiatric ward outside the context of an interview, it was established that patients

with schizophrenia more often than mentally healthy persons avoid social contact with personnel and other patients [39].

Psychobiologists and ethologists have long known that stereotypies of behaviour and thought in schizophrenia, in particular catatonia, and autism are very similar to ethological CFAPs, which are included in the structure of animal and human social displays and have a relaxing function [46]. However, researchers later demonstrated that the stereotypies in schizophrenia reflect an imbalance in neurochemical systems' activity: namely, the striatum, striosomes and extrastriosomal matrix [47, 48]. Observation revealed that stereotypies are frequently fragments of complex sequences and forms of behaviour, According to a "chunking" principle, these fragments can take the place of demonstration of a large ensemble of behaviours; hence, stereotypies possess an adaptive function and cannot always be considered as indicative of pathology [49]. The development and refinement of functional magnetic resonance imaging (fMRI) has created further opportunities for the study of some models of behaviour. In particular, contagious pandiculation, which is unusual for individuals with schizotypal disorder and schizophrenia, is related to neuronal activity in the cingulate and precuneus. Thus, it is hypothesised that this area is involved in imitative behaviour in general and empathy in particular, which are lacking in schizophrenia [50].

The use of ethological principles for diagnosis and classification of schizophrenia is not yet justified. The sole achievement of ethological research on schizophrenia is the diagnosis in a group of patients with schizophrenia, schizoaffective disorder and affective psychosis of limbic psychotic trigger reactions (LTPRs), which result from frontal-limbic imbalance. LTPRs entail marked homicidal and destructive behaviour and incidental reduction of serotonin. Their diagnostic criteria include episodes of hyperactivity, cognitive and vegetative aura, absence of consciousness changes and amnesia, bland affect, incidental psychoses with hallucination in several modalities and delusion [51].

It is not clear if patients with schizophrenia are impaired in their display of emotions, in particular as expressed in nonverbal behaviour and facial expression, or if they incorrectly appraise social stimuli and consequently enact inadequate behaviours in response [52]. However, disturbed recognition of others' emotions as displayed by facial expression and vocal tone as well as a distorted ability to understand hints, logic, intentions, deceit, metaphor, irony and tact in social relations among schizophrenics are part of the distinctive cognitive and behavioural phenotype of the disorder [53]. It is believed that the emotional centre in the amygdala, by cooperating with sensory, prefrontal and motor cortex, can generate adequate affective conditions and motivation, and its suppression results in the negative signs of schizophrenia as it integrates other centres [54]. However, the same multisensory integrator for auditory and visual communications in primates is the ventrolateral prefrontal cortex (VLPFC) [55], and, as was established earlier, frontotemporal interaction and the local failure of prefrontal functioning are among the main neuronal mechanisms of hallucination in schizophrenia [56]. Nevertheless, it is not clear how the actual positive and negative signs of schizophrenia are connected with the system of interacting CPGs involving different cortical and subcortical structures or how clinical signs are related to the observed behaviour. In the most complete

review devoted to ethological studies of depression and schizophrenia, Geerts and Brune [41] express the expectation that in the future psychiatry will find the answers to four fundamental questions posed by Tinbergen [4]: what are the reasons for the behaviour, its ontogenesis, its survival value and its evolutionary trajectory?

Today, the theory of endophenotypes connects hypothetical genes to clinical symptoms of schizophrenia [57, 58]. The hierarchy of gene – protein – cellular system and signalling pathway – local neuronal dysfunction – cognitive dysfunction – symptom – syndrome clearly enough describes the deficiency of working memory in schizophrenia, which is associated with the prefrontal cortex. This deficiency may act as an inherent diathesis and a candidate endophenotypic marker in schizophrenia [59]. A number of such candidates are related to the inability of individuals with schizophrenia to sustain movement of the eye following a moving object, known as smooth pursuit eye movement dysfunction (SPEMD) [60], and some combine SPEMD with the results of a memory test (continuous performance task) [61]. A reduction of prepulse inhibition (PPI) also holds promise as an indicator of sensor filtration [62, 63] because the high frequency of this phenomenon among mentally healthy relatives of individuals with schizophrenia and its connection with neurotransmitters has been demonstrated. In addition, similar changes have been reported in animals raised under deprived conditions [49]. This means that is possible to study the connection between PPI and other biomarkers and behaviour in schizophrenia because deprivational models of this pathology are convincing. A number of possible endophenotypic markers involve neuroanatomical attributes revealed with neurovisualisation, "soft" indicators of CNS dysfunction, physiological and electrophysiological indicators, biochemical or immunological markers, and psychological or neurocognitive deficiencies (for review, see [57]). At present, 38 markers of the endophenotype exist. These attributes can be connected in a hierarchy from prospective genetic loci to biochemical, sensory and cognitive processes and further to the clinical spectrum of schizophrenia. The problem arises that, from the neuropsychological level to the level of clinical signs, the degree of subjectivity progressively increases and is impossible to overcome by testing.

Though human ethology describes behaviour under non-experimental conditions, its methods allow the addition of an objective description to a clinical picture, which can be compared to biological models. Behavioural patterns established by non-experimental methods are possible endophenotypic markers that can relate genetics and biochemistry to clinical attributes of schizophrenia.

The Crimean Neuroethology Project

The Crimea Neuroethology Project was initiated in 1986 [64–84]. The purpose of the project was the description of basic mental diseases using ethological methods. The tasks of the project included: (a) compilation of a behaviour glossary for general ethological description of primates, including humans, in normative terms and in the context of mental pathology; (b) the description of a behavioural structure of

schizophrenia by ethological methods; (c) comparison between the behaviour of monkeys and humans in normative terms and in schizophrenia; and (d) searching for candidate endophenotypes among neuroethologically relevant features of the behaviour of persons with schizophrenia.

Method

Design

Typology of behaviour was recorded for various mental disorders, including schizophrenia, in mentally healthy respondents, and also in mentally healthy mothers of individuals with schizophrenia during interactions both with a psychiatrist and with their children. Substance- and alcohol-addicted patients during periods of intoxication and abstinence and patients with affective disorders and neurotic disorders were used as controls. All patients included in the study met the criteria for a diagnosis of schizophrenia according to the diagnostic guidelines of the DSM-IV. Patients with current or past neurological pathology verified by neurological examination, computer tomography and EEG, those using drugs and/or alcohol, and those with a Macey-Burke index of hand functioning [85] lower than 30 were excluded.

Participants

Samples of patients with schizophrenia and mentally healthy persons in Crimea, Cherson, Zaporozhye (Ukraine) and Surguts (East Siberia, Russia) were studied. Participants were categorised into the ethnic groups of Slavs (Russian, Ukrainian, Byelorussians), Turkic peoples (Crimean tatars) and natives of the Far North (Khanty, Mansi, Selkupy, Nenets) (Table 6.1).

The sample of individuals with schizophrenia included 410 women with an average age of 35.4 years (± 10.6) and 436 men with an average age of 37.1 years (± 11.4). The paranoid type of schizophrenia was most common (N = 634; 74.9%). The average age of 250 mentally healthy controls (120 men and 130 women) was 32.7 years (± 5.2), and that of 117 mentally healthy mothers of schizophrenia patients was 56.4 years (± 4.1). All patients took typical neuroleptics and combinations thereof in small to average doses. The mentally healthy persons were hospitalised for observational purposes unrelated to the present research and consequently were observed under the same conditions of a clinical ward.

Anthropologists and psychiatrists together carried out ethological observation of 100 mentally healthy persons and 100 patients with schizophrenia (50 men and 50 women in both groups) during contact with a doctor. All patients had suffered from schizophrenia for longer than 10 years, had not remained out of the hospital for any period longer than 3 years and exhibited negative symptoms.

For comparative purposes, the data of M.A. Derjagina [68] who studied the behaviour of monkeys by ethological methods worldwide over a period of 25 years,

Table 6.1 Samples of the study

Groups	Characteristics	Total
Control groups: Healthy persons		250 (50)
Mental disorders	Substance-related disorders (303.90, 305.00, 303.00, 291.0, 291.3, 292.89, 292.0)	120 (20)
	Mood disorders (296.xx)	134 (25)
	Anxiety, somatoform and dissociative disorders (300.xx, 307.xx, 308.3, 309.81)	245 (30)
	Schizophrenia (295.30, 295.10, 295.20, 295.90, 295.60)	846 (100)
Mentally healthy mothers of individuals with schizophrenia		117 (10)
Monkeys [67, 68]	2 species of Prosimii, 10 species of Platyrrhini, 9 species of Catarrhini, 5 species of Hominidae	1,046 (40)
Acute emotional stress [67, 68]	The Rhesus Monkey (Macaca mulatta)	21(3)
	The Hamadryas Baboon (Papio hamadryas)	29 (7)
Healthy persons[a]		100
Patients with schizophrenia[a]		100

Note: In brackets the number of objects' supervision allowing to construct a glossary and to calculate probabilities of diagnostics of elements, patterns and complex forms of behaviour is specified. Further this glossary has been applied to comparative evolutionary researches.
[a]Ethological observation was conducted by both anthropologist and psychiatrist.

were used. Two senior psychiatrists (the author of the present chapter and A.A. Korobov) participated in the observation of the monkeys alongside primatologists and anthropologists.

Assessments

(A) Clinical diagnosis of schizophrenia on the basis of DSM-IV criteria [86]
(B) Patients with schizophrenia were divided into two groups according to Crow's criteria [87–89]: Type 1 (Sch I) (482 patients, 57.0%), with prevalent productive symptoms, delusions and hallucinations appropriate to paranoid schizophrenia; and type 2 (Sch II) (364 patients, 43.0%), with prevalent negative and cognitive deficit symptoms appropriate to non-paranoid schizophrenia.
(C) A general glossary of behaviour was compiled on the basis of ethograms for every patient observable during a 20-min interview as well as behaviour outside of the interview setting during observation in the hospital unit. Ethograms included visual and removed record of behaviour in the protocols. The probabilities of particular behaviours in a series of actual observations in comparison with control participants were calculated. During observation of monkeys, the similar principle of ethogram fixing on channels of facial expression, posture, gesture, manipulative activity (MA) and vocalisation [68] was used (Table 6.2). Ethograms included elements and patterns of behaviour translated to a context of behaviour.

Table 6.2 The example of ethogram record of behaviour and vocalization

Number of transition in dynamics of behaviour	Facial expression M	Posture P	Gesture G	Manipulation activity MA	Vocalization and speech S
1[a]	Smile				
2	Half-proboscis	Inclination forward			
3	Eyebrow flash	both shoulders raised	Fist		
4	Look bottom left	both shoulders lowered	Hold right hand forward	Manipulation if earlap	

Note: [a]Examples of number of transition: 1 = single (channel M), 2 = double (M + P), 3 = triple (M + P + G), and 4 = quadruple (M + P + G + MA) complexes on communication channels were designated.

(D) Tests of manipulative activity (MA) included:

(a) spontaneous MA by recording of spontaneous gestures with an estimation of the kind of manipulation and degree of intensity. Mapping of MA ethograms was carried out according to the standard protocols, with marks for separate elemental motions based on a technique by McNeil [90] in which the topography of space of a manipulation and gesture are taken into account. The duration of observation was 20 min, the distance between the examinee and the researcher was 100–150 cm, and the plane of visual contact was frontal.

(b) The experimental 2-serial manipulation task was carried out with the help of standard sets of 4 objects of neutral (grey – black) colour used in primatological research [66, 67]: stick, sphere, ring, rag. The first and second choices were estimated, and the structure and sequence of forms of a manipulation, ethological figure and level of hierarchy of a manipulation were analysed. Finger index (FI) was calculated (Appendix 1). Within categories of actions, types of actions, forms of categories and variants of circuits of a manipulation were created.

(E) Method of estimation of oculomotorics. Oculomotorics were measured during a 10-min experimental MA in which a videorecording of eye movements in different sectors of space, with the subsequent account of its frequency in bits per 1 min in each direction of space was created.

(F) Techniques of speech analysis during a manipulation. Participants' speech was recorded on a Dictaphone during a task, and the recording was transcribed. On the basis of text fragments including at least 70 words, the basic lexical and grammatical characteristics, general length of the utterance (number of words), and parts of speech were determined. In spontaneous speech, the quantities of nouns (as parts of speech designating a subject), verbs (describing actions), and adjectives (reflecting a condition of a subject and its attributes) were determined. The shares of the specified parts of speech were presented in relation to the total number of words in a researched fragment of speech. The rate of speech was registered by counting the number of words spoken per minute. Psycholinguistic indexes were also investigated [70, 91–94] (Appendix 1).

(G) Alongside with traditional statistics and determination of the reliability of our distinctions, the: finite-state machine (FSM) ideology [95] was used. The transitions from one complex form of behaviour to another allow transforming the ethogram in the vector structure. In FSM, the transition from one condition to another (i.e., from one behaviour to another) is not determined unequivocally, and there is some distribution of transitional probabilities from a certain condition at any time that deviates from an equiprobable distribution.

Results

The observations yielded a glossary of behaviour consisting of 184 elements, 17 patterns and 15 complex forms of behaviour. Unlike ECSI, displacement is not included because, along with readdressing, vacuum of activity, and ritualisation, it was considered as a mechanism of behaviour (Appendix 2).

Elements of Behaviour

On the basis of comparisons of the frequencies of elementary units and patterns of behaviour in the study sample, the attributes authentically prevailing in schizophrenia in comparison with mentally healthy controls were determined (see Tables 6.3, 6.4, 6.5 and 6.6). Identification of these attributes permitted the development of an ethological profile of schizophrenia that differs from the controls' profile on many attributes that prevail in two types of illness or are seldom observed.

Table 6.3 The glossary of elements of behaviour and probability of recognition of elements during the interview

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
P	*General characteristics of a posture*				
P.1	*Postures in a standing position:*				
P.1.1	With item held in hands,	0.22	0.15	0.35	0.32
P.1.2	With holding on object by the hands,	0.12	0.10	0.20	0.22
P.1.3	With displacement of the trunk,	0.16	0.14	0.12	0.14
P.1.3	Relaxed,	0.27	0.32	0.35	0.34
P.1.4	With crossed arms (Napoleon's posture),	0.06	–	0.04	0.06
P.1.5	Submissive,	0.08	0.44*	0.06	0.24
P.1.6	Aggressive,	0.36*	0.02	0.02	0.12
P.1.7	Supporting the head with one hand (thoughtfulness),	0.24*	0.10	0.12	0.20
P.1.8	Squatting.	–	0.06	–	–
P.2	*Postures in sitting position:*				
P.2.1	Static with straightened back,	0.23	0.52*	0.02	0.04
P.2.2	Relaxed,	0.11	0.14	0.03	0.06
P.2.3	Supporting the head with one hand (thoughtfulness),	0.14	–	0.12	0.22
P.2.4	With hands to the sides,	–	0.12*	–	–
P.2.5	Foetal position,	–	0.08	–	–
P.2.6	Posture of an equestrian,	–	0.10	0.02	–

Table 6.3 (continued)

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
P.2.7	Pleading posture with one or both hands extended forward,	0.02	–	–	0.06
P.2.8	Aggressive,	0.26*	0.04	0.02	0.12
P.2.9	Posture of the Buddha,	–	0.01	–	–
P.2.10	Leaning: forward,	0.02	0.16	–	0.01
P.2.11	Back,	0.02	0.04	0.18	0.12
P.2.12	to the right,	0.10	0.12	0.12	0.16
P.2.13	To the left,	0.02	0.04	0.15	0.19
P.2.14	Hunched forward (camptocormia),	–	0.02	–	0.05
P.2.15	Mating posture (lordosis),	0.02	0.16*	–	0.08
P.2.16	Shrinking (reduction of body size).	0.04	0.26*	–	0.12
P.3	*Sleeping postures:*				
P.3.1	On back,	0.82	0.45	?	?
P.3.2	Extension posture on back (decerebrate),	0.08	0.07	?	?
P.3.3	On one side,	0.26	0.34	?	?
P.3.4	On stomach,	0.08	0.12	?	?
P.3.5	Foetal position,	–	0.16*	?	?
P.3.6	Frequent changes in posture.	0.16	0.02	?	?
P.4	*Head components:*				
P.4.1	Looking directly ahead,	0.78	0.82	0.88	0.87
P.4.2	Leaning the head forward aggressively,	0.16*	–	0.02	–
P.4.2	Inclination: forward,	0.12	0.14	19	18
P.4.3	Back,	0.12	0.07	0.06	0.10
P.4.4	to the right,	0.06	0.11	0.06	0.05
P.4.5	To the left.	0.06	0.04	0.02	0.03
P.6	*Components of shoulders:*				
P.6.1	Parallel to the pelvis,	0.82	0.88	0.87	0.89
P.6.2	One or both shoulder(s) raised,	0.18*	–	0.04	0.02
P.6.3	One or both shoulder(s) lowered,	0.01	0.13*	0.02	0.02
P.6.4	Distortion (lack of parallelism),	0.04	0.16	0.08	0.12
P.6.5	Shoulders thrown back,	0.24*	0.03	0.03	0.04
P.6.6	Shoulders adduced forward,	0.11	0.23	0.13	0.14
P.6.7	Hypertonus of shoulder	0.02	0.26*	–	0.03
P.7	*Trunk components:*				
P.7.1	Inclination: forward,	0.12	0.13	0.12	0.16
P.7.2	To the right,	0.14	0.14	0.15	0.13
P.7.3	To the left,	0.16	0.14	0.16	0.18
P.7.4	Facing forward,	0.76	0.78	0.83	0.84
P.7.5	Demonstration of genitals.	–	0.03	–	–
P.8	*Components of hands.*				
P.8.1	One hand placed on: an item or object,	0.46	0.52	0.37	0.56

Table 6.3 (continued)

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
P.8.2	The head,	0.12	0.02	0.08	0.08
P.8.3	Throat,	0.02	0.16*	–	0.08
P.8.4	Trunk,	0.12	0.14	0.16	0.06
P.8.5	Groin, or	0.02	0.02	–	–
P.8.6	Hip,	0.14	0.12	0.14	0.14
P.8.7	One hand not placed on anything,	0.10	0.20*	–	–
P.8.8	Both hands placed on: an item or object,	0.02	0.02	0.03	0.08
P.8.9	Trunk,	0.01	0.09	0.01	0.07
P.8.10	Groin,	0.03	0.06	–	–
P.8.11	Hip,	0.01	0.02	0.04	0.04
P.8.12	Both hands not placed on anything,	–	0.12	–	0.6
P.8.13	Special positions of one hand: a fist,	0.14*	0.02	0.02	0.02
P.8.14	Fig,	–	0.04	–	–
P.8.15	Pinch,	–	0.06	0.02	0.04
P.8.16	Low mobility of one palm (hand of a monkey),	0.02	0.24*	–	0.12
P.8.16	Scraping movements (sharp-clawed hand),	–	0.14*	–	0.04
P.8.17	Palm as a boat,	–	0.02	0.02	0.01
P.8.18	Thumb abduction,	0.12	–	0.06	0.02
P.8.19	Special positions of both hands: one hand compressing the fingers of the other hand,	0.02	0.12	–	0.08
P.8.20	Fingers interlaced,	0.14	0.16	0.14	0.12
P.8.21	Hands in sleeves,	0.10	0.12	0.11	0.13
P.8.22	palm of one hand to back of other hand,	0.12	0.14	0.10	0.08
P.8.23	Both hands in fists,	0.14	0.06	0.01	0.12
P.8.24	Palm to palm.	0.12	0.07	0.08	0.14
P.9	*Components of feet:*				
P.9.1	Crossing of shins,	0.03	0.12	0.06	0.08
P.9.2	Shin of one leg on the other thigh,	0.02	–	–	–
P.9.3	Knees: abduction,	0.28	0.31	0.10	0.08
P.9.4	Knees: adduction,	0.72	0.69	0.90	0.92
P.9.5	Foot: abduction	0.15	0.26	0.14	0.14
P.9.6	Foot: adduction,	0.85	0.74	0.86	0.86
P.9.7.1	Knee bent less than 90 degrees: right leg	0.34	0.46	0.44	0.46
P.9.7.2	– Left leg,	0.36	0.45	0.34	0.37
P.9.7.3	– Both legs,	0.12	0.16	0.01	0.03
P.9.8.1	Exactly 90 degrees: right leg,	0.01	0.02	0.01	–
P.9.8.2	– Left leg	–	0.04	–	–
P.9.8.3	– Both legs	0.12	0.06	–	0.01

Table 6.3 (continued)

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
P.9.9	more than 90 degrees: right leg	0.08	0.12	0.34	0.48
	– Left leg,	0.14	0.12	0.32	0.15
	– Both legs,	0.12	0.10	0.33	0.48
P.9.10	Jumping,	–	0.06	–	–
P.9.11	Stomping foot	0.02	0.12	–	0.02
M	*Facial expression*				
M.1	*Components of eye contact*				
M.1.1	Looking at partner's face,	0.82	0.52**	1,00	0.98
M.1.2	Staring at partner's face (absence of blinking longer than 2 min while looking at a face without looking away),	0.26*	0.02	0.10	0.12
M.1.3	Staring to the side,	0.12	0.36*	–	0.27
M.1.4	Looking around or at the corners of the room,	0.15	0.14	0.34	0.23
M.1.5.1	Looking at hands,	0.08	0.35*	0.08	0.12
M.1.5.2	At objects	0.14	0.12	0.01	0.12
M.1.5.3	At a window or light source	0.12	0.21	0.08	0.08
M.1.5.4	At the ceiling	–	0.04	–	0.02
M.2	*Components of eyelids:*				
M.2.1	Closed eyes,	–	0.02	–	–
M.2.2	Blinking (fluctuations of sizes of the orbital fissures without full closing of the eyes),	0.88	0.75	1.00	0.99
M.2.3	Winking (fluctuations of the sizes of one orbital fissure with full closing of the eye),	0.36	0.14**	0.52	0.28
M.2.4	Unilateral blinking (winking),	0.01	–	0.01	–
M.2.5	Veraguth's fold (descended external corner of the eye with overhanging upper eyelid) (98),	0.01	–	–	0.06
M.2.6	Considerable widening of eyelids (protruding eyes),	0.04	0.02	–	0.01
M.2.7	Tightly closed: both eyes,	0.10	–	0.01	0.01
M.2.7	Right eye	0.08	0.06	0.02	–
M.2.8	Left eye	0.02	0.02	–	–
M.2.9	Tears,	0.02	–	–	0.13
M.2.10	Baggy skin below the eyes.	0.01	0.02	0.02	0.06
M.3	*Eyeball components:*				
M.3.1	Leaden shine of eyes, shining eyes,	0.01	–	–	0.01
M.3.2	Dim eyes,	0.02	0.12	–	0.08
M.3.3	Sad eyes.	0.02	0.02	0.01	0.14

Table 6.3 (continued)

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
M.4	*Components of the forehead and eyebrow area:*				
M.4.1	Lifted: both eyebrows,	0.02	0.01	0.04	0.08
M.4.2	Right eyebrow	0.01	0.01	0.04	0.06
M.4.3	Left eyebrow	0.01	0.01	0.04	0.06
M.4.4	Eyebrow flash (i.e., movement),	0.16**	0.01**	0.87	0.45
M.4.5	Movement of the ears,	0.01	0.10*	–	–
M.4.6	Eyebrows furrowed,	0.16*	0.01	0.01	0.14
M.4.7	Lowered external ends of: both eyebrows,	0.02	0.02	0.01	0.08
M.4.8	Right eyebrow	0.01	0.01	–	0.06
M.4.9	Left eyebrow	0.02	0.01	0.01	0.01
M.4.10	Longitudinal wrinkles on the forehead,	0.02	0.14*	0.02	0.08
M.4.11	Vertical wrinkles on the forehead,	0.16*	0.02	0.02	0.10
M.4.12	Asymmetry of forehead wrinkles,	0.07	0.12	0.04	0.02
M.4.13	Movement of the forehead,	0.02	0.12*	–	–
M.4.14	Amimia of the top of the face.	0.11	0.34*	–	0.12
M.5	*Components of the mouth area:*				
M.5.1	Smile,	0.14	0.02**	0.47	0.23
M.5.2	Grin,	0.26*	0.03	0.11	0.02
M.5.3	Half-grin,	0.18	0.12	0.19	0.10
M.5.4	Half-smile,	0.13	0.08	0.04	0.06
M.5.5	Asymmetrical smile,	0.08	0.12	0.06	0.09
M.5.6	Trembling of corners of mouth,	0.16	0.09	0.01	0.13
M.5.7	Trembling of the lower lip,	0.08	0.06	–	0.08
M.5.8	Square mouth,	0.02	–	–	0.01
M.5.9	Bell mouth,	0.01	0.08	–	–
M.5.10	Lengthened mouth,	0.07	0.05	–	0.01
M.5.11	Slit-like	–	0.01	–	0.01
M.5.12	Intention to bite,	0.09	–	–	–
M.5.13	Biting a hand or clothes,	–	0.06	–	–
M.5.14	Uplifted lips	0.01	0.07	0.01	0.02
M.5.15	Biting of the lips,	0.02	0.04	0.01	0.02
M.5.16	Compressed lips,	0.16*	0.02	0.01	0.09
M.5.17	Lips pressed inside,	–	0.06	0.01	0.08
M.5.18	Spitting,	–	0.06	–	–
M.5.19	Kissing,	–	0.01	–	–
M.5.20	Chewing,	0.12*	0.04	0.01	0.01
M.5.21	Tongue visible between lips in the centre of the mouth,	–	0.01	–	0.01
M.5.22	Tongue visible between lips in a corner of the mouth,	0.02	0.02	0.02	0.01
M.5.23	Intention to speak,	0.06	–	0.12	0.14
M.5.24	Relative displacement of lips,	0.05	0.14*	0.02	0.04

Table 6.3 (continued)

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
M.5.25	Displacement of lips with protrusion of the tongue,	–	0.08	–	–
M.5.26	Oscitation,	0.11*	0.02	–	–
M.5.27	Licking lips,	0.16*	0.14*	0.02	0.02
M.5.28	Inflation of cheeks,	–	0.02	–	–
M.5.29	Drooped lower lip,	0.02	0.08	–	–
M.5.30	Proboscis,	0.07	0.17*	0.01	0.01
M.5.31	Protruding lower lip,	0.12	0.03	0.05	–
M.5.32	Protruding lower jaw,	0.16*	0.02	0.01	0.01
M.5.33	Combination of semi-proboscis with an open mouth (giving the appearance of the mouth of a fish),	0.02	0.09	–	0.02
M.5.34	Lip-smacking,	0.02	–	–	0.02
M.5.35	Teeth chattering,	–	0.01	–	0.01
M.5.36	Bruxism (grinding the teeth),	0.01	–	–	0.01
M.5.37	Relaxed mouth.	0.22*	0.33*	0.01	0.25
G.	*Gestures with the free hand:*				
G.1	Gesture underlining speech (gesture accent),	0.35	0.02**	0.26	0.15
G.2	Indicating gesture,	0.18*	0.04	0.04	0.05
G.3	Gesture directed to the interlocutor (reference gesture),	0.13*	–	0.09	0.12
G.4	Gesture with hand fixing: On the head (thoughtfulness gesture),	0.08	0.04	0.04	0.18
G.5	On the neck (gesture of latent anxiety),	0.20*	0.06	0.02	0.12
G.6	Abdomen,	–	0.02	–	0.02
G.7	Genitals,	–	0.02	–	–
G.8	Gesture of removal,	0.06	–	–	–
G.9	Gesture with rubbing hands,	0.02	–	–	–
G.10	Clapping,	0.02	–	–	–
G.11	Raising a hand to threaten another person,	0.01	0.02	–	–
G.12	Obscuring the face or its parts with the hands.	0.01	–	–	0.08
G.13	Gestures of autogrooming: Hair,	0.12	0.11	0.14	0.12
G.14	Ear,	0.06	0.02	0.02	0.01
G.15	Neck,	0.12*	0.02	0.01	0.01
G.16	Forehead,	0.25*	0.06	0.09	0.12
G.17	Eye,	0.14*	0.01	0.02	0.10
G.18	Nose,	–	0.06	0.02	0.01
G.19	Mouth,	0.03	0.18*	–	0.01
G.20	Shoulder,	0.16*	0.01	–	0.01
G.21	Hand,	0.12*	0.04	0.02	0.02
G.22	Trunk,	0.01	–	–	–

Table 6.3 (continued)

	Glossary	Probability			
Code	The channel and the element of communication	Sch I	Sch II	Control	Mentally healthy mothers
G.23	Genitals,	–	0.01	–	–
G.24	Feet,	–	0.01	–	–
G.25	Game by fingers	–	0.13*	–	–
G.26	Gesture of unfinished grooming (aspiration to put interlocutor's clothes in order or to touch him).	0.01	–	–	–
G.27	Gesture of grooming (tactile communications)[a]	0.14	0.02**	0.66	?
O	*Olfactory*				
O.1	Sniffing: parts of a body – hands after touching the face,	0.02	0.14*	–	0.02
O.2	Feet,	–	0.02	–	–
O.3	Armpits,	–	0.02	–	–
O.4	Objects,	–	0.04	–	–
O.5	Sniffing one's surroundings,	0.02	0.02	–	–
O.6	Sniffing one's meal	0.02	0.28*	?	?

Note: P-probability of recognition, Sch I-II group of schizophrenia according to Crow's criteria [87–89].

*$p < 0.05$.

**$p < 0.001$.

[a]the total number of elements of communication from the interview includes 37 elements of tactile communication connected with the dialogue of the patient with another subject, including: mutual or unilateral embraces by the shoulders or waist, a touch to the head, face, hand, chest, or back, donation of objects, cigarettes, or food, exchange of objects, and manipulation of the hands. All elements of tactile communications were not marked during the interview.

Postures with elements typical of aggressive-precautionary behaviour, with hunched shoulders, shoulders thrown back to expose the chest, head-first attack, and also postures appropriate for meditation are characteristic for Sch I. For Sch II, with its prevalence of negative symptoms, characteristic postures were of submission, including standing and sitting postures with elements of mating posture (named lordosis) or dropping of the shoulders and hypertonus of the shoulder zone muscles as an attribute displaying fixed submission. The postures of the legs, hands, and trunk did not differ at all between the two types of schizophrenia, the controls and mothers of patients with schizophrenia. Among the special hand elements typical of Sch I were low mobility of the palm despite sufficient mobility of the fingers ("monkey" hand), scraping movement with the fingers ("sharp-clawed" hand), and pinching (hand of "accoucheur"). These attributes are similar to experimentally described "soft" neurological indicators. The absence of placing a hand on the body, typical of submission, was also characteristic. In Sch II, marked compression of a hand in a fist was frequently observed as an aggressive-precautionary attribute.

Table 6.4 Probability of recognition of patterns of behaviour

Code	Pattern	Sch I	Sch II	Control	Mentally healthy mothers
1	Proxemics	Individual distance (cm)			
		220±40	320±120*	170±25	300±105
		Probability of recognition of patterns			
2	Greeting at a distance	0.27	0.13**	0.92	0.62
3	Orientation at contact				
3.1.	Kinesis	0.34	0.30	0.25	0.22
3.2.	Taxis	0.66	0.70	0.75	0.78
3.2.1	– Phobotaxis	0.34*	0.27*	–	0.12
3.2.2	– Menotaxis	0.12	0.30*	–	0.15
3.2.3	– Mnemotaxis	0.10	0.13	0.16	0.24
3.2.4	– Telotaxis	0.04**	–**	0.59	0.27
4	Reaction of a shoulder	0.02	0.08	–	0.01
5	Eye contact and reaction of a pupil				
5.1	– Constant contact	0.85	0.52	1.00	0.82
5.2	– Very rare (2–3 times during 20 min)	0.13	0.45*	–	0.12
5.3	– Pupil reaction depends on external stimulus	?	0.01	0.24	?
5.4	– Spontaneous reaction of the pupil	0.06	0.04	–	?
6	Guttural tussiculation	–	–	0.01	–
7	“Aha” expression	–	–	0.02	0.01
8	Attraction to mirrors	–	0.07	–	?
9	Mumbling	–	0.06	0.02	–
10	Trophallaxis	–	0.15	?	0.15

Note: Sch I–II group of schizophrenia according to Crow’s criteria [87–89].
*$p < 0.05$.
**$p < 0.001$.

Table 6.5 Probability of recognition of the dynamic phenomena of behaviour

	Probability			
Phenomenon	Sch I	Sch II	Control	Mentally healthy mothers
Stereotypy	0.12	0.44*	0.01	0.03
Hyperkinesias	–	0.01	–	–
Tics	0.02	0.04	0.01	0.04
Tremor	0.11	0.18*	–	–

Note: Sch I–II group of schizophrenia according to Crow’s criteria [87–89].
*$p < 0.05$.

Patients with Sch II made eye contact with the interviewer almost half as much as others. Blinking was rare, but looks to the side or at the hands following eye contact with the interviewer were observed. Thus eyes were dim. Patients’ mothers exhibited similar eye contact behaviour. In Sch I, extended eye contact with blinking

Table 6.6 Finger index at spontaneous manipulation

Choice stages	Sex	Schizophrenia		Control	
		Mean	SD	Mean	SD
Choice of the first item	Men	0.83*	0.01	0.42	0.02
	Women	0.76*	0.04	0.40	0.02
Choice of the second item	Men	0.74*	0.03	0.52	0.01
	Women	0.65	0.02	0.48	0.02

Note: Choice of items from a set: a sphere, a stick, a rag, a circle, * – reliability of distinctions $p < 0.05$ [69]. Sample size: schizophrenia (35 males, 35 females); control subjects (25 males, 25 females).

was typical. These findings support studies that connect sociality with avoidance of eye contact in schizophrenia and assume that such behaviours can serve as markers of disease [42]. As a whole, in schizophrenia, the absence or reduction of the eyebrow flash (EBF) reflects hypomimia of the top of the face, which is almost completely absent in Sch II and in one half of patients' mothers. For negative symptoms of schizophrenia, movements of the forehead, hair and ears were typical, none of which were observed in the control group. Comparative research has shown that characteristic attributes of facial expression should be referred to as regressive. Among the elements characteristic of the mouth area in Sch I are a marked grin, compressed lips, chewing and yawning, and jutting of the mandibula, all of which are aggressive-precautionary. In Sch II, the relative displacement of the lips and proboscis, and lowered angles of the mouth were typical. Licking of the lips and a relaxed half-open mouth were observed with identical frequency in both types but were not observed in the controls, indicating that these behaviours were caused by dryness of the mouth connected with neuroleptic treatment. The qualitative analysis of facial expressions in Sch I revealed asymmetry of facial expressions between the right and left halves of the face; for example, Veraguth's fold [96] only on one side or lowering of one corner of the mouth. In Sch II, marked dissociation of the facial expressions of the top and bottom of the face was observed; for example, sad eyes with a half-smile.

Observation of gestures showed that, for Sch II, gestures underlining speech and directed to the side of an interlocutor are not typical, demonstrating a dissociation between gesture and speech communication. Autogrooming gestures such as rubbing of the mouth are observed, but there were practically no gestures connected with tactile social communication. In Sch I, gestures are directed to an interlocutor, and autogrooming gestures are focused on the neck, forehead and eye areas. Comparison with clinical data has shown that the gesture of hand fixing on separate parts of the body is related to basic experienced emotion. Placing a hand on the throat, apex of the nose, or ear lobe is characteristic of anxiety; on the chest, depression; and on the stomach, fear. The gesture of "game by fingers" can be described as special stereotypy specific to Sch II [77]. In this gesture, with low mobility of the palm, the fingers engage in continuous stereotyped movement in a vertical plane.

The separate elements of behaviour in combination with clinical features comprise clinical-ethological syndromes. For example, at apathic states in Sch II, behaviour marked by lowering the shoulders with reduction of one shoulder was combined with turning away and a peculiar posture of the neck. This behaviour pattern is typologically similar to submissive behaviour observable in many evolutionarily dissimilar kinds of animals [97]. During a period of acute psychosis with auditory hallucination in Sch I, a pattern was observed in which sharp turns of the head from side to side were combined with cessation of blinking and hunching of the shoulders. The pattern was reminiscent of "hiding" from a sudden stimulus, visual image or sound [12]. In the Sch II group, a combination of poorly expressed motor catatonic symptoms with hypertonus of the shoulder muscles, increased static character of a posture, game by fingers, inclination of the head and a fixed look to the side was observed. In the same patient, marked mating posture (lordosis), amimia and a spontaneously arising proboscis were observed. Such displays were regarded as microcatatonic. Similar patterns were not observed in the Sch I group. Observation of dynamics revealed that the majority of nonverbal elements of Sch I disappear during periods of remission; however, the ethological markers of Sch II are retained. Especially consistent are dissociation of facial expression with hypomimia in the forehead and eyes, a lack of eye contact with the appearance of avoidance of a look or an unblinking removed look, and the appearance or amplification of stereotypies of gesture or posture. The gradual regression and disintegration of speech up to schizophasia is marked after a period of activation of gesture and prevalence of expansive forms in Sch II. In the stage of catatonic mutism, gesture regresses after speech. Attributes of regression of gesture are reduced involvement of the hands, indeductibility of gesture from the context of speech and emotional condition, stereotypy, presence in one gesture of various typological elements, gesticulation behind one's back, and regression of gesture up to the kinematics of the fingers.

Olfactory communications were not unique to the control group and were very actively shown in Sch II. The patients sniffed their meals and also their fingers after touching their face and other parts of their body. As olfactory communication is the most phylogenetically ancient form of communication, these features were also considered as regressive.

Patterns and Dynamic Phenomena of Behaviour

The study of simple complexes (patterns) of behaviour showed that proxemic distance at contact among mentally healthy individuals was 170 ± 25 cm; in the Sch I type, 220 ± 40 cm, and in the Sch II type, 320 ± 120 cm. This group's large deviation from the average testifies that the prevalence of negative symptoms is related to a patient's desire to sit either closer or farther away than the "normative" distance. The mean distance of mentally healthy patients' mothers was 300 ± 105 cm. The increase in individual distance among the mentally ill patients was correlated with fear intensity, but also with observed delusional disorders. During conversations

with mentally healthy individuals, the individual distance initially remains steady during the whole conversation. As the conversation concludes it is increased due to changes in the posture of the patient or doctor prior to discontinuing contact. It is notable that insignificant dynamics of individual distance during dialogue due to changes in posture are always present, so the final distance between conversation partners is never equal to the initial distance (Table 6.4).

Patients with delusional experiences aspire to increase their distance from a conversation partner, and this increase is a quantitative criterion of delusional dissimulation. With delusional affective involvement, the distance decreases sharply. In Sch II, the distance is already much greater at the initial stage of the interview and does not vary during the conversation.

Individual distance is always dynamic and involves some spatial geometry. The geometry of individual behaviour is part of a complex geometry of social spaces. Distance does not exist outside of specific realised behaviours; therefore differ proxemic characteristics were observed during a game, during a conversation, while not communicating and during communications accompanied only by exchanges of looks.

The pattern of greeting from a distance in Sch II is reduced, and the posture, facial expression and gesture components are absent. All characteristic complexes of facial expression and gesture in healthy people are shown within the first seconds of contact with a doctor, but in schizophrenia these complexes arise more often after 30–60 s. A greeting from a distance, like individual distance, reflects social distancing, which is characteristic of the negative symptoms at schizophrenia.

Rigidity of the shoulders and trunk is especially characteristic of neuroleptic intoxication. An objective criterion of a high level of fear and anxiety among the patients with schizophrenia was reaction of the shoulders. A combination of a lowered head and raised shoulders results in a stoop, which is characteristic of patients with schizophrenia. A stoop, probably, is the fixed reaction of a shoulder. With the involvement of acute psychopathological experiences, it is possible to reveal one more nonverbal attribute – convulsions of the shoulder due to tension of the shoulder's zone muscles.

The study of orientation patterns has shown that menotaxis prevails in schizophrenia, as does mnemotaxis orientation, which is observed in response to new stimuli after a latency period. Telotaxis was not observed in schizophrenia, but after careful telemetering observation and subsequent analysis, it was established that telotaxis is nevertheless present in patients with schizophrenia in the form of moving only the eyes without changes in posture or the position of the head. This attribute, as well as rare eye contact and spontaneous expansion of the pupil in response to an external stimulus in Sch II, is likely to be connected to the known biomarker SPEMD, and taxes and kineses as a whole stem from PPI, as revealed under experimental conditions.

Patterns of guttural tussiculation were not observed in schizophrenia, though they were observed in six healthy controls. The biological value of guttural tussiculation lies in its alarm or warning function – therefore it amplifies during periods of anxiety, representing a signal of danger. Guttural tussiculation has been shown

to be amplified in humans during confusion, when intending to speak, and when discontent. The loss of this attribute in schizophrenia testifies to the regression of the biological alarm social function. Individuals with schizophrenia did not display "Aha!"-expression connected with emotivity and the sociobiological alarm sense.

Inclination toward mirrors as a special obsession was noted in 12 schizophrenia cases, but not in other diagnostic groups. The majority of male and female schizophrenic patients showed a reduction of interest in their appearance, but with increasing negative symptoms, interest in mirrors grows.

The phenomenon of muttering together with talking to oneself was three times as frequent among the Sch II group as among healthy controls; it was usually combined with schizophasia. Trofollaxis, which is characteristic in normal individuals only for early ontogenetic periods, was observed among patients of the Sch II group and their mothers. In this behaviour, a mother's chewed food is transferred to her child by mouth or by hand.

The dynamic phenomena of behaviour – stereotypies and tics – were observed among mentally healthy persons also; however, they did not exhibit tremor or hyperkinesias (Table 6.5).

Stereotypy is considered a microcatatonic element [98], and in biological experimental models it is always regarded as a pathological attribute [99, 100]. The supervision of dynamics of stereotypy development, both in the clinical picture of schizophrenia and in neuroleptic intoxication, has shown that stereotypies are developed in the following sequence in schizophrenia: (a) stereotypy of manipulation, writing and drawing (b) legs (c) posture (jactation) (d) facial expression and nonverbal components of speech. In neuroleptic intoxication, the sequence is: (a) stereotypies of manipulation, writing and drawing (b) facial expression stereotypy in the oral area (c) stereotypes of legs and posture (d) a combination of stereotypies with hyperkinesis and tremor. It was difficult to differentiate neuroleptic origins of dynamic patterns from probable latent subcortical organic pathology. Stereotypy among Sch II includes practically all elements of facial expression, posture, gesture, patterns of a greeting, orientation movement and shoulder movement. It is conditionally possible to consider a rigid and stable system of delusions in Sch I as a cognitive stereotypy.

Manipulation Activity

The MA study revealed that, in schizophrenia, active spontaneous manipulation is realised using the fingers of both hands, parts of the face, and one's clothes. This behaviour coincides with impoverishment of speech and reductions of a VAQ (Verb-Adjective Quotient), an index of direction, a factor of objectifying actions and an index of a dictionary variety. Thus, the structural complexity of gestures and manipulations in schizophrenia is an early sign of cognitive impairment.

Among the healthy examinees and female patients with schizophrenia, spontaneous MA is exhibited via autogrooming movements – contact, "beating" of the

hair, winding it around a finger, touching a corner of the mouth, or smoothing of the clothing. Among male patients and healthy men, MA targets everyday household objects found in pockets as well as manipulations in the genital area.

Among healthy individuals, MA involving clothes had the appearance of putting them in order – namely shaking off or straightening out, without any clichéd appearance. Among patients with schizophrenia, these actions were stereotyped with bizarre elements. The intensity of spontaneous manipulations in the Sch I group was higher than among the Sch II group.

It was also observed that eye movements among patients with schizophrenia and healthy individuals during the MA task were correlated with questions and instructions. A right-side orientation prevailed, reflecting the prevalence of right-handed persons among the sample. In schizophrenia, the prevailing orientations of looks were to the bottom, lower left and lower right areas, and to the patient's own hands (Fig. 6.1). These features corresponded to frequencies of orientation of a look without manipulation and revealed systematic avoidance of eye contact in schizophrenia.

The parameter of the central orientation of a look was especially characteristic for the patients in Sch I and had an aggressive or warning character.

Experimental manipulations revealed that, in schizophrenia as well as in healthy controls, gender-specific preferences are exhibited in the choice of manipulation objects. The women preferred soft and rounded subjects, and men firm and oblong. The same sexual preference in object manipulation is noted in higher primates [66, 68].

Among male patients with schizophrenia, FI (finger index) was higher than in the controls (Table 6.6). This finding testifies to the increased participation of fingers in object manipulation. The high FI parameters, as evolutionary attributes of the development of the hand, reflected a reduction of the precision necessary for exact capture and manipulation. Thus, FI was anti-correlated with all psycholinguistic factors, meaning that speech impoverishment corresponded to an increase in manipulation activity.

The spontaneous speech during a manipulation was characterised by reduction of all parameters, except for VAQ, which was increased in schizophrenia with a prevalence of productive symptoms (Table 6.7).

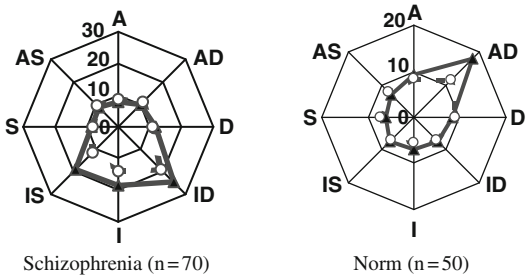

Fig. 6.1 Peripheral orientation of gaze in a spontaneous manipulation. The note: Sector of a direction of a look: *A* – top, *AD* – top right, *D* – right, *ID* – bottom right, *I* – bottom, *IS* – bottom left, *S* – left, *AS* – top left. Gradation of the scale is in bits per minute [69]

Table 6.7 Speech parameters during manipulation

Index	Sex	Schizophrenia		Control	
		mean	SD	Mean	SD
Speech tempo (words/min)	Men	69.1*	0.9	81.3	1.4
	Women	72.1*	1.3	82.4	1.5
VAQ	Men	2.5*	0.05	1.4	0.04
	Woman	2.8*	0.04	1.3	0.02
VNQ	Men	0.82	0.02	1.2	0.03
	Woman	0.6*	0.03	1.4	0.01
CD	Men	0.2	0.01	0.5	0.01
	Woman	0.2	0.01	0.3	0.01
VD	Men	3.9*	0.04	7.0	0.03
	Woman	3.6*	0.02	6.6	0.02

Note: Comparison between schizophrenia and control subjects: * $p < 0.05$. Indices: VAQ – Verb-Adjective Quotient; VNQ – Verb-Noun Quotient; CD – Coefficient of dogmatisms; VD – Vocabulary diversity index.
Sample size: schizophrenia (50 males, 50 females); control subjects (50 males, 50 females).

Table 6.8 The verbal elements of stimulated speech during experimental manipulation

Speech elements	Sex	Schizophrenia (%)	Control (%)
Simple sentences	Man	5.7	22.0
	Woman	8.5	16.0
Compound sentences	Men	4.2	18.0
	Woman	2.8[a]	26.0
Incoherent statements	Men	24.2[a]	–
	Woman	20.0[a]	–
Interjections	Men	12.8	4.0
	Woman	14.2	6.0
Verbal refusal	Men	7.1	–
	Woman	5.7	–
Silence	Men	2.8	6.0
	Woman	4.2	2.0

Note: Percentage of linguistic elements relative to total number of respondents in the group.
Sample size: schizophrenia (35 males, 35 females); control subjects (25 males, 25 females).
[a]Reliability of distinctions relative to controls – $p < 0.05$ [69].

Among patients with schizophrenia, speech stimulated by manipulative actions revealed the prevalence of incoherent statements (Table 6.8).

The kinetic-linguistic interrelation data were rated on a three-point scale. In Fig. 6.2, the mutual distributions of types of manipulations and characteristics of speech activity in patients with schizophrenia and in the control group are depicted.

The results reveal kinetic-linguistic parallelism between the intensity of manipulation and the complexity of speech activity. In other words, in healthy controls,

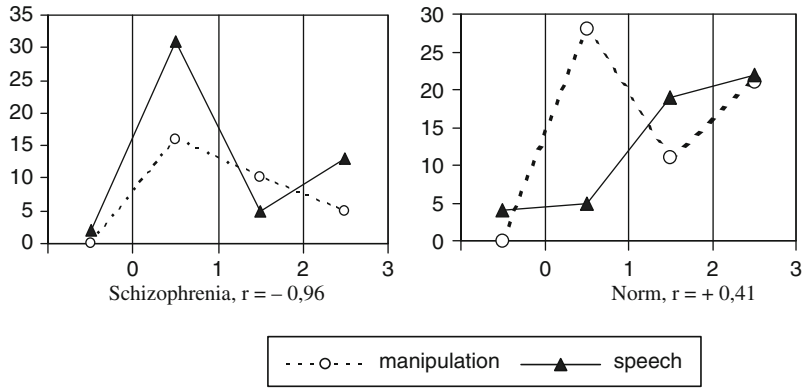

Fig. 6.2 Distribution of types of chains of manipulation and character of speech activity. Note: *X-axis* – number of patients, *Y-axis* – degree of complexity of manipulating or speech activity. Refusal of manipulations corresponded to numerical value 0, a simple linear chain of manipulation – 1, a complex linear chain – 2, a nonlinear chain – 3. Verbal reactions: silence – 0, incoherent statements and/or interjections – 1, simple sentences – 2, compound sentences – 3. r – correlation factor between degree of complexity of manipulations and characteristics of speech activity [69]

increased speech complexity corresponds to increased manipulation intensity. However, in schizophrenia, a negative correlation between MA and speech is observed in which the disintegration and regression of speech are accompanied by increased MA [68, 70]. In particular, incoherent speech statements are combined with impulsive variants of a spontaneous manipulation and complex speech statements with simple linear manipulative circuits, revealing a high degree of anticorrelation ($r = -0.96$).

The phenomenon of manipulative behaviour is associated with systems involving the centres of speech. Thus, we can estimate the degree of connectivity between speech motor centres and behavioural control by observing MA structures [14].

In schizophrenia, the most notable attribute is impulsivity of manipulations. The examination of items has a regressive character and is carried out with the fingers of both hands, frequently with participation of one palm. This pattern of actions may be explained by the releasing of a prehensile reflex from descending inhibitory control, but similar phenomena are observed in organic lesions of the VLPFC and DLPFC. The tendency to avoid contact by instead looking down is probably are related to structural connections to the cortical second frontal convolution, which controls rotation of the eye on a vertical axis.

The study of MA features testifies to the relative independence and autonomy of the functioning of speech centres and CGP manipulation at schizophrenia, which involves the limbic system and brain stem.

Many observed features of manipulation in schizophrenia could be explained by neuroleptic intake, making it impossible to discern whether they are true markers of schizophrenia. If so, at present there is no explanation for the steady independence of manipulation in schizophrenia from structural impairments of speech.

Typology and Dynamics of Complex Forms of Behaviour

The highest hierarchical level of individual human behaviour consists of its complex forms, which are observable in the deployment of series of behaviour patterns. With observation of such complex forms of individual behaviour as sleep, territorial behaviour, migratory behaviour, domination and hierarchy, comfort behaviour, aggressive behaviour, ingestive (food and drinking) behaviour, imitative behaviour, sexual behaviour, parental behaviour, exchange and possession, information seeking behaviour and game-playing behaviour, typological features can emerge, allowing the relative specificity of the separate forms of behaviour specific to schizophrenia to be determined. Nevertheless, unlike individual elements of behaviour, the complex forms of behaviour are poorly investigated not only at schizophrenia, but also in healthy individuals as they differ considerably depending on ethnicity, age, sex, social relations and ecological environment.

Ethological observation permits the discussion of a special "behavioural syndrome" characteristic of schizophrenia – neophobia, which is reflected in all complex forms of behaviour and is an "axial" syndrome for negative symptoms in the Sch II group [77]. Neophobia is indicated by behavioural elements and patterns signalling avoidance and submission, in particular in posture, facial expression, eye contact, gesture, avoidance of heterogrooming, decrease in rank, and reduction of telotaxis. A comprehensive display of neophobia's attributes does not exist in healthy individuals, but elements of neophobia are appreciable among mentally healthy mothers of patients with schizophrenia. Neophobia is likely to be an integrating attribute related to deficiencies in attention, working memory, visual and verbal motor memory, and executive functioning. However, it is quite probable that these cognitive impairments are secondary to avoidance of new stimuli. In addition, it is necessary to take into account that data about cognitive functions are collected only via neuropsychological testing and thus do not correspond to natural human social functioning. It is possible to consider neophobic behaviour patterns as energy-efficient because avoidance of new stimuli and conservatism allow the individual to adapt better in conditions of chronic stress, though it can be detrimental during acute stress (Table 6.9).

For patients with schizophrenia, reduced imitative behaviour was characteristic, as determined by synchronous observations of patients and their mothers, other patients and psychiatrists. No marked "audience effect" is observed in schizophrenia; that is, schizophrenia involves an objective parameter of social isolation and the absence of social induction. To the extent that inductance and imitation are related to teachability, their reduction may result in cognitive deficiencies [84].

The systems of hierarchy and domination in schizophrenia are characterised by decreased rank among Sch II individuals, but exacerbation of a psychosis and the first episode of acute psychosis in Sch I, which can have a ritual character, increase the patient's rank [80]. Changes in rank from α to δ occurred in the context of increases of negative symptoms, while the opposite sequence from δ to α reflected reversal of social regression. However, fixation of negative symptoms in schizophrenia also means fixation of attributes related to low rank. Patients

Table 6.9 Recognition of complex form (context) of behaviour

No	Form of behaviour	Probability			
		Sch I	Sch II	Control	Mentally healthy mothers
1	Neophobia	0.12	0.68*	–	0.16
2	Imitating behaviour	0.02	0.02	0.22	0.25
3	Rank and dominance behaviour				
3.1.	– α rank	0.35	0.01	0.14	0.15
3.2.	– γ, δ rank	0.25	0.70*	0.08	0.28
4	Aggressive behaviour				
4.1.	– aggressive-precautionary	0.27	0.16	0.16	0.14
4.2.	– aggressive-conflicted	0.19*	0.01	–	0.01
4.3.	– aggressive-contact actions	0.01	–	–	–
5	Comfort behaviour	0.15	0.13	0.19	0.14
6	Eating and drinking behaviour	0.17	0.18	0.09	0.11
7	Grooming				
7.1	Autogrooming	0.13	0.15	0.21	0.22
7.2	Heterogrooming	0.18	0.02**	0.24	?
8	Research behaviour	0.11	0.09	0.14	0.23
9	Manipulation	0.12	0.18	0.05	0.12
10	Attention behaviour	0.46	0.22**	0.62	0.64
11	Intentional behaviour	0.18	0.36*	0.11	0.16

Note: Sch I–II group of schizophrenia according to Crow's criteria [87–89].
*$p < 0.05$, **$p < 0.001$.

with schizophrenia residing in psychiatric wards alongside patients with dementia have the lowest rank and continue to support other patients' rank relations with the help of a system of exchange. Nevertheless, the level of heterogrooming and social dialogue in this environment is much lower than among healthy controls.

The system of aggressive behaviour in schizophrenia does not differ from similar systems among the mentally healthy. However, aggressive-precautionary elements are frequently stereotyped. As the stereotyped aggressive-precautionary actions are thought to "buffer" and ritualise aggression, it is possible to assert that, for schizophrenia as a whole, avoidance of aggressive-conflict and aggressive-contact actions is characteristic. During comparative ethological observation of female patients with paranoid schizophrenia interacting with a doctor and with their mothers, the degree of behaviour polymorphism (single, double, triple, and quadruple complexes) and intensity of behaviour did not differ. The greatest numbers of aggressive-precautionary elements were observed for facial expression and gesture. However, during interaction with a doctor, these elements were observed reliably more often in posture and gesture, and during communication of patients with their mothers, in facial expression and speech (e.g., severe tone of voice, threats, insults) (Table 6.10).

Table 6.10 Quantity of aggressive-precautionary elements in patients with schizophrenia on communication channels

Dual communication		Facial expression	Posture	Gesture	Speech	Total
Patient-doctor	N	539	130	271	1	941
	Mean±SD	57, 3±12, 9	13, 8±5, 1*	28, 8±10, 1*	0, 1±0, 0	100, 0
Patient-mother	N	849	94	235	14	1,192
	Mean± SD	71, 2 ± 18, 6*	7, 9 ±5, 7	19, 7±6, 3	1, 2±0, 3*	100,0

Note: In cells, the sum of aggressive-precautionary elements (see Appendix 2) and average values in 100 women with paranoid schizophrenia during a first interview with a doctor (10 min) and contact with their mother (10 min) is designated. Of these patients, 64 were in a condition of exacerbation of schizophrenia.
*$p < 0.05$ [64].

These features indirectly indicate an early ontogenesis of aggression as a result of contact with the mother, in which the identification of facial expressions by the child plays a very important role [17, 19].

The absence of grooming is a poor prognostic attribute related to an increase of negative symptoms or addition of secondary catatonia in schizophrenia. In our collateral observation, it was noted that when a doctor touched a patient, especially on his shoulders, autogrooming was intensified; however, this attribute was very seldom observed among Sch II patients. Stereotyped grooming in patients with schizophrenia is performed with the palm and high mobility of the fingers.

Observation of patients revealed that such components of attentional behaviour as making eye contact with a manipulated object, orientation of the trunk and hands toward this object, facial expressions of concentration, and gesturing to the side of an object of attention as elements of search behaviour in schizophrenia are constructed by other principle. In particular, most looking is concentrated on one side, and the orientation of the head and speech are aimed toward the other side. Furthermore, gesture is not in harmony with looking or with orientation of the trunk and head.

In ingestive behaviour in schizophrenia, the increased consumption of liquids is characteristic and related to side effects of neuroleptics or lithium. However, the consumption of liquids is also increased in acute psychosis before administration of neuroleptics, corresponding to an ethological increased in thirst appreciable in many kinds of animals during periods of excitation and fear. Such displaced activity to drinking during stressful times is known as Saugtrinken, “a symptom of water-pump” [101]. Increased liquid use is accompanied by an increase in the number of chewing and swallowing movements. Among the prominent negative symptoms of Sch II is marked choking and reduction of the number of swallowing movements, which can result in food asphyxia.

Reduced display of eating behaviour, without the dryness of mucous tissue observable in neuroleptic intoxication, involves licking, chewing movements,

swallowing, touch touching objects to the mouth, and movement of the oral area without speech. All of these features of behaviour are caused by mechanisms of displacement activity. In schizophrenia with a prevalence of negative symptoms, these features of behaviour have a stereotyped character.

Some psychopathological impairment in schizophrenia is reflected in food behaviour in a different way. In hypochondriac delusional syndromes, marked changes in the rhythm of food consumption, such as delusion of poisoning, selective preference for particular foods, aspiration to manipulate food and desire to eat alone, are observed. In apathic depression, an absolute lack of fastidiousness in eating is observed. Patients report that the taste of their food is lost, so they consume their meals "as cotton wool".

The intention movements in comparison with healthy controls are marked in schizophrenia more often, especially movements with stereotyped activity, for example, scratching, manipulation and tramping before leaving. These variations of behaviour indicate activation of alternative and ambivalent programs of the completed actions in schizophrenia.

The majority of basic human behaviour patterns, despite some quantitative and qualitative distinctions related to genetics, ecology and culture, are similar in even the most removed ethnoses [12, 17]. The typology of ethological communication, patterns and complex forms of behavior in persons with schizophrenia of Slavs, Turkic (Crimean tatar) ethnic group and natives of the Far North within and without acute psychosis were similar [71–73, 82].

The study of the dynamics of behavioural contexts in schizophrenia with the FSM has permitted us to construct a model of the structure of mutual relations of behavioural forms. For model creation, 50 mentally healthy respondents and 50 patients with schizophrenia with prevalence of negative symptoms (Sch II) were observed during 30-min interviews. Ethograms consisting of a circuit of supervision elements were recoded in the contexts of behaviour designated in Figs. 6.3 and 6.4.

Research has shown that the structure and dynamics of behaviour in schizophrenia structurally differ from behaviour in healthy controls. The number of "forbidden" transitions of behaviour, that is, those taking place when switching of contexts is impossible, is almost doubled in schizophrenia ($N = 10$ in controls; $N = 17$ in schizophrenia), indicating increased rigidity of behaviour and decreased variety. During interviews with a mentally healthy respondent, any form of behaviour passes to consolidation of attention and contact (h), while in schizophrenia there is a displacement of attention to eating behaviour (d) and autogrooming (e). As attention is associated with frontal mechanisms and grooming and eating behaviour with the limbic system and brain stem, the model is a quantitative reflection of the imbalance of evolutionarily new and archaic brain structures, the latter of which are involved in phyloontogenetically earlier forms of communication. Though the consolidation of attention in schizophrenia occurs, alternative variants indicating an absence of frontolimbic balance or relative independence of brain structures of various phylogenetic depths connected with various CFAP are observed regularly. At

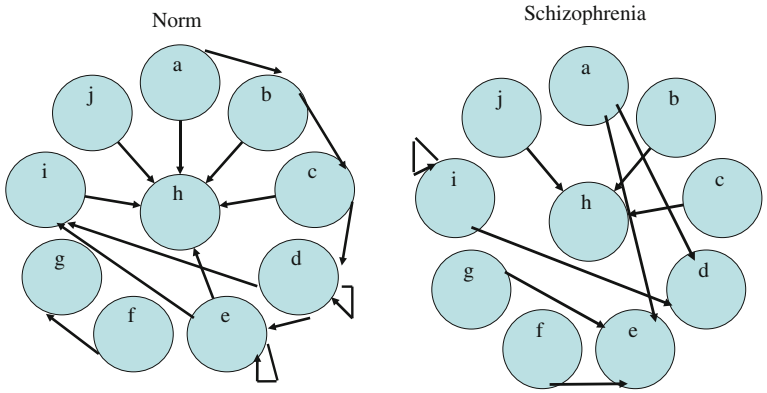

Fig. 6.3 Structure and dynamics of behaviour of the recipient in the FSM model without an additional stimulus

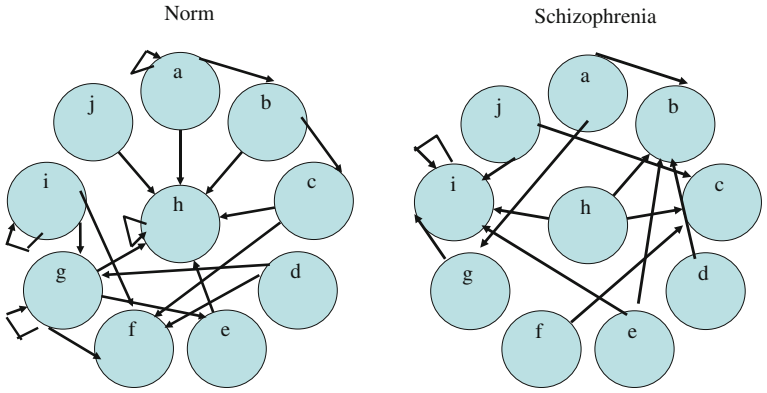

Fig. 6.4 Structure and dynamics of behaviour of the recipient in the FSM model in response to an additional stimulus. Note: in *bubbles* – complex forms of behaviour: a – comfortable, b – neophobia, c – aggressive-precautionary signs, d – food, e – autogrooming, f – information seeking behaviour, g – spontaneous manipulation, h – attention and contact, i – imitating, j – intentional behaviour. Pointers designate transitions from one form of behaviour to another or behaviour stereotypification (angular pointers) with probability ($p < 0.01$) exceeding equiprobable transitions P, which were calculated based on possible stereotypification (one transition) and switching possibilities on other forms (nine transitions) as $P = 1/10 = 0.10$

the appearance of new natural stimulus (change of posture, doctor's gesticulation, appearance of a new unexpected sound, appearance of a new person in a room), attention is not affected among mentally healthy individuals; also, the number of transitions (N = 21) – that is, the plasticity of behaviour – remains at or above its usual level. Some transitions consolidating information seeking behaviour (f) and a manipulation (g) were observed. The same dynamics of behaviour remain in schizophrenia also (N = 13), but the consolidation occurs with behaviour signifying neophobia (b); with aggressive-precautionary attributes (c), that is, on the system of

aggression-escape, which is connected to territorial behaviour or hypersensitivity to stress; or with imitative behaviour (i), which is an original system of social mimicry. These systems probably function independent of cortical control in schizophrenia. Interpersonal contact itself is not a sufficient stimulus for the consolidation of attention in schizophrenia, and any additional stimulus results in avoidance of contact. Thus, there is a generated and stable regressive functional mechanism inhibiting cortical control of behaviour. It is completely typologically similar to CFAP, which arises in early ontogenesis and earlier phylogenetic stages of evolution. Therefore, it is possible to argue that the brain in schizophrenia is not pathological but is functionally constructed by completely different laws, in which previous stages of evolution of behaviour and brain structures documented by MacLean [15] continue to act as a special adaptive mechanism intended by evolution for situations of chronic stress.

Comparative Evolutionary Research

Comparison of glossaries for monkeys and humans observed outside of the interview context allowed us to specify some laws that were not apparent during glossary development in the interview context. During the interviews, tactile communication was not at all observed due to the social distance between the doctor and patient, but it was appreciable when observing the patient in the psychiatric ward. In this sense, the conditions of observation in humans (outside of the interview context) and monkeys were similar as both were in groups but under conditions of partial isolation.

The maximal number of observable elements of communication included in the glossary of patients with schizophrenia was 1.5 times more than in healthy controls (Table 6.11).

Table 6.11 The sizes of glossaries of communication of primates in evolutionary comparative studies

Channel of communication	Rhesus Monkey (Macaca mulatta)	Hamadryas Baboon (Papio hamadryas)	Chimpanzee (Pan troglodytes)	Human (Sch)	Human (norm)	Total
Facial expression	24	18	79	100	86	112
Posture	24	12	54	22	8	65
Gesture and MA	14	7	48	68	53	68
Tactile	7	11	19	36	2	37
Olfactory	2	2	4	6	0	6
Total	71	50	204	232	149	288

Note: the general glossary was made on the basis of observation of 27 species of monkeys, mentally healthy humans, and patients with schizophrenia during communication in a psychiatric ward.

In schizophrenia relative to healthy controls, the numbers of elements in glossaries of facial expressions, postures and gestures are considerably increased, tactile communication is more varied, and elements of olfactory communication are present that are absent in healthy adults but exist in monkeys. In particular, marked sniffing of hands, fingers, hair, objects, preliminary sniffing of food, and also such primitive forms of dialogue as nasal-nasal and nasal-anal contact and diffusive sniffing of others' bodies were observed.

For facial expression, among patients with schizophrenia, the appearance of archaic facial expression elements, such as an open mouth as a part of an aggressive context of behaviour, as observed in primates were characteristic. For example, closed grin, grin with displacement of the jaw, and also infantile facial expression elements such as sucking of a finger or item, sucking movements made by lips rolling in proboscis, and movement of the ears and hair were observed. For postural elements of communication, pendulous walking, stereotyped swinging by the trunk, jumping, somersaults, and certain postures are characteristic in schizophrenia: demonstration of aggression (for example, jumping and lunging, raising the head, display of genitals). The gestural communications of patients with schizophrenia contain stereotyped movements of the whole hand and palm as well as gestures related to displacement aggression. For example, the patient may strike an object with the hand and then shake it. The differentiation of elements of tactile communication is an important marker of pathological behaviour. Patients may touch an interaction partner on the lips, body, or hand, eat from the other's mouths, and also use tactile elements in an aggressive context, such as by pushing, pinching, or biting each other.

In patients with schizophrenia, the specificity of nonverbal behaviour is connected, first of all, with the appearance of ritual, stereotyped elements of facial expressions, gestures and postures: for example, chewing with displacement of the jaw, rocking of the hands, wiping of the fingers, percussion on the forehead and so on. There is appreciable miscoordination and differentiation of elements of facial expression and gestures. For example, the various facial expression variants with an open mouth are similar to facial expression variants observed in the hamadryas baboon and rhesus macaque after acute emotional stress (AES), which has been used as an animal model of schizophrenia [67, 68] as well as in chimpanzees living in cages in a zoo. Analogous to the spatial deprivation of monkeys in an AES, compensatory amplification of facial expression occurs due to movement restrictions. It is necessary to note the rather small probability of appearance of composite complexes of communication, which are characteristic of higher levels of development of the communication system in the primate phylogenesis. Association of two communicative elements (60% of cases) is most common, threefold complexes less frequent (34%), and quadruple complexes were observed only in 6% of cases, demonstrating the disorganisation of the communication system in patients with schizophrenia [68].

As a whole, parallelism in behaviour between the lowest monkeys (macaque, baboon) in the hours immediately following AES, chimpanzees in conditions of spatial and object deprivation in a zoo (variant of chronic stress) and in patients with

Sch II type is apparent. In all clinical cases, the differentiation of facial expression elements, appearance of stereotypies in facial expression, gestures, manipulations, postures, inadequate use of communicative elements and disintegration of speech were typical. These features are similar across schizophrenia and AES in humanoid monkeys. In particular, the grin with displacement of the jaw in monkeys is identical to the smile with displacement of the jaw in patients with schizophrenia.

Discussion and Future Directions

Ethological research has shown that for objectification of psychometric diagnostics it is necessary to use a glossary of behaviour that describes the whole system of nonverbal communication from elements up to complex forms. Its advantages are its objectivity, correspondence to brain structures and evolutionary validity. According to our data, the ethological structure of behaviour in schizophrenia differs qualitatively from the behaviour of healthy individuals and in other mental disorders. Especially clearly, ethological specificity of schizophrenia is shown in the form of negative symptoms in Sch II, in which consist of stable submission, signals of decreased rank in the hierarchy, neophobia, and stereotyped fixation of behavioural dynamics. Thus in schizophrenia, as well as in animals subjected to AES, there is not impoverishment of nonverbal behaviour, but rather an increase in its variety comprised by regressive, in particular olfactory, elements, as well as the appearance of new elements caused by displaced, ritualised and readdressed behaviours. These behavioural changes are distinctive and possibly explain associated regressive changes of speech and cognitive deficiency. This finding supports an earlier report of displaced activity in alexithymia, in which dissociation between cognitive and nonverbal levels is revealed [102], as well as a connection between neurocognitive data and expressivity of nonverbal behaviour as measured by facial expression and decreased social competence [103].

Recently the interpretation of schizophrenia as a frontostriatal disease has been argued, in which abnormalities of projections from the ventral tegmental area to the ventral striatum (nucleus accumbens) as well as connections of amygdala and substantia nigra to the basal ganglia play significant roles. Dysfunctions of the fronto-orbital area are realized in disintegration of consciousness, other clinical signs and disintegration of biochemical structures [104, 105]. As a whole, in schizophrenia there is a reduction in the functioning of interneurons of the ventral striatum, which terminate in the prefrontal cortex. However, the striatum is associated with creativity, which is not completely absent but only altered in schizophrenia [106]. Besides, frontoorbital dysfunction is associated not only with schizophrenia, but also with immorality and with personality disorders [107]. The dynamics of frontal-limbic imbalance may be objectified with the help of ethological research, which testifies that individuals with schizophrenia exhibit a qualitatively different system of communication, including gesture, facial expression, posture and manipulation activity. Use of the study's systems of behavioural dynamics, such as FSM,

will permit the creation of computer models of pathological behaviour similar to existing computer models of structural networks within the brain [108].

Thus, ethological research shows that systems of behaviour in schizophrenia are based on a unique organisation of brain processes in which there is relative autonomy of brain stem, limbic and cortical processes. Revival of evolutionary ancient CFAPs results, on one hand, in actualisation of regressive adaptive mechanisms, but on the other hand in an increase of a diverse assortment of behavioural variations. This arrangement is an example of a "cost-benefit" tradeoff as described in sociobiology, but it could also mean that most schizophrenia spectrum disorders represent a special subspecies of *Homo sapiens* having both advantages and deficiencies in the evolutionary process. Until we advance in the study of genetics of separate patterns of behaviour in schizophrenia in association with other biological markers, we are compelled to consider the brains of patients with schizophrenia as pathological.

The large volume of existing pathophysiological research on schizophrenia cannot yet answer the question of how candidate endophenotypes are embodied in the clinical spectrum of schizophrenia, that is, in its phenotypes, because clinical descriptions are always subjective. The search for biomarkers in systems of natural behaviour and the description of a complete ethological structure of schizophrenia will allow this problem to be solved in the future.

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Appendix 1: Research Indices

Methods	Definition
Finger index (FI) [66]	The ratio of the number of fingers participating in holding an object to the total number of fingers being used on the manipulating hand was counted as: FI = A/N FI – finger index (in standard units) A – number of fingers participating in holding of object N – number of fingers being used on the manipulating hand
Macey-Burke index [85]	Functional valuation of palm movements on a 70-point scale that considers general palm proprioception and stability to cold, pain, force and dexterity carpal capture, flexibility during radiocarpal [brachiocarpal] articulation, and performance of a handling activity. Low levels of palm functioning as a result of neuroorthopaedic defects, pain, congenital anomalies and appreciable signs of neuroleptic intoxication correspond to scores of 10–30, average – scores of 31–50, high – scores of 51–70
Verb-adjective quotient (VAQ) [89]	The ratio of quantity of verbs to quantity of adjectives in a text unit
Verb-noun quotient (VNQ) [70]	The ratio of quantity of verbs to quantity of nouns in a text unit
Coefficient of dogmatisms (CD) [92, 93]	The ratio of the quantity of words such as “should”, “absolutely, “undoubtedly”, “always” and other expressions with a high level of dogmatism to the total quantity of words in a text unit
Vocabulary diversity index (VD) [94]	The ratio of the quantity of nonrepeating words (n) to the total number of words (N) according to the formula: $VD = n/\sqrt{2N}$

Appendix 2: Some Ethological Definitions in the Crimean Neuroethology Project

Dynamic Valuation of Behaviour

No	Phenomenon	Definition
1	Stereotypies	Steady and aimless repetition of movements with small amplitudes. Stereotypies of postures (jactation), facial expression, head nodding, head wobbling, shoulder movements, gesturing, manipulation of a object, clothes, or parts of the face, grooming (effleurage, rubbing), manual stereotypies ("game by fingers"), stereotypies of the feet (abduction and adduction, tapping the heels, rocking), stereotypies of writing and drawing, stereotypies of nonverbal components of speech (tussiculation, mumbling, muttering)
2	Hyperkinesis	Suddenly arising involuntary forced movements in various groups of muscles with considerable amplitude. Facial (grimaces), head, trunk, hands, feet, or a combination
3	Tics	Involuntary and short-term trembling of separate groups of muscles
4	Tremor	Fast and rhythmic muscular movements with a frequency of about 10 Hz. Can occur in the head, lips, tongue, trunk, feet, or a combination

Patterns of Behaviour

N	Patterns	Definition
1	Proxemics	Proxemics is the sum of measures related to interaction distance. Includes the initial and final distances between dyads interacting
2	Greeting at a distance	The complex includes facial (EBF – smiling – convergence of eyebrows) and gestural components (uplifted hands), as well as posture components (bowing, nodding the head). The complex is thought to be meaningfully and unconsciously caused by biological factors as a number of elements of the complex are observed among anthropoids also
3	Orientation at contact	The position adopted by the subject in relation to the interlocutor or another source of stimulus. The orientation form is rarely steady. Orientation movements include taxis and kinesis
3.1		Kinesis – changes of postures dependent only on the intensity of the stimulus, not its direction. They are observed when the patient, while answering a question, notices a stranger, a shrill sound or an unexpected movement. Usually a rapid sequence of two to three postures is observed: complexes of displacement behaviour and the subsequent return to a posture of attention. All postures adopted in this case do not depend on the stimulus' location

(continued)

N	Patterns	Definition
3.2		Taxis – changes of postures in an effort to increase comfort, dependent on the kind, intensity and direction of a stimulus
3.2.1		Phobotaxis – avoidance reaction with the tendency to a turn the trunk away from a new stimulus,
3.2.2		Menotaxis – angular orientation in relation to a stimulus, including the interlocutor,
3.2.3		Mnemotaxis – orientation in relation to a new stimulus throughout the latent period,
3.2.4		Telotaxis – orientation following the movement of a stimulus
4	Reaction of a shoulder	Uplift of one or both shoulders, representing reduced startle at a sudden extraneous sound or emotionally significant question, hunching of the shoulders (a shoulder convulsion)
5	Eye contact and reaction of a pupil	Features of eye contact. Presence or absence of blinking and winking, periodic and visually appreciable widening of a pupil without removal from a light source
5.1		– Constant contact
5.2		– Very rare (2–3 times during 20 min)
5.3		– Pupil reaction depends on external stimulus
5.4		– Spontaneous reaction of the pupil
6	Guttural tussiculation	Combination of confused gestures, facial indications of confusion or helplessness, and nonverbal components of speech such as mumbling, coughing, or smacking the lips
7	"Aha" expression	Behaviour described as the behavioural display of "Aha-experience" in response to a sudden understanding of previously unknown circumstances. Includes a gestural component with different degree of expressiveness, from throwing up the hands to various variants of gesture-accent; a facial component (a smile, a half-opened mouth, EBF); a posture component (turn and/or nod); and specific nonverbal components of speech: "ah", "aha", "well". "Aha"-expression in a biological sense is close to a guttural tussiculation
8	Attraction to mirrors	The behaviour was originally described in fishes, who settle down separately from their group and remain near images in glass or a mirror [73]. The mirror has a relaxing effect in groups of fishes, but a stimulating effect for a single fish. Effects of mirror stimulation and calming have been described in birds and mammals [74]
9	Mumbling	The nonverbal component of speech ascending in ontogenesis to cooing and babbling, sounds preceding the development of speech. It is known that cooing begins at 2 months of age and takes place when interacting with objects and having contact with an adult. In adults, muttering is an indicator of speech restraint: for example, during concentration, muttering or the movement of lips simulating speech are sometimes observed
10	Trophallaxis	Transfer of food from mouth to mouth. Such transfer is characteristic of social insects. In humans, it is only observed during the stage of transition from nursing to solid food, when the mother transfers her chewed food into the mouth of the child. This is thought to be the origin of kisses

Some Complex Forms (Contexts) of Behaviour

N	Form of behaviour	Definition
1	Neophobia	Neophobia – is nonspecific avoidance of contact via increase proxemic distances. Avoidance is shown by averting the head, avoiding eye contact, looking to the side with rare blinking during direct speech contact, changing of orientation of the body to the side at social contact (a type of menotaxis), shoulder dropping, and a submissive posture [63, 64]
		Partial neophobia is shown as homoneophobia, which is a regressive ethological sign – "fear of strangers" typical of young children. Further, homoneophobia can be seen as a game: an interested look is directed toward a stranger when he or she looks away [12]. Neophobia is shown in stereotypic food preferences and avoiding not only strangers, but also pets. The territorial neophobia in schizophrenia is expressed in avoidance of new places to take walks, premises, and aspiration to territory restriction. The syndrome is also shown in the avoiding of new clothes. It generally takes place in a submissive context in primates
2	Imitating behaviour	Imitating behaviour is expressed in the repetition of others' nonverbal behaviour. For example, it may take the form of reciprocating when an interaction partner smiles, an induction of oscitation, or repetition of the interlocutor's gesture. The "audience effect", when any action is more intensively performed when people nearby perform similar actions, is another form of imitative behaviour
3	Rank order and dominance behaviour	Marks of rank, in particular in primates, by the balance of aggression (domination) – submission (escape). Human ranks are similarly (α, β, γ, δ) established; they are obviously distinguishable in the conditions of isolation of a psychiatric hospital on the basis of following signs: (1) On access to significant stimulus, for example, to food or the medical personnel; and (2) On a number of markers of domination
3.1		α, β typical straightened posture, shoulders raised, staring, other aggressive-precautionary signs, a choice of the best territory for a sleeping, the maximum use of speech, a low timbre of the voice, and unusual – in particular, ritualised – behaviour are characteristic
3.2		γ, δ ranks are signified by signs of submission in facial expression, posture and gesture as a whole, corresponding to neophobias
4	Aggressive behaviour	Aggression stages consist of:
4.1		– aggressive-precautionary elements (staring, shoulder raising, hand compression in a fist, furrowed eyebrows, raising of the open hand, pointed gestures),

(continued)

N	Form of behaviour	Definition
4.2		– aggressive-conflicted (invective and verbal threats, threatening and swinging hands, reduction of individual distance, genital display, attacking with the head),
4.3		– aggressive-contact actions (a direct attack)
5	Comfort behaviour	Complexes of movements directed at increasing comfort. Includes pandiculation, oscitation, putting clothes in order, changes of posture
6	Eating and drinking behaviour	Eating, drinking, deglutition, chewing, licking of lips, spitting, trophallaxis
7	Grooming	Autogrooming: Arranging or pulling the hair,
7.1		trichotillomania, scratching and rubbing parts of the body, the face, or the head, onychophagy, scraping movements
7.2		Heterogrooming: desire to groom an interlocutor, system of tactile communications, including embraces, snuggling up, touching the interlocutor. Symbolic grooming includes verbal encouragements, donations and mutual exchanges
8	Research behaviour	Examination of the space, contents of pockets, sniffing, switching attention to a new image or a sound, transformation of taxes in relation to a new stimulus
9	Manipulation	Manipulating by hand an object (item), body parts, clothes, meals (a spontaneous manipulation) and the presented standard items (a sphere, a circle, a stick, a fabric) (an experimental manipulation)
10	Attention behaviour	Greeting from a distance. Eye contact with an interlocutor, widening of the eyelids, the game face, fixing of taxes in relation to an interlocutor. Elements of a facial expression of concentration on contact. Gestures directed to an interlocutor. In a broad sense, corresponds to a friendly context in primates
11	Intentional behaviour	The initial movements prior to a finishing movement represent the complexes of preparatory movements that are not similar to either previous or subsequent behaviour. In particular, before rising, the person moves their head and looks round; before asking a question, movement of the lips is marked. The part of such movements is considered as the displaced activity

Note: based on dictionaries and guidelines [12, 28, 101, 109].

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Chapter 7
Quality of Life Deficit Is a Core Presentation of Functional Psychoses

Michael S. Ritsner

Abstract Patients with functional psychoses (FP) exhibit an exceedingly wide range of symptoms, and a broad spectrum of cognitive and functional impairments. In addition, it has become increasingly apparent that functional psychoses are, to variable degrees, accompanied by health-related quality of life (HRQL) impairments. This chapter addresses the question of whether the HRQL impairment or deficit is a syndrome in FP. The literature, as well as new and previously published findings from the Shaar Menashe Longitudinal Study of Quality of Life will be presented. I argue that a HRQL deficit is highly prevalent and fairly marked in FP patients. The HRQL impairment has been observed before individuals exhibit signs and psychotic symptoms of schizophrenia and it is relatively stable throughout the course of the illness. This syndrome appears to be relatively independent of symptomatology and neurocognitive deficits. Finally, the author suggests that impairment in general and domain-specific quality of life in particular are sufficiently reliable, stable, and specific enough syndrome to warrant inclusion in the diagnostic criteria for FP. Limitations in the current knowledge in this area are identified, and suggestions for future research are provided.

Keywords Schizophrenia · Schizoaffective disorder · Major depression · Bipolar disorder · Quality of life · Impairment · Model · Long-term follow up · Symptoms

Abbreviations

BPD	Bipolar disorder
BSI	Brief symptom inventory
CGI-S	Clinical global impression severity scale
DSAS	Distress scale for adverse symptoms
DSM-IV	Diagnostic and statistical manual of mental disorders – 4th edition

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FGAs	First generation antipsychotic agents
FP	Functional psychoses
GAF	Global assessment of functioning scale
HRQL	Health-related quality of life
MD	Mood disorders (MDD and BPD)
MDD	Major depression disorder
PANSS	Positive and negative syndromes scale
Q-LES-Q	Quality of life enjoyment and life satisfaction questionnaire
QLS	Quality of life scale for rating the schizophrenic deficit syndrome
QOL	Quality of life
SA	Schizoaffective disorder
SGAs	Second generation antipsychotics
SZ	Schizophrenia
TBDI	Talbieh brief distress inventory

Health Related Quality of Life

The concept of quality of life (QOL) has both objective (social functioning and environment) and subjective (well being, life satisfaction or happiness) components. Broadly speaking, the subjective approach centers on issues such as life satisfaction, contentment with defined needs, happiness, self-realization and growth [1]. Maslow's theory [2] uses the concept of human needs (physiological, safety, belonging, love, self-esteem and the need for self-actualization) as the basis for development of happiness and true being. Conceptualization, operationalization and measurement of quality of life have been the subject of many publications (reviewed in [3]).

The term health-related quality of life (HRQL) refers to the physical, psychological, and social domains of health. In other words, HRQL includes dimensions of physical and social functioning: mental health and general health perceptions including such important concepts as energy, fatigue, pain, and cognitive functioning [4]. The quality of life concept has many definitions that vary in the degree of emphasis on subjective or objective aspects of quality. Measurement of HRQL is based on a multidimensional approach, which uses patients' statements on satisfaction with major life domains of daily functioning [5–7].

HRQL is multidimensional in the sense that the subjects may simultaneously evaluate several facets of life to arrive at an overall judgment. Two persons with the same mental health status may have different levels of HRQL since personality differences and illness related factors influence one's assessments of health and satisfaction with life. Perceptions of HRQL are based on a cognitive process, which involves identifying the relevant domains that contribute to QOL, determining which domains are relevant to one's self and integrating the specific domain evaluations into an overall QOL assessment [8]. Each domain of health has many components that need to be measured.

HRQL is a heterogeneous concept, as reflected in the different perceptions of this construct by psychiatrists and their patients in observer rated and self-report instruments, respectively. Observer-rated and self report HRQL data provide distinct types of information, and appear to have different indicators for HRQL [7, 9–15]. There are several limitations in the interpretation of self reported measures of HRQL, namely, self-report bias, the lack of universally accepted measures, the lack of reliability and validity data for many of the scales, and difficulty in generalizing findings from the various instruments. Observer-rated instruments are based mostly on negative and deficit symptom items. There is a general consensus regarding the importance of using both self-report and observer-rated measures of HRQL.

HRQL in Functional Psychoses

Most prior studies of factors that affect HRQL of patients with functional psychoses (FP) that included schizophrenia (SZ), schizoaffective (SA) and mood disorders (MD) were cross-sectional. These studies showed that dissatisfaction with life quality of patients is clearly associated with a number of distressing factors, including expression of depressive and negative symptoms [16–21], side effects of antipsychotic agents [22–24], and high levels of emotional distress [16, 24, 25] (for review see [17, 26–29]). Short-term longitudinal design was used to examine HRQL among specific groups of patients, for instance, those discharged from hospitals [30–34], or patients involved in special therapy programs [35, 36], and to identify predictors [34, 37, 38]. Although findings from these studies show that SZ and SA are associated with marked reduction in perceived HRQL compared with healthy subjects [16, 39, 40], changes in satisfaction of these individuals in specific domains of quality of life together with disorder-related dimension scores across time have not been adequately addressed [41]. Indeed, a few studies reported contradictory findings: some researchers did not find statistically significant improvement in subjective HRQL of SZ patients 9 months [34], 7 years [42], and 10 years [43] following baseline assessments, whereas others report positive changes in HRQL domains during 1–3 years of follow up [44, 45]. Findings from these studies have limited applicability because of the short follow–up periods and small sample sizes. They also did not evaluate medication side effects or psychosocial variables throughout the follow up period. In order to address these limitations the Sha'ar Menashe Quality of Life Project was initiated in 1998.

Shaar Menashe Quality of Life Project

Design

This is a large ongoing naturalistic prospective investigation whose aim is to examine HRQL impairment and related factors among patients with FP. A detailed description of the study design, data collection, and measures was reported

elsewhere [16, 17, 46, 47]. In brief, the participants met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia (SZ), schizoaffective (SA), major depression (MDD) or bipolar disorder (BPD); they were age 18–65, inpatients, and able to provide written informed consent for participation in the study. Patients with comorbid mental retardation, organic brain diseases, severe physical disorders, drug/alcohol abuse, and those with low comprehension skills were not enrolled. Overall, the main features of this project are: (i) a systematic ascertainment of inpatients with FP consecutively admitted to closed, open, and rehabilitation hospital settings of a university affiliated hospital (Sha'ar Menashe Mental Health Center); (ii) a wide battery of multidimensional, observer-rated and self-report instruments for evaluating HRQL, psychopathology, treatment, cognitive and general functioning, psychological and social-related variables; (iii) naturalistic follow-up of the same patients for 10 years from the initial assessment. This longitudinal design allows for a more stringent examination of potentially causal interactions between independent factors and their influence on HRQL measures.

Participants

Figure 7.1 presents a flow diagram of the study population. For 1998–2000 years 339 inpatients were assessed in the beginning of the stabilization phase of the illness: 237 persons with SZ, 70 patients with SA disorder, and 32 patients with mood disorders (initial sample). The first follow-up evaluation was at *the second year of follow up* (199 of 339 patients were examined). At the 10-year follow-up (during 2008–2009), 307 patients with SZ/SA disorders from the initial sample were invited for follow up assessment. Among them 99 persons were not evaluable or had died (22 could not be evaluated because of severe mental status, 47 were too physically ill to complete an interview, 30 died), 30 could not be located, and 178 patients were available for the 10-year assessment. Seventy persons did not consent to further participation, thus 108 persons were evaluated (the response rate in this follow-up assessment was 108/178 or 60.7%). Patients did not receive financial incentives for their follow-up assessments. Comparisons between the 108 remaining patients and the total number of dropouts, 70 patients, showed no significant differences regarding initial background characteristics such as sex, age, civil status, level of education, and living situation.

Thus, the database of the project included the following samples of patients with FP and healthy subjects [16, 17, 47].

1. The initial sample includes data for 339 patients with FP.
2. The 2-year follow-up sample represented 199 patients with FP.
3. The 10-year follow-up sample represented 108 patients with SZ/SA.
4. The community based sample includes data for 133 schizophrenia outpatients examined during the stabilization phase of the illness.
5. The control sample included 175 hospital staff members excluding physicians. Inclusion was based on the availability of respondents for the interview.

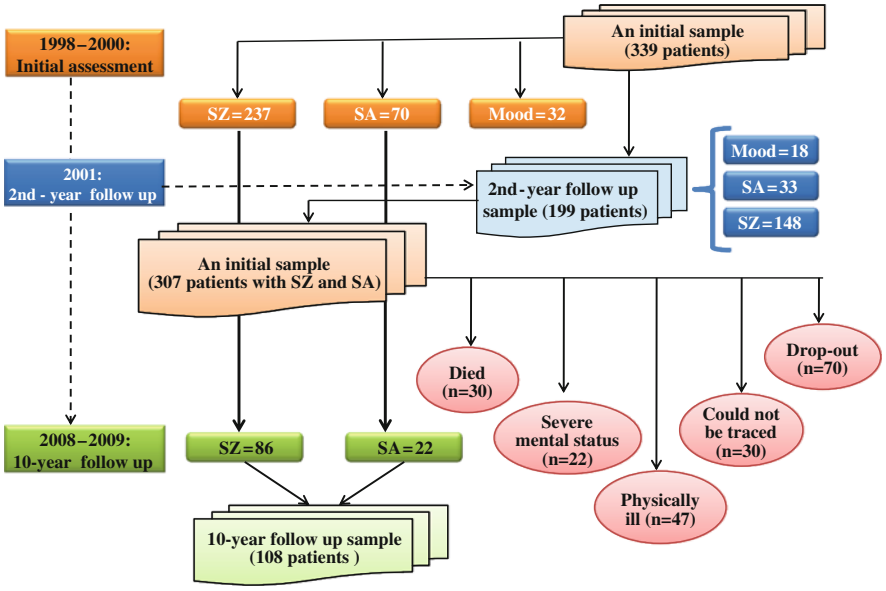

Fig. 7.1 A flow diagram of the study population in the framework of the Sha'ar Menashe Quality of Life Project [47]

Instruments

All respondents participated in the initial interview; diagnoses were according to DSM-IV criteria. The Schedule for Assessment of Mental Disorder (SAMD) [16], a semi-structured interview, was used for collecting data covering background and demographic characteristics, family psychiatric history, personal psychiatric history, details of the present illness and medication, general medical history, and current laboratory tests. Information from a patient's relative, close companion, or file records supplemented the SAMD. The Checklist for Patients not Entered into Database (SAMD-0) was used to register non-enrolled patients.

Today there is no universal instrument that can be recommended for all studies. Specific features and psychometric properties of self-report, observer-rated, and combined (observer and self-report) instruments have been reviewed [7]. Differences between these instruments in terms of the underlying HRQL concepts and data collection procedures are substantial.

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [48], and the Quality of Life Scale for schizophrenia (QLS) [49] present both self-report and observer-rated scores of the main quality of life domains, respectively.

The Q-LES-Q_{93} is a self-report questionnaire comprised of 93-items grouped into ten summary scales as follows: Physical Health, Subjective Feelings, Leisure Time Activities, Social Relationships, and General Activities, Work, Household Duties, Medication Satisfaction, and School/Course Work, and Life Satisfaction and Enjoyment. Responses are scored on a 1- to 5-point scale, with higher scores

indicating better HRQL. We added the general Q-LES-Q_{index}, which was an average of the scores of the 60 items of the seven Q-LES-Q domains (Cronbach's $\alpha = 0.95$). Recently [50] a parsimonious subset of items from Q-LES-Q_{93} was sought and evaluated in 339 patients with FP (Q-LES-Q_{18}). It was found that 18-items predicted basic Q-LES-Q_{93} domains (physical health, subjective feelings, leisure time activities, social relationships) and general index scores with high accuracy. The Q-LES-Q_{18} indicated that the test-retest ratings had high reliability, validity, and stability. Thus, Q-LES-Q_{18}, a brief, self-administered questionnaire, may aid in monitoring the quality of life outcomes of schizophrenia, schizoaffective, and mood disorder patients (Appendix 1).

Quality of life was operationally defined as *severely impaired* when Q-LES-Q scores decreased more than two standard deviations below the healthy subjects (control sample, $n = 175$): <2.72 for physical health, <3.28 for subjective feelings, <2.68 for leisure-time activities, <2.96 for social relationships, <3.28 for general activities, and <3.41 for Q-LES-Q_{index} scores [51].

The observer-rated *Quality of Life Scale* includes 21 items rated by the clinician on a 7-point scale (0–1 severe impairment to 5–6 normal or unimpaired functioning) and includes four domains: interpersonal relations, instrumental role, intrapsychic foundations, common objects, and activities [49]. We tested and validated a condensed QLS_5, based on QLS_{21}, which is briefer and thus easier to administer than the complete rating scale (QLS_5) [52]. The analyses suggest that QLS_5 has been shown to be a valid predictor of the QLS_{21} total scores. Psychometric properties (inter-rater, test-retest reliability, and sensitivity to change) for QLS_5 were also high and comparable to QLS_{21}. In addition, QLS_5 does not reflect the presence of psychiatric symptoms as does the QLS_{21}. The most reliable items in QLS_5 are social initiatives, adequacy, acquaintances, time utilization, and motivation. Thus, the five-item condensed Quality of Life Scale for schizophrenia maintains the validity of the full QLS, and has the advantage of shorter administration time. Utilization of the revised QLS_5 in routine care and clinical trials may potentially facilitate evaluation of treatment outcomes in SZ.

The overall level of functioning was assessed with the *Global Assessment of Functioning Scale* (GAF) [53]. Severity of psychopathology was assessed using 30 items of the *Positive and Negative Syndromes Scale* (PANSS), which were analyzed by 5-factor models [54–58].

Neurocognitive functions were assessed using tests from the computerized *Cambridge Automated Neuropsychological Test Battery* (CANTAB; for a description of the nature of these tests, the performance measures used and how the test scores are derived, see (http://www.cantab.com/camcog/default.asp).

For assessment of insight for illness, the *Insight and Treatment Attitudes Questionnaire* [59] was employed. Responses are scored on a 3-point scale (0 – no, 1 –questionable, and 2 – good insight). Participants also completed the *Insight Self-report Scale* [60] with Cronbach's $\alpha = 0.86$.

The presence and severity of adverse effects of medication as well as psychological responses to them were measured with the *Distress Scale for Adverse Symptoms* (DSAS; Appendix 2) [16, 61]. The DSAS is a 22-item checklist covering mental,

neurological, somatic, and autonomic dysfunctions caused by current medication. Adverse symptoms are rated in a face-to-face interview on a 5-point intensity scale (0-none or questionable symptom to 4-extreme expressions of the symptom). The patient is then asked "How much discomfort has each of these symptoms caused you during the previous week?" Responses are scored in the same way, with higher mean scores indicating greater intensity of associated distress. Three DSAS indices related to adverse events were computed: Number of Adverse Symptoms (NAS), Mental Distress Index (MDI, Cronbach's $\alpha = 0.89$), Somatic Distress Index (SDI, Cronbach's $\alpha = 0.81$), and the DSAS index that covers both observer-rated and self-report items of the DSAS. Higher index scores indicate a greater number of adverse events (NAS) and that higher distress levels are attributed to a given side effect (MDI, SDI).

Assessment of emotional distress was done using the *Talbieh Brief Distress Inventory* (TBDI). Construction, properties of the TBDI, its internal consistency, and validity are reported in detail elsewhere [62, 63]. The TBDI is a 24-item questionnaire covering the six psychological symptoms: obsessiveness, hostility, anxiety, and paranoid ideation (each with 3 items), sensitivity (4 items), and depression (7 items). Responses are scored on a 0 to 4-point scale, with higher scores indicating greater intensity of distress, and particular symptom severity (Appendix 3). A general TBDI index, the average of 24 items, is computed (range = 0–4). To analyze specific psychological symptoms, differential criteria thresholds for each of the TBDI subscales were established and validated elsewhere [64]. The threshold magnitudes of the mean scores for the following symptom subscales were obsessiveness and hostility (both >1.3), sensitivity (>0.8), anxiety (>1.5), paranoid ideation (>0.9), and depression (>1.4). Thus, subjects who scored above these thresholds were considered to have the symptom, and those scoring lower than the threshold were asymptomatic. For each respondent, we calculated the TBDI mean number of symptoms independent of modality. The rationale for the symptom count is the observation that the number of symptoms increases with the intensity of psychological distress.

The *Somatization Scale* is derived from the *Brief Symptom Inventory* (BSI) [65]. The BSI-somatization scale reflects distress arising from perceptions of bodily dysfunction. Task-, emotion-, and avoidance-oriented coping styles were evaluated with the *Coping Inventory for Stressful Situations* [66]. The *Rosenberg Self-Esteem scale* is a well-known 10-item self-report questionnaire for measuring self-esteem and self-regard [67]. The *General Self-Efficacy Scale* is a 10-item scale for evaluating a sense of personal competence in stressful situations [68]. The *Multidimensional Scale of Perceived Social Support* (MSPSS) [69] was used as a measure of social support. The *Level of Expressed Emotion* scale (LEE) was developed to provide an index of the perceived emotional climate in a person's influential relationships [70, 71]. Personality traits were measured with the *Tridimensional Personality Questionnaire* [72], a 100-question self-report instrument that discriminates between different major temperament traits using three dimensions: novelty seeking, harm avoidance, and reward dependence.

SZ/SA Patients Versus Healthy Subjects

Evidence is accumulating that FP are associated with substantial impairments in HRQL. Individuals with SZ, SA, MDD and BPD have substantially poorer quality of life than community comparison cohorts (reviewed in [3, 17, 73, 74]). 339 patients with FP patients from the database of the Shaar Menashe HRQL study were significantly less satisfied with general and domain-specific HRQL compared with 175 healthy subjects (MANOVA, $F = 13.4$, $df = 6,501$, $p < 0.001$). SZ/SA patients are significantly impaired across general and all domain-specific life qualities compared with healthy subjects (MANOVA, $F = 17.2$, $df = 14,1056$, $p < 0.001$; Fig. 7.2) [17]. SA patients were significantly impaired in general and on all domain-related HRQL compared with healthy subjects (MANOVA, $F = 14.1$, $df = 6,236$, $p < 0.001$). Patients with depressive and mixed types of SA disorders had lower levels of HRQL compared with controls, whereas those with manic type reported high satisfaction with HRQL, which in part may be symptomatic of the illness. Indeed, the correlation coefficient of the Manic Rating Scale scores with leisure time activities was $r = 0.51$ ($p = 0.011$), and with social relationships, $r = 0.42$ ($p = 0.042$), while with other HRQL domains r ranged from 0.16 to 0.31 ($p > 0.05$).

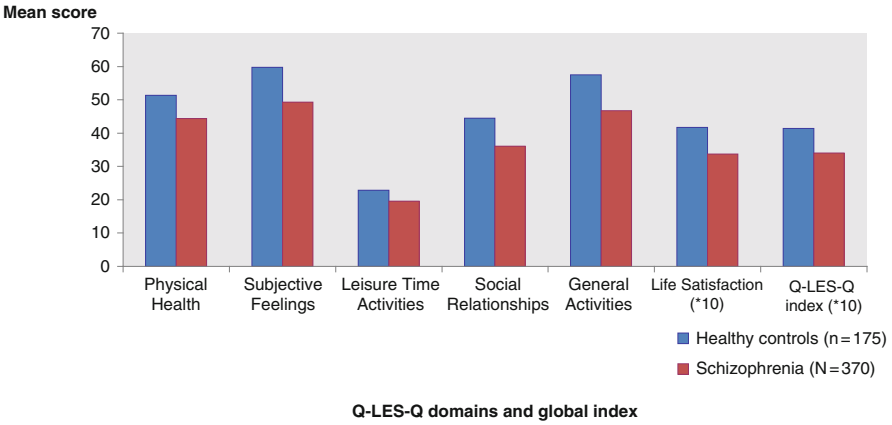

Fig. 7.2 Quality of life scores among schizophrenia patients and healthy subjects [17]

Comparison Between Functional Psychoses

For current analysis data for 339 inpatients and 175 healthy subjects were used (initial sample). A total of 70 patients were diagnosed with SA (28 patients with depressive type, 24 patients with manic type, and 18 patients with mixed episode), 237 patients with SZ and the remaining 32 patients with mood disorders (MD). Comparative literature about HRQL in FP is scant. Some cross-sectional studies failed to find considerable differences in general HRQL between SZ and SA/MD

disordered patients [16, 17, 46, 75, 76]. Depressed patients reported greater dissatisfaction with HRQL than SZ patients [77]. Rudolf and Priebe [78] demonstrated that depressive women expressed dissatisfaction with 4 out of 8 life domains and with life in general, and had lower HRQL than women with SZ. Differences remain statistically significant when controlling for the influence of age and anxiety/depression, and therefore, changes in depressive symptoms do not fully explain HRQL changes. When anxiety (n = 139), depression (n = 349) and SZ (n = 403) were concurrently investigated, SZ patients recorded better life satisfaction than patients with major depression and anxiety disorder [79].

Inasmuch as different subtypes of FP may be accompanied by various clinical and psychosocial factors, it is of interest to establish whether they could also be distinguished on the basis of HRQL measures. We found that *SA* patients were significantly more satisfied than SZ patients in the domains of subjective feelings ($F = 3.1$, $p < 0.05$), and social relationships ($F = 5.8$, $p < 0.05$). At the same time, SA and MD patients had quite similar ratings on all life quality domains (Table 7.1). Differences between SA and SZ disorder patients regarding social relationships remained significant when controlling for the confounding effect of various PANSS factors, emotional distress, side effects, suicide risk, coping styles, self-variables and illness duration [51].

Course of HRQL Deficits

A 2-Year Follow Up Study

For longitudinal analysis the median cut-off point scores obtained from 175 healthy subjects were used to split the HRQL domain and index scores into two levels: dissatisfaction and satisfaction with HRQL (4.08 = physical health, 4.36 = subjective feelings, 4.0 = leisure time activities, 4.09 = social relationships, 4.21 = general activities, and 4.18 = perceived Q-LES-Q index). Over 16 months 62.8% (125 of 199) patients with FP remained dissatisfied, and 10% patients (20 of 199) remained satisfied with general HRQL. Improvement in HRQL was observed among 16.1% patients (32/199), while worsening in life quality was reported by 11.1% patients (22/199). Thus, about 74% of the patients with FP were dissatisfied with their HRQL. Differences between SZ, SA, and mood disorder patients in the course of HRQL throughout 16-month period did not reach significant levels (Fig. 7.3)

A 10-Year Follow Up Study

The 10-year follow up sample included 82 (75.9%) men, mean age 48.1 years (SD = 9.3), 63 people (58.3%) were single, 23 (21.3%) were married, and the rest 22 (20.4%) were divorced, separated or widowed. Mean extent of education was 10.6 years (SD = 2.6); 11 (10.2%) lived alone independently, 21 (19.5%) with their own

Table 7.1 General and domain-related quality of life scores across patients with functional psychoses (initial sample) [51]

	Schizophrenia (N = 237)		Schizoaffective disorders (N = 70)		Mood disorders (N = 32)		ANCOVA (df = 2,339)[a]		Sex (df = 1,339)	
Q-LES-Q	Mean	SD	Mean	SD	Mean	SD	F	p	F	P
Physical Health	3.4	0.9	3.4	0.8	3.3	0.9	0.4	0.66	2.5	0.12
Subjective feelings	3.5	0.9	3.7	0.9	3.3	1.0	3.1	0.044	8.4	0.004
Leisure time activities	3.3	1.1	3.5	1.1	3.4	1.1	1.5	0.23	2.9	0.091
Social relationships	3.3	0.9	3.8	0.8	3.5	1.1	5.8	0.003[b]	4.1	0.043
General activities	3.4	0.9	3.5	0.8	3.3	1.0	1.1	0.32	3.6	0.057
Satisfaction with medication	3.5	1.2	3.8	1.1	3.7	1.0	1.7	0.18	2.1	0.14
General Q-LES-Q index	3.4	0.8	3.6	0.8	3.3	0.9	2.4	0.090	6.1	0.014

[a]Two-way ANCOVA controlling for gender and age.
[b]Schizoaffective disorders better than schizophrenia.

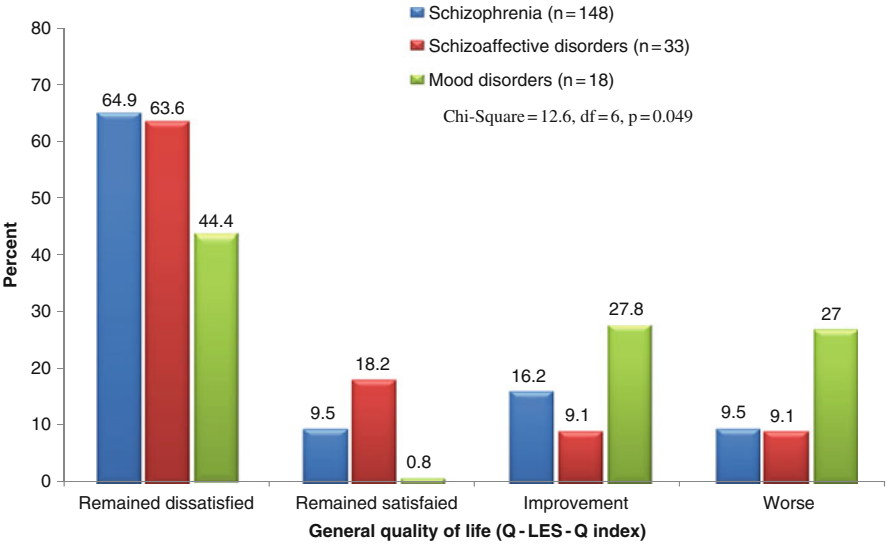

Fig. 7.3 Change in satisfaction of patients with general quality of life over 16 months [51]

families, 15 (13.9%) with parents, 21 (19.5%) in a group home, and 40 (37.0%) in a hostel. 71 patients (65.7%) were unemployed, 26 (24.1%) in sheltered employment, 9 (8.3%) paid or self-employed, and 2 (1.8%) were retired. Mean age of application for psychiatric care was 22.9 years (SD = 7.6), and mean duration of disorder was 25.1 years (SD = 9.2). None of the participants had exacerbation of their physical disorders at the follow up assessment (16 persons had endocrine disorders, 13 – cardiovascular, 15 – pulmonary, 8 – gastrointestinal, 4 – urinary disorders, and 49 patients were physically healthy). During the follow up period all patients were treated with a variety of antipsychotic medications (FGAs, SGAs, and combination) and additional medications (benzodiazepines, antidepressants, and mood stabilizers) as clinically indicated. In particular, 57 patients were treated with first generation antipsychotic agents (FGAs), 25 – with second generation antipsychotics (SGAs), and 26 – with a combination of FGAs and SGAs, and additional medications; 46 patients received benzodiazepines, 28 – antidepressants, 45 – mood stabilizers, and 74 – anti-Parkinson agents.

Table 7.2 presents socio-demographic and background characteristics of initial and follow up samples. The patients were followed up for a mean of 10.3 (SD = 0.6) years after initial assessment. At the last follow up, 42 patients were reassessed in the outpatient clinic, 25 – in the hostel, and 41 at discharge from an additional admission. Among 108 patients in the 10-year follow up sample 62 (57.4%) presented with paranoid type, 20 were with residual type, 1 with disorganized type, 3 with undifferentiated type of SZ, and 22 with SA disorders. Notably, no significant differences were found with respect to patients' sex, civil status and education, age at onset, diagnosis, and duration of illness. Thus, our follow-up sample of 108 patients proved to be quite representative of the full sample.

Table 7.2 Background characteristics of the initial sample and 10-year follow-up sample (at initial and 10-year follow-up assessments) [47]

			A 10-year follow up data			
	An initial sample (n = 307)[a]		Initial assessment (n = 108)		10-year assessment (n = 108)	
Characteristics	**N**	%	**N**	%	**N**	%
Sex						
Male	224	73.0	82	75.9	82	75.9
Female	83	27.0	26	24.1	26	24.1
Civil status						
Never married	175	57.0	64	59.2	63	58.3
Married	70	22.8	26	24.1	23	21.3
Divorced, separated, widowed	62	20.2	18	16.7	22	20.4
Diagnosis (DSM-IV)						
Schizophrenia, disorganized type (295.1)	12	3.9	5	4.6	1	0.9
Schizophrenia, paranoid type (295.3)	174	56.7	64	59.3	62	57.4
Schizophreniform disorder (295.4)	2	0.6	1	0.9	0	0
Schizophrenia, residual type (295.6)	38	12.4	14	13.0	20	18.5
Schizophrenia, undifferentiated type (295.9)	11	3.6	3	2.8	3	2.8
Schizoaffective disorder (295.7)	70	22.8	21	19.4	22	20.4
	Mean	SD	Mean	SD	Mean	SD
Education (yr.)	10.5	2.8	10.4	2.7	10.6	2.6
Age (yr.)	38.3	10.1	38.5	9.4	48.1	9.3
Age of onset (yr.)	23.9	7.9	22.9	7.6	22.9	7.6
Duration of illness (yr.)	14.2	9.7	14.5	8.8	25.1	9.2
CGI-S score	4.4	0.9	4.3	0.9	4.1	1.0
PANSS, total score	82.8	20.2	81.8	20.0	77.9	17.2

[a]All patients with mood disorders (n = 32) were excluded in this study.

The research question addresses the association between variability in quality of life domain scores and variability in disorder-related dimension scores throughout the 10-year follow up period. To answer this question Pearson correlation coefficients between Q-LES-Q and disorder-related dimensions were computed using: (a) raw scores obtained at the 10-year follow up assessment (“cross”) (b) changes in scores across the 10-year period (“changes”), and (c) changes in scores across the

10-year period with partial variables (TBDI, PANSS), that were "partialled out" of the correlation matrix. From the correlation matrix shown in Table 7.3, we can see that at follow up assessment Q-LES-Q domains are negatively associated with the Clinical Global Impression Scale (CGI-S; *r* ranged from –0.21 to –0.24), PANSS total scores (*r* ranged from –0.19 to –0.35), general psychopathology (*r* ranged from –0.27 to –0.44) and negative symptoms (*r* ranged from –0.21 to –0.33), side effects (*r* ranged from –0.24 to –0.51), emotional distress index (*r* ranged from –0.22 to –0.66), and somatization (*r* ranged from –0.22 to –0.51). By contrast, there is a positive relationship to Global Assessment of Functioning Scale (GAF) scores (*r* ranged from 0.17 to 0.33), while positive symptoms are not significantly associated with quality of life domains.

In the patient group, changes in most Q-LES-Q dimensions are negatively associated with changes in the CGI-S (*r* ranged from –0.20 to – 0.31), PANSS total scores (*r* ranged from –0.21 to –0.24), positive symptoms ($r = -0.26$; physical health) side effects (*r* ranged from –0.23 to –0.33), severity of emotional distress (*r* ranged from –0.32 to –0.63), somatization (*r* ranged from –0.30 to –0.43). Improvement in general functioning (GAF) correlates positively with changes in quality of life domains (*r* ranged from 0.20 to 0.25) excluding physical health and medicine satisfaction. By contrast, changes in negative symptom and general psychopathology scores are not significantly associated with changes in Q-LES-Q measures over time. Age at examination, age of onset, and illness duration are not significantly associated with changes in Q-LES-Q domains and index.

Since the correlation between changes in TBDI and PANSS total scores was $r = 0.21$ ($p = 0.032$), we tested the concurrent effects of these variables on correlation coefficients by partial correlation analysis. The findings indicate that when the influence of changes in TBDI scores was "partialled out" of the correlation matrix, the correlation of Q-LES-Q dimensions with CGI-S scores decreased from significant levels in 7 domains to a significant level in one domain; with DSAS and BSI-S scores – from 7 domains to 3 domains. After adjusting for TBDI scores the correlation of Q-LES-Q domains with GAF and PANSS total ratings did not reach a significant level. Contrarily, after adjusting for PANSS total ratings the correlation of Q-LES-Q domains with other disorder-related variables remained significant, excepting GAF scores.

It would be reasonable to assume that symptoms are cardinal factors, and thus, effective predictors of HRQL. Nevertheless, both sets of correlations show significant negative associations of Q-LES-Q domains with emotional distress, side effects, somatization, illness severity, PANSS total scores, and positive association with general functioning. These findings are consistent with previous studies linking HRQL outcomes with a number of distressing factors, including expression of emotional distress [16], and side effects of antipsychotic agents [22, 24, 80]. As shown in previous studies, there is no consensus regarding associations of HRQL with positive [81, 82], and general psychopathology ratings [83, 84].

In the present study changes in PANSS negative and general psychopathology scores are not significantly correlated with changes in Q-LES-Q measures over a 10-year period, a finding supported by previous reports [34, 85]. Furthermore,

Table 7.3 Pearson correlation coefficients s between Q-LES-Q domain and disorders related dimension scores (n = 108)

Measures	Data[a]	Physical health	Subjective feelings	Leisure time activities	Social relationships	General activities	Life satisfaction	Medicine satisfaction	Q-LES-Q index
Illness severity (CGI-S)	Cross	–0.15	–0.13	–0.21*	–0.17	–0.14	–0.16	–0.21*	–0.24*
	Changes	–0.21*	–0.17	–0.21*	–0.21*	–0.21*	–0.31***	–0.20*	–0.27**
	TBDI	–0.12	–0.02	–0.10	–0.06	–0.05	–0.23*	–0.18	–0.11
PANSS, total	Cross	–0.24**	–0.22*	–0.19*	–0.22*	–0.21*	–0.23*	–0.35***	–0.31***
	Changes	–0.21*	–0.14	–0.10	–0.22*	–0.18	–0.22*	–0.18	–0.24*
	TBDI	–0.15	–0.02	–0.01	–0.12	–0.07	–0.14	–0.19	–0.02
Negative subscale	Cross	–0.06	–0.17	–0.24*	–0.21*	–0.11	–0.04	–0.33***	–0.21*
	Changes	–0.15	–0.07	0.06	–0.12	–0.18	–0.17	–0.09	–0.12
	TBDI	–0.10	–0.004	0.15	–0.06	–0.12	–0.12	–0.07	–0.04
Positive subscale	Cross	–0.11	–0.05	–0.13	–0.14	–0.08	–0.16	–0.15	–0.16
	Changes	–0.26**	0.14	–0.02	0.03	–0.13	–0.00	0.03	0.07
	TBDI	0.31***	0.14	0.04	0.11	–0.09	0.04	0.04	0.18
General Psychopathology	Cross	–0.34***	–0.29**	–0.09	–0.16	–0.27**	–0.28**	–0.32***	–0.32***
	Changes	0.07	0.02	–0.03	–0.03	–0.10	–0.07	–0.04	–0.02
	TBDI	0.13	0.08	0.01	0.02	–0.05	–0.04	–0.05	0.06

Table 7.3 (continued)

Measures	Data[a]	Physical health	Subjective feelings	Leisure time activities	Social relationships	General activities	Life satisfaction	Medicine satisfaction	Q-LES-Q index
Side effects (DSAS)	Cross	–0.51***	–0.39***	–0.24*	–0.17	–0.35***	–0.36***	–0.18	–0.41***
	Changes	–0.29**	–0.23*	–0.33***	–0.24*	–0.27**	–0.27**	–0.16	–0.33***
	TBDI	–0.23*	–0.12	–0.26**	–0.11	–0.16	–0.19	–0.14	–0.28*
Emotional distress	Cross	–0.65***	–0.55***	–0.40***	–0.41***	–0.64***	–0.60***	–0.30**	–0.66***
	Changes	–0.32***	–0.49***	–0.43***	–0.57***	–0.56***	–0.39***	–0.08	–0.63***
	PANSS	–0.28**	–0.48***	–0.42***	–0.54***	–0.54***	–0.36***	–0.03	–0.60***
Somatization	Cross	–0.51***	–0.33***	–0.18	–0.22*	–0.46***	–0.50***	–0.16	–0.40***
	Changes	–0.34***	–0.31**	–0.37***	–0.37***	–0.30**	–0.36***	–0.09	–0.43***
	TBDI	–0.22*	–0.08	–0.20*	–0.13	–0.04	–0.20*	–0.06	–0.18
General functioning	Cross	0.20*	0.19	0.29**	0.26**	0.25**	0.21*	0.27**	0.33***
	Changes	0.11	0.23*	0.21*	0.23*	0.20*	0.18	0.24*	0.25*
	TBDI	0.04	0.13	0.14	0.16	0.12	0.12	0.24*	0.16
	PANSS	0.02	0.17	0.18	0.17	0.15	0.11	0.19	0.17

[a]Three types of correlation coefficients were computed: (a) raw scores obtained at 10-year follow up assessment ("cross") (b) changes in scores over 10-year period ("changes"), and (c) changes in scores over 10-year period with partial variables (TBDI, PANSS), that were "partialled out" of the correlation matrix.
*$p < 0.5$; **$p < 0.01$; ***$p < 0.001$.

a partial correlation analysis showed that (1) the negative relationship between changes in TBDI and Q-LES-Q dimensions over time remains significant when the effect of severity of symptoms (PANSS) was removed from the correlation matrix, but not vice verse; and (2) the positive relationship between changes in both GAF and Q-LES-Q dimension scores over time does not remain significant when the effect of severity of emotional distress (TBDI) or symptoms (PANSS) was removed from the correlation matrix that may have a moderating/mediating effect on the influence of general functioning on changes in satisfaction with quality of life over time. These findings may suggest that factors other than changes in psychopathological symptoms could influence satisfaction with HRQL during the course of the illness.

HRQL Models

Despite the increasing importance of quality of life in the mental health field, the theoretical conceptualization of the construct remains poorly developed. The rationale for a HRQL assessment in psychiatric research should be outlined in an analytic model that tests the relationship between predictors and response variables.

A Conceptual Integrative Model

According to the Conceptual Integrative Model, HRQL is the outcome of interaction between three major determinants (symptoms, side effects, and psychosocial performance) and several modulators such as personality characteristics, premorbid adjustment, values and attitudes toward health and illness, resources and their availability [86]. Testing the validity of this model indicated that the severity of symptoms was the main predictor of HRQL, explaining 32% of its variance, while neuroleptic side effects explained 17%. The contribution of psychosocial indicators and modulators, however, was not significant.

Mediational Model

This model links subjective HRQL with self-related constructs. Zissi and associates [87] tested this model and concluded that the extended mediational model of HRQL for individuals with long-term mental health problems appears to have important implications for the planning and delivery of mental health programs. However, this model needs further development, testing and validation.

Distress/Protection Vulnerability Model

This model postulates that subjective HRQL is an outcome of the interaction of an array of distress factors, on the one hand, and protective factors, on the

other [16, 17]. It suggests that satisfaction with HRQL decreases when distress factors outweigh protective factors, and vice versa. The data included measures of satisfaction with general and domain-specific HRQL such as physical health, subjective feelings, leisure activities, social relationships, general activities, medication, as well as severity of psychopathology, adverse events, psychological distress, expressed emotions, personality traits, self-constructs, coping styles, and perceived social support. In order to validate the Distress/Protection Vulnerability model, two types of multivariate analyses were conducted using cross-sectional and longitudinal data. Since 2000, the Distress/Protection Vulnerability model has been extensively used by our team to compare HRQL impairment among patients with severe mental disorders [16, 17, 46], to examine the role of side effects [24], to predict quality of life impairment in chronic schizophrenia from cognitive variables [88], to test mediating effects of coping styles [89], to search for longitudinal predictors of general and domain-specific quality of life [90–92], to explore the association of HRQL impairment with suicidal behavior [93], temperament factors [94, 95], and sleep quality [96], and to examine the impact of antipsychotic agents [97, 98].

In addition, findings of other research groups also highlighted the importance of addressing psychosocial issues and their interrelationships in the structures of HRQL that have supported this model [99–103].

Thus, the Distress/Protection Vulnerability model integrated previously defined HRQL models [87, 104, 105] and postulated that (1) dissatisfaction with HRQL is a particular syndrome observed in the FP; (2) this syndrome is an outcome of the interaction of an array of distressing factors, on the one hand, and putative stress process protective factors, on the other hand; and (3) dissatisfaction with quality of life increases if distressing factors overweigh protective factors, and vice versa (Fig. 7.4).

HRQL Impairment Syndrome

A number of empirical findings of HRQL impairments in FP that were obtained from earlier stages of this project [17, 26, 27, 29, 51, 106, 107] prompted the following suggestions.

- Subjects who met criteria for vulnerability to FP showed lower total ratings on the QLS [49] with significantly higher psychological distress scores [108, 109].
- Despite the absence of psychotic symptoms, individuals with prodromal symptoms (ultra-high-risk) for SZ experience significant HRQL impairments in a manner parallel to that observed in patients with established psychotic illness [110, 111].
- There is an association between poor premorbid adjustment and poor HRQL levels in SZ [112–114].
- Poor HRQL is associated with long duration of untreated first-episode SZ [112, 115].

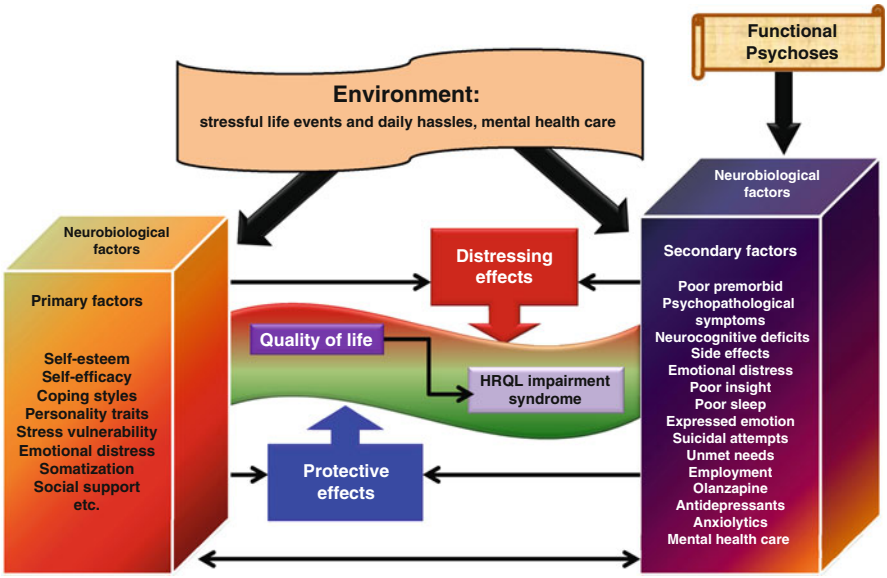

Fig. 7.4 The Distress/Protection Vulnerability model of HRQL impairment in functional psychoses (HRQL – health-related quality of life)

- There are significant differences in HRQL levels between patients with SZ, SA, MDD and BPD [17, 116].
- Taken together, HRQL findings underscore the relatively stable character of HRQL disturbances with mild fluctuations in the general and domain-specific quality of life scores throughout the course of FP [17, 34, 42–44, 117].
- HRQL of patients with FP is associated with "stress related factors" such as some personality traits, low self-esteem, and self-efficacy, emotion-oriented coping style, and emotional or somatic distress rather than with psychopathological symptoms, and side effects [16, 17, 24, 51].
- Psychopathological symptoms explained a relatively small proportion of the variance in HRQL scores among people with depression or anxiety disorders [116].
- Some temperament traits, which are not necessarily part of the deterioration process of the illness, are significantly associated with HRQL in schizophrenia [95].
- Logistic regression analysis with stress process-related variables, symptom severity, demographic and background data of SZ patients at initial examination (1st model) and at 2-year follow-up examination (2nd model) was applied to search for predictors of severe HRQL impairment. Table 7.4 presents a summary of the regression analysis for two groups of patients: those with severe impairment versus those with mild or no impairment. The 1st model indicates 6 significant predictors: three negative (emotional distress, somatization, and age), and three positive (self-esteem, self-efficacy, and social support). The 2nd revealed only three significant predictors of severe HRQL impairment syndrome (emotional

Table 7.4 Summary of logistic regression analysis for discrimination between severe and mild quality of life impairment in schizophrenia patients (follow-up sample, n = 148) [17]

Regression model	β[a]	χ^2	p	Last R^{2b}
Initial examination (1st model)				
Intercept	–3.89	8.3	0.004	0.0351
Emotional distress	–0.75	5.8	0.016	0.0247
Somatization	–0.81	6.2	0.012	0.0263
Self-esteem	0.13	6.1	0.013	0.0258
Self-efficacy	0.12	16.1	0.001	0.0658
Social support	0.02	4.4	0.035	0.0189
Age at examination	–0.04	4.9	0.027	0.0208
Severe HRQL impairment = 117 patients, mild – 120 patients. Model's properties: $R^2 = 0.36$, df = 6, $\chi^2 = 130.9$, $p < 0.001$; correctly classified = 79.2%				
Follow-up examination (2nd model)				
Intercept	–3.97	4.6	0.032	0.0310
Emotional distress	–1.22	9.4	0.002	0.0613
Self-esteem	0.16	3.9	0.049	0.0262
Self-efficacy	0.11	7.2	0.007	0.0478
Severe HRQL impairment = 58 patients, mild – 90 patients. Model's properties: $R^2 = 0.37$, df = 3, $\chi^2 = 85.7$, $p < 0.001$; correctly classified = 81.8%.				

[a]β is the estimated value of regression coefficient that was calculated using the Newton-Raphson method to solve the nonlinear, maximum likelihood equations.
[b]Last R^2 reflects the amount that this variable adds to the overall R^2 when it is added to the logistic regression equation.

distress, self-esteem, and self-efficacy). Both models correctly classified about 80% of the patients as being severely impaired versus those with mild or no impairment. Symptom severity did not reach a significant level in these prediction models [17].

Thus, according to our hypothesis, the HRQL deficit in FP refers to the vulnerability to illness, and, consequently, should be viewed as a definitive expression or *a particular syndrome*, such as psychopathology or cognitive impairment. The stress-vulnerability model postulates the vulnerability to illness as stable, enduring, and largely attributable to genetic and environmental factors [118–120]. Greater vulnerability is associated with higher risk for developing FP, but the actual expression of this predisposition depends on a host of personal and environmental factors, some of which are noxious, while others are protective. It is the interaction of vulnerability, stressors and protective factors that influences both the onset and the course of the disorder.

Conclusions and Future Directions

There is growing interest in HRQL impairment among persons with FP that provides new insights and challenges for understanding and treating severe mental disorders. In recent years there has been an exponential rise in the study of HRQL of FP

leading to a torrent of information, sometimes conflicting, regarding various HRQL associations with the exceedingly heterogeneous FP symptoms. This chapter is focused on findings from the Shaar Menashe Longitudinal Study of Quality of Life, the Distress/Protection Vulnerability model and HRQL presentation in FP. The Distress/Protection Vulnerability model [106] suggests that (Fig. 7.4):

- HRQL impairment is a particular syndrome observed in severe mental disorders. This syndrome occurs before the first psychotic episode and persists throughout the course of FP. It involves every aspect of quality of life and has an important impact on long-term social and occupational outcomes.
- This syndrome is an outcome of the interaction of an array of distressing factors, on the one hand, and putative stress process protective factors, on the other hand.
- HRQL impairment increases if distressing factors overweigh protective factors, and vice versa.
- There are primary and secondary factors. Primary or vulnerability related factors are those usually considered inborn or personal characteristics, while secondary factors are related to the illness and the environment [91]. Such primary factors as harm avoidance, high levels of neuroticism, poor coping skills, elevated emotional distress, emotion-oriented coping, and weak self-constructs [121–123] might lower the vulnerability threshold, and, consequently, result in severe HRQL impairment. Secondary factors influence HRQL impairment via primary factors. Identified factors can potentially be ameliorated thereby enhancing the well being of FP disordered patients.

Integration of the quality of life and neurobiological investigations may provide new vistas for the HRQL impairment syndrome in mental disorders and may lead to improved understanding of FP and more effective treatment decisions. Nonetheless, many issues warrant further investigation. The primary question is how to integrate the quality of life and neurobiological investigations in FP? What are the diagnostic implications? Finally, do we offer pharmacological treatment targets for HRQL impairment? Perhaps it would aid us in the selection of a specific treatment modality (pharmacological, psycho-social, cognitive remediation etc.) in accordance with the specific HRQL domains? We leave these various reflections unanswered for now as we await future study and deliberation.

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Appendix 1: Quality of Life Enjoyment and Satisfaction Questionnaire – Abbreviated Version (Q-LES-Q-18)

This questionnaire is designed to help assess the degree of enjoyment and satisfaction experienced during the past week [50].

		Not at all or Never	Rarely	Sometimes	Often or most of the time	Frequently or all the time
	During the past week how much of the time have you. . .					
(1)	Felt at least in very good physical health	1	2	3	4	5
(2)	Been free of worry about your physical health	1	2	3	4	5
(3)	Felt good physically	1	2	3	4	5
(4)	Felt full of pep and vitality	1	2	3	4	5
(5)	Felt satisfied with your life	1	2	3	4	5
(6)	Felt happy or cheerful	1	2	3	4	5
(7)	Felt able to communicate with others	1	2	3	4	5
(8)	Felt able to travel about to get things done when needed (walk, use car, bus, train, or whatever is available as needed)?	1	2	3	4	5
(9)	Felt able to take care of yourself?	1	2	3	4	5
	The following questions refer to leisure time-activities such as watching T.V., reading the paper or magazines, tending house plants or gardening, hobbies, going to museums or the movies, or to sports events, etc.?					
(10)	How often did you enjoy the leisure activities?	1	2	3	4	5
(11)	How often did you concentrate on the leisure activities and pay attention to them?	1	2	3	4	5
(12)	If a problem arose in your leisure activities, how often did you solve it or deal with it without undue stress?	1	2	3	4	5
	During the past week how often have you. . .					
(13)	Looked forward to getting together with friends or relatives?	1	2	3	4	5
(14)	Enjoyed talking with co-workers or neighbors?	1	2	3	4	5
(15)	Felt affection toward one or more people?	1	2	3	4	5
(16)	Joked or laughed with other people?	1	2	3	4	5

(continued)

		Not at all or Never	Rarely	Sometimes	Often or most of the time	Frequently or all the time
(17)	Felt you met the needs of friends or relatives?	1	2	3	4	5
	Taking everything into consideration, during the past week how satisfied have you been with your. . .					
(18)	Medication? (If not taking any, check here ____and leave item blank)	1	2	3	4	5

Appendix 2: Distress Scale for Adverse Symptoms (DSAS)

The scale consists of 22 drug induced adverse symptoms, each to be rated on 5-point scale of intensity. For each symptom, please mark the rating that best describes the patient's current status, and ask how much discomfort (subjective distress) that symptom has caused the patient during the past week including today. Use following scale: 0 – absent or questionable; 1 – mild; 2 – moderate; 3 – marked; 4 – severe [16, 24, 61].

	Symptom	Symptom intensity	Subjective distress
1	Headache	0 1 2 3 4	0 1 2 3 4
2	Fatigue	0 1 2 3 4	0 1 2 3 4
3	Nervousness	0 1 2 3 4	0 1 2 3 4
4	Dizziness	0 1 2 3 4	0 1 2 3 4
5	Sleep disturbances	0 1 2 3 4	0 1 2 3 4
6	Somnolence	0 1 2 3 4	0 1 2 3 4
7	Tremor	0 1 2 3 4	0 1 2 3 4
8	Akathisia	0 1 2 3 4	0 1 2 3 4
9	Ataxia	0 1 2 3 4	0 1 2 3 4
10	Dyskinetic movements	0 1 2 3 4	0 1 2 3 4
11	Hypokinesia/Bradykinesia	0 1 2 3 4	0 1 2 3 4
12	Hypersalivation/ Dry mouth	0 1 2 3 4	0 1 2 3 4
13	Nausea/ Vomiting	0 1 2 3 4	0 1 2 3 4
14	Appetite disturbances	0 1 2 3 4	0 1 2 3 4
15	Gastric discomfort	0 1 2 3 4	0 1 2 3 4
16	Constipation/Diarrhea	0 1 2 3 4	0 1 2 3 4
17	Weight loss/ Weight gain	0 1 2 3 4	0 1 2 3 4
18	Tachycardia	0 1 2 3 4	0 1 2 3 4
19	Hypotension/ Hypertension	0 1 2 3 4	0 1 2 3 4

(continued)

	Symptom	Symptom intensity	Subjective distress
20	Polyuria/Disuria	0 1 2 3 4	0 1 2 3 4
21	Skin sensitivity/ Dry skin	0 1 2 3 4	0 1 2 3 4
22	Sexual dysfunction	0 1 2 3 4	0 1 2 3 4

Scoring:
Three DSAS indices related to adverse events were computed:
Severity of Adverse Symptoms = AVERAGE (1:22) from "symptom intensity"
Mental Distress Index = AVERAGE (1:11) from "subjective distress"
Somatic Distress Index = AVERAGE (12:22) from "subjective distress"
Global Distress Index = AVERAGE (1:22) from "subjective distress"
Higher index scores indicate a greater severity of adverse events and higher distress levels are attributed to a given side effect.

Appendix 3: Talbieh Brief Distress Inventory (TBDI)

Below is a list of problems and complaints that people sometimes have. Read each one carefully, and select one of the numbered descriptors that best describe HOW MUCH DISCOMFORT THAT PROBLEM HAS CAUSED YOU DURING THE PAST MONTH INCLUDING TODAY. Place that number on the line to the right of the problem. Please do not skip any items, and print your number clearly [62–64].

How much were you distressed by:

1. Trouble remembering things
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
2. Feeling easily annoyed or irritated
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
3. Pains in heart or chest
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
4. Feeling that most people can not be trusted
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
5. Temper outbursts that you could not control
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
6. Feeling lonely even when you are with people
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
7. Your feelings being easily hurt
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
8. Feeling that people are unfriendly or dislike you
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
9. Difficulty making decisions
   0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
10. Getting into frequent arguments
    0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely

(continued)

11. Others not giving you proper credit for your achievements
    0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
12. Feelings of worthlessness
    0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely
13. Feelings of guilt
    0 – Not at all; 1 – A little bit; 2 – Moderately; 3 – Quite a bit; 4 – Extremely

During the past month, how often have you. . .

14. Had attacks of sudden fear or panic?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
15. Been bothered by feeling of sadness or depression – feeling blue?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
16. Been bothered by nervousness, being fidgety or tense?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
17. Felt useless?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
18. Felt anxious?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
19. Felt that nothing turns out for you the way you want it to, would you say. . .
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
20. Felt completely hopeless about everything, would you say. . .
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
21. Felt completely helpless?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
22. Had times when you couldn't help wondering if anything was worthwhile any more?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
23. Had trouble concentrating or keeping your mind on what you were doing?
    0 – never; 1 – almost never; 2 – sometimes; 3 – fairly often; 4 – very often
24. In general, how satisfied have you been with yourself during the last month?
    0 – very satisfied; 1 – somewhat satisfied; 3 – somewhat dissatisfied; 4 – very dissatisfied

Scoring (average):
Obsessiveness 1,9,23
Hostility 2,5,10
Sensitiveness 7,8,12,13
Depression 15,17,19,20,21,22,24
Anxiety 14,16,18
Paranoid Ideation 4,6,11

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Chapter 8
Early Onset Schizophrenia

Vishal Madaan, Yael Dvir, Durga Prasad Bestha, and Daniel R. Wilson

Abstract Early onset schizophrenia (EOS) describes onset of the first episode of psychosis before age 18 years. Such an earlier onset of symptoms is often associated with a severe and chronic course of the illness, a poorer prognosis and a potentially significant negative impact on recovery and rehabilitation. A recent emphasis on early intervention by utilizing the advances in neurobiological and psychosocial domains along with psychopharmacological effectiveness research in managing this chronic psychotic disorder is paving the way for a more rigorous study of this chronic disabling disorder. This chapter reviews recent literature on diagnostic assessment and management of schizophrenia when it strikes during formative years, and provides future directions for further research in the area.

Keywords Schizophrenia · Early onset · Childhood onset · Prodromal phase · First episode psychosis · Typical and atypical antipsychotics

Abbreviations

AOS	Adult onset schizophrenia
APRS	Attenuated psychotic symptoms syndrome
BPRS	Brief psychiatric rating scale
CGI	Clinical global impression
CHR	Clinical high risk
CNV	Copy-number variation
COS	Childhood onset schizophrenia
DLPFC	Dorsolateral prefrontal cortex
DSM-IV TR	Diagnostic and statistical manual of mental disorders, Fourth edition, Text revision
EPSE	Extrapyramidal side effects

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FDA	Food and Drug Administration
FEP	First episode of psychosis
ICD-10	International statistical classification of diseases and related health problems 10th revision
MRI	Magnetic resonance imaging
NIMH	National Institute of Mental Health
PANNS	Positive and negative syndrome scale
PRS	Psychosis risk syndrome
TSH	Thyroid stimulating hormone
UHR	Ultra high risk
VEOS	Very early onset schizophrenia

Introduction

Schizophrenia is a chronic, heterogeneous disorder that constitutes a significant challenge not only for patients but also for family members, friends, and mental health professionals involved in the care of persons who suffer from this devastating illness. According to the DSM-IV TR [1], the usual age of onset of schizophrenia is from late teens to mid-30s. However, in a majority of cases, psychotic symptoms come to the forefront during adolescence or young adulthood (ages 15–24). In fact, several studies have reported nearly one-third of patients with schizophrenia have their first episode of psychosis (FEP) before age 19 [2, 3]. The term "early onset schizophrenia" (EOS) is used to identify patients who develop FEP before the age of 18. The term "very early onset Schizophrenia" (VEOS) and "childhood onset schizophrenia" (COS) are used interchangeably to identify patients in whom the illness manifests before the age of 13. While VEOS is a rare phenomenon, with prevalence of about 1 in 10,000, EOS is more common with an estimated prevalence of 0.5% [4].

VEOS/COS is thought to be a more severe phenotype of schizophrenia with poor premorbid functioning, numerous developmental abnormalities, and stronger epigenetic, biological vulnerabilities to develop illness as compared to adult onset schizophrenia (AOS) [5, 6]. Since the age of onset of schizophrenia is earlier in males than females by about 5 years, there is often an over-representation of males in VEOS/EOS; however, this ratio evens out in epidemiological studies that analyze the sex ratio in adult patients with schizophrenia. Research indicates that while EOS may have a better prognosis than VEOS, both have poorer outcomes when compared to AOS [7]. While schizophrenia continues to be understood as an inevitably progressive, chronic, and debilitating illness, evidence from recent research reinforces the importance of early identification and treatment of psychosis. Such early identification may not only shorten the psychotic episodes but may also alter the natural untreated course of the illness and thus improve prognosis [8]. This impetus towards early diagnosis and treatment of schizophrenia further underscores the

importance of a more sophisticated understanding of EOS. Furthermore, this also highlights several challenges in the assessment and treatment process of EOS that are discussed in the following sections.

Symptoms and Diagnosis

DSM-IV TR and ICD-10[9] do not differentiate between AOS and EOS or VEOS. Hence, essentially the same diagnostic criteria are applied during the evaluation of a child/adolescent or an adult with psychotic symptoms to confirm or refute these varied diagnoses of schizophrenia. Though it appears the broad subcategories of positive and negative symptoms as well as a decline in functioning hold true across the continuum, there are several subtle yet important differences in the symptom profiles of EOS/VEOS compared to AOS. These are largely dependent on the developmental stage of the patient. EOS can either have an acute or insidious onset while VEOS is usually characterized by gradual onset [10, 11]. Patients with an insidious onset usually have a variety of non-specific symptoms often recognized in retrospect only late in the course of illness, especially with progression to a florid psychotic stage that is a significant deviation from normal functioning. These non-specific elements, often referred to as "prodromal phase symptoms" may include social withdrawal or isolation, irritability, bizarre idiosyncratic behaviors, decline in academic performance and/or personal hygiene, affective or anxiety symptoms, and changes in personality [12, 13]. In most cases, attenuated psychotic symptoms such as perceptual abnormalities, suspiciousness, ideas of reference, and changes in experiences of self, others or the world occur late in prodromal phase before the onset of florid psychotic symptoms [14]. In fact, the task force on DSM-V is debating the inclusion of an "attenuated psychotic symptoms syndrome (APRS)" [15] as these might promote earlier recognition of symptoms, referral to appropriate treatment agencies, and possibly reduced burden of disease. A variety of similar concepts exist in the literature, including the "at-risk mental state (ARMS)", "psychosis risk syndrome (PRS)", "ultra high risk (UHR)" [16] and "clinical high risk (CHR)"; all of which aim at identification of subjects who experience sub-threshold psychotic symptoms or brief psychotic symptoms (lasting < 1 week) associated with a decline in functioning. These patients often have strong family history of psychosis and hence are at a high risk of developing psychotic illness. Early and successful detection along with intervention for such prodromal phase patients potentially might increase the likelihood of preventing or delaying onset of psychotic symptoms. More importantly, such early detection may prevent a progressive decline in functioning that is associated with untreated course of illness. High degrees of clinical suspicion with early detection may also result in better prognosis [17]. However, even though the concept of Psychosis risk syndrome and the goal to delay, prevent FEP is very likeable, Yung et al state that several factors such as reliability, validity and cost-benefit analysis of this new proposed syndrome have to be properly studied

before adding this to the DSM-V [18]. Similarly, Correll [19] adds that while studies looking at PRS have yielded crucial information at research level, currently, there is not enough evidence to include this into clinical practice.

Among the actual psychotic symptoms seen in EOS, auditory hallucinations are the most common perceptual abnormality which often begins as elementary sounds. Delusions are vague and not systematized or complex such as those seen in AOS [20]. Disorganized speech and behavior is also commonly seen in patients with EOS. It has also been reported that children with VEOS may have more visual hallucinations compared to adults with schizophrenia. However, the presence of negative symptoms and cognitive deficits at an early stage along with numerous premorbid difficulties such as anxiety or affective symptoms, history of substance abuse, and abnormal personality traits (such as schizotypal), often characterize EOS and VEOS [21, 22]. Furthermore, some of the non-specific prodromal symptoms in children with VEOS may overlap with autism spectrum disorders; in fact, many of these children are initially misdiagnosed as having pervasive developmental disorders. These details are discussed at length in another chapter in the book. Neurocognitive studies indicate that in adolescents with schizophrenia compared to control subjects, there is a large to moderate effect size impairment in IQ, attention, memory and executive function [23].

Etiology and Pathophysiology

Schizophrenia is considered a heterogeneous group of disorders caused by a complex interaction of multiple genes, epigenetic, and environmental factors [24] that lead to variable presentations, courses and responses to available treatment options. Several studies of EOS compared to AOS have attempted to identify etiological factors of particular significance to each, but the difficulty of enrolling subjects from this patient population at an earlier stage of the illness has constrained sample sizes in most studies. However as a consequence of these efforts, several interesting pathophysiological changes and genetic abnormalities have been identified. A number of maternal factors have been hypothesized to be critical factors in the future development of schizophrenia, notably hypoxia, malnutrition, infection, stress, and other effects on fetal development. However, not only are maternal factors not apparent in all patients with schizophrenia; furthermore, perinatal factors have not been shown to be as significant in EOS compared to AOS. Neuroimaging studies have shown that schizophrenia is associated with regional gray matter brain volume reductions irrespective of age of onset. In fact, multiple regional brain volumetric reductions have been described in schizophrenia at first diagnosis regardless of age, especially in temporal lobe [24]. These volumetric reductions in gray matter are hypothesized to be due to disruption of specific neurodevelopmental processes during adolescence. Shaw et al [25] note childhood onset schizophrenia is associated with a marked increase in rate of loss of cerebral gray matter during adolescence. Another interesting factor noted in patients with childhood onset schizophrenia was

the "the almost complete silencing of white matter growth" during adolescence. Addington and Rapoport [26] reviewed the role of genetics in COS and inferred that it is difficult to be certain that EOS is due to more penetrant genetic variations. They did identify a higher occurrence of a variety of copy number variations (CNVs) in EOS when compared to AOS. These included 16p11.2 duplication, MYT1L duplication, NRXN1 deletion as well as genetic abnormalities such as 45 X atypical/mosaic, 22q11 deletion, and 47 XXX. Gothelf et al [27] looked at 22q11 (Velocardiofacial syndrome) and reported COMT genotype, low IQ, anxiety or depressive symptoms and sub-threshold psychotic symptoms predicted a higher rate of emergence of psychotic illness in this patient population. Bennett examined synapse formation and regression in schizophrenia and found synapse loss in dorsolateral prefrontal cortex (DLPFC) is about 60% in patients with schizophrenia whereas it is about 30% in normal adolescents. The exact mechanism is not yet known but the "Disrupted in schizophrenia 1" (DISC 1) gene that encodes a scaffold protein, and Neuregulin 1 that is involved in expression and function of neurotransmitter receptors including glutamate, are involved in processes of synapse formation [28]. Walsh et al noted in patients with both AOS and EOS schizophrenia that microdeletions and microduplications (CNV) affect multiple genes involved in formation of neural pathways. Such microdeletion and microduplication effects could induce abnormalities in synapse formation, neural migration, and glutamate receptor signaling [29]. A link between cannabis use and psychosis has been researched over at least the last 15 years. In their extensive review, Moore et al [30] reported that it is difficult to provide a direct cause-effect relationship between cannabis and psychosis; nevertheless, report there is sufficient evidence that continued cannabis use – in combination with other risk factors – increases risk of psychotic illness and they caution adolescents and young adults against such substance misuse.

Assessment

Any child or adolescent initially presenting with psychotic symptoms should have a comprehensive evaluation to promote correct diagnosis. A detailed history should include information as to onset, course of symptoms, history of prodromal phase symptoms, premorbid abnormalities as well as personal and family history of neurological or psychiatric illness, especially first degree relatives with schizophrenia or affective disorders, especially bipolar disorder or major depressive disorder with or without psychotic features. The presence of substance induced psychotic symptoms is important in the differential diagnosis and thus, thorough exploration of any illicit substance or herbal use and a urine drug screen are indicated. A review of symptoms, with attention to symptoms suggestive of infection, seizure, neurological, metabolic and endocrine conditions, should be conducted. When evaluating a patient with FEP, it is advisable to obtain a brain MRI and electroencephalogram (EEG) in addition to blood tests such as complete blood count, complete metabolic profile and serum TSH. Clinicians should also consider pervasive developmental disorder, bipolar

disorder, major depressive disorder with psychotic features, post-traumatic stress disorder, and other anxiety disorders. In many instances, a provisional diagnosis of psychotic disorder not otherwise specified (Psychosis NOS) is used before collating history from collateral resources and while waiting for results of investigations needed for conclusive diagnosis.

Treatment

Treatment of EOS is best accomplished by using a multimodal approach. Once the diagnosis of either AOS or EOS is established, treatment with antipsychotic medication remains the cornerstone. Currently, atypical antipsychotics are first line agents for EOS. For use in adolescents with schizophrenia, the FDA approved risperidone [31] and aripiprazole [32] in 2007, then olanzapine [33] and quetiapine [34] in December 2009. As to the efficacy of atypical antipsychotics in EOS, there are only several short-term and a very few extended studies [4, 35].

The FDA approval of risperidone for schizophrenia in adolescents is based on two short term (6 and 8 week duration) randomized, double-blind, placebo-controlled studies using doses between 0.15 and 6 mg/day [36, 37]. In both studies, individuals in the risperidone group had a statistically significant decrease in the primary outcome measure – the Positive and Negative Syndrome Scale (PANNS). Adverse effects of risperidone at lower doses (< 3 mg/day) included dizziness, somnolence, and agitation. In the higher dose group (3-mg/day), there was an increased incidence of extrapyramidal side effects (EPSE), weight gain, and prolactin elevation (for further details, the reader is referred to other available resources [38]). Another pivotal multicentric, randomized, double-blind, placebo-controlled study [39] looking at the efficacy and tolerability of aripiprazole (either 10 mg or 30 mg/day) in adolescents with schizophrenia, found both doses were well tolerated and achieved statistical significance in reducing PANNS scores when compared to placebo. The most common adverse effects included extrapyramidal symptoms, somnolence, and tremor. There were no significant changes in glucose or lipid profiles; of note, there was a decrease in prolactin levels from baseline seen with both the doses. The FDA approval of olanzapine was based on a 6-week randomized, double-blind, placebo-controlled trial in which olanzapine was found to be statistically significant and superior to placebo in the primary outcome measure, Brief Psychiatric Rating Scale (BPRS) and also in secondary outcome measures, including PANNS and clinical global impression (CGI) scales [40]. However, adolescents taking olanzapine were more likely than adults to experience weight gain, hyperlipidemia, somnolence, and changes in the levels of hepatic enzymes. The efficacy of quetiapine in treatment of schizophrenia in adolescents (13–17 years of age) was demonstrated in a 6-week, double-blind, placebo-controlled trial [41]. In this study, subjects were randomized to three groups and received either quetiapine 400 or 800 mg (initiated at 50 mg and titrated to target dose) or placebo. It was found that quetiapine was superior to placebo in reduction of PANSS total score

at dosages of both 400 and 800 mg/day. Safety and tolerability of quetiapine in adolescents was assessed in placebo-controlled trials in schizophrenia and bipolar mania. Interestingly, changes in blood pressure, >20 mm Hg systolic in 40.6% and >10 mm Hg diastolic in 40.6% of subjects treated with quetiapine were noted [35]. There was one reported case of hypertensive crisis in the open label continuation phase of the studies.

In a recent review of EOS, Mattai et al [42] note a higher risk of EPSE, akathisia, prolactin elevation, sedation, and metabolic effects due to atypical antipsychotic therapy in adolescents than adults. In the landmark Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) cohort study, Correll et al [43] found that increased weight gain occurred with all the four atypical antipsychotics (risperidone, olanzapine, aripiprazole and quetiapine) approved for use in adolescents. Variable but significant changes in lipid profile also occurred with the above agents. Correll [44] commented on the importance of the findings of a 10 year retrospective cohort study of children and adolescents exposed to antipsychotics conducted by McIntyre and Jerrell and highlighted an increased risk of metabolic and cardiovascular adverse events. This was especially so when multiple antipsychotics were prescribed or when mood stabilizers and antidepressants were co-prescribed with antipsychotics. Hence, careful risk–benefit evaluation should be conducted before prescribing any antipsychotic. In addition, routine monitoring and active management of cardio-metabolic adverse effects should be a routine part of a clinic visits. Recently, a retrospective study using U.S. Medicaid claims data for atypical antipsychotics prescribed in patients aged 6–17 years, across three states, found children did not get recommended screening for metabolic syndrome [45]. In a review of childhood-onset schizophrenia, Madaan et al [4] note that, while studies report efficacy of typical agents such as haloperidol, loxapine, thiothixene and thioridazine, high incidence of side effects such as EPSE, elevated prolactin, sedation, akathisia, dystonias, and tardive dyskinesia appear to almost preclude use of these agents as a first line among children and adolescents.

However, the recently completed NIMH-funded Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS), two atypical agents, olanzapine and risperidone were compared to one typical agent, molindone. Results of this study raise questions regarding the tolerability, safety, and efficacy of atypical agents in children and adolescents [46, 47]. After an 8 week initial "acute trial" [46], subjects continued in "maintenance trial" for up to another 44 weeks [47]. Risperidone and olanzapine did not demonstrate superior efficacy over molindone for early-onset schizophrenia while olanzapine resulted in more weight gain, increased lipids, and insulin levels than comparator medications. When compared to baseline, risperidone was also associated with elevated prolactin levels and akathisia. Only 12% of subjects completed the trial on their originally randomized treatment. Furthermore, molindone was associated with an increase in total cholesterol, LDL cholesterol, insulin, alanine aminotransferase, and aspartate aminotransferase. These researchers concluded that there is a need for improved treatments for early-onset schizophrenia spectrum disorders.

Although clozapine is often considered a treatment of last resort, it has been efficacious in treating early onset schizophrenia [48]. Because of clinicians' concern regarding clozapine's serious adverse effects including agranulocytosis, and a reluctance on the part of patients and families for frequent blood testing, Kumra et al believe that clozapine therapy remains underutilized [49]. Despite some research indicating the probability of developing agranulocytosis in this pediatric sample being similar to adult population [50], more information is required in this area of research.

In addition to the use of medications, psychoeducation is another essential treatment component. Psychoeducation of patients and family members is best tailored to needs on a case by case basis but concerns a variety of important topics including symptom identification and reduction, relapse prevention, role of psychosocial factors, and importance of medication adherence. The use of social skills training along with academic and vocational rehabilitation go a long way in re-integrating recovering patients in day to day living in community setting. In a 2 year follow up of EOS patients, Eack et al [51] applied cognitive enhancement therapy (CET) and noted early application of these techniques maybe an effective approach to remediate cognitive deficits in early schizophrenia. Furthermore, CET may help reduce disability in this population.

Conclusion and Future Directions

Schizophrenia is a complex, heterogeneous group of neuropsychiatric disorders and VEOS/EOS represents a particularly severe phenotype characterized by predominance of cognitive deficits and negative symptoms emerging at an earlier stage, in addition to the more dramatic positive symptoms that typically bring this patient population into contact with treatment services. Comprehensive assessment to rule out other medical and psychiatric disorders constitutes an important first step in management. Using psycho-educational approaches, an effort should be made to engage the patient and his social supportive network in treatment as this is a critical factor to sustain long term treatment. At present, atypical antipsychotic agents form the cornerstone for treating positive symptoms of early onset schizophrenia, even though their long term use has inherent risk of both metabolic syndrome and extrapyramidal adverse effects. Significant unmet needs persist for demonstrably safe and effective treatments for negative symptoms and cognitive deficits in youth (and, indeed, adults). In a descriptive review, Townsend and Findling [52] weigh metabolic and cardiovascular risks associated with atypical antipsychotics against negative consequences of untreated schizophrenia. They conclude that, at present, the most effective treatment choice for adolescents with schizophrenia is to treat with atypicals even while aiming to minimize risks associated with drug treatment via promotion of healthy lifestyles, education, regular monitoring, and early recognition and treatment of cardiovascular and metabolic problems.

The future is one of much optimism as to more timely intervention and treatment of early onset schizophrenia. While the first step would involve consolidating the current knowledge base to promote early recognition and treatment of VEOS/EOS, future phases of research should address novel avenues such as identification of biomarkers for conversion to psychosis, exploration of newer pharmacological agents with efficacy for negative symptoms and cognitive deficits, means that lessen side effect burdens and, optimally, those that afford neuroprotection. Further research to help reach more meaningful social and functional outcomes will also compare at risk subjects who develop schizophrenia despite early interventions to those who do not convert.

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Chapter 9
Prediction and Early Detection of First-Episode Psychosis

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Abstract It has long been known that first episode psychosis is generally preceded by a prodromal phase that can even last up to decades. Different conceptualizations and models have been suggested during the last century. An early detection of first episode psychosis within this prodromal phase, however, was long thought to be impossible due to the assumed unspecific nature of complaints within the pre-psychotic period. This view has started to change during the last two decades. Since the late 1990s, increasing international research activities on an early detection have resulted in first promising findings. Within this new area of research, two main approaches can be identified, the German basic symptom concept, first introduced by Gerd Huber, and the Australo-American ultra-high risk concept, originally introduced by Patrick McGorry and Alison Yung. Another important step was the shift from a prodrome focussed to a risk focussed approach. Meanwhile, results from several studies indicate that both concepts have the ability to define samples with a considerably increased risk for developing a florid psychosis. The chapter will introduce the early and current concepts and review the evidence provided by the available studies.

Keywords First-episode psychosis · Prediction · Early detection · Prodrome · At-risk mental state · Basic symptoms · Ultra-high risk

Abbreviations

APS	Attenuated psychotic symptoms
ARMS	At-risk mental state
BLIPS	Brief limited intermittent psychotic symptoms
BPRS	Brief psychiatric rating scale
BS	Basic symptoms
BSABS	Bonn scale for the assessment of basic symptoms

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CAARMS	Comprehensive assessment of at-risk mental states
CHR	Clinical high risk
COGDIS	Basic symptom high risk criterion “cognitive disturbances”
COPER	Basic symptom risk criterion “cognitive-perceptive basic symptoms”
COPS	Criteria of Prodromal Syndromes
DUP	Duration of untreated psychosis
EIPS	Early initial prodromal state
FEP	First-episode psychosis
FEPSY	Früherkennung von Psychosen
LIPS	Late initial prodromal state
NAPLS	North american prodrome longitudinal study
PACE	Personal assessment and clinical evaluation
PANSS	Positive and negative syndrome scale
PI	Prognostic index
PRIME	Prevention through risk identification, management and education
RAP	Recognition and prevention
SIPS	Structured interview for prodromal/psychosis-risk syndromes
SOPS	Scale for prodromal syndromes
SPI-A	Schizophrenia proneness instrument, Adult version
SPI-CY	Schizophrenia proneness instrument, child & youth version
UHR	Ultra-high risk

Prevention of Psychiatric Disorders

Both the World Health Organization [1] and the European Commission [2] have given the prevention of mental disorders high priority, because, in light of the current limitations in effectiveness of treatment modalities for decreasing disability due to mental and behavioural disorders, they consider prevention “the only sustainable method for reducing the burden caused by these disorders” [1, p. 13]. In addition, individuals and families affected by mental disorders, in particular by psychotic disorders, continue to suffer from intense and pervasive stigma and discrimination. At least partially, these result from the general perception of a lack of effective preventive or treatment modalities. Thus an effective prevention might positively alter these negative and rather fatalistic perceptions and hence change the way mental disorders are looked upon by society [1]. In pursuit of this aim, the conceptual framework of prevention by Mrazek and Haggerty [3] that pays special attention to the characteristics of mental disorders is mainly applied nowadays. At the general aim of reducing the incidence rate of the disorder, 3 approaches to prevention are distinguished therein: universal, selective and indicated prevention.

While the universal and selective approach target populations with no signs of a mental disorder but, in case of the selective approach, with a known increased biological and/or psychosocial risk of developing the disorder, the indicated approach targets populations that already show prodromal or subthreshold signs of the

disorder but do not (yet) meet diagnostic criteria. This focus on persons already suffering from mental problems brings about two main advantages, in particular in infrequent disorders with prolonged prodromes like psychoses: First, from a research point of view, the resulting risk enrichment that allows the observation of sufficient numbers of transitions to the full-blown disorder within the generally restricted time frames of early detection and/or intervention studies. Second, from a clinical point of view, persons with first signs of mental disorder are more likely to seek help and, consequently, to come in contact with specialized services. Therefore, an indicated approach has been predominately followed in the prevention of mental disorders, particularly psychoses [4]. Despite these considerable advantages, however, it was also argued that a universal or selective prevention targeting rather general risk factors, such as functional, emotional and behavioural disturbances [5], not specific to a single mental disorder might nevertheless be efficient strategies for reducing the incidence of mental disorders as a whole [5–7].

The Prodrome of Psychosis

In medicine, the term "prodrome" (Greek: πρόδρομος; precursor) describes the early phase of an illness, in which unspecific and early symptoms occur that herald the future illness before it develops into its full-blown clinical picture, i.e., before its diagnostic criteria are met. Therewith, strictly speaking, a prodrome can only be assessed and determined in retrospect, after the onset of the first episode of the disorder. Hence first descriptions and models of the prodrome of psychosis, particularly schizophrenia [8–31], mainly relied on the retrospective examination of patients with the manifest disorder.

Descriptions of schizophrenic psychoses have noted a prodromal phase of considerable length, which already results in deficits in psychosocial functioning, i.e., in a "kink in the life line" [32], before the onset of positive psychotic symptoms, ever since their first description as "dementia praecox" by Kraepelin [33]; and the prodrome is explicitly allowed for as part of the time criteria of schizophrenia in DSM-IV [34], though not ICD-10[35]. A first methodologically thorough retrospective study of the prodrome of first-episode schizophrenia, the Age-Beginning-Course study [36], conducted between 1987 and 1989 in a semi-rural German area, confirmed early clinical observations by showing a prodromal phase of 5 years on average in 73% of the 232 inpatients along with an onset of first psychosocial deficits and delays already more than 1 year before the onset of first positive symptoms. Nearly 15 years later, these findings were largely corroborated by a second German study on 128 inpatients with non-affective and affective first-episode psychosis (FEP), mainly schizophrenia [37]. Therein, even 98% of the FEP patients reported a prodrome of at least 1-month duration and of nearly 6 years on average. Further, both studies reported a mean duration of untreated psychosis (DUP; time between onset of first psychotic symptoms and of first inpatient treatment for psychosis) of slightly more than 1 and 2 years, respectively [36, 37].

First and foremost conducted in the 1990s, a multitude of studies on DUP and outcome evidenced extensive DUP and a discrete association between the length of DUP and various measures of poor outcome [38–40]. The, compared to adult-onset psychosis, much extended DUP has also been assumed to underlie the frequently reported more unfavourable course of early-onset psychosis [41]. Further, negative associations with favourable outcome were likewise found for the total duration of untreated illness, including the prodrome [42], as well as the duration of untreated prodromal symptoms itself [43].

The findings of an early onset of functional deficits and of the unfavourable effects of treatment delay that had started to accumulate in the 1990s gave great impetus to preventive efforts in FEP. To the majority of researchers and clinicians, such efforts had long appeared fruitless for the alleged unspecific nature of prodromal symptoms, though the possible benefits of an early detection and intervention had early and repeatedly been voiced: e.g., in 1932, the German psychiatrist Wilhelm Mayer-Gross "wondered why, hitherto, one has so infrequently made use of the impressive experience that is represented by the first irruption of a thought disorder, a decrease in activity, an aberration in sympathy and other emotions into the healthy personality" ([8, p. 296]; translation by FSL), while, already in 1927, the American psychiatrist Harry Stack Sullivan had critically observed that "The psychiatrist sees too many end states and deals professionally with too few of the pre-psychotic." [9, p. 135].

Prediction of First-Episode Psychosis

The presumed unspecific nature of prodromal symptoms, however, had also been challenged early. In 1957, the Scottish psychiatrist Hunter Gillies expressed his conviction that the early symptoms were "more specific than it would at first appear." ([44, p. 47]). To him, thought, affective and volitional disorders as well as autistic withdrawal represented "the most pathognomonic signs. But they must be looked for. During a lengthy interview they may emerge once only, or not at all. [. . .] The early case does not show these [authors' comment: Bleuler's secondary symptoms, i.e., positive symptoms] often, except in an embryonic form, and when they are present the diagnostic is obvious. [. . .] It is, therefore, to the primary signs [authors' comment: Bleuler's primary symptoms, i.e., negative symptoms], and to the non-specific signs that precede even the primary signs, that we must direct our attention." [44, p. 50].

Prodromal Criteria of the DSM-III and Its Revision

Despite the generally assumed unspecificity of prodromal symptoms of FEP, an attempt to define a prodromal phase of schizophrenia was made based on an expert consensus decision of the American Psychiatric Association in DSM-III and

DSM-III-R [45, 46]. The DSM-III-R provided a list of 9 symptoms in its description of prodromal and, simultaneously, of residual symptoms of Schizophrenia. These were attenuated forms of negative symptoms and of positive symptoms, the latter corresponding to the respective criteria of Schizotypal Personality Disorder in DSM-III-R and DSM-IV (Table 9.1). In case of the occurrence of 2 of the 9 prodromal symptoms for at least 6 months and of the additional presence of psychotic symptoms during this time for at least 1 week (note: in DSM-IV, a duration of psychotic symptoms of 1 month, or less if successfully treated, is required for the diagnosis of Schizophrenia), the diagnosis of "prodromal" Schizophrenia was given [46].

Most DSM-III-R prodromal symptoms, i.e., symptoms 1–6 and 9 (Table 9.1), were completely based on observable behavioural changes. Further, the seventh prodromal symptom, although requiring the presence of unusual thought content, also required this to influence behaviour, thus an observable element was again necessary. Subjective disturbances were not taken into account, as the inclusion of mainly observable phenomena in this operationalization of the schizophrenic prodrome was intended to increase the reliability of the diagnosis [47].

Subsequent studies of the specificity, prevalence and reliability of the DSM-III-R prodromal symptoms, however, showed discouraging results [49–55]. And in 1996, the Melbourne workgroup of Patrick D. McGorry concluded that the decision to not continue prodromal criteria in DSM-IV was justified not only for their unclear validity and specificity as well as their partly unreasonably high prevalence in non-psychotic samples but also for the relative unreliability of their assessment [51]. They reasoned that other prodromal symptoms as already suggested by other authors (a review was given by Yung and McGorry [56]), "when taken in concert with one another, may have greater sensitivity and specificity, and more importantly, greater positive and negative predictive powers for psychosis, but obviously more empirical work needs to be undertaken as regards such symptoms." [51, p. 503f].

Ultra-High Risk Criteria

As a direct result of their studies of the DSM-III-R prodromal symptoms, the Melbourne group of the "Personal Assessment and Clinical Evaluation" (PACE) clinic [57] gradually developed the "ultra-high risk" (UHR) criteria [4, 48] (Table 9.2). Thereby, they aimed "to identify people with high likelihood of transition to psychosis within a follow-up period of 12 months" [4, p. 14]. Their studies resulted in the formulation of 3 different sets of criteria, which – though in different operationalization – have been most widely used in the early detection of FEP (Tables 9.2 and 9.3):

1. attenuated psychotic symptoms (APS): experience of subthreshold, attenuated positive psychotic symptoms including schizotypal symptoms (Table 9.1)

Table 9.1 Comparison of the prodromal symptoms of schizophrenia according to DSM-III-R, criteria of schizotypal personality disorder according to DSM-IV and attenuated psychotic symptoms (APS) according to the UHR criteria [4, 48]

Prodromal/residual symptoms of schizophrenia according to DSM-III-R	Diagnostic criteria of schizotypal personality disorder according to DSM-IV	APS of the UHR criteria
(1) Marked social isolation or withdrawal	(8) Lack of close friends or confidants other than first-degree relatives	
(2) Marked impairment in role functioning		
(3) Markedly peculiar behaviour	(7) Behaviour or appearance that is odd, eccentric, or peculiar	
(4) Marked impairment in personal hygiene and grooming		
(5) Blunted or inappropriate affect	(6) Inappropriate or constricted affect	
(6) Digressive, vague, overelaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech	(4) Odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped)	(5) Odd thinking and speech
(7) Odd beliefs or magical thinking (incl. ideas of reference)	(2) Odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms	(2) Magical thinking (incl. grandiose ideas)
	(1) Ideas of reference (excluding delusions of reference)	(1) Ideas of reference
(8) Unusual perceptual experiences	(3) Unusual perceptual experiences, including bodily illusions	(3) Perceptual disturbance
(9) Marked lack of initiative, interests, or energy		
	(5) Suspiciousness or paranoid ideation	(4) Paranoid ideation
	(9) Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self	

Table 9.2 Operationalizations of the PACE/CAAR MS UHR criteria over time; changes between subsequent operationalizations are indicated by bold type

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/Vulnerability
Phillips et al. 2000[48] *Pilot Study criteria* (1994-not specified; age 16–30 yrs)	Group 2 Subjects had experienced a definite change from their usual self or functioning as defined by presence of **at least two** of the features of the DSM-III-R schizophrenia prodrome criteria: **(1) Marked social isolation or withdrawal,** **(2) Marked impairment in role functioning** (3) Markedly peculiar behaviour, **(4) Marked impairment in personal hygiene and grooming,** **(5) Blunted or inappropriate affect,** (6) Digressive, vague, overelaborate to circumstantial speech, or poverty of speech or poverty of content of speech, (7) Odd beliefs or magical thinking, (8) Unusual perceptual experiences, **(9) Marked lack of initiative, interests or energy** However, subjects who exhibited only one "positive" prodromal feature (attenuated psychotic symptoms) were also included.		Group 1 Having a first- or second-degree relative with any psychotic disorder or Schizotypal or **Schizoid Personality Disorder** in conjunction with a change in mental state or functioning indicating the potential development of a probable prodromal state: (1) Two or more of the nine criteria for DSM-III-R prodrome, (2) **Moderate depression according to the score on the BDI[a]** or (3) **Having experienced any items on the EWSS[b] several times per week.** OR Group 3 Subjects met DSM-III-R criteria for either Schizotypal or **Schizoid Personality Disorder**

Table 9.2 (continued)

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/Vulnerability
Yung et al. 1996 [60] (starting 1994 over 20-month period; age: 16–30 yrs)	Group 2 Those who had developed attenuated or subthreshold psychotic symptoms, that is, who had **one or more** of the positive **prodromal features of DSM-III-R criteria** for schizophrenia prodrome: (3) Markedly peculiar behaviour, (6) Digressive, vague, overelaborate, or metaphorical speech, (7) Odd or bizarre ideation or magical thinking, (8) Unusual perceptual experiences as assessed for presence with the **RPMIP**[c]	**Group 3** **History of fleeting psychotic experiences that spontaneously resolved (called brief limited intermittent psychotic symptoms, or BLIPS) within 1 week.**	Group 1 Combination of trait risk factors and state risk factors, that is, a first- **or second-degree** relative with a history of any psychotic disorder or a Schizotypal Personality Disorder, both **as defined by DSM-III-R,** combined with a change in mental state or functioning indicating development of a probable prodromal state as defined by the presence of two or more of the nine criteria for DSM-III-R schizophrenic prodrome
Yung et al. 1998 [4] (05/1995–07/1996; age 16–30 yrs)	Presence of at least one of the following **symptoms as defined in DSM-IV Schizotypal Personality Disorder:** **(1) ideas of reference,** (2) magical thinking, (3) perceptual disturbance, **(4) paranoid ideation,** (5) odd thinking and speech (6) odd behaviour or appearance	History of transient psychotic symptoms as defined by the presence of at least one of the following symptoms: (1) Hallucinations, (2) Delusions, (3) Formal thought disorder	First degree relative with a psychotic disorder or Schizotypal Personality Disorder **as defined by DSM-IV** or **individual has DSM-IV Schizotypal Personality Disorder;** **Significant decrease in mental state or functioning – maintained for at least one month (reduction in GAF Scale of 30 points from premorbid level)**

Table 9.2 (continued)

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/Vulnerability
	(2–3 on unusual thought content scale; 1–2 on hallucinations scale; 2–3 on suspiciousness scale of BPRS[d]); **Held with a reasonable degree of conviction, as defined by a score of 2 on the CASH[e] rating scale for delusions;** **Frequency of symptoms – several times per week;** The change in mental state has been **present** for **at least 1 week.**	**(3+ on hallucinations scale; 4+ on unusual thought content scale or 4+ on suspiciousness scale (or it is held strong conviction, as defined by a score of 3 or more on the CASH rating scale for delusions); or 4+ on conceptual disorganization scale of BPRS);** Duration of episode of less than 1 week; Symptoms resolve spontaneously	
Phillips et al. 2000 [48] *Prediction study criteria* (not specified; age **14**–30 yrs)	Low-grade psychotic symptoms: (1) Ideas of reference, (2) Magical thinking, (3) Perceptual disturbance, (4) Paranoid ideation, (5) Odd thinking and speech (2–3 on Unusual thought content scale; 1–2 on hallucinations scale; **3 on suspiciousness scale** or 1–3 on conceptual disorganization scale of BPRS); Held with a reasonable degree of conviction, as defined by a score of 2 on the CASH rating scale for delusions; Frequency of symptoms – several times per week; The change in mental state has been present for at least 1 week **within the past year and not more than 5 years**.	Transient psychotic symptoms: (1) Ideas of reference, (2) Magical thinking, (3) Perceptual disturbance, (4) Paranoid ideation, (5) Odd thinking and speech (4+ on unusual thought content scale; 3+ on hallucinations scale; 4+ on suspiciousness scale (or it is held strong conviction, as defined by a score of 3 or more on the CASH rating scale for delusions) or 4+ on conceptual disorganization scale of **BPRS**); Duration of episode of less than 1 week; Symptoms resolve spontaneously; **The symptoms occurred within the past year**	First degree relative with a psychotic disorder or Schizotypal Personality Disorder or individual has Schizotypal Personality Disorder; Significant decrease in mental state or functioning – maintained for at least a month (reduction in GAF Scale of 30 points from premorbid level); **Decrease in functioning maintained for at least a month and for not more than 5 years**

Table 9.2 (continued)

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/Vulnerability
Yung et al. [76] (03/1995–01/1999; age 14–30 yrs)	Presence of at least one of the following symptoms: (1) Ideas of reference, (2) Odd beliefs or magical thinking, (3) Perceptual disturbance, (4) Paranoid ideation, (5) Odd thinking and speech, **(6) Odd behaviour and appearance** (2–3 on unusual thought content scale; 1–2 on hallucinations scale; **2–3 on suspiciousness scale** or 1–3 on conceptual disorganization scale of **BPRS**); Held with a reasonable degree of conviction, as defined by a score of 2 on the CASH rating scale for delusions; Frequency of symptoms - at least several times per week; The period in which attenuated psychotic symptoms are **present** is **at least 1 week and not longer than 5 years**	Presence of at least one of the following: (1) Ideas of reference, (2) Magical thinking, (3) Perceptual disturbance, (4) Paranoid ideation, (5) Odd thinking and speech (4+ on unusual thought content scale; 3+ on hallucinations scale; 4+ on Suspiciousness scale (or it is held strong conviction, as defined by a score of 3 or more on the CASH rating scale for delusions) or 4+ on conceptual disorganization scale of **BPRS**); Duration of episode of less than 1 week; symptoms resolve spontaneously; The BLIPS must have occurred within the past year	Schizotypal Personality Disorder (as defined by DSM-IV) or **a first-degree relative with a DSM-IV psychotic disorder** Significant decrease in mental state or functioning – maintained for at least a month and not longer than 5 years (reduction in GAF Scale of 30 points from pre-morbid level) **The decrease in functioning occurred within the past year**

Table 9.2 (continued)

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/Vulnerability
Yung et al. [64] (not specified; not specified)	(i) Subthreshold intensity: Severity scale score of 3–5 on disorders of thought content subscale, 3–4 on perceptual abnormalities subscale and/or 4–5 on disorganized speech subscale of the **CAARMS**[f]; Frequency scale score of 3–6 on disorders of thought content, perceptual abnormalities and/or disorganized speech subscale of the CAARMS for at least 1 week; OR **Frequency scale* score of 2 on disorders of thought content, perceptual abnormalities and disorganized speech subscale of the CAARMS on more than two occasions.** **(ii) Subthreshold frequency:** **Severity scale score of 6 on disorders of thought content subscale, 5–6 on perceptual abnormalities subscale and/or 6 on disorganized speech subscale of the CAARMS;** **Frequency scale score of 3 on disorders of thought content, perceptual abnormalities and/or disorganized speech subscale of the CAARMS;** (for both categories) Symptoms **present in past year and for not longer than 5 years**	Severity scale score of 6 on disorders of thought content subscale, 5 or 6 on perceptual abnormalities subscale and/or 6 on disorganized speech subscale of the **CAARMS**; **Frequency scale[g] score of 4–6 on disorders of thought content, perceptual abnormalities and/or disorganized speech subscale;** Each episode of symptoms is present for less than 1 week and symptoms spontaneously remit on every occasion; Symptoms occurred during last year **and for not longer than 5 years**	Family history of psychosis in first degree relative or schizotypal personality disorder in identified patient; **30% drop in GAF score from premorbid level**, sustained for 1 month; Change in functioning occurred within last year and **maintained at least 1 month**

Table 9.2 (continued)

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/ Vulnerability
Yung et al. unpublished CAARMS, version by 12/2006	*This criterion identifies young people at risk of psychosis due to a subthreshold psychotic syndrome. That is, they have symptoms which do not reach threshold levels for psychosis due to subthreshold intensity (the symptoms are not severe enough) or they have psychotic symptoms but at a subthreshold frequency (the symptoms do not occur often enough).* (a) Subthreshold intensity: Global rating scale score of 3–5 on unusual thought content subscale, **3–5 on non-bizarre ideas subscale,** 3–4 on perceptual abnormalities subscale and/or 4–5 on disorganised speech subscales of the CAARMS *PLUS* Frequency scale score of 3–6 on unusual thought content, non-bizarre ideas, perceptual abnormalities and/or disorganised speech subscales of the CAARMS for at least a week (b) Subthreshold frequency: Global rating scale score of 6 on unusual thought content, **6 on non-bizarre ideas**, 5–6 on perceptual abnormalities and/or 6 on disorganised speech subscales of the CAARMS	*This criterion identifies young people at risk of psychosis due to a recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within one week.* Global rating scale score of 6 on unusual thought content subscale, **6 on non-bizarre ideas**, 5 or 6 on perceptual abnormalities subscale and/or 6 on disorganised speech subscales of the CAARMS *PLUS* Frequency scale score of 4–6 on unusual thought content, non-bizarre ideas, perceptual abnormalities and/or disorganised speech subscales *PLUS* Each episode of symptoms is present for less than one week and symptoms spontaneously remit on every occasion.	*This criterion identifies young people at risk of psychosis due to the combination of a trait risk factor and a significant deterioration in mental state and/or functioning* Family history of psychosis in first degree relative OR Schizotypal Personality Disorder in identified patient *PLUS* **30% drop in SOFAS score** from premorbid level, sustained for a month, occurred within past 12 months ***OR*** **SOFAS score of 50 or less for past 12 months or longer**

Table 9.2 (continued)

Study (recruitment period; targeted age group)	Attenuated (psychotic) symptoms (APS)	Brief limited intermittent psychotic symptoms (BLIPS)	Trait-state risk factors/ Vulnerability
	PLUS Frequency scale score of 3 on unusual thought content, non-bizarre ideas, perceptual abnormalities and/or disorganised speech subscales of the CAARMS *PLUS* (for both categories) Symptoms present in past year ***PLUS*** **(for both categories)** **30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months** ***OR*** **SOFAS score of 50 or less for past 12 months or longer**	*PLUS* Symptoms occurred during last year ***PLUS*** **30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months** ***OR*** **SOFAS score of 50 or less for past 12 months or longer**	

[a]Beck Depression Inventory [58].
[b]Early Warning Signs Survey [59].
[c]Royal Park Multidiagnostic Instrument for Psychosis [54, 55].
[d]Brief Psychiatric Rating Scale [61].
[e]Comprehensive Assessment of Symptoms and History [62, 63].
[f]Comprehensive Assessment of At-Risk Mental States CAARMS. Comprehensive Assessment of At Risk Mental States, Version December, 2006, unpublished; Severity scores: 3 = moderate; 4 = moderately severe; 5 = severe; 6 = psychotic and severe.
[g]CAARMS Frequency scores: 2 = Once a month to twice a week – less than 1 h per occasion; 3 = Once a month to twice a week – more than 1 h per occasion OR 3–6 times a week – less than 1 h per occasion; 4 = 3–6 times a week – more than an hour per occasion OR daily – less than an hour per occasion; 5 = Daily – more than an hour per occasion OR several times a day; 6 = Continuous.

Table 9.3 Operationalizations of UHR criteria by different instruments

	Criteria of prodromal syndromes (COPS)	PACE (since 1998)/FEPSY	PACE (CAARMS[a],12/2006 version)	Morrison et al. [65, 66] and Amminger et al. [67]
Instrument	Structured interview for/scale of prodromal syndromes (**SIPS/SOPS**)	Brief psychiatric rating scale (**BPRS**)	Comprehensive Assessment of At-Risk Mental States (**CAARMS**)	Positive and negative syndrome scale (**PANSS**)
Attenuated psychotic symptoms (APS)	Unusual thought content/delusional ideas (P1-score 3–5) Grandiosity (P3-score 3–5)	Unusual thought content PACE: score 2–3 FEPSY: score 3–4	(a) Subthreshold intensity: Unusual thought content subscale (score 3–5) Non-bizarre ideas subscale (score 3–5) (b) Subthreshold frequency: Unusual thought content subscale (score 6) Non-bizarre ideas subscale (score 6)	Delusions (P1- AND/OR P5-score 3)
	Suspiciousness/persecutory ideas (P2-score 3–5)	Suspiciousness PACE: score 3 FEPSY: score 3–4		Suspiciousness (P6-score 3–4)
	Perceptual abnormalities/hallucinations (P4-score 3–5)	Hallucination PACE: score 1–2 FEPSY: score 2–3	(a) Subthreshold intensity: Perceptual Abnormalities subscale (score 3–4) (b) Subthreshold frequency: Perceptual Abnormalities subscale (score 5–6)	Hallucinations (P3-score 2–3)
	Disorganized communication (P5-score 3–5)	Conceptual disorganisation PACE: score 1–3 FEPSY: not considered	(a) Subthreshold intensity: Disorganised speech subscale (score 4–5) (b) Subthreshold frequency: Disorganised speech subscale (score 6)	Conceptual disorganisation (P2-score 3–4)

Table 9.3 (continued)

	Criteria of prodromal syndromes (COPS)	PACE (since 1998)/FEPSY	PACE (CAARMS[a],12/2006 version)	Morrison et al. [65, 66] and Amminger et al. [67]
General requirements for APS	Average frequency of at least once per week in the past month ***PLUS*** development or increase by 1 point in severity within the past year	PACE: Frequency of several times per week ***PLUS*** present for at least 1 week within the past year and not more than 5 years FEPSY: Frequency of several times per week ***PLUS*** present for at least 1 week	(a) Subthreshold intensity: Frequency Scale Score of 3-6 on the respective subscale of the CAARMS for at least a week b) Subthreshold frequency: Frequency Scale Score of 3 on the respective subscale of the CAARMS ***PLUS*** a & b) Symptoms present in past year ***PLUS*** 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months ***OR*** SOFAS score of 50 or less for past 12 months or longer	Frequency of several times per week ***PLUS*** change in mental state present for 1 week

Table 9.3 (continued)

	Criteria of prodromal syndromes (COPS)	PACE (since 1998)/FEPSY	PACE (CAARMS[a],12/2006 version)	Morrison et al. [65, 66] and Amminger et al. [67]
Brief limited intermittent psychotic symptoms (BLIPS)	Unusual thought content/delusional ideas (P1-score 6) Grandiosity (P3-score 6) Suspiciousness/ persecutory ideas (P2-score 6) Perceptual abnormalities/hallucinations (P4-score 6) Disorganized communication (P5-score 6)	Unusual thought content PACE: score ≥4 FEPSY: score ≥5 Suspiciousness PACE: score ≥4 FEPSY: score ≥5 Hallucination PACE: score ≥3 FEPSY: score ≥4 Conceptual disorganisation PACE: score ≥4 FEPSY: score ≥5	Unusual thought content subscale (score 6) Non-bizarre ideas subscale (score 6) Perceptual Abnormalities subscale (score 6) Disorganised speech subscale (score 6)	Delusions (P1-AND/OR P5-score 4–7) Persecutory ideas (P6-score 5–7) Hallucinations (P3-score 4–7)

Table 9.3 (continued)

	Criteria of prodromal syndromes (COPS)	PACE (since 1998)/FEPSY	PACE (CAARMS[a],12/2006 version)	Morrison et al. [65, 66] and Amminger et al. [67]
General requirements for BLIPS	No less than several minutes a day at least once per month and no more than 1 hour a day for 4 days a week (on average) for 1 month ***PLUS*** development within the past 3 months ***PLUS*** symptoms not seriously disorganizing or dangerous	PACE: Duration of episode less than a week ***PLUS*** symptoms spontaneously resolve ***PLUS*** occurrence within the past year FEPSY: Duration of episode less than a week ***PLUS*** symptoms spontaneously resolve	Frequency scale score of 4–6 on respective subscale of the CAARMS ***PLUS*** each episode of symptoms is present for less than 1 week ***PLUS*** symptoms occurred during last year ***PLUS*** symptoms spontaneously remit on every occasion ***PLUS*** 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months ***OR*** SOFAS score of 50 or less for past 12 months or longer	Present for less than 1 week prior to spontaneous resolution

Table 9.3 (continued)

	Criteria of prodromal syndromes (COPS)	PACE (since 1998)/FEPSY	PACE (CAARMS[a],12/2006 version)	Morrison et al. [65, 66] and Amminger et al. [67]
Trait-state risk factor	First-degree relative with any psychotic disorder ***OR*** patient has a Schizotypal Personality Disorder ***PLUS*** reduction of functioning on the GAF Scale of at least 30 points for at least 1 month as compared to 12 months ago	PACE: First-degree relative with a psychotic disorder or schizotypal personality disorder ***OR*** patient has a schizotypal personality disorder ***PLUS*** reduction of functioning on the GAF Scale of at least 30 points from premorbid level for at least 1 month and not more than 5 years FEPSY: at least one first- or second-degree relative with a psychotic disorder ***PLUS*** at least two of the following risk factors ***OR*** low number and combination of these risk factors without family history of psychosis: ■ "Kink in the life line" with a significant decline in functioning over the last 5 years ■ Regular use of cannabis, hallucinogenic drugs, cocaine, amphetamines, inhalations, opiods, phenylcyclidines, or designer drugs within the last 2 years ■ Previous psychiatric disorders or problems ■ Referral for suspected developing psychosis and presence of other prodromal symptoms with onset within the past 2 years, i.e., DSM-III-R prodromal symptoms (Table 9.1), concentration, attention or sleep disturbances, depressive mood, anxiety, nervousness, restlessness, hypersensitivity, derealisation, depersonalisation	Family history of psychosis in first-degree relative ***OR*** patient has a Schizotypal Personality Disorder ***PLUS*** 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months ***OR*** SOFAS score of 50 or less for past 12 months or longer	Family history of psychosis ***OR*** patient has a schizotypal personality disorder ***PLUS*** functional deterioration

[a]see Table 9.2 for description of CAARMS severity and frequency ratings.

2. brief limited intermittent psychotic symptoms' (BLIPS): frank psychotic symptoms that last no longer than 1 week and remit spontaneously
3. trait-state risk factors: presence of a risk factor of psychosis and a significant decrease in functioning.

For the symptomatic assessment of the UHR criteria, the PACE group first used the DSM-III-R prodromal symptoms and next a combination of the "Brief Psychiatric Rating Scale" (BPRS) [61] and the "Comprehensive Assessment of Symptoms and History Interview" (CASH) [62, 63]. From 1999 to 2006, a specialized instrument, the "Comprehensive Assessment of At Risk Mental States" (CAARMS) [64], CAARMS. Comprehensive Assessment of At Risk Mental States, Version December, 2006, unpublished, had gradually been developed to assess all relevant domains within one tool, i.e., symptoms, their intensity, frequency, duration and recency [64] (Table 9.2).

Based on the Australian definition of the UHR criteria and modelled after the "Positive And Negative Syndrome Scale" (PANSS) [68], within the "Prevention through Risk Identification, Management and Education" (PRIME) clinic at Yale University, USA, the "Structured Interview for Prodromal Syndromes" (SIPS) along with its rating scale "Scale for Prodromal Syndromes" (SOPS) and, later on, the "Criteria of Prodromal Syndromes" (COPS; Table 9.3) was developed [69, 70] and recently published as the "Structured Interview for Psychosis-Risk Syndromes" (SIPS) [71]. Though the domains of negative, disorganized and general symptoms underwent significant changes from the second to the third version of the SIPS by changing from a frequency- to a symptom-based severity rating, the positive syndrome section and, therewith, the assessment of UHR or COPS criteria has remained mostly unchanged.

Although developed in close reference to each other, the UHR operationalizations of the PACE and the PRIME group vary in some respects: Whereas the assessment of UHR criteria had earlier differed between the PACE criteria and the COPS mainly in terms of the maximum duration of presence of APS and BLIPS, with more emphasis on recency in COPS (Table 9.3), during the last couple of years, not only attenuated but also infrequent frank psychotic experiences are captured as APS in the CAARMS/PACE criteria (Tables 9.2 and 9.3), while these continue to be rated as BLIPS in the COPS. Furthermore, a significant decline in psychosocial functioning has newly been introduced as an obligate criterion of APS and BLIPS in the CAARMS. Comprehensive Assessment of At Risk Mental States, Version December, 2006, unpublished (Table 9.2).

Transition Rates in UHR Samples

While these differences in UHR operationalizations, which occur between centres and scales as well as within centres and scales over time, are often obscured in study reports by general descriptions of UHR criteria in terms of APS, BLIPS and "trait-state", they do seem to have an effect on transition rates. In a recent long-term follow-up of participants of PACE studies conducted between 1994 and

2006 [72] that used the UHR criteria valid at the time of first intake into a PACE study, significantly higher transition rates in patients recruited between 1994 and 2000 compared to those recruited between 2001 and 2006 showed (Table 9.4).

Studies conducted with the different PACE/CAARMS definitions of UHR criteria found 6-month transition rates to frank psychosis of participants not part of the treatment group of a pharmacological intervention study of between 10% [73, 74] and 40% [4] and, weighted for the reported sample size but not controlled for overlapping samples, of 20.1% on average [4, 64, 73–77]. First year's transition rates varied between 12% [78] and 41% [48] and were 23% on average [48, 72, 75, 76, 78, 79] (Table 9.4). For studies conducted with the SIPS, the reported 6-month transition rates were 46% [70] and 13% [90] with a sample-size adjusted mean rate of 14%. First year's rates ranged from 12% [88] to 54% [70] at an average transition rate of 22% [70, 86–88, 90–92] (Table 9.4) that is almost equal to that of PACE/CAARMS operationalizations. Thus, irrespective of the variation of PACE/CAARMS criteria across time, the 2 main UHR operationalizations predict psychosis at an almost equal mean 12-month transition rate of 22 to 23%.

Some differences between the 2 operationalizations, however, might exist with regard to the lag time to transition and long-term transition rates. The 2 large multisample studies of the PACE/CAARMS criteria [72] and the COPS [90] indicate that the rise in transition rates over time might be slower initially but steadier when applying the COPS, thus resulting in a transition rate of 35% at 30 months [90] using the COPS compared to 25% at 36 months and 29% at 60 months or later using the PACE/CAARMS criteria [72] (Table 9.4). Yet, differences in transition rates might not only be due to differences in the operationalization of UHR criteria, but also due to differences in exclusion and/or transition criteria (Table 9.6) as well as to other unsystematic sampling biases such as service utilization biases, e.g., towards persons of higher education and/or lack of migration background [108], variable treatments and unequal follow-up and/or drop-out rates.

Another operationalization of UHR criteria that had only been used in two smaller intervention studies [65–67, 95] relies on the PANSS (Table 9.3). This operationalization had led to 1-year transition rates in the control groups of 38% [95] and 29% [67], respectively (Table 9.4).

UHR-Like Approaches

Clinical High Risk Criteria

A different UHR-related approach to an early detection of FEP, particularly Schizophrenia, was developed by the "Hillside Recognition and Prevention" (RAP) programme in New York [109] that operates within a child and adolescent psychiatric setting and only exceptionally takes in young adults above the age of 18. Dropping the trait-state criterion of the UHR criteria altogether, the "clinical high risk" (CHR) criteria are conceptually related to the neurodevelopmental model [110] and distinguish between 3 at-risk criteria operationalized by the SIPS:

Table 9.4 Transition rates to psychosis in at-risk samples

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Studies conducted at the personal assessment and crisis evaluation (PACE) clinic					
Yung et al. [60] (1994, over 20-mth period)	$N = 33$ (UHR acc. to DSM-III-R) suspiciousness/magical ideation = 21 perceptual abnormalities = 17 digressive/vague speech = 3 markedly peculiar behaviour = 4	15–26; mean: 19.0; 74% males	≤20 mth	21.2% within 20 mth	No specific antipsychotic treatment
Phillips et al. [48] *Pilot Study* (1994-not specified)	$N = 21$ (UHR acc. to DSM-III-R) participants of Yung et al. [60]	16–30 Gender not specified	24 mth	33% within 24 mth	Not specified
Yung et al. [4] (05/1995–07/1996)	$N = 20$ (UHR acc. to BPRS/CASH)	16–30 Gender not specified	≥6 mth	25% within 1 mth 40% within 6 mth	No specific antipsychotic treatment
Phillips et al. [48] *Prediction study*; Yung et al. [79] (03/1995–10/1996)	$N1 = 49$ (UHR acc. to BPRS/CASH) APS, no BLIPS = 29 BLIPS = 12 only "trait-state" = 8	15–29; mean: 19.1; 51.0% male		28.6% within 4.5 mth 40.8% within 12 mth further $n = 2$ of not entire sample after 12 mth	No neuroleptic treatment

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
McGorry et al. [76] and Phillips et al. [80] (10/1996–01/1999)	N1 = 59 (UHR acc. to BPRS/CASH) N2 = 33 (UHR acc. to BPRS/CASH but refusing study participation)	14–28; N1: mean 20; 58% male. N2: mean: 20; 42% male	approx. 6 and 12 mth and, of N1, 3–4 years	36% within 6 and 12 mth (N1, NBI); 12.1% within 6 mth (N2) 18.2% within 12 mth (N2) 10% within 6 mth (N1, Risperidone) 19% within 12 mth (N1, Risp. plus NBI) 41.2% within 3–4 years (N1, NBI; $n = 17$; 11 drop-outs) 45.8% within 3–4 years (N1, Risperidone plus NBI; $n = 24$; 7 drop-outs)	n1 = 28: needs-based intervene-tion (NBI) only N2: NBI n1 = 31: 1–2 mg/d Risperidone for 6 mth followed by NBI
Yung et al. [73] (03/1995–01/1999)	$N = 104$ (UHR acc. to BPRS/CASH) APS, no BLIPS = 55 BLIPS = 29 only "trait-state" = 20 incl. participants of earlier studies	14–28; mean:19.4; 49% male	≥6 mth	27.9% within 6 mth 7.1% within 6–12 mth ($n = 98$; 6 drop-outs) further $n = 5$ of not entire sample after 12 mth	No neuroleptic treatment

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Yung et al. [64] (not specified for N2, N3)	N1 = 49 (UHR acc. to BPRS/CASH; same participants as in [48, 79]) N2 = 43 (UHR acc. to CAARMS) N3 = 107 (no-UHR acc. to CAARMS)	N2: 15–24	6 mth	11.6% within 6 mth (N2) 0.9% within 6 mth (N3)	Not specified
Yung et al. [81] (04/1995–08/2000)	*N* = 142 (UHR acc. to CAARMS) only participants of 3 previous PACE research studies	mean: 19.3	5 years	35.9% within 5 years	Not specified
Yung et al. [73] and Yung et al. [74] (04/2003–10/2003)	N1 = 119 (UHR acc. to CAARMS) N2 = 173 (no-UHR acc. to CAARMS)	15–24; mean: 18.1 49% male	6 and 24 mth	10.1% within 6 mth (N1) 16.0% within 24 mth (N1) 0.6% within 6 mth (N2) 1.2% within 6 mth (N2)	Treatment not recorded

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Nelson et al. [72] (1994–2006)	$N = 411$ (UHR acc. to different operationalizations; Table 9.2) only participants of previous PACE research studies	not specified	5–15 years note: follow-up period of 2005 and 2006 samples not specified	17.1% within 1 year 20.9% within 2 years 25.0% within 3 years 29.3% within ≥5 years significantly higher transition rate in patients recruited between 1994 and 2000 than of those recruited between 2001 and 2006	Not specified in abstract
Studies using CAARMS/PACE criteria					
Carr et al. [82] (1997-not specified)	$N = 23$ (UHR acc. to BPRS/CASH)	total UHR-sample of $N = 60$: mean:17.6; 61.7% male	4–34 mth	9% within an average period of 14.6 mth	No neuroleptic treatment
Mason et al. [83] (1997–2002)	$N = 74$ (UHR acc. to CAARMS) APS, no BLIPS = 38 BLIPS = 23 only "trait-state" = 13 incl. participants of Carr et al. [82]	13–28; mean: 17.3; 52.7% male	≥12 mth; mean: 26 mth	50.0% within a mean observation period of 26 mth 55.3% with APS, no BLIPS 60.9% with BLIPS 15.4% with only "trait-state"	No neuroleptic treatment
Broome et al. [84] (not specified; 30 mth)	$N = 58$ (UHR acc. to CAARMS) APS, no BLIPS = 45 BLIPS = 12 only "trait-state" = 1	14–35; mean: 24.1; 65.5% male	≥6 mth	11.3% within unspecified observation period ($n = 53$)	Various treatments incl. neuroleptic medication

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Kéri et al. [85] (not specified in abstract)	$N = 42$ (UHR acc. to PACE; assessment not specified in abstract)	not specified in abstract	12 mth	7.1% within 6 and 12 mth	Low-dose neuroleptic treatment plus supportive therapy for 6 mth followed by 6-mth monitoring
Lam et al. [77] (06/2002–04/2003)	$N = 62$ (UHR acc. to CAARMS) APS, no BLIPS = 46 BLIPS = 12 only "trait-state" = 4	9–25; mean: 16.2; 58.1% male	6 mth	25.8% within 3 mth 29.0% within 6 mth 32.6% within 6 mth (APS, no BLIPS) 25.0% within 6 mth (BLIPS) 0% within 6 mth (only "trait-state")	NBI, no neuroleptic treatment
Miyakoshi et al. [78] (not specified)	$N = 33$ (UHR acc. to CAARMS)	14–35; 69.7% male	6 mth	12.1% within 12 mth 15.0% within 12 mth ($n =$ 20; antipsychotic-naïve)	Various treatments incl. neuroleptic medication
Studies using SIPS/COPS criteria					
[a]Miller et al. [69] (not specified)	$N = 10$ (UHR acc. to SIPS) participants of McGlashan et al. [86]	not specified	not specified	30% within an unspecified observation period	Olanzapine vs. placebo
[a]Miller et al. [70] (01/1998–06/2000)	N1 = 13 (UHR acc. to SIPS) APS, no BLIPS = 12 BLIPS = 1 N2 = 16 (no-UHR acc. to SIPS)	mean: 17.8; 66% male	12 mth	46% within 6 mth (N1) 54% within 12 mth (N1) 0% within 12 mth (N2)	Not specified

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
[a]McGlashan et al. [86] (01/1998–07/2001)	$N = 60$ (UHR acc. to SIPS) APS, no BLIPS = 57 BLIPS = 0 only "trait-state" = 3	12–36; mean: 17.8; 65% male	24 mth	26.7% within 12 mth 29.4% within 13–24 mth ($n = 17$) 37.9% within 12 mth (placebo) 25.0% within 13–24 mth ($n = 8$; placebo) 16.1% within 12 mth (Olanzapine) 33.3% within 13–24 mth ($n = 9$; Olanza.)	PRIME clinical trial: $n = 31$: 5–15 mg/d Olanzapine vs. $n = 29$: placebo Each for 12 mth followed by no treatment for 12 mth
Lemos et al. [87] (not specified)	$N = 30$ (UHR acc. to SIPS)	15–31 mean: 21.7; 56.7% male	12 mth	incidence rate of 26.7% within 12 mth ($n = 22$)	Cognitive- behavioural therapy and drug treatment
[a]Kristensen and Cadenhead [88] (2000–2005)	$N = 48$ (UHR acc. to SIPS)	12–30; mean: 18.6; 54.2% male	12 mth	12.5% within 12 mth	Various treatments incl. neuroleptic medication
[a]Pinkham et al. [89] (not specified)	$N = 19$ (UHR acc. to SIPS) APS, no BLIPS = 17 BLIPS = 2	mean: 21.7; 32% male	not specified	26% within a median time to conversion of 12 mth	Neuroleptic treatment possible

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Cannon et al. [90] (1998–2005)	$N = 291$ (UHR acc. to SIPS) APS, no BLIPS = 282 BLIPS = 7 only "trait-state" = 2 NAPLS: pooled data from 8 independently conceived research projects [107]	mean: 18.1; 58.4% male	6–30 mth	12.7% within 6 mth, 21.7% within 12 mth, 26.8% within 18 mth, 32.6% within 24 mth, 35.3% within 30 mth % adjusted at follow-ups beyond month 6 for not reported drop-outs	Various treatments incl. neuroleptic medication
Lemos-Giráldez et al. [91] (2002-not specified)	$N = 61$ (UHR acc. to SIPS) APS, no BLIPS = 52 BLIPS = 3 only "trait-state" = 6 incl. participants of Lemos et al., 2006	17–31; mean: 21.7; 65.6% male	1 and 3 years	18.0% within 12 mth ($n = 45$), 22.9% within 36 mth ($n = 27$)	Cognitive- behavioural therapy and drug treatment
Simon and Umbricht [92] (not specified)	$N = 72$ (UHR acc. to SIPS) APS, no BLIPS = 67 BLIPS = 3 only "trait-state" = 2	14–40; mean: 20.3; 59.7% male	12 mth	14.3% within 12 mth ($n = 49$; 23 drop-outs) 59.2% remission from UHR status 26.5% maintenance of UHR status	Various treatments incl. neuroleptic medication

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Kwon et al. [93] (11/2004–08/2009)	$N = 69$ (UHR acc. to SIPS and/or CAARMS) APS, no BLIPS = 61 BLIPS = 1 only "trait-state" = 7	15–35; mean: 21.2; 60.9% male	mean: 16 mth	24.1% within a mean time to conversion of 1.3 years ($n = 54$; 13 drop-outs)	Antipsychotic and/or antidepressive pharmacological treatment
Studies using a different UHR/UHR-like operationalization					
Morrison et al. [65] (2000–2002)	$N = 23$ (UHR acc. to PANSS)	16–36	≥6 mth	17.4% within 6 mth (all APS) $n = 1$ within 6–12 mth	Cognitive therapy (CT) or treatment as usual (TAU); neuroleptic medication possible after baseline
[a]Cornblatt et al. [94] (1998–2001)	$N = 62$ (CHR acc. to SIPS) only attenuated negative symptoms = 20 ($n = 14$) APS = 42 ($n = 34$)	18–22; mean: 16.4; 71% male	≥6 mth	18.8% within a mean time to conversion of approximately 1 year ($n = 48$; 14 with ≤6-mth follow-up) 0% with attenuated negative symptoms 26.5% with APS	Various treatments incl. neuroleptic medication

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Morrison et al. [95, 66] (2000-not specified)	$N = 58$ (UHR acc. to PANSS) APS, no BLIPS = 48 BLIPS = 6 only "trait-state" = 4 incl. participants of Morrison et al. [65]	16–36; mean: 22; 70% male	12 and 36 mth	12.0% within 6 mth (– = 50; 8 drop-outs) 25.0% within 12 mth ($n = 32$; 26 drop-outs) 52% within 36 mth ($n = 27$; 31 drop-outs) 21.1% within 6 mth ($n = 19$; TAU; 4 drop-outs) 37.5% within 12 mth ($n = 16$; TAU; 7 drop-outs) 70% within 36 mth ($n = 10$; TAU; 13 drop-outs) 6.5% within 6 mth ($n = 31$; CT; 4 drop-outs) 7.7% within 12 mth ($n = 26$; CT; 9 drop-outs) 41% within 36 mth ($n = 17$; CT; 18 drop-outs)	$n = 35$: cognitive therapy (CT) vs. $n = 23$: treatment as usual (TAU) for 6 mth followed by 6-mth monitoring; neuroleptic medication possible after baseline
Nordentoft et al. [96] (01/1998–12/2000)	$N = 79$ (ICD-10 Schizotypal Disorder)	18–45; mean: 24.9; 67.1% male	24 mth	19.4% within 12 mth ($n = 67$; 12 drop-outs) 35.4% within 24 mth ($n = 65$; 14 drop-outs)	Assertive community treatment ($n = 42$) or standard treatment ($n = 37$)

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
[a]Lencz et al. [97] (01/1998–07/2001)	$N = 38$ (only APS acc. to SIPS)	mean: 16.5; 58% male	6–68 mth	36.4% within a mean time to conversion of 22 mth (6–68; $n = 33$; 5 drop-outs)	Various treatments incl. neuroleptic medication
[a]Cornblatt et al. [98] (01/1998–06/2005)	$N = 48$ (only APS acc. to SIPS) incl. participants of Cornblatt et al. [94] and Lencz et al. [97]	12–18 (or, in exceptional cases, 22); 60.4% male	2–88 mth; mean: 30.5 mth	25.9% within 2–66 mth 1 within 6 mth, 2 within 7–12 mth, 6 within 13–24 mth, 1 within 25–36 mth and 1 in 66th mth	Neuroleptic and/or antidepressive medication
Riecher-Rössler et al. [99, 100] (03/2000–02/2003)	$N = 58$ (FEPSY criteria; $n = 50$; 8 drop-outs)	≥18; mean: 26; 58.6% male	2–5 years	14.0% within 6 mth 10.0% within 6–12 mth 2.0% within 12–24 mth 32.0% within 2–5 years (of all $n = 50$)	No neuroleptic treatment
[a]Mittal et al. [101] (not specified)	$N = 40$ (DSM-IV Schizotypal Personality Disorder)	11–18; mean: 14.2; 70.0% male	3 years	25.0% within 36 mth	Various treatments incl. neuroleptic medication
Amminger et al. [67] (04/2004–05/2006)	$N = 81$ (UHR acc. to PANSS) APS, no BLIPS = 44 BLIPS = 35 only "trait-state" = 2	13–25; mean: 16; 33.3% male	12 mth	17.1% within 12 mth ($n = 76$; 5 drop-outs) 28.9% within 12 mth ($n = 38$; 2 drop-outs; placebo) 5.3% within 12 mth ($n = 38$; 3 drop-outs; ω-3 PUFA)	$n = 41$: 1.2 g/d ω-3 PUFA vs. $n = 40$: placebo each for 12 weeks followed by 40-week monitoring

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Studies using basic symptom criteria (COPER and/or COGDIS)					
Klosterkötter et al. [102] (1987–1991)	$N = 110$ ($\geq$1 basic symptom acc. to BSABS, i.e., irrespective of recency and frequency of basic symptoms) COPER = 106 COGDIS = 67 $N = 50$ (no basic symptom)	15–54; mean: 28.8; 53.6% male	mean: 9.6 years	70.0% within a mean time to conversion of 1.9 years (1–13 yrs) 19.8% within 12 mth (COPER) 36.8% within 24 mth (COPER) 50.0% within 36 mth (COPER) 65.1% within >36 mth (COPER) 23.9% within 12 mth (COGDIS) 46.3% within 24 mth (COGDIS) 61.2% within 36 mth (COGDIS) 79.1% within >36 mth (COGDIS) 4.0% within no basic symptom group	Various treatments
Schultze-Lutter et al. [103]; updated by first author (2000–2003)	$N = 146$ (COPER acc. to SPI-A) COGDIS = 124	16–39; mean: 24.4; 69.2% male	$\leq$48 mth	30.6% within 12 mth ($n = 124$; 22 drop-outs) 45.5% within 24 mth ($n = 110$; 36 drop-outs) 59.6% within 36 mth ($n = 89$; 57 drop-outs) 86.2% within 48 mth ($n = 65$; 81 drop-outs) 31.4% within 12 mth ($n = 105$; COGDIS; 19 drop-outs) 46.2% within 24 mth ($n = 93$; COGDIS; 31 drop-outs) 60.8% within 36 mth ($n = 74$; COGDIS; 50 drop-outs) 87.3% within 48 mth ($n = 55$; COGDIS; 69 drop-outs)	Various treatments incl. neuroleptic medication

Table 9.4 (continued)

Study (recruitment period)	Sample	Age (in yrs) gender	Follow-up period	Transition rate	Treatment
Studies using UHR and basic symptom criteria (COPER and/or COGDIS)					
Koutsouleris et al. [104] (not specified)	$N = 45$ (EIPS, LIPS[b]) early = 20 late = 25	mean: 25.1; 62.2% male	≤48 mth	45.5% within a mean time to conversion of 6 (2–26) ($n = 33$)	Not specified
Velthorst et al. [105] (not specified)	$N = 73$ (UHR acc. to SIPS and COGDIS acc. to SPI-A)	mean: 19.2; 64.4% male	36 mth	27.7% within 36 mth ($n = 65$; 8 drop-outs)	Various treatments incl. neuroleptic medication
Ruhrmann et al. [106] (08/2002–04/2006)	$N = 183$ (UHR acc. to SIPS and COGDIS acc. to SPI-A) incl. approx. 50 participants of Velthorst et al. [105]	16–35; mean: 23.6; 54.1% male	18 mth	20.2% within 18 mth	Various treatments incl. neuroleptic medication

[a]included in NAPLS [90, 107].
[b]EIPS: COPER and/or "trait-state" criterion of the UHR criteria in absence of both APS and BLIPS; LIPS: APS and/or BLIPS.

1. CHR-negative: attenuated negative symptoms, i.e., at least 1 negative syndrome item of the SIPS with a score of 3–5
2. CHR-positive: APS according to COPS (Table 9.3); additional differentiation between moderate APS (sum score of all SIPS positive syndrome items of 9 at most) and severe APS (sum score of all SIPS positive syndrome items of at least 10)
3. "schizophrenia-like psychosis" (SLP): at least any 1 SIPS positive syndrome item with a score of 6 but not meeting DSM-IV criteria of Schizophrenia, e.g., BLIPS (Table 9.3), Psychosis NOS and Brief Psychotic Episode.

It was hypothesised that Schizophrenia would rather regularly develop from CHR-negative via CHR-positive (APS) and SLP. In an observational study of the first 48 RAP clients with at least 6-month available follow-up, this developmental model was supported: 1 of 14 subjects of the CHR-negative group developed moderate APS, 1 of the 19 subjects with moderate APS developed severe APS and another 1 even progressed to frank psychosis after having developed severe APS; a third developed psychosis from moderate APS without developing detectable severe APS prior to it. Further, altogether 7 of the 15 subjects with severe APS developed psychosis within an average 1-year period [94] (Table 9.4). In addition, in a sample of 26 SLP-subjects (12–22 years, mean: 16.2; 66% male) with a follow-up of at least 6 and 23 months on average, a transition rate to Schizophrenia or Schizoaffective Disorder of 27% showed [111]. Additional 3 subjects (11.5%) developed Bipolar Disorder with Psychotic Features. The transition rate, however, fell behind expectations for this assumed highest risk group, particularly as only 2 of those not making the transition (8%) retained their SLP status, while 6 (23%) improved to CHR-positive or APS level and 10 (38%) even to CHR-negative or no-CHR symptoms level [111].

FEPSY Criteria

In the Basel "Früherkennung von Psychosen" (FEPSY) study, criteria for an at-risk mental state (ARMS) following the UHR criteria [4] and results from the Age-Beginning-Course study [36] were defined according to the BPRS and distinguish APS, BLIPS, genetic risk and non-genetic risk groups [99, 100] (Table 9.3). Compared to the BPRS-based definition of the PACE group [4] (Table 9.3), not only the additional risk factors but also the definitions of APS and BLIPS differ. In the FEPSY study, these mainly require a minimum score on the respective BPRS scales that is 1 point higher than required by the PACE criteria. In addition, according to the gender differences in age of onset of schizophrenia, the maximum age was set as below 25 years of age for men and below 30 years of age for women [99, 100]. In a first observation period of 2–5 years, 32% of the FEPSY at-risk persons developed a florid psychosis, 23% in the first year [100] (Table 9.4).

Basic Symptom Criteria

A different approach to an early detection of FEP is based on the basic symptom concept [112], developed by Gerd Huber in the 1960s [16, 17, 113]. Basic symptoms (BS) are subtle, subclinical, self-experienced disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action that, by definition, do not occur as the result of a general medical condition or substance use including psychopharmaca. BS can be present before the first psychotic episode, between and after psychotic episodes, even during psychotic episodes themselves. They were thought to be the most immediate psychopathological expression of the somatic disturbance underlying the development of psychosis – thus the term "basic" [112]. BS were first operationalised as a semi-structured clinical interview in the "Bonn Scale for the Assessment of Basic Symptoms" (BSABS) [114]. Shorter versions for adults and children and adolescents, respectively, i.e., the "Schizophrenia Proneness Instrument, Adult version" (SPI-A) [115] and "Schizophrenia Proneness Instrument, Child and Youth version" (SPI-CY) [116], were later developed from dimensional analyses [117, 118]. While the BSABS only allows a rating of presence, SPI-A and SPI-CY also allow severity ratings according to the maximum frequency of occurrence within the past 3 months.

BS are phenomenologically different from mental states known to the patient from what s/he considers his/her "normal" self and thus are clearly distinguishable from subtle disturbances described as traits in those at genetic high-risk [119, 120]. In addition, BS are phenomenologically clearly distinct from APS and BLIPS as they are not necessarily observable by others as are odd thinking and speech and formal thought disorders; and unlike schizotypal perceptual disturbances and hallucinations, BS are regarded by the patient as originating in him-/herself. Further, BS do not primarily affect thought content as do magical thinking, ideas of reference, paranoid ideation, suspiciousness, delusions and *Ich-Störungen* (i.e., thought broadcasting, insertion and withdrawal and delusion of alien control). Moreover, negative symptoms in their current understanding as functional and observable deficits [121] are also clearly distinct from phenomenologically similar BS, because BS do not have to be observable to others but can remain completely in the self-perception of the patient [112, 115, 116].

BS were first examined for their Schizophrenia-predictive value in the "Cologne Early Recognition" (CER) study [102, 122]. Therein, 385 patients who were presumably in the prodromal phase of Schizophrenia were followed up on average 9.6 ($\pm$7.6) years past baseline. By this time, 49% of the former patients who agreed to follow-up ($n = 160$; 50 had not reported any BS at baseline) had meanwhile developed Schizophrenia. Only 2 of these had not reported any BS at baseline. The overall presence/absence of at least any 1 BS correctly predicted presence/absence of subsequent transition to Schizophrenia in 78.1% [102, 122].

From further analyses, 2 partially overlapping BS criteria for defining an ARMS of psychosis, primarily Schizophrenia, were developed [122]. The first criterion that consists of 10 cognitive-perceptive BS and is abbreviated as COPER (Table 9.5)

Table 9.5 Basic symptom based definitions of an at-risk mental state of psychosis and their predictive accuracy in the CER study [3, 12]

Criterion	Predictive accuracy[a]
Cognitive-perceptive basic symptoms (COPER):	
➲ at least any 1 of the following 10 BS with a SPI-A/SPI-CY score of ≥3 within the last 3 months and first occurrence ≥12 months ago:	Sensitivity = 0.87 Specificity = 0.54 Positive predictive value = 0.65 Negative predictive value = 0.82 Positive likelihood ratio = 1.89 Negative likelihood ratio = 0.24 Odds ratio = 7.86 False positives = 23.1% False negatives = 6.3%
• Thought interference	
• Thought perseveration	
• Thought pressure	
• Thought blockages	
• Disturbance of receptive speech	
• Decreased ability to discriminate between ideas and perception, fantasy and true memories	
• Unstable ideas of reference	
• Derealisation	
• Visual perception disturbances (excl. blurred vision and hypersensitivity to light)	
• Acoustic perception disturbances (excl. hypersensitivity to sounds/noises)	
Cognitive disturbances (COGDIS)	
➲ At least any 2 of the following 9 BS with a SPI-A/SPI-CY score of ≥ 3 within the last 3 months:	Sensitivity = 0.67 Specificity = 0.83 Positive predictive value = 0.79 Negative predictive value = 0.72 Positive likelihood ratio = 3.94 Negative likelihood ratio = 0.40 Odds ratio = 9.91 False positives = 8.8% False negatives = 16.3%
• Inability to divide attention	
• Thought interference	
• Thought pressure	
• Thought blockages	
• Disturbance of receptive speech	
• Disturbance of expressive speech	
• Unstable ideas of reference	
• Disturbances of abstract thinking	
• Captivation of attention by details of the visual field	

[a]for BSABS-rating of presence, irrespective of recency and frequency.

was based on findings on the predictive accuracy of single BS [102, 122]. The second was based on a methodological study of the same data in that a cluster of 9 cognitive BS had repeatedly been selected as the most predictive of all 7 examined clusters [123]. This cluster was called "Cognitive Disturbances" (COGDIS; Table 9.5) [122, 123].

In the matter of general predictive accuracy, the 2 criteria slightly differed in the CER study as COGDIS tended to be more conservative than COPER, i.e., to perform better in ruling in subsequent Schizophrenia at the cost of performing worse in ruling it out (Table 9.5 [122]). The transition rate throughout the average follow-up period of roughly 10 years was 65% for COPER and even 79% for COGDIS with the majority of transitions occurring within the first 3 years past baseline (Table 9.4).

In a second prospective study conducted with the SPI-A and with a systematic follow-up of 24 months [103] (Table 9.5), altogether 38% of the initially included 146 at-risk subjects according to COPER developed a frank psychosis, mainly Schizophrenia, within 12.3 (±10.4) months on average (1–48; Median = 9). Thus, the positive results of the CER study were confirmed for the first years past baseline. This included the fact that, again, COGDIS appeared to be more specific but less sensitive than COPER (Table 9.4).

Integrative Approaches

Early and Late Initial Prodromal State Criteria

Within the early detection and intervention projects of the German Research Network on Schizophrenia [124], the BS and UHR approach were combined to define an "early initial prodromal state" (EIPS) and a "late initial prodromal state" (LIPS). The EIPS criterion attempts to define an at-risk group at incipient but not imminent or immediate risk of psychosis and is defined alternatively by COPER and the "trait-state" criterion of the UHR criteria (Tables 9.3 and 9.5), with the peculiarity that the risk factor "Schizotypal Personality Disorder" was exchanged for "obstetric complications". In line with the initial description of UHR criteria as describing a most imminent risk of transition within 12 month, the LIPS criterion attempts to identify people at an imminent risk of psychosis and, alternatively, includes APS and BLIPS [125]. It was hypothesised that, following unspecific signs of the beginning psychotic disorder, EIPS would precede LIPS prior to the onset of the full-blown psychotic disorder [124–127].

Taking COPER as a measure for EIPS and APS as a measure for LIPS, this 2-stage ARMS model was retrospectively examined in a sample of 128 FEP inpatients and broadly confirmed [37]. Further, it showed that both COPER and APS were frequently reported for their prodromal phase by FEP inpatients, thus showing excellent sensitivities for both criteria of 0.80 and 0.74, respectively, and even of 0.87 for either one. This indicates that, in terms of sensitivity, both criteria would be suitable for the early detection of psychosis – even in the majority of FEP patients who do not seek help for mental problems prior to the onset of frank psychosis and accounted for 70% of the sample [37, 128, 129].

UHR-BS Criteria

UHR and BS criteria were first combined alternatively to define an ARMS in the Cologne early detection and intervention centre (FETZ) where they showed a large overlap with UHR criteria as assessed with the SIPS [108]. Thereby, UHR criteria rarely occurred without COPER and/or COGDIS, whereas BS criteria occurred without UHR criteria in about 14% of at-risk patients.

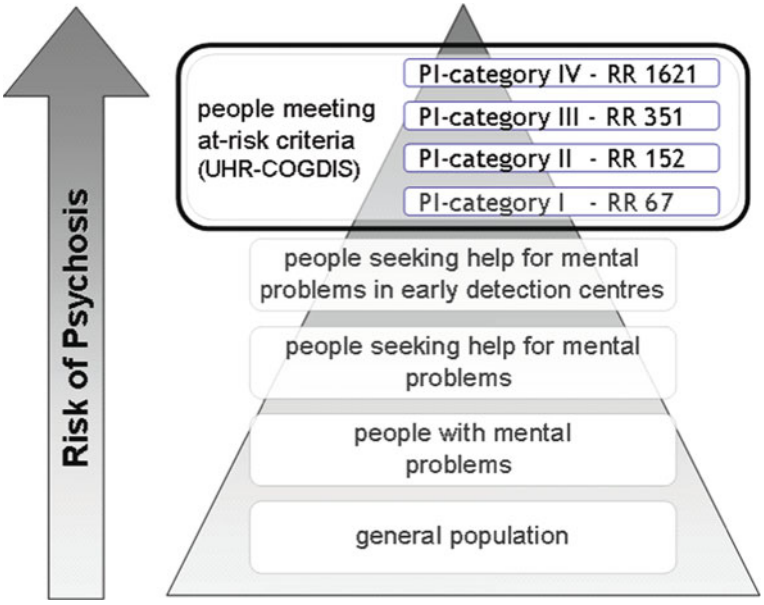

Fig. 9.1 The risk stratification strategy, exemplified by the EPOS results [106]. PI-category: risk class according to the prognostic score RR: relative risk for transition within 18 months related to the 12-month incidence rate in a UK general population sample of 0.035% for any psychosis [172]

The first study explicitly relying on BS and UHR criteria as alternative intake criteria was the naturalistic observational "European Prediction of Psychosis Study" (EPOS) [130]. Therein, the COPS, i.e., the UHR definition of the SIPS, and COGDIS were used to predict a transition within 18 months past baseline [106, 131]. It showed that the concurrent presence of COGDIS and UHR criteria at baseline was most sensitive (0.68) and most frequent in 1 of 4 risk groups that exhibited the highest risk of transition (Fig. 9.1; see also below), thus predicting transition to psychosis within 18 months better than the presence of COGDIS or UHR alone [106].

Exclusion Criteria

Early detection of FEP studies, naturally, have agreed in excluding current or past psychotic disorders or episodes of more than 1 week, exceptionally even of more than a few hours [96]; and most even state so explicitly (Table 9.6). Further, they generally have agreed on excluding general medical conditions from that relevant symptoms might arise. Other exclusion criteria – not always explicitly mentioned – were related to the assessability of at-risk and other symptoms and mainly involved

Table 9.6 Transition and exclusion criteria of early detection studies

Reference	Transition criteria	Exclusion criteria
Studies conducted at the personal assessment and crisis evaluation (PACE) clinic		
Yung et al. [60] and Phillips et al. [48] *Pilot Study, Prediction study*	Presence of at least 1 of the following symptoms: • ≥3 on Hallucinations scale of the BPRS • ≥4 on Unusual thought content scale of BPRS, or ≥3 (strong conviction) on the CASH rating scale for delusions • ≥4 on Formal Thought Disorder scale of BPRS **Frequency: At least once a day** Duration: Longer than 1 week	• Previous psychotic episode of longer than 1 week (treated or untreated) • Organic brain disorder
McGorry et al. [76]	Presence of at least 1 of the following symptoms: • ≥3 on Hallucinations scale of the BPRS • ≥4 on Unusual thought content scale of BPRS, or ≥3 (strong conviction) on the CASH rating scale for delusions • ≥4 on Formal Thought Disorder scale of BPRS Duration: Longer than 1 week	• Previous psychotic or manic episode (incl. substance – induced psychotic disorder) • Previous treatment with an antipsychotic or mood stabilizing agent • IQ < 70 • Lack of adequate English
Yung et al. [4]	Presence of at least 1 of the following symptoms: • **≥2 on hallucinations scale of the BPRS** • ≥4 on unusual thought content scale of BPRS, or **≥4 on the Suspiciousness** scale of the BPRS, or ≥3 (strong conviction) on the CASH rating scale for delusions • ≥4 on formal thought disorder scale of BPRS **Frequency: more than twice a week** Duration: longer than 1 week	• Previous psychotic episode of longer than 1 week (treated or untreated) • Previous or current treatment with neuroleptic given in sufficient time and at a dose that would lead to a clinical response in the average first-episode psychosis patient, defined as 5 mg haloperidol (or equivalent) for 3 weeks • Lack of adequate English

Table 9.6 (continued)

Reference	Transition criteria	Exclusion criteria
Yung et al. [79, 75, 64, 81] and Lam et al. [77]	Presence of at least 1 of the following symptoms: • **≥3 on hallucinations scale of the BPRS** • ≥4 on unusual thought content scale of BPRS, or ≥3 (strong conviction) on the CASH rating scale for delusions • ≥4 on formal thought disorder scale of BPRS Frequency: several times a week Duration: longer than 1 week	Previous psychotic episode for longer than 1 week (treated or untreated) Organic brain disorder Intellectual disability Lack of adequate English
Yung et al. CAARMS. Comprehensive Assessment of At Risk Mental States, Version December, 2006, unpublished, [64, 74] and Nelson et al. [72]	Presence of at least 1 psychotic symptom according to the respective **subscales of the CAARMS**: • 6 on unusual thought content subscale, • 6 on non-bizarre ideas, • ≥5 on perceptual abnormalities subscale, • 6 on disorganised speech Frequency scale score of ≥4 Duration: longer than 1 week	• Presence of psychotic disorder • Known organic cause of presentation • IQ < 70 • Lack of adequate English
Studies using CAARMS/PACE criteria		
Carr et al. [82]	Presence of any psychotic symptom Duration: more than 1 week	Not specified
Mason et al. [83]	Any psychotic disorder according to the diagnostic interview for psychosis	Not specified
Miyakoshi et al. [78]	Presence of at least 1 psychotic symptom according to the respective subscales of the CAARMS: • 6 on unusual thought content subscale, • 6 on non-bizarre ideas, • ≥5 on perceptual abnormalities subscale, • 6 on disorganised speech Frequency scale score of ≥4[a] Duration: longer than 1 week	• Previous history of apparent psychotic or maniac episode (incl. drug induced psychosis) • Personality disorder with severe acting-out behaviour • Mental retardation

Table 9.6 (continued)

Reference	Transition criteria	Exclusion criteria
Studies using SIPS/COPS criteria		
Miller et al. [69, 70]; McGlashan et al. [86]; Lemos et al. [87]; Cannon et al. [90]; Pinkham et al. [89]	Presence of at least 1 psychotic symptom according to the respective subscales of the SIPS: • 6 on unusual thought content/delusional ideas, • 6 on grandiosity, • 6 on suspiciousness/persecutory ideas, • 6 on perceptual abnormalities/hallucinations • 6 on disorganized communication Frequency: ≥1 h/day Duration: ≥4 days per week during past month OR Particular impact: seriously disorganizing or dangerous	• Past or current psychotic disorder • Prodromal symptoms sequelae of drug or alcohol use • Treatable psychiatric disorder that could account for the prodromal symptoms • Suicidal or homicidal
Kristensen and Cadenhead [88]	DSM-IV criteria	• History of a DSM-IV psychotic disorder • Neurological disorder or a serious head injury • Subjects meeting DSM-IV criteria for drug or alcohol dependence at the time of initial evaluation • Use of illicit drugs (with the exception of cannabis) within 30 days of the initial assessment
Lemos-Giráldez et al. [91]	DSM-IV-RT criteria	• Presence of neurological disorder • IQ < 70
Simon and Umbricht [92]	Not specified	• Present or a past psychotic episode • Traumatic brain injury, epilepsy or other known neurological disorder • IQ < 70 • Age below 14 years
Kwon et al. [93]	DSM-IV criteria	Not specified

Table 9.6 (continued)

Reference	Transition criteria	Exclusion criteria
Studies using a different UHR/UHR-like operationalization		
Nordentoft et al. [96]	ICD-10 diagnosis of a psychotic disorder within the F2 spectrum: F20, F22, F23, F25 or F29	• Psychotic symptoms lasting more than few hours
Morrison et al. [65, 66]	Presence of at least 1 psychotic symptom according to the respective item of the PANSS: • ≥4 on hallucinations (P3), • ≥4 on delusions (P1, P5) • ≥5 on persecutory Ideas (P6) • ≥5 on conceptual disorganisation (P2) Frequency: several times a week Duration: longer than 1 week	• Current or past receipt of antipsychotic medication
Lencz et al. [97] and Cornblatt et al. [98]	Presence of at least 1 psychotic symptom according to the respective subscales of the SIPS: • 6 on unusual thought content/delusional ideas, • 6 on grandiosity, • 6 on suspiciousness/persecutory ideas, • 6 on perceptual abnormalities/hallucinations • 6 on disorganized communication Duration: minimum 2 weeks	Presence of at least 1 psychotic symptom according to the respective subscales of the SIPS at baseline: • 6 on Unusual Thought Content/delusional ideas, • 6 on Grandiosity, • 6 on Suspiciousness/Persecutory Ideas, • 6 on Perceptual Abnormalities/Hallucinations • 6 on Disorganized Communication
Riecher-Rössler et al. [99, 100]	Presence of at least 1 of the following symptoms according to the respective subscales of the BPRS: • ≥4 on hallucinations OR visual illusions >2/week or with functional impairment • ≥5 on unusual thought content OR some areas of functioning disrupted • ≥5 on suspiciousness with partly delusional conviction • ≥5 on conceptual disorganization Frequency: several times a week Duration: longer than 1 week	• Previous episode of schizophrenic psychosis (treated with major tranquillisers for >3 weeks) • Psychosis due to organic reasons, substance abuse, or psychotic symptomatology within clearly diagnosed affective psychosis or borderline personality disorder • IQ > 70 • Insufficient knowledge of German • Age below 18 years

Table 9.6 (continued)

Reference	Transition criteria	Exclusion criteria
Mittal et al. [101]	Presence of at least 1 psychotic symptom according to the respective subscales of the SIPS: • 6 on unusual thought content/delusional ideas, • 6 on grandiosity, • 6 on suspiciousness/persecutory ideas, • 6 on perceptual abnormalities/hallucinations • 6 on disorganized communication	• Neurological disorder • Current Axis I disorder • Substance abuse/addiction • Mental Retardation • Other disruptive behaviour disorders
Amminger et al. [67]	Presence of at least 1 psychotic symptom according to the respective item of the PANSS: • ≥4 on hallucinations (P3), • ≥4 on delusions (P1, P5,P6) • ≥5 on conceptual disorganisation (P2) Duration: longer than 1 week	• Previous psychotic disorder (incl. substance-induced psychotic disorder) or manic episode • Neurological disorders or structural brain changes • Current DSM-IV diagnosis of substance dependence (except cannabis dependence) • Previous treatment with an antipsychotic or mood-stabilizing agent of >1 week • Intake of >3 supplements within 8 weeks of being included in the trial • IQ < 70 • Acute suicidal or aggressive behaviour • Laboratory values more than 10% outside the normal range for transaminases, thyroid hormones, C-reactive protein, or bleeding parameters • Another severe intercurrent illness that may have put the person at risk or influenced the results of the trial or affected their ability to take part in the trial

Table 9.6 (continued)

Reference	Transition criteria	Exclusion criteria
Studies using basic symptom criteria (COPER and/or COGDIS)		
Klosterkötter et al. [102]	DSM-IV criteria of schizophrenia	• DSM-IV criteria of schizophrenia, delusional or psychotic disorder not elsewhere classified • Organic mental disorder • Substance-induced disorder • Mental retardation • ≥50 years at first examination
Schultze-Lutter et al. [103]	Presence of at least 1 psychotic symptom according to the respective item of the PANSS: • ≥4 on hallucinations (P3), • ≥4 on delusions (P1, P5) • ≥4 for paranoid ideas and ≥5 for increased mistrust without paranoid ideation (P6) • ≥4 on conceptual disorganisation (P2) Duration: more than 7 days	• Current or past psychotic disorder • Diagnosis of delirium, dementia amnestic; other neurological cognitive disorders; psychiatric disorders due to somatic factor or diseases of the central nervous system • Any substance-induced disorder • Alcohol or drug abuse or dependence within the last 3 months • Mental retardation
Studies using UHR and basic symptoms criteria (COPER and/or COGDIS)		
Koutsouleris et al. [104]	According to Yung et al. [4]	• Past or present diagnosis of schizophrenia spectrum and bipolar disorders • Past or present inflammatory, traumatic, or epileptic disease of the central nervous system or psychiatric disorders due to a somatic factor, delirium, dementia, amnestic or other cognitive disorders • Alcohol or drug abuse within 3 months before examination • Any previous treatment with antipsychotics • Mental retardation

Table 9.6 (continued)

Reference	Transition criteria	Exclusion criteria
Velthorst et al. [105]	Presence of at least 1 psychotic symptom according to the respective item of the PANSS: • ≥4 on hallucinations (P3), • ≥4 on delusions (P1, P5, P6) • ≥4 on conceptual disorganisation (P2) Duration: longer than 1 week	• Presence or history of a psychotic disorder for more than 1 week • Symptoms due to a known general medical disorder or intoxication with drugs or alcohol • Other drugs than cannabis or if cannabis caused the UHR • IQ < 85
Ruhrmann et al. [106] (08/2002–04/2006)	Presence of at least 1 psychotic symptom according to the respective subscales of the SIPS: • 6 on unusual thought content/delusional ideas, • 6 on grandiosity, • 6 on suspiciousness/persecutory ideas, • 6 on perceptual abnormalities/hallucinations • 6 on disorganized communication Duration: longer than 1 week	• Psychotic episode for more than 1 week (i.e., fulfilling DSM-IV criteria of a brief psychotic episode not only for more than 1 day but for more than 7 days, assessed with the Structured Clinical Interview for DSM-IV) • Having symptoms relevant for inclusion arising from a known general medical disorder • Drugs or alcohol dependency • Verbal IQ < 85

[a]For CAARMS frequency ratings see Table 9.2.

insufficient knowledge of the respective language and/or an IQ below a certain threshold that varied between 85, i.e., borderline intellectual functioning, and 70, i.e., mental retardation (Table 9.6).

In the matter of drug use, misuse and dependency, exclusion criteria have varied greatly (Table 9.6). While some studies have considered these, when present currently or until recently and particularly if involving illicit drugs, to different degrees as an exclusion criterion [67, 69, 70, 86–90, 101–106], others have not taken them into account at all [4, 48, 56, 64–66, 72–74, 76, 77, 79, 91, 92, 96], explicitly have not excluded cannabis [67, 88] or even have incorporated the regular use of illicit drugs into ARMS criteria as one of the risk factors [99, 100] (Table 9.3, FEPSY criteria).

Similarly inconsistent has been the consideration of other psychiatric disorders (Table 9.6) that have been listed as an exclusion criterion in many studies using the SIPS, if they could fully account for the at-risk symptoms [69, 70, 86, 87, 89, 90, 101], or, in case of personality disorders, have been excluded when accompanied by severe acting-out behaviour in a Japanese study [78]. In addition, suicidality and homocidality/aggressive behaviour or disruptive behaviour have served as exclusion criteria in some studies [67, 69, 70, 86, 87, 89, 90, 101] (Table 9.6).

Moreover, some studies have excluded subjects with past or current neuroleptic – rarely also mood-stabilizing – medication at baseline [4, 104], though this has been most frequent in intervention studies [65–67, 76]. Other exclusion criteria have rarely been described and, if so, have been related to the study's aims, e.g., certain laboratory values in the ω-3 fatty acid intervention study [67].

In all, it has to be assumed that, besides differences in ARMS criteria and/or their operationalizations, differences in exclusion criteria have also added to the differences in reported transition rate.

Transition Criteria

General transition criteria of early detection studies aiming at the prediction of any affective or non-affective psychotic disorder, and not specifically of Schizophrenia [102] or schizophrenia-spectrum disorder [97, 98], almost consistently have required the presence of positive psychotic symptoms, i.e., delusion, hallucination and formal thought disorder, for more than 1 week (Table 9.6). Exceptions to this have been the transition criteria according to the SIPS, i.e., the "Presence of Psychotic Syndromes, POPS" criteria, with a minimum duration of positive symptoms of 4 days a week [69, 70, 86, 90, 97] and the transition criterion used by Mittal and colleagues [101] that has solely required the occurrence of psychotic symptoms.

While most groups have also made explicit requirements for a minimum frequency of occurrence of psychotic symptoms (Table 9.6), others have not [97, 98, 103, 105, 106] or have required that the minimum psychotic symptom severity had to be sustained throughout the crucial period defining transition [67]. The definition of symptom severity, however, has shown the greatest variance across studies because various assessments of psychotic symptoms have been used, e.g.,

the BPRS with or without the CASH, the CAARMS, the SIPS, the PANSS or the "Present State Examination, 9th version" [102, 131] (Table 9.6). But even if the same instrument for the assessment of frank psychotic symptoms was used, the required minimum cut-off score for the rating of a frank psychotic symptom has partly been incongruent between different studies: e.g., the required minimum score on the hallucination subscale of BPRS varied between 2 [4] and 3 [75] across the PACE studies, in which, moreover, the minimum BPRS scores have been generally 1 point below the respective thresholds required in the FEPSY study [99, 100] (Table 9.6). Still other studies have employed no general transition criterion but diagnostic criteria of psychotic disorders according to DSM-IV [88, 91, 93] or ICD-10 [96] or structured interviews for their assessment [83], such as the "Diagnostic Interview for Psychosis" [132].

Thus, aside from the inconsistent inclusion and exclusion criteria (see above), differences in transition criteria, too, have to be assumed to add to the differences in results of early detection studies.

Résumé of Current Early Detection

Contrary to the pessimistic view of the possibility to detect emerging FEP early, i.e., already in its prodromal state, that dominated psychiatric research and clinic for almost a century, the past 2 decades have evidenced the emergence of encouraging results with regard to the detection of persons with a substantially increased risk of developing FEP. Inconsistencies in ARMS criteria and their operationalization, in exclusion as well as transition criteria and in follow-up periods that sometimes are only reported as means, however, obstruct the comparability of results and, thereby, reliable conclusions about the amount of risk of transition to psychosis delineated by current at-risk criteria. Changes in the operationalization of intake, exclusion and transition criteria might also underlie, at least in parts, reports of declining conversion rates in recent UHR studies [72, 81]. These have mainly been reasoned to possibly result from an earlier help-seeking or referral to specialized services and, thus, an earlier and thereby potentially more effective early intervention [81, 133]. Additionally, a longer lag time to transition has been suggested as a consequence of earlier help-seeking, which, consequently, would necessitate longer follow-ups to detect similar transition rates [81, 133].

Further, other unsystematic sampling and/or referral biases such as overinclusive referral strategies and a consequential dilution of at-risk samples have been put forward as an additional or alternative explanation of declining transition rates [133]. This line of argument, however, implies that ARMS criteria are in truth less specific than indicated by early studies and that they are met by a significant proportion of persons not actually at an increased risk of developing FEP. A possibly low specificity of UHR criteria, in particular of APS and BLIPS, has indeed be argued from studies reporting a high prevalence of psychotic-like experiences in the general population and non-psychotic clinical samples alongside a low prevalence of

clinically significant psychotic symptoms [134–137]. Yet, these studies used self-report questionnaires or fully structured interviews administered by lay interviewers designed for the assessment of psychotic symptoms but not APS [135, 138–144] that are therefore most likely no valid estimation of APS. This is even more likely as even the degree to that psychotic-like experiences reflect clinically relevant psychotic symptoms has been questioned [141, 145]. Indeed, first studies of the prevalence rates of ARMS criteria indicate that these, when assessed in a clinical manner, are rather uncommon in the general population: A study of BS as assessed only for presence/absence with the BSABS in 96 adolescents from the Swiss general population [146] found 6-month prevalence rates of COPER and COGDIS symptoms in sufficient number, though potentially not sufficient frequency of occurrence, of 8 and 3%, respectively [118]. And in a pilot study on 58 subjects between 16 and 35 years of age also from the Swiss general population, none reported COPER or COGDIS symptoms in sufficient number and frequency as assessed with the SPI-A for the past 3 months, BLIPS were also never reported in the clinical telephone interview, and APS criteria according to COPS were only once fulfilled (1%) [147]. Though large epidemiological studies of the prevalence of ARMS criteria in the age-defined risk segment of the general population, assessed within a clinical interview, are still wanting, these first results give preliminary indication that ARMS criteria might not – as feared – "reflect behaviours so common among adolescents and young adults that a valid distinction between ill and nonill persons is difficult" [134, p. 841].

Yet, even if it will be proven that at-risk criteria delineate psychopathological states, with the current focus on FEP as the main outcome of interest, it will be important for future planning of service provision to characterize in long-term studies the subgroups of at-risk patients who do not transit to FEP but show other diagnostic outcomes and remain impaired and/or continue to fulfil at-risk criteria and of those who fully recover over time with or without treatmen [133].

Future Directions

Risk Enrichment and Stratification

Current ARMS criteria, though a promising starting point for an accurate early detection of FEP, still result in considerable proportions of false-positive predictions. Thus, in the search for risk enhancing factors, potential additional predictors have already been investigated in great number. Yet, only recently, longitudinal analyses of sufficiently large at-risk samples with sufficiently large subsamples of transited subjects have been available. While the body of literature for the majority of potential additional predictors is scarce or inconclusive, there is increasing evidence that deficits in psychosocial functioning and more severe APS as well as measures of verbal and working memory and of processing speed might be promising candidates for the enhancement of accuracy of prediction of transition to FEP

in at-risk samples [133, 148]. Comprehensive overviews of potential clinical and biological risk factors for psychosis in at-risk samples have recently been provided by Correll and colleagues [133] and, of neurocognitive parameters, by Pukrop and Klosterkötter [148].

Most approaches to risk enhancement using regression models and single cut-offs to improve prediction by UHR criteria, however, resulted in an unfavourable loss of sensitivity and, consequently, in an undesirable exclusion of patients below the cut-off, who might, in fact, be in an ARMS and would benefit from an early intervention [75, 90, 122, 149]. Thus, for the frequent lack of validation of findings and the loss of sensitivity, the search for additional predictors has so far not resulted in a modification of ARMS criteria, except for the introduction of a reduced psychosocial functioning as an obligate criterion of the APS and BLIPS criteria in the latest PACE/CAARMS operationalization of the UHR criteria CAARMS. Comprehensive Assessment of At Risk Mental States, Version December, 2006, unpublished (Table 9.2). It yet remains to be shown that this UHR operationalization will indeed result in a rise of transition rates and will not overly lower sensitivity by particularly excluding at-risk subjects with still sufficient coping strategies.

In somatic medicine such as oncology or pneumology [150–152], a well-established and widespread risk modeling procedure, which does not result in a loss of sensitivity, is the use of prognostic indices (PI) for a multivariate clinical staging by risk stratification. This risk stratification approach has recently been introduced into early detection research by the EPOS group [106]. They developed a clinical model based on a Cox regression equation including 6 variables (SIPS-Positive score, SIPS bizarre thinking score, SIPS sleep disturbances score, SIPS schizotypal personality disorder, highest GAF-M score in the past year and years of education). Based on the individual regression scores, a multivariate PI for further classifying the risk of transition to psychosis into 4 risk classes was suggested – each delineating a significantly increased relative risk, compared to that of the general population, rising with each class (Fig. 9.1) [106]. Thereby, the PI has not been suggested to replace initial intake criteria; rather it is meant to facilitate a better and more individualized risk estimation in the whole at-risk sample. This 4-class model was argued to significantly improve the prediction of psychosis by enabling a differentiation of the individual risk in terms of magnitude and time [106].

Such a more individualized risk estimation or clinical staging of risk – if validated in future studies – could significantly advance the development of risk-adapted inclusion criteria for future randomized preventive trials [106, 149]. All the more, because risk stratification approaches have two major advantages over risk enhancement strategies introducing additional conditions to the initial at-risk criteria: First, no matter his/her prognostic score, a patient continues to be considered “at-risk” once screened positive on the applied at-risk criteria. Thus, no loss of sensitivity occurs with this approach, in which current ARMS criteria would remain to serve as a first-step detection tool of a generally increased risk. Second, instead of a binary one-fits-all risk estimate based on current ARMS criteria, an individual PI provides a detailed definition of the patient’s risk at a given time by serving as a multivariate

second-step and change-sensitive tool for risk classification in terms of magnitude and time [106]. While in the first application of this risk stratification approach in EPOS, only certain clinical and demographic variables had been considered [106], next, it will have to be investigated, whether a multilevel model including neurocognitive, neurobiological, socio-biographical or environmental variables will increase the predictive accuracy even further. In addition, future studies will have to examine whether such models can also be applied to the prediction of psychosis within different time frames [106].

At-Risk Criteria and DSM-V

A consistent finding across the different operationalizations of UHR criteria is that APS accounted for the highest proportion of at-risk patients (Table 9.4). This was particularly pronounced in COPS [70, 86, 89–92, 112] and had led to the proposal of introducing a "Prodromal Risk Syndrome for First Psychosis" based on APS and their operationalization according to the SIPS into DSM-V[153]. By this, it had been argued, future research on the psychosis would be greatly stimulated, thereby, continuously enhancing the benefits while reducing the risks of such a prodromal diagnosis [153, 154]. This proposal, however, had been heatedly debated [118, 134, 137, 154–167]. Critics mainly argued with the high rate of false-positive predictions of 60–70% even in specialist clinics that would have to be expected to increase to up to 90% in general outpatient clinics [157, 159].

Another concern was voiced regarding the still unknown validity of current ARMS criteria in child and adolescent samples as the majority of early detection studies were conducted in adult or mixed, i.e., adult and adolescent, samples, without special examination of age or developmental effects [118]. Further, the general differential validity of such an exclusively APS-based diagnostic category has been doubted, particularly with regard to Psychosis NOS and dissociative disorders [163]. In line with this and in light of the encouraging results of BS research, it had been proposed to include COGDIS as a group of symptoms clearly distinct from diagnostically relevant symptoms of any other DSM disorder [156, 157]. Further, incorporating COGDIS would be much in line with the suggested inclusion of cognitive impairments into DSM-V criteria of schizophrenia [164, 165, 168–171] (Appendix).

In the matter of intervention, it was demanded that the inclusion of such a prodromal risk syndrome should be accompanied already by the provision of adequate treatment strategies [157]. Preventive intervention studies, mostly anti-psychotic medication and/or cognitive behavioural therapy, have already shown encouraging results on active treatment [133]. However, the lower risk for transition to psychosis compared to the control condition was not maintained in 3 of the 4 studies with available longer-term data [66, 80, 86]. Thus, first prevention studies have mainly failed to produce satisfying long-term results [133] (see also Volume III, chapter 42).

Other critics of a risk syndrome argued that, while a need for treatment in help-seeking at-risk samples was most certainly given, a related diagnostic class should not attempt to define an end-stage syndrome when, in fact, any kind of outcome was possible [160, 164, 165]. Such a diagnostic class in terms of a psychosis spectrum disorder – alike ICD-10's Schizotypal Disorder (F.21) – that could be diagnosed independently of any potentially associated risk of psychosis was first proposed by Ruhrmann and colleagues [164, 165] and preliminarily defined by APS and COGDIS. Their suggestion of an independent psychosis spectrum disorder has been seized in the latest draft of an "Attenuated Psychotic Symptoms Syndrome" (Appendix) recommended by the DSM-V work group – either for inclusion in the main DSM-V manual or in an appendix for further research. Although modelled on APS according to COPS in terms of frequency and currency (criterion B) and progression (criterion C), the suggested operationalization of APS does not follow the SIPS – or any other operationalization used so far – and makes no reference to schizotypal features originally underlying the definition of APS but, as for BLIPS, to psychotic symptoms (Appendix).

Conclusion

Over the last 15 years, the prediction and early detection of psychotic disorders has much advanced, and current ARMS criteria seem to offer an excellent starting point for an accurate risk estimation in future – at least in patient populations seeking help for mental problems in specialized early detection services or being referred to these. Yet, several questions remain:

- What ARMS criterion or combination of ARMS criteria and in what operationalization performs best in predicting transition to FEP? And within what time frame?
- Do certain ARMS criteria or their combination perform differently in predicting different types of psychosis? And can they also be used to predict other severe psychiatric disorders such as bipolar disorders?
- Can current ARMS criteria, which have mainly been studied in adult or mixed adult-adolescent samples, be transferred to children and adolescents? Or do developmental aspects need to be considered? In particular, how can newly occurred schizotypal features in adolescents that might signify the development of a Schizotypal Personality Disorder be reliably distinguished from APS signifying the development of FEP?
- What other predictors, which preferably should broadly be applicable in clinical settings, can enhance individual risk estimation?
- Can current ARMS criteria maintain their predictive accuracy in other clinical settings? And how can the reliability of the assessment of ARMS criteria that currently rely on special scales requiring rater training be ensured in these other clinical settings?

Appendix: Criteria of the Attenuated Psychotic Symptoms Syndrome Recommended by the DSM-V Development Work Group as of May-17-2010 (http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=412#)

All six of the following:

(a) Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored:

  (i) delusions
  (ii) hallucinations
  (iii) disorganized speech

(b) Frequency/Currency: symptoms meeting criterion A must be present in the past month and occur at an average frequency of at least once per week in past month
(c) Progression: symptoms meeting criterion A must have begun in or significantly worsened in the past year;
(d) Distress/Disability/Treatment seeking: symptoms meeting criterion A are sufficiently distressing and/or disabling to the patient and/or others to lead to help-seeking
(e) Symptoms meeting criterion A are not better explained by any DSM-5 diagnosis, including substance-related disorder.
(f) Clinical criteria for any DSM-V psychotic disorder have never been met

Dimensions will be assessed on a 0–4 scale cross-sectionally, with severity assessment based on past month. There are distinct psychopathological domains in psychotic illnesses (most clearly noted in schizophrenia) with distinctive patterns of treatment-response, prognostic implications, and course. The relative severity of symptoms across these domains varies across the course of illness and among patients. This is a major change that will potentially be of great clinical value and will also be of additional research utility.

	Hallucinations	Delusions	Dis-organization	Abnormal psychomotor behavior	Restricted emotional expression	Avolition	Impaired cognition	Depression	Mania
0	Not present	Not present	Not present	Not present	Not present	Not present	Not present	Not present	Not present
1	Equivocal (severity or duration not sufficient to be considered psychosis)	Equivocal (severity or duration not sufficient to be considered psychosis)	Equivocal (severity or duration not sufficient to be considered disorganization)	Equivocal (severity or duration not sufficient to be considered abnormal psychomotor behavior)	Equivocal decrease in facial expressivity, prosody, or gestures	Equivocal decrease in self-initiated behavior	Equivocal (cognitive function not clearly outside the range expected for age or SES, i.e., within 1 SD of mean)	Equivocal (some depressed mood, but insufficient symptoms, duration or severity to meet diagnostic criteria)	Equivocal (some inflated or irritable mood, but insufficient symptoms, duration, or severity to meet diagnostic criteria)
2	Present, but mild (little pressure to act upon voices, not very bothered by voices)	Present, but mild (delusions are not bizarre, or little pressure to act upon de-lusional beliefs, not very bothered by beliefs)	Present, but mild (some difficulty following speech and/or occasional bizarre behavior)	Present, but mild (occasional abnormal motor behavior)	Present, but mild decrease in facial expressivity, prosody, or gestures	Present, but mild in self-initiated behavior	Present, but mild (some reduction in cognitive function below expected for age and SES, b/w 1 and 2 SD from mean)	Present, but mild (meets criteria for major depression, with minimum number of symptoms, duration, and severity)	Present, but mild (meets criteria for Mania with minimum number of symptoms, duration, and severity)

	Hallucinations	Delusions	Dis-organization	Abnormal psychomotor behavior	Restricted emotional expression	Avolition	Impaired cognition	Depression	Mania
3	Present and moderate (some pressure to respond to voices, or is somewhat bothered by voices)	Present and moderate (some pressure to act upon beliefs, or is somewhat bothered by beliefs)	Present and moderate (speech often difficult to follow and/or frequent bizarre behavior)	Present and moderate (frequent abnormal motor behavior)	Present and moderate decrease in facial expressivity, prosody, or gestures	Present and moderate in self-initiated behavior	Present and moderate (clear reduction in cognitive function below expected for age and SES, b/w 2 and 3 SD from mean)	Present and moderate (meets criteria for Major Depression with somewhat more than the minimum number of symptoms, duration, and/or severity)	Present and moderate (meets criteria for Mania with some-what more than the minimum number of symptoms, duration, and/or severity)
4	Present and severe (severe pressure to respond to voices, or is very bothered by voices)	Present and severe (severe pressure to act upon beliefs, or is very bothered by beliefs)	Present and severe (speech almost impossible to follow and/or behavior almost always bizarre)	Present and severe (abnormal motor behavior almost constant)	Present and severe decrease in facial expressivity, prosody, or gestures	Present and severe in self-initiated behavior	Present and severe (severe reduction in cognitive function below expected for age and SES, > 3SD from mean)	Present and severe (meets criteria for major depression with many more than the minimum number of symptoms and/or severity)	Present and severe (meets criteria for Mania with many more than the minimum umber of symptoms and/or severity)

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Chapter 10
Schizophrenia Spectrum Disorders in Relation to the *Totality* of Psychosis: From First Episode to Long-Term Outcome

Tara Kingston, Olabisi Owoeye, Anthony Kinsella, Vincent Russell, Eadbhard O'Callaghan, and John L. Waddington

Abstract "Schizophrenia spectrum disorders", however broadly defined, still fail to capture large tranches of psychotic illness whose epidemiological, psychopathological and pathobiological characteristics are likely important for holistic understanding of psychosis. We outline preliminary findings from the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) that suspends a priori diagnostic criteria, incepts "*all*" cases of first episode psychosis on an epidemiologically complete basis, follows cases prospectively over several years and evaluates the extent to which putative post hoc diagnostic distinctions are actually sustained or refuted by the data. Findings from CAMFEPS elaborate a dimensional as distinct from a categorical concept of psychotic symptomatology. What we currently diagnose operationally as schizophrenia/"schizophrenia spectrum disorders" may constitute not a discrete entity/collective but, rather, a domain characterised by certain epidemiological, psychopathological, pathobiological and functional characteristics; the boundaries of this domain appear arbitrary and in continuity with other operational psychotic and non-psychotic, particularly affective diagnoses and, perhaps, with the limits of "normal" adult human behaviour that include non-clinical, psychotic-like experiences.

Keywords Psychosis · Schizophrenia · Schizophrenia spectrum · Affective disorder · Epidemiology · Psychopathology · Pathobiology · Dimensional model

Abbreviations

CAMFEPS	Cavan-Monaghan first episode psychosis study
CI	Confidence interval
DSM-IV	Diagnostic and statistical manual of mental disorders, Fourth edition

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DUP	Duration of untreated psychosis
EXIT	Executive interview
NES	Neurological evaluation scale
NSS	Neurological soft signs
PANSS	Positive and negative syndrome scale
QoL	Quality of life
RR	Relative risk
SD	Standard deviation
SE	Service engagement

Introduction

While the impact of in vivo neuroimaging, postmortem cytoarchitectonic and molecular genetics on our understanding of the pathobiology of schizophrenia is substantial, our underlying concept of the disorder also continues to evolve [1–4] (see also Ritsner and Gottesman, this volume). Clinical reality has long made it apparent that the diagnostic entity of *Schizophrenia*, however defined [for this article, DSM-IV terminology and criteria are adopted], captures only a modest proportion of cases characterised clinically by psychotic illness and related abnormalities of mentation and behaviour.

The notion of "schizophrenia spectrum disorders" typically encompasses also *Schizophreniform disorder*, *Schizoaffective disorder* and *Schizotypal personality disorder*, with the status of *Delusional disorder* and *Schizoid personality disorder* remaining unclear in the absence of biological validators for either individual or collective diagnostic categories [1–4] (see also Mamah and Barch, this volume). Yet even "schizophrenia spectrum disorders", however broadly defined, still fails to capture large tranches of psychotic illness, most notably the affective psychoses [*Bipolar disorder* and *Major depressive disorder – with psychotic features*] and *Brief psychotic disorder* (see also Chapter 15 by Castagnini and Berrios, this volume) but also *Substance-induced psychosis*, *Substance-induced mood disorder – with manic features*, *Psychosis due to a general medical condition* and *Mood disorder due to a general medical condition – with manic features*; there endures also the enigma of *Psychosis not otherwise specified*.

We have argued previously [5, 6] that a critical route to addressing these challenges is to: (i) suspend such diagnostic criteria; (ii) incept into a research study "*all*" cases of first episode psychosis on an epidemiologically complete basis; (iii) conduct demographic, psychopathological, cognitive, functional and biological assessments unencumbered by diagnosis; (iv) follow cases prospectively over several years; (v) apply such diagnoses not as a criterion for entry into/exclusion from the study but, rather, as an integral component of prospective assessment; and (vi) evaluate the extent to which such diagnostic distinctions are sustained or refuted by the data on a longitudinal basis. To exemplify this approach and illuminate some of the issues outlined above, we present a further update on preliminary

findings from the still ongoing Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) [5–7], which is specifically structured, in an unusually favourable social/demographic/administrative setting, to approach these ideals.

The Cavan-Monaghan First Episode Psychosis Study

As described previously in detail [5], CAMFEPS involves two rural border counties in the Republic of Ireland, Cavan and Monaghan, having an ethnically homogeneous population totalling 109,139. It utilises the following ascertainment procedures: mental health care provided on a strict catchment area basis, involving a home-base treatment model with minimal recourse to inpatient care [8, 9]; cases identified from (a) all treatment teams in the catchment area, including services for the elderly and those with learning disability (b) cases from the catchment area who present privately to St. Patrick's Hospital, Dublin, or St. John of God Hospital, Dublin, which together account for > 95% of all national private psychiatric admissions, and (c) cases from the catchment area having forensic admission to the Central Mental Hospital, Dublin; primary entry criterion of a first lifetime episode of any psychotic illness, to include a first manic episode; no exclusion criteria other than a previously treated episode of psychosis/mania or psychosis/mania occurring with a prior, overriding diagnosis of gross neurodegenerative disease [e.g. Alzheimer's disease, Huntington's disease or Parkinson's disease]; presentation at age 16 or above, with no upper age cut-off; no loss of cases to services for the elderly or those with learning disability; demographic, psychopathological, cognitive, functional and biological assessments, including DSM-IV diagnosis; follow-up assessments at 6 months and 6 years; Research Ethics Committee approvals for all procedures, to include obtaining diagnostic/demographic information from case notes/treating teams for those declining formal assessment.

Epidemiology

During the interim period [1995–2008] we incepted 372 cases of first episode psychosis, to include a first manic episode [mean age, 38.4 (SD 19.5; range 16–92); 215 males, age 35.6 (18.4); 157 females, age 42.3 (20.2); age at inception was younger in males than in females, $P < 0.05$. The incidence of psychosis was 33.5 (95% CI 30.1–37.0)/100,000 of population age > 15 [males, 38.9; females, 28.0; risk for psychosis was greater in males than in females, relative risk (RR) = 1.4 (95% CI 1.1–1.7), $P < 0.01$].

DSM-IV diagnoses at 6 months post-inception were: *Schizophrenia*, N = 73; *Schizoaffective disorder*, N = 19; *Schizophreniform disorder*, N = 21; *Brief psychotic disorder*, N = 20; *Delusional disorder*, N = 22; *Bipolar I disorder*, N = 73; *Bipolar II disorder – depressed with psychotic features*, N = 1; *Major depressive disorder – with psychotic features*, N = 77; *Substance-induced psychosis*, N = 20;

Substance-induced mood disorder – with manic features, N = 6; *Psychosis due to a general medical condition*, N = 11; *Mood disorder due to a general medical condition – with manic features*, N = 3; *Psychosis not otherwise specified*, N = 23; there were two cases of "Simple deteriorative disorder" [a DSM-IV (Appendix B) exploratory entity relating to all the hallmarks of schizophrenia in terms of negative symptoms and functional decline but without sufficiently prominent positive symptoms to satisfy criteria for schizophrenia]; one case having an inception diagnosis of *Brief psychotic disorder* defaulted from care immediately following inception, hence his status at 6 months could not be determined. There were three cases of completed suicide over the first 6 months following inception, with the "last observation" diagnosis prior to demise being carried forward.

At 6 months post-inception, the three largest diagnostic nodes were: *Schizophrenia* [N = 73, mean age 30.9 (SD 14.5; range 16–79), incidence 6.4 (95% CI 5.0–8.1)/100,000 of population age > 15; 54 males, age 28.6 (13.3); 19 females, age 37.4 (16.3)]; *Bipolar I disorder* [N = 73, age 32.6 (14.0; range 16–80), incidence 6.6 (5.2–8.3); 38 males, age 31.2 (13.3); 35 females, age 34.2 (14.7)]; and *Major depressive disorder – with psychotic features* [N = 77, age 51.2 (22.1; range 16–87), incidence 6.6 (5.2–8.3); 36 males, age 49.6 (23.0); 41 females, age 52.6 (21.4)]. For *Schizophrenia*, risk in males exceeded that in females [RR = 2.9 (1.7–5.0), P < 0.001]; conversely, risk for *Bipolar I disorder* and *Major depressive disorder – with psychotic features* was indistinguishable between males and females.

Duration of Untreated Psychosis

As assessed using the scale of Beiser and colleagues [10], mean durations of untreated psychosis (DUP) across diagnoses at 6 months post-inception were: *Schizophrenia* 21.6 months (SD 37.2, range 0–192; N = 43); *Bipolar I disorder* [duration of untreated mania] 1.4 months (SD 7.0, range 0–43; N = 38); *Major depressive disorder – with psychotic features* 1.7 (SD 2.4, range 0–9; N = 29). For other diagnoses, DUP was available only for limited numbers of subjects.

Psychopathology

Focussing on the seven positive symptom items on the Positive and Negative Syndrome Scale (PANSS), scores were similar for cases of *Schizophrenia* [17.4 (6.4), N = 54], *Schizoaffective disorder* [15.4 (6.2), N = 17]; *Schizophreniform disorder* [14.1 (6.0), N = 10]; *Delusional disorder* [15.5 (6.2), N = 6]; *Bipolar I disorder* [16.3 (8.1), N = 45; on disassembling cases of *Bipolar I disorder* on the basis of DSM-IV specifiers, PANSS-positive scores were somewhat higher for cases of *Bipolar I disorder – with psychotic features* [17.3 (8.3), N = 38] than for cases of *Bipolar I disorder – without psychotic features* [10.9 (5.0), N = 7, P < 0.05]]; *Major depressive disorder – with psychotic features*

[14.6 (6.5), N = 37]; *Substance-induced psychosis* [13.3 (7.1), N = 12]; *Psychosis due to a general medical condition* [19.0 (5.5), N = 4]; *Psychosis not otherwise specified* [13.3 (5.0), N = 11]. Only for *Brief psychotic disorder* [8.6 (3.3), N = 11] were PANSS-positive scores materially lower than for other diagnoses. For the remaining diagnoses PANSS was available only for limited numbers of subjects.

Neuropsychology and Neurological Soft Signs

Application of the Executive Interview (EXIT) [11] indicated frontal lobe function to be poorer in *Major depressive disorder – with psychotic features* [9.9 (SD 4.2), N = 33] than in *Bipolar I disorder* [6.9 (5.3), N = 39, P < 0.05], with *Schizophrenia* evidencing intermediate values [8.4 (4.5), N = 46] that did not differ from either of these two other diagnoses. There were no significant differences between *Bipolar I disorder – with psychotic features* and *Bipolar I disorder – without psychotic features*.

Assessment of neurological soft signs (NSS) using the Neurological Evaluation Scale (NES) [12] revealed no evidence of gross neurological dysfunction across diagnoses having meaningful numbers of subjects. However, among the three largest diagnostic nodes NES scores indicated NSS to be more evident in *Major depressive disorder – with psychotic features* [18.7 (SD 11.0), N = 30] than in *Bipolar I disorder* [10.3 (8.0), N = 34, P < 0.05], with *Schizophrenia* evidencing intermediate values [14.2 (8.1), N = 47, P < 0.05 *vs Bipolar I disorder*]. There were no significant differences between *Bipolar I disorder – with psychotic features* and *Bipolar I disorder – without psychotic features*.

Interim Synthesis – At the First Episode

Post hoc application of DSM-IV criteria at 6 months to CAMFEPS cases, in the absence of a priori diagnostic restriction, revealed psychotic illness to be approximately 40% more common in men than in women, as noted on meta-analysis of studies carried out over several decades and which applied diverse diagnostic criteria [13]. As expected, *Schizophrenia* and *Bipolar I disorder* constitute two major diagnostic nodes. However, these diagnoses each accounted only for approximately a fifth of cases. Extension to "schizophrenia spectrum" diagnoses [*Schizophrenia*, *Schizophreniform disorder*, *Schizoaffective disorder*] increased the proportion only to approximately a third of cases. In considerable part, this arose because of the unexpectedly high incidence of a third major diagnostic node: *Major depressive disorder – with psychotic features*. The remaining diagnoses were: *Delusional disorder*, *Brief psychotic disorder*, *Substance-induced psychosis*, *Substance-induced mood disorder – with manic features*, *Psychosis due to a general medical condition*, *Mood disorder due to a general medical condition – with manic*

features, and *Psychosis not otherwise specified*; there were also a small number of cases who showed the hallmark features of negative symptoms and functional decline but without sufficiently prominent positive symptoms to satisfy criteria for schizophrenia, i.e. the putative DSM-IV exploratory diagnosis "Simple deteriorative disorder".

Among the three major diagnostic nodes, incepting cases without any arbitrary upper age cut-off revealed the following epidemiological "signatures": For *Schizophrenia*, risk was threefold greater in men than in women; mean age at inception was in the early 30s, younger in men than in women, but with a median in the 20s indicating emergence primarily in early adulthood but extending throughout the lifespan. For *Bipolar I disorder*, risk was similar between the sexes; mean age at inception was in the early 30s for both sexes, but with a median in the 20s indicating emergence primarily in early adulthood but extending throughout the lifespan. For *Major depressive disorder – with psychotic features* risk was similar between the sexes; mean age at inception was at approximately 50 for both sexes, with a similar median indicating emergence throughout the lifespan.

However, these three superficially distinct epidemiological "signatures" should not be interpreted as validation of these diagnoses: they show substantive homogeneity in terms of indistinguishable overall incidence and presentation throughout the lifespan, with differences being quantitative across continuous measures, rather than indicating any fundamental, qualitative differences. Importantly, these are population-based profiles that are of no diagnostic utility on an individual case basis. Additionally, these three diagnostic categories, together with *Schizoaffective disorder* and *Schizophreniform disorder*, were characterised by indistinguishable positive symptom scores. Furthermore, dichotomization of bipolar disorder into two subgroups on the basis of the DSM-IV qualifier "– *with psychotic features*" revealed only the expected modest difference in terms of scores for positive symptoms, with no evidence for bimodality that might indicate heterogeneity. Psychosis in bipolar disorder appears to be a generic characteristic, likely evident along a continuum, rather than any basis for arbitrary subtyping of the disorder.

While mean DUP appeared substantially more prolonged for *Schizophrenia* than for either *Bipolar I disorder* or *Major depressive disorder – with psychotic features*, this was somewhat less apparent in terms of medians due to inflation of the mean by a small number of extremely large DUP values in the *Schizophrenia* group. Nevertheless, these data indicate that the nature of co-morbid affective, rather than psychotic, disturbance may be an important determinant of these differences. While *Schizophrenia* evidenced EXIT and NSS scores that did not differ from those for *Bipolar I disorder* or *Major depressive disorder – with psychotic features*, EXIT and NSS scores did indicate greater impairment in *Major depressive disorder – with psychotic features* than in *Bipolar I disorder*. These data indicate further that the nature of co-morbid affective, rather than psychotic, disturbance may be an important determinant of these differences.

Long-Term Follow-Up

Our concept of psychotic illness can be clarified using an alternative approach, namely how do the diverse diagnoses allocated over the early phase of illness evolve longitudinally: in the long-term, do they show the profiles of stable, discrete entities or do they ultimately converge on a much smaller number of more uniform diagnostic nodes; to what extend might these diagnostic resolutions be associated with similar or different psychopathological and functional outcomes? We have recently conducted such a long-term follow-up of the first 8 years of cases incepted into CAMFEPS [N = 202]. Of these 202, long-term follow-up was possible for 196 subjects at a mean of 6.4 years (SD 2.3) after inception. At follow-up 13 subjects, all male, were deceased: 4 by suicide, 1 by accident and 8 from natural causes.

Diagnostic Stability

Diagnostic stabilities, with transitions, between 6 months and 6 years were as follows: ***Schizophrenia***, 37 of 42 cases having this diagnosis at 6 months retaining the diagnosis at 6 years [88%], with 3 evolving to *Schizoaffective disorder*, 1 to *Bipolar I disorder*, 1 to *Substance-induced psychosis*; ***Schizoaffective disorder***: 9 of 11 [82%], with 1 *Schizophrenia*, 1 *Major depressive disorder – with psychotic features*; ***Schizophreniform disorder***: 3 of 11 [27%], with 5 *Schizophrenia*, 2 *Substance-induced psychosis*, 1 deceased; ***Brief psychotic disorder***: 2 of 10 [20%], with 2 *Schizophrenia*, 1 *Schizoaffective disorder*, 2 *Bipolar disorder*, 2 *Major depressive disorder – with psychotic features*, 1 *Delusional disorder*; ***Delusional disorder***: 2 of 10 [20%], with 5 *Schizophrenia*, 1 *Schizoaffective disorder*, 1 *Major depressive disorder – with psychotic features*, 1 *Psychosis due to a general medical condition*; ***Bipolar I disorder***: 26 of 34 [76%], with 2 *Schizophrenia*, 3 *Schizoaffective disorder*, 1 *Substance-induced mood disorder – with manic features*, 2 deceased; ***Major depressive disorder – with psychotic features***: 22 of 40 [55%], with 2 *Schizophrenia*, 3 *Schizoaffective disorder*, 4 *Bipolar I disorder*, 1 *Substance-induced psychosis*,7 deceased [2 by suicide]; ***Substance-induced psychosis***: 4 of 11 [36%], with 1 *Schizophrenia*, 1 *Brief psychotic disorder*, 2 *Schizoaffective disorder*, 1 *Bipolar I disorder*, 1 deceased; ***Psychosis not otherwise specified***: 4 of 13 [31%], with 3 *Schizophrenia*, 3 *Schizoaffective disorder*, 1 *Major depressive disorder – with psychotic features*, 1 *Substance-induced mood disorder – with manic features*, 1 Alzheimer's disease. For other diagnoses, follow-up involved only limited numbers of subjects.

Psychopathology

At follow-up, the three largest diagnostic nodes were: *Schizophrenia* [N = 60]; *Bipolar I disorder* [N = 35]; and *Major depressive disorder – with psychotic features* [N = 27]. Using the PANSS, positive symptom scores were lower ($P < 0.001$)

for *Bipolar I disorder* [8.8 (3.2), N = 33] and *Major depressive disorder – with psychotic features* [7.8 (1.8), N = 26] than for *Schizophrenia* [13.0 (5.5), N = 60].

Global Assessment of Functioning

Global Assessment of Functioning was higher (P < 0.001) for *Bipolar I disorder* [66.7 (12.4), N = 35] and *Major depressive disorder – with psychotic features* [68.2 (10.6), N = 27] than for *Schizophrenia* [52.5 (12.8), N = 60].

Quality of Life

Using the Quality of Life (QoL) scale [14], QoL was higher (P < 0.001) for *Bipolar I disorder* [100.7 (19.5), N = 33] and *Major depressive disorder – with psychotic features* [97.6 (24.4), N = 26] than for *Schizophrenia* [70.2 (27.1), N = 60].

Service Engagement

Using the Service Engagement (SE) scale [15] SE was higher (P < 0.01) for *Bipolar I disorder* [12.2 (12.2), N = 33] and particularly (P < 0.001) for *Major depressive disorder – with psychotic features* [8.7 (10.1), N = 26] than for *Schizophrenia* [20.4 (12.5), N = 60].

Interim Synthesis – At Long-Term Follow-Up

Re-application of DSM-IV criteria to CAMFEPS cases at 6 year follow-up indicated a diagnosis of *Schizophrenia* at 6 months to be substantially stable thereafter, with accretion of cases via transitions from other categories, primarily *Schizophreniform disorder*, *Delusional disorder* and *Psychosis not otherwise specified*. However, even at 6 years, *Schizophrenia* remained a minority diagnosis: *Schizoaffective disorder* showed substantial diagnostic stability, with few transitions to and little accretion from other categories; *Bipolar I disorder* also showed substantial diagnostic stability, with limited transitions to other categories, primarily *Schizophrenia* and *Schizoaffective disorder*, and limited accretion from other categories, primarily *Major depressive disorder – with psychotic features*; *Major depressive disorder – with psychotic features* remained a substantive diagnostic category but was somewhat less stable, with transitions to other categories, primarily *Bipolar I disorder* and *Schizoaffective disorder*, and limited accretion from other categories. Worryingly, mortality at 6 years was highest for *Major depressive disorder – with psychotic features* and appeared only partly explicable in terms of somewhat older age at inception.

While there were few difference in positive symptom scores between diagnostic categories at 6 months, at 6 years these scores were lower for *Bipolar I disorder*

and *Major depressive disorder – with psychotic features* than for *Schizophrenia*; this pattern generalised to poorer global assessment of functioning, reduced quality of life and lower service engagement in *Schizophrenia* relative to these other two major diagnostic nodes. However, while *Schizophrenia* appears to be an increasingly portentous entity over the several subsequent years, this does not in itself constitute evidence for it being a "singularity". It is notable that while *Brief psychotic disorder* was a relatively stable diagnosis between inception and 6 months, it was particularly unstable thereafter, showing numerous transitions to other categories, primarily *Schizophrenia*, *Bipolar I disorder* and *Major depressive disorder – with psychotic features*. *Brief psychotic disorder* may be a far from benign occurrence that is more often the harbinger of long-term evolution to serious psychotic illness, the diagnostic diversity of which extends beyond not only *Schizophrenia* but also the "schizophrenia spectrum". Irrespective of these important but theoretical considerations, at a clinical level *Brief psychotic disorder* may repay more vigorous, sustained intervention following presentation.

Conclusions and Future Directions

It remains to be determined whether a diagnosis of *Schizophrenia*, or indeed the "schizophrenia spectrum" as currently conceptualised, represents a categorical entity or captures, within arbitrary limits, the more severe end of a dimension of psychotic illness. However, the above preliminary findings from CAMFEPS elaborate contemporary theorising that posits a dimensional as distinct from a categorical concept of psychotic symptomatology: what we currently diagnose operationally as *Schizophrenia*/"schizophrenia spectrum" may constitute not a discrete entity but, rather, a domain characterised by certain epidemiological, psychopathological, pathobiological and functional characteristics, the boundaries of which are arbitrary and in continuity with other operational psychotic and non-psychotic, particularly affective diagnoses [4, 16]. Furthermore, these boundaries may extend to the limits of "normal" adult human behaviour that include non-clinical, psychotic-like experiences [16]; particularly in children, adolescents and young adults, such psychotic-like experiences may constitute an "at-risk mental state" associated with increased likelihood of future clinical conversion to diagnosable psychotic illness [17–19].

As a primary example, increasing evidence points to substantive pathobiological overlap between *Schizophrenia* and at least *Bipolar I disorder* in terms of (i) genetic risk, whether involving several common background genes of small effect and/or multiple but individually rare copy number variations [20–22] (ii) structural and functional brain abnormalities [23–26] and (iii) "hard" biological indices of early developmental disruption, such as craniofacial dysmorphology [27, 28]. The challenge is to clarify the extent to which such findings in *Schizophrenia*, the most widely investigated psychotic diagnosis, might generalise not only to "schizophrenia spectrum" diagnoses and *Bipolar I disorder* but also to *Major depressive*

disorder – with psychotic features and, provocatively, *Brief psychotic disorder* and "at-risk-mental states".

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Chapter 11
Course of Schizophrenia: What Has Been Learned from Longitudinal Studies?

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Abstract Understanding the course of schizophrenia is essential to improve prophylaxis, early diagnosis, diagnostic validity, and prognosis. While the majority of the longitudinal studies of schizophrenia report that 50–70% of patients have a chronic, generally persistent course of illness, the rest of the patients present with a heterogeneous course. Furthermore, there are no clear course predictors at the time of the initial diagnosis. In this chapter we discuss likely contributors to the reported course heterogeneity of schizophrenia. Schizophrenia longitudinal studies are based on heterogeneous patient samples, using different inclusion criteria to define the type and severity of the disease. Different diagnostic approaches as described by Kraepelin, Bleuler, Schneider, Conrad and DSM, amongst others, have been used over time. The implications of different diagnostic systems on course and outcome are discussed.

Keywords Longitudinal studies · Schizophrenia · Prognosis · Schizophrenia course

Abbreviations

DSM	Diagnostic and statistical manual of mental disorders
EEG	Electroencephalography
ICD	International classification of diseases
IPSS	International pilot study of schizophrenia
IQ	Intelligence quotient
RDC	Research diagnostic criteria
SCID	Structured clinical interview for DSM disorders
SOC	Sense of coherence
SOHO	Schizophrenia health outcomes
WHO	World Health Organization

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Introduction

To understand the course of schizophrenia we will review evidence based on longitudinal, prospective (cohort) and retrospective (case control), studies of the illness. A few preliminary considerations on the strengths and limitations of such a review, as specifically applied to schizophrenia, are in place.

First, any historical review needs to consider if the subject of the review is the same throughout the considered historical period. Changes in diagnostic criteria imply that different clinical populations can be spuriously defined as being similar. Assumed diagnostic homogeneity might in fact "cover" diagnostic and course heterogeneity. For example, when two studies using different diagnostic criteria report differences in course, the found differences might be the result of the change in diagnosis rather than true course differences. This issue is of special relevance to schizophrenia, an illness which definition has been changed multiple times.

Secondly, with the exception of natural course studies, a review of longitudinal studies should account for the effects of treatment on course variation. The estimation of treatment effect as a potential course modifier is further complicated when treatment efficacy changes over time, which is the case in schizophrenia. Studies have used one or several diagnostic tools, such as those of Kraepelin, Eugene and M. Bleuler, Schneider, DSM 1 and 2, DSM 3 and 4 and revisions and ICD criteria, with some overlap as well. Several other tools, worth mentioning, such as St. Louis, Taylor, Vienna Research Criteria, Research Diagnostic Criteria (RDC), Feighner, Taylor-Abrams 1978 criteria, Washington IPSS 12-Point Flexible System and Astrup's process/nonprocess distinction are used in some of the studies either alone or along with other tools.

Hypothesized Protective Factors

Protective factors can be understood as a variety of functions or events that contribute to an optimal level of operations. Vaillant [1, 2] and Stephens et al. [3] identified several factors that predicted recovery. These factors included the presence of affective symptoms at hospital admission, shorter duration of symptoms and functional deterioration before the hospitalization (e.g. acute onset and work history) and lack of family history of mental illness.

Antonovsky and Sagy describe a "sense of coherence" (SOC) concept [4], which defines the individual resources to maintain psychological health and well-being that can be used to define the continuum health/disease state, including comprehensibility, manageability and "meaning". Bergstein suggested the use of the SOC scale as prognostic tool in acute delusional states and recommends specific interventions aimed toward improving the SOC score [5].

Suddendorf describes "foresight" as the ability to consider the long-term effects of behavior to guide present and future actions as they relate to a functional outcome [6]. Eack and Keshavan [7, 8] found that the baseline level of foresight predicts the functional outcome, even after adjusting for psychopathology, treatment received

and neurocognitive functioning [9]. Higher metacognitive ability of schizophrenia patients correlates with better work performance [10].

In a 18 month prospective study Ritsner et al. [11] showed that social support, self-efficacy and self-esteem correlated positively with the general quality of life index.

Perception of emotion in patients with schizophrenia has been correlated with better work functioning and independent living at 1 year, but not with social functioning and family relationships [12]. Troisi et al. [13] showed that patients with more spontaneous facial expression during the clinical interview generally had a better score on Global Assessment of Functioning, suggesting that programs aimed at this could improve the functional outcome of patients.

General cognitive ability (measured by intelligence quotient) has been positively correlated with functional outcome [14]. Subjects with higher IQ were more liable to have deterioration at the first hospitalization but return to the previous level at 10 years reassessment, while the subjects with lower IQ maintained a more stable score over the observed period [15].

Previous research has suggested that women with schizophrenia have a milder course of illness than men [16–18]. Grossman et al. examined the gender differences in the course of the illness in schizophrenia in a longitudinal study [19]. Ninety-seven patients, 43 women and 54 men were assessed during index hospitalization (acute phase of the illness), and then re-assessed prospectively at 6 consecutive follow-up visits over a 20 year period using a series of standardized measures. Compared to men, women had a lower percentage of psychotic episodes over the course of the illness and a significant improvement in psychotic activity over 20 years. In addition, women showed significantly better global function, higher percentages of recovery, and a greater percentage of a having a period of recovery at some point during the 20 year period (61% women versus 41% for men).

Hypothesized Negative Factors

The male to female risk ratio is 1.4:1 [20] suggesting that male sex increases the risk for schizophrenia.

A higher disease incidence has been reported in urban and low-income populations versus rural and higher income groups [21–23]. Migrant status [24] in countries with higher immigration has a higher risk than migrant status in countries with lower immigration [25].

Affected persons have been found to be more likely to have been born in the winter versus the spring or summer seasons, but this data is controversial [26, 27]. No variation in prevalence has been found with certainty between ethnic groups [28]. A higher prevalence has been suggested in the northeastern and western regions of the US [29].

A family history of schizophrenia is a strong risk factor [30, 31]. While there is no one risk factor for developing schizophrenia [32] and the genes discovered account only a fraction of variability and risk of schizophrenia, the closer the family

relationship to an affected relative, the higher the risk [33, 34]. Different deficits may be linked to genes and some symptoms are found in asymptomatic relatives of patients with schizophrenia (e.g., poor psychosocial functioning, change in brain volume over time) [35–37]. Family history has a small but significant effect on decreasing the age-at-onset as well as increasing the risk for negative symptoms [38].

Substance misuse has been reported to be the most prevalent co morbid condition associated with schizophrenia [39]. Cannabis is the most frequently used substance [40] and schizophrenia patients have significantly higher rates of abusing marijuana when compared to the general population or patients with other mental illness [41]. However it is unclear if cannabis use is a risk factor reflecting either a cause and effect relationship or an increase of risk for those already at risk for developing a psychotic disorder [42–45] or a protective factor (where increased use is due to beneficial effects on psychotic symptoms) [46].

Earlier onset of the illness, more insidious debut and absence of perceived stress at onset are associated with worse prognosis [47]. Patients diagnosed with developmental language disorder as children demonstrated a 6.4% risk of developing schizophrenia spectrum disorders vs. 1.8%; $P < 0.0001$ in general population [48].

In a large (over 1.3 million men) longitudinal Swedish study both height and BMI in young adulthood were strongly and inversely correlated with the risk of developing schizophrenia [49].

Tools Used

Psychosis have historically been dichotomized as originally in Emil Kraepelin's classification of dementia praecox (schizophrenia) and manic depressive insanity (bipolar disorder). However, Kraepelin recognized that many patients presented symptoms from both disorders [50]. As a response to the "in-between" patients, Kasanin introduced the concept of schizoaffective disorder in 1933, describing the concept of acute admixtures of features [51]. While such "in-between" disorders, lying between schizophrenia and manic-depressive disorders, challenge the fundamental Kraepelin dichotomous core of current DSM and ICD diagnostic systems [52]. According to the DSM-IV classification, schizophrenia and schizoaffective disorder are considered to be similar disorders in terms of chronicity, severity, rates of co-morbidity and relatively young onset [53–57].

Current leading international taxonomies represented by the American Psychiatric Association's DSM and World Health Organization's ICD systems use clinical, descriptive and phenomenological systems of diagnosis rather than objective, biologically-based methods to support psychiatric diagnoses [58–60]. Because of the poor reliability of assessment, sources of new information, longitudinal observation of the symptoms and the evolution of the illness, diagnostic instability may occur over time [61]. Salvatore et al. [52] evaluated the diagnostic stability of a broad range of DSM-IV psychotic disorders of 517 patients enrolled in the International First-Episode Project, by using the SCID assessment at baseline and

at 24 months. They found that the DSM-IV diagnosis of schizophrenia (75%) had relatively high levels of diagnostic stability. Schizoaffective disorders were rarely diagnosed initially (0.20%), indicating low diagnostic sensitivity without prolonged observation. However, schizoaffective disorders accounted for 12.2% of all 500 diagnoses at 2-years, and 53.6% of new diagnoses, a 61-fold increase.

The definition of schizophrenia and schizoaffective disorder has changed over time. Furthermore, these diagnoses are defined differently by the DSM and ICD diagnostic systems. For the schizoaffective disorder the DSM-IV TR requires a co-occurrence of an affective episode and a schizophrenia active phase and at least 2 weeks without mood symptoms whereas the ICD-10 classification defines the co-occurrence of an affective syndrome and schizophrenia symptoms for 2 weeks of about the same extent and intensity as the affective symptoms [58, 60]. The differences in the definitions highlight the potential overlapping symptom presentations between bipolar disorder and schizophrenia and possibly challenge the dichotomy as proposed by Kraepelin.

Studies challenging the concept of dichotomization have shown that both disorders have similar risk factors, including a family history of psychiatric disorders, child birth, perinatal complications, and recent stress [32, 62–65].

From a genetic standpoint, recent research studies support that neither schizophrenia nor bipolar disorders are results of a single cause or single gene, but this may be the result of epistatic effects with a number of genes with relatively small impact compounded by environmental hazards [66]. Some of the genes may confer susceptibility towards both disorders while other genes may only increase the risk of one the disorders, but the results from studies on the overlap are inconclusive [67–69].

Laursen et al. [70] investigated the magnitude of the overlap between the clinical diagnoses of bipolar disorder, schizoaffective disorder, and schizophrenia by looking at a register-based prospective cohort study of more than 2.5 million persons born in Denmark over a 35-year period. Risks for the 3 psychiatric disorders were estimated by survival analysis using the Aalen-Johansen method. It was concluded that a large co morbidity index between schizophrenia and schizoaffective disorder was found as well as a large index between bipolar disorder and schizoaffective disorder. More surprisingly, it was clear that a substantial co morbidity index between bipolar disorder and schizophrenia was present. The study supported the existence of an overlap between bipolar disorder and schizophrenia, thus challenging the strict categorical approach used in both DSM-IV and ICD-10 classification systems based on Kraepelin's dichotomous concept.

There are different theories that oppose the Kraepelin dichotomous concept. The developmental model proposes shared susceptibility genes between bipolar disorder and schizophrenia but different environmental factors operate to cause a person to develop either bipolar disorder or schizophrenia [71]. The continuum model suggests that all the major psychiatric disorders are linked by the existence of a continuum across a spectrum, from unipolar disorder, to bipolar disorder, to schizoaffective disorder, and to schizophrenia, with increasing severity across the spectrum [72, 73].

Longitudinal Studies

In order to reduce the potential impact of historical change of the diagnostic criteria and treatment effects we grouped schizophrenia course studies according to their historical time periods. We divided the history timeline in the following periods: 1. a pre-antipsychotic medications institutionalization period, 2. a post antipsychotic medications institutionalization period and 3. a deinstitutionalization period. Due to the longitudinal nature of the reviewed studies, in some cases these periods overlap.

Pre-antipsychotic Era Institutionalization Studies

Harris and Lublin [74] using the Kraepelin diagnostic system, followed 289 patients over 18 years. They reported that 56% had a poor outcome at follow up. In their sample of 294 patients with schizophrenia followed up for 16–17 years Mayer-Gross [75] reports that of 42% showed a remission. However, 42% of patients died during a food shortage in Heidelberg during World War I. Freyhan [76] reports on two groups of 100 patients each, one hospitalized in 1920 and the other one in 1940 followed up until 1953. In the first group, 65% of the patients were still hospitalized and 11% were dead in 1933; from the second group 43% were still hospitalized and 4% were dead in 1953.

Achte [77, 78] identified two groups of patients diagnosed with schizophrenic psychosis, the first group hospitalized between 1950 and 1952 (before the neuroleptic era) and the second group hospitalized between 1957 and 1959 (neuroleptic era). They reported that the percent of patients without improvement was higher in the 1950–1952 group.

Noreik et al. [79] followed a cohort of 148 patients hospitalized between 1938 and 1961 and another cohort of patients with schizophrenia (acute onset) between 1955 and 1957. The average follow up was 22 years. They reported that 16% of patients recovered, 38% improved (including the relapse remitting course) and 46% did not improve. Using Feighner's criteria for 139 patients admitted during 1934–1944 Tsuang and Winokur [80] reported that 47% were unimproved, 35% improved to a degree and 19% recovered and diagnosed at 40 years follow up.

In a retrospective study of 99 patients that remained institutionalized in the decades following deinstitutionalization Mancevski and collegues [81] found that early onset (age < 25) was associated with more negative symptoms at any given age, female gender was associated with more positive symptoms, and over time, the positive symptoms decreased and negative symptoms increased. Bland and Parker [82] in a 10 year prospective study of 88 patients diagnosed with schizophrenia using DSM II criteria reported the following outcomes: 51% patients had normal economic productivity, 69% had good to fair social adjustment, and only 17% of patients were unimproved.

The Burgholzli Hospital Study [83] which was conducted in Switzerland was a prospective study conducted over 23 years. 208 patients were selected as representative sample of 653 patients admitted between 1942 and 1943 to the hospital

for schizophrenia. The diagnostic criteria used were designed by M. Bleuler, using a narrower version as compared with the ones used by his father, E. Bleuler. 53% of these patients recovered or were significantly improved and 46% of sample had minimal or no impairment in social functioning.

Post-antipsychotic Era Institutionalization Studies

The Lausanne Investigations in Switzerland, led by Ciompi and Muller [84], examined the effect of aging on schizophrenia. The investigators selected 289 patients, as a representative sample of 1,642 patients with schizophrenia with first admission before the age of 65 and who were older than 65 in 1963. These patients were diagnosed initially using criteria of Kraepelin and E. Bleuler and ultimately M. Bleuler. The average duration of individual data was 37 years. This data included direct evaluation, hospital records and collateral informants. Twenty-three percent of the patients were hospitalized for over 20 years. Forty-seven percent of patients had one hospitalization after 1963 of less than 1 year. "Undulating course types" were described in half of the patients, 27% were reported recovered and 23% mildly dysfunctional. There were 24% of patients in the moderate-severe category and 18% in the severe category, with 9% of patients course described as "uncertain".

The Vermont Longitudinal Research Project [85, 86] followed 269 patients with schizophrenia over an average of 32 years. Of these patients, 118 met retrospectively the DSM III criteria for schizophrenia. Outcome was rated using the Strauss-Carpenter Levels of Functioning Outcome Scale [87]. Overall, 34% of patients were fully recovered and another 34% had considerable improvement.

Huber et al. [88] studied 758 patients admitted between 1945 and 1959. Of these, 502 patients were systematically followed up for up to 14 years (1967–1973). Of the sample, 77% received the diagnosis using the first-rank symptoms and 23% using second-rank (expression) symptoms. The average duration of illness was 22.4 years at the time of the last follow up. At the end of the study 87% of the group lived in communities and were not permanently hospitalized. Overall, 22.1% of the patients had remission of symptoms, 43.2% had "pure residual syndromes" and "structural deformity without psychosis" and 34.7% had characteristic residual syndromes [89]. The authors concluded that "predictions are possible only when several factors that have a similar influence on the long-term prognosis occur in combination, and when factors with contrary prognostic influence are absent. Even under these circumstances, the individual course is by no means certain" (p. 603). The long-term prognosis appeared to be independent of the duration of illness.

Retterstöl [90] followed 94 patients diagnosed with of schizophrenia at the time of their first admission and 47 patients with a diagnosis of schizoaffective disorder. They then reevaluated these patients approximately 10 years later. Opjordsmoen [91] evaluated 110 of these patients (diagnosed with schizophrenia) at a mean 31 years after the first hospitalization. Patients with long term hospitalizations had a worse prognosis when compared with patients with first hospitalization between 1958 and 1961. At the 10 year evaluation there was no difference between men and

woman in terms of prognosis, but at 31 years (mean) follow up women had deteriorated more. At the first follow up 65% were without psychosis as compared to 44% at the last examination. When DSM III criteria were used for diagnosis, the prognosis was, from best to worse as follows: schizoaffective psychosis, schizophreniform disorders and schizophrenia, which led the authors to conclude that prognosis is dependent on diagnosis, not on the type of delusions. Approximately one third of patients with Kraepelin's paranoia had no psychosis at the last follow up. Breier et al. [92] states that in a sample of 58 patients of patients with schizophrenia, only 20% had a good prognosis and 78% had at least one relapse at 2–12 years follow up.

Endicott et al. [93] reported on differences on short term outcome prediction for a schizophrenia sample when using (seven) different diagnostic systems. No system or symptom predicted strongly the prognosis, but DSM III and Schneiderian First Rank Symptoms performed better. However in another study using DSM II versus DSM III diagnostic criteria for 153 patients prognosis differed depending on the diagnostic scheme used [94]. Using the broader DSM II criteria resulted in a better prognosis. Of note, some of the predictive factors, such as gender, had a higher predictive value, in the authors' opinion, because some of the females with better prognosis in the study did not meet the stricter DSM III criteria. Patients diagnosed with schizophrenia using DSM III were more homogenous and had a worse prognosis overall [95]. This view was also supported by Servaes [96].

Modestin et al., used clinical notes and patient charts from the 1972 M. Bleuler study [97] recalculated prognosis after rediagnosing patients based on DSM III and IV, ICD 10, RDC, Schneider criteria's, and an operationalized version of Eugen Bleuler's criteria. For 30% of these patients, the diagnosis of schizophrenia was not confirmed; most of these patients being rediagnosed with schizoaffective disorder (37–66% depending on the tool used). Of note the authors find high diagnostic agreement between DSM III and IV, ICD-10 and RDC schemes, but not with Schneider and Bleuler criteria. Slightly different trajectories of illness course were reported when only the patients with a confirmed schizophrenia diagnosis were considered (145 out of 205 patients). The percentage of patients that had a "severe end state" increased slightly, while recovery for patients with undulating course decreased by approximately 10%. For "moderate/mild end state" patients the percentage increased for the chronic onset category and decreased slightly for acute onset patients, when re-diagnosed with DSM III and IV, ICD-10 and RDC when compared with Schneider and Bleuler criteria.

De-institutionalization Studies

Carpenter et al. [98] utilizing the International Pilot Study of Schizophrenia's Washington cohort, looked at the prognostic variables after the index admission of 40 patients with schizophrenia followed up over 11 years. Initial prognostic variables such as social, occupational, hospital utilization, and symptom areas of functioning were modestly correlated with one another. These variables can predict to a degree the long-term outcome but were not correlated with cross sectional

symptom presentation. The follow up data suggest that the illness reaches a plateau early in the course, with an equal number of patents who then either improve or deteriorate.

Eaton et al. looked at the longitudinal course from the first hospitalization, finding that the hospitalizations cluster early in the illness, with an amelioration in symptoms occurring over time, when adjusted for the chronicity [99].

In their comprehensive review of literature regarding the outcome of schizoaffective disorder, Harrow and Grossman [100], concluded that the evidence supporting the hypothesis that the prognosis of schizoaffective disorder is better than in schizophrenia but worse than in affective disorders is mixed. This view is also supported by Shanda et al. [101] by looking at 90 patients (followed up for 6–9 years) evaluated using a polydiagnostic approach. Harrow and Grossman also suggested that mood incongruent psychotic symptoms are associated with either poor prognosis or with other factors that are suggestive of a poor prognosis. In their 7 years longitudinal study of 186 patients diagnosed with functional psychosis based on ICD-9, RDC and DSM-III schemes, Lenz et al. [102] reported significant diagnosis stability for schizophrenia. However, the data for schizoaffective disorder was not as robust, with better diagnostic stability for schizoaffective bipolar as schizoaffective depressed patients. Tsuang and Coryell [103] in an 8 years follow up study showed that the outcome for schizoaffective disorder and schizophrenia, diagnosed using DSM III R, was similar.

The Prudo and Blum [104] study of 100 patients with schizophrenia hospitalized in London area psychiatric hospitals found that 49% had good symptomatic outcome and 42% had good social outcome at a 5 year follow up.

Based on the SOHO (Schizophrenia Health Outcomes) Haro et al. [105] defined three distinct courses of schizophrenia: a prolonged course with no remission; remission followed by relapse; and persistent. The SOHO study, a 3-year prospective observational study, describes course and outcomes in outpatients with a diagnosis of schizophrenia. Conducted in 10 European countries, with 1,096 participating psychiatrists, and 5950 analyzed patients (out of an original sample of 6,770 patients) SOHO is one of the largest longitudinal studies of schizophrenia to date. During the 3-year follow-up 2,301 (38.7%) of the SOHO outpatients did not achieve remission (prolonged course); 933 (15.7%) achieved remission but relapsed (remission and relapse); and 2,716 (45.7%) achieved and maintained remission (persistent remission).

The proportion of males in the prolonged course group was higher than in the persistent remission group. Patients with a prolonged course had worse social functioning at baseline and a longer mean duration of illness (years since onset). As expected, patients in the prolonged course group had a higher symptom severity at baseline while there were no differences in baseline global severity scores between the patients who achieved persistent remission and those who relapsed after remission. The most important predictor of the course of schizophrenia was social functioning at baseline. Socially active, employed patients, in a stable relationship had a better prognosis. Females had a significantly higher chance of achieving persistent remission than having a prolonged course, but there were no gender

differences between the prolonged course and the achieving remission and relapse course. Patients who experienced a psychotic relapse with longer duration of illness had fewer chances to recover than patients with a shorter course of illness.

In short, Haro et al. concluded that characterization of the course of schizophrenia with a combination of remission and relapse periods provided a richer description of the patient outcomes than the use of simple dichotomous outcomes.

Negative symptoms have been associated with deficits in functional outcome and poor treatment response [106]. The deficit syndrome, defined as the presence of primary and enduring (>1 year) negative symptoms [107, 108], has been found to be particularly resistant to current pharmacological and psychosocial treatments [109–111]. In previous longitudinal studies of persistently impaired patients with schizophrenia, the deficit syndrome appears to be associated with poor long-term outcome, worsening of negative symptoms, and possibly an increasing severity of disorganized symptoms over time [112–115]. These findings on the deficit syndrome, contrast with more recent findings, indicating that at least some patients with schizophrenia may show improvement in symptoms and global functioning throughout the course of the disorder.

Strauss et al. [116] compared a sample of schizophrenia versus nonpsychotic depressed patients on symptom progression, functional outcome, and recovery over a 20-year period. The study reported that patients with deficit syndrome were more likely to experience a persistently impaired course of illness and had poorer long-term outcome than nondeficit schizophrenia patients. More specifically, patients with deficit syndrome had increased disorganized thinking and greater worker disability over time. Global recovery was seldom achieved among deficit patients and was even less likely later in the course of the illness.

Harvey et al. looked at 28 predictors and several categorical and continuous outcome measurements for 114 patients over almost 5 years. They reported that 33% of patients were worse and 62% were better overall at the end of follow up period, with the best negative predictors being social isolation, apart from relatives, longer illness and being hospitalized at the first assessment [117].

While the previous study recruited younger patients (a mean age of approximately 23 years) in private and public hospitals, Mancevski et al. examined 99 chronic inpatients that remained in the state institutions until the 1970s and subsequently died in those institutions [81]. By examining data from the onset of illness until death, this study was unique in examining the entire course of schizophrenia in a relatively large number of closely observed subjects. The study found that the lifetime course of schizophrenia in the chronically institutionalized patients is characterized by a decrease in positive symptoms and an increase in negative symptoms. Schizophrenia with earlier onset (before the age of 25) was associated with more negative symptoms throughout life.

Schultz et al. [118] examined the course of schizophrenia over the lifespan by comparing symptoms of patients aged 14–73. Three symptom dimensions (psychotic, disorganized, and negative) were examined separately in relation to age. Age was specifically associated with a decrease in hallucinations, delusions, bizarre

behavior and inappropriate affect. Male gender was associated with greater severity of negative symptoms. Schultz et al. concluded that psychotic and disorganized symptoms were likely to be of lesser severity in older patients with schizophrenia, while negative symptoms tended to persist.

These longitudinal studies suggest that negative symptoms increase later in life. Long term stability (ranging from 4 years [56] to 10 years [119]) of the cognitive impairment in schizophrenia has been reported. Hoff et al. [120] also found that the cognitive changes occur prior to the debut of schizophrenia illness.

Bergstein et al. [5] looked at the relationship of sense of coherence and expressed emotion, depression and delusions as prognostic factors. From 48 acute delusional patients followed over 18 months, 23% of them had a chronic course, 42% relapsed after initial improvement, 8% had late remission and 23% had stable remission.

The Danish National Schizophrenia Project [121, 122] is a prospective, comparative, longitudinal study with a minimum intervention period of 2 years and assessment of patients with a first psychotic episode of a schizophrenic spectrum disorder at baseline and at 1, 2 and 5 years after inclusion. From 562 patients randomized to three treatments, 119 patients received supportive psychodynamic psychotherapy, 139 received "integrated treatment", an integrated program consisting of assertive community treatment, psychoeducational multifamily treatment, social skills training, and antipsychotic medication, and 304 received "treatment as usual". The three cohorts were similar at baseline. After 1 year, patients in the two intervention groups improved more in terms of symptoms and social function than patients in the treatment-as-usual group. This improvement continued into the second year. Patients that received the integrated assertive treatment fared better than those being treated with supportive psychodynamic psychotherapy. This study suggests that more intensive psychotherapeutic modalities may improve the outcome for patients with first psychotic episodes. Jager et al. [123] reports that in an 8 week naturalistic study of 280 patients with schizophrenia (DSM-IV criteria) 78.5% achieved the criteria for response and 44.6% of these patients achieved criteria for remission. Thirthalli et al. [124] identified 215 patients with schizophrenia, diagnosed using ICD-10 criteria. This study is unique for our time, as 58% of these patients did not receive antipsychotic medication over the 1 year follow up period. Thirthalli et al. report that the level of disability in untreated patients did not change, and, the continuous treatment with antipsychotic medication decreased the disability significantly.

During the Camden Schizophrenia Surveys Harvey et al. evaluated 114 patients with schizophrenia in a community setting over a 5 year period [117]. After 5 years, 62% of the patients were better overall while 33% were worse. There were four best negative predictors of outcome: social isolation, longer illness, living apart from relatives, and being an inpatient at first census, which together accounted for 32% of the outcome variance. The authors concluded that social relationships during the course of the illness were important predictors of overall outcome. Furthermore, relationships with friends and family also positively contributed to a better outcome.

Discussion

An increasing body of evidence suggests that the uniformly poor prognosis of schizophrenia conceptualized over a century ago [125] no longer accurately describes the course and outcome of schizophrenia. We will discuss the most likely explanations of this apparent paradigm change.

First, a change in the diagnostic criteria schemes used over time effectively pares an apparently homogeneous entity in smaller and likely different biopsychological constructs. It is conceivable that the very differences between such constructs, previously lumped together, are now manifesting in differences of course and prognosis. For example, Stephens et al. [126], using 9 diagnostic systems to analyze the medical records of 283 patients discharged from the hospital with diagnosis of schizophrenia, schizoaffective disorder and paranoid state found that except for 3 schemes (the New York Research Diagnostic Criteria (RDC), DSM-III, and St. Louis criteria), the overall diagnostic agreement between the other 6 diagnostic schemes was low. Modestin [97] also reported diagnosis agreement between DSM III and IV, ICD-10 and RDC but not with either Schneider's or Bleuler's criteria. Lenz et al [102] also reported that there is a good diagnosis stability with the ICD-9, RDC and DSM III systems. However, in another study [93], from 7 tested diagnostic systems, only two (DSM III and Schneider's first rank) performed somewhat better in predicting prognosis. One study suggested that schizophrenia diagnosed with DSM II might have a better prognosis when compared with schizophrenia according to the DSM III system [94].

While both over and under inclusive criteria, i.e. a broad or narrow diagnosis, may serve a purpose at a particular time of use, only time can reveal their long term shortcomings, as in the case of Langfeldt's schizophreniform psychosis [127].

Secondly, a sufficiently long period of follow up is necessary to differentiate between remission and recovery. Brief follow up might spuriously report recovery in patients who might be in a state of temporary remission. Torgalsboen and Rund [128], looking at a small patient population diagnosed with remission 10 years before, reported that only half of these patients maintain a recovery diagnosis.

Thirdly, the effect of evolving treatments, in addition to other factors (e.g. the individual's level and perception of stress, alimentation, exposure to toxins and other environmental factors) need to be carefully considered when data in captured longitudinally, over extended periods of time. Koshland describe a "paradigm challenge" [129] as new data emerges which may be incongruous with the existing theories. Such factors should at least be acknowledged as possible confounders; in certain cases a more direct, disease modifying effect might need to be considered. We will use two examples to illustrate this point. First, the oldest longitudinal studies of schizophrenia reported a smaller percent of patients who dropped out than the more recent studies [75, 76, 81, 104]. Interestingly, this fact cannot be accounted by the longer hospitalizations of the period as, in several of these studies, the patients were traced post hospitalization and in between hospitalizations. This is a case where other confounders should be considered, such as changes in the nature of the therapeutic relationship (with a more authoritarian physician stance in the past), or the nature of family dynamics (with more "connected" extended

families in the past) among others. A different example: when compared with the past, modern day schizophrenia seems to have much fewer cases of the catatonic type [130]. This is a rather drastic change in a clinical phenotype. In this case, in addition to considering confounders, one might also consider a more direct effect of a potentially disease/phenotype/gene expression modifying factor (i.e. a cumulative medical treatment/other interventions effect at the individual and his/her offspring's level).

To illustrate, out of a group of patients with frequent hospitalizations over a period of 4 years, those offered boarding homes (with an average stay of 11 months) had significantly less hospitalizations during the boarding home period and years after, as well as a lower hospitalization rate [131] than the non-boarding home control group. It should be acknowledged that the protective effects of structure have been demonstrated over decades. In their state hospital study, Peterson and Olson [132] report that between 1936 and 1945 39% out of 4,254 of Warren State Hospital patients were not released 5 years after the fist hospitalization. The same investigators report that following the introduction of neuroleptics from 170 patients at the Anoka State Hospital only 11% were never released at 5 years. However, when they looked at patients never released and readmitted at 5 years the proportion changed to 39 and 21% respectively. In terms of the stability of improvement, McWalter et al. [133] reports that 46% of patients in the preneuroleptic era and 49% of patients in postneuroleptic era were not readmitted during the year following discharge. Therefore, although a shorter duration of symptoms is noted with neuroleptic therapy, the time to rehospitalization is not significantly increased, when most of other factors are the same.

Conclusion and Future Directions

In the earliest longitudinal studies [134] 39% of the patients admitted for the first time with schizophrenia continued to be hospitalized at 5 years. The percent of patients having a particular outcome largely depended on the type of schizophrenia, with worse prognosis reported for hebephrenic type (55% unimproved) and process status (54% unimproved at follow up) [135]. In general, using similar diagnostic criteria, 18–35% of patients had a severe outcome, 24–46% moderately severe outcome and 22–34% are recovered [5, 85, 86, 88, 97, 105, 136, 137].

The development of neuroleptic medication contributed significantly to deinstitutionalization by allowing a faster stabilization period but did not prove to be superior when compared to previous interventions in preventing hospitalization at 1 year post-discharge [133] or clearly improving long term course or prognosis.

Although there are ongoing divergences, there is currently a general consensus regarding the diagnostic approach to schizophrenia. DSM IV and ICD, the most used diagnostic schemes for schizophrenia, offer uniformity in diagnosis and good reliability, amongst other benefits. However, more specific categories along a diagnostic spectrum may help researchers to individualize treatment. Furthermore, a dimensional approach might improve the predictive power of diagnostic criteria.

Further prospective, long terms studies, with carefully selected and validated diagnostic criteria, including endophenotypes (cognitive and negative symptoms clusters, EEG, electrophysiology and brain imaging data) in addition to clinical criteria, are recommended to clarify the course and prognosis of schizophrenia.

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Chapter 12
Late-Onset Schizophrenia: Epidemiology, Clinical Profile, Prognosis, and Treatment Considerations

Emilio Sacchetti, Cesare Turrina, Luca De Peri, and Antonio Vita

Abstract Historically, the possibility that schizophrenia can arise in middle or old age was supported by Emil Kraepelin, Eugene Bleuler and Manfred Bleuler. For very late-onset cases the British school used a specific diagnosis like late paraphrenia. However, until DSM-IIIR, clinicians in the United States did not consider a diagnosis of schizophrenia in patients with more than 45 years of age. In 2000 a consensus was reached to give a specific definition to late-onset schizophrenia (LOS) for cases in the 40–60 year age range, and very late-onset schizophrenia-like psychosis (VLOSLP) for cases aged 60 years or more. There have been few community surveys of LOS, and few reported estimates for broadly defined psychotic symptoms, or, at best, for the overall prevalence of schizophrenia in the elderly. Analyses of the clinical surveys indicate that, among patients with schizophrenia, 20–30% had an onset of illness after age 40 years. The symptom profile was generally investigated through matching patients with LOS with those with early onset schizophrenia (EOS). Some studies outlined the similarities between LOS and EOS, but often LOS had fewer negative symptoms, less disorganization, and better social performance. These comparisons must be weighted for the deterioration and selective mortality of schizophrenia with early onset. Patients with LOS have a worse neuropsychological performance than healthy controls, but for some tests they show an intermediate performance between EOS and controls. Genetic studies are very few and often not specifically designed, but evidence from the larger studies indicates a lower rate of first-degree relatives affected by schizophrenia in LOS compared with EOS. Brain imaging has found that LOS has abnormalities similar to EOS, although not all studies are concordant. Indices of cerebrovascular illness did not seem to be specific. Brain imaging, EEG and neuropathological studies do not indicate that

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neurodegeneration or cerebrovascular illness play a major role in LOS. Evidence-based guidelines for the treatment of LOS do not exist, for these patients are too few in randomized clinical trials. The indications from experts are to treat these late-onset patients with at least half the doses used for elderly patients with EOS. After 2000 more follow-up studies on LOS were published on whether patients with schizophrenia progressed to a dementia illness. Most did not find such evidence, but some studies suggested that, for a subgroup of patients, this possibility must be considered. Theories on the etiopathology of LOS have generally hypothesized a cerebral neurodevelopmental damage, similar to EOS, that predisposes an individual to the later development of psychosis when other insults occur in later life. Future research should probably concentrate on middle-age patients with LOS, because it is difficult to find patients with VLOSLP, should correct comparisons with aged patients with EOS for factors such as selective mortality and cognitive deterioration, and clarify the paradox of good premorbid functioning of patients with LOS despite existing neurodevelopmental deficits.

Keywords Late-onset schizophrenia · Very late-onset schizophrenia-like psychosis · Elderly · Late paraphrenia · Late-onset psychosis

Abbreviations

LOS	Late-onset schizophrenia
EOS	Early-onset schizophrenia
VLOSLP	Very late-onset schizophrenia-like psychosis

Late-Onset Schizophrenia, Historical and Diagnostic Issues

The clinical and scientific debate on late-onset schizophrenia (LOS) can be traced back to at least the beginning of modern psychiatry, despite the firm consensus that the disorder typically begins in youth and early adulthood.

The concept of Kraepelin [1] of dementia praecox as a mental decline starting in early adulthood was soon revised by the same author to allow for the possibility of illness onset after adolescence or in early adulthood (“. . . a not unconsiderable number of cases still reach development in the fourth, fifth and even in the sixth decade”).

Eugene Bleuler [2], in his textbook of psychiatry reported a second peak in the incidence of schizophrenia at the time of climaterium, and the occurrence of chronic paranoid forms around the fourth decade. The issue was then addressed by Manfred Bleuler [3] in a series of chronic institutionalized patients. He reported a rate of onset after 40 years of 15%. Minor phenomenological differences were observed in the comparison with patients with early-onset schizophrenia (EOS), namely milder symptom severity, and lower frequency of affective flattening and formal thought disorders.

For patients with an onset after 60 years of age the British literature [4–6] has used the construct of "late paraphrenia", which identifies a psychosis with a lack of negative symptoms and without a deteriorating course. In a review of 1995 [7], the available literature was criticized for mixing two different diseases, the Bleulerian LOS and the British late paraphrenia. It was also advocated that there should be clear boundaries between LOS and other delusional disorders with onset in late age, and it was pointed out that late paraphrenias may be "disguised diagnoses" for disorders with an organic origin.

Although DSM-III [8] did not allow a diagnosis of schizophrenia after the age of 45 years, DSM-IIIR [9] did specify the possibility of LOS after the age of 45 years. DSM-IV [10] and DSM-IVTR deleted any specification related to the timing of schizophrenia onset and ICD-10[11] dropped the diagnosis of late paraphrenia. Lack of age limits for the onset of schizophrenia in the two classifications is largely based on the assumption that onset in old age does not give specificity to the disorder.

The lack of a valid diagnostic construct for schizophrenia-like symptoms starting in old age has led to an authoritative consensus [12], published in 2000, that stated "after much discussion, a consensus was reached that cases in which onset occurs between age 40 and 60 be called late-onset schizophrenia and that cases in which onset occurs after the age of 60 should be called very late-onset schizophrenia-like psychosis (VLOSLP). In terms of epidemiology, symptom profile, and identified pathophysiologies, the diagnosis of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis have face validity and clinical utility". This work has somehow changed the way to conceptualize late-onset schizophrenia and sometimes was a reference for authors publishing thereafter. Among its assumptions were that there are three peaks in the incidence of schizophrenia, young, middle and old age, and that this last is possibly more linked to organic etiology.

The Differential Diagnoses

Table 12.1 lists some of the more frequent psychotic disorders starting in old age, and their differential diagnosis according to some authors [13–17]. Among these disorders are: dementia with delusions and hallucinations (psychosis of Alzheimer's disease), delusional disorder, psychotic disorder due to a general medical condition, brief reactive psychosis, mood disorder with psychotic features, delirium, substance abuse and psychosis. Particularly, the first two have been discussed by authors interested in late-onset schizophrenia.

The term psychosis of Alzheimer disease [16, 17] has recently gained credit over the more general diagnosis of behavioral and psychological symptoms of dementia. The diagnostic criteria are: (1) characteristic symptoms: presence of visual or auditory hallucinations or delusions; (2) primary diagnosis: dementia of the Alzheimer's type; (3) chronology: onset of dementia precedes or coincides with that of psychosis; (4) duration and severity: the symptoms of psychosis have been present, at least intermittently, for 1 month or longer, and are severe enough to cause some disruption

Table 12.1 The differential diagnoses of schizophrenia with onset in old age

Disorder	Clinical features
Dementia, Alzheimer type with delusions and hallucinations	Impaired memory, typical neuropsychological performance, everyday functioning does not improves with treatment [13], simple paranoid believes [14, 15, 16, 17], misidentifications are common [16, 17]
Delusional disorder	No bizarre delusions and/or hallucinations [13], poor response to antipsychotics [14]
Mood disorder with psychotic features	Hystory is positive for major depression or manic/hypomanic symptoms, affect is not blunted or flat [13]
Brief reactive psychosis	Short psychotic symptoms, after a stressful event [13]
Delirium	Clouded consciousness or difficulties to sustain attention [14]
Psychotic disorder due to a general medical condition	Patients history, physical examination, and laboratory assessment are positive [13], visual hallucinations in Parkinson disease, especially if treated with anticholinergic or dopaminergic drug [14]
Substance abuse and psychosis	Positive drug screen [14]

in functioning; (5) exclusion of schizophrenia, delusional disorder, psychotic mood disorder, another medical condition, or substance- or medication-induced psychosis; and (6) delirium: the psychosis does not occur exclusively during the course of a delirium. Misidentification of caregivers and delusions of theft are more common; schneiderian first rank symptoms are rare. It tends to remit in the later stages of dementia.

Delusional disorder is another psychiatric disorder with onset after 40 years of age. In common with LOS schizophrenia, the symptoms include a lack of disorganized speech and behavior and the absence of negative symptoms, with onset typically in middle or late adulthood. The average age of onset is 40–49 years for men and 60–69 years for women [15]. Although the distinction between LOS and delusional disorder looks rather easy (presence/absence of bizarre delusions and hallucinations), some authors [18] have questioned the validity of this distinction on a descriptive and predictive basis.

The heterogeneity of late-onset psychoses is well illustrated in a 10-year follow-up [19] of 47 cases diagnosed as persistent paranoid psychosis, with onset after 60 years. After a clinical review, these patients had distinct features that allowed them to be categorized into 6 subgroups: schizophreniform, paranoid, schizoaffective, organic, symptomatic and affective. In another study [20] with details of differential diagnosis after referral of 74 patients with an onset of psychotic symptoms after 45 years (DSM-IIIR threshold) to a university psychiatric service, 3 had a psychosis secondary to drug abuse, 4 had onset of a dementia disorder, 11 had delusional

disorder, 9 had a mood disorder with psychotic features, and 6 were not otherwise specified psychosis.

Prevalence and Incidence of LOS and VLOSLP

In a community survey, the mere distinction between early- and late-onset psychosis may not be scheduled in the study design, and lay interviewers have poor knowledge of the differential diagnosis between the many types of psychotic illnesses of the elderly. Hence, population studies report on the prevalence of psychotic symptoms in general, while clinical epidemiology can make estimates of the relative contribution of LOS in the overall number of patients with schizophrenia.

Community Surveys

In a community survey [21] of elderly people that aimed at diagnosing auditory hallucinations and paranoid ideation, it was found that 65 of 935 subjects (7.0%) had at least one psychotic symptom; of these subjects, 40 (4.3%) were judged to be cognitively intact.

In a two-wave community study [22] of 5,222 persons aged 65 years or more, the incidence of schizophrenia was defined by those subjects who were negative at the first assessment but with schizophrenic symptoms after 2 years (wave 2). Only two subjects were found, but these were relapses of schizophrenia already diagnosed before the age of 65 years. The annual incidence of 3.0/100,000 (CI 0.00–110.7) was computed from another case with a provisional diagnosis of schizophreniform disorder, with some depressive features, who developed dementia after 4 years. In this study, the prevalence of all cases of schizophrenia, with no distinction between early and late-onset, was 0.12%.

The heterogeneity of causes of psychotic symptoms in the elderly detected by community surveys is apparent in a Swedish study [23] on psychotic symptoms and paranoid ideation in a nondemented population of very old subjects (85+ years). The prevalence of any psychotic symptom was high (10.1%), but these symptoms were associated with incident dementia and major depression syndrome.

A recent, two-wave community incidence study [24] (age range 18–64 years) identified three age groups: young (18–34 years), middle (35–49 years) and old age (50–64 years). Of the 4,637 subjects investigated, 56 had incident psychosis (34 in the young, 44 in the middle, and 21 in the old). The cumulative incidence of late-onset psychosis was 0.3%.

Clinical Studies

In a review [25] of clinical studies published between 1913 and 1986, 8 studies were selected that reported on the occurrence of LOS (40+ years) among patients from

various age groups. A weighted mean proportion of 23.5% was computed, ranging from 15.4 to 32.0%.

A case-register study [26], serving the Camberwell catchment area, investigated first contacts with an ICD-9 diagnosis of schizophrenia, paraphrenia and other non-organic psychosis made between 1965 and 1984. The chart review also considered a more stringent diagnosis of DSM-IIIR schizophrenia, and it was found that both ICD and DSM identified a peak of incidence in the 16–25-year-old group, a slight second peak in the 46–55 year group, and a third peak in the over 65 years age group (10–20/100,000 population). Twenty-eight percent of the collected sample had an onset of illness after age 44 years, and 12% after age 64 years. Surprisingly, diagnosing schizophrenia according to DSM criteria was easier in late-onset cases.

It has been reported that admission rates for non-affective, non-organic psychoses in elderly people are influenced by age. A study [27] on first admission to hospital of people age 60+ years in a large population in the Netherlands, England and Wales, showed a linear association with age, with an 11% increase in the incidence with each 5-year increase in age. A connection between degenerative brain processes and what were called non-affective psychoses in the elderly was supported.

The setting of clinical studies may influence estimate rates. A survey [28] conducted in Illinois state hospitals detected a very low prevalence of late-onset DSM-IIIR schizophrenia, with an estimate of 4.1% of all patients aged 45 years and older with diagnoses of schizophrenia or schizoaffective disorder. It was hypothesized that patients with LOS had had a better working performance during adulthood, which could have resulted in better health coverage and admission to private facilities.

In a review [29] of clinical reports on the age at onset of first psychiatric admission for schizophrenia, it was reported from the analysis of 8 studies that 77% of patients had onset before the age of 40 years, 13% between 41 and 50 years, 7% between 51 and 60 years, and 3% after the age of 60 years.

Epidemiology should also be kept in mind for those studies that compare late-onset cases with aged patients with schizophrenia who had early onset of their illness. The 25-year mortality of people with schizophrenia has recently been estimated in a cohort of 370 patients [30], and it was found that the standardized mortality ratio was 289 (i.e. three times higher than a control population). Of all patients, 164 (44.3%) were dead at follow-up, and most deaths were from common causes seen in the general population. Considering the typical onset of schizophrenia in the twenties, the chances of getting through 40 years of illness to the age threshold for very-late-onset schizophrenia like psychosis look very gloomy, so that any comparison with early-onset cases who have aged is biased by this selective mortality.

Risk Factors

The literature [10, 12, 20, 31, 32] is sufficiently consistent in indicating a preponderance of females among subjects with LOS exceeding the over representation of women in the general elderly population. A pattern of the relationship between age

and sex was reported in one study [33] that showed the number of cases in men decreased from 45 to 75 years. In the Camberwell catchment area [26], a study on patients with first contact for non-organic, non-affective psychotic disorder found that the male/female ratio fell dramatically after the age of 35 years: before the age of 35 years it was greater than 1, but then dropped to 3:20 in the group over the age of 75 years. In the ABC study [34] on the age distribution of onset of schizophrenia, there was a peak in the number of women in the 45–49 year-old age group, which was significantly higher compared with men. In the NEMESIS study [24], no greater risk was found for females, and this result, at odds with previous studies, was interpreted as being due to lower likelihood that men come to professional attention, so that they are missed in clinical studies.

Sex may interact with ethnicity because, although VLOSLP is traditionally associated with female sex, migrant populations in the United Kingdom have shown a preponderance of males (52% of males in migrants vs 18% in native subjects) [35]. The incidence of VLOSLP in African- and Caribbean-born subjects was compared with that of native subjects in London, identifying all new referrals over the course of 5 years. Rates for migrants were 12 times higher in migrant females and 24 times higher in migrant males [36]. The same group [37, 38] reported that Caribbean born patients were significantly younger and had a lower mean age of illness onset. This suggested that risk factors for VLOSLP may be different in migrants compared with British-born elders, as a result of additional psychosocial risk factors such as social isolation, loss of social status and loss of social networks.

Hearing impairment is usually associated with the risk of psychosis [5, 12], but a higher rate of hearing impairment was not found [39] in subjects with LOS when compared with controls (mild + moderate/severe 40.7 vs 38.2%). In this study only a few subjects had severe hearing loss, which may be more likely associated with psychosis. In the NEMESIS study [24] a statistical trend only was found for the association between psychosis and hearing impairment. This was defined by a subject's self-report of being treated or monitored by a physician. The measure of hearing impairment was probably too stringent and this sample (<65 years) could be too young for these variables to exert significant differences.

Research has also investigated the possible influence of psychosocial stress in childhood, such as that of child survivors of the holocaust. In a review [40] of 93 subjects there were 12 cases of LOS. A significant association was reported with severity of stress; for example, detention in a concentration camp and the loss of parents and siblings.

Psychopathology of LOS and VLOSLP

Very little, if anything, is known from research about the pattern of onset of psychotic symptoms in old age. EOS is a disorder that often starts with a prodromal phase, followed by true psychotic symptoms. How LOS and VLOSLP progress

has not been understood until now. More is known about psychopathology, where comparisons have been made with elderly patients with EOS.

Studies on psychopathological differences between LOS and EOS have reported mixed results, probably because of the inclusion of psychotic disorders other than schizophrenia, or the inclusion of chronically ill schizophrenia patients with multiple hospitalizations [41]. These studies are summarized in Table 12.2.

In a comparative study [33] of 470 first-contact cases with EOS or LOS that analyzed a large number of symptoms of psychosis, the conclusion was that, notwithstanding the presence of phenomenological similarities, the number of symptom differences between the two patient groups was sufficient to support the hypothesis that cases of EOS and LOS are not phenotypically homogenous. In particular, the two groups did not differ in the prevalence of delusion of reference, bizarre delusions, delusional perceptions, and lack of insight. Instead, patients with EOS presented more positive and negative formal thought disorders, affective symptoms, inappropriate affect, delusions of grandiosity or passivity, primary delusions other than delusional perception, thought insertion, and thought withdrawal. Patients with LOS had increased prevalence of persecutory delusions with and without hallucinations, organized delusions, third person auditory hallucination, abusive or accusatory voices, and running commentary (Fig. 12.1).

Although the results of a study [20] on LOS (45+ years) showed many similarities with EOS ("late-onset schizophrenia is as much schizophrenia as early-onset schizophrenia is"), an atypical result was that patients with LOS had a long life of normal social adjustment, but premorbid childhood maladjustment.

Analysis of the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) for a small sample of patients [39] with DSM-III-R schizophrenia (early-onset 35 years or less, late-onset 50 years or more) did not find symptom differences after Bonferroni correction except for the presence of more negative symptoms overall in the early-onset group. Three- and five-factor analyses of SAPS and SANS data also failed to demonstrate differences between patients with EOS and LOS. Overall functioning was also evaluated in this study and the Global Assessment of Functioning scores were much lower in EOS (17.7) versus LOS (27.8) versus controls (86.6); scores for instrumental activities of daily living were higher (poorer performance) in EOS (2.3) versus LOS (1.8) versus controls (1.0).

In a large study [41] of first-episode, antipsychotic drug-naive patients with schizophrenia, affective flattening and social withdrawal were more severe in subjects with an onset before 40 years of age. Systematic persecutory delusions presented higher scores in the group of patients with onset after 40 years of age. Differences in affective flattening and social withdrawal between patients with EOS and LOS persisted after controlling for several secondary sources of negative symptoms, thus supporting some role of primary negative symptoms in this finding. These authors are among the few that discuss the possibility of a prodromal phase in LOS, leaving the question for future research.

Table 12.2 Differences between early and late onset schizophrenia

Author	Study features	Female sex	Paranoid symptoms	Affective flattening	Cognitive performance	RMN/CT	Antipsychotic doses	Prognosis, Performance
Howard et al. [33]	Symptom profile in EO and LO first-contacts	Higher rate in LO	Higher in LO	Lower in LO	–	–	–	–
Jeste et al. [20]	Symptom profile, neuropsychology	Higher rate in LO	SAPS: LO > NC EO > NC	SANS: LO > NC, EO > NC Affective blunting: LO<EO	LO=EO<NC	–	–	–
Brodaty et al. [39][a]	Symptom profile in EO and LO and risk factors	Females=males	EO=LO	SANS: LO<EO	–	–	–	Better living functioning in LO
Sato et al. [41]	Symtom profile of LO vs. EO, first episode patients	–	Higher systematic persecu-tory delusions in LO	Lower in LO	–	–	Lower in LO	Less social withdrawal in LO
Vahia et al. [42]	Symptom profile, functioning and neuropsychology	Higher rate in LO	Less positive symptoms	LO=EO	CVLT, WCST, Digit symbol, and block design: LO > EO Other 5 variables: LO=EO	–	Lower in LO	Better everyday functioning in LO

EO: early onset schizophrenia; LO: late onset schizophrenia; VLOSLP: very late onset schizophrenia like psychosis; NC: normal controls.
[a]Early onset if before 35 years, late onset if after 50.

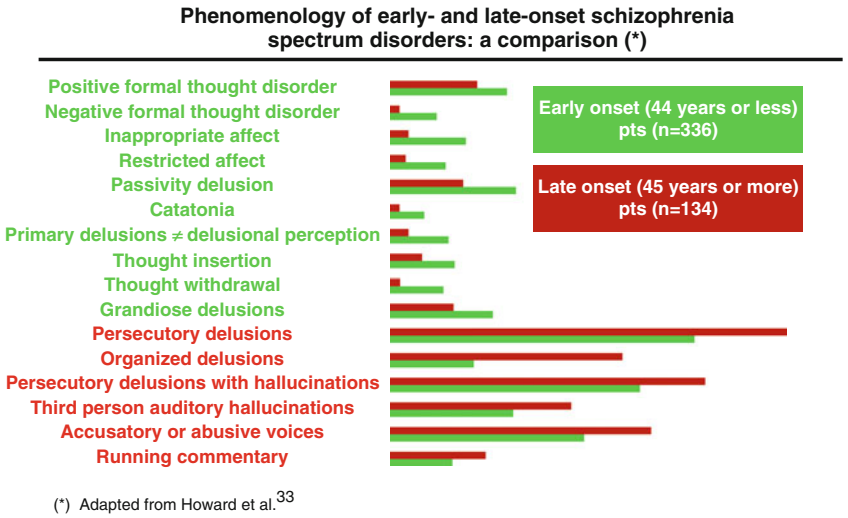

Fig. 12.1 Phenomenology of early- and late-onset schizophrenia spectrum disorders: a comparison (adapted from Howard et al. [33])

In a study [42] on psychopathological profiles, functioning and cognition of 744 patients with EOS and 110 patients with LOS (40+ years), one of the largest studies to date, both similarities (prevalence of negative, deficit and depressive symptoms) and differences (in LOS less positive symptoms and general psychopathology, better processing speed, abstraction, verbal memory and everyday functioning) were found. The authors commented that these differences were enough to consider LOS a subtype of schizophrenia. The worse performance in subjects with EOS was interpreted as due to the effects of schizophrenia starting in adolescence or early adulthood, when many of the normal psychosocial and developmental tasks are interrupted. If onset is delayed until mid-/late-life, functional skills are established and integrated.

A hint about the complex phenomenology of LOS may come from a well-discussed clinical case [43], in which the patient with a "late-onset schizophrenia like psychosis" had an onset in his early fifties, a juvenile history of epilepsy, his first psychotic symptoms after imprisonment, a treatment that coupled an antipsychotic with 100 mg of nortriptyline, blunted affect in the evaluation of two episodes, discontinuation of antipsychotic treatment too quickly after clinical response, and 2 years of remission while drug-free.

Thus, psychopathological differences are sometimes found, pointing to less negative symptoms in cases of LOS and more organized paranoid ideation, but this comparison must be viewed cautiously, both for selective mortality and for the deteriorating course of the illness in control cases of EOS.

Neuropsychology

Neuropsychological performance is of special interest in LOS because it can test similarities (or differences) with EOS and assist in the differentiation of LOS with dementia of the Alzheimer type.

A study in San Diego [20] investigated 15 neuropsychological variables that covered overall intellectual ability, executive functions, learning and memory, motor skills, verbal ability, perceptual- motor skills and sensory abilities. Almost all tests showed that patients with LOS performed significantly worse than normal controls. Only in two variables (perseverative responses at the Winsconsin Card Sorting Test (WCST) and trials 1–5 of the California Verbal Learning Test (CVLT)) did patients with LOS perform better than those with EOS.

In a comparison [44] of 32 patients with DSM-IV schizophrenia, with onset after 45 years, with 32 patients with Alzheimer disease, it was found that the long-delay free recall of the CVLT was significantly better in patients with LOS (3.50) than those with Alzheimer disease (0.84). Notably, performance on most other tests was "predominantly similar" among the two groups. The study had no control subjects, such as healthy elderly or patients with EOS and one-third of patients with Alzheimer disease had psychotic symptoms.

The analysis [45] of some cognitive styles, such as probabilistic reasoning, causal attribution styles and mentalizing ability, showed that in VLOSLP only mentalizing errors were higher than in patients with depression and controls (mean first order deception 79.8 in VLOSLP, 91.7 in depression, 96.7 in healthy controls). Because evidence exists that all these variables are defective in EOS, a less severe cognitive bias could be an indication of differences between very-late-onset schizophrenia-like patients and deluded patients with early-onset psychosis.

A study [42] in the United States investigated psychopathology and neurocognition in patients with LOS, EOS and normal controls. Both the EOS and the LOS groups had worse cognitive scores than normal control subjects. Patients with EOS and LOS were similar on verbal knowledge and auditory working memory, but the LOS group was less impaired than the EOS group on tests of processing speed, abstraction/cognition flexibility and verbal memory.

Genetics

In general, most of the scant literature on familial load suggests that LOS runs in families with a lower aggregation in comparison with EOS [25]. Research in this area is very poor, because family genetic studies are difficult to carry out and interpret, due to the difficulties in collecting relatives of older subjects, and the possible underestimated risk when the entire life span has to be considered.

In a clinical and neuropsychological study [20] of 25 patients with LOS (45+ years), 39 patients with EOS, and 35 normal subjects, family history was collected in a semi-structured clinical interview with subjects and informants. Patients with

LOS and EOS had a similar proportion of first-degree relatives with schizophrenia (12 vs. 13%).

A unique family study [46] of late-onset non-affective psychoses investigated the psychiatric morbidity of 269 first-degree relatives of patients with schizophrenia or delusional disorder (onset at 60+ years) and 272 relatives of healthy controls. Both a narrow (15–50 years) and a wider (15–90 years) age range for schizophrenia were considered, but the lifetime risks were very similar in index relatives and controls (narrow 1.3 vs. 1.3%; wider 2.3 vs. 2.2%). Unexpectedly, the risk for depression was significantly higher in relatives of patients with late-onset psychosis.

In a study [39] on the phenomenology of schizophrenia with onset after 50 years, the family psychiatric history was investigated using a structured interview. It was found that only 3.7% of 27 patients with LOS had a positive family history for schizophrenia, compared with 40% of 20 patients with EOS.

A recent genetic association study [47] has found that the deletion of CCR5 32-bp allele, a chemokine receptor, was more frequent in a subgroup of schizophrenia patients with first admission after the age of 40 years compared with those admitted earlier and with healthy controls (8 vs. 2 vs. 1% were homozygous for the deletion allele, respectively). This deletion could be present in subjects with a genetically higher sensitivity to the prenatal viral effects on neurodevelopment, leading to neuronal damages and a predisposition to a specific form of schizophrenia with late-onset.

Brain Imaging

Early studies started to look for differences between LOS and normal controls, following research on structural brain changes in EOS. In a study [48] that included patients with LOS (55+ years) DSM-IIIR schizophrenia, EOS, patients with Alzheimer disease, and normal controls, 11 MRI measures of atrophy in the comparison of EOS and LOS patients were similar. Furthermore, LOS patients had higher dopamine D2 receptor density than normal controls.

In a study [49] on neurological soft signs, neuropsychological defects and MRI abnormalities, it was found that 30 patients with EOS and 27 patients with LOS (45+ years) had similar neurological soft signs, and similar larger lateral ventricles. Patients with LOS had more cortical atrophy in the anterior temporal and mid parietal regions, and more subcortical signal hyperintensities.

A study [50] on regional cerebral blood flow on 15 subjects with LOS (50+ years), 7 EOS (<35 years) and 27 healthy controls found that patients with LOS had a lower cerebral perfusion in the frontal and temporal areas compared with controls, but only right temporal perfusion was significantly different compared with EOS. The authors commented that finding similar abnormalities in late-onset and early-onset could help in understanding schizophrenia, but did not answer questions on why onset is late in life in some patients.

In a study [51] on 25 subjects with LOS, age- and sex-matched with EOS and normal controls, hyperintensities on MRI were computed. Subjects with LOS had a

mean age of 74.5 years and were tested 8 years after onset. Although the research hypothesis was that hyperintensities were higher in the prefrontal, temporal, and basal ganglia circuits, significant differences were found in the periventricular white matter (total periventricular hyperintensities: in the left hemisphere 0.153 LOS, 0.084 EOS, 0.048 normal controls; in the right hemisphere 0.156 LOS, 0.076 EOS, 0.054 normal controls). In discussing the higher rates of periventricular hyperintensities in LOS compared with EOS, the authors did not consider them to be specific to LOS. They hypothesized a predisposition to the development of psychosis that becomes manifest after the occurrence of additional brain pathology, such as cerebrovascular disease. They purported that a subgroup of patients with LOS will progress to vascular dementia if followed up over a sufficiently long period.

Looking for mid-sagittal differences in the corpus callosum and the cerebellum, the same group [52] compared 25 patients with LOS (50+ years), 24 with EOS, and 30 normal controls. Differences in the size of the corpus callosum between the three groups were no longer significant after covarying for age and education. Cerebellar areas and the cerebellum were also not significantly different; the pons was smaller in patients with EOS and LOS.

In a study [53] aimed at differentiating MRI findings in 14 patients with LOS (45+ years), age-matched bipolar and unipolar subjects (early-onset allowed), it was found that LOS patients had a significant right temporal horn and third ventricular enlargement. Unfortunately this study did not include patients with EOS but the authors reported that findings possibly paralleled existing data on EOS. The right-sided temporal abnormalities could explain the lack of thought disorganization in LOS.

In a clinical study [54] that examined the imaging characteristics of 21 VLOSLP and 21 controls with EOS, the cerebellum ventricular/brain ratio (0.165) was significantly higher in patients with VLOSLP compared with EOS controls (0.118). Other parameters computed in axial sections, such as cortical atrophy, periventricular white matter leucoencephalopathy, ventricle-to-brain ratio were all similar to EOS patients.

In the only diffusion tensor MRI study [55] of 14 VLOSLP patients and 15 healthy elderly volunteers, both fractional anisotropy and mean diffusivity were found to be similar to those of healthy controls. These results are remarkable, because reduction in fractional anisotropy was reported in various white matter areas in EOS patients.

Other Studies on Organicity

A study [56] of 10 patients with a DSM-IV diagnosis of schizophrenia and onset between 40 and 60 years of age examined whether EEG abnormalities were similar to those of patients with EOS. Quantitative EEG parameters, such as absolute and relative power, overall mean frequency, mean frequency of each band,

and interhemispheric coherence were not significantly different from a normative database of age-matched normal subjects.

In a relatively recent neuropathological study [57], 13 patients with LOS (40+ years) had more alterations in the gray/white matter ratio of the hippocampal gyrus compared with 8 normal controls and 13 patients with EOS (average gray/white ratio 17% greater than EOS patients and 27% greater than controls in the left anterior hyppocampal gyrus; 23% greater than EOS and 21% greater than controls in the right anterior hyppocampal gyrus). Authors interpreted this as preservation of gray matter and a concomitant reduction of white matter. The shrinkage of the white matter of parahippocampal gyri in LOS was viewed as a possible dying back neuropathy.

In a neuropathologic study [58] of 8 patients with LOS (40+ years), compared with 10 EOS, it was found that the density of neurofibrillary tangles was similar in five different brain regions. Furthermore, density of tangles was comparable with that of normal controls.

Treatment of LOS and VLOSLP

An early case report [59] of 5 patients with DSM-IIIR (45+ years) LOS detected "some symptomatic improvement with relatively low doses of neuroleptics". Lower antipsychotic doses have generally been recommended for LOS, with some differences among studies. For example, in the 2000 consensus statement [12], the recommendation about treatment of VLOSLP was to give doses as low as one-tenth of those given in young adults.

An open study [54] on treatment with risperidone (mean dose 2.1 mg/day) of 21 patients with VLOSLP and 21 with EOS found clinical improvement (CGI <=3) in 71.4 and 57.1% of subjects, respectively. The authors suggested that the use of an atypical antipsychotic contributed to the high response, quoting lower rates of response with typical antipsychotics.

The Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients [60] recommended, in older patients with schizophrenia, an upper limit (risperidone 3.5 mg/day, quetiapine 300 mg/day) of about one-half the doses for younger patients, while for other drugs the upper limit was somewhat higher (olanzapine 15 mg/day, aripiprazole 30 mg/day).

To date, the only study [61] on the treatment of LOS and VLOSLP is an open trial with amisulpride that included a sample of 26 patients with good cognitive performance (Mini-Mental State Examination > 26). At the end of treatment all patients were "considerably improved" (PANNS total improvement 46.6% over 5 weeks).

In a recent Cochrane review [62] on antipsychotic drug treatment for elderly people with LOS, it was concluded that there is no trial-based evidence on which to base guidelines for the treatment of LOS. The major difficulty for authors in finding some evidence was that in almost all placebo (or active arm) controlled trials the number of cases of LOS was too small.

One case was reported in the literature [63] of a woman with onset at 53 years of age, who did not respond to 4 adequate antipsychotic trials; remission was achieved with transcranial magnetic stimulation.

The Prognosis for LOS and VLOSLP

Results of studies on the course of LOS were found to be "rare and very contradictory" in a review [32] in 1997. This was echoed in a 1999 review [64] on LOS, which reported "a dearth of follow-up studies". After 10 years, more data are available and some indications on the time course of the illness are available. The issue is not a minor one, because it may well be that in the early stages of Alzheimer disease, when MMSE scores are normal, a schizophrenia-like psychosis will develop and only after some years it will be diagnosed as psychosis of Alzheimer disease. Follow-up studies are fundamental to investigate this possibility. Furthermore, symptoms may be followed by the typical cognitive, affective, and behavioral deterioration of schizophrenia. Mixed results were found in follow-up studies of LOS or VLOSLP, but most (Table 12.3) pointed to a favorable outcome of the psychotic disorder.

In a 5-year follow-up [65] of patients with LOS (50+ years), 9 cases of dementia were found out of 19 patients (no cases were found in a control group). Notably, the evaluation of global functioning (GAS) did not find a significant decline (41.0 baseline score, 45.7 at 5 years), but when subjects who developed dementia at follow-up were omitted, the mean score of those patients without dementia rose from 41.4 to 61.6. The investigators reported that this was likely due to the "full or partial resolution of psychosis in many cases".

In a study [66] on schizophrenia spectrum disorders with late-onset (45+ years), that included controls with early-onset psychosis, and subjects with Alzheimer disease with and without psychosis, it was found at 1-year follow-up that MMSE scores did not decline in late-onset psychosis (baseline 27.2, 1-year 27.6); decline was significant in patients with dementia. These results led the investigators to define LOS as "static encephalopathies".

In a long-term follow-up study [67] (120-month), three groups were compared: dementia with psychosis, late-onset major depression, and LOS (40+ years). The likelihood of developing dementia after 10 years was similar in patients with LOS and major depression. The authors did not outline that the chances of being free from dementia after 10 years were less than 50%.

In a 30-month follow-up [68] of 21 patients with VLOSLP, 13 of the 16 still living were judged to be cognitively intact by their caregiver. This led authors to comment that "in the majority of patients, cognitive and functional deterioration that could suggest psychotic illness as part of a dementia syndrome were not found". The concluding comments suggested a similar course for patients with EOS and LOS, but data did show stable neuropsychological deficits in LOS and worsening deficits in those with EOS. The worse pattern in patients with EOS was significant after weighing for a proxy score of deterioration.

Table 12.3 Outcome studies of late-onset schizophrenia

Author	No. of subjects	Criteria for late onset	Length of follow-up	Outcome variable	Results
Brodaty et al. [65]	27 LOS	Aged 50+ years, dementia ruled out	5 years	BPRS, Clinical Dementia Rat., MMSE, CAMDEX	9 patients developed dementia
Palmer et al. [66]	37 LOS 69 earlier onset, 56 normal controls	Aged 45+ years	1–2 years	MMSE, Mattis Dementia Rating Scale	Cognitive changes in LO=EO=controls
Rabins and Lavrisha [67]	28 "late life psychosis" 48 major depression 47 dementia + psychosis	Aged 45+ years	84 months (death) 129 months (dementia)	MMSE, DSM-IV criteria for dementia	Psychosis and depression had similar rates of dementia
Mazeh et al. [68]	21 VLOSLP 21 life-long schizophrenia	Aged 70+ years	30 months	CGI (caregiver)	No cognitive and functional deterioration in 13 of 16 patients
Laks et al. [69]	13 LOS	Aged 50+ years	1 year	MMSE, CAMCOG, PANNS, ADL, NPI	Stable cognition and ADL, no dementia at follow-up

LOS: late onset schizophrenia; VLOSLP: very late onset schizophrenia like psychosis.

In a Brazilian study [69] of schizophrenia with onset after 50 years of age (13 patients), MMSE scores and activities of daily living were stable at the 1-year follow–up (MMSE baseline 21.3, 1-year follow-up 20.8; PFAQ baseline 4.3, follow-up 5.9). Authors speculated that, given the mean duration of the disease at study entry (6.7 years), a neurodegenerative illness would have produced a marked impairment in baseline or follow-up estimates.

Most studies [66, 68, 69] have found stable cognitive performance at follow-up, but at least 2 [65, 67] studies warned about the possibility of cognitive deterioration. These results are probably due to differences in study design, length of follow-up and the quality of exclusion criteria for cognitive disorders at study entry.

The Etiopathology of LOS and VLOSLP

Hypotheses about the etiopathology of LOS can be grouped as follows: the effects of cerebral lesions similar to those of EOS, due to a neurodevelopmental deficit; the effects of neurodegeneration in later life; the combined effects of neurodevelopmental deficits, which remain compensated until old age, and later life neurodegeneration [12].

In advocating that the atypical features of LOS may provide research clues to illuminate its pathogenesis, Rabins and Lavrisha [67] hypothesized that severe thought disorders and affective blunting (rare in LOS) are linked to lesions before language system development and frontal lobe myelinization; symptoms such as hallucinations and delusions (more frequent in LOS) may be linked to neuronal plasticity and abnormal neural connections that form in response to injury.

In reviewing the literature on cerebrovascular disease in delusional disorder and schizophrenia, Almeida and Starkstein [70] concluded that existing data are not supportive of the hypothesis that schizophrenia and delusional disorder with onset in later life are strongly associated with cerebrovascular disease, and that “cerebrovascular disease per se plays a limited role in the development of schizophrenia-like symptoms in later life”.

The impairment, although less severe, among patients with LOS in abstraction/cognitive flexibility and verbal memory compared with normal controls, has led some authors [42] to speculate about a similar involvement in EOS and LOS of prefrontal and temporal lobe regions. The authors hypothesize that “neurobiological changes occurring in mid or later life may also be important in the phenotypic manifestations of schizophrenia in some individuals”.

The high prevalence of LOS in women in the (pre)menopause years had lead to the estrogen theory [32, 34] that neuromodulatory and antidopaminergic effects of estradiol can delay schizophrenia onset in woman, until estrogen levels drop quickly.

One of the most articulate speculations about the etiopatology of LOS is reported in Jeste et al. [29] who hypothesized that there are different lesions according to symptom differences between patients with EOS, LOS and normal controls. In particular, it was hypothesized that the similarities in positive symptoms could be due

to disruption in orbitofrontal cortex circuits, the fewer negative symptoms in LOS to less disruption in anterior cingulate cortex circuits, and the neuropsychological performance of LOS, intermediate between EOS and controls, to lesions in the dorsolateral prefrontal cortex.

Conclusions and Future Directions

Robust epidemiological data for LOS and VLOSLP in the community are still not available; community surveys are probably inadequate to identify non-organic, non-affective psychoses, given the low frequency of this illness. Furthermore, lay interviewers should rule out at least 5–6 different diagnoses, and it is commonly believed that the most frequent psychotic disorder with onset in old age is the psychosis of Alzheimer disease. Clinical epidemiology, looking for first-contact rates is probably in a better position to give estimates of this illness, especially if a catchment area is clearly defined.

More recent studies on the symptom profile of LOS seem to confirm what was previously reported by many investigators, that LOS patients have less thought disorganization, less negative symptoms, better premorbid social adjustment, and a better response to antipsychotics. Reports in the 1990s, after DSM-IIIR dropped the 45 years upper limit for the diagnosis of schizophrenia, outlined some similarities between EOS and LOS such as a similar severity of positive symptoms, a similar genetic loading, the chronicity of course and a poor response to antipsychotics ("... these similarities suggest that what we call LOS is indeed schizophrenia; it is neither a mood disorder nor a progressive dementia" [29]). Later research, more interested in subtyping LOS, outlined more differences (less negative symptoms, more favorable response, less family history of schizophrenia, better course).

Accordingly, brain imaging has moved along three main research lines: looking for differences between LOS and healthy controls, similarities between LOS and EOS, and differences between LOS and EOS. The most frequent finding was that LOS and EOS had similar neuroimaging abnormalities [48–54] or few differences [49, 51, 54]. One study was discordant in that LOS subjects were found to be similar to healthy controls [55]. These findings reinforce the relatively recent changes in diagnostic systems that allow for the possibility of a typical schizophrenic syndrome in old age, but are at odds with data on the good response to treatment and the overall good prognosis in LOS.

A serious flaw of the studies on LOS is that a true control group is probably impossible. The choice of controls for LOS was done in almost all studies by matching subjects for age, so that controls were schizophrenia patients with a long duration of illness. Although this could balance the effect of age on the symptom profile, the results may be biased by the deteriorating effect of the illness. Vahia et al. [42] found, for example, that differences in cognitive flexibility (WCST) and verbal memory (CVLT) were no longer significant after weighing for duration of illness. It was estimated that aged patients with schizophrenia have a loss of 3 MMSE points

for each decade of life and that for verbal and visuomotor skills patients with EOS are more impaired than patients with Alzheimer disease with similar score at the MMSE [71]. Furthermore, aged patients with schizophrenia are not good representatives of their illness, because they are a group of better functioning psychotics who have survived decades of illness. In discussing the definitely lower prevalence of schizophrenia in old age, like the 0.1% of the Liverpool study [22], the investigators considered selective mortality as one of the first hypotheses.

Recent follow-up studies suggest a favorable course for LOS, both for the stability of cognitive performance, and for the improvement in global functioning. However, a few reports leave open the possibility of cognitive deterioration, at least in a subgroup of patients. This reminds us that the definition of LOS as a non-affective non-organic psychosis is a relative concept, at least as far as organicity is concerned. Those few cases who developed dementia had probably already started an Alzheimer disease that could not be detected with a MMSE, but with other, more sophisticated neuropsychological tests.

The premises of 2000 [12], that laid down the basis for at least an age threshold for LOS and VLOSLP, look now, after 10 years, probably too ambitious. Some assumptions were made, such as the distinction of a very late subgroup, possibly linked to an organic etiology. Unfortunately, this distinction was not often used in the papers that followed. One of the most recent, larger studies [42] on LOS (110 LOS vs 744 EOS) included patients with illness onset at 48.1 years, with a standard deviation of 7.3, so that only a few patients are expected to be 60+ at onset. To the best of our knowledge, of 22 experimental papers published after 2000, 13 considered only a broad category of LOS that included all patients with onset after 40 years of age. The remaining 9 papers dealt with VLOSLP, but most (6) were published by the same London group that proposed the criteria for VLOSLP [12].

One of the major paradoxes to be addressed by future research is the finding of a relatively good performance before the onset of LOS and data from neurobiology that would indicate the existence of neurodevelopmental defects, similar to EOS. One hypothesis is that social functioning in these subjects was indeed suboptimal [29], but data are definitely lacking. This could have some interest also for the identification of behavioral premorbid features, and possibly identifiable risk factors.

It is probable that, with progress in diagnostic techniques and testing, more cases with VLOSLP will be found to have an organic basis, and will no longer be diagnosed as schizophrenia-like. A proposal [72] to subtype LOS into 2 clusters, one (type A) with less cognitive impairment and complex psychotic symptoms, and the other (type B) with more cognitive impairment and more widespread signs of cerebrovascular disease, was criticized because type B LOS should be more properly diagnosed as a psychosis secondary to a general medical condition [73].

Notably, Emil Kraepelin [1] foresaw that "... the clinical forms of dementia praecox not only exhibit in themselves an extraordinary variety, but also, as formerly mentioned in detail, are distinctly influenced by age. The decision as to which

morbid disorders of the age of involution are to be reckoned with dementia praecox and which are to be regarded as psychoses of another kind, will therefore always depend on the question, how far the differences in the form of the clinical phenomena are conditioned by the character of the morbid process and how far by the changes of advancing age in the personality”... “It must remain for the future to decide whether, as I for the present consider more probable, it must be broken up into various groups according to the points of view indicated”.

More research in multisite studies is necessary, given the low numbers available for this population. Fewer numbers do not mean low clinical relevance, because the special features of this illness have attracted the interest of many authors for its heuristic connections. In the meantime, a more positive attitude toward non-organic, non-affective psychotic illness in the elderly is the strongest suggestion coming from recent literature, and its practical implications may be of great benefit to patients suffering from this disorder.

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Chapter 13
Neurological and Neuropsychological Endophenotypes in Schizophrenia Spectrum Disorders

Raymond C.K. Chan, William S. Stone, and Xiaolu Hsi

Abstract Increasing efforts to identify alternate expressions of mental disorders that are broader than the DSM or ICD diagnostic criteria needed to diagnose them reflects a growing consensus that multidimensional expressions of psychiatric disorders may advance the search for underlying etiological or modulatory factors. These alternate phenotypes or "endophenotypes" (e.g., social, psychophysiological or neuropsychological abnormalities) of disorders may be more specific and amenable to objective measurement than clinical symptoms, which presumably reflects variation among smaller numbers of genes than more distal clinical symptoms. These features support the current usefulness of endophenotypes in genetic studies, and their potential usefulness in the development of strategies for early intervention. In this chapter, we review potential neurological and neuropsychological endophenotypes for schizophrenia and for schizophrenia spectrum disorders, with an emphasis on key conceptual criteria for assessing endophenotypes, including their relationships to schizophrenia, to non-psychotic relatives, and to heritability. Future directions for establishing the validity of endophenotype research are also discussed.

Keywords Endophenotypes · Neurological makers · Behavioral markers · Schizophrenia

Abbreviations

COGS	Consortium on the genetics of schizophrenia
CPT	Continuous performance test
CVLT	California verbal learning test
DSM-IV	Diagnostic statistical manual 4th edition
ICD-10	International classification of disease 10th edition

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IQ	Intelligence quotient
MPAs	Minor physical anomalies
NSS	Neurological soft signs
VDM	Deficits in verbal declarative memory
WAIS-IV	Wechsler adult intelligence test 4th edition
WCST	Wisconsin card sorting test
WMS	Wechsler memory scale

Although genetic contributions to schizophrenia are well-accepted [1–4], the identity of most genes that increase susceptibility to the disorder, and the biological mechanisms by which they act, are largely unknown. One approach to understanding how genetic determinants of schizophrenia leads to the disorder emphasizes the idea that schizophrenia is broader than the DSM-IV or ICD-10 syndromes that are required for diagnosis [5]. The importance of identifying "endophenotypes" (e.g., social, psychophysiological or neuropsychological abnormalities) [6] reflects a growing awareness that multidimensional expressions of psychiatric disorders can advance the search for underlying etiological or modulatory factors [1, 6–11]. Moreover, endophenotypes may be more specific and amenable to objective measurement than symptoms, presumably reflecting variation among smaller numbers of genes than do more distal clinical symptoms [6, 12, 13], and are heritable [14, 15]. While the underlying genetic etiology of many putative endophenotypes have turned out to be quite complex themselves [16], these features all support the usefulness of endophenotypes in genetic studies [12, 13, 17].

Attempts to identify useful endophenotypes have focused largely on abnormalities in, or presumed to derive from, the central nervous system. This chapter focuses on two important classes of endophenotypes that reflect this focus: neurological endophenotypes and neuropsychological endophenotypes. In addition to their relationships to underlying neurobiological etiologies, neurological and neuropsychological share other common features. Both, for example, involve measures that are amenable to objective definition and measurement, and both have been studied intensively [8, 10, 18]. This review will highlight recent, representative findings in both of these areas. We will emphasize the utility of proposed neurological and neuropsychological endophenotypes in the context of key conceptual features that includes their association with the illness, their heritability, and their appearance in "unaffected" biological relatives.

Neurological Endophenotypes

Schizophrenia is conceptualized as a neurodevelopmental disorder characterized by anomalies of peripheral ectodermal structures that are formed simultaneously with the cerebral cortex during intrauterine development [19]. Both the neurological soft signs (NSS) and the minor physical anomalies (MPAs) are suggested to be very important direct and/or indirect evidence for cerebral maldevelopment in

schizophrenia [20]. Recent studies have demonstrated that these two neural manifestations are higher in schizophrenia but not in other mood disordered patients, when compared with healthy volunteers [21–24], and have been proposed as neurological endophenotypes for schizophrenia [8, 25–27].

NSS in Schizophrenia

Traditionally, NSS are defined as the minor neurological indicators of non-specific cerebral dysfunction and contrast with hard neurological signs, which are indicative of localized brain deficit. However, this distinction is artificial and may reflect an inability to define the brain-behaviour relationship that underlies the presence of NSS [28, 29]. Typically, NSS are classified into motor coordination, complex motor sequencing tasks, sensory integration, and disinhibition [28, 30].

Recent studies suggest schizophrenia is likely to have a polygenic mode of inheritance in which each gene carries a minor effect. The phenotypic expressions of some contributing genes may be widespread in the normal population. Consistent with this, NSS are also found in the normal population with a base-rate ranging from 5 to 59% [28, 29, 31, 32]. Tsuang and colleagues [33, 34] have considered NSS as the target features for schizophrenia and have argued that these NSS reflect genetic and nongenetic processes underpinning the predisposition to psychotic illness. Most recently, NSS have been considered to be one of the promising endophenotypes for schizophrenia [8].

Heritability and Genetic Correlates of NSS

There are two main sources for the heritability of NSS in schizophrenia, namely the direct evidence from the calculation of inheritability of NSS and the indirect evidence from the familial association. For the heritability calculation, Sanders and colleagues [35] specifically tested the heritability of NSS items in a group of 96 participants coming from eight extended families, each consisting of two first-degree relatives with schizophrenia spectrum disorders, as well as available first- to fifth-degree relatives. To a large extent, statistically significant heritability estimates were obtained for neurological abnormalities, particularly in items concerning motor coordination and complex motor sequencing such as the alternating fist-palm test (h^2 0,77 $\pm$ 0.19 for completion time; h^2 0.7 $\pm$ 0.32 fro errors), and go-ongo task (h^2 0.93 $\pm$ 0.33 for correct responses), and rapid alternating movement (h^2 0.99 $\pm$ 0.19 for completion time). Only audio-visual integration (h^2 0.79 $\pm$ 0.54) from the sensory integration signs was found to be heritable in this sample. These findings are consistent with recent findings that motor speed may be specifically heritable [36, 37]. These findings are limited to Caucasian sample. Given that NSS may be subject to cultural and ethnic variations [31, 38], these findings may not be generalized to non-Caucasian samples. However, our preliminary data from Chinese

healthy twins indicates that a similar heritability of NSS in the motor coordination (h^2 0.58) and sensory integration (h^2 0.57) subscales of the Cambridge Neurological Inventory [30].

For the familial association, data from twin studies generally support the idea that NSS are associated with schizophrenia. For example, Cantor-Graae et al. [39] demonstrated there was a significant difference among the patients with schizophrenia, monozygotic co-twins, and healthy monozygotic twins in NSS, with patients showing the highest prevalence of NSS and the healthy co-twins having the lowest prevalence of NSS. Niethammer et al. [40] also found that the twins with schizophrenia exhibited higher total scores of NSS than did the comparison participants. Moreover, the total scores for NSS of the nonaffected discordant twins were significantly higher than those of the comparison twins. The affected discordant twins showed higher total scores of NSS than the nonaffected discordant twins. Like the heritability of NSS, these differences between the three subgroups were limited to motor coordination signs.

Substantial findings other than the twin studies also support the argument of familial association of NSS with schizophrenia [29]. A recent meta-analysis indicates that there are already large effect sizes of the prevalence rate differences between first-onset schizophrenia and healthy controls, with Cohen's d ranging from 0.77 to 1.65, indicating that NSS are associated with the illness of schizophrenia and are not caused by medication effect. Moreover, another meta-analysis comparing the prevalence rate of NSS in nonpsychotic first-degree relatives of schizophrenia, patients with schizophrenia, and healthy controls also indicate that the NSS differences yield a mean effect size of 0.81 for schizophrenia patients and their non-psychotic first-degree relatives, and 0.97 for nonpsychotic relatives and healthy controls [18]. These two meta-analyses show that there large group differences in NSS prevalence between patients with schizophrenia, their nonpyschotic first-degree relatives, and healthy controls. However, there is a dearth of studies that have looked at NSS in at-risk individuals with schizophrenia such as those with schizotypal personality features [41, 42]. Barkus et al. [43] and Chan et al. [44] showed that at-risk individuals with schizotypal personality features exhibited significantly more NSS deficits than healthy controls. A re-analysis of our laboratory data on 75 individuals with schizotypal personality features, 104 patients with schizophrenia, and 93 healthy controls also revealed that prevalence of NSS in participants with schizotypal personality features was intermediate between healthy controls and patients with schizophrenia (Fig. 13.1). Schizotypal personality features and clinical symptoms of schizophrenia were positively associated with ratings of motor coordination, sensory integration and total soft signs. Taken together, these results are consistent with the argument that NSS are familial in nature, segregate with the illness and may be valid and useful endophenotypes.

Very few studies have been conducted to examine the genetic correlates of NSS in schizophrenia. Galderisi et al. [36] found that COMT Val 158 Met polymorphism is associated with cognitive and motor coordination soft signs in schizophrenia. They further showed that COMT polymorphism accounted for 6.6% of the cognitive performance variance, while patients with Val/Val genotype performed significantly

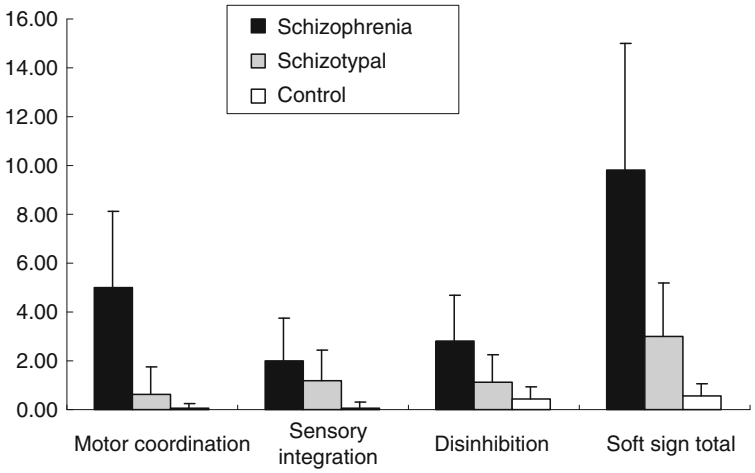

Fig. 13.1 Neurological soft signs between participants with schizophrenia, schizotypal and healthy controls

worse than patients with the Val/Met or Met/Met genotype. The COMT polymorphism also shared 15.6% of the motor coordination soft signs variance in patients with deficit syndrome but no such an association in patients with nondeficit syndrome. On the other hand, Chen et al. [45] also found that there was a significant association with small to modest effect size between genotype 102T/102C and patients with better verbal fluency and less motor coordination soft signs. However, these findings should be interpreted cautiously because there is strong genetic differences and noncombatility of data between European and East Asian populations on the C allele or CC homozygosity [46].

In sum, these findings suggest that although not all neurological abnormalities were heritable, there were at least familial influences on motor neurological soft signs in schizophrenia, and these heritable measures were also associated with specific genes in schizophrenia.

Clinical and Cognitive Correlates of NSS

Several studies examined the relation between NSS and clinical symptoms in schizophrenia. King et al. [47] first found NSS scores were correlated positively with both positive and negative schizophrenic symptoms; and it was also found in other studies [48, 49]. However, more studies found NSS were correlated with negative symptoms but not positive symptoms [50–54]. A recent meta-analysis comprehensively reviewed the literature and showed that correlation between NSS total score and symptom total score was significant ($r = 0.327$, 95% CI 0.213–0.432), relation between motor coordination subscale, sensory integration subscale and

motor sequencing subscale and symptom total score were all significant; correlation between NSS total score and positive symptoms were significant but weaker ($r = 0.192$, 95% CI 0.067–0.312), relationship between sensory integration, motor sequencing and positive symptoms were not significant; correlation between NSS total score and negative symptoms were significant ($r = 0.346$, 95% CI 0.260–0.426), relationship between motor coordination, sensory integration and motor sequencing and negative symptoms were all significant [18]. These findings suggest that NSS (including total scores and subscale scores) have significant relationship with clinical symptoms in schizophrenia patients, particularly negative symptoms. These may indicate NSS share similar neural substrates with negative symptoms, e.g. frontal lobes [55, 56].

There were some follow-up studies examining the stability of relationship between NSS and clinical symptoms or the relation between changes of NSS and clinical symptoms. For example, Mittal et al. [48] revealed that after 6 weeks of haloperidol treatment, the relation pattern was similar to baseline; NSS score was positively correlated with positive ratings, and negatively correlated with Brief Psychiatric Rating Scale (BPRS) psychological discomfort subscale. A study with 4-year follow-up found patients with schizophrenia showed NSS score correlated with negative symptoms at the follow-up [49]. Studies examining the relation between change in NSS and symptoms revealed that 6 weeks after treatment, changes in motor coordination, sequencing of complex motor acts, and sensory integration ratings were significantly correlated with changes in both total and positive subscale scores of BPRS, and change in total NES measures was significantly correlated with the change in total BPRS scores [57]. Whitty et al. [58] found that Improvements at 6 months follow-up in total NES and in motor coordination subscales were associated with improvements in positive, negative and total symptom scores; sequencing of complex motor acts was associated with improvement in positive and negative symptom scores; sensory integration was also associated with improvement in positive, but not negative symptom scores. These findings suggested that the relationship between NSS and clinical symptoms were also stable.

Increasing trend of studies has been started looking at the relationship between NSS and cognitive dysfunction in an attempt to identify a common neurobiological process that underlies both of these indexes of brain function in schizophrenia despite the fact that associations between cognitive domains and brain regions are complex. It has been stated that NSS have been conventionally considered to be neurological signs not reliably point to a specific brain region or network that could be associated with cognitive impairment. However, recent studies have suggested that neurobiological dysfunctions of NSS and cognitive impairments may share the same underlying neural bases. For example, Bersani et al. [59] found that there was a significant association between Wisconsin Card Sorting Test performance and motor sequencing items of NSS. Das et al. [60] further showed that patients with schizophrenia exhibiting high NSS abnormalities had lower IQ and greater impaired cognitive function, including executive function, memory, attention, psychomotor ability than those patients with fewer NSS abnormalities. More interestingly, even though both groups showed significant improvements on cognitive function

followed administration of atypical antipsychotics over a 6 month period, the low NSS group exhibited more improvement suggesting to the authors that the presence of high NSS in schizophrenia patients impedes the improvement in cognitive function with atypical antipsychotics treatment.

A most recent meta-analysis [18] also indicates that there is a modest correlation between NSS and neurocognitive function impairments in schizophrenia. The NSS total score was inversely correlated with the composite score of cognitive abilities (with Cohen's d ranging from 0.31 to 0.37). In particular, motor coordination signs were specifically associated with impairments in action and attention inhibition as well as verbal performance, whereas sensory integration signs were significantly associated with general intellectual functioning. Adopting a structural equation modeling approach, Chan et al. [61] further showed that NSS was more or less at a similar level to capture conventional neurocognitive functioning tests.

From a neuroanatomical perspective, Dazzan and Murray [62] found that frontal release NSS correlated with perseverative errors on Wisconsin Card Sorting Test in patients with schizophrenia and thus suggested that these signs may be frontal cortical in origin. Similarly, Keshavan et al. [63] also found that NSS concerning cognitive-perceptual domain correlated with the volume of heteromodal association cortex whereas NSS concerning repetitive motor coordination associated with caudate and cerebellum regions. These authors thus suggested that there was a relatively specific regional structural alteration association with NSS in schizophrenia.

Most recent structural brain imaging studies also indicated that NSS, especially the motor coordination signs and sensory integration signs, were significantly associated with a reduction of grey matter volume of subcortical structures, including putamen, globus pallidus and thalamus, in both first-onset schizophrenia and healthy volunteers [64, 65].

Taken together, the findings suggest that the correlations between NSS clinical symptoms of schizophrenia were relatively modest but significant. Although the assessment methods are different, NSS are also more or less equivalent to conventional neurocognitive functioning tests in capturing the deficits of central nervous system. Most recent imaging studies also provide evidence of these two presumably distinct constructs share the similar underlying neural bases.

Effects of Medication on NSS

As the presence of antipsychotic medication may confound the results, studies on medication free patients are particularly valuable. Evidence has been consistently reported there is no effect of neuroleptic treatment on NSS in schizophrenia [28, 62, 63, 65, 66]. King et al. [47] found a positive correlation between NSS and duration of neuroleptic treatment and current neuroleptic dose, which means the medication would worsen the NSS. Most other studies found medication did not have an effect on NSS. Poole et al. [67] found neuroleptic dose was unrelated to NSS. A study found there were no significant differences of NSS between baseline and 6 weeks post-treatment, except for a significant worsening of the glabellar reflex [57]. Other

studies found different types of medication did not affect NSS performance either. Smith et al. [68] found a change from a typical to an atypical neuroleptic medication did not consistently lead to lower NSS scores; and patients on clozapine monotherapy were compared with the patients receiving standard conventional neuroleptics, the NSS total score and the sub-scores were almost identical [69].

Chen et al. [66] examined NSS in 138 patients with first-onset medication-naïve schizophrenia and longitudinally tracked the expression of motor coordination NSS in the following 3 years. They found that the level of NSS at clinical stabilization was lower for patients with a shorter duration of untreated psychosis. However, the quantity of NSS abnormalities did not change significantly in the subsequent 3 years that followed the first initial episode. These findings further support the argument that there is not obvious progression in the level of motor coordination NSS in schizophrenia, at least in the first 3 years of the illness, that followed the first psychotic episode. Medication dose does not affect the prevalence of NSS in schizophrenia.

In a recent paper [18], relationship between treatment and NSS were comprehensively reviewed, among those reported data on correlation between NSS and treatment, 5 out of 6 found nonsignificant results, only one found significant correlation. Among those studies did not reported data on correlation between NSS and treatment, 9 out 10 found nonsignificant relationship, only 1 found both significant and also nonsignificant results. Most of the studies which contrast low dose and high dose medication found nonsignificant difference on NSS. These findings suggested that medication did not improve the NSS, and the NSS impairments were stable in patients with schizophrenia.

MPAs in Schizophrenia

MPAs are another set of risk markers for schizophrenia that are characterized by slight developmental and morphological abnormalities [70]. MPAs are typically described as subtle morphological deviations that have no serious medical or cosmetic significance to an individual, but are of great value to the clinicians because they can be utilized as risk markers for underlying disease susceptibility or disturbed development [71, 72]. This is thought to be particularly true when multiple MPAs occur together in a given individual and when an individual is already at high risk. Recent studies have suggested that schizophrenia is associated with a wide range of MPAs [22, 26, 73, 74].

MPAs are usually evaluated by clinical ratings [22, 75] and include items capturing the anomalies in different regions such as head and facial, eyes, ears, mouth, hands, feet, and torso. Classically, MPAs are exemplified by items such as protruding or recessing supraorbital ridge, confluent eyebrows, hypertelorism, adherent ear lobes. MPAs are a heterogeneous group of morphologic markers with both genetic and environmental determinants. The developmental timing of MPA formation limits their potential causes to prenatal and/or genetic/epigenetic factors that have the potential to disrupt fetal development [26]. Empirical findings have

been demonstrated that MPAs are commonly found in patients with schizophrenia than in healthy controls [22, 73, 76–78]. Two most recent meta-analytical studies indicate that the pooled effect size was 1.13, indicating that a high degree of difference in MPAs between patients with schizophrenia and healthy controls [74, 79].

Moreover, MPAs have also been demonstrated at a higher frequency in at-risk individuals such as those characterized with schizotypal personality features. For example, Weinstein et al. [80] found that at-risk adolescents characterized with schizotypal personality features exhibited more MPAs than adolescents with other personality disorders and those without psychiatric illnesses. Bollini et al. [42] further adopted a very rigorous methodology to examine the relationships between schizotypal personality features and MPAs as well as NSS. To maintain representativeness of the sample, Axis II schizotypal personality disorder symptoms were assessed using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) [81] in addition to the administration of the Schizotypal Personality Questionnaire [82]. MPAs were recorded using a structured scale adapted from Lane et al. [22] and Waldrop and Halverson [75], and NSS were assessed by the Neurological Evaluation Scale [83]. Twenty-six first-degree relatives of schizophrenia patients (characterized by the schizotypal personality features) and 38 healthy controls without schizotypal personality features were recruited. The authors found that the mean schizotypal scores did not different between relatives and controls. However, both NSS and MPAs were associated with the level of interviewer-assessed schizotypal personality features in controls but not in relatives of patients with schizophrenia. MPAs and NSS were note associated with self-reported schizotypal personality features in either group. These findings suggested that both MPAs and NSS were associated with interview-based schizotypal personality features, at least in non-psychiatric participants.

A recent meta-analysis done by Xu et al. [79] also shows that there is a medium effect size of the prevalence rate between patients and first-degree relatives of schizophrenia (Cohen's $d = 0.45$). Taken together, the aforementioned studies indicate that MPAs are found in patients with schizophrenia and also unaffected relatives (though to a lesser extent), which is consistent with the idea that MPAs may represent a potential endophenotype for schizophrenia.

Heritability and Genetic Correlates of MPAs

There is also evidence of a link between heritability of MPAs though the effect size is not as strong as that of NSS [21]. However, these findings should be interpreted with cautious because there are only very limited empirical evidence from twin study and large large-scale molecular genetic studies. Moreover, MPAs may come from both the inherited genetic risk and acquired genetic risk. For example, Griffiths and colleagues [84] found that families with a single case of schizophrenia might manifest more MPAs than multiplex families, suggesting that MPAs result from an insult during fetal development rather than from a genetic liability of schizophrenia.

Future studies should aim at identifying the heritable and nonheritable determinants of MPAs in schizophrenia and the nature of their association with schizophrenia.

Clinical and Cognitive Correlates of MPAs

Relatively few studies have been conducted to examine the relationship between MPAs and clinical symptoms in schizophrenia. Of the limited studies, empirical findings suggest that there is no correlation found between MPAs and clinical symptoms of schizophrenia [24, 85–87] as well as neurocognitive performances in schizophrenia [24]. A number of studies have been conducted to examine the potential associations between MPAs and NSS in schizophrenia. However, most of them indicate that MPAs and NSS are not correlated with each other [21, 24, 50, 54, 88–90], though there are few reports of a positive association [21]. Gourion and colleagues [21] have examined specifically the relationship between NSS and MPA in schizophrenia. In particular, they classified the nonpsychotic parents of patients with schizophrenia into "presumed carriers" and "non-presumed carriers". Presumed carriers referred to those parents if they had a second relative with schizophrenia in their ascendants, collaterals (first or second degree), whereas presumed non-carriers referred to those parents without a genetic loading. They found that NSS scores and MPA scores correctly classified 71% of nonpsychotic parents into presumed carriers or presumed non-carriers. However, in another study, Gourion [50] found there was no support for intrafamilial transmission of MPAs in 18 patients with schizophrenia and 36 nonpsychotic parents. These authors only found that NSS showed similar patterns of deficits in the two groups but not MPAs. In general, these findings suggest that neurological soft signs and MPAs are distinct risk markers. However, a co-assessment of both the MPAs and NSS may represent a composite endophenotype of developmental markers for schizophrenia [21, 91].

Neuropsychological Endophenotypes

Neuropsychological deficits are both hallmarks and core features of dysfunction in schizophrenia. Quantitative studies over the last decade demonstrate significant cognitive impairment across a broad range of cognitive domains [92–94]. Cognitive deficits are associated with both impaired quality of life and with poor functional outcomes [95–97]. They are stable and present in all phases of the illness. This section focuses on neuropsychological deficits considered broadly first, and then considered more discretely in particular cognitive domains. We will focus on representative areas that are both significantly impaired and well-studied: overall cognitive abilities, learning and memory, attention, and executive function. We will also emphasize specific representative tests/variables within each domain to identify the most valid endophenotype candidates.

Broad/Generalized Deficits. The notion of broad or more generalized deficits can be viewed in at least two ways. One is to consider single measures that are presumed to assess more generalized functioning, such as Full Scale IQ scores derived from Wechsler intelligence tests. Impairments in broad measures of cognition, however, occur in the context of broad neuropsychological impairments across many domains in schizophrenia [98, 99]. This raises the question of whether separable cognitive deficits really occur, or whether they reflect a more generalized deficit that is evident in whichever cognitive domain is assessed. These choices are not mutually exclusive, however, as recent studies reveal both general and more specific cognitive deficits in schizophrenia [100–102]. We will focus on IQ scores as a general measure of cognitive function because they are relatively discrete measures that can be assessed/compared more easily across studies.

Aylward et al. showed in a 1984 meta-analysis that overall cognitive ability as measured by IQ scores in subjects who subsequently developed schizophrenia or related disorders, was lower than in comparison samples [103]. The effect size (Cohen's d) was small to medium (–0.43). More recently, Woodberry et al., performed a meta-analysis on 18 studies in which subjects subsequently developed schizophrenia, schizoaffective disorder or schizophreniform disorder, using more recent diagnostic criteria [104]. Consistent with Aylward et al., these subjects showed lower overall cognitive abilities, as measured by IQ scores, with a moderate effect size relative to comparison samples (–0.54). This effect size is about half the magnitude of the overall cognitive deficit in schizophrenia [28], which shows that a substantial portion of the deficit appears premorbidly. Sorenson et al. also showed that children 10–13 years who later developed a disorder in the schizophrenia spectrum had lower IQ scores compared to a group who did not develop a psychiatric disorder [105].

Mesholam et al. included data from 47 studies in a meta-analysis of first-episode schizophrenia [106]. They showed medium to large deficits across 10 neuropsychological domains (effect sizes from –0.64 to –1.20), including an overall cognitive domain (effect size = –0.91) that was composed mainly of IQ tests. They also found that the magnitude and extent of cognitive deficits at the first episode was similar to the level of deficits observed in chronic schizophrenia [93, 94], which demonstrates further the stability of these deficits.

Nonpsychotic relatives of patients with schizophrenia also show stable, cognitive deficits [107–109]. A meta-analysis that assessed 43 neuropsychological test scores from 58 studies showed smaller differences from control subjects than generally occur with patients [109]. Differences in overall cognitive ability, using the WAIS-R, however, were significant, with a small effect size (0.31).

A meta-analysis of IQ showed moderate levels of heritability (0.48) [110]. At least one study assessed the heritability of IQ in schizophrenia, and also showed significant findings. Husted et al. assessed the heritability of neuropsychological measures in 17 multiplex Canadian families. Most cognitive measures showed small to moderate heritabilities (0.31–0.62), with the highest heritability shown by IQ (0.64–0.74; the estimates varied slightly in different statistical models) [15].

Verbal Learning and Memory

Deficits in verbal declarative memory (VDM) are among the most consistent and severe neuropsychological deficits in schizophrenia [92–94, 99, 111]. The putative endophenotype usually refers to performance on tests of learning and memory that assess the abilities to learn, retain and retrieve specified information. Its association with the illness is robust. Effect sizes versus appropriate comparison populations are often large, in the 1.0–1.5 standard deviations range [92–94, 111, 112]. Deficits in VDM are thus associated closely with schizophrenic illness.

Deficits in VDM are also stable. They occur at different phases of the disorder, including the prodrome and prior to frank psychosis, and after remission from psychotic symptoms [104, 111, 113–118]. Mesholam et al. showed a large effect size (–1.20) for an Immediate Verbal Memory composite score in their meta-analysis at the time of the first episode, and even larger effect sizes for specific test measures [106]. Among these, immediate recall of short stories on the Wechsler Memory Scale (WMS) Logical Memory Test was –1.47, while the total number of words recalled correctly over the course of 5 trials on the California Verbal Learning Test (CVLT) was –1.34. One of the largest evaluations of this same measure of learning on the CVLT was performed at 7 sites as part of the Consortium on the Genetics of Schizophrenia (COGS), with 509 control subjects, 309 subjects with schizophrenia, 449 sibling relatives and 232 parent relatives [119]. The effect size for subjects with schizophrenia was again large, consistent with the results obtained by Mesholam et al.

Deficits in VDM occur independently of deficits in overall cognitive ability [118], are mainly independent of clinical state [111], and are largest in the learning/encoding stage [111], with milder deficits evident in rates of forgetting and in recognition, similar quantitatively to that observed in other conditions with mild medial temporal lobe damage [120, 121]. Moreover, VDM deficits prior to treatment show that the deficits were not caused by antipsychotic medications, which may palliate them to a modest degree [122, 123].

Non-psychotic biological relatives of individuals with schizophrenia also show impaired encoding on VDM, but the deficits are milder, and do not involve the rate of forgetting [10, 107, 108, 111, 119, 124–128]. The qualitative similarity of the deficits to those that occur in patients adds to the view that impairments in VDM reflect intrinsic features of the disorder (i.e. endophenotypes) rather than secondary phenomena related to effects of medication, psychosis or other cognitive dysfunctions.

Memory in healthy adults is moderately heritable [129, 130], and evidence is growing that deficits in VDM in schizophrenia are similarly heritable. As noted above, for example, Husted et al. assessed heritability of several neuropsychological functions, and IQ [15]. Immediate recall on the WMS Logical Memory Test was among the measures that showed significant heritability (0.40–0.49). Wang et al. showed that performance on the Logical Memory Test was the most heritable neuropsychological measures assessed (0.34) in a sample of first-episode, drug naïve, Han Chinese patients with schizophrenia and their siblings and parents, in

relation to controls [102]. Calkins et al. assessed the heritability of several neuropsychological functions in African-American probands with schizophrenia or schizoaffective disorder, their biological relatives and in control subjects [131]. They showed significant heritability for several composite neuropsychological functions, including verbal memory (about 0.50). Performance on this verbal memory composite also showed significant heritability (0.66) in a previous multiplex, family study of schizophrenia from the same group [132]. Greenwood et al. demonstrated significant heritability for CVLT performance (0.25) in the COGS study, which included subjects with schizophrenia or schizoaffective disorder, depressed, and their biological siblings and parents [14].

Attention

Deficits in attention have long been considered central features of schizophrenia, and are among the most extensively studied [131–137]. Several overlapping dimensions of attention are impaired. These include, among others: (1) attention span, which refers to the extent of information that can held in mind; (2) selective attention, which refers to an ability to focus on particular stimuli; (3) cognitive control of attention, which refers to the abilities to organize and direct attention in relation to task demands; and (4) sustained attention and concentration, which refer to the abilities to sustain focus over time, sometimes in the presence of interfering or prepotent stimuli. Many of these aspects of attention are impaired in schizophrenia. Heinrichs and Zakzanis showed medium to large deficits in their meta-analysis of 22 measures derived from 204 studies [94], for example, including medium-sized deficits in auditory attention span (0.62) and large deficits in measures of sustained attention (1.18). Henirichs also showed a large effect size (of over 1.0) for deficits in sustained attention more recently [93].

Mesholam et al. divided attention into three composite (i.e. subdomain scores) in their recent first episode study [106]. In the first of these, tests of attention also emphasized processing speed and produced an Attention: Processing Speed composite score that showed a large deficit compared to controls (–0.96). A second dimension of attention was assessed with an Attention: Vigilance subdomain that included scores from computerized continuous performance tests (e.g. omission errors, commission errors, and d'). This composite demonstrated a medium effect size versus control subjects (–0.72). The third subdomain emphasized "working memory", which refers to the abilities to both hold information in mind consciously and manipulate it to solve problems or make decisions. The type of tests that comprise the Attention: Working Memory subdomain, which will also be considered in the next section (Executive Function), showed a medium to large effect sized deficit relative to control subjects (–0.79).

Different dimensions of attention overlap with each other to varying degrees, and with other neuropsychological deficits. Cohen et al., for example, showed that cognitive control of attention was closely related to mechanisms involved in the representation and maintenance of contextual information needed for the

efficient selection of task-appropriate actions (i.e. working memory) [138]. The overlap between cognitive dimensions of function or dysfunction again raise questions about the prominence of general cognitive deficits in schizophrenia, as opposed to definable, more specific deficits. Consistent with other recent findings, however [100, 102], Nuechterlein et al., in their review of 13 factor analytic studies, also demonstrated support for separate cognitive deficits, including a separate attention/vigilance factor that focused on sustained, focused attention [10, 101].

Progress in defining and validating deficits in sustained attention separate from other, related cognitive dysfunction, together with consistent evidence of medium to large deficits, has contributed to a focus on sustained attention as an endophenotype in schizophrenia [133, 139]. Continuous performance tests (CPT) are the most widely utilized measures to assess sustained attention [10]. While different versions of the test are differentially sensitive to related cognitive dysfunctions (e.g. in working memory or perceptual processing) in schizophrenia, even simpler versions show consistent, medium to large deficits in vigilance, in most studies [106, 140, 141].

Performance stability has been demonstrated for several versions of CPTs. Among these, the degraded stimulus CPT and the CPT, identical pairs version, showed good reliability across sites, nationally and internationally [10, 142]. Deficits in these tests occur in medication naive subjects and in subjects taking antipsychotic medications [143, 144], and they occur in different stages of illness [145–147].

Like their ill relatives, nonpsychotic biological relatives of individuals with schizophrenia also show deficits in CPTs [10, 108]. Snitz et al. showed small to medium effect sizes for several variables [109]. Among these, a quantitative measure of the ability to distinguish target from non-target stimuli (d') showed a medium deficit in the CPT, identical pairs version (–0.53), as did false alarm responses (–0.54). Recent large studies using the Penn Battery version of the CPT have also demonstrated significant deficits in nonpsychotic relatives [131, 132]. Nonpsychotic relatives show smaller deficits on simpler versions of CPTs, rather than on more complex versions that contain higher "loads" of working memory, interference and or perceptual processing [108], but still show significant impairments in vigilance with minimal working memory and perceptual processing loads [140].

A growing literature shows that performance deficits in attention are significantly heritable. Cornblatt et al. showed heritabilities for the CPT, identical pairs version, of 0.39 (using digits as verbal stimuli) and 0.49 (using shapes as visual, nonverbal stimuli) in healthy families [142]. Chen et al. showed heritabilities of 0.48–0.62 in relatives of patients with schizophrenia [148]. Greenwood demonstrated a significant level of heritability for the degraded stimulus version of the CPT (0.38) in the COGS project [14], while Gur et al. and Calkins et al. showed significant heritability using the Penn Battery CPT (0.50 and 0.40, respectively) [131, 132]. Interestingly, a recent study that assessed heritability for performance in tests of attention that did not utilize CPT tests did not show significant levels of heritability [102], which validates the use of CPTs as endophenotypes further.

Executive Function

Executive functions refer to a family of cognitive abilities that include, among others, the acquisition, organization, maintenance, transformation, updating and retrieval of information, and also its protection from interference. These properties underlie and contribute to many adaptive cognitive and functional activities, such as learning, problem solving, fluency, processing speed, mental persistence and resistance to interference. Like the other cognitive domains reviewed in this discussion, executive functions are involved in the normal performance of many cognitive tasks. Also similar to the other cognitive domains reviewed in this section, executive functions are often robustly impaired in schizophrenia [10, 99, 108, 132, 145, 149, 150], but separable from other cognitive abilities [101] in at least some dimensions.

Many studies documented deficits in executive function in schizophrenia. Among several that quantified the magnitude of the dysfunctions, Henrichs et al. used an executive function composite score based on performance on the Wisconsin Card Sorting Test (WCST), which showed a large deficit (effect size = 0.95) compared to control subjects. Heinrichs also showed deficits with large effect sizes in a 2005 meta-analysis for performance on the WCST and on tests of verbal fluency (both > 1.0). Mesholam et al. also used an executive function composite based on WCST function their meta-analysis of first episode schizophrenia and showed a large deficit (–0.83). Other aspects of executive function have also shown significant deficits. Lee and Park, for example, showed small to medium deficits in visual-nonverbal (–0.46) and in verbal (–0.45) working memory tasks. Wang et al. showed medium to large effect-sized deficits (–0.73 to –1.33) for prospective memory tasks (i.e. remembering to carry out intended actions) [151].

Despite the large deficits shown in schizophrenic subjects for several measures of executive function, they do not have equal potential as endophenotypes. Deficits on the WCST, for example, though large and studied extensively, may have limited value as an endophenotype. Heritability studies for WCST performance have been inconsistent, with several studies failing to show significant heritability estimates in schizophrenia families [132]. Kremen et al. performed the largest adult twin study to date on the heritability of the WCST, using the Vietnam Era Twin Registry sample, and failed to show either significant heritability or monozygotic – dizygotic differences [152]. Several factors probably contribute to inconsistent WCST heritability levels in the context of large deficits in performance, including the complexity of the test and a multitude of cognitive factors that contribute to performance [152].

Working memory tests provide another paradigm that emphasizes executive function, has been studied extensively in schizophrenia [153], and is more promising as an endophenotype. There are two broad classes of working memory studies. As noted above, the first one emphasizes vigilance and the transient maintenance of information (e.g. WAIS-IV Digit Span Forward). The second class involves vigilance and maintenance of information as well, but it also involves the manipulation of information (e.g. WAIS IV Letter-Number Span). It is the second type of working memory task that emphasizes executive functions, and which will be considered here in more detail as a putative endophenotype for schizophrenia. This paradigm

also corresponds to the more complex working memory tasks referred to in the Attention section, above [106].

Effect sizes for all working memory paradigms considered together [153] are smaller than they are for the cognitive endophenotypes reviewed above in overall cognitive ability, verbal declarative memory and sustained attention. More complex paradigms with heavier executive function deficits, however, often demonstrate large effect sizes [132]. This point was demonstrated, for example, in a recent, large COGS study that compared performance on simple and more complex verbal working memory paradigms in schizophrenia probands, their relatives, and control subjects [154]. Effect sizes for the probands versus controls were large (–0.94) for the more "executive" paradigm, and were medium (–0.54) for the simpler paradigm that emphasized vigilance.

Deficits in working memory show other features similar to the strong endophenotype candidates discussed above. These include stability. Deficits in working memory are present at all stages of the illness [10, 106, 146, 153, 155], are present with and without antipsychotic medication [156, 157] and are not secondary to clinical symptoms of schizophrenia [155].

Non-psychotic relatives of patients with schizophrenia show smaller, but significant deficits in working memory. Snitz showed, for example, small (e.g. –0.27, digit span, backward condition) to medium (e.g. –0.55, spatial delayed response tasks – accuracy). Like patients with schizophrenia, working memory tasks that emphasize executive function show greater effect sizes in relatives. Conklin et al. showed, for example, that effect size increased from a digit span forward (–0.43) to a digit span backward (–0.56) to a letter-number span (–0.66) paradigm [158]. Horan et al. showed similar findings, with a larger effect size in a letter-number span paradigm that required re-ordering (–0.36) than a letter-number span that did not require re-ordering (–0.22) [154].

Performance on working memory tasks shows significant heritability in both healthy subjects (0.43–0.49) [159, 160] and in families with schizophrenia (0.36–0.42) [161]. Recent studies by Husted et al., Calkins et al., and Greenwood et al., provide additional evidence for heritability of working memory performance in schizophrenia families (0.32–0.50) [14, 15, 131].

Conclusions and Future Directions

This review confirms that schizophrenic illness is associated with numerous neurological and neuropsychological abnormalities that are not related formally to DSM-IV or ICD-10 diagnostic criteria for schizophrenia or for other disorders in the schizophrenia spectrum. Many of these abnormalities do meet some or all criteria proposed for endophenotypes, however [6]. It is equally notable that the demonstration of NSS, MFA and neuropsychological deficits reviewed here represent only a few of the potentially important endophenotypes in these areas. Moreover, endophenotypes reflecting other types of brain (e.g. psychophyiological abnormalities and

other abnormalities in brain structure and function), clinical and social function, and other dimensions of functional capacity, are at least equally important. Together, they open new windows of investigation into the etiology of schizophrenia, and perhaps even more importantly, into new strategies for intervention and prevention.

Particular neurological and neuropsychological endophenotypes are important functionally, irrespective of their relationships to other measures. Individuals with significant IQ, VDM, sustained attention and/or working memory deficits will be disadvantaged in coping with their environments, for example, regardless of whether they have schizophrenia. Yet the functional importance of the endophenotype, coupled with a lack of specificity for schizophrenia, limits the potential value of the endophenotype. This is even truer of NSS and MFA that may not have obvious functional correlates, and it raises the question of how to maximize the utility of multiple endophenotypes.

At least two related directions for future research should be emphasized. The first involves a need to further validate the utility of potential individual endophenotypes. In addition to assessing whether potential response measures meet proposed criteria for endophenotypes, for example, it will be essential to determine epidemiological properties that include their base rates, their sensitivity to detect truly affected individuals, and their specificity to reject truly unaffected individuals.

These principles of psychiatric epidemiology are also inherent in the second direction for future research, which involves the development of liability syndromes. Neurological, neuropsychological and other types of endophenotypes offer a significant opportunity to identify and establish such syndromes, which helps to bridge the gap between genotypes and clinical symptoms of schizophrenia (and other disorders). In addition to sensitivity and specificity, other principles of epidemiology, such as a syndrome's positive predictive power (i.e. the probability that someone who meets criteria for the syndrome will actually develop schizophrenia or a related disorder) and negative predictive power (i.e. the probability that someone who does not meet criteria for the syndrome will not develop schizophrenia or a related disorder) will also help establish the syndrome's utility. At this point, many endophenotypes have been proposed [13], but few diagnostic criteria have been put forth, and even fewer have been validated.

Nevertheless, the development of liability syndromes that utilize multidimensional endophenotypes from diverse areas of function has the potential to capitalize on advances in genetics and neuroscience and relate them to multiple clinical domains in ways that transcend traditional nosology and increase opportunities for effective intervention. In one such approach, Tsuang and colleagues proposed a reformulation of Meehl's concept of liability for schizophrenia (called "schizotaxia") [162] to include measurable, clinically meaningful symptoms, including neuropsychological deficits and negative symptoms, in adult, non-psychotic, first-degree, biological relatives of patients with schizophrenia [5, 34, 163, 164]. While initial attempts at concurrent validation of the syndrome are encouraging [165], the real potential importance of the syndrome and the endophenoypes that comprise it derives from its broader view of the population at risk for schizophrenia, and its potential to identify novel treatment targets that might reduce both the risk and the

expression of the disorder. Whether the field adopts this version or another version of schizotaxia for this purpose is unimportant. In contrast, the ability to capitalize on the potential of endophenotypes to improve our understanding of both diagnosis and treatment may be critical to our progress in both areas.

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Chapter 14
The Association of Metacognition with Neurocognition and Function in Schizophrenia: Advances from the Study of Personal Narratives

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Abstract Research has confirmed that many with schizophrenia experience deficits in metacognitive capacity defined as impairments in the ability to think about thinking, both with regards to their own thinking and the thinking of others. These difficulties are related to but not reducible to symptoms. One question posed here for contemporary research regards how these deficits are linked to other forms of cognitive deficits, including deficits in neurocognition, and how they and other forms of cognitive deficits are related to the ability to function. As neurocognition is degraded during the early course of schizophrenia, does the ability to think about one's own thinking diminish? Furthermore, even if related to deficits in neurocognition, do deficits in metacognition affect function in a manner independent of deficits in neurocognition? Does metacognitive function mediate the impact of neurocognitive deficits on daily functioning? To explore these possibilities, this chapter reviews recent studies which have advanced our understanding of these issues by studying metacognition as it occurs spontaneously within personal narratives of self and illness by adults with schizophrenia spectrum disorders. Results are presented which suggest that impairments in verbal memory and executive function may interfere with the ability to form and sustain representation of one's own internal state as well as the internal states of others. Additionally, results are detailed which suggest that metacognitive deficits directly affect function prospectively and may mediate the impact of neurocognitive deficits on functioning.

Keywords Schizophrenia · Psychotherapy · Recovery · Narrative · Metacognition · Recovery · Psychosis · Quality of life · Self

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Introduction

The term "Metacognition" refers to an individual's general ability to think about his or her own thinking. This capacity is thought to reflect a wide range of semi-independent faculties which allow the individual to form representations of his or her own mental states and the mental states of others. Metacognitive ability allows one to form, challenge, and revise ideas of what is believed, felt, dreamt of, or feared in a number of rapidly evolving contexts. This critical function allows the individual to sustain more enduring ideas about the person one is across different situations, which then lays the groundwork for an evolving, nuanced personal narrative [1].

Over the last two decades, research has suggested that deficits in metacognitive capacity are common in persons with schizophrenia. Relative to those without psychosis or significant mental illness, persons with schizophrenia have difficulties distinguishing the source of internal experiences, perceiving themselves as agents in the world and detecting the intention and emotions of others from verbal and visual cues [2–7]. These deficits appear to be relatively stable over time and, while correlated with severity of psychopathology, are not simply a straight forward consequence of symptoms or other clinical features of schizophrenia [8–11].

The discovery of metacognitive deficits has led to interest in their relationships with other aspects of the disorder and with their potentially significant role in determining long term outcome. In this chapter we will explore advances in this area made through the study of metacognition as it is manifest in the personal narratives of persons with schizophrenia. Specifically we will explore whether deficits in neurocognition, including impaired capacity for storing and processing information, has a deleterious effect on an individual's ability to consider his or her own mental states and the mental states of others when assessed using these methods. We will then examine whether deficits in metacognition could affect function in a manner independent of deficits of neurocognition and whether metacognition may mediate the impact of neurocognitive deficits on functioning in people with schizophrenia. As a matter of intuition, it seems likely that reduced capacity to think about thinking would be related to neurocognitive deficits and might determine in part the extent to which these difficulties affect functioning, but the nature of this relationship is yet unclear. A nuanced understanding of these issues could have important implications for clinical issues ranging from prevention to remediation, as well as for emerging neurobiological models of social function.

Accordingly, this chapter will be divided into five sections. In the first we will broadly discuss the relation between neurocognition and metacognition. In the second we will describe the rationale for, development of, and psychometric properties of a method for assessing metacognition from personal narratives of self and illness. In the third section we will present results of recent work using these methods that has demonstrated links between metacognition as so assessed and neurocognition. In the fourth section we will turn to the relation of metacognition and social and vocational function and present studies suggesting that metacognitive capacity affects functional outcome and mediates the impact of neurocognition on those outcomes. Finally, implications and future research direction will be discussed.

Theoretical Impetus for Investigating the Relation Between Neurocognition and Metacognition

Impairments in neurocognition are believed to appear early in the course of schizophrenia and include losses in previously held levels of ability to sustain attention, sort relevant from irrelevant stimuli, recall and recognize visual or verbal material, and think in a flexible and abstract manner (e.g., David and colleagues [12]). The loss of these capacities has been widely suggested as limiting the ability to learn new material and to adaptively solve problems [13, 14]. Given the pervasive nature of these deficits, it seems plausible to hypothesize that as neurocognitive abilities decline, there may be a point at which metacognitive capacity is degraded. Intact neurocognitive function may not be necessarily sufficient for full metacognitive function; however, certain levels of neurocognitive function may be necessary to perform some basic metacognitive acts. Indirect evidence for this hypothesis includes findings that more severe deficits in flexibility of abstract thought and context processing limit both social cognition and the acquisition of social skills in rehabilitation [15–17].

The possibility that cognitive decline in schizophrenia could underpin some deficits in metacognition is also consistent with research in other types of mental illness. With the general loss of cognitive function, many with dementia experience familiar social situations as increasingly confusing and difficult to decode [18]. The loss of neurocognitive abilities as a result of traumatic brain injury has also been suggested to lead to reduced ability to perform basic self-monitoring tasks and to shift mentally between different self-representations and sustain a functional sense of self [19, 20]. In Asperger's syndrome, difficulty with interpreting the thoughts and feelings of others has been linked to difficulties with integrating contextual information, as well as to impairments in executive function which compromise persons' abilities to shift back and forth from two different viewpoints of the same event [21]. Finally, developmental studies of young children suggest that executive functions emerge prior to the ability to think about the mental states of others, and may form the basis for this metacognitive ability [22]. Thus, in the least, there is a broad literature consistent with the possibility that declines in neurocognition might limit the capacity for metacognition to some extent.

Limitations of Current Research on Metacognition and Neurocognition

Despite the intuitive and theoretical grounds leading to the presumption that neurocognitive impairments contribute to metacognitive deficits in schizophrenia, research on this subject has been hampered to date by a number of methodological issues. For one, most studies have assessed metacognition by measuring performance on a laboratory task which simulates social interaction or a self-reflective task. Participants might be asked, for instance, to discern the intentions of characters

in a story or cartoon. In another task, they might be asked to determine whether movements they were watching on a screen were mimicking the movement of their own limbs [2, 23]. Yet, in daily life, metacognitive acts often occur in emotion-laden contexts. Judgments in real time about mental states often involve others and situations for which one has strong feelings. Thus, performance on tests using impersonal stimuli may not accurately describe persons' abilities to engage in metacognitive acts when sensitive personal issues are involved.

A second problem is that these laboratory-based tasks cue or call for specific metacognitive acts at specific times; participants make responses after an explicit request for a judgment. Thus, another problem is that these tasks may be measuring how persons respond to cues for metacognition but not necessarily how they think and act spontaneously. A third difficulty is that metacognition is often studied as a one-dimensional phenomenon. Metacognitive acts, however, which have different foci (e.g., thoughts about one's own thoughts vs. interpreting another person's intentions) may involve capacities which are not only conceptually distinct but also involve semi-independent neurocognitive functions. Research suggests that creating a mental image of oneself activates a range of cortical structures, some of which are common with those utilized when creating an image of another, but others which may be unique to self-reflection [24–26]. Accordingly, an examination of only a single axis of metacognition carries the risk of missing the possibility that the capacity to perform different metacognitive acts are linked with separable neurocognitive functions and that some groups of persons may exist in which certain domains of metacognition are impaired while others are more relatively intact (e.g. persons able to discern their own emotions but have little sense of others emotions).

To measure metacognitive function as it might exist in emotionally salient tasks which do not cue for responses, we have proposed a method to rate metacognitive ability from a spontaneously generated speech sample. That speech sample is obtained through a semi-structured interview called the Indiana Psychiatry Illness Interview (IPII), which elicits a narrative of self and illness and typically lasts between 30 and 60 min [27]. Responses are audio taped and later transcribed.

The IPII is divided into five sections. First, participants are asked to tell the story of their lives in as much detail as possible, beginning with their earliest memory. Second, participants are asked if they think they have a mental illness and, if so, how they understand it. This is followed with questions about what has and has not been affected by their condition in terms of interpersonal, vocational, and psychological experiences. In the third section, participants are asked if their condition "controls" their life and if and how well they "control" their condition. Fourth, participants are asked how much their illness is affected by others and to what degree others have been affected by their illness. Finally, participants are asked what they expect to stay the same and what they expect to change in the future, again in terms of interpersonal and psychological function.

The IPII differs from other psychiatric interviews in that the interviewer is instructed not to introduce content. Interviewers do not ask participants about symptoms, for instance, whether they hear or see things other people do not hear or see. The interviewer may ask for minor clarification when confused and also may query

non-directively, however he or she may not pose questions about specific matters nor ask for historical details to anchor the story. The IPII thus produces a self-narrative in which specific metacognitive acts may appear spontaneously. As a life story is told, there are a number of opportunities in that story where participants may demonstrate the ability to think about their own thinking, the thinking of others, or how certain challenges are best faced. Furthermore, because one's personal narrative is accompanied by descriptions of other people who played critical parts in that narrative, the IPII allows the participant to demonstrate a wide range of metacognitive ability, and thereby avoids assessing only one dimension of metacognition. For example, individuals are not only prompted to reflect on their own experiences, but to describe their relationships with others as well as others' relationships that are independent of the participant. Thus, different dimensions of metacognitive capacity may be evaluated from the same interview.

To quantify metacognitive capacity within IPII narratives, we have used a modified version of the *Metacognition Assessment Scale* (MAS) [28]. The MAS was originally designed to detect changes in the ability of persons with severe personality disorders to think about their own thinking by evaluating transcripts from psychotherapy sessions. In consultation with the original authors, the MAS has been adapted for the study of IPII transcripts [29].

The MAS contains four scales which pertain to different foci of metacognitive acts: "Self Reflectivity," or the comprehension of one's own mental states, "Understanding of others' minds," or the comprehension of other individuals' mental states, "Decentration," which is the ability to see the world as existing with others having independent motives, and "Mastery," which is the ability to use one's mental states to implement effective action strategies in order to accomplish cognitive tasks or cope with psychological distress. It is assumed that metacognitive capacity can vary along a continuum, and each of the four MAS subscales are accordingly broken down into a series of steps which are arranged in order of increasing complexity. Thus, once a step is not attained, no higher steps on that scale should be able to be obtained. For example, self reflectivity is divided into nine steps. If one does not recognize one's emotions, for instance (step four out of a total of nine), then it should not be possible to obtain higher levels, such as the capacity to understand links between one's thoughts and emotions (step seven out of a total of nine).

To assess narratives using the MAS, the rater looks for evidence of the steps within each scale. If evidence is found that the capacity to perform a specific step is present, a point is awarded and the rater then searches for evidence that the participant can perform the next step. If no evidence is found that the participant is capable of performing the metacognitive act described in the next step, the rater ceases his or her search for subsequent higher capacities and the score for that scale is the number of steps already achieved. As an example, after a rater has judged that a participant had achieved the first three steps of the MAS Self Reflectivity scale, the rater would turn to the next step within this scale: the ability to define and distinguish one's own emotions. To do this the rater would search the IPII transcript for places where the participant described different ways he or she felt. If the rater then found several places in the transcript where the participant described his or her own emotions, this

would constitute evidence that the participant was able to identify his or her own emotions and a point would be awarded. The rater would then start to search for evidence of the next step: recognition that one's own thoughts are fallible and/or one's representation of the self and world is subjective and changeable. If this next level of capacity was achieved, another point would be awarded (giving the subject 5 points so far) and the rater would search for evidence of the sixth step. Once a rater determines there is no evidence of a capacity to perform a step, no higher ratings are considered and the final score is the number of steps the participant was judged to be capable of performing. In this way, increasing scores reflect increasingly complex metacognitive operations. A final score of "5" for a given scale would reflect more complex levels of metacognition in this domain than a "4," but less complex metacognition than a "6".

Evidence of the reliability of these methods for quantitatively assessing metacognition includes findings of good interrater reliability for blind raters and internal consistency among the four MAS scales [30]. Concerning its validity, MAS scores have been linked with independent assessments of awareness of illness as well as self-reports of coping strategies and self-reflectivity [29, 31]. Regarding convergent and divergent validity performance of the MAS, MAS scores have been found to be correlated with performance on the Scale to Assess Narrative Development, which measures depth of personal narrative. This assessment also demonstrates discriminant validity, as it is uncorrelated with theoretically unrelated aspects of self-experience such as internalized stigma [32]. In another study, we have found MAS scores are linked with assessments of social cognition that tap the extent to which persons can construct a complex story about an imagined social interaction, independent of symptom level [33]. Finally, in a study that is now underway, preliminary observations suggest that persons with schizophrenia experience graver deficits in metacognition as assessed within narratives compared to comparable persons with chronic medical conditions in the absence of psychosis. These results suggest that deficits in metacognition observed in schizophrenia are more severe than the metacognitive deficits associated with serious medical conditions, conditions also known to affect how persons feel and think about themselves [34]. Formal results of this study are expected in summer 2011.

Three Studies: Neurocognition and Metacognitive Capacities

Study 1a. To study the relationship between neurocognitive and metacognitive capacities, we sought to determine whether ratings on three of the domains assessed by the MAS were linked with performance on a range of neurocognitive functions [29]. Our central questions were twofold: (i) do poorer levels of metacognition assessed within narratives of persons with schizophrenia correlate with poorer neurocognitive test performance and (ii) if so, do certain types of metacognitive deficits have unique links with poorer performance on certain types of neurocognitive tests? Participants were 61 men with DSM-IV diagnoses of a schizophrenia spectrum disorder enrolled in a larger study seeking to develop a cognitive behavioral therapy

targeting work function in schizophrenia. All were initially recruited from an outpatient treatment setting and were in a post-acute phase of illness as defined by having no hospitalizations or changes in medication or housing in the month prior to entering the study.

Participants were administered the IPII along with a battery of neurocognitive tests which included the Wisconsin Card Sorting Test (WCST) [35], a test of flexibility in abstract thought; the Hopkins Verbal Learning Test (HVLT) [36], an auditory verbal memory test; the Vocabulary subtest from the Wechsler Adult Intelligence Scale III (WAIS III) [37], which assesses global verbal intellectual function; the Digit Symbol subtest from the WAIS III which assesses processing speed; and the Visual Reproduction subtest of the Wechsler Memory Scale III (WMS III) [38] which assesses visual memory.

To assess the relation between metacognition and neurocognition, we next correlated MAS scores for Self Reflectivity, Awareness of the other's mind, and Mastery. Results revealed that participants with greater metacognitive capacity for self-reflectivity had better performance on the HVLT, the Vocabulary and Digit Symbol subtest of the WAIS III, and the Visual Reproduction subtest of the WMS III. When entered into a regression, the Vocabulary and Digit Symbol scores predicted a quarter of the variance in Self Reflectivity. Participants rated as having greater metacognitive capacities for Awareness of the other's mind and for Mastery tended to have better performance on the HVLT. No measures were related to the WCST.

We concluded that deficits in self-reflectivity may be influenced by possible risk factors for schizophrenia, such as pre-morbid intellectual function and cognitive impairments linked to the disease progress, such as processing speed. The finding that verbal memory was linked with all three domains may suggest that these deficits also interfere with the ability to form and hold onto mental representations of internal states as objects for contemplation. Perhaps with greater difficulty encoding verbal material it may be more difficult to maintain the larger cognitive structures needed to make meaning of experience and frame a personal sense of self.

Study 2a. As a follow-up to these findings, we conducted a second study exploring whether attaining certain levels of specific metacognitive function is related to possessing certain levels of neurocognition [30]. Here the question was: do certain elements of metacognition require a minimum threshold level of neurocognitive function? To address this question, we compared the neurocognitive profiles of three different types of participants from a second sample: (i) those who had achieved basic self-reflectivity, (ii) those with basic self-reflectivity but without decentration and (iii) those with both basic self-reflectivity and decentration.

Participants in this second sample were 61 adult men and 8 women with a diagnosis of a schizophrenia spectrum disorder. All were recruited from an outpatient treatment center and were in a post-acute phase of illness according to the same definition as in Study 1. The neurocognitive test battery differed from the first study in that it also utilized the Block Design subtest from the WAIS III, which assesses visual spatial processing and the Arithmetic subtest from the WAIS III which taps

working memory. From the WMS III, we added the Logical Memory subtest, a test of verbal memory.

To divide participants into those who possessed versus those who did not possess basic self-reflectivity and decentration, we used the Self Reflectivity (with a range of 0–9) and the Decentration scales (with a range of 0–3) of the MAS. Participants were rated on an a priori basis as having basic self-reflective capacity if they obtained scores of "4" or higher and as not having basic self-reflectivity if they scored lower than "4" on the MAS Self Reflectivity scale. They were rated on an a priori basis as having achieved decentration if they achieved a score of "2" or higher and as not having achieved decentration if they achieved scores of less than "2" on the MAS Decentration scale. This categorization process resulted in participants being placed into three groups: (i) minimal self-reflectivity/not decentered ($n = 25$); (ii) basic self-reflectivity/not decentered ($n = 33$); and (iii) basic self-reflectivity/decentered ($n = 11$). As expected, there were no participants who were decentered and lacked basic self-reflectivity.

The three groups were not found to differ according to diagnosis or other demographic information, but the groups did significantly differ from one another in neurocognitive capacity. Participants with basic self-reflectivity had generally better performance on the WCST and the WAIS III Arithmetic subtest, while participants rated as having also achieved basic decentration had better performance on the Visual reproduction subtest of the WMS III. The basic self-reflectivity/decentered group also had better performance on the Vocabulary and Block Design subtest than the minimal reflectivity group.

We interpreted these results as suggesting that difficulties distinguishing internal states in schizophrenia can emerge when there are significant deficits in executive function, such as holding abstract matters in mind and shifting fluidly between such concepts. Whereas flexibility in abstract thought may aid in self-awareness, the ability to see that others have their own unique views is associated with relatively intact visual memory.

Study 3a. In our third study, we planned to follow up our previous findings linking absence of full self-awareness with deficits in executive function [39]. One of the limitations of Study 1 is that it assessed executive function exclusively using the WCST. Though a reasonable measure of global executive function, the WCST is widely seen as unable to distinguish between the multiple and semi-independent elements of executive function [40]. Success at the task, for instance, requires a range of different capacities, including the ability to form an idea, then to inhibit that idea and shift to another. Thus, it is unclear whether specific aspects of executive function are more closely linked than others to different forms of metacognition. This seems to be especially important because of all the neurocognitive capacities studied so far, executive function intuitively seems likely to play a significant role in the construction of a complex and flexible idea of the self.

To address this issue, we examined whether MAS scores were linked with selected subtests of the Delis Kaplan Executive Function System (DKEFS) [41, 42]. The DKEFS assesses multiple domains of executive function potentially relevant for

metacognitive acts, including (i) tests of inhibition and set shifting – the ability to willfully inhibit a thought or feeling and switch to another in a goal directed manner and (ii) mental flexibility – the ability to form and reform ideas about how different stimuli can be related to one another in a goal-directed manner. In this study, we chose six specific DKEFS subtests, three because of their links to inhibition switching: Design Fluency Switching, Category-Switching on the Verbal Fluency Task and Inhibition-Switching from the Color-Word Task; and three because of their links with mental flexibility: total correct sorts from the Sorting Task, total score for the Word Context Task – and the total correct score of the Twenty Questions Test.

This sample consisted of 49 participants drawn from the first two IPII studies above, who had completed the DKEFS as part of another study. For this reason it is notable that the DKEFS and MAS were not administered concurrently and could have taken place potentially up to 6 months apart (an aspect of the methodology that may weaken the relationship and is unlikely to strengthen or produce spurious correlations).

Two specific analyses were undertaken. First, Spearman Rho correlations were calculated between the six DKEFS scores and four scores from the MAS: Self Reflectivity, Understanding the other's mind, Mastery, and Total score. These revealed that greater levels of self-reflectivity were linked to better performance on the Sorting, Word Context, and Twenty Questions tests. Also, attaining higher levels of Understanding the others' mind was linked to better performance on the Design Fluency Switching and Twenty Questions tests. Greater Mastery was linked to better performance on the Verbal Fluency Switching and Twenty Questions tests.

Second, since the MAS Decentration scores showed a skewed range, we treated this as a categorical variable and classified participants as having high Decentration if their Decentration scores were greater than "1" or low Decentration if the scores were "1" or less. Scores of greater than "1" suggest the ability to see the world as involving others' unique thoughts and feelings. An ANOVA was then conducted comparing the DKEFS scores of participants with high ($n = 7$) vs. low ($n = 42$) decentration. Results revealed that participants with high Decentration had significantly higher Verbal Fluency, Color Word Switching, and Word Context scores.

These results suggest that self-reflectivity is more closely linked to mental flexibility than the other domains assessed by the MAS. The DKEFS tests linked to the ability to inhibit a response were more closely linked to Decentration and somewhat linked to Awareness of the other's mind and Mastery. This is consistent with the hypothesis that as persons with schizophrenia are less able to move flexibly between abstract ideas, they cannot detect the nuances and different patterns present in how they think and feel. Without being able to define thoughts and feelings in multiple ways, awareness of internal complexity may be difficult to sustain. Similarly, without an ability to inhibit thoughts about one's own circumstances, some may find it difficult to call to mind the perspectives of others and to detect a range of possible meanings in rapidly evolving but ambiguous situations.

Metacognition, Neurocognition and Functioning

As noted above, neurocognitive deficits have been widely observed to be predictive of poorer psychosocial functioning. In light of the findings above, the question can be raised as to whether metacognitive deficits are also linked to functional impairment. If so, it is of further interest as to whether that link is independent of neurocognitive capacity. To explore this final issue we have conducted three studies.

Study 1b. In the first study concerned with function, metacognition was assessed using the methods described in the previous section and participants were offered a placement in a work program lasting 6 months [43]. Work performance was then assessed biweekly using the Work Behavior Inventory [44]. At the conclusion of the study, participants were classified as having high, medium or low self-reflectivity. High self-reflectivity was defined as having a MAS Self Reflectivity score of 5 or higher (signifying awareness of one's different emotions and the recognition that one's ideas about the world are fallible). Medium self-reflectivity group was defined as having a MAS Self Reflectivity score of 4 (signifying awareness of one's different emotions but not the recognition that one's ideas about the world are fallible). The low self-reflectivity group was defined as having a MAS Self Reflectivity score of 3 or lower (signifying a lack of awareness of one's own different emotions and a lack of recognition that one's ideas about the world are fallible). Of an original total of 100 participants, 56 worked enough weeks to allow a meaningful analysis of their work performance (i.e. a minimum of 9 of 13 work behavior observations were completed).

The research questions in this study were twofold: (i) would the group with high self-reflectivity have better work performance than the other groups over time and (ii) would those differences persist when we controlled for a neurocognitive variable often linked to work function and metacognition: performance on the WCST. We then conducted a repeated measures ANOVA comparing the three groups on 13 biweekly Work Behavior Inventory total scores. This revealed a significant effect of time, with scores generally increasing over the course of the program, and a significant group effect with the high self-reflectivity group showing generally better work performance than either of the other two groups. A significant interaction was also observed suggesting the high self-reflectivity group improved faster and then sustained those gains relative to the other groups. Looking at specific weeks across the 26 week span we found that the high self-reflectivity group began to demonstrate better work performance than either of the other group intermittently beginning in the fifth week and had persistently better work performance from week 11 on. When the repeated measures ANOVA were performed again as an ANCOVA covarying for WCST performance, the group with the highest level of self-reflectivity continued to have better work performance over time and to improve more quickly that the other groups as well.

We interpreted these results as suggesting that indeed metacognitive function in the realm of self-reflectivity affects vocational function and, importantly, that the relationship of metacognition to vocational function exists independently of deficits in executive function. We speculated in particular that without an ability to reflect

upon and correct one's thinking about work related matters, it is more difficult to learn and adapt to changing vocational demands. For instance, persons in the high self-reflectivity group could initially perform job tasks well if given the requisite training and if they possessed a reasonable capacity for working memory. However, if those same persons were relatively unable to recognize the fallibility of their own thinking they might not be able to correct inaccurate interpretations they made impulsively about the meaning of other people's words and actions or find a new way to think about their strengths and weaknesses at work.

Study 2b. In the second study, we examined the same sample but with a different set of questions in mind. In particular, we asked whether metacognition is linked to the quality and quantity of social relationships, and whether metacognition mediates the impact of neurocognition upon these indices of social function. Specifically, in Study 2b we examined through structural equation modeling whether Mastery, the domain of metacognition as noted above that reflects the ability to use knowledge about mental states to respond to psychological challenges, mediated the effects of neurocognition on the frequency of social contact and persons' capacity for social relatedness [45].

Participants were 102 adults with a schizophrenia spectrum disorder. Frequency and quality of social relationships was assessed using two subscales from the Quality of Life Scale: Interpersonal Relationships and Intrapsychic Foundations [46]. Neurocognitive function was represented by a factor score that resulted from a Principal Components Analysis (PCA) conducted on participant's scores on the WCST, HVLT, WAIS III Vocabulary, WAIS Digit Symbol Subtest and WMS III visual reproduction. All of the neurocognitive tests included here have all been linked in the previous studies reported above to metacognition. All assessments were obtained concurrently.

To test the hypothesis that neurocognition affects mastery which then affects social function we used a measured-variable path analysis. This model revealed an acceptable fit to the observed data, which persisted after controlling for negative and cognitive symptoms. These results indicate that metacognitive ability mediates the relationship between neurocognitive capacity and social function.

Study 3b. As a follow up, in our third and final study to be considered here, we conducted a second path analysis to determine whether the cross sectional relationships observed above persisted over time [47]. Specifically we measured the two assessments of social function (Interpersonal Relations and Intrapsychic Foundations) and metacognition for 72 of the original 102 participants conducted 5 months apart. Here we specified a model in which mastery predicted concurrent social function, and that mastery at baseline affected mastery 5 months later which similarly affected social function 5 months later. As in the first path analysis, acceptable levels of fit were found for the proposed model. We interpreted results as providing some of the first empirical evidence that elements of metacognition may mediate the impact of deficits in neurocognition on daily life. We speculated that it may be the level of metacognitive capacity which determines the extent to which neurocognitive deficits complicate efforts to relate to others.

Summary, Limitations and Conclusions

In this chapter we have examined the associations of metacognition, neurocognition and function, focusing exclusively on the contributions of the study of metacognition as it occurs within the personal narratives of persons with schizophrenia. Three studies suggested that better performance on tests of neurocognition was linked to better performance on a range of measures of metacognition. Specific findings were suggestive of the possibility that certain levels of neurocognitive capacity are necessary for successfully performing certain metacognitive acts. An additional three studies suggested that metacognitive function is linked to psychosocial function in a manner which is independent of the effects of neurocognition. Self-reflectivity was found to predict work function regardless of levels of deficits in executive function while mastery was linked to social function over time and seemed to mediate the effects of neurocognition on social function.

Of note, while we have focused here exclusively on research studying metacognition within personal narratives, others have found similar results using laboratory tasks to assess metacognition; Bora and colleagues [48] demonstrated that patients who were high in metacognitive ability as indicated by the "Eyes" and "Hinting" tests demonstrated significantly better social outcome compared to those with poor metacognitive ability. Similarly, another group found that high performance on the "Eyes" test predicted better social outcomes, and that metacognition appears to mediate the effect of neurocognition on social function [49].

There are nevertheless several limitations to the studies we have reviewed. Certainly the correlational nature of five of these studies precludes drawing any firm conclusions, and all interpretations of the observed relationships are intended as speculative and as a basis for hypotheses for future study. Furthermore, there are alternative hypotheses that cannot be ruled out. It is possible that different neurocognitive deficits in schizophrenia are in part the result of different forms of metacognitive deficits. In other words, it is possible that different metacognitive dysfunctions interact with each other to generate neurocognitive dysfunctions, or perhaps deficits in neurocognition and metacognition magnify one another in a cyclical manner.

Generalization of findings also is limited by sample composition. Participants were mostly persons in their 40s, all of whom were involved in treatment. It may well be that a different relationship exists between neurocognition and metacognition among younger persons with schizophrenia, or in particular, persons who decline treatment. Additionally, thus far we have only examined a subset of the many possible aspects of metacognitive capacity in schizophrenia, and more study is called for to explore a wider range of possible patterns of deficits. Thus, more research is necessary which involves the collection of data exploring other aspects of neurocognition and metacognition at multiple time points using broader samples. Comparisons of metacognition as assessed within narratives and as assessed with more traditional laboratory methods are needed. Finally, results should not be taken to suggest that impairments in neurocognition are the only or even the main causal force in the development of deficits in metacognition. There is much evidence that

there are multiple paths which lead to deficits in metacognition among adults with severe mental illness; at best, neurocognitive impairment plays a role along with many other forces.

Regarding the clinical implications of this work, it seems worth noting that if impairments in different aspects of neurocognition are linked to decrements in certain metacognitive acts, then interventions aimed at improving cognitive capacity and flexibility might be necessary before patients are able to better think about their own thinking. This, at the very least, may point to the possibility of the development of psychotherapeutic and rehabilitative interventions that support persons learning to perform neurocognitive tasks linked to specific aspects of metacognition. Furthermore, it may be that interventions which can address deficits in metacognition may also open new opportunities for improving function.

These and many other questions await longitudinal research.

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Chapter 15
The Relationship of Acute Transient Psychoses and Schizophrenia

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Abstract This chapter deals with the historical, clinical and nosographic aspects of the acute transient psychoses and discusses the implications arising from the introduction in current classifications of diagnostic categories such as ICD-10 "Acute and transient psychotic disorder" (ATPD) and DSM-IV-TR "Brief psychotic disorder". The first part focuses on earlier concepts of European psychiatry such as *bouffée délirante,* cycloid psychosis and the reactive and schizophreniform psychoses, and examines the process whereby they were incorporated into ATPD. The second part reports empirical data on ATPD pointing out differences from schizophrenia in terms of epidemiology, clinical features, course and outcome.

Keywords Acute transient psychosis · Bouffée délirante · Cycloid psychosis · Psychiatric classification · Reactive psychosis · Schizophreniform psychosis

Abbreviations

ADPD	Acute predominantly delusional psychotic disorder
APPD	Acute polymorphic psychotic disorder
ASPD	Acute schizophrenia-like psychotic disorder
ATPD	Acute and transient psychotic disorders
BD	Bouffée délirante
BPD	Brief psychotic disorder
CP	Cycloid psychosis
DSM	Diagnostic and statistical manual of mental disorders
FRS	Schneider's first-rank symptoms
ICD-8	International classification of diseases, Eighth Revision
ICD-9	International classification of diseases, Ninth Revision
ICD-10	International classification of diseases, Tenth Revision
NARP	Non-affective acute remitting psychosis

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RP	Psychogenic or reactive psychosis
SFD	Schizophreniform disorder
WHO	World Health Organization

Introduction

The inability of the received Kraepelinian [1] dichotomy of *dementia praecox* (later renamed schizophrenia) and *manic-depressive insanity* to encompass all known forms of psychosis has encouraged the formulation of additional categories and concealed Schneider [2] old question, namely, "whether [in all such cases] a psychic reaction or a psychosis is present". This because descriptions of "atypical" psychoses often triggered by stress (e.g. *bouffée délirante,* reactive psychosis, schizophreniform psychosis, etc.) seem to abound in the psychiatric literature. Although such categories tend to converge on a common clinical phenomenon, they belong in different psychiatric traditions that have given rise to a fragmented body of evidence causing difficulties in classification and nomenclature, e.g. ICD-10 ATPD [3] and DSM-IV-TR BPD and SFD [4].

European Views on Acute Transient Psychoses

Bouffée Délirante

Bouffée délirante (BD) names a late nineteenth century French clinical concept developed in the wake of degeneration theory [5]. Magnan [6] and followers (e.g. Legrain and Saury) differentiated between "transient delusional disorders" (*bouffées délirantes polymorphe des dégénérés*) and more stable and uniform conditions leading to mental deterioration (*délire chronique à évolution systématique*) on the basis of their sudden onset and the fleeting nature of chaotic delusions (*délire d'emblée)*, which they attributed to a constitutional predisposition; external factors, Magnan believed played only a minor role. This formulation bears striking similarities to Ey's [7] considered BD as a form of acute delusional psychosis. According to his "organo-dynamic" theory BD resulted from a destructuration of consciousness somewhat intermediate between manic depression and confusional-oneroid states. Until recently, under "Transient delusional states" the French classification of mental disorders [8] was listing: (1) acute delusional psychosis (typical *bouffée délirante*); and (2) reactive delusional psychosis (*bouffée délirante réactionelle*) which was brought about by stressful events. To improve reliability French psychiatrists offered explicit definitions of: (a) abrupt onset; (b) polymorphic delusions; (c) emotional changes, mood swings, depersonalisation, derealisation and/or hallucinations; (d) complete remission within weeks or few months; (e) exclusion of organic causation, alcohol or drug abuse; (f) no psychiatric antecedent other than BD

[9, 10]. Studies on the natural course of BD have variously reported that 30–40% reach full recovery but a similar proportion recur or switch onto affective disorders or schizophrenia [11–15]. It is also believed that since the 1980s its frequency has decreased accounting only for a small proportion of psychiatric admissions [16]; migrants usually from Africa and the French-speaking Caribbean are more likely to be diagnosed with BD [17–19]. Of late there has been a paucity of work on BD. This lack of specific interest may reflect the fact that BD is currently included in studies of "first-episode" psychosis [20, 21].

Cycloid Psychoses

Drawing on the concepts of "amentia" (Meynert) and "motility psychosis" (Wernicke), Kleist [22] introduced the term *zykloide Psychosen* (CP) to denote "phasic illnesses which come and go autochthonously like manic depression, frequently in dual, contrasting phases of confused excitement and stupor, or hyperkinesis and akinesis, running their course and leaving behind no residual defects" (p. 300). Leonhard [23] added the "anxiety-happiness psychosis" which resulted from the combination of "anxiety psychosis" and "revelation psychosis" (categories borrowed from Wernicke and Kleist). Different from both schizophrenia and manic-depression, CP comprised the "anxiety-happiness psychosis", "confusion psychosis" and "motility psychosis"; these conditions were characterized by an impairment of affect, thinking, and psychomotor activity, respectively.

In Anglophone psychiatry, the concept of CP became known through the work of Perris [24, 25] who provided an operational diagnosis and criteria [26]. Perris's [27] "cycloid psychotic disorder" referred to a condition "polymorphous in its clinical manifestations" sharing common features with BD which eventually were incorporated into the checklist of ATPD.

Cycloid psychoses are reported as being prevalent in females and not associated with genetic factors or stress [24, 28]. They also are more responsive to Lithium than to antipsychotics [27]; the latter must be used with caution because of a greater risk of neuroleptic syndrome and catatonia [28]. Follow-up studies have lent support to Leonhard's clinical observations that CP may be distinct from schizophrenia in course and outcome [27–30]. Yet Cutting [31] has posited that CP be an "atypical variant" of the affective disorders. Kendell [32] in turn claimed that their "distinctive features" from manic-depression were due to "their unusually sudden onset" (p. 464).

Research to date has provided a link between CP and changes in auditory P300 amplitude, brain scan, cerebral blood flow, and gestational respiratory infections but their relationship with affective disorders remains unclear [28, 33, 34]. In Japan, Mitsuda [35] described "atypical" or "episodic" psychoses; acute onset, bipolar features, confusion, recurrent course and favourable outcome were characteristic features [36].

Psychogenic or Reactive Psychosis

Based on the behaviour of "abreacting" hysterical patients and the variegated symptomatology of subjects affected with "traumatic" and "war neuroses", the concept of "psychogenic illness" appeared in the late nineteenth century as a challenge to the predominant view that mental symptoms resulted from damage to central nervous system brought about by physical stimuli [37, 38]. Soon after, under reactive psychosis (RP) Jaspers [39] separated clinical phenomena typically triggered by a psychological trauma from what he called disease "processes" (e.g. schizophrenia). In RP symptoms were meaningfully connected to: (a) extent of trauma, (b) semantic or symbolic role (defence, escape, wish fulfilment), and (c) content. Jaspers went on to propose a threefold classification of RP in terms of: (1) "precipitating factors" (imprisonment, war, catastrophes, homesickness, linguistic isolation, etc.; (2) clinical features (depressive, paranoid, confused, hysterical, etc.); and (3) "psychic constitution" (irritable, sensitive, psychopathic, manic-depressive, etc). (p. 391). Although of great theoretical value, Jaspers' criteria were criticized on account of their "subjective" character. This is perhaps best shown in the group of cases described by Kretschmer [40] as affected with the "sensitive delusion of reference" (*sensitiver Benziehungswahn*), in which qualitative differences in symptoms and behaviour are rendered intelligible in terms of premorbid personality and the circumstances of the illness.

The concept of RP was further developed in Scandinavia through successive work of Wimmer [41], Strömgren [42], Færgeman [43] and Retterstøl [44]. By the late 1970s up to a third of psychiatric admissions with functional psychoses were diagnosed as "reactive" in these countries [45]. However, its clear differentiation from schizophrenia and manic depression was hampered by the fact that the boundaries of RP as a relatively homogenous category showing affective, confusional and paranoid symptoms could not be fully drawn [46, 47]. It was also felt that the causal role of psychological factors in RP was not so determinant and in subsequent episodes about 30–50% of patients changed diagnosis [48–51].

In addition to the Nordic countries, RP was accepted in Japan, the former Soviet Union and in some developing countries [42], but it made little headway in Continental (European) and British psychiatry, where its diffusion was hindered by a long term opposition to the concept of "psychological causation" [52, 53] – a similar controversy had taken place earlier in regards to the putative distinction between reactive and endogenous depression [54, 55].

Schneider's [2] view that all the psychoses had "somatic" basis was also influential and contributed to reject the concept of reactivity to life events [56]. After World War II, the distinction between "reaction" and "psychosis" became increasingly important and was to have significant implications for psychiatric classification [57–59].

Although the psychological mechanism of "reactivity" – on which RP is based – has been deftly re-defined in terms of stress vulnerability, life events, social adversities, nowadays interest in psychical trauma seems to have been monopolized by

"Post-traumatic stress disorder" (perhaps because it is the only condition in which compensation can be paid). The consolidation of the cognitivist paradigm since the early 1980s [60] has not helped in this regard.

Schizophreniform States

The concept of "schizophreniform psychosis" was coined by Langfeldt [61] to refer to schizophrenia-like disorders with rapid remission in response to "shock" treatment. Acute onset, precipitating stress, mental confusion, affective symptoms, and extroversion rather than schizoid personality differentiated schizophreniform psychosis from "nuclear" schizophrenia; others have called this group "remitting schizophrenia" or "good prognosis schizophrenia" [62–64]. Related conditions were the "schizophrenia-like emotion psychosis" (*schizophrenieähnliche Emotionspsychose)* reported by Staehelin and Labhardt [65] and the "acute schizoaffective psychoses" that Kasanin [66] described in patients presenting mixed symptoms triggered by stressful events.

In North-American psychiatry, research on outcome prediction helped to shape the DSM-III [67] criteria of schizophrenia which in addition to including Schneider's first-rank symptoms (FRS) was based on deterioration in occupational and/or social functions, a tendency to develop a persistent course and absence of affective features. As the diagnosis of schizophrenia required at least 6-month duration, it was introduced in DSM-III the category "Brief reactive psychosis" (duration shorter than 2 weeks) and "Schizophreniform disorder" (SFD) (typical schizophrenia with a duration longer than 2 weeks but less than 6 months). After the establishment of DSM III, only occasional reports can be found on RP [68] and cases meeting Langfeldt's criteria tended to be diagnosed as "schizoaffective disorder" or "mood-incongruent affective psychosis" [69].

Modern Psychiatric Classifications

Under the heading of "Other psychoses", ICD-8 [70] featured a number of "conditions attributable to a recent life experience" such as "Reactive depressive psychosis", "Reactive excitation", "Reactive confusion" and "Acute paranoid reaction". A series of international seminars (WHO "Programme A" 1965–1972) that included diagnosis of case histories and interview videos preceded the development of IDC-9 [71]. The second 1966 Oslo meeting dealt with those psychotic disorders that had been classified as "reactive" in ICD-8 [72]. It is likely that the diagnostic differences which arose between the WHO experts and the Scandinavian psychiatrists attending the seminar led the draftsmen of ICD-9 to restrict this category to the "small group of psychotic conditions that are largely or entirely attributable to a recent life experience" [71].

In ICD-10 [3], the inclusion under F2 "Schizophrenia and related disorders" of ATPD may have been due both to the need to avoid diagnostic criteria based on aetiological assumptions and the findings of the WHO collaborative study on acute psychoses [73]. Conducted in 14 centres totting up more than a 1,000 cases, this study reported that only in about half of patients exhibiting typical schizophrenic symptoms stress had precipitated their condition. These subjects showed rapid remission (often within few weeks) and in two-thirds there had been no relapse after a year. Accordingly, the draftsmen of ICD-10 [3] wrote: "The limited data and clinical traditions... do not give rise to concepts that can be clearly defined and separated from each other [...]. The nomenclature of these acute disorders is as uncertain as their nosological status".

ATPD was characterized by: (a) acute onset (within 2 weeks); (b) presence of polymorphic, schizophrenic or predominantly delusional symptoms; and (c) association (or not) with psychological stress. Complete recovery was expected within 1 or 3 months and this set it apart from schizophrenia and persistent delusional disorder (Table 15.1).

Furthermore, psychotic disorders induced by substance or alcohol intoxication and organic mental diseases (concussion, delirium, dementia) were excluded. Lastly, in spite of the frequent presence of emotional changes and affective features, ATPD was not to be considered as a variant of depressive or manic disorder.

Developed in parallel with ICD-10, DSM-IV [4] characterized "Brief psychotic disorder" (BPD) as having: (a) sudden onset; (b) duration of less than 1 month; (c) at least one of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour. It "may follow marked stressors" or may have its "onset in the post-partum period". This claim has been criticized on the basis that it assumes the presence of precipitating events, or a condition rather different is being described (perhaps cycloid psychosis) [74]. (Table 15.2)

To accommodate psychotic disorders with good prognosis that have an intermediate duration between BPD and schizophrenia, DSM-IV also included SFD. This category, however, has little to do with Langfeldt's original formulation [75].

Acute and Transient Psychotic Disorders (ICD-10 F23)

Shortcomings of ATPD

ATPD Is a Composite Category

At the core of the six ATPD subcategories, is F23.0 "Acute polymorphic psychotic disorder" (APPD), which can include schizophrenic symptoms (F23.1). Reminiscent of BD and Kleist and Leonhard's CP, its clinical profile includes varied delusions, hallucinations, perceptual disturbances, perplexity and emotional turmoil that shift from day to day or even from hour to hour. F23.2 "Acute schizophrenia-like psychotic disorder" (ASPD) has replaced the ICD-9 category "Acute schizophrenic

Table 15.1 ICD-10 F23 Acute and transient psychotic disorders (WHO, 1992)

F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia

An acute psychotic disorder in which hallucinations, delusions and perceptual disturbances are obvious but markedly variable, changing from day to day or even from hour to hour. Emotional turmoil, with intense transient feelings of happiness or ecstasy or anxiety and irritability, is also frequently present. This polymorphic and instable, changing clinical picture is characteristic, and even though individual affective or psychotic symptoms may at times be present, the criteria for manic episode (F30.-), depressive episode (F32.-), or schizophrenia (F20.-) are not fulfilled. This disorder is particularly likely to have an abrupt onset (within 48 h) and a rapid resolution of symptoms; in a large proportion there is no obvious precipitating stress. If the symptoms persist for more than 3 months the diagnosis should be changed. Persistent delusional disorder (F22.-) or other nonorganic psychotic disorder (F28) is likely to be the most appropriate.

Diagnostic guidelines

(a) the onset must be acute (from a nonpsychotic state to a clearly psychotic state within 2 weeks or less);
(b) there must be several types of hallucination or delusion, changing in both type and intensity from day to day or within the same day;
(c) there should be a similarly varying emotional state; and
(d) in spite of the variety of symptoms none should be present with sufficient consistency to fulfill the criteria for schizophrenia (F20.-) or for manic (F30) or depressive episode (F32.-).

Includes: bouffée délirante without symptoms of schizophrenia
cycloid psychosis without symptoms of schizophrenia

F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia

An acute psychotic disorder which meets the descriptive criteria for polymorphic psychotic disorder (F23.0) but in which typically schizophrenic symptoms are also consistently present.

Diagnostic guidelines

For a define diagnosis, criteria (a), (b) and (C) specified for polymorphic psychotic disorder (F23.0) must be fulfilled; in addition, symptoms that fulfill the criteria for schizophrenia (F20.-) must have been present for the majority of time since the establishment of an obviously psychotic clinical picture.

If the schizophrenic symptoms persist for more than 1 month the diagnosis should be changed to schizophrenia (F20.-).

Includes: bouffée délirante with symptoms of schizophrenia
cycloid psychosis with symptoms of schizophrenia

F23.2 Acute schizophrenia-like psychotic disorder

An acute psychotic disorder in which the psychotic symptoms are comparatively stable and fulfill the criteria for schizophrenia (F20.-), but have lasted for less than 1 month. Some degree of emotional variability or instability may be present, but not to the extent described in acute polymorphic psychotic disorder (F23.0).

Diagnostic guidelines

(a) the onset of psychotic symptoms must be acute (2 weeks or less from a nonpsychotic to a clearly psychotic state);
(b) symptoms that fulfill the criteria for schizophrenia must have been present for the majority of the time since the establishment of an obviously psychotic clinical picture;
(c) the criteria for acute polymorphic psychotic disorder (F23.0) are not fulfilled.

If the schizophrenic symptoms last for more than 1 month the diagnosis should be changed to schizophrenia (F20.-).

Table 15.1 (continued)

Includes: acute (undifferentiated) schizophrenia
brief schizophreniform disorder
brief schizophreniform psychosis
oneirophrenia
schizophrenic reaction
Excludes: organic delusional [schizophrenia-like] disorder (F06.2) schizophreniform disorders NOS (F20.8)

F23.3 Other acute predominantly delusional psychotic disorders

Acute psychotic disorders in which comparatively stable delusions or hallucinations are the main clinical features, but do not fulfill the criteria for schizophrenia (F20.-). Delusions of persecution or reference are common, and hallucinations are usually auditory (voices talking directly to the patient).

Diagnostic guidelines

(a) the onset of psychotic symptoms must be acute (2 weeks or less from a nonpsychotic to a clearly psychotic state);
(b) delusions and hallucinations must have been present for the majority of the time since the establishment of an obviously psychotic state; and
(c) the criteria for neither schizophrenia (F20.-) nor an acute polymorphic psychotic disorder (F23.0) are fulfilled.

If delusions persist for more than 3 months the diagnosis should be changed to persistent delusional disorder (F22.-). If only hallucinations persist for more than 3 months the diagnosis should be changed to other non-organic psychotic disorder (F28).

Includes: Paranoid reaction
Psychogenic paranoid psychosis

F23.8 Other acute and transient psychotic disorders

Any other acute psychotic disorders that are unclassifiable under any other category in F23 (such as acute states in which definite delusions or hallucinations occur but persist for only small proportion of time) should be coded here. States of undifferentiated excitement should also be coded here if more detailed information about the patient's mental state is not available, provided that there is no evidence of organic causation.

F23.9 Acute and transient psychotic disorder, unspecified

Includes: (brief) reactive psychosis NOS.

episode"; F23.3 "Acute predominantly delusional psychotic disorder" (ADPD) involves relatively stable delusions and hallucinations. The remaining are residual classes for cases that cannot be accommodated elsewhere.

The Subcategories Have Poor Reliability

Apart from ASPD, the field trials of ICD-10 DCR [76] reported that ATPD subcategories failed to achieve established standards of reliability (kappa value range 0.42–0.54). This may be ascribed to the instability of its "polymorphic" symptoms;

Table 15.2 DSM-IV-TR criteria for Brief Psychotic Disorder (APA, 2000)

A. Presence of one (or more) of the following symptoms:
   (1) delusions
   (2) hallucinations
   (3) disorganized speech (e.g. frequent derailment or incoherence)
   (4) grossly disorganized or catatonic behaviour

Note: do not include a symptom if it is culturally sanctioned response pattern.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.

C. The disturbance is not better accounted for by a mood disorder with psychotic features, schizoaffective disorder, or schizophrenia and is not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition.

Specify if:

With marked stressor(s) (brief reactive psychosis): if symptoms occur shortly after and apparently in response to events that, simply or together, would be markedly stressful to almost anyone in similar circumstance in the person's culture

Without marked stressor: if symptoms do *not* occur shortly after, and apparently in response to events that, simply or together, would be markedly stressful to almost anyone in similar circumstance in the person's culture

With postpartum onset: if onset within 4 weeks postpartum

to its over-short duration criterion of less than 1-month; and to fact that ADPD is a diagnosis by exclusion from APPD, persistent delusional disorder or schizophrenia.

ATPD Bears Little Continuity with the Traditional Categories of European Psychiatry

Marneros and Pillmann [77] reported that 55% of their cases with ATPD fulfilled Perris and Brockington's [26] criteria for CP; Peralta and Cuesta [34] and van der Heijden et al. [78] found that only a minority showed a positive diagnosis for both disorders. A closer overlap emerged when comparison involved only the polymorphic subtypes of ATPD [77, 79]; or "sudden onset" (as per Perris and Brockington) was extended from "within a few hours or days" to "2 weeks" [77]; or those with prominent affective symptoms were withdrawn [34]. A further study comparing ATPD with the French concept of BD indicated that only 29% of those with ATPD fulfil the criteria for BD [77].

Lastly, a comparison with the ICD-8 category of RP resulted in significantly less patients with ATPD and more patients being diagnosed as schizophrenia, persistent delusional disorder or affective disorders according to ICD-10 [80]. This may be due to the fact that: (1) the psychological mechanism of "reactivity" has been neglected; (2) emotional syndromes, formerly the main group of RP, are now subsumed under affective disorders; (3) paranoid psychoses lasting longer than 3 months changed to "persistent delusional disorder"; (4) reactive confusional states are listed as either dissociative or organic mental disorders [81].

ATPD Does Not Conform to Any Specific Category in DSM-IV

The DSM-IV field trial for schizophrenia and other psychotic disorders reported that 42% of those with SFD, 21% with psychotic disorder NOS, and 13% with BPD also met the criteria for ATPD [82].

Likewise Jørgensen et al. [83] found that only a third of their series of cases with ATPD fulfilled the criteria for BPD, 41% were diagnosed with SFD, and 25% with psychotic disorder NOS. Among the various subcategories, APPD only partly overlapped with BPD, while a closer concordance emerged between ASPD and SFD. Such findings are consistent with the study of van der Heijden et al. [78] that a minority of patients with APPD meet criteria for BPD.

This contrasts with Marneros and Pillmann [77] that 62% of their patients with ATPD satisfied the criteria for BPD, though a number of cases either presented a different mode of onset or exceeded duration criteria. There was only a moderate overlap between BPD and APPD, and between SFD and ASPD.

An earlier study reported that an unusually high proportion of cases shared the diagnosis of ATPD and BPD [84].

Clinical Features

Patients affected with ATPD are more likely to experience fleeting polymorphic features such as varied delusions, mood fluctuations, etc. and fewer negative symptoms than subjects with schizophrenia [77]. Although Schneiderian FRS were found to occur more frequently in the latter condition, attempts to differentiate schizophrenia from ATPD failed because FRS were present in both clinical groups. Only negative symptoms can distinguish schizophrenia from ATPD [85].

Epidemiology

Singh et al. [86] identified 32 subjects with ATPD out of 168 cases with first-episode psychosis in Nottingham; the authors calculated an annual rate of 3.9 per 100.000 population. A more recent study based on 503 cases of ATPD obtained from the Danish National Register reported a rate of 9.6 per 100.000 [87] Reports on prevalence are equally varied with higher rates observed in first-episode psychosis studies [88, 89]. Likewise, hospital admissions in Denmark show higher rates for ATPD than in Germany; such difference may relate to the lingering importance of RP and an unwillingness to diagnose schizophrenia on fist admission [90].

Although ATPD is reported as being commoner in females during early and middle adulthood [77, 91–95], cases showing earlier age of onset and schizophrenic features tend to be more prevalent in males [87]; this suggests a closer relationship to schizophrenia [95].

There is in ATPD an increased mortality from both natural and unnatural causes; suicide during the acute stage of illness being the principal cause of premature death [96]. Yet late-onset ATPD (over 60 years) seems to be associated with a greater risk of dementia; in some of these cases, a differential diagnosis with delirium is particularly difficult [97].

Predisposing Factors

Das et al. [92] reported that whereas ATPD was 3 times more frequent in first-degree relatives of patients with ATPD, the risk of schizophrenia or affective disorders did not exceed that in the general population. This can be contrasted with the much higher risk of schizophrenia in the family of schizophrenic patients. Likewise, first-degree relatives of ASPD patients were more likely to develop schizophrenia than ATPD. A later study by Das et al. [98] found that ATPD patients with a family-history of mental disorder exhibited fewer life events before illness onset than those without. It has been suggested that familial predisposition renders such patients less likely to cope with adverse events [99]. Yet in stressful circumstances people with mild intellectual disability seem proner to ATPD [100].

Marneros and Pillmann [77] observed higher psychiatric morbidity in family members of patients with ATPD than in relatives of healthy controls but no significantly increased risk compared with relatives of schizophrenics.

Studies since then have lent support to the view that ATPD is neither associated with a family-history of schizophrenia nor premorbid dysfunctions [86, 94, 101]. Jørgensen et al. [91] reported that almost two-thirds of their patients with ATPD had a concomitant diagnosis of personality disorder, but they did not find a relationship with any specific disorder. It is noteworthy that this rate had dropped significantly 1 year later. Since most patients were taking neuroleptic medication on hospital discharge, it has been argued that "personality disorder" resulted from psychotic decompensation or pharmacological treatment [83].

Marneros and Pillmann [77] carried out a comparison with schizophrenia, schizoaffective disorder and healthy controls using the 5-NEO Factor Inventory (neuroticism, extraversion, openness to experience, agreeableness, conscientiousness). No relevant difference between ATPD and healthy controls emerged, whereas schizoaffective patients, and particularly those with schizophrenia, showed higher neuroticism and lower extroversion and conscientiousness. The latter also showed fewer premorbid social relations and more difficulty in developing stable relationships.

There is no convincing evidence of neurobiological factors apart from reports of metabolic changes in amino acid pathways associated with APPD – by analogy with the clinical phenomena induced by psychedelic drugs [102]; and increased serum levels of bilirubin compared with schizophrenia and schizoaffective disorder [103]. Rottig et al. [104] examined EEG recordings of patients with ATPD, but no significant change was observed.

Precipitating Factors

Although ICD-10 excluded the notion of RP, an additional code (F23.×1) may be used to indicate whether ATPD is associated with "acute stress". This is defined as events: (a) regarded as stressful to most people in similar circumstances such as bereavement, unexpected loss of partner or job, etc.; (b) that occur less than 2 weeks before onset of psychotic symptoms.

Despite methodological differences and geographical variations, higher rates of life events have been reported in developing countries and consequently social and cultural factors seem more often to be associated with acute psychoses [105–107]. According to Sajith et al. [93] life events are involved in two-thirds of cases of psychosis, particularly in those with sudden onset. Okasha et al. [108] have reported that 74% of Egyptian patients with acute psychosis experienced stressful events. There is also evidence that life events are more frequently associated with ATPD than manic disorder [109].

On the other hand, in industrialized countries ATPD tended to have an abrupt onset with stress factors being found only in a small number of cases [77, 83, 86, 87, 110].

These findings raise the need of defining stress in a more refined way and of specifying further its temporal associations with illness onset; they also suggest that the role of "acute stress" has been underestimated because coded as an additional "diagnostic feature" [80]. For example, examination of the impact of the Welsh religious experience in 1904–1905 revealed a significant increase in admission rates for APPD pointing out that "environmental" factors may play a part in their causation [111]. This suggests that whilst short-lived psychotic disorders would be mediated by emotion-driven pathways, the cognitive impairment involved in insidious-onset psychoses would be associated with negative symptoms and poorer outcome [112].

Diagnostic Stability and Outcome

The natural history of ATPD has been mapped by about 14 papers with follow-up periods from 1 to 15 years (Table 15.3). In developing countries, ATPD shows a higher diagnostic stability and low rates of relapse [93, 108, 112–114]. In a cohort of Indian patients first admitted with APPD, Sajith et al. [93] found that 73% retained the initial diagnosis, and more than half had only one brief psychotic decompensation followed by stable remission. Abrupt onset and brief duration (less than 1 month) predicted good stability over 3 years. Another follow-up from India showed that more than two-thirds of those with ATPD had complete remission 1 year later [115].

In industrialized countries, at least 50% of those with ATPD changed diagnosis into another F2 category "Schizophrenia and related disorders" or affective disorders and showed higher rates of relapse than in developing countries [77, 83, 86, 87, 101, 110].

Table 15.3 Follow-up studies of ATPD (see text for details)

Study	Cases (M/F)	Follow-up	Stability	Outcome/comments
Abe et al. [118]	16 (8/8)	>12 years	63%	2/3 multiple episodes, 30% SCZ. Retrospective case-note study
Amini et al. [114]	10	1 year	100%	FEP study of 26 patients from Iran
Chang et al. [101]	17	5 years	35%	35% SCZ, 18% BP, 12% SAD. FEP study of 166 cases in Hong-Kong
Castagnini et al. [87]	503 (243/260)	6 years	39%	18% mono episodic course, 11% relapsed true to type, 30% SCZ or PDD, 11% AD. Register-based study
Jäger et al. [110]	94 (49/45)	3–7 years	NR	Of 73 cases followed-up: 42% single episode, 58% recurrent course, 12% persistent impairment (DAS-S score 4–5). Higher Strauss-Carpenter scale score, negative and/or depressive symptoms associated with unfavourable prognosis
Möller et al. [117]	30	15 years	47%	30% single episode, 50% episodic-remittent course, 20% chronic course
Jørgensen [131]	15 (6/9)	8 years	87%	First-admissions with delusional disorder. GAF score $\geq$ 70
Jørgensen et al. [83]	51 (12/39)	1 year	52%	Of 46 cases followed-up: 17% SCZ or PPD, 28% AD, 33% recurrent course. GAF score $\geq$ 70
Marneros et al. [77]	42 (9/33)	7 years	54%	Of 39 cases followed-up: 3/4 multiple episodes, 30% AD, 10% SAD, 8% SCZ. One-third stable remission after 7 year. GAS score $\geq$ 80
Okasha et al. [108]	50 (25/25)	1 year	54%	2/3 full remission, 14% relapsed, 22% residual or persistent symptoms
Sajith et al. [93]	45 (13/32)	3 years	73%	Of 42 cases followed-up: 10 BP. Short duration (<1 month) and abrupt onset predicted diagnostic stability. GAF score >70
Singh et al. [86]	32 (21/11)	3 years	35%	35% SCZ or PDD, 19% AD, 9%SIP; 2/3 multiple episodes. GAS score $\geq$ 70. Female gender and good premorbid functioning predicted good outcome
Suda et al. [84]	25 (6/19)	>5 years	60%	Better premorbid functioning and episodic course with longer remission than SCZ
Thangadurai et al. [115]	87 (45/42)	13 months	64%	26% SCZ, 9% AD. 11% recurrent form

AD: Affective disorders; BP: Bipolar affective disorder; DAS-S: Short disability assessment schedule; FEP: First episode psychosis; GAF: Global assessment of functioning; PDD: Persistent delusional disorder; SAD: Schizoaffective disorder; SCZ: Schizophrenia; SIP: Substance induced psychosis.

Marneros and Pillmann [77] reported that three quarters of their cases with ATPD had subsequent affective or psychotic episodes, 30% developed mood disorders, and a relatively small number converted into either schizophrenia or schizoaffective disorder. Although only one third enjoyed a stable remission and discontinued medication after 7 years [116], they fared better than schizophrenic and schizoaffective patients in terms of clinical and social outcome.

Jäger et al. [110] conducted a follow-up of 73 patients with ATPD within 3–7 years since admission and found that 42% had a single episode, 46% experienced recurrent relapse and a minority persistent disability. Further evidence from the Munich first-admission study showed a favourable long-term prognosis and as compared with those affected with schizophrenia or delusional disorder only few cases showed a chronic course [117].

Abe et al. [118] and Suda et al. [94] reported that patients with a stable diagnosis of APPD are more likely to have an episodic course with longer remissions than those who developed schizophrenia. According to the Japanese tradition they may be regarded as having "atypical" or "periodical" psychoses [36].

According to the Nottingham first-episode psychosis study, the outcome of ATPD proved more favourable than that of schizophrenia although on the 3 year follow up two-thirds of cases had changed diagnosis [86]. Female gender and good premorbid adjustment predicted favourable outcome. It was also found that neither diagnostic stability nor good outcome are significantly associated with any particular subcategory.

Although most of these studies used standardised instruments for data collection and assessment of outcome, methodological differences make meaningful comparisons difficult. Further limitations are due to the paucity of prospective studies with adequate numbers of cases and diversity in ATPD subcategories.

The Non-affective Acute Remitting Psychoses

International collaborative research coordinated by the Mental Health Division of WHO indicated that schizophrenia fared better in developing countries than in developed ones [119]. Such diversity is to be expected as transient psychotic disorders are more common in the former countries and seem influenced by cultural factors [106].

Reanalysis of data from the WHO Determinants of Outcome Study by Susser and Wanderling [120] suggested that the incidence of the so-called "non affective acute remitting psychoses" (NARP) (characterized by: (1) acute onset (within 2 weeks) of broadly-defined psychotic symptoms, (2) a duration of less than 6 months; and (3) no relapse over 2 years) is 10 times higher in developing countries than in developed ones; and is twice as high in females. Subsequent studies reported that NARP did not conform with the profile of the other remitting psychoses or with the atypical affective disorders [121], and often occurred in the wake of a febrile illness or systemic infection [122].

Further findings from the Suffolk County (New York) suggest that only 6% of patients with NARP compared with 77% of those with non-acute remitting psychosis changed diagnosis to schizophrenia or schizoaffective disorder at 24-month follow-up and almost half of them enjoyed complete remission over 4 years [123]. In this regard, evidence has been marshalled that in NARP there is post-synaptic down-regulation in serotonergic receptors supporting the view that it is not a primary mood disorder [124].

Conclusions and Future Directions

Available evidence suggests that due to the heterogeneous and infrequent nature of its clinical features, case identification and follow-up are difficult in ATPD. It also seems to be the case that ATPD have an uneven geographical distribution with a higher frequency in developing countries and in ethnic minority groups in industrialized countries [125, 126]. Transcultural research suggests that these disorders are associated with phenomena of mass-urbanization and cultural adaptation reminiscent of the socio-clinical conditions that characterized the early stages of industrialization in nineteenth century European countries [107, 127].

Acuteness of onset, polymorphic symptoms and early remission are the characteristic features, but it may result problematic to differentiate ATPD from other F2 categories because of the fleeting nature of its symptoms. Yet no evidence seems to support the subdivision of polymorphic disorder into those "with" or "without" schizophrenic symptoms – based on 1 or 3 month duration, respectively. Likewise ADPD is likely to be an artificial diagnosis. These issues have implications both for clinical practice and research where accuracy of diagnostic assessment is essential for data clarity. Research findings seem to indicate that:

(a) ATPD may be more common in females with onset in the early-middle adulthood as opposed to schizophrenia that tends to occur in young males;
(b) Despite high rates of relapse and poor prognostic validity ATPD has better clinical and social outcome than schizophrenia;
(c) Absence of historical and empirical continuity between ATPD and earlier European psychiatry such as BD, CP and RP makes it simplistic to conflate them under the general heading of ATPD.
(d) On account of its different criteria (onset and duration), ATPD overlaps only partially with the BPD DSM-IV-TR.

ATPD seems to be a speculative category whose poor predictive power and obscure defining features argue against a premature separation from borderland disorders.

To improve the validity and reliability of ATPD the following has been suggested: (a) subcategories with schizophrenic features should be moved to schizophrenia as a distinct group; (b) the criterion of emotional turmoil and confusion (perplexity)

should be withdrawn; and (c) the temporal cut-off should be increased to 6 months so as to include acute psychotic disorders lasting typically longer than 1–3 months [128, 129]. Although such changes would make ATPD closer to DSM-IV BPD and SFD, respectively [82], it would be difficult to extend the duration criterion any further as that would require changes in schizophrenia and persistent delusional disorder [130]. It remains the case that diagnostic concepts meeting these criteria cannot be accommodated in the same category as schizophrenia when the latter starts insidiously and lasts for several months.

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Chapter 16
Schizophrenia and Depression – Challenging the Paradigm of Two Separate Diseases

Heinz Häfner and Wolfram an der Heiden

Abstract Affective symptoms, depression in particular, show high rates in schizophrenia. When occurring in combination with subclinical psychotic symptoms they are precursors of psychosis risk. Their increase over time is associated with an increase in psychosis risk and their decrease with a fall therein. The prodromal stage of severe depression and the prepsychotic prodromal stage of schizophrenia show, in the mean, more or less identical symptoms, but are diagnostically distinguishable from each other only after the onset of psychotic symptoms. In the course of full-blown schizophrenia depressive mood is the most frequent symptom, even more frequent than the positive symptoms specific to schizophrenia. In psychotic relapse episodes depressive symptoms, too, increase and to some extent also decrease when the psychosis remits. 15–20% of the relapse episodes are characterised by affective symptoms without psychotic symptoms. Attempts to identify a depressive prodrome in psychotic relapses have not yielded consistent results. The Kraepelinian model of two discrete illness groups does not provide an adequate description of the functional association between affective and psychotic symptoms observable throughout the illness course. A model of schizophrenia based on symptom dimensions, which are in part functionally related and differ in their shares in individual illness, seems to be closer to reality. Since the currently available antipsychotic and antidepressant medications and specific psychotherapeutic techniques act on symptom dimensions rather than the Kraepelinian disease concepts, a dimensional model of schizophrenia seems more useful in therapeutic respect as well.

Keywords Psychosis · Schizophrenia · Depression in schizophrenia · Subclinical symptoms · Prodromal stage · Long-term course · Symptom dimensions in schizophrenia

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Abbreviations

ICD	International classification of diseases
DSM	Diagnostic and statistical manual
EDSP Study	Early developmental stages of psychopathology study
IRAOS	Interview for the retrospective assessment of the onset of schizophrenia
NEMESIS	Netherlands mental health survey and incidence study

Introduction

In 1896, proposing his theory of natural disease entities and applying it to functional psychoses – dementia praecox, which E. Bleuler [1] later termed schizophrenia, and manic-depressive insanity, today called bipolar I – the young Emil Kraepelin [2] founded a tradition that has survived until today. Kraepelin's dichotomy of discrete disorders is reflected for example in the fact that according to ICD-10 F20 a "diagnosis of schizophrenia should not be made in the presence of extensive depressive or manic symptoms" unless the affective symptoms preceded the psychotic ones [3].

Clinical experience and a growing number of studies, however, have shown that affective symptoms, depressive symptoms in particular, are very frequent in the course of schizophrenia and that psychotic symptoms may occur in severe affective psychosis. But in judging these study results it should be kept in mind that the pharmacotherapy administered to patients suffering from pronounced psychotic and/or affective symptoms influences the number and intensity of these symptoms. Therefore, it is only rarely that the natural course of schizophrenia and its symptoms can be studied in a drug-naive state. Longitudinal studies usually report on treated illness.

Categorical Versus Dimensional Definitions

According to the Kraepelinian disease construct and the categorical diagnoses based on it affective symptoms of diagnostic relevance occurring in schizophrenia are usually classified as comorbidity, that is, as reflecting a discrete illness in its own right.

The criticism recently levied on the categorical diagnoses of functional psychoses has brought to the limelight the role of empirical symptom dimensions. Attempts to break down the conglomerate of schizophrenic and affective symptoms into a few underlying clusters or dimensions go far back in time.

A first step in that direction was the distinction between positive and negative symptoms, prompting a wealth of studies analysing their stability and dependence vs. independence in the course of schizophrenia. As a result of their factor-analytic studies Liddle [4, 5] and Liddle and Barnes [6] proposed a three-factor model of

schizophrenic symptomatology. Included were only factors pertaining to the core symptoms of schizophrenia, namely "psychomotor poverty", which mainly comprised negative symptoms, "reality distortion", which covered positive symptoms, and as a third factor "disorganization" including thought disorder.

The results of such factor analyses depend, among other things, on the types of symptoms entered in the analysis. Since the instruments commonly used for assessing schizophrenia symptoms comprise only few items measuring affective symptoms, the factor analyses conducted on such basis have failed to produce an affective factor. In contrast, instruments adequately covering affective symptoms, too, all produce depression as a fourth factor [7], already detectable in first-admission samples [8–12].

These factors reflecting the empirical symptom dimensions permit us to study not only cross-sectional, but also longitudinal aspects of schizophrenia. The literature on this topic is still scarce. Liddle's [6] three-factor model was tested in a follow-up study covering 2 years by Arndt et al. [13] and in another study covering 5 years by Salokangas [11], both based on samples of first-onset patients with schizophrenia. Löffler and Häfner [14] tested the stability of Liddle's three factors by following up a sample of 115 patients in their first illness episodes of schizophrenia at six cross sections over 5 years. In all these studies the "psychomotor poverty" factor showed the greatest degree of stability and a course independent of the other factors. These studies did not yield a factor for affective symptoms yet. However, their results indicated the potential of detailed analyses of the empirical symptom dimensions not restricted to the traditional disease construct or the categorical diagnoses.

Depressive Symptoms in Schizophrenia

Misgivings about schizophrenia and affective psychosis neatly splitting into discrete disorders as postulated in his dichotomy theory were already voiced by Kraepelin [15] himself in his later works. A frequent occurrence of depression in the course of schizophrenia has also been reported by E. Bleuler [1], McGlashan and Carpenter [16] and more recently by a number of authors. According to Siris and Bench [17] and Buckley et al. [18] the rate for depression in schizophrenia ranges from 6–75%. In a population-based sample Häfner et al. [19] found that 74% (point prevalence for 2 weeks) of the patients in their first psychotic episodes – when symptoms were at their maximum – also suffered from depression. 6 months later the rate had fallen to 27%. The great variation in the rates reported is accounted for by differences in how depression is defined, e.g. by diagnosis from different classification systems (DSM or ICD), by single depressive symptoms versus syndromes or diagnoses, by operational measures such as point, period or lifetime prevalence, and by the stage of illness in schizophrenia at the time of assessment. And whether or not schizoaffective psychosis is included in the diagnosis of schizophrenia also has an impact on the rate of affective symptoms.

Reviewing a series of studies Siris and Bench [17] estimated a modal rate of 25% for a concurrent occurrence of depression and schizophrenia.

Classifying a syndrome as comorbidity causes problems, even if categorical diagnoses were applied, when frequencies of 50% or more are found for the syndrome in question. Depending on the methodological prerequisites mentioned, rates of that magnitude for depression in schizophrenia are quite common. Concerning the possible causes for the frequent observation of such high rates of depression in the course of schizophrenia, an extrinsic genesis is probable only in part of the cases. The causation of depressive and dysphoric syndromes, frequently in combination with akathisia and akinesia during treatment with first-generation antipsychotics [20–23], an issue intensively debated in the 1970s and 1980s, has almost lost its relevance in the wake of the widespread transition to the new generation of antipsychotic medications in the treatment of schizophrenia. A random occurrence of depression or bipolar psychosis as a discrete disorder in schizophrenia is reasonable to presume only in a small proportion of cases. Studies conducted on the topic have invariably shown significantly higher frequencies for depressive symptoms in manifest schizophrenia compared with healthy controls. Hence, there must be more into the association between schizophrenia and affective disorder than just a mere coincidence of the two in psychotic illness.

Affective Symptoms as Risk Factors and Precursors of Psychosis

Depression or depressive symptoms are common not only in full-blown schizophrenia, but also in initial states and at the prodromal stage of the disorder. A few recent birth-cohort and population studies have prospectively analysed symptom development prior to illness onset. Among them are a birth-cohort study from New-Zealand [24], covering age up to 26 years, the Dutch NEMESIS study [25], based on a representative population sample aged 18–64 years, and the Munich EDSP study [26, 27] of a representative sample of adolescents and young adults aged 14–24 years. The New Zealand study showed that the risk for developing schizophrenia spectrum disorder by age 26 years was frequently associated with an experience of single hallucinatory symptoms without manifest illness at age 11. Of the young adults experiencing subclinical hallucinations in childhood 25% developed a schizophrenia spectrum disorder, but 75% did not. In the Dutch NEMESIS study, 8% of the adult probands presenting at least one psychotic symptom (hallucination) at initial assessment went on to develop a psychosis in need of treatment by 3-year follow-up [28]. That risk rose to 21.7% for probands reporting not only psychotic symptoms, but also depression during the observation period [29].

Population studies have found high rates of subclinical affective symptoms in persons with subclinical psychotic symptoms. When depressive and anxiety symptoms are included, the rates reach high values. In a population-based adult sample (Utrecht Health Project; mean age: 39 years) the figure was 89%, compared with 11% for controls free of preclinical psychotic symptoms [30]. Another analysis of

the correlation between affective and subclinical psychotic symptoms found that bizarre experiences and persecutory ideas were strongly associated with depression [31].

According to long-term follow-up studies, subclinical psychotic symptoms as precursors of schizophrenia are mostly transitory in nature, that is, they remit, thus resulting in a symptom-free state, or persist without transition to psychosis over the follow-up period. It can be considered established that depressive and manic symptoms, which the authors of the EDSP study termed "affective dysregulation" when these symptoms occurred in association with subclinical positive symptoms [26], are associated with an increased risk for transition to psychosis over a follow-up period of 10 years. An increase in affective symptoms, depression and anxiety in particular, leads to an increase in psychosis risk, whereas a decrease in affective symptoms lowers the risk for psychosis [27]. A dose-effect relationship demonstrated between the change in the number of affective symptoms and psychosis risk – active in both directions – indicates a possible causal association between the affective and the psychotic symptom dimension.

Concerning the nature of that relationship, we can as yet offer only a rudimentary speculative hypothesis. Depression or depressive symptoms might reflect early stages of neurobiological dysfunction. As that dysfunction deteriorates, they may transit to psychosis; more often, however, they remit. But the affective symptoms described can be both risk factors for and precursors of psychosis and, irrespective of the psychosis risk, occur in other aetiological constellations as well.

In this context it should be kept in mind that affective symptoms are among the most prevalent psychopathology in the population, whereas the lifetime risk for full-blown schizophrenia is 2% at the most. From that it can be concluded that the probability of depression transiting to psychosis is low.

Genetic predisposition is probably required for the risk of subclinical psychotic symptoms to transit to psychosis. That predisposition might be reflected in the occurrence of subclinical psychotic symptoms prior to psychosis onset. Some authors [26], hence, presume that subclinical psychotic symptoms are indicative of an increased genetic vulnerability for psychosis. In the case of subclinical affective symptoms the association with psychosis risk indicates that the relationship is probably of a more complex nature, given the greater prevalence of depressive symptoms than that of subclinical psychotic symptoms in the population.

Depression at the Prodromal Stage of Schizophrenia

The clear evidence for an association between the occurrence of the psychotic and the depressive dimension in schizophrenia prompt the question of their sequence. Learning which symptom dimension manifests itself first and which follows we gain a hint at the direction of causality.

In a retrospective analysis of the prodromal stages of schizophrenia, of the early course from symptom onset to first admission, in a representative cohort of first

illness episodes of schizophrenia (N = 232) in the ABC Schizophrenia Study [32] depression, depressive mood in particular, at 19%, turned out to be the most frequent initial symptom in both male and female probands (Table 16.1).

In that same study early illness course was also compared between a subsample of 130 first admissions for schizophrenia, 130 first admissions for severe and moderately severe depression and 130 healthy population controls, matched by age and sex [33]. The mean duration of the early illness course from first sign of illness to first admission was 5.2 years (median: 2.2) in the schizophrenia group and 7.2 years in the depression group. The most frequent initial symptom in both illness groups was depressive mood.

A comparison of the lifetime prevalence of four depressive symptoms – each of them of at least 2 weeks' duration – at age determined by first admission between the two illness groups and population controls illustrates the role depression plays in schizophrenia (Table 16.2).

In the depression group the lifetime prevalence rate for depression was 100% for diagnostic reasons, but in the schizophrenia group, too, it was only slightly lower: 84.9% had experienced at least one 2-week episode of depressed mood. Another remarkable finding was the rate for attempted suicide at this early stage: at 18% in the schizophrenia group it lay between that for the depression group (29%) and healthy controls (11%). The highly significantly lower rate among healthy controls was as expected.

In a recent study of 170 first episodes of schizophrenia Barrett et al. [34] found markedly elevated rates for attempted suicide (14%) and suicidal ideation (70%) particularly in the pre-treatment phase, and clinical studies seem to confirm that, although discrepant findings do exist. In any case early intervention aiming at

Table 16.1 The ten most frequent earliest signs of schizophrenia (independent of the course) reported by the patients[a]

	Total (n = 232) (%)	Men (n = 108) (%)	Women (n = 124) (%)	P
Restlessness	19	15	22	
Depression	19	15	22	
Anxiety	18	17	19	
Trouble with thinking and concentration	16	19	14	
Worrying	15	9	20	*
Lack of self-confidence	13	10	15	
Lack of energy, slowness	12	8	15	
Poor work performance	11	12	10	
Social withdrawal, distrust	10	8	12	
Social withdrawal, communication	10	8	12	

[a]Based on closed questions, multiple counting possible. All items tested for sex differences
*:$p < 0.05$
Source: Häfner [32]

Table 16.2 Comparison of four IRAOS depression items in patients with schizophrenia, depression and healthy controls. Lifetime prevalence rates at first admission; both control groups matched by age and sex

IRAOS item	Patients with schizophrenia (n = 130)	Patients with depression (n = 130)	"Healthy" controls (n = 130)	Cochran's Q-test
Depressive mood	84.9	100.0	46.9	***
Feelings of guilt	33.6	55.4	12.3	***
Loss of self-confidence	68.3	89.2	35.7	***
Attempted suicide	18.5	29.2	10.8	**

**: $p < 0.01$, ***: $p < 0.001$

shortening the duration of untreated psychosis also offers an opportunity of reducing the risk of attempted suicide and suicidal ideation [35, 36].

The chronology of symptom manifestation revealed not only that depressive mood was the most frequent initial symptom both in schizophrenia and severe depression, but also that depressive symptoms preceded psychotic symptoms in 75% of schizophrenia cases. Only in 6.5% did psychotic symptoms appear first. The sequence and type of symptoms leading to psychosis onset showed a high degree of similarity to those in depression (Fig. 16.1) [37].

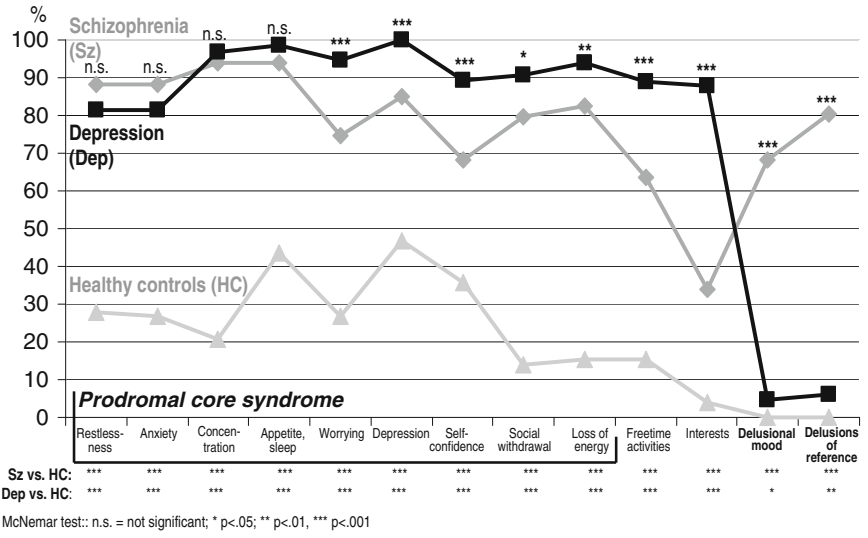

Fig. 16.1 Frequency of symptoms (period prevalences %) in patients with schizophrenia, depression and in healthy controls; symptoms with ranks 1–10 and prevalences > 5% in any of the three groups. Source: Häfner [37]

It was not until the onset of a sufficient number of psychotic symptoms that a diagnostic discrimination between unipolar depression and schizophrenic psychosis in keeping with the Kraepelinian dichotomy and the categorical diagnoses of ICD-10 and DSM-IV became possible. These findings on the affective precursors of schizophrenia at the prepsychotic prodromal stage, the similarity of those phenomena in severe unipolar depression and the central role depressive symptoms play in the early course of psychotic illness provide important insights for a better understanding of these disorders, presumably not at all mutually exclusive as postulated by Kraepelin. They also have important implications for early recognition and early intervention before transition to full-blown illness. The unfeasibility of a diagnostic distinction between schizophrenia and affective disorder at the prepsychotic prodromal stage of schizophrenia or in the early course of depression does not have any disadvantageous consequences for early intervention. Since both psychotropic drugs and specific psychotherapies act on syndromes rather than illnesses or diagnoses, early intervention targeted at syndromes is justifiable and meaningful [38].

Depressive Symptoms in Full-Blown Schizophrenia

If the first psychotic episode is frequently preceded by a prodromal stage characterised by affective symptoms it is reasonable to presume that that might also be the case in psychotic relapses, particularly since the affective symptoms of the prodromal stage continue to persist in the further course of schizophrenia. Study results on this topic differ and do not allow clear-cut conclusions. Hirsch and Jolley [39], Tarrier et al. [40] and Tollefson et al. [41] found an increase in depressive symptoms prior to a relapse, frequently concomitantly with social withdrawal, anxiety and dysphoric states. An der Heiden et al. [42] could not confirm this finding. Especially after the remission of the first episode depressive symptoms tend to reduce the well-being and quality of life of patients with schizophrenia [43].

Several studies indicate that depressive symptoms increase in number and/or severity in psychotic episodes and decrease, though often more slowly than psychotic symptoms, to lower or even initial values in the psychosis-free interval. In a survey of practicing psychiatrists Siris et al. [44] found surprisingly similar values for the frequency of depression in schizophrenia on the basis of heterogeneous stages of illness: the figure for first-admission patients was 33%, for relapsed patients 38% and for clinically stable chronic patients 29%.

Detailed analyses of the temporal associations between depressive and psychotic symptoms in psychotic relapses were conducted by an der Heiden et al. [42] on the basis of 333 psychotic relapse episodes of 107 patients over a homogenous follow-up period of 134 months after first admission. The authors found that the prevalence of depressive symptoms increased clearly and more or less simultaneously with the onset of a psychotic exacerbation, but not prior to in the sense of a prodrome. The analysis focused on symptom dimensions as based on four core symptoms with no

or little overlap with the other symptom dimensions. The depression dimension was defined by depressive mood, loss of self-confidence, feelings of guilt and suicidal ideation.

The partially parallel course of positive and depressive symptoms indicates that affective symptoms do play a part in psychotic relapses, too. And that association emerged in another context as well: The long-term course of schizophrenia followed up over 134 months in the cited study showed that besides 333 (range: 0–29, mean: 3) psychotic relapse episodes the authors also counted 73 (= 18% of the total number of episodes) relapse episodes free of psychotic symptoms and mainly characterised by depressive symptoms.

Similar results were reported by Jablensky [45] from a 2-year follow-up of the WHO 10-country study: he found 16% affective episodes. In the IPSS cohort [46] with a diagnosis of schizophrenia according to ICD-8 17% of the probands suffered clear-cut depressive episodes over a period of 2 years [47] and 15% over a period of 5 years [48]. Bressan et al. [49], who assessed a sample of 80 clinically stable outpatients with schizophrenia over 1.5 years, reported that 16.3% of these patients met the criteria for a major depressive episode according to DSM-IV. The similarity of the rates reported indicates that depressive relapse episodes in schizophrenia are a fairly regular phenomenon.

In the long-term follow-up study covering 134 months an der Heiden et al. [42] calculated mean values for the clinical symptom dimensions characteristic of schizophrenia as based on the number of months in which patients presented symptoms from each dimension. Table 16.3 shows that depressive symptoms were the most frequent type of symptoms in the long-term course of schizophrenia, followed by negative and positive symptoms. The analysis was based on IRAOS [50].

The authors also found out that the proportion patients presenting depressive symptoms after the remission of the first episode remained more or less unchanged over the entire follow-up period [37, 42]. In interpreting these results it is important to note that the symptoms from the five dimensions show partial overlap, i.e. a symptom may be classified in more than one group, for example negative symptoms such as lack of concentration, slowness and social withdrawal can also be symptoms of a severe depression. This effect might have bloated the figure for depressive symptoms disproportionately. For this reason the authors repeated the

Table 16.3 Number of months spent with at least one symptom of the main clinical categories in the 134-month (11.2-year) follow-up period

Symptom	Mean	SD
Depressive	76.9	56.2
Manic	9.0	24.8
Negative	45.1	54.5
Positive	26.7	42.6
Disorganization	6.3	19.2

Source: Häfner et al. [51]

analysis with symptoms that showed no or minimal overlap between the dimensions. The most frequent symptom in schizophrenia turned out to be "depressive mood". Considering the occurrence of depressive symptoms in the prephase and at the prodromal stage of schizophrenia, considering their persistence in the further illness course and the increase of depressive symptoms in psychotic relapse episodes this finding strongly suggests that depressive symptoms do not represent affective comorbidity of schizophrenia, but frequently an integral element of the disorder over the entire illness course.

The question whether depressive symptoms have an impact on the illness course in schizophrenia has not yet been answered conclusively [52, 53]. Some studies report a favourable impact, others no significant influence, still others postulate a differential impact of depressive symptoms depending on whether they occur in psychotic episodes or in the interval [54]. Depressive symptoms occurring mainly in the psychosis-free interval seem to be associated with an unfavourable illness course – probably by reducing wellbeing and active behaviour-, whereas those occurring mainly in psychotic episodes tend to have a favourable effect [53, 55, 56].

The association of depressive symptoms with an increased risk for suicide – already visible at the prodromal stage – has been widely reported [57, 58]. Buckley et al. [18] described an unfavourable prognostic impact on illness course not related to a particular stage of illness. The prospective analyses conducted by Häfner et al. [59], in which they compared first-onset schizophrenia patients with and patients without depressive symptoms over a 5-year period showed that only affective blunting was influenced significantly: the symptom was less frequent in the depression group.

The authors explained this finding by differences in patients' affective responsivity. Patients with greater affective responsivity are bound to develop less symptoms of affective blunting and more affective symptoms.

Analysing the long-term course over 134 months an der Heiden et al. [42] tested whether depressive symptoms occurring in psychotic episodes and in the interval between the episodes influence the length of inpatient treatment. In agreement with the results of Olfson et al. [56] a moderate, but significant correlation emerged between the amount of depressive symptoms experienced in psychotic episodes and the frequency of inpatient treatment spells and total time spent in inpatient treatment. No significant correlation was found between depressive symptoms occurring in psychosis-free intervals and the frequency or total length of inpatient treatment.

Conclusions and Future Directions

The onset of schizophrenic psychosis is usually preceded by a lengthy period of even several years in which subclinical premonitory sings of affective and psychotic type manifest themselves. With their persistence and increase over time the risk for transition to psychosis increases. With their decrease or remission the psychosis risk, too, falls.

The prepsychotic prodromal stage of schizophrenia and the preclinical early course of severe and moderately severe depression cannot be reliably distinguished

from each other on the basis of mean symptom values and type of course. A diagnosis of schizophrenia is possible only after the manifestation of a sufficient amount of psychotic symptoms marking the end of the prepsychotic prodromal stage. Early recognition at this early stage is possible, provided that it focuses on symptoms and impairment, but a diagnostic differentiation is only possible after the appearance of psychotic symptoms. Early intervention at the prodromal stage is recommendable with therapies targeted at the symptom dimensions in need of treatment, especially since the efficacies of the therapies available have been ascertained for the symptom dimensions and not for the complex disease construct.

In the overall course of full-blown schizophrenia depression and depressive symptoms are very frequent. When psychotic symptoms increase, in psychotic relapses in particular, depressive symptoms, too, increase slightly or moderately and decrease to some extent in the psychosis-free interval. There is no reliable evidence indicating the existence of an affective prodrome in psychotic relapses. In contrast, several follow-up studies have demonstrated the occurrence of non-psychotic relapses characterised mainly by depressive symptoms. Their frequency is estimated at 15–20% of total relapses.

The high frequency of depression has long been ignored by both patients and clinicians. A reason may be the tradition of psychopathology shaped by Karl Jaspers [60]. In that hierarchical disease model affective symptoms were deemed secondary to psychotic symptoms. Another reason may be a selective perception of psychiatric symptoms. Depressive symptoms do not trigger help-seeking behaviour as readily as psychotic symptoms do. Murphy et al. [61] demonstrated in a recent population-based study that subclinical positive symptoms such as thought control, strange experiences and paranoia in particular cause people to consult their doctors for emotional problems.

The simultaneous occurrence of depression and psychosis, the fact that depressive symptoms frequently precede a transition to psychosis and the dose-effect relationship of the two symptom dimensions at the early stage of illness development and in the early illness course suggest that these symptom dimensions are functionally linked with each other.

Kraepelin's dichotomy model, surviving in the contemporary international classification systems, does not permit an adequate description of this association. A series of genes have been detected, which, straddling the boundary between the diagnoses, are associated with risks for both types of psychopathology [62, 63].

The disease construct of schizophrenia seems to consist of several symptom dimensions: a depressive, a manic, a psychotic and a negative dimension. The shares of these dimensions in individual presentations of the disorder differ greatly in size and severity. For example, there are illness courses characterised by a high frequency and a great severity of positive symptoms, but also courses characterised by persistent depressive symptoms and more or less pronounced negative symptoms. The characteristics of these symptom dimensions and the role they play in individual cases, the long neglected depression dimension in particular, call for attempts to improve treatment by therapies targeted specifically at these dimensions.

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Chapter 17
Schizo-Obsessive Disorder

Ruth Cunill and Xavier Castells

Abstract Obsessive-compulsive features are common in schizophrenia. The term schizo-obsessive has been proposed to delineate this subgroup of schizophrenia patients who also present OCS/OCD. Research into clinical, neuropsychological and functional profiles of schizo-obsessive patients has been extensive during these last years although a specific profile has yet to emerge. In addition, the neurobiological and genetic underpinnings of this association have recently begun to be investigated with preliminary but promising results. This chapter reviews the validity of schizo-obsessive disorder. The clinical and neuropsychological profile is elucidated and possible pathophysiological mechanisms and etiologic factors are discussed. Finally, a suitable therapeutic approach is also suggested.

Keywords Schizo-obsessive · Schizophrenia · Obsessive-compulsive · Antipsychotic · Neuropsychology · Genetics · Pathophysiology · Treatment

Abbreviations

AP	Antipsychotic
CANTAB	Cambridge automated neuropsychological test battery
COMT	Catechol-O-methyltransferase
DLPC	Dorsolateral prefrontal cortex
DSM	Diagnostic and statistical manual for mental disorders
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
MRI	Magnetic resonance imaging
OFC	Orbito-frontal Cortex
OC	Obsessive-compulsive
OCD	Obsessive compulsive disorder

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OCPD	Obsessive-compulsive personality disorder
OCS	Obsessive-compulsive symptoms
SSRI	Selective serotonin reuptake inhibitor
UHR	Ultra high risk
WCST	Wisconsin card sorting test
YBOCS	Yale Brown obsessive-compulsive scale

Introduction

Obsessive–compulsive (OC) features are common in patients with schizophrenia. Up to almost one half of schizophrenia patients show obsessive-compulsive symptoms (OCS) [1–3] and one fourth may qualify for obsessive-compulsive disorder (OCD) [4–6]. The term schizo-obsessive has been proposed to delineate these schizophrenia patients who also have OCS/OCD [7]. Since the first reports of schizophrenia patients with OC phenomena in the past century, [8–10] research into schizo-obsessive patients has burgeoned. Epidemiological and clinical studies have estimated that prevalence of OC features in schizophrenia is higher than in the general population, but reported rates varied between studies [11–13]. The clinical and cognitive profile of these patients has also been extensively investigated [3, 14–19] although results have been heterogeneous and no specific profile has been established yet. Difficulties in identifying obsessions and compulsions in schizophrenia together with heterogeneity in the definition of schizo-obsessive patients may account for these inconclusive results.

The neurobiological basis and genetic underpinnings of this association have been explored recently with encouraging although provisional results. It has been suggested that similarities in neurocircuitry, anatomic structures and neurotransmitters involved in each disorder may account for symptom co-expression [20, 21]. There is also evidence of a contribution of genetic factors [22–24].

Finally, although research on therapeutics of schizo-obsessive patients is still scarce, it has been shown that both atypical antipsychotics (AP) and adjunctive antiobsessive agents may be efficacious in ameliorating OC features in these patients [25–27]. Nevertheless, some controversy has emerged since these former drugs have also shown some propensity to induce OCS in schizophrenia patients [28].

In this chapter we aim to review the validity of schizo-obsessive disorder. A clinical and neuropsychological profile will be outlined and putative underlying pathophysiological substrates and etiologic factors will be discussed. Finally, a suitable therapeutic approach will be suggested.

Concept and Diagnosis

The concept of schizo-obsessive disorder delineates a subgroup of schizophrenia patients characterized by the presence of OCS or OCD in addition to positive, negative and disorganized psychotic symptoms [7]. Three different groups of

schizo-obsessive patients have been described, those diagnosed with OCD before the development of schizophrenia, those who begin to exhibit OCS around the onset of schizophrenia or at any time during the course of the illness, and finally, those who show transient OCS at different stages of their disease, or under specific conditions such as infection or the use of antipsychotic [29].

Identification of schizo-obsessive patients is complex due to difficulties in recognizing obsessions and compulsions in schizophrenia [21, 26]. OCS may resemble psychotic symptoms so, for example, it can be hard to distinguish obsessions with poor insight from delusions, compulsions from mannerisms, and obsessional slowness from thought blocking [30]. Moreover, there is no universally accepted method for identifying OCS in patients with schizophrenia, although some recommendations have been suggested in order to facilitate this task. It has been proposed that a recurrent, intrusive, ego-dystonic thought should not be considered an obsession if it revolves exclusively around delusional themes, and that a repetitious act should only be considered a compulsion if it occurs in response to an obsession, not if it occurs in response to a delusion [21]. Most studies carried out in schizo-obsessive patients attempted to exclude those patients whose OCS were exclusively related to psychotic symptoms [31]. Additionally, in a great deal of studies, identification of OCS has been performed using the Yale Brown Obsessive-Compulsive Scale (YBOCS) [3, 11, 14, 15, 32, 33]. This instrument has been demonstrated to have good internal consistency and interrater reliability in this population [34]. These measures would be expected to reduce diagnostic bias, mitigate confounding variables and consequently enhance diagnostic accuracy [21].

Diagnosis of schizo-obsessive patients has been performed using both categorical and dimensional definitions of OC features. Studies using a categorical definition considered that schizo-obsessive patients are those who, in addition to a diagnosis of schizophrenia, meet full Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for OCD or symptomatic DSM criteria for OCS [2–6, 12, 13, 16–19, 35–62]. In order to identify OCS/OCD, most of them used structured clinical interviews. In contrast, studies using a dimensional definition of OC features have employed scales that measure the severity of OCS to diagnose schizo-obsessive patients. Most of these studies administered the YBOCS [3, 11, 14, 15, 32, 33, 63, 64] although other instruments have also been used [65–69]. Different cut-off scores in the YBOCS have been applied to determine OCS significance and thus to diagnose schizo-obsessive patients.

It has been proposed that dimensional approaches may have particular relevance for the study of OCS in schizophrenia because they appear to be a way of conceptualizing intricate psychiatric symptomatology [52]. Evidence favoring a dimensional definition of schizo-obsessive disorder has been pointed out since it has a prognostic value in terms of severity of psychotic symptoms [31] and it captures the complexity of both schizophrenia and OCD [70].

In conclusion, despite the above-mentioned, obsessions and compulsions can be reliably identified in schizophrenia patients. These schizophrenia patients with both psychotic and OC features have been named schizo-obsessive but they do not represent a homogenous group since both categorical and dimensional definitions have been given. Preliminary support for a dimensional definition has been noted.

Epidemiology

Presence of OC features has been extensively assessed in schizophrenia and they have been reported at all stages of life and in all phases of the illness. OC features have been identified in adults, [2–6, 11, 12, 15–18, 32, 33, 35–40, 43, 46, 47, 49–53, 55–69] in adolescents [41, 48, 54] and in elderly people [13] with schizophrenia. They have been found in stable phase, [3, 14, 15, 36, 37, 40, 50, 61, 62, 64, 66, 67] in active phase, [5, 13, 38, 39, 46, 48, 63] during prodromal stage, [71–73] in first psychotic episode [12, 17, 46, 57–60] and in chronic stage [4, 11, 18, 52, 65].

The first attempt to estimate the prevalence of OC features was early in the previous century. Before the introduction of DSM criteria, the prevalence of OCS in schizophrenia was found to be low, ranging from 1.1% to 3.5% [8, 9, 74]. These studies assessed OCS retrospectively by means of patient's medical records and did not use standardized criteria to describe these symptoms. Since chart reviews rely on the recognition and documentation of symptoms, underestimation is not unusual.

Fenton and McGlashan [75] ran the first study that applied operational criteria to assess the prevalence of OCS and found that 12.5% of schizophrenic patients also had OCS. Subsequently, studies using defined OCS/OCD criteria and structured interviews to assess these phenomena have been carried out. The characteristics of studies that have investigated the prevalence of OCS/OCD in patients with schizophrenia are presented in Table 17.1.

These studies have reported widely varying prevalence rates. OCS may be present in 2.5–64% of schizophrenia patients and OCD in 0–37.5%. Recently, a meta-analysis investigating the prevalence of anxiety disorders in schizophrenia has reported a pooled prevalence rate of OCD in schizophrenia of 12.1% (95% CI 7.0–17.1%) [76]. Since prevalence of OCD in the general population has been reported to be 1.6% [77] it appears that OC features occur in schizophrenia more often that would be expected [20, 21, 26]. Nevertheless, it must be noted that most studies that have investigated the prevalence of OC features in schizophrenic patients have used clinical samples that are known to lead to an overestimation of the prevalence because schizo-obsessive patients have a more severe disorder than those with schizophrenia, and therefore they are more likely to be visited as outpatients or admitted into the hospital.

It seems that variation in diagnostic criteria employed to diagnose schizo-obsessive patients may have contributed to this wide range in prevalence estimates. Most studies that have applied a categorical definition of OC features have used DSM-IV to assess OCD but some have employed DSM-IIIR. It appears that those studies that applied DSM-IIIR criteria generally found lower prevalence rates than those studies that used DSM-IV criteria, with these last showing rates higher than 15% [2, 4, 6, 13, 16, 18, 36, 37, 39, 48, 50, 52, 61, 67] while the former studies showed rates lower than 15% [12, 38, 40, 43, 59, 60] (for details see Table 17.1). This may reflect in part some important differences between DSM-III-R and DSM-IV OCD criteria. DSM-IV is less restrictive than DSM-IIIR regarding the diagnosis of OCD in patients with schizophrenia. DSM-IIIR only allows diagnosis of OCD in patients with another axis I disorder when the content of obsessions

Table 17.1 Characteristics of studies assessing the prevalence of OCS/OCD in schizophrenia

Author	Study characteristics	Sample characteristics	Diagnostic criteria for OCS/OCD	Prevalence
Berman et al. [65]	Cross-sectional	Chronic outpatients	OCS: two or more of Fenton and McGlashan operationalized symptom criteria and 6 mo. duration	P OCS 25% LTP OCS 30%
Berman et al. [11]	Cross-sectional	Chronic inpatients	OCS: YBOCS checklist and minimum YBOCS total score of 10	P OCS 46.6%
Bermanzohn et al. [4]	Cross-sectional	Day treatment hospital patients	OCD: DSM-IV (assessed by means of SCID)	LTP OCD 29.7%
Bland et al. [1]	Cross-sectional	Community residents	OCS: DSM-III symptomatic criteria	P OCS 59.2%
Braga et al. [36]	Cross-sectional	Outpatients	OCD: DSM-IV (assessed by means of SCID)	LTP OCD 15.1%
Byerly et al. [67]	Cross-sectional	Outpatients	OCS: Two or more OCS identified by FOCI, present for at least 6 mo.	P OCS 30%
			OCD: DSM-IV	P OCD 23%
Cassano et al. [5]	Cross-sectional	Inpatients	OCD: DSM-IIIR (assessed by means of SCID)	P OCD 29%
Ciapparelli et al. [37]	Longitudinal (12 mo.) (prevalence only assessed at one time point)	Outpatients	OCD: DSM-IV (assessed by means of SCID)	P OCD 23.8%
Cosoff et al. [38]	Cross-sectional	Acute inpatients	OCD: DSM-III R (assessed by means of SCID)	P OCD 13.8%
Craig et al. [12]	Longitudinal (24 mo.) (prevalence only assessed at one time point)	Acute inpatients	OCS: DSM-IIIR symptomatic criteria (assessed by means of SCID)	LTP OCS 16.9%
		First episode	OCD: DSM-IIIR (assessed by means of SCID)	LTP OCD 4%

Table 17.1 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for OCS/OCD	Prevalence
De Haan et al. [39]	Longitudinal (6 weeks)	Acute inpatients	OCS: DSM-IV symptomatic criteria (assessed by means of SCID-P)	P OCS T1 29.2%; T2 31.9%
			OCD: DSM-IV (assessed by means of SCID-P)	P OCD T1 15%; T2 15%
Dominguez et al. [66]	Cross-sectional	Outpatients	OCS: MMOCI (non specified)	P OCS 33%
Eisen et al. [40]	Cross-sectional	Chronic outpatients	OCD: DSM-IIIR (assessed by means of SCID)	P OCD 7.8%
Fabisch et al. [63]	Longitudinal (during acute psychotic exacerbation)	Acute inpatients	OCS: YBOCS checklist (not specified)	P OCS (acute phase) 11% P OCS (at discharge) 9%
Goodwin et al. [43]	Cross-sectional	Inpatients in research unit	OCD: DSM-IIIR (assessed by means of SCID)	P OCD 5.4%
Huppert et al. [6]	Cross-sectional	Outpatients	OCD: DSM-IV (assessed by means of SCID)	P OCD 37.5%
Karno et al. [45]	Cross-sectional	Community residents	OCD: DSM-III	P OCD 12. 2%
Kayahan et al. [2]	Cross-sectional	Inpatients and outpatients	OCS: DSM-IV symptomatic criteria (assessed by means of SCID-P)	P OCS 64%
			OCD: DSM-IV (assessed by means of SCID), minimum YBOCS total score of 7 and 6-mo. duration	P OCD 30%
Koen et al. [46]	Cross-sectional	Acute inpatients South African	OCD: DSM-IV (assessed by means of SCID/DIGS)	P OCD 1.1%

Table 17.1 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for OCS/OCD	Prevalence
Kruger et al. [47]	Cross-sectional	Inpatients after resolution of acute phase	OCD: DSM-III-R (assessed by means of SCID)	P OCD 15.8%
Lysaker et al. [3]	Cross-sectional	Outpatients	OCS: Minimum YBOCS obsession or YBOCS compulsion scores of 8	P OCS 45%
Lysaker et al. [14]	Cross-sectional	Outpatients	OCS: Minimum YBOCS total score of 17	P OCS 17.4%
Nechman et al. [48]	Cross-sectional	Acute inpatients Adolescents	OCD: DSM-IV, minimum YBOCS total score of 7 and 6- mo. duration.	P OCD 26%
Niehaus et al. [49]	Cross-sectional	Inpatients and outpatients Xhosa-speaking South African	OCD: DSM-IV (assessed by means of DIGS)	LTP OCD 0.5%
Ohta et al. [16]	Cross-sectional	Inpatients and outpatients	OCD: DSM-IV (assessed by means of SCID) and YBOCS (non specified)	P OCD 18.3%
Ongur and Goff [15]	Cross-sectional	Outpatients	OCS: Minimum YBOCS total score of 16	P OCS 8.8%
Pallanti et al. [50]	Cross-sectional	Outpatients	OCD: DSM-IV (assessed by means of SCID)	P OCD 22.5%
Porto et al. [52]	Cross-sectional	Chronic patients in day treatment program	OCS: DSM-IV symptomatic criteria (assessed by means of SCID) but not enough distressing or time consuming OCD: DSM-IV (assessed by means of SCID)	LTP OCS 26 % LTP OCD 26%
Poyurovsky et al. [17]	Cross-sectional	First episode acute inpatients	OCD: DSM-IV (assessed by means of SCID-P)	P OCD 14%

Table 17.1 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for OCS/OCD	Prevalence
Poyurovsky et al. [18]	Cross-sectional	Inpatients in long term unit	OCD: DSM-IV (assessed by means of SCID), minimum YBOCS total score of 7 and 6-mo. duration	P OCD 23.5%
Poyurovsky et al. [13]	Cross-sectional	Acute inpatients 63–83 years	OCD: DSM-IV (assessed by means of SCID), minimum YBOCS total score of 15 and 12-mo. duration	P OCD 16%
Seedat et al. [56]	Cross-sectional	Inpatients and outpatients	OCD: DSM-IV (assessed by means of DIGS)	LTP OCD 10.7%
Sim et al. [57]	Cross-sectional	First episode inpatients Asian	OCD: DSM-IV (assessed by means of SCID-P)	P OCD 2%
Sim et al. [58]	Longitudinal (24 mo.) (prevalence only assessed at one time point)	First episode inpatients Asian	OCD: DSM-IV (assessed by means of SCID-P)	P OCD 6.3%
Strakowsky et al. [59]	Cross-sectional	First episode inpatients	OCD: DSM-IIIR (assessed by means of SCID)	P OCD 13.7%
Strakowsky et al. [60]	Cross-sectional	First episode Inpatients and outpatients	OCD: DSM-IIIR (assessed by means of SCID)	P OCD 11%
Tibbo et al. [61]	Cross-sectional	Stable outpatients	OCD: DSM-IV (assessed by means of SCID)	P OCD 25%

DIGS: Diagnostic Interview for Genetic Studies; FOCI: Florida Obsessive Compulsive Inventory; LTP: Lifetime Prevalence; Mo: Month; MMOCI= Modified Maudsley Obsessive Compulsive Inventory; P: Point Prevalence; SCID: Structured Clinical Interview for DSM-III-R/DSM-IV Axis I Disorders; SCID-P: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition; T1: at admission; T2: at 6 weeks; YBOCS: Yale Brown Obsessive Compulsive Scale.

and compulsions is not related to this other diagnosis. In contrast, DSM-IV allows the diagnosis of OCD despite having another axis one disorder if the content of obsessions and compulsions is not restricted to that single disorder. It could be that those studies using DSM-III R criteria may not have searched for further OCS in those patients with obsessions and compulsions related to psychotic symptoms, and thus produced a lower estimate of the prevalence of OCD [52]. In addition, unlike DSM-III R, DSM-IV permits insight to be present or absent in varying degrees in OCD, therefore allowing this diagnosis in patients whose insight into their OCS is poor.

Variation in diagnostic criteria in those studies applying a dimensional definition of OC features depended mostly on the instrument used to assess OCS and also on the cutoff scores selected to identify OCS (for details see Table 17.1). Most studies employed the YBOCS, [3, 11, 14, 15, 63] but other instruments have also been used [65–67]. Amongst the studies that used the YBOCS, those that chose lower cutoff points [3, 11] found higher prevalence rates than those that used higher scores [14, 15]. Prevalence of OCS in the first group was found to be around 40% while in the second it was lower than 20%.

In addition to differences in the diagnostic criteria, it seems that another factor that may help to explain this variability in prevalence estimates is ethnicity. It appears that the prevalence of OC features is generally lower in non-Caucasian samples [46, 49, 57, 58] than in Caucasian ones [2, 4, 6, 13, 16, 18, 36, 37, 39, 48, 50, 52, 61, 67]. While most studies performed in Caucasian samples have found the prevalence of OCD to be higher than 15%, in all studies that have enrolled non-Caucasian subjects it was lower than 10% (for details see Table 17.1). Although both schizophrenia and OCD have been shown to be present in people of different cultures and ethnic groups, [78, 79] evidence also suggests that OCD may be less common in certain communities [80]. This lower prevalence of OC features in non-Caucasian schizophrenia patients raises interesting questions about the role of genetic and cultural factors in the expression of OC phenomena in schizophrenia.

Unlike prevalence, incidence of OC features has been little assessed. It has been found that incidence rate at 24 months is between 3.5 and 4.3% for OCS and between 0 and 1.8% for OCD in first episode schizophrenia patients [12]. These findings could suggest that lifetime rate comorbidity may increase with age and chronicity of the disorder. Nevertheless, it should be noted that prevalence rates of OCD in first episode psychotic patients [17, 59, 60] and in adolescent schizophrenia patients [48] have been shown to be similar to those found in chronic patients [18] and in elderly schizophrenia patients [13]. Moreover, after 24 months follow up, only one third of those schizophrenia patients with OCS/OCD at baseline still had symptoms suggesting that OCS are fluctuating [12]. While the reason for this fluctuation of OCS in schizophrenia is not clear, this finding is consistent with studies suggesting that the course of OCD without comorbid psychosis is variable and unpredictable [81]. In contrast, no change in either prevalence or severity of OCS/OCD during stabilization of active psychotic phase has been demonstrated in schizo-obsessive patients [39, 63].

In conclusion, OC features have been shown to be present throughout the course of schizophrenia, across life-span and in different ethnic groups and, despite varying reported prevalence estimates, compelling evidence suggests that the rate of occurrence of OC features in schizophrenia is considerably higher than in the general population. This higher-than-expected comorbidity supports the validity of an association between OC features and schizophrenia. However, long term longitudinal studies with accurate definition of OC features that assess incidence and changes in OCS/OCD prevalence during different stages and phases of illness are needed. Additionally, epidemiological research in non-Caucasian samples is required in order to replicate preliminary findings of the possible role of ethnicity in the expression of OC features in schizophrenia.

Ethiology

Genetic Factors

Research on the contribution of genetic factors in the etiology of OC features in schizophrenia is scarce and it has been limited to the assessment of the role of a common catechol-O-methyltransferase (COMT) gene polymorphism and to the evaluation of familial transmission of OC-associated disorders.

Since both schizophrenia and OCD strongly aggregates in families, [82–84] familial transmission has been investigated in schizo-obsessive patients. In one study, [22] aggregation of schizophrenia-spectrum, schizo-obsessive disorder and OC-associated disorders, such as OCD and obsessive-compulsive personality disorder (OCPD) was assessed in first degree relatives of schizophrenia probands with and without OCD and in first degree relatives of community subjects. Relatives of schizophrenia patients with OCD showed significantly higher morbid risks than relatives of schizophrenia patients without OCD for schizo-obsessive disorder (2.2% versus 0%; $p = 0.033$) and OCPD (7.14% versus 1.90%; $p = 0.014$) and a trend towards higher morbid risk for OCD (4.41% versus 1.43%; $p = 0.08$). When morbid risks for OCD, OCPD and schizo-obsessive disorder were pooled together, the significant between group difference became robust (13.4% vs 3.3%; $p = 0.0002$). No statistically significant difference in morbid risk for schizophrenia spectrum disorders or any other axis I or axis II disorders was found between relatives of schizophrenia patients with and without OCD. As expected, relatives of both schizophrenia groups had significantly higher morbid risks for schizophrenia and pooled schizophrenia-spectrum disorders than relatives of community-based control subjects. These preliminary findings suggested that schizo-obsessive patients may have a differential familial aggregation and transmission of OC-associated disorders than schizophrenia patients.

Research on specific candidate genes for schizo-obsessive disorder has been conducted recently. The COMT gene has been considered a candidate for both schizophrenia and OCD because it encodes a key catabolic enzyme with an essential

role in dopaminergic neurotransmition [85] which has been implicated in both disorders [86, 87]. Furthermore, this gene is located at the q11 band of chromosome 22. This region is deleted in velocardio-facial syndrome (VCFS) which has been associated with predisposition to schizophrenia [88] and with higher prevalence of OCD [89]. The COMT gene contains a common polymorphism (valine to methionine substitution at codon 158) that causes variation in its activity (high activity in Val/Val, intermediate activity in Val/Met and low activity in Met/Met). Val 158 Met polymorphism has been studied in schizo-obsessive patients since a possible contribution of this polymorphism to both schizophrenia and OCD has been suggested, although negative results have also been reported [90]. In one case-control association study, [23] COMT Val 158 Met polymorphism (Val/Val, Val/Met and Met/Met) was assessed in schizophrenia patients with OCD, pure OCD patients and in healthy controls and no significant difference in allele and genotype distribution of the COMT gene between the three groups was found. Prevalence of Val/Val, Val/Met and Met/Met in schizophrenia patients with OCD, OCD patients and in healthy controls was found to be 31%, 23% and 28%, 45%, 47% and 52%, and 24%, 30% and 20%, respectively. In contrast, a significant effect of COMT genotype on severity of OCS has been shown in another study performed in adolescent schizophrenia male patients [24]. In this study, schizophrenia patients were divided into three groups according to the COMT genotype (Val/Val, Val/Met and Met/Me) and the severity of OCS was assessed in each group by means of the YBOCS. The Val/Val genotype was associated with the highest YBOCS scores whereas patients with Met/Met genotype had the lowest YBOCS scores (mean YBOCS = 7.32 vs 0, $Z = -2.58$, $P = 0.010$) suggesting that COMT high activity Val allele is associated with more sever OCS. Variation in methodology and definition of OC features between these two studies make comparison of results difficult.

In summary, despite the limited published genetic research into schizo-obsessive disorder, preliminary evidence suggests that genetic factors may contribute. Preferential familial aggregation of OC-spectrum disorders in schizo-obsessive patients and an association between COMT high activity Val allele and OCS in schizophrenia patients have been shown. These findings give additional support to the validity of a putative schizo-obsessive entity although replication is required. To further support the validity of this phenotype large-scale family studies that assess familial aggregation of additional OCD spectrum disorders and association studies that encompass all pertinent candidate gens are needed.

Environmental Factors

Research into the involvement of environmental factors in the etiology of OCS in schizophrenia has been limited to the assessment of the role of AP. Since the introduction of atypical AP, case reports and retrospective studies have indicated that some atypical AP may induce or exacerbate OC features in patients with schizophrenia [28, 91–93]. It has been suggested that this effect may be related to the serotonin and dopamine interactions, particularly the 5-HT 2A/ dopamine

antagonist ratios [20]. On the contrary, prospective and controlled studies with some atypical AP have failed to find a relationship between these drugs and appearance or exacerbation of OC features [94–97].

A recent systematic review of case reports describing atypical AP-induced OCS identified 30 reports that included 55 cases, 30 of which were with clozapine, 16 with risperidone, 8 with olanzapine and 1 with quetiapine [28]. Besides this, cross-sectional and retrospective studies have also described the presence of OC features in schizophrenia patients treated with clozapine. It has been found that up to 28 % of schizophrenia patients treated with clozapine may show *de novo* appearance or exacerbation of OC features [91, 93, 98–101]. In one of these studies, [101] a relation between plasma concentration of clozapine and the emergence of OCS was suggested since clozapine-treated schizophrenia patients with OCS had higher plasma concentration of clozapine and its metabolites norclozapine and clozapine-N-oxide than those patients without OCS. It should be noted that other studies have failed to show a relation between dose of clozapine and appearance of OCS [93, 99].

The prevalence of OC features in patients treated with clozapine or typical AP has been compared in cross-sectional and retrospective studies. Higher prevalence of OC features was found in clozapine-treated patients compared to those treated with typical AP in two studies [102, 103] but another one [104] showed no significant difference between these two groups. However, this last study found that schizophrenia patients treated with clozapine showed greater severity of OCS compared to those treated with typical AP [104].

The design of these studies limits conclusions about a causal relationship between clozapine and the appearance or exacerbation of OC features because these assessments were performed retrospectively. Besides this, the prevalence of OCS/OCD reported in clozapine-treated schizophrenia patients is between the range of that found in epidemiological and clinical studies, regardless of treatment. The major limitation of these studies is that patients receiving clozapine differ from those receiving atypical AP. Therefore, the possibility that these baseline differences could explain the finding of higher prevalence of OCS in clozapine-treated patients cannot be ruled out.

The effect of other atypical AP on OCS has also been investigated. Case reports, retrospective and cross-sectional studies have shown the appearance of OC features in schizophrenia patients treated with olanzapine, risperidone, quetiapine, ziprazidone and aripiprazole [28, 91, 92, 105, 106] However, prospective and controlled studies with olanzapine and risperidone have failed to confirm a relationship between these drugs and OC features in schizophrenia patients. In a small 6-week, double-blind, placebo-controlled clinical trial, [94] schizophrenia patients were randomly assigned to either olanzapine in two fixed daily doses (1 mg vs 10 mg) or to placebo. Fifty-six percent of these patients had OCS at baseline. No changes in severity of OCS from baseline to endpoint were found in any of the three groups. With regard to risperidone, a single-blind, 2-month length prospective study showed that schizophrenia patients assigned to the drug (mean dose at baseline and at study completion was 2.6 and 3.5 mg, respectively) rather than showing an increase of OCS severity, in fact showed a reduction [97].

The propensity of olanzapine and risperidone to induce or exacerbate OC features has also been compared. In a 6-week prospective study [95] performed in schizophrenia patients taking risperidone (mean dose at baseline and at the end of 6th week was 14.2 mg) or olanzapine (mean dose at baseline and at the end of 6th week was 4.1 mg) no differences were found in their short term propensity to induce or exacerbate OCS. However, the duration of the treatment with olanzapine was related to severity of OCS suggesting that olanzapine may be associated with a delayed expression of OCS. Nevertheless, olanzapine was associated with a reduction in OCS severity in a later randomized double-blind prospective study [96] that compared the propensity of olanzapine and risperidone to induced OC features in schizophrenia patients. Olanzapine (mean dose of 11.3 mg) was associated with larger improvements of OCS than risperidone (mean dose 3 mg).

There does not appear to be any other controlled study that has investigated the development of atypical AP-induced OCS with the use of drugs other than risperidone and olanzapine. Nevertheless, both aripiprazol and amisulpiride have been associated with a decrease in OCS severity in two small open label studies performed in schizo-obsessive patients [25, 27].

To conclude, although it has been suggested that atypical AP may induce or exacerbate OC features in schizophrenia patients, available controlled data with olanzapine and risperidone have failed to confirm these findings. Furthermore, reduction in OCS severity with both drugs has been shown. In the absence of additional controlled data, caution is needed when inferring a causal relationship between atypical AP and the appearance of OC features. Additional controlled studies with longer follow-up periods which investigate different atypical AP at varying doses are needed in order to confirm or reject any casual association.

Phatophysiology

On the basis of available data from neurobiological studies of schizophrenia and OCD it has been hypothesized that similarities in neurocircuitry, anatomic structures and neurotransmitters involved in both disorders may account for the overlap in symptom expression [20, 21] But neurobiological research in schizo-obsessive patients is still lacking.

The cortico-strial-thalamic-cortical circuitry is known to be involved in the pathophysiology of OCD [107]. Specific structures implicated in this pathway include orbitofrontal cortex (OFC), anterior cingulated, caudate nucleus, globus pallidus and thalamus [108, 109]. Dorsolateral prefrontal cortex (DLPC) circuitry has been largely associated with schizophrenia [110] and it shares some anatomic substrates with the OFC circuitry, including prefrontal cortex, anterior cingulated and thalamus [20, 21, 111]. It has been suggested that these similarities in the underlying cortico-subcortical pathways raise the possibility that a common functional alteration may lead to the co-expression of OCS and psychotic symptoms [20].

Studies assessing these common brain areas in schizo-obsessive patients are few. The Prefrontal cortex has been assessed using functional magnetic imaging (fMRI) [112] and neuropsychological test [44, 64]. It has been suggested that if the hypothesis of the overlapping common substrates is correct, schizo-obsessive patients should show deficits in both DLPC and OFC function while schizophrenia patients should only show deficits in DLPC function but not in OFC function [64]. One neuropsychological study failed to identify any difference between schizo-obsessive and schizophrenia patients in either OBF function or DLPC function, which were assessed by means of Object Alternation Learning Test and the Wisconsin Card Sorting Test (WCST) respectively [44]. Another study found that schizo-obsessive patients compared to schizophrenia patients showed greater deficits in both DLPC and OFC functions, that were assessed by means of the WCST and the Bechara Gambling Task respectively, but these differences did not reach the conventional level of statistical significance [64].

Activation of DLPC has been measured using fMRI during a word-fluency challenge test in schizophrenia patients with different degrees of OCS severity [112]. Two distinct groups of schizophrenic patients were found with regard to the relationship between OCS severity and fMRI signal change. In one group, a negative correlation between DLPC activation and OCS severity was found amongst those patients with higher OCS severity. In the other group, no association was found between OCS and fMRI signal. However, since this last group had more severe psychopathology it could be that the relationship between OCS and fMRI activation was masked.

There do not seem to be further published neuroimaging studies assessing other overlapping brain regions in schizo-obsessive patients. In contrast, two neuroimaging studies have shown specific structural brain abnormalities in these patients that differ from those seen in each disorder individually. Using magnetic resonance imaging (MRI), both enlargement of the anterior horn of the lateral and the third ventricle [113] and smaller left hippocampus [114] have been demonstrated in patients with juvenile-onset schizophrenia with OCS compared to those patients without OCS. It has also been suggested that young schizophrenic patients with OCS may be predisposed to develop frontal lobe atrophy, since an inverse correlation between illness duration and frontal lobe size was also found in the group of schizophrenia with OCS but not in the group without OCS [114].

An overlap in neurotransmitter systems in schizophrenia and OCD has also been suggested since both serotonin and dopamine have been implicated in the pathophysiology of both disorders [20, 21] but there is little data involving schizo-obsessive patients. Whole blood serotonin concentration has been compared between schizophrenia patients with and without OCS, OCD patients, clozapine-treated patients who developed OCS and those who did not, and healthy controls [115]. The results revealed that the three groups with OCS, namely, OCD, schizophrenia with OCS and patients with clozapine-induced OCS had lower serotonin concentration than the other groups. All patients with OCS demonstrated similar levels of whole blood serotonin. These findings suggest the existence of an association between OCS and low levels of serotonin and indicate some common

underlying biological mechanism for OCS regardless of its origin, neurotic, schizo-obsessive or clozapine-induced.

In summary, there is still a dearth of neurobiological data concerning schizo-obsessive disorder to draw any conclusion about its pathophysiology. It has been proposed that similarities between cortico-subcortical pathways and neurotransmitters involved in schizophrenia and OCD may account for this overlap in symptom expression. Although an altered serotonin metabolism has been found in schizo-obsessive patients, neuroimaging and neuropsychological studies assessing these common substrates have come to inconclusive results. In contrast, specific structural brain abnormalities that differ from those seen in each disorder individually have been found in schizo-obsessive patients. Whether these findings suggest a specific pattern of dysfunction unique to this comorbid group or a more severe form of illness with greater brain dysfunction is still unclear.

Psychopathology

Obsessive-Compulsive Symptoms

The characterization of OCS in schizo-obsessive patients has shown clinical similarities with those OCS presented in OCD. More than two thirds of schizo-obsessive patients exhibited both obsessions and compulsions [17–19, 40, 41, 53, 54, 56]. The assessment of the type of obsessions and compulsions has shown that aggressive and contamination obsessions are the most prevalent [13, 16–19, 41, 47, 52, 53] but sexual and somatic obsessions have also been documented [17, 19, 39, 47, 53]. The most prevalent compulsions are washing and checking [13, 16–19, 41, 47, 52] but repeating and hoarding compulsions have also been reported [39, 41, 47, 53]. Type and severity of obsessions and compulsions have been assessed mostly by means of YBOCS [13, 16–19, 39, 47, 52–54]. Mean YBOCS total scores of schizo-obsessive patients have been shown to range from 15 to 28, indicating moderate to severe OCS [11, 13, 16–19, 39, 47, 48, 51, 53, 61, 68]. These findings suggest that the characteristics of OCS in schizo-obsessive patients are similar to those presented in OCD patients.

Taking into account these similarities, one study evaluated the factor structure of OCS in schizo-obsessive patients in order to determine whether it was comparable to that revealed previously in OCD [42]. Five symptom dimensions emerged: (1) aggressive, sexual, religious/ counting; (2) symmetry/ordering, hoarding compulsion; (3) cleanliness/washing; (4) somatic/repeating rituals and (5) hoarding obsession/ checking. Despite the fact that hoarding obsession and compulsion were not loaded on the same factor as in most factor analytical studies performed in OCD patients [116] these five symptom dimensions are to a large extent comparable to those revealed in OCD patients.

Traditionally it has been considered that OCS were distinct and separable from psychotic symptoms on the basis of insight since patients recognize obsessions and

compulsions as excessive or unreasonable and foreign to them [21]. Whereas it has been shown that between 10 and 39% of patients with OCD may show poor insight into their OCS [117, 118]. Evaluation of insight in schizo-obsessive patients has also found that 15% of them showed poor insight [41, 53]. This proportion is within the range observed in OCD [53].

Based on the interrelationship between OCS and psychotic symptoms, Poyurovsky et al. [19] identified two groups of schizo-obsessive patients. The first group had classical ego-dystonic obsessions and/or compulsions that were unrelated to the content of psychotic symptoms and the second included patients with classical ego-dystonic obsessions and/or compulsions unrelated to the content of psychotic symptoms together with obsessions and/or compulsions related to delusional and/or hallucinatory content. An additional group was defined by Porto et al. [52] to describe those schizophrenic patients who presented obsessions and compulsions on a continuum with psychotic symptoms. In a recent study, specific relationships between psychotic dimensions and OCS dimensions have been reported in schizophrenia patients [70]. In this study, schizophrenia symptoms scores were collapsed into four dimensional scores (disorganization, bizarre delusions, auditory hallucinations and diminished expression) and OCS into four other dimensional scores (obsessions, compulsions, somatic obsessions and hoarding/collecting compulsions). The latter were entered as explanatory variables to determine their associations with schizophrenia dimension scores. The results showed that bizarre delusions and obsessions were positively correlated, supporting the view that they reflect a manifestation of the same mechanism [119]. This mechanism could be expressed as over-valued ideas lying on a continuum of obsessional doubts to delusional certainty [120]. Hallucinations were also positively correlated with compulsions, also suggesting a common underlying mechanism that may be related to a decreased capacity to inhibit behaviors or thoughts [70].

The identification of these three distinct subgroups of schizo-obsessive patients indicates a substantial heterogeneity of this patient population. It has been suggested that those patients with typical ego-dystonic OCS may represent a distinct comorbid disorder while delusion-related OCS/OCD may represent a specific dimension of schizophrenia [26].

To conclude, studies assessing the characteristics of OCS presented in schizo-obsessive patients have shown that they are comparable to those seen in OCD patients. The proportion of schizo-obsessive patients with poor insight is within the range observed in OCD. These similarities suggest that OCS appear to be an identifiable dimension of psychopatology in schizophrenia [41, 53]. Based on the interrelationship between OCS and psychotic symptoms, three subgroups of patients have been identified, those with classical ego-dystonic OCS unrelated to psychotic symptoms, those with ego-dystonic OCS related to psychotic symptoms in addition to OCS unrelated to psychotic symptoms and those that presented OCS on a continuum with psychotic symptoms. Further delineation of these subgroups of schizo-obsessive patients is warranted since it may help to improve current understanding of the interrelationship between OCS and schizophrenia in this population [26].

Psychotic Symptoms

The impact of OC features on psychotic symptoms in schizophrenia patients has been widely assessed although the results have been inconsistent. The characteristics of studies assessing psychotic symptoms severity in schizo-obsessive patients are presented in Table 17.2.

Some studies have found no differences in psychotic symptom severity between schizophrenia patients with and without OC features [11, 13, 16, 18, 33, 35, 41, 53, 54, 62, 64, 67, 121] or, at most, they have found differences in one specific psychotic symptom but not in overall positive or negative symptoms. Regarding positive psychotic symptoms, greater severity of bizarre behavior [19, 47] and lower severity of delusions and hallucinations [47] and formal thought disorder [17] have been reported. Regarding negative psychotic symptoms, both greater and lesser severity of affective flattening [17, 48] and lower anergia [55] have been shown.

In contrast, other studies have found differences in overall positive or negative psychotic symptom severity between schizo-obsessive and schizophrenia patients. Greater overall severity of positive and negative psychotic symptoms in schizo-obsessive patients has been shown in some studies [3, 14, 15, 68] but others have reported lesser severity in negative symptoms [32, 39, 61]. One study reported that the effect of OCS upon severity of negative symptoms was dependent on psychosocial function [32]. Schizo-obsessive patients with good psychosocial function had fewer negative symptoms than those with poorer function. Another study that reported lower severity of negative symptoms in schizo-obsessive patients than in those with schizophrenia showed that these differences were only present during the acute phase of the illness and they faded away after a few weeks of treatment [39].

Differences in definition of OC features (dimensional versus categorical) may account for these discrepant results and may in consequence have made it difficult to reach conclusions about the impact of OC phenomena on psychotic severity. To address this issue, a systematic review followed by a meta-analysis has been published recently [31]. Eighteen studies comparing schizophrenia patients with and without OCS/OCD with information regarding psychotic severity were included in the analysis, which was carried out separately for those studies using a dimensional versus a categorical definition of OC features. The results showed that the impact of OCS/OCD on the severity of psychotic symptoms was dependent on the definition of OC features. When a categorical definition was used, no differences were found between schizo-obsessive patients and pure schizophrenia patients, whereas when using a dimensional one, schizo-obsessive patients showed greater severity of positive, negative and global psychotic symptoms. Since a dimensional definition of OC features is less restrictive than a categorical one, patients with OCS who may not fulfill diagnostic criteria for OCD would be classified in the schizo-obsessive group if a dimensional definition is used but would be placed in the schizophrenia group if a categorical definition is applied. Thus, the control group will differ in terms of OC severity depending on the definition, with a greater severity of OC features when using a categorical definition because it would include patients with varying degrees of OCS. This may lead to a dilution of the effect of OCS over psychotic severity.

Table 17.2 Characteristics of studies assessing psychotic symptoms severity in schizo-obsessive patients

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Berman et al. 1998 [11]	Cross-sectional Consecutive sampling	N = 30 Schizophrenia Chronically hospitalized inpatients	Schizophrenia: DSM-III-R OCS: YBOCS checklist and minimum YBOCS total score of 10	PANSS	No difference in positive, negative and global symptoms between OCS-SCZ and non-OCS- SCZ groups No correlation between OCS and positive or negative symptoms
Borkowska et al. 2003 [35]	Cross-sectional Sample was stratified in 4 groups: OCD-SCZ, non-OCD-SCZ, OCD and HC matched for age and level of education	N = 60 Schizophrenia with OCD (N = 13), schizophrenia without OCD (N = 15), OCD (N = 17) and HC (N = 15) Inpatients and outpatients	Schizophrenia: DSM-IV and ICD-10 OCD: DSM-IV and ICD-10	PANSS	No difference in global and negative symptoms between OCD-SCZ and non-OCD-SCZ groups Positive symptoms were not assessed
Byerly et al. 2005 [67]	Cross-sectional Consecutive sampling in first 82 patients and non-consecutive sampling in the 18 patients left	N = 100 Schizophrenia (N = 78) and schizoaffective disorder (N = 22) Outpatients	Schizophrenia: DSM-IV OCS: Two or more OCS identified by FOCI and present for at least 6 mo.	PANSS	No differences in positive, negative and global symptoms between OCS-SCZ and non-OCS-SCZ groups

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Craig et al. 2002 [12]	Prospective (24 mo. follow-up) Sampling: NR	N = 450 Schizophrenia and schizoaffective disorder (N = 225), Bipolar disorder with psychosis (N = 138) and Major depression with psychosis (N = 87) Inpatients Acute phase First episode or current admission within 6 mo. of first	Schizophrenia: DSM-III-R (assessed by means of SCID). OCS: DSM III-R symptomatic criteria assessed by means of SCID OCD: DSM III-R full diagnostic criteria assessed by means of SCID	SAPS and SANS	No association between the presence of OCS or OCD at baseline and the severity of positive and negative symptoms at 24 mo. follow-up
De Haan et al. 2005 [39]	Prospective (6 weeks) Consecutive sampling	N = 113 Schizophrenia (N = 97), schizoaffective disorder (N = 9) and schizophreniform disorder (N = 7) Inpatients Acute phase Recent onset of psychotic disorder	Schizophrenia: DSM-IV OCS: DSM-IV symptomatic criteria (assessed by means of SCID-P) OCD: DSM-IV full criteria (assessed by means of SCID-P)	PANSS	Lesser negative symptoms in OCS-SCZ group compared to OCD-SCZ and non-OC-SCZ groups at baseline No difference in positive and negative symptoms after 6 weeks of treatment in OCS-SCZ, OCD-SCZ and non-OC-SCZ groups

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Fabisch et al. 2001 [63]	Prospective study (acute psychotic exacerbation) Sampling: NR	N = 150 Schizophrenia (N = 128) and schizoaffective disorder (N = 22) Inpatients Acute phase	Schizophrenia: DSM-IV OCS: YBOCS checklist (non specified)	PANSS	No association between OCS and severity of psychotic symptoms
Faragian et al. 2008 [41]	Cross-sectional Sample was stratified in 2 groups: OCD-SCZ and non-OCD-SCZ matched for age, gender and number of hospitalizations	N = 44 Schizophrenia with OCD (N = 22) and schizophrenia without OCD (N = 22) Inpatients Acute unit Adolescents	Schizophrenia: DSM-IV (assessed by means of SCID-P) OCD: DSM-IV criteria (assessed by means of SCID-P)	SAPS and SANS	No difference in positive or negative symptoms between OCD-SCZ and non-OCD-SCZ
Hwang et al. 2000 [68]	Cross-sectional Sample was stratified in 2 groups: OCS-SCZ and non-OCS-SCZ matched for age and gender	N = 20 Schizophrenia with OCS (N = 10) and schizophrenia without OCS (N = 10) Inpatients After 4 weeks of symptom stabilization with optimal AP dose	Schizophrenia: DSM-III-R OCS: At least 3 of the operationalized symptom criteria described by Fenton and McGlashan present for at least 6 mo.	PANSS	No difference in positive symptoms between OCS-SCZ and non-OCS-SCZ groups Greater negative symptoms and general psychopathology in OCS-SCZ group compared to non-OCS-SCZ

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Kayahan et al. 2005 [2]	Cross-sectional Sampling: NR	N = 100 Schizophrenia Inpatients and outpatients	Schizophrenia: DSM-IV (assessed by means of SCID-P) OCS: DSM IV symptomatic criteria assessed by means of SCID-P OCD: DSM-IV criteria (assessed by means of SCID-P), a minimum YBOCS total score of 7 and 6- mo. duration	PANSS	Positive correlation between OCS and general psychopathology, positive and global symptoms No correlation between OCS and negative symptoms
Krüger et al. 2000 [47]	Cross-sectional. Consecutive sampling	N = 76 Schizophrenia Inpatients Interviewed after resolution of acute phase	Schizophrenia: DSM-III-R OCD: DSM-III-R criteria (assessed by means of SCID)	SAPS, SANS and BPRS	No differences in overall negative and positive symptoms between OCD-SCZ and non-OC-SCZ groups Greater general psychopathology in OCD-SCZ group compared to non-OCD-SCZ Lesser hallucinations, delusions and poverty of speech in OC-SCZ group compared to non- OCD-SCZ Greater bizarre behavior, lack of vocal inflection circumstantiality and pressure of speech in OCD-SCZ group compared to non- OCD-SCZ

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Lysaker et al. 2000 [3]	Cross-sectional. Consecutive sampling	N = 46 Schizophrenia (N = 35) and schizoaffective disorder (N = 11) Outpatients Stable or post acute phase	Schizophrenia: DSM-IV OCS: Minimum YBOCS obsessions or YBOCS compulsions scores of 8	Factor analytical derived PANSS scales	Greater positive and emotional discomfort symptoms in OCS-SCZ group compared to non-OCS-SCZ No differences in negative symptoms between OCS-SCZ and non-OCS-SCZ groups
Lysaker et al. 2002 [14]	Cross-sectional. Consecutive sampling	N = 63 Schizophrenia and schizoaffective disorder Outpatients Post acute phase	Schizophrenia: DSM-IV OCS: Minimum YBOCS total score of 17	Factor analytical derived PANSS scales	No differences in positive symptoms between OCS-SCZ and non-OCS-SCZ groups Greater negative symptoms and emotional discomfort symptoms in OCS-SCZ group compared to non-OCS-SCZ
Lysaker et al. 2004 [32]	Cross-sectional Sample was stratified in 4 groups: OCS-SCZ/good function, OCS-SCZ/poor function, non-OCS-SCZ moderate function and non-OCS-SCZ/poor function	N = 66 Schizophrenia (N = 41) and schizoaffective disorder (N = 25) Outpatients Stable or post acute phase	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: Cluster analysis based on YBOCS total scores	Factor analytical derived PANSS scales	Lesser negative symptoms in OCS-SCZ/good function group compared to OC-SCZ/poor function and non-OCS groups No differences in positive symptoms between the four groups

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Lysaker et al. 2006 [33]	Cross-sectional. Sampling: NR	N = 67 Schizophrenia (N = 43) and schizoaffective disorder (N = 25) Outpatients Stable or post acute phase	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: 2 or items in YBOCS obsessions or YBOCS compulsion subscales rated as moderate	Factor analytical derived PANSS scales	No differences in global symptoms between OCS-SCZ and non-OCS-SCZ groups
Nechman et al. 2003 [48]	Cross-sectional. Consecutive sampling	N = 50 Schizophrenia (N = 39) and schizoaffective disorder (N = 11) Inpatients Acute phase Adolescent	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV criteria, a minimum YBOCS total score of 7 and 6-mo duration	SAPS and SANS	No difference in overall positive and negative symptoms between OCD-SCZ and non-OCD-SCZ groups Greater affective flattening in OCD-SCZ group compared to non-OCD-SCZ Positive correlation between OCS and negative symptoms
Ohta et al. 2003 [16]	Cross-sectional. Sampling: NR	N = 71 Schizophrenia Inpatients (N = 60) and outpatients (N = 11)	Schizophrenia: DSM-IV OCD: DSM-IV (assessed by means of SCID) and YBOCS rating (non specified)	PANSS	No difference in psychotic symptoms between OCD-SCZ and non-OCD-SCZ groups
Ongur and Goff 2005 [15]	Cross-sectional. Consecutive sampling	N = 118 Schizophrenia and schizoaffective disorder Outpatients Stable phase	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: YBOCS total score between 1 and 11; and YBOCS total score equal or greater than 12	PANSS	Greater positive symptoms in the OCS-SCZ group with higher OCS compared to other two groups No difference in negative and global symptoms between the three groups

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Poyurovsky et al. 1999 [17]	Cross-sectional. Consecutive sampling	N = 50 Schizophrenia (N = 37), schizoaffective (N = 4) and schizophreniform (N = 9) disorders. Inpatients Acute phase First episode	Schizophrenia: DSM-IV (assessed by means of SCID-P) OCD: DSM-IV criteria (assessed by means of SCID-P)	SAPS and SANS	Lesser formal thought disorder and affective flattening in OCD-SCZ group compared to non-OCD-SCZ No correlation between OCS and positive or negative symptoms
Poyurovsky et al. 2001 [18]	Cross-sectional Sampling: NR	N = 68 Schizophrenia. Inpatients in long-term rehabilitation unit	Schizophrenia: DSM-IV (assessed by means of SCID-P) OCD: DSM-IV criteria (assessed by means of SCID-P), a minimum YBOCS total score of 7 and 6-mo. duration	SAPS and SANS	No difference in positive or negative symptoms between OCD-SCZ and non-OCD-SCZ groups No correlation between OCS and positive or negative symptoms
Poyurovsky et al. 2003 [19]	Cross-sectional. Sample was stratified in 2 groups: OCD-SCZ and non-OCD-SCZ, matched for age and number of hospitalizations	N = 110 Schizophrenia with OCD (N = 55) and schizophrenia without OCD (N = 55) Inpatients Interviewed after resolution of acute phase	Schizophrenia: DSM-IV (assessed by means of SCID-P) OCD: DSM-IV (assessed by means of SCID-P)	SAPS and SANS	No differences in overall positive and negative symptoms between OCD-SCZ and non-OCD-SCZ groups Greater bizarre behavior and lower delusions and formal thought disorder in OCD-SCZ group Positive correlation between compulsions and bizarre behavior

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Poyurovsky et al. 2006 [13]	Cross-sectional. Consecutive sampling	N = 50 Schizophrenia (N = 41) and schizoaffective disorder (N = 9) Inpatients Acute phase 63-83 years old	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV criteria (assessed by means of SCID), a minimum YBOCS total score of 15 and a 12-mo.duration	SAPS and SANS	No differences in positive or negative symptoms between OCD-SCZ and non-OCD-SCZ groups No correlation between OCS and positive or negative symptoms
Poyurovsky et al. 2007 [53]	Cross-sectional Sample was stratified in 2 groups: OCD-SCZ and non-OCD-SCZ	N = 137 Schizophrenia with OCD (n = 57) and schizophrenia without OCD (N = 80)	SCZ: DSM-IV (assessed by means of SCID-P) OCD: DSM-IV (assessed by means of SCID-P), typical OCS on YBOCS checklist that last more than 1 h/day and, 6 mo. duration	SAPS and SANS	No differences in positive or negative psychotic symptoms between OCD-SCZ and non-OCD-SCZ
Poyurovsky et al. 2008 [54]	Cross-sectional Sample was stratified in 2 groups: OCD-SCZ and non-OCD- SCZ, similar in age, gender and number of hospitalizations	N = 44 Schizophrenia with OCD (n = 22) and schizophrenia without OCD (N = 22) Inpatients Adolescent	SCZ: DSM-IV (assessed by means of SCID-P) OCD: DSM-IV criteria (assessed by means of SCID), a minimum YBOCS total score of 7 and a 6-mo. duration	SAPS and SANS	No differences in positive or negative symptoms between OCD-SCZ and non-OCD-SCZ groups

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Rajkumar et al. 2008 [55]	Cross-sectional Consecutive sampling Sample was stratified in 2 groups: OCD-SCZ and non-OCD-SCZ	N = 100 Schizophrenia with OCD (n = 50) and schizophrenia without OCD (n = 50)	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV	PANSS	No differences in positive and negative symptoms between OCD-SCZ and non-OCD-SCZ groups Lesser anergia and higher depression in OCD-SCZ compared to non-OC-SCZ Positive correlation between YBOCS insight and positive, negative and general psychotic symptoms
Sevincok et al. 2004 [121]	Cross-sectional. Sampling: NR	N = 77 Schizophrenia (N = 53) and healthy subjects (N = 25)	Schizophrenia: DSM-IV OCD: DSM-IV criteria and a minimum YBOCS total score of 7	SAPS and SANS	No differences in positive or negative symptoms between OCD-SCZ and non-OCD-SCZ groups No correlation between OCS and positive or negative symptoms
Tumkaya et al. 2009 [62]	Cross-sectional Sampling: NR	N = 89 Schizophrenia with OCD (N =16), schizophrenia without OCD (N = 30), OCD (N = 30), OCD with poor insight (N = 13) Outpatients	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV (assessed by means of SCID)	SAPS and SANS	No difference in positive and negative symptoms between OCD-SCZ and non-OCD-SCZ groups

Table 17.2 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Psychotic severity assessment	Results
Tibbo et al. 2000 [61]	Cross-sectional. Sampling: by advertisement	N = 52 Schizophrenia Outpatients Stable on AP dose for the prior mo.	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV criteria (assessed by means of SCID)	PANSS	Lesser negative symptoms in OCD-SCZ group compared to non-OCD-SCZ No difference in general psychopathology, positive and global symptoms between OCD-SCZ and non-OCD-SCZ groups
Whitney et al. 2004 [64]	Cross-sectional Sampling: NR	N = 65 Schizophrenia (N = 40), schizoaffective (N = 14) disorder and OCD (N = 11) Outpatients Stable phase	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: Minimum YBOCS obsessions or YBOCS compulsions scores of 8	PANSS	No differences in global, positive or negative symptoms between OCS-SCZ and non-OCS-SCZ groups

FOCI: Florida Obsessive Compulsive Inventor; HC: Healthy Controls; Mo: Month; Non-OC-SCZ: Schizophrenia Without OCS or OCD; Non-OCD-SCZ: Schizophrenia Without OCD; Non OCS-SCZ: Schizophrenia Without OCS; NR: Non Referred; OCD: Obsessive-Compulsive Disorder; OCS: Obsessive-Compulsive Symptoms; OCD-SCZ: Schizophrenia with OCD; OCS-SCZ: Schizophrenia with OCS; PANSS: Positive and Negative Syndrome Scale; SCID: Structured Clinical Interview for DSM-III-R/DSM-IV Axis I Disorders; SCID-P: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition; SANS: The Scale for the Assessment of Positive Symptoms; SAPS: The Scale for the Assessment of Positive Symptoms; YBOCS: Yale Brown Obsessive Compulsive Scale.

These findings appear to favor a dimensional conceptualization of schizo-obsessive disorder since it has a prognostic value.

In this line, a study [72] investigating OCS/OCD in psychosis prodrome found that, when OCD was examined from a DSM-IV categorical perspective, ultra high risk (UHR) individuals with OCD did not differ from UHR individuals without OCD in either positive or negative psychotic symptom severity. In contrast, when the effects of OCS were examined from a dimensional perspective, by means of the Padua Inventory, it was found that OCS were associated with higher severity of positive symptoms and also with negative symptoms, at a statistical trend.

In summary, despite inconclusive findings from individual studies regarding psychotic severity in schizo-obsessive patients, it appears that the presence of OCS may increase global, positive and negative psychotic symptom severity. This effect seems to be dependent on the definition of OC features, since it was only found when OCS were assessed from a dimensional perspective. Therefore, these results favor a dimensional view of schizo-obsessive disorder.

Neurocognition

The neurocognitive function of schizo-obsessive patients has been extensively assessed. The first neuropsychological study of schizo-obsessive patients [11] showed that schizophrenia patients with OCS performed worse than pure schizophrenia patients in a number of domains that have been reported as abnormal in both schizophrenia and OCD, such as visual memory, cognitive and motor shifting abilities and visual-spatial skills. No differences were found in domains reported to be impaired in schizophrenia but not in OCD such as visual and auditory memory, attention and motor abilities. Eighty-one percent of cases could be correctly classified as either OC or non-OC based on neurocognitive performance. In OC group, severity of OCS correlated with perseverative errors and with more perseverative responses in the WCST as well as with poor performance on Trail Making Test A and B.

Subsequent research into the neuropsychological profile of schizo-obsessive patients has produced heterogeneous results, hindering the delineation of any specific profile. The characteristics of studies assessing neurocognitive function are presented in Table 17.3.

Greater deficits in executive function in schizo-obsessive patients compared to those with schizophrenia have been shown in some studies [3, 14, 51, 64, 68]. More perseverative [64, 68] and non-perseverative errors, [14, 64] and fewer categories completed [14, 68] in the WCST, along with a greater total number of errors [51] in the Cambridge Automated Neuropsychological Test Battery (CANTAB) have been reported. In addition, an association between poorer executive functioning and OCS has been shown in a recently published longitudinal study [69]. In this study, schizophrenia patients were assessed for the presence of OCS at baseline and at 6 months follow up by means of the YBOCS. Executive function was assessed at

Table 17.3 Characteristics of studies assessing neurocognitive function in schizo-obsessive patients

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Neuropsychological assessment	Results
Berman et al. [11]	Cross-sectional Consecutive sampling	N = 30 Schizophrenia Chronically hospitalized inpatients	Schizophrenia: DSM-III-R OCS: YBOCS checklist and minimum YBOCS total score of 10	WCST TMT A and B Controlled oral word association test Weshcler delayed visual memory test Weschler immediate visual memory test WAIS-R (block design. similarities tests, digit symbol tests and digit span) MMSE	OCS-SCZ performed worse in TMT A and B and in Weshcler delayed visual memory than non-OCS-SCZ No difference between OCS-SCZ and non-OCS-SCZ groups in any other neuropsychological test Positive correlation between YBOCS and perseverative errors and responses in WCST Association between YBOCS and poor performance on TMT B
Borkowska et al. [35]	Cross-sectional. Sample was stratified in 4 groups: OCD-SCZ, non-OCD-SCZ, OCD and HC matched for age and level of education	N = 60 Schizophrenia with OCD (N = 13), schizophrenia without OCD (N = 15), OCD (N = 17) and healthy subjects (N = 15) Inpatients and outpatients	Schizophrenia: DSM-IV and ICD-10. OCD: DSM-IV and ICD-10	TMT A and B Stroup color word interference test Controlled oral word association test	OCD-SCZ performed better in TMT A and B and in FAS than non-OCD-SCZ No difference in Stroop color word interference test between OCD-SCZ and non-OCD-SCZ

Table 17.3 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Neuropsychological assessment	Results
Hermesh et al. [44]	Cross-sectional Sample was stratified in 2 groups: OCD-SCZ and non-OCD-SCZ matched for age, IQ and depressive and psychotic severity	N = 40 Schizophrenia with OCD (N = 21) and schizophrenia without OCD (N = 19) Inpatients and outpatients	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV (assessed by means of SCID)	WCST Alternation learning Standard progressive matrices sets A, B, C, D and E	No difference in WCST and alternation learning between OCD-SCZ and non-OCD-SCZ Positive correlation between YBOCS and alternation learning in high range OCD-SCZ group No correlation between YBOCS and WCST
Hwang et al. [68]	Cross-sectional Sample was stratified in 2 groups: OC-SCZ and non-OC-SCZ matched for age and gender	N = 20 Schizophrenia with OCS (N = 10) and schizophrenia without OCS (N = 10) Inpatients After 4 weeks of symptom stabilization with optimal AP dose	Schizophrenia: DSM-III-R OCS: At least 3 of the operationalized symptom criteria described by Fenton and McGlashan present for at least 6 mo.	WCST Mini Mental State Examination	More perseverative errors and fewer categories completed in WCST in OCS-SCZ than in non-OCS-SCZ No difference in Mini Mental State Examination between OCD-SCZ and non-OCD-SCZ groups
Lysaker et al. [3]	Cross-sectional Consecutive sampling	N = 46 Schizophrenia (N = 35) and schizoaffective disorder (N = 11) Outpatients Stable or post acute phase	Schizophrenia: DSM-IV OCS: Minimum YBOCS obsession or YBOCS compulsion scores of 8	WCST Symbol search subtest of WAIS-III Hopkins Verbal Learning Test	OCS-SCZ group completed fewer categories in WCST than non-OCS-SCZ No differences in any other neuropsychological test between OCS-SCZ and non-OCS-SCZ

Table 17.3 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Neuropsychological assessment	Results
Lysaker et al. [14]	Cross-sectional Consecutive sampling	N = 63 Schizophrenia (N = 42) and schizoaffective disorder (N = 21) Outpatients Post acute phase	Schizophrenia: DSM-IV OCS: Minimum YBOCS total score of 17	WCST Visual reproduction test immediate recall Continuous Performance Task	OCS-SCZ group made more non-perseverative errors in WCST than non-OCS-SCZ OCS-SCZ group made fewer correct response and more false alarms in Continuous Performance Task than non- OC-SCZ OCS-SCZ group reproduced details in Visual reproduction test immediate recall more correctly than non-OC-SCZ
Lysaker et al. [32]	Cross-sectional Sample was stratified in 4 groups: OCS-SCZ/good function, OCS-SCZ/poor function, non-OCS-SCZ moderate function and non-OCS-SCZ/poor function	N = 66 Schizophrenia (N = 41) and schizoaffective disorder (N = 25). Outpatients Stable or post acute phase	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: Cluster analysis based on YBOCS total scores	WCST Continuous Performance Task	OC/poor function group completed fewer categories in WCST and made more errors of commission in Continuous Performance Task than other 3 groups

Table 17.3 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Neuropsychological assessment	Results
Lysaker et al. [69]	Longitudinal (6 months) Sampling: NR	N = 41 Schizophrenia (N = 20) and schizoaffective disorder (N = 21) Outpatients Stable or postacute	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: MOCI	Delis Kaplan Executive Function system	Positive correlation between MOCI and Delis Kaplan Executive Function system at baseline and at 6 moths
Ongur and Goff [15]	Cross-sectional Consecutive sampling	N = 118 Schizophrenia and schizoaffective disorder Outpatients Stable phase.	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: YBOCS total score between 1 and 11; and YBOCS total score equal or greater than 12	WCST Stroup color word interference test TMT A and B Continuous Verbal Learning Test WAIS-IIIR	No differences in any neuropsychological test between the three groups
Patel et al. [51]	Cross-sectional Sample was stratified in 2 groups: OCD-SCZ and non-OCD-SCZ matched for age, gender, medication, IQ and duration of illness	N = 28 Chronic schizophrenia treated with clozapine	Schizophrenia: DSM-IV (assessed by means of MINI) OCD: DSM-IV (assessed by means of MINI)	Intra and extradimensional Set-shift test from CANTAB Stocking of Cambridge from CANTAB Cambridge gambling task from CANTAB Affective go/no go task from CANTAB	OCD-SCZ group made more errors at the intradimensional set-shift than non-OCD-SCZ No difference in any other neuropsychological test between OCD-SCZ and non-OCS-SCZ groups

Table 17.3 (continued)

Author	Study characteristics	Sample characteristics	Diagnostic criteria for schizophrenia and OCS/OCD	Neuropsychological assessment	Results
Tumyaka et al. [62]	Cross-sectional Sampling: NR	N = 89 Schizophrenia with OCD (N = 16), schizophrenia without OCD (N = 30), OCD (N = 30), OCD with poor insight (N = 13) Outpatients	Schizophrenia: DSM-IV (assessed by means of SCID) OCD: DSM-IV (assessed by means of SCID) OCD poor insight: OVIS greater than 6	WCST Stroup color word interference test TMT A and B Verbal memory process test Visual reproduction test	No differences between OCD-SCZ and non-OCD-SCZ groups in any neuropsychological test
Whitney et al. [64]	Cross-sectional. Sampling: NR	N = 65 Schizophrenia (N = 40), schizoaffective disorder (N = 14) and OCD (N = 11) Outpatients Stable phase	Schizophrenia: DSM-IV (assessed by means of SCID) OCS: Minimum YBOCS obsession or YBOCS compulsion scores of 8	WCST Bechara Gambling task California verbal learning test Complex figure test Continuous Performance Task Visual spatial skill index from WAIS-III block design subtest and time in TMT A	OCS-SCZ group performed worse than non OCS-SCZ in all neuropsychological tests with the exception of visual spatial skills index No correlation between YBOCS and any neuropsychological tests

CANTAB: Cambridge Automated Neuropsychological Test Battery; IQ: Intelligence Quotient; MINI: Mini International Neuropsychiatric Inventory; Mo: Month; MOCI: Maudsley Obsessive Compulsive Inventory; Non-ODC-SCZ: Schizophrenia Without OCD; Non-OCS-SCZ: Schizophrenia Without OCS; OCD: Obsessive-Compulsive Disorder; OCS: Obsessive-Compulsive Symptoms; OCD-SCZ: Schizophrenia with OCD; OCS-SCZ: Schizophrenia with OCS; SCID: Structured Clinical Interview for DSM-III-R/DSM-IV Axis I Disorders; SCID-P: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition; TMT A and B: Trail Making Test A and B; WAIS: Weschler Adults Intelligence Scale; WCST: Wisconsin Card Sorting Test; YBOCS: Yale Brown obsessive compulsive scale.

baseline by means of Delis Kaplan Executive Function System. Using factor analysis, a single score was produced that estimated overall executive function. Results revealed that poorer executive function predicted higher levels of OCS both concurrently and prospectively. This finding persisted even when controlling for general level of anxiety.

In contrast, other studies have failed to find differences in executive function between schizo-obsessive and schizophrenia patients [15, 44, 62] and one study has even reported better executive function in schizophrenia patients with OCD compared to pure schizophrenia patients [35]. In this last study, schizo-obsessive patients fell between OCD and schizophrenia patients in terms of frontal lobe dysfunction. This finding has been supported by a recent study [122] comparing cognitive event-related potentials (ERP) in patients with schizophrenia, schizo-obsessive patients and OCD patients. When compared with the other groups, schizo-obsessive patients showed a distinct ERP pattern: abnormally increased target activation, akin to that found in OCD patients but unlike the pattern often shown in schizophrenia; and reduced P300 amplitude, akin to schizophrenia but unlike OCD. Nevertheless, schizo-obsessive patients have also shown greater cognitive impairment compared to OCD patients in two other studies [62, 64].

Differences in the definition of OC features may account for these ambiguous results since most studies that showed graver neurocognitive deficits in schizo-obsessive patients applied a dimensional definition while most studies showing no differences in executive deficits used a categorical one (for details see Table 17.3). This finding is consistent with the results of the aboved-mentioned meta-analysis [31] that showed that the effect of OCS in psychotic severity was dependent on the definition of OC features. Greater psychotic severity in schizo-obsessive patients compared with schizophrenia patients was found when a dimensional definition of OC features was applied but not when a categorical definition was used.

It has also been proposed that there may be two groups of schizo-obsessive patients depending on psychosocial function, one with poor psychosocial function in whom OCS are linked with greater cognitive deficits and another with good psychosocial function from whom OCS are linked with better cognitive function [32]. These hypotheses have only been partially confirmed in one study [32] that assessed neuropsychological function in four groups of schizophrenia patients on the basis of their level of OCS and global psychosocial function. Schizo-obsessive patients with poor psychosocial function showed more severe neurocognitive deficits than pure schizophrenia patients, irrespective of their psychosocial function. However, schizo-obsessive patients with good psychosocial function did not demonstrate better cognitive performance than either non-OC groups.

Findings regarding other neuropsychological domains such as memory and attention are also inconsistent. On the one hand, some studies have found greater impairments in verbal and spatial memory [64] and in attention [14, 64] in schizo-obsessive patients compared to pure schizophrenia patients. On the other hand, other studies have shown lesser impairments in visual memory in schizo-obsessive patients compared to those with pure schizophrenia [14] and still others reported no

difference in verbal [3, 15, 62] and visual memory [62] and in attention [3] between these two groups.

In summary, although that any specific pattern of neurocognitive dysfunction has been identified yet, it seems that schizo-obsessive patients have a more severe neurocognitive impairment than those with schizophrenia alone, one which fundamentally affects the executive functions. Interestingly, it seems that the type of definition of OC features may influence the pattern of neuropsychological findings: greater executive impairment has been mostly shown in studies applying a dimensional definition of OC features while most studies using a categorical one failed to find any difference. These results may provide additional support to the dimensional definition of schizo-obsessive disorder.

Treatment

Although it is widely accepted that OC features are often seen in schizophrenia, their treatment has only been minimally studied. Evidence that AP alone or in combination with antiobsessional drugs may be effective for the treatment of OCS in schizophrenia patients has been pointed out [25–27] but controlled studies are still far and between.

Since both selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressants have been demonstrated to work for the treatment of OCD, [123] their efficacy with regard to OC features in schizophrenia has also been studied. Two randomized controlled trials have shown that both clomipramine and fluvoxamine improved OCS in schizophrenia patients [124, 125]. In the first study [124] schizophrenia patients with OCS previously stabilized with psychotropic medication were assigned to either placebo or clomipramine and then switched to the other agent. Reduction of OCS severity was significantly greater with clomipramine than with placebo. Patients treated with clomipramine also showed an improvement in psychotic symptoms. In the second study, [125] schizophrenia patients stabilized with AP medication and showing OCS were randomized to fluvoxamine (100–200 mg/day) or placebo. After 8 weeks of treatment, patients receiving fluvoxamine showed a greater reduction in OCS severity than the control group. Open label studies investigating effectiveness of fluxovamine are also available [126, 127]. In these studies, schizophrenia patients with OCS/OCD received fluvoxamine in doses of 100–200 mg/day [127] and up to 150 mg/day [126] in addition to their ongoing AP treatment for 8 weeks [127] and 12 weeks [126]. A significant reduction of the severity of OCS was reported in both studies, with one reporting a decrease in YBOCS scores of 50% [126] and the other of 33% [127]. Fluvoxamine was well tolerated but acute psychotic exacerbation (1 patient) and increased aggressiveness (2 patients) were reported in one study [126]. In addition, positive case reports with clomipramine and with other SSRI such as fluoxetine, paroxetine and sertraline have also been published, although negative results also exist [26].

Due to their effectiveness in treating resistant OCD, [128] the use of atypical AP for OC features in schizophrenia is beginning to be considered. By contrast, there do not appear to be any investigations into treatment efficacy of typical AP[129] even though these drugs have also proved to be effective in refractory OCD [130]. We are not aware of any controlled trial with atypical AP but open label studies investigating aripiprazol and amisulpiride are available. In a small 6-week, open-label, flexible-dose trial with aripiprazole [25] (up to 30 mg/day), six out of seven schizophrenia patients with OCS showed a decrease in YBOCS scores of more than 35%. In another open label 12 week prospective study [27] performed on schizophrenia patients with OCS, 75% of these patients showed a decrease in YBOCS scores of more than 50% after switching their previous treatment to amisulpiride. A significant reduction on the severity of psychotic symptoms was also observed in both studies.

Further to this, risperidone and olanzapine have also been shown to reduce OCS severity in two studies designed to determine whether these drugs were associated with increased severity of OC features [96, 97]. Case reports of successful treatment of OCS in schizo-obsessive patients with clozapine, [131–134] olanzapine, [135] amisulpiride, [106] paliperidone, [136] and aripiprazole [137, 138] have also been published.

Other therapeutic options have also been assessed. An open-label trial with 9 schizophrenia patients receiving AP medication showed that lamotrigine reduced the severity of OCS [139]. Fifty-five percent of these patients showed a decrease in YBOCS scores equal or greater than 35%. Besides this, the benefit of electroconvulsive therapy [140–142] and deep brain stimulation [143] has also been reported.

Even though cognitive behavioral therapy has an important role in the treatment of OCD [144] we are not aware of any study assessing its efficacy in reducing OC features in schizo-obsessive patients.

In the absence of more evidence-based data, some recommendations for the pharmacotherapy of schizo-obsessive patients have been made [26]. It has been suggested that OCS/OCD in schizophrenia should only be treated when the severity of symptoms outweigh the potential risks of adjunctive pharmacotherapy and after stabilization with AP medication. The first-line treatment should be atypical AP. SSRI should be added if there is no response to atypical AP monotherapy. If there is still no response, an alternative combination of atypical/SSRI or clomipramine combination could be considered. Before introducing clozapine, which should be reserved for treatment-resistant schizo-obsessive patients, a combination of typical AP and SSRI should be initiated. It has been suggested that schizophrenic patients who began to exhibit OCS within the course of the psychotic process may be successfully treated with clozapine alone [133]. However, for those whose OCS preceded the development of the psychotic process, clozapine monotherapy may not be effective and therefore, it should be administered concomitantly with specific anti-obsessive agents [133].

In conclusion, there is a paucity of controlled data assessing management of OC features in schizophrenia. Antiobsessional drugs such as fluvoxamine and

clomipramine have been shown to be effective as an adjunctive treatment for OC features in schizophrenia. Preliminary evidence has also suggested a beneficial effect of atypical AP in improving OC features in schizo-obsessive patients. Until additional controlled trials are carried out, the above-mentioned recommendation may be useful. In addition to this, research into psychotherapeutic treatment is also requested.

Prognosis

Although a better prognosis was suggested by early literature, it appears that schizo-obsessive patients have poorer prognosis than their schizophrenia counterparts. Early studies reported that the presence of OC features was an indicator of good prognosis, since it was thought they may retard the "personality disintegration" associated with schizophrenia, prevent the development of malignant schizophrenia and even indicate the remission of psychotic illness [9, 10]. Most subsequent research has failed to confirm these early findings. Schizo-obsessive patients have been shown to have poorer social and vocational functioning [18, 65, 75] and poorer general quality of life [36, 145] than those with schizophrenia. The presence of OCS has also been associated with greater levels of hopelessness and with avoidant focused coping strategies [33]. Additionally, suicidal ideations and attempts are more frequent in schizo-obsessive patients than in patients with schizophrenia alone [146].

Conclusions and Future Directions

OC features have been shown to occur in schizophrenia at a rate far beyond that expected in the general population. OCS/OCD in schizophrenia patients have been observed across life span, in different ethnic groups and in all psychotic stages. Thus, epidemiological data suggests that the association between OC features and schizophrenia is not artifactual or spurious [20, 21, 26]. Putative etiological factors responsible for the presence of OC features in schizophrenia are still to be clarified. Although atypical AP have been involved in the development of OCS in schizophrenia patients, these drugs do not seem responsible for the high prevalence of OC features in schizophrenia. These features have been shown in AP naïve schizophrenia patients and controlled studies with atypical AP have failed to find a relationship between these drugs and appearance or exacerbation OCS. Preliminary findings from family and association studies have suggested the contribution of genetic factors in the expression of OCS in schizophrenia, further supporting the validity of schizo-obsessive disorder.

Despite the heterogeneity in the definition of schizo-obsessive disorder, preliminary evidence favors the use of a dimensional definition. Such a definition appears to capture the complexity of both disorders and it may also facilitate

prognosis. Firstly, it seems to have a prognostic value concerning the severity of psychotic symptoms. Secondly, it may also have a prognostic value in terms of cognitive impairment. Studies that used a dimensional definition of OC features found that schizo-obsessive patients showed greater cognitive impairment than pure schizophrenia patients, while those using a categorical definition could not distinguish between the two groups.

The clinical profile of schizo-obsessive patients appears to be different from that of schizophrenia patients. OCS in schizophrenia have been linked to greater severity of psychotic symptoms and with more severe impairment in executive functioning. Moreover, greater suicide risk and poorer social and vocational function have also been shown. These findings suggest that schizo-obsessive patients have a poorer prognosis.

Research into neurobiological substrates of schizo-obsessive patients is scarce and its underlying mechanism remains unknown. Although structural and functional brain abnormalities have been found in these patients it is still unclear whether these findings reflect a specific pattern of dysfunction unique in these patients, or a more severe form of illness with greater brain dysfunction caused by common neurodevelopmental predisposing factors.

The validity of schizo-obsessive disorder seems to be confirmed by: (1) higher than expected prevalence; (2) different clinical and functional outcomes compared to pure schizophrenia and; (3) familial transmission of OC-related disorders. Additional support can be drawn from preferential aggregation of OCD-spectrum disorders, primarily body dysmorphic disorder, chronic tic disorder and trichotillomania, in schizo-obsessive patients compared to schizophrenia patients [7]. Whether schizo-obsessive disorder represents a dimension or subtype of schizophrenia, or a new diagnosis remains still unresolved.

It is also unclear whether distinct groups of schizo-obsessive patients exist. It has been suggested that patients who experience OCS prior to the onset of schizophrenia may be a very different group to those who develop OCS after the onset of illness [29]. Similarly, it has been suggested that there may also be a group of patients with schizophrenia for whom OCS are closely linked to negative symptoms and neurocognitive deficits and another one who experience OCS but have significantly higher levels of psychosocial function and lesser levels of cognitive deficits [32]. Still, depending on the relation between OCS and psychotic symptoms three additional groups have been identified: those with OCS not related to the content of psychotic symptoms; those with OCS both related and unrelated to the content of psychotic symptoms; and finally those whose OCS lie on a continuum with psychotic symptoms [19, 52]. It has been suggested that these groups may have distinct pathophysiology and may even need different therapeutic approach [29, 129]. Comprehensive phenotyping of homogeneous subgroups and its further characterization in terms of course of illness, prognosis and response to pharmacological interventions may help to shed light on the interrelation between schizophrenia and OC features [26]. It could also aid the identification of common and unique genetic and environmental factors that might contribute to the delineation of schizo-obsessive disorder [147].

Although the presence of OCS is an aspect that can determine the selection of the treatment of patients with schizophrenia, research into therapeutics is limited. Atypical AP alone or in combination with SSRI or tricyclic antidepressants appears to be effective in reducing OC features in these patients.

Future research could benefit from longitudinal studies that include schizo-obsessive patients with differing severity of OCS and multiple-time clinical, neuropsychological and functional assessments [129]. Further to this, identification of specific biological markers and genetic underpinnings would contribute to further validation of this complex schizo-obsessive entity. In this line, it has been suggested that research into endophenotypic markers could improve understanding of this association [147]. Moreover, structural and functional brain imaging techniques may also be of particular importance in delineating schizo-obsessive disorder. Finally, controlled trials of psychopharmacological and psychotherapeutic interventions are also needed in order to achieve better evidence-based treatment recommendations and to improve the prognosis of these patients.

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Chapter 18
Neurophysiology of Cognitive Dysfunction in Schizophrenia

Corinna Haenschel and David Linden

Abstract Cognitive neurophysiology, the investigation of perceptual and cognitive tasks with EEG or MEG, is a key technique for the investigation of information processing in schizophrenia. In the present chapter we first provide an introduction to the techniques and signals of non-invasive electrophysiology (Part 1) and then explain its application to perceptual (2) and cognitive processes (3). We discuss some of the most widely investigated and replicated electrophysiological features of schizophrenia, including the P50, P1, MMN and P3. Recent applications of time frequency analysis techniques have allowed for a more detailed investigation of the neural mechanisms of cognition and its dysfunction through measures of oscillatory activity (4). We finally introduce some of the current approaches that combine non-invasive neurophysiology, pharmacology and genetics. We will discuss their findings in the context of cellular and molecular models of schizophrenia, particularly in relation to several neurotransmitter systems (5). We argue that cognitive neurophysiology can provide interesting intermediate phenotypes of schizophrenia.

Keywords Schizophrenia · Cognition · ERPs · Synchronised oscillatory activity

Abbreviations

AEP	Auditory evoked potential
ERP	Event-related potentials
EP	Evoked potentials
EEG/MEG	Electro-/Magnetoencephalography
fMRI	functional magnetic resonance imaging
GABA	Gamma-amino butyric acid
MMN	Mismatch negativity
NMDA	N-methyl-D-aspartate

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NRG1	Neuregulin 1
PV	Parvalbumin
(SS)VEP	Visual (steady-state) evoked potential

Introduction

Schizophrenia is probably the mental disorder that is most difficult to capture in animal models. Most of its core symptoms are related to language, thought and complex social interaction and thus only accessible in humans. Direct correlates of these symptoms can therefore only be investigated in humans with non-invasive techniques. Similarly, correlates of the disorders' complex cognitive deficits are only accessible to investigation in humans. Cognitive neurophysiology, which assesses the brain correlates of information processing with electro- or magnetoencephalography (EEG or MEG), has therefore gained an established place in schizophrenia research. Although their spatial resolution and reliability of localisation is inferior to advanced functional imaging techniques, they have the advantage of superior temporal resolution. Of particular relevance to the comparison with animal and cellular studies, their temporal profile is similar to that of invasive or in-vitro recordings. Results of neurophysiological studies are thus generally easier to interpret in relation to cellular and molecular models of altered neural processing in schizophrenia than those of functional imaging studies.

Another more practical benefit of EEG is its wide availability and relatively low cost. Simple EP and ERP studies can even be conducted with the same equipment as used for standard clinical neurophysiology. This makes it a particularly attractive tool for the investigations of large samples of patients and controls that will be required for the investigation of neural endophenotypes and association with quantitative trait loci. Knowledge of the principles of non-invasive neurophysiology and its application to schizophrenia, including recently developed links with pharmacology and genetics, is therefore essential for researchers and clinicians in the field of schizophrenia.

Basic Neurophysiology

EEG/MEG studies can be conducted with or without external stimulation. In the latter case, difference in intrinsic activity, for example power in particular frequency bands or topographic patterns, can be compared between groups. It is the easiest type of studies to set up, and even segments of EEG recorded for clinical purposes can be used for such an analysis, provided the recording conditions (e.g. eyes close vs. open) were homogenous. Pharmacological manipulation can be used as well. However, such resting state studies cannot directly investigate correlates of information processing. These require application of external stimuli or cognitive tasks, which then allow for the computation of neural responses that are linked to the stimulus, task phases, or a response. The most widely used example are evoked

potentials/event-related potentials (EP/ERP), which are time-locked averages over multiple trials. The principle behind EP/ERP studies is that averaging will reduce the contribution of noise, which will vary randomly across trials, and preserve the signal that reflects neural processing. A third, less commonly used technique aims at the correlation of neural activity and psychopathological symptoms. Here symptoms are induced by the experimenter, or reported by the patients when they occur spontaneously, and neural correlates compared to a baseline, for example power changes in particular frequency bands.

Sensory stimuli evoke synchronous activity in the central nervous system that can be measured on the scalp by EEG electrodes. These so-called evoked potentials (EPs) have mainly been described for the visual, auditory and tactile domain, but can in principle be measured for all sensory channels. EPs are normally described as positive or negative going (denoted with the letters P or N), according to the direction of the deflection in standard referencing procedures. This convention is unrelated to the contribution from excitatory vs. inhibitory neural activity, though. The letter is followed by a number that denotes the latency in milliseconds or the position in a sequence of positive or negative deflections. For example, the P100 (or P1), generated in primary and higher visual areas, is a positive deflection with latency from stimulus onset of about 100 ms. Exceptions of this terminology are the very first brainstem-generated components of the auditory evoked potential (AEP), which are labeled with Roman numerals (I-VI), and the mid-latency AEPs between 10 and 50 ms (Fig. 18.1).

These probably reflect activity in the auditory pathway from inferior colliculus via the medial geniculate body to the auditory cortex. The late AEPs from P1 to N2 reflect cortical activity, although it has been difficult to localize their source to specific parts of temporal cortex, and contributions from multiple sources are likely. The detection of EPs on the scalp requires the recordings of hundreds or thousands (for brainstem potentials) of trials of basic sensory stimulation.

The earliest visual evoked potential (VEP), the C1 at ca. 50 ms post-stimulus, reflects activity in primary visual cortex. Its polarity changes with the quadrant of the visual field that is stimulated. The component that is most widely used for clinical purposes is the P100 or P1, which arises between 100 and 130 ms after a stimulus, with the exact latency depending on stimulus contrast. In clinical settings, whole field checkerboard stimulation is normally used, and delayed latencies may indicate a central demyelinating process such as multiple sclerosis. Later parts of the VEP include the N1 (sometimes equated with the face-responsive N170 and other) and the P2. The P300 or P3 is a classic “event-related potential” (ERP). ERPs differ from EPs in that they are less dependent on stimulus properties than on the cognitive context or expectancy of the subject. However, the classical divide between the exogenous and endogenous components is less clear, because of all the evidence that has shown an influence of cognitive factors (like attention), on the early components (e.g. P1). For example, the P3 is recorded after rare “oddball” events in repetitive stimulus trains and even when an expected stimulus does not occur, and thus in the absence of sensory stimulation. Another interesting feature of the P3 is that it can be evoked by visual, auditory, tactile and even olfactory or gustatory paradigms.

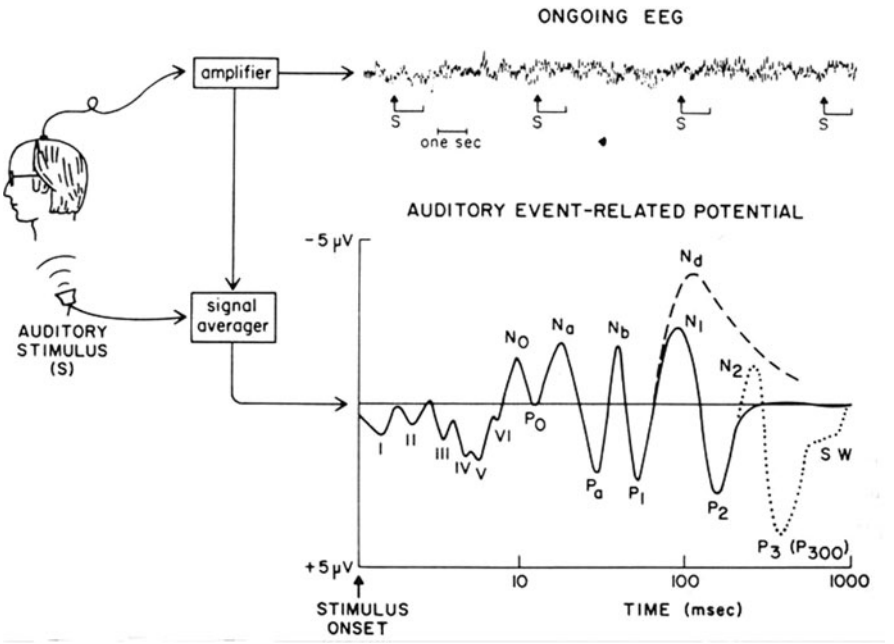

Fig. 18.1 Basics of ERPs. The *upper row* show the recording of continuous EEG activity during the presentation of auditory stimuli (denote with "S"). This original signal is segmented into epochs containing a defined time period following the stimulus and a pre-stimulus baseline. The averaged signal change compared to baseline is shown in the *bottom row* and yields the standard components of the EP/ERP. Note that the time scale is logarithmic. The component denoted as auditory P1 is also called P50 in parts of the clinical literature and in this chapter. From ref [190]. Reproduced with permission from the Annual Review of Psychology, Volume 34 (c) 1983 by Annual Reviews

Similar paradigms, albeit typically passively presented, in the auditory domain evoke the mismatch negativity (MMN), a modulation of the auditory N2. Interestingly, MMN and possibly even P3 can be evoked during sleep. The P3 and MMN are probably the most frequently investigated ERPs in psychiatric research, and they are also used to probe the depth of coma and the prognosis after brain damage. Pharmacological influences on these potentials are of considerable interest for the study of psychiatric and neurological disorders and their treatment responses. The sequence of EPs/ ERPs may reflect serial stages of sensory and cognitive processing and can thus help unravel mental chronometry, the timing of information processing in the brain [1]. Their modulation by cognitive manipulations can help identify the stages at which cognitive and perceptual processes interact. For example, the investigation of attentional modulation of the P1 has made a considerable contribution to the debate on early vs. late selection in visual attention. Finally, information derived from ERPs, if backprojected in to the cortex by means of source localization algorithms, can add to the temporal resolution of functional imaging techniques [2] as well as improve the spatial resolution of

ERPs. For example, different sources may contribute to subcomponents of the P3 and overlap in their scalp topographies. One limitation of this approach is that the solutions of source models of scalp EEG activity are never unique, and additional assumptions have to be made. Unless it is anatomically relatively obvious where a generator should be placed (which is really only the case for the early AEPs), constraints from other domains, for example functional magnetic resonance imaging (fMRI), need to be implemented. This procedure, backed up by lesion studies, has led to the successful localization the generators of the visual P3 to higher visual, frontal and parietal areas [3]. The P3 complex can be subdivided further into an early and more frontal P3a and a later and more posterior P3b. The P3a is evoked by tasks that demand more active allocation of attention, such as the orienting response, whereas the P3b is more associated with the bottom-up driven monitoring system. P3b generators were particularly prominent in parietal and inferior temporal cortex, whereas P3a had strong contributions from the insula and premotor cortex [4].

EEG can be recorded simultaneously with fMRI, although different filtering techniques need to be applied for artefact correction. Furthermore, ERP equivalents (termed event-related fields, ERF) can also be recorded with Magnetoencephalography (MEG), potentially allowing for higher spatial resolution, although here simultaneous combination with imaging is not possible. Because of the considerable cost and low availability of this technique, it is unlikely to replace EEG in the near future. Furthermore, MEG only captures sources that are tangential to the scalp and thus does not necessarily reflect the same neural signals as EEG.

The analysis of ERP only captures the small part of the information contained in EEG data that is highly time-locked to the stimulus across trials and exhausts itself in a single cortical potential change. These components are very good signatures of the initial phases of sensory processing and of some clearly defined cognitive processes, but cannot capture the complexity of the neural code. Currently, there are two potential mechanisms that can explain the generation of the ERPs. Classically, the ERP have been suggested to reflect a transient response to the stimulus that is superimposed on the background EEG. In addition, it is assumed that the sensory stimulus induces phase resetting of ongoing rhythmic activity in each trial and that averaging these phase-coherent rhythms produces the ERP [5, 6]. The current literature suggests that these two mechanisms coexist [7].

In addition to the analysis of the averaged ERPs, time frequency analysis (TFA), dividing the EEG activity into several frequency bands and assessing the changes of relative power over time, permits the investigation of the patterns of oscillatory activity that provide potentially rich and versatile means of information storage and processing.

One proposed mechanism is that functional networks are created transiently by the synchronisation of periodic firing of groups of neurons (termed oscillatory activity) within and between cortical areas [8–10]. Such a dynamic integration into neuronal assemblies may range from local networks for early sensory processing to large-scale networks responsible for cognitive processes such as memory

formation [11, 12]. This proposal enables neurons to flexibly contribute to many different networks implementing a variety of cognitive tasks. This can be measured by analysing synchronous oscillatory activity in a broad range of frequencies (theta: 3–8 Hz; alpha: 8–12 Hz, beta: 12–30 Hz, gamma: >30 Hz) on a trial by trial basis. The last decade has demonstrated that synchronous oscillatory activity is related to a multitude of perceptual and cognitive tasks There is evidence that suggest that synchronous oscillatory activity is related to feature binding in perception [13], working memory [14], object representation [15] and attention [16].

Theorists distinguish between three main forms of synchronized oscillatory activity: evoked activity, induced activity and long-range synchrony. Evoked oscillatory activity is tightly time and phase-locked to the onset of the stimulus and has been especially related to early, stimulus-driven encoding processes, which is commonly measured by averaging the response across all trials and then examining power in a specific frequency band (Fig. 18.2.). It can also be measured by examining the variability in the phase of a stimulus elicited response at a specific

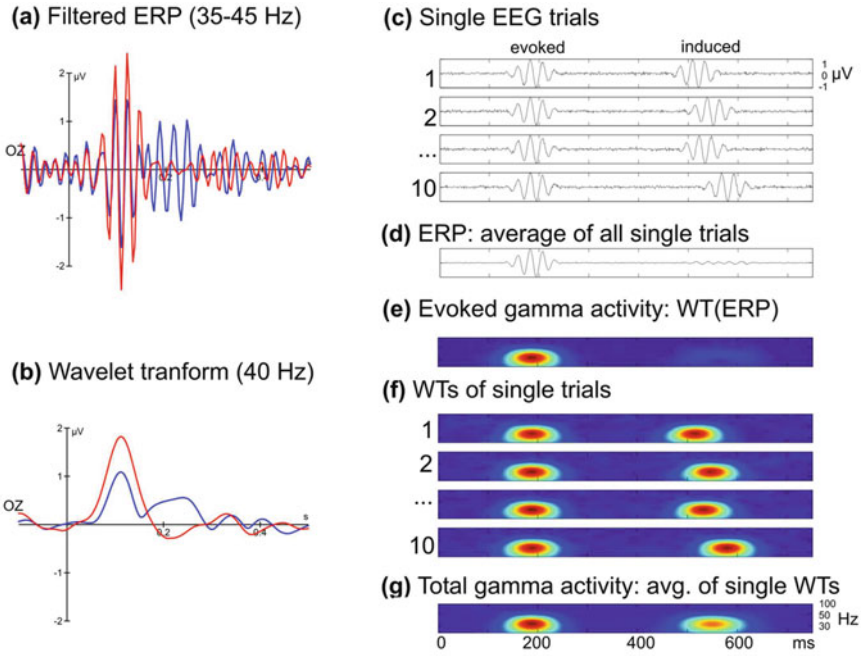

Fig. 18.2 From ERPs to induced activity. (**a**) Oscillatory patterns in ERPs can be detected by band-pass filtering. A narrow filter of 35–45 Hz as applied here reveals differences in gamma oscillations over time in two experimental conditions (*blue* and *red curves*). (**b**) The quantitative assessment of such differences is aided by the wavelet transform. (**c**–**g**) If oscillations are time- and phase-locked to a stimulus or event, averaging across trials yields the ERP in the time domain (**d**) and the power or evoked oscillatory activity in the time-frequency domain (**e**). The detection of non-locked ("induced") activity requires averaging after the single-trial wavelet transforms have been applied (**f**, **g**). From [191] with kind permission of Elsevier

electrode across individual trials (termed inter-trial phase locking or inter-trial coherence (ITC).

Although induced activity is also elicited in direct response to the appearance of the stimulus its timing reflects internal network processes[1] and is therefore less tightly linked to stimulus onset, which is commonly measured by examining the power in each frequency band for individual trials and then averaging this power across trials (Fig. 18.2).

Finally, long-range synchrony measures phase coupling between electrodes, which reflects the degree to which activity at those sites form part of a common functional network of activity. All these forms of synchronised oscillatory activity integrate neural activities that can instantiate stable, salient and coherent representations of mental objects. They furthermore provide a mechanism that can sustain their activity for working memory processes even when information is no longer available in the environment [17].

In summary, ERPs provide a measure of the peak neural response in a particular processing unit in response to a particular stimulus or task [1], whereas synchronized oscillatory activity provides a mechanism for dynamic formation of networks during cognitive tasks. Learning more about the relationship and precise signature of ERPs, evoked and induced oscillatory power and the inter-trial- and inter electrode phase synchrony may help to unravel the dysfunctional mechanisms underlying the cognitive deficits associated with schizophrenia and may help to find biological markers for these deficits. The study of cognitive biological markers of mental disorders is mainly interested in the stability and replicability of the measure. The ideal biological marker will be one that can be evoked by any number of stimulus conditions in any sensory modality. However, such a marker will only contribute in a very global fashion to our understanding of the mechanisms underlying cognitive deficits. For this purpose, techniques that are sensitive to subtle variations in the paradigm and capture the neural processes involved at high temporal and informational resolution, are required. Ideally, such a technique should also allow for comparison with animal and cellular models of signal processing. The time frequency analysis of EEG or MEG data fulfils all these requirements and can thus help to translate what is known from basic neuroscience about the modulation of the oscillations to human EEG studies and to elucidate the mechanisms underlying altered cognitive functions. It is therefore not surprising that over the last 10 years evidence for aberrant cortical oscillatory activity in schizophrenia has accumulated. This evidence comes from experiments probing early-sensory systems, like steady-state, sensory gating and backward masking experiments and from more cognitive event-related paradigms, like the auditory oddball, visual binding and working memory experiments.

[1] Following the recent report of Yuval-Greenberg et al. [17] the possibility of a relationship between induced gamma band activity and microsaccades should also be considered (but see also [18]).

Neurophysiology of Perceptual Processes in Schizophrenia

It has long been assumed that only late components of the ERP like the P3 would be abnormal in schizophrenia while early VEPs would be unimpaired. This view has recently been challenged [18]. A growing body of evidence from patients with schizophrenia indicates abnormalities of both early visual P1 and the early auditory P50 wave. However, these abnormalities appear to be task-dependent. Although standard checkerboard stimulation does not normally result in reduced VEPs in schizophrenia, stimulation biased for the magnocellular pathway revealed impaired P1 generation, which correlated with reduced fiber integrity of visual pathways [19]. Our study with a visual working memory paradigm yielded a severely impaired P1 [20]. This highlighted possible links with abnormalities in thalamocortical circuits discussed in the anatomical literature and opened up a new avenue of investigation, focusing on the contribution of perceptual systems to cognitive deficits. The deficits in magnocellular processing that have been linked to reduced P1 could also lead to reduced precision with which temporal transients are signaled and thus to reductions in response timing (synchrony).

The analysis of synchronised oscillatory activity provides an additional tool to elucidate the mechanisms underlying impaired ERPs. For instance, it can be hypothesized that the impaired P1 can be explained by reduced phase reset of the on-going EEG activity, which however is not the case [21]. Nevertheless, this is a good example of how the use of oscillatory activity will provide further insights into the pathological mechanisms underlying impaired cognition in schizophrenia

Interestingly, the rapid and transient signal transmission in the magnocellular pathway makes it ideal for quick links between early visual and higher cognitive areas. In fact, recent models of visual perception posit that the efficiency and speed of everyday vision largely rely on early bottom-up/top-down interactions between occipital and prefrontal areas of the cortex which are driven by magnocellular projections from early visual areas [22, 23]. As a consequence magnocellular pathway deficits might contribute to encoding problems by causing basic difficulties in perceptual discriminability or top-down enhancement of earlier representations. Nevertheless, the contribution of basic sensory deficits to higher cognitive functions remains relatively unexplored [24]. In the following section we will discuss the evidence from ERP research and synchronous oscillatory activity demonstrating deficits both at a basic sensory as well as higher cognitive level, which have been associated with a variety of perceptual and cognitive impairments.

Neural Correlates of Visual Processing

Evidence for deficits in early visual processing in schizophrenia comes from studies investigating the steady-state visual evoked potential (SSVEP) and the early ERPs (P1, N1). The entrainment of the EEG to externally driven rhythmic stimulation elicits the steady-state response that resonates at the stimulating frequency. Steady state VEP paradigms have been used to probe the ability of cortical networks to generate and maintain oscillatory activity in patients with schizophrenia [25]. A stimulus is

flickered at a specific temporal frequency and elicits modulation in neural activity in early visual areas that is synchronized to the flicker in frequency and phase. Krishnan et al. [26] showed that compared to controls patients with schizophrenia exhibited significantly reduced SSVEPs at high flicker frequencies (17 Hz, 23 Hz, and 30 Hz) but not at low frequencies.

Steady state VEPs have also been used to investigate the hypothesis that patients' with schizophrenia show impairments in response to stimuli biased towards the magnocellular (low-spatial-frequency, moving, and rapidly flickering), but not to stimuli biased towards parvocellular (high-spatial frequency, chromatic contrast and static stimuli) visual responses [18, 27] (but see Skottun BC, Skoyles J. for an alternative view). The results with the classical ERPs, especially the P1, provide further evidence for altered visual processing in schizophrenia. For example, the P1 was reduced in response to low-luminance-contrast, but not to chromatic-contrast e.g [25]. , supporting a deficit in the magnocellular pathway. There is also evidence for impairments in the P1 ERP in response to fragmented stimuli designed to address perceptual closure [28] and in response to illusory Kanizsa-figures [29]. Finally, a recent study used a texture segregation task in order to study feedback processes necessary for stimulus integration. Results showed a trend for a smaller P1, but a larger N160 compared to controls indicating that patients engage more in processing of stimulus detail [30]. There is also evidence for a reduced P1 in first-episode patients [31], in patients with early onset schizophrenia [20] (Fig. 18.3), in unaffected first degree relatives [32] and in individuals with high

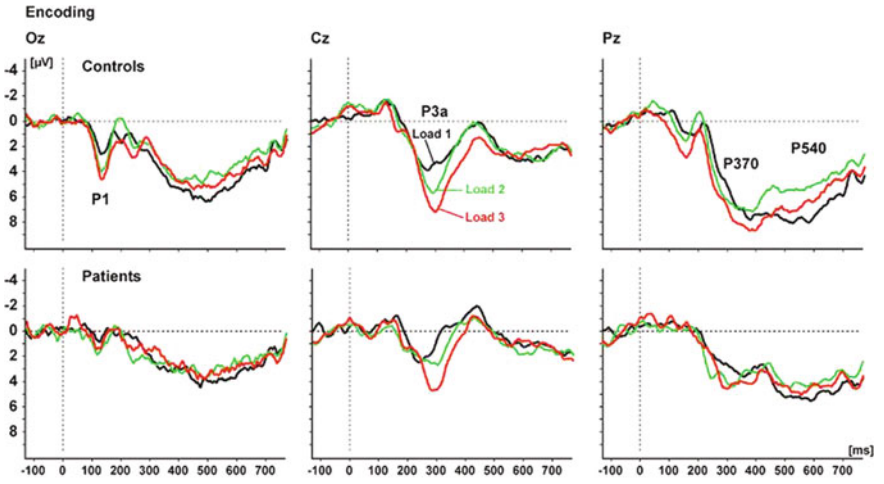

Fig. 18.3 ERPs during WM encoding in patients with early-onset schizophrenia (*bottom*) and healthy age-matched controls (*top*). The ERP responses after the first sample stimulus for WM load 1 (*black line*), the second stimulus for WM load 2 (*green line*), and the third stimulus for WM load 3 (*red line*) are shown at the central occipital electrode (Oz), the vertex electrode (Cz) and the central parietal electrode (Pz). The P1 can be seen at Oz, P3a at Cz, and P370 and P570 (subcomponents of the P3b) at Pz. From [20] with kind permission. Copyright © 2007, American Medical Association. All right reserved

schizotypy [33]. These results point to a role of such neurophysiological changes as trait markers of schizophrenia, or indeed of a psychosis spectrum [34], considering that similar effects have also been reported in bipolar disorder [35].

Alterations of evoked synchronized activity in schizophrenia were also observed in response to stable non-flickering visual stimuli [29, 36, 37]. Spencer et al. [29] examined responses to illusory Kanizsa triangles, which they showed in normal participants evoked gamma frequency oscillations and a high-degree of inter-trial phase locking at electrodes associated with visual processing but these responses were considerably attenuated in patients. Furthermore, Uhlhaas et al. [37] provided evidence for a close relationship between impaired neural synchrony in schizophrenia and specific cognitive deficits using Mooney face stimuli. Mooney faces consist of degraded pictures of human faces where all shades of gray are removed, leaving only black and white contours. Perception of Mooney faces requires the grouping of the fragmentary parts into coherent images. Schizophrenia patients exhibited a deficit in the perception of Mooney faces and reduced phase-synchrony in the beta-band (20–30 Hz) while the power of induced gamma-band oscillations was in the normal range.

Finally, patients show reduced evoked [38] and induced [39] gamma band oscillations in response to backward visual masking. Visual masking is a procedure that is used to assess the earliest components of visual processing. In backward masking, the identification of an initial stimulus (the target) is disrupted by a later stimulus (the mask). In comparison to controls patients showed a specific deficit in evoked gamma-band activity for masked targets in the right hemisphere but not unmasked targets.

In summary, there is strong evidence for impairments in early visual processing in schizophrenia. Specifically, the data point to an impairment in the magnocellular (m-) pathway that utilizes precise temporal information. However, the precise direction of the relationship is not yet clear. The impairments in the precise timing demonstrated in evoked activity (ERPs, oscillations and phase locking) could be explained by an abnormality in the m-pathway. Alternatively, the m-pathway could be normal, but higher cortical mechanisms permitting processing of precisely timed signals could be deficient. Finally, these deficits could also be explained by cortical deficiencies in handling precise temporal codes, which may result in deficits in the integration of the information. In the next section we will review the evidence for early auditory deficits, which calls the specificity for the magnocellular visual pathway into question and argues for a more global deficit. For instance deficits in thalamocortical projections may underlie impairments in both stimulus-driven ERPs and oscillations.

Neural Processing of Auditory Information

Evidence for early auditory deficits have been demonstrated in studies investigating the steady-state auditory evoked potential (ssAEP), sensory gating and the N1 using both ERPs and measures of synchronised oscillatory activity.

The Steady-State Response

The auditory steady-state response is measured at the level of the middle latency auditory evoked potentials [40]. With higher rates of stimulus presentation the overlapping midlatency response sums up to the auditory steady state response (SSR). The entrainment of the EEG to externally driven rhythmic stimulation elicits the SSR that resonates at the stimulating frequency. The auditory SSR is typically of largest amplitude when the stimulation is presented at 40 Hz. Lower or higher rates of stimulation produce a response of smaller amplitude [41–45], suggesting that 40-Hz is a "preferred" working frequency of the auditory network, reflecting the increased phase locking of individual trials [46] and the synchronized activation of thalamocortical loops.

Patients with schizophrenia failed to show evoked EEG oscillations to steady-state auditory trains in the beta- and gamma-frequency range, but they were present at the lower frequencies [47]. Patients also exhibited delays in both the onset of phase synchronization and desynchronization in response to the auditory click trains. Light et al. [48] extended these results by showing that the inter-trial coherence was reduced in response to 30 and 40 Hz oscillations. In addition, they showed a modest correlation between reduced working memory performance (measured with the Letter-Number Sequencing test) and the patients' 40-Hz intertrial phase synchronization. This suggests that deficits in early sensory processing are owed to failed entrainment of synchronized responses by higher frequency stimuli. The reduction in intertrial synchrony was attributed to increased EEG response variability [49–51]. Furthermore, disruption of auditory SSR is consistent with anatomical abnormalities in the auditory cortex [45].

Sensory Gating

Sensory gating refers to the ability to attenuate irrelevant sensory input in order to avoid flooding with irrelevant information [52] or to modulate its sensitivity to incoming sensory stimuli [53]. Failures in sensory gating are a classical feature of schizophrenia and the resulting sensory overload may actually give rise to the disorder [54]. Sensory gating is typically measured using the paired-click paradigm, where an auditory stimulus, typically a click, is repeated within 500 ms. In healthy participants the P50 to the second click is suppressed compared to the P50 to first click. This is referred to as P50 gating. Patients with schizophrenia typically show either no or only a small amount of gating (i.e. no major reduction of the P50 to the second tone compared to that evoked by the first), which may reflect deficits in inhibitory processes.[2] This neurophysiological evidence was later followed by studies linking sensory gating deficits to cholinergic function and the gene for the

[2]Interestingly, Dakin et al. [55] showed that individuals with schizophrenia are less prone to the visual "contrast–contrast" illusion, which suggests that they have weaker visual contextual suppression resulting from impaired lateral inhibition. Thus, deficits in inhibitory processes might be a general deficit across sensory domains.

alpha-7 nicotinic receptor subunit [55–57]. In addition to investigating changes in the averaged ERPs in response to auditory gating, examination of the underlying evoked responses in the frequency domain across single trials may further help to elucidate the mechanisms underlying the sensory gating. First evidence for a relationship between abnormalities in high-frequency oscillation and altered P50 was provided by Clementz et al. [58]. They found a relationship between auditory early phase-locked gamma band activity and P50 suppression and showed that the evoked gamma band response may account for poor P50 suppression. This was later extended by Hong et al. [59] showing that reduced evoked beta-band activity to the first click was inversely correlated to the second click P50 response. This was based on the finding that showed evoked beta and gamma in response to novel tones, but habituation of the beta activity in response to repeated tones [60]. Finally, Johannesen et al. [61] subdivided the patients according to the sensory gating inventory into a group with either large or normal perceptual disturbances. Results indicated that patients with large perceptual disturbances showed smaller P50 amplitudes and weaker gamma band attenuation. These results suggest that reductions in gamma and beta activity contribute to P50 impairments. In addition there is evidence that reductions in the theta- and alpha band contribute to the later N1 and P2 ERP sensory gating impairments found in response to the first stimulus [62, 63]. Furthermore, whereas N1 and P2 amplitudes correlated with phase synchronisation in controls, this relationship was not present in patients with schizophrenia (see [64], for corroborating evidence).

N1

In addition to deficits in P50, there are also deficits in auditory N100/N1 generation [65], but these have been studied less. Deficits in N1 are larger with interstimulus intervals longer than 1 s [66]. Furthermore, patients with schizophrenia typically do not show an increase of N1 with attention [66].

The N1 generators have been localized primarily to infragranular layers of auditory cortex using intracranial studies [27, 67, 68] and can be inhibited by direct application of NMDA antagonists. Impairments in N1 have consequently been related to NMDA receptor dysfunction in schizophrenia [67].

There is some evidence demonstrating that N1 amplitude is reduced when healthy volunteers are talking, rather than listening. This has been taken as evidence for a modulation of the N1 by top-down “corollary discharge” from speech areas. This modulation has been shown to be impaired in patients with schizophrenia [69]. This lack of N1 suppression may be linked to structural damage to the white-matter (WM) arcuate fasciculus measured with fractional anisotropy (FA) using diffusion tensor imaging (DTI) [70]. Furthermore, during acute auditory hallucinations the N1 amplitude is reduced in response to auditory stimuli compared to periods without hallucinations [71, 72]. These data provide complementary evidence to functional imaging findings of increased auditory cortex activity during hallucinations [73]. This activation may cause a lower capacity to respond to external stimulation,

leading to the ERP findings as well as to impaired communication abilities during hallucinations.

Ford and Mathalon [74] further investigated the hypothesis that impaired generation of efference copies (corollary discharges) might be also related to impaired neural synchrony in these patients. Results demonstrated that gamma band coherence between frontal and temporal lobes was greater during talking than listening and was disrupted by distorted feedback during talking in healthy controls. In contrast, patients did not show this pattern for EEG gamma coherence, which supports the notion of reduced connectivity in patients. However, in this study the relationship between neurobiological indicators of dysfunctional corollary discharge and the extent of current auditory hallucinations was not clear [74].

In summary, impairments in both basic visual and auditory processing indicate a breakdown of at least some of the processing at early stages of stimulus evaluation [75]. These abnormalities, in turn, may contribute to some of the cognitive deficits in schizophrenia. Since higher order cognitive processes are largely dependent on the fidelity of information input from early sensory-perceptual stages of processing, it is likely that some cognitive dysfunctions will trace their origins to sensory-perceptual deficits [76]. Furthermore, some researchers have argued that early perceptual deficits should be seen as part of the reciprocal interactions between hierarchical levels of sensory systems [77]. Such a deficit would express itself as a dysfunctional information integration system that affects higher order processes.

In the next section we will therefore review evidence for neural mechanisms of cognitive dysfunctions in schizophrenia.

Neurophysiological Cognitive Markers of Schizophrenia

Neurophysiological markers have also been widely used to study altered cognitive processes in schizophrenia, for example sensory memory formation, attention and working memory. The mismatch negativity (MMN) and P3 are two prominent examples, which have also been extensively studied with pharmacological manipulations intended to model aspects of the neurochemistry of schizophrenia.

MMN

The MMN is an electrophysiological tool that reflects the sensory trace formation and passive detection of change. This ERP falls on the interface between sensory perceptual and cognitive processing. MMN impairment has been consistently observed in schizophrenia (see meta-analysis and review in [78, 79]. MMN impairment in patients increase with illness duration [78], correlates with the global-assessment of function (GAF) and predict level of independence living [80, 81].

MMN is elicited during passive listening to deviant sounds interrupting a sequence of repeated standard stimuli [82]. This suggests that a pre-attentive echoic

memory trace of the preceding stimuli is used as a template against which incoming sounds are compared. MMN increases progressively with the number of standard stimulus repetitions [68, 83–85], suggesting that MMN reflects the strength of the underlying echoic memory trace, termed the "MMN memory trace effect". However, MMN is elicited after a trace for preceding standards has been formed, hence it only indirectly probes trace strength. A candidate ERP component for trace formation was observed when the standard sounds were changed in frequency between consecutive stimulus trains (roving standard protocol introduced by Cowan et al. [86] and Winkler et al. [87]). A fronto-central ERP positivity from 50 to 220 ms post-stimulus increased in amplitude with repetition of each new standard sound [88, 89] (Fig. 18.4). This repetition positivity (RP) was observed during both passive and active frequency discrimination tasks and accounted for the largest part of the MMN memory trace effect in those studies, suggesting that it is a marker of the formation and strengthening of echoic memory traces. A candidate neuronal

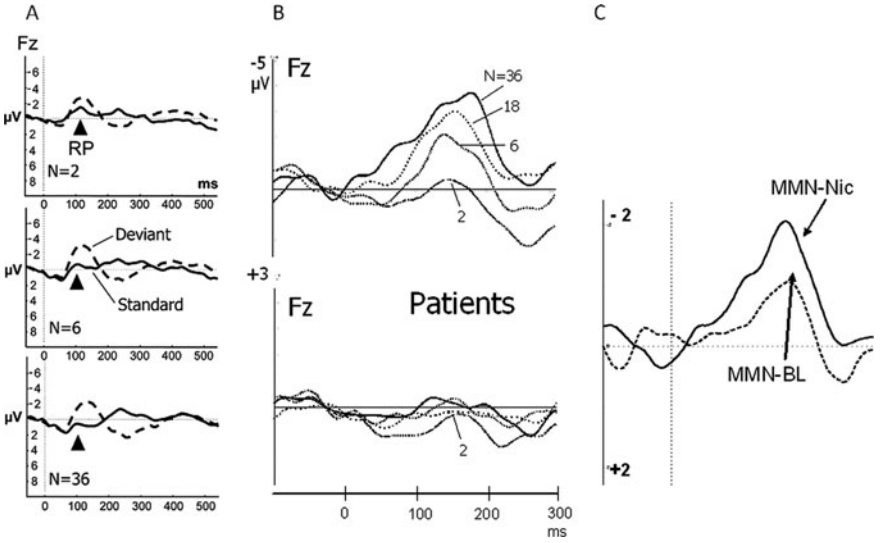

Fig. 18.4 Formation of sensory memory traces and therapy effects. (**a**) Formation of a sensory memory trace in healthy volunteers. The standard (*black lines*) and deviant (*dashed lines*) responses are shown after 2 (*top*), 6 (*middle*), and 36 (*bottom*) standard repetitions for the passive conditions for the central Frontal electrode. The *arrowheads* indicate where the repetition positivity (RP) can be seen (adapted from [89]). (**b**) MMN memory trace effect in patients with schizophrenia (*bottom*) and matched healthy controls (*top*). In controls the effect of increasing number of standard stimulus repetitions on MMN difference waves is due to increasing magnitude of the deviant negativity as well as an increasing positivity to standards (repetition positivity RP, see text). In patients, the MMN memory trace effect was diminished because of an attenuation of both ERP effects. Data are shown for the central-frontal electrode Fz (adapted from [88]). (**c**) Effect of a single dose of nicotine on the MMN, comparing the nicotine (MMN-Nic) and placebo (MMN-BL) groups (adapted from [103])

mechanism for echoic memory has recently been described in the cat primary auditory cortex [90] and also in the auditory thalamus [91] of mice and in the inferior colliculus of rats [92], suggesting that these arise from subcortical levels. These studies observed stimulus specific adaptation (SSA) of neuronal responses with repetition of frequent standard sounds, while responses to rare (frequency) deviants did not adapt.

The adaptation effects underlying RP are a basic form of cortical plasticity and might serve as useful markers of aberrant synaptic function in schizophrenia reviewed in [93]. The major part of this MMN deficit is owed to selective attenuation of the frontal MMN component [94–96]. The loss of adaptive properties of this frontal component (including RP) is robustly correlated with measures of cognitive impairment and social dysfunction in chronic schizophrenia [81, 88] (Fig. 18.4).

Näätänen and Kähkönen [79] recently suggested that the attenuated responses of the frontal MMN generator might indicate dampened frontal attention-switching function and might contribute to the negative symptoms such as social withdrawal, whereas abnormalities in the temporal MMN generator process might contribute to dysfunctions in auditory perception and might be associated with patients' positive symptoms.

At the pharmacological level, impairments in sensory memory trace formation underlying MMN have been related to NMDA receptor dysfunction [97, 98]. It is therefore of interest to determine if the MMN can be restored by modulator of glutamatergic activity.

There is some evidence for an improvement of MMN following 6 week administration of N-acetyl-cysteine, a gluthathione precursor that can increase NMDA receptor activity [79, 99]. Conversely, high doses of glycine, a co-transmitter at the NMDA receptor, can attenuate the MMN in healthy volunteers [100]. Given the preliminary evidence that glycine may reduce negative symptoms in schizophrenia, this indicates that these effects may depend on the optimal stimulation and integrity of the NMDA receptor system. In addition to effects on the NMDA receptor, there is some evidence for the GABA and serotonin being involved in modulating MMN [79, 101, 102]. Furthermore, acute administration of nicotine augments MMN in healthy volunteers in a manner that has been found deficient in patients with schizophrenia [103] (Fig. 18.4). Nicotine administration augmented MMN amplitude in the treatment group compared to the baseline recording, while no MMN change was found in the placebo group. The drug effect was due to a selective enhancement of the RP, while the negativity to deviants remained unaffected. These results suggest that nicotine agonists may ameliorate the MMN impairment by improving stimulus encoding and sensory memory trace formation.

Leitman et al. [24] recently addressed the question whether the sensory deficits measured with MMN would also contribute to higher cortical dysfunctions as measured with P3 in patients with schizophrenia. In their study, the MMN deficit predicted reduced P3 amplitude. One reason for correlation between different ERPs may be a shared neurochemical mechanism.

P3

Although schizophrenia patients are generally not impaired in the detection of targets in active oddball tasks, both the amplitude and latency of the P3 can be reduced, particularly in the auditory domain. Weisbrod and colleagues [104] found reduced amplitude of the auditory P3b both in patients with schizophrenia and their unaffected twins. The study of unaffected relatives (and/or unmedicated patients) is also important to rule out medication effects. Further support for P3 abnormalities across the schizophrenia spectrum came from studies of schizotypal personality disorder [105] and of healthy individuals with high scores on a schizotypy scale [106]. However, P3 impairments may not be specific for schizophrenic psychosis, because they have also been reported for bipolar disorder albeit with slightly different topographies [107]. There is some evidence that individuals with schizoaffective disorder have no impairment in P3 amplitude, but have similarly delayed latencies compared to patients with schizophrenia [108].

The heritability of P3 amplitude has been estimated at 60%. Although it is difficult to link a quantitative trait such as an ERP amplitude with a categorical on ("caseness" of schizophrenia), heritability is one of the prerequisites of an endophenotype, and the observation of these changes in relatives might suggest that P3 deficits are, indeed, a biological marker of schizophrenia. If this could be corroborated further, for example through the investigation of co-segregation in families with both affected and unaffected members, the P3 might become an attractive trait to probe for association with specific genetic loci, which may then turn out to be relevant for schizophrenia as well. Because numbers of participants in ERP studies are normally too small to allow for genome wide screens, this approach has so far only been taken with candidate genes. Associations with P3 alterations have been observed for several genes that are also implicated in the disease mechanism of schizophrenia or code for proteins that are targeted by treatment. These include the genes for the dopamine D2 and D3 receptors, the Catechol-O-Methyltransferase enzyme, which degrades intracellular dopamine, and the Disrupted in Schizophrenia (DISC) 1 and 2 genes [57]. The next challenge will be to find associations with loci that have not yet been implicated in schizophrenia or other neuropsychiatric disorders, in order to fulfill the promise of the endophenotype concept that it will aid the discovery of new genes based on its more strictly defined and reliable phenotypes.

Several studies investigated the relationship between the auditory oddball paradigm (typically used to assess MMN and P3) and synchronised oscillatory activity. A few studies examined the relationship between reduced P3 and oscillatory activity directly and demonstrated deficits in the delta and theta frequency range in patients [109–111]. Ford et al. [111] showed that gamma synchrony predicted P3 in healthy individuals but not in patients. In addition, Doege et al. [109] showed a correlation between evoked delta and theta activity and the variability of reaction times and performance levels. They suggested that the timing of oscillations in patients is less precise leading to smaller evoked amplitudes and more variable reaction time.

In addition oddball paradigms have also produced evidence for reduced gamma band activity. These studies reported a reduction of evoked gamma band activity (i) in response to standards [112] (ii) to novel targets associated with increased autonomic arousal [113] and (iii) in a late latency range (220–350 ms) in response to targets in unmedicated schizophrenic patients [49]. Interestingly, this last study tested the effect of smoking in patients and found higher early gamma activity in response to targets in smokers compared to non-smokers. Furthermore, induced gamma band activity was reduced in response to targets over the left hemisphere and increased over right hemisphere [112]. Finally, reduced gamma band phase synchronization was evident in response to the target in first-episode patients and chronic patients [114, 115]. In contrast, there is also some evidence for normal evoked gamma oscillations in response to simple tones in chronic medicated patients with schizophrenia [116].

Some of the variability across studies may be explained by genetic differences between patients. Common variants with small effects make a considerable contribution to the heritability of schizophrenia, and combinations of such common variants are likely to differ between patients and overlap across disorders [117]. If one or several of these common variants have a major effect on an intermediate phenotype, for example a neurophysiological measure, differences between these phenotypes across patient groups and studies would be expected. In fact, such an intermediate phenotype would be a particularly attractive endophenotype, if it can be shown to be heritable, because it might lead researchers to new genetic risk loci. Another translational application of non-invasive neurophysiology is the investigation of neural mechanisms of specific cognitive deficits (below Part 4) in relation to the underlying neuropharmacology (Part 5).

Mechanisms of Cognitive Deficits: The Example of Working Memory

Working memory (WM) encompasses processes that form, maintain, and manipulate short-term representations, which are crucial for comprehension, learning, reasoning and many everyday tasks [118]. Working memory impairments, particularly in the visuospatial and verbal domain, are amongst the most consistent cognitive deficits already in the schizophrenia prodrome and are considered a core deficit in the disorder.

Neurophysiological and functional neuroimaging studies of visual WM in normal participants emphasise its dependence upon an extended network of neural areas including the prefrontal, parietal, primary and higher sensory cortices. This raises the possibility that abnormalities in network integration by synchronous oscillatory activity [119] may provide a parsimonious account for the working memory problems and many of the cognitive deficits observed in schizophrenia [120, 121]. As a consequence a number of researchers propose that core aspects of the pathophysiology of the disorder arise from a dysfunction in the integration and coordination of

distributed neural activity [121–123]. This disconnection hypothesis is supported by reports of altered functional connectivity in schizophrenia during WM particularly between prefrontal and parietal areas [124–126] which indicates that perceptual deficits may in part result from impairments in reciprocal interactions between sensory and higher cortical areas [77]. Our own recent results confirm the important contribution of early visual processes to successful WM performance in healthy subjects and deficits in patients with schizophrenia [20, 127].

In a recent series of studies we have directly examined the effects of WM encoding deficits in schizophrenia, which are assumed to arise in large part due to the visual processing difficulties described above. We first measured neural activity with event-related potentials (ERPs) during WM encoding of up to three abstract test shapes that were presented sequentially and followed by a probe shape, which was either drawn from the test shapes (50%) or was a non match (a visual delayed discrimination task). For control participants, but not patients, a prominent early P1 (related to stimulus encoding) increased with WM load and predicted performance. Furthermore, the P1 reduction in patients was mirrored by reduced activation of visual areas in fMRI [20] (see Fig. 18.3). A reduced P1 during WM encoding has recently also been reported in participants with high schizotypy compared to low schizotypy [33].

In a subsequent paper we examined these deficits in patients with schizophrenia in greater detail by looking at the effects of oscillatory activity in a broad frequency range. We demonstrated that patients show reduced evoked theta, alpha, and beta oscillatory activity during WM encoding [127]. Importantly, in contrast to ERPs and evoked oscillatory activity, induced oscillatory activity can be used to directly assess processes during the maintenance period. Our result suggest that induced gamma activity increased monotonically across all tested loads in controls, but reached an asymptote at load 2 in patients reflecting a greater impact of task difficulty in patients [127] (see Fig. 18.5).

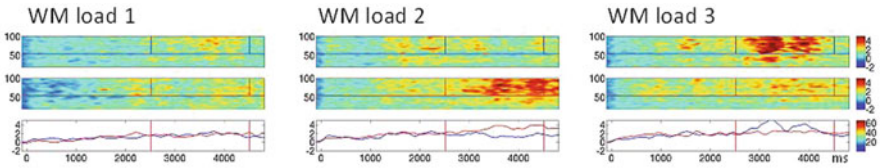

Fig. 18.5 Time frequency analysis of the maintenance period from the experiment shown in Fig. 18.2. Induced oscillatory activity at anterior electrodes following the offset of the first sample stimulus for WM load 1 (*left*), the offset of the second stimulus for WM load 2 (*center*), and the offset of the third stimulus for WM load 3 (*right*) are shown for controls (CT, *top row*) and patients with early-onset schizophrenia (SZ, *middle row*). The *bottom row* shows the line graph for high gamma activity (55–100 Hz) in the two groups (controls: *blue*; patients: *red*). Please note that during the later delay (2500–4500 ms) periods controls show an increase in induced gamma activity only for WM load 3, whereas patients show an increase for WM load 2 and then fail to further sustain the gamma band activity. Modified from [127] with kind permission of the Society for Neuroscience

If some key neural processes are deficient, how can patients still perform most cognitive tasks at reasonable levels, even at high loads? One possibility is that patients use selective attention to enhance the salience of items to be encoded into WM, which can show a surprisingly degree of preservation in patients [128]. Consistent with this proposal we recently demonstrated that alpha phase-locking during encoding correlates with working memory performance in patients (but not controls) [21]. Activity in this frequency band has been linked to selective visual attention [129, 130]. In a related finding Bachman et al. [131, 132] have reported enhanced alpha activity during WM maintenance for patients compared to controls, which may reflect the operation of compensatory attentional mechanisms during this process. The extremely long stimulus presentation time of that study may have helped to reduce encoding difficulties (as suggested above) and may indicate why compensatory mechanisms are recruited later in the WM process.

In addition to the delayed discrimination studies described above [127, 132] that looked at the different component processes separately, some studies investigated the relationship between reduced oscillatory activity and tasks that require a high degree of top down control [133] such as the cognitive control and N-back paradigms [134–136]. Cho et al. [135] examined the relationship between executive processes and gamma-band oscillations in a cognitive control paradigm that required participants to inhibit a pre-potent response. Patients with schizophrenia were characterized by a significant decrease of induced gamma-band power over frontal electrodes sites relative to controls during this cognitive control task. This impairment was significantly correlated with their reduced performance.

Basar-Eroglu et al. [134] and Schmiedt et al. [136] used an N-back task in which the stimuli were selected from three possible numbers. In addition they manipulated demands on executive function by having one number require a response with the opposing hand. In conditions requiring high cognitive control (respond with opposing hand) they found evoked frontal theta (not apparent in other conditions) and evoked gamma activity that increased with WM load in the healthy participants. In contrast, patients with schizophrenia showed attenuated evoked theta activity and high gamma band activity but neither increased with WM load. Finally, there is also evidence for impairments in functional connectivity in WM using both correlation-coefficients and theoretical graph approaches to study "small-world properties (for details see [137]).

In summary, the reviewed studies suggest a relationship between impairments in synchronized oscillatory activity and perceptual and higher-level cognitive processing contributing to WM deficits in schizophrenia. Additionally, correlations in synchronized activity and performance may also indicate the use of compensatory mechanisms to perform the task, e.g. increased alpha phase locking as an indicator of increased attention [21]. In the next section we review the evidence for a link between impairments in oscillatory activity and neurotransmitter dysfunctions. For a more detailed discussion how these may specifically affect working memory and its subprocesses see [138].

Neurophysiology and Molecular Mechanisms of Schizophrenia

Altered oscillatory patterns are potential intermediate phenotypes of schizophrenia. It is thus of great interest to understand the underlying neurochemical mechanisms, and the combination of evidence from pharmacological EEG studies in humans and in-vitro studies can be very fruitful.

GABA

Several studies have suggested alterations of the GABA system in the brains of patients with schizophrenia for reviews [138–140] providing evidence of a dysfunction of inhibitory interneurons in schizophrenia [141]. Postmortem studies have shown that the 67-kDa isoform of glutamic acid decarboxylase (GAD67) responsible for the synthesis of GABA is reduced in patients with schizophrenia [142].

More recently impairments in patients with schizophrenia have been linked to specific subtypes of GABAergic interneurons, especially those containing the Ca2+-binding protein parvalbumin (PV) in the dorsolateral prefrontal cortex (DLPFC) [139]. Importantly, these neurons are characterized by a fast-spiking pattern and control the excitability of pyramidal neurons [143]. The release of GABA from PV neurons is controlled by the growth factor neuregulin 1 (NRG1) through its ErbB4 receptor. Selective ablation of these receptors in mice resulted in a phenotype with schizophrenia-like features, including impaired working memory, reduced pre-pulse inhibition and hyperactivity. Some of these features normalized after treatment with diazepam, an allosteric positive modulator of the GABA-A receptor. Thus, reduced GABA-ergic activity can lead to schizophrenia-like phenotypes in experimental animals. It is interesting that both NRG1 and ErbB4 have been suggested to be susceptibility genes for schizophrenia [144, 145].

Networks of GABA-ergic interneurons, especially those containing parvalbumin, are important for supporting gamma oscillatory activity, Furthermore, blocking GABA-A receptors alters the dynamic profile of gamma oscillatory activity to changes in the network drive [146, 147]. Recently, a direct link between alterations in markers of GABAergic and glutamatergic neurotransmission and, in particular, gamma oscillatory activity has been found in animal models of schizophrenia [148, 149], demonstrating a deficit in rhythmogenesis. It has therefore been suggested that the abnormalities of GABA-ergic networks in schizophrenic patients may lead to reduced gamma band synchrony and thus to WM and other cognitive deficits.

Using network simulation Vierling-Classen et al. [150] showed that increasing the decay time at the GABA-A synapse from interneuron to pyramidal neuron can model the gamma band deficits found in schizophrenia. Increasing the decay time of the extended inhibitory postsynaptic current (IPSCs) resulted in longer inhibition and a reduced probability of pyramidal cell spiking for a longer duration. As expected from these simulations, patients showed a pronounced response at 20 Hz, but reductions at 40 Hz using an auditory steady state paradigm. Interestingly, these

authors also noted that the fidelity of the networks is not only dependent on the GABAergic interneuron functioning, but also on the strength of the drive of the input to the network. If the drive is too strong, this would overshadow any extended inhibition. They gave an example of a loud auditory stimulus that may provoke sufficient excitation in the auditory cortex to overpower the effects of extended inhibition. This raises the question whether a sufficiently salient or motivating stimulus may also be enough to overcome extended inhibition and enhance weak synchronization, in this instance the diminished gamma activity.

Glutamate

A role for NMDA receptor activity in schizophrenia is based on the finding that NMDA antagonists, such as ketamine or Phencyclidine (PCP), mimic both positive and negative symptoms of schizophrenia [151]. The NMDA receptor has consistently been related to the cognitive symptoms of schizophrenia.

NMDA receptors play a crucial role in neuronal communication and plasticity. Blocking NMDA does not only interfere with excitatory transmission and synaptic plasticity, but it also reduces the drive to inhibitory interneurons [152]. Several recent studies suggest that altered GABA neurotransmission may be secondary to abnormalities in NMDA receptor functioning [153, 154]. This is based on the finding that ketamine has been shown to reduce the activity of GABA interneurons and a consequence to disinbibit pyramidal neurons [155]. In addition to the effect of acute intake, chronic ketamine exposure has been shown to result in a reduction in the number of PV-containing axoaxonic cartridges, the synaptic terminals of inhibitory chandelier cells [156].

There is evidence both from in vivo recordings from mouse hippocampus [157] and from human EEG [158] using the auditory paired-click gating paradigm that ketamine increases gamma oscillatory activity and reduces slow frequency activity. However, there is also in-vitro evidence for reduced oscillatory high-frequency activity in response to ketamine as well [148, 149]. Roopun et al. [149] showed that ketamine can have region-specific effects with an increase in gamma in one region and a reduced or no effect in another. They argued that reduced power in one region may lead to phase delays between oscillating networks across the cortex and changes in long-range synchrony.

However, differential effects of acute or chronic ketamine have to be taken into account when using alterations of NMDA receptor function as a model for schizophrenia (see [158, 159]. Whereas acute ketamine augments glutamate concentration measured with MR-spectroscopy in humans [160], it is the chronic use of ketamine that results in NMDA receptor hypofunction. Indeed, glutamate concentration has been shown to be higher in patients with recent onset of schizophrenia [161], but reduced in chronic schizophrenia [162].

In addition to the abnormalities of excitatory NMDA-receptor transmission on shaping the inhibitory GABAergic transmission, these functional impairments may also interact with structural abnormalities [45], such as reductions in amount of

cortical neuropil, axon terminals and dentritic spines density on cortical pyramidal neurons in schizophrenia [163, 164]. Dendritic spines are the principal targets of excitatory synapses to pyramidal neurons. These abnormalities have mainly been found in deep layer 3 pyramidal neurons in DLPFC and other areas as well [139, 164], which suggests an involvement in primarily intracortical circuits, and thus recurrent excitation [165]. This is in line with the dysconnection theory, according to which reduced synaptic connectivity results in abnormal functional integration of neural systems [123, 166].

Dopamine

It has been suggested that dopaminergic signaling through D1-type receptors modulates the cortical signal-to-noise ratio by enhancing selective inputs to both pyramidal cells and inhibitory interneurons [167] and it has been shown that reduced D1-receptor signaling on prefrontal pyramidal cells attenuates GABA-A- and NMDA- receptor induced currents [168–170]. Dopamine may thus modulate frequency-dependent signal transmission and thereby adjust oscillations in cortical networks [171]. Dopaminergic input can have inhibitory or excitatory effects on pyramidal neurons because activation of D2-type receptors (D2, D3, D4) decreases concentrations of cyclic adenosine monophosphate, an important second messenger, whereas activation of D1-type receptors (D1, D5) increases it. Increased synaptic dopamine may thus reduce or enhance oscillatory activity. A study of the effects of functional polymorphisms in the dopamine transporter and D4 receptor genes has provided first EEG evidence for such divergence [172], but further receptor-specific studies are needed to determine the direction of the effects of dopamine on gamma oscillations.

Dopamine modulates glutamatergic and GABAergic transmission, and is also under the influence of the same synaptic proteins. Dystrobrevin-binding protein-1 (dysbindin-1) regulates both dopamine and glutamate release and trafficking. The neurophysiological effects of *dysbindin-1* variants have been investigated with both early/perceptual ERPs (P1) [173, 174] and indices of (prefrontal) cognitive control [175]. These findings underline the importance of looking beyond the classical neurotransmitter pathways of synthesis, release, receptor binding, transport and degradation and assess functional differences in the synaptic apparatus, which is likely to be crucial for the maintenance of oscillatory activity as well.

Cholinergic System

Nicotine normalizes the auditory sensory gating (P50) deficit in patients with schizophrenia, improves deficits in spatial WM [176], sustained attention [176] and performance in the N-back task [177]. Evidence is starting to emerge that can explain these network functions. The alpha-7 nicotinic receptors are concentrated on

interneurons [178] and, by enhancing the excitation of the GABAergic interneurons, they may enhance their inhibitory output [179, 180]. Indeed, nicotine increases the gamma oscillations that are dependent on interneuron function in rat hippocampal slices [181]. Furthermore, cholinergic modulation (mainly via muscarinic receptors) has also been shown to increase oscillatory activity [182].

Interestingly, animal studies have shown that oscillatory activity can be increased by stimulation of the mesencephalic reticular formation [183, 184] which triggers increased levels of ACh in the cortex [185], and by direct cholinergic stimulation of the visual cortex [182]. In addition, stimulation of the nucleus basalis of Meynert, the main source of cortical ACh, also induced high-frequency oscillations [186]. Stimulation of the mesopontine cholinergic nuclei in the brainstem that project to the thalamus also facilitates oscillatory activity [187].

Alterations in the cholinergic system can thus contribute to deficits in oscillatory activity. Gallinat et al. [49] tested the effect of smoking in patients and found higher early gamma activity in response to targets in smokers compared to non-smokers. Given that the α7 nicotinic receptor functioning has been shown to be impaired in schizophrenia; it is not surprising that patients can benefit from nicotine in some domains.

Conclusions and Future Directions

The neurophysiology of schizophrenia has recently received important boosts from the combination with molecular genetics and pharmacology and impulses from in-vitro study. It is still the only methodology that permits the investigation of neural processing in real-time and in signals that are biophysically close to those measured in invasive animal recording and cellular pharmacology studies. Attractive combinations with other noninvasive tools are also emerging. For example, Muthukumaraswamy et al. [188] showed a correlation between the individual gamma frequency and the GABA concentration measured in visual cortex with MR-spectroscopy [188, 189].

Several important predictions about links between neurotransmitter systems (particularly GABA, glutamate and acetylcholine) and cortical oscillations that were based on in-vitro studies have been borne out by human EEG studies. Furthermore, for several of these mechanisms, for example hypofunction of the NMDA glutamate receptor and the alpha-7 nicotinic receptor subunit, links with schizophrenia have been established through model psychoses, endophenotype and treatment studies. One hope is that by learning more about how to normalize oscillations by pharmacological intervention, which can be studied in-vitro, in animals and in human EEG, we will find out how to treat the cognitive and clinical symptoms of schizophrenia, many of which are related to altered oscillatory patterns, more efficiently. Although concrete treatment trials are still far off, several suggestions for such translational research have been made, in particular in relation to the GABA, acetylcholine and glutamate systems. Finally, the traditional approach of cognitive neurophysiology with biological markers such as the P50 sensory gating suppression and reduced

P1, MMN and P3 is experiencing a revival based on its potential use in family and genetic association studies, where they may serve as important endophenotypes and help with the search for new schizophrenia risk loci.

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Chapter 19
Schizophrenia Spectrum Disorders and Risk for Cancer Morbidity and Mortality

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Abstract This chapter reviews recent epidemiological studies on the relationship between schizophrenia spectrum disorders and cancer morbidity and mortality. Three sorts of findings are discussed: (1) reduced risk for cancer morbidity and mortality among patients diagnosed with schizophrenia and their first-degree relatives; (2) enhanced risk for cancer morbidity among patients with bipolar spectrum disorders, and (3) no increased risk for cancer morbidity among patients suffering from schizoaffective disorders. The genetic hypothesis suggests that the presence of genes with the dual effect of reducing the cancer risk and disrupting neurodevelopment is a plausible explanation for this association in schizophrenia patients. The environmental contributors to malignancy include health behavior, psychotropic medications, and metabolic syndrome, are suggested to explain the increased cancer risk among bipolar patients. The identification of risk and protective genes that mediate the development of malignant processes in some major psychiatric disorders is a new challenge in the field of psycho-oncology.

Keywords Schizophrenia · Bipolar disorder · Schizoaffective disorder · Cancer · Morbidity · Mortality

Abbreviations

APC	Adenomatous polyposis coli
CYP	Cytochrome P450
MET	*MET* proto-Oncogene
MspI	A four base cutter (C decrease CGG) restriction endonuclease
MRS	31p Nuclear magnetic resonance spectroscopy
PDK1	3-Phosphoinositol-dependent kinase 1
PI3K	Phosphatidylinositide 3-kinase
PKB	Protein kinase B

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PtIns3,4,5P3	Phosphatidyl Inositol 3,4,5 triphosphate
NQO1	NAD(P)H: Quinone oxidoreductase 1
SMR	Standardized mortality ratio
SIR	Standardized incidence ratio
PTEN	Tumorsuppressor phosphatase with tensin homology
SOD	Superoxide dismutase
SSRI	Selective serotonin reuptake inhibitor
TGFBR2	Transforming growth factor-B receptor

Introduction

In recent years there has been increased interest in the investigation of the co-occurrence between schizophrenia spectrum disorders and cancer morbidity and mortality. This interest was promoted by conflicting findings of large-scale, register-based epidemiological studies conducted worldwide. The studies have demonstrated that despite the presence of multiple risk factors noted in the population of mentally ill individuals, they may reveal increased, reduced or similar cancer incidence compared to the general population. In this chapter we will review the most recent findings in this field and will discuss possible explanations of this "epidemiological puzzle". We prearranged our review according to traditional nosological distinction into schizophrenias, schizoaffective disorders and bipolar disorder, despite all the complexity of this classification of serious mental illnesses.

Schizophrenia is a major mental disorder with polymorphic symptomatology, unknown etiology and complex pathophysiology [1]. Of other mental disorders (schizoaffective and mood disorders), schizophrenia seems the most severe illness: most patients need treatment and care for the rest of their lives [2]. Symptomatology of the illness is traditionally divided into positive symptoms such as delusions, hallucinations, and thought disturbances, and negative symptoms such as apathy, alogia, flattened affect and social withdrawal [3–7]. The positive-negative dichotomy does not cover the entire spectrum of schizophrenic psychopathology (e.g., cognitive, mood, and motor symptoms) and therefore may be considered a simplification of the clinical phenotype. Nonetheless, it has an important clinical and prognostic significance: while the positive symptoms are preponderant at onset of the illness or in phases of acute exacerbation and can be improved with antipsychotic drug therapy, the negative symptoms appear generally in the chronic deteriorating course and are generally treatment-resistant (even with novel antipsychotic agents) and responsible for most of disability in the disease [6].

Over the past six decades the introduction and wide use of new psychopharmacological agents (antipsychotics, antidepressants, anxiolytics, and mood stabilizers) for effective treatment of serious mental disorders changed the face of traditional clinical psychiatry. As a consequence, the deinstitutionalization movement has been occurred signifying the transition of treatment from the state psychiatric hospitals to the community. The reform of the mental health system has offered mentally ill

people an opportunity to be no longer isolated in hospital from their healthy counterparts and hence to share the common patterns of behavior including substance use and other risk factors for physical comorbidity [2]. On the other hand, the development of comprehensive rehabilitation programs and community-based psychiatric and psychosocial services has enhanced their skills and abilities for help-seeking and access to medical services. Thus, hazards and benefits of the community living could be counter-balanced.

Risk Factors

Life Style

Patients with schizophrenia have high rates of unrecognized and untreated medical conditions and substantially elevated mortality rates due to medical illness [8, 9]. They are more likely to smoke than the general population even more than lower socioeconomic class population groups [9, 10]. The costs associated with tobacco use also render them economically poorer, with further consequences for their physical health [11]. Theories for the increased smoking rates in people with schizophrenia include a therapeutic effect of nicotine on psychotic symptoms and cognitive deficits as well as a propensity for smoking in an attempt to increase the metabolism of antipsychotic drugs, thus reducing their side effects [10, 12].

Patients with chronic psychoses maintain the sedentary or indoor way of life and are less likely to exercise and more likely to use diets higher in fat and lower in fiber compared to the general population [9]. Some studies have shown that the rates of obesity and alcohol misuse are comparable in patients with chronic psychosis and in the general population [8]. However, there is an association between schizophrenia and alcohol and drug misuse [13, 14]. Smoking, alcohol misuse and lifestyle risks do not represent the full picture of risk factors for cancer. A more important risk factor for cancer than smoking or eating less fruit and vegetables that suggested by current health guidelines, [15] is being exposed to carcinogenic chemical compounds in the workplace. As patients with schizophrenia as a rule are usually unemployed, this could decrease their cancer morbidity.

Medication

Psychotropic medication is associated with a host of physical complications and side effects, the discussion of which is beyond the scope of this review. Antipsychotic medication in particular may induce endocrinologic (e.g., galactorrhea), neurologic (e.g., tardive dyskinesia), and cardiovascular (e.g., prolongation of the QT interval) side effects [16]. Although novel antipsychotic agents are safer and less toxic than the conventional medications, they have their own potential for worsening physical health. In particular, their propensity to cause overweight may jeopardize both the patient's physical health and compliance with therapy [17, 18].

At the same time, there is a somewhat paradoxical protective action of antipsychotic pharmacotherapy, both direct (anticancer effects) and indirect (actions of antipsychotic drugs on hormones by inhibition of dopamine) that might contribute to the lower rate of cancer occurrence in schizophrenia [19].

Service-Related Risks

Growing evidence shows that there exist barriers to receiving adequate medical care among patients with schizophrenia [20–22]. Psychiatrists and family physicians are fairly poor at recognizing and treating physical conditions in psychiatric patients [23–25]. Because physical complaints may occur as part of a psychiatric illness, some physicians might neglect physical assessment in their psychiatric patients, wrongly assuming that their symptoms are psychological. Alternatively, the psychiatric symptoms may render patients less able or less likely to communicate their physical needs [24, 26, 27]. Attending physicians may be uncomfortable dealing with patients with psychiatric problems, which might impair their clinical assessment. The stigma of mental illness may be another barrier preventing patients from seeking and receiving the correct treatment [25]. For example, in the United States many people with mental disorders report difficulty in obtaining insurance. Therefore, cost is the barrier that prevents them from obtaining the right medical care when it is needed [28–30]. However, this is not the case for Israel, where medical insurance is available practically for all citizens [31].

Use of medical care varies by psychiatric diagnosis, with young adults with schizophrenia and adults of all ages with bipolar disorder having an especially high risk of not receiving general medical services [32]. Few researchers have studied whether psychiatric patients are offered general screening measures, such as mammography and cervical smears, as often as the general population. For instance, women with schizophrenia are less likely to receive appropriate cervical cancer screening and this situation may mitigate good continuity of care by primary care physicians with psychiatrists assisting [33, 34].

The aforementioned factors could account for the fact that schizophrenia is associated with the rate of premature mortality that is 2–3 times higher than in the general population, [35, 36] however, the role of cancer in this excess mortality remains unclear.

Cancer Morbidity

Lower than expected rates of cancer have sporadically been reported for psychiatric patients over almost a century [37]. In recent years, when population-based studies have become available, an analysis of the data by specific types of cancer and by specific psychiatric diagnoses allows to obtain more valid and reliable results. Paradoxically, however, the recent studies bring controversial results, depending upon both type of cancer and type of disorder [38]. Therefore, we reviewed

systematically the epidemiological findings by aggregated cancer sites and by cancer type and localization as well.

Aggregated Rates

Controversy concerning cancer incidence in schizophrenia exists because of heterogeneous findings. In the USA, Carney et al. [39], using a large pool of insurance claims, reported that overall individuals with mental disorders were no more or less likely to develop a malignancy than those without such diagnoses. Analyzing the types of cancer, they found that there was a slightly greater chance of respiratory system cancers, which was explained by the increased rate of smoking in this population. Grinshpoon et al. [40] reviewed six population-based studies conducted in the USA, Australia, Denmark, Finland and Japan and found reduced cancer incidence rates in four of them [41–46]. The exceptions were the USA (Honolulu) and Japan's (Hagasaki) studies [41] and Finnish study, [44] where standardized incidence ratios (SIRs) were higher for the patients with schizophrenia than for the respective general population. In their own large-scale epidemiological study carried out in Israel, Grinshpoon and associates [40] found a slightly decreased overall rate of cancer in persons with schizophrenia, although risks for specific types of cancer varied.

Breast Cancer

Similar to the case of overall cancer rates, epidemiological studies examining the incidence of breast cancer in patients with schizophrenia report increased as well as reduced or similar incidence compared to the general population. Recently, Bushe and colleagues [47] performed a meta-analysis of 13 published studies to investigate possible reasons for the variable findings [48–55]. Data were extracted for over 6,000 female patients who were compared to age-matched general populations from the relevant country from 1986 to 2008. Only 6 studies reported an increased or marginally increased incidence of breast cancer. These tend to be studies with more than 100 incident cases of breast cancer, greater than 100,000 person years follow up and older populations. The authors of the meta-analysis concluded that inconsistencies in study findings may be due to methodological issues such as low statistical power and the age range of cohorts studied. Reduced gender parity and hyperprolactinaemia were suggested to play a part of putative etiological factors for increased breast cancer in women with schizophrenia.

Factors associated with breast cancer are consistent across epidemiologic studies. Breast cancer's risks increased with age to a maximum for women in their 60s; the rate of increase slowed for women in later decades of life, and it began to decline beyond the seventh decade; hormonal factors such as menopause and decreased surveillance and diagnosis among the elderly may underlie these findings [56]. Similarly, the lower risk among poor women (eligible for Medicaid) was explained by differences in reproductive patterns (e.g., greater parity, lower age at

first birth, and lower age at menarche) or surveillance and diagnosis [57]. Also, increased hazards for women was associated with benign breast disease, [58] obesity, [59] and non-breast malignancies [60]. The increased risk in patients with more comorbid illness and more outpatient medical visits may be due to higher levels of surveillance for breast cancer in these populations.

Lung Cancer

In Denmark, Dalton et al. [52] found marginally reduced risk for lung cancer in male patients with schizophrenia that was due to a reduction in risk for older patients, and increased risk for breast cancer in female patients with schizophrenia. Despite decreased overall rate of cancer in persons with schizophrenia in Israel, Grinshpoon et al. [40] reported elevated risk for lung cancer for male but not female schizophrenia inpatients, particularly for those originated from Asia and Africa. In contrast, Lichtermann et al.'s study [44] in Finland reported increased overall cancer risk, with half of the excess cases attributed to lung cancer and with the strongest relative increase in risk in pharyngeal cancer. The standard explanation for such findings is an excessive tobacco smoking of men suffering from schizophrenia, exceeding potential anticancer effects of other factors.

Prostate Cancer

The best evidence of the lower risk of cancer in patients with schizophrenia is that with prostate cancer, a condition exposed to a substantial effect of the hormones affected by antipsychotic medication. Fuller Torrey [61] undertook a systematic review of the relevant literature on the incidence of prostate cancer in individuals with schizophrenia. He revealed 5 studies that reported age-standardized and site-specific cancer data [40, 44, 50, 52, 53]. Although, the incidence of cancer at other sites varied across the studies, all the five studies found a lower SIR for prostate cancer, ranging from 0.49 to 0.76. Possible explanations included ascertainment bias; genetic factors; antipsychotic drug effects, either by being cancer protective or decreasing testosterone, or both; and lifestyle differences, such as prolonged hospitalization resulting in a decreased opportunity for heterosexual intercourse.

Until recently, most men with schizophrenia were hospitalized on gender-segregated wards. They thus had little opportunity for heterosexual intercourse or for becoming infected with sexually transmitted diseases, which, in some studies, have been associated with an increased risk of prostate cancer. In one study, for example, 43% of men with severe psychoses had never had a sexual relationship [62]. In another study, 32% of men with schizophrenia had never had a sexual relationship [63]. Additional support for this hypothesis also comes from the decreased incidence of cervical cancer in women with schizophrenia reported in three studies [50–52] but not in two others [44, 53]. In recent years, as psychiatric patients have been deinstitutionalized, their pattern of sexual activity has more closely approximated that of the general population.

Family Studies

Given that genetic causes have been proposed as an explanation of findings of a reduced risk of cancer among people with schizophrenia, one would expect that the risk of cancer among first-degree relatives would be similarly reduced. In order to test this hypothesis, Levav and associates [64] investigated the risk of cancer among the biological parents and full siblings of a large cohort of inpatients with schizophrenia in Israel. Linkage analysis was carried out between national population, psychiatric and cancer databanks. SIRs for aggregated cancer sites were calculated by comparing the incident rates among schizophrenia patients and their first-degree relatives with national incidence rates. Reduced SIRs were found across all groups examined. Among parents, whose numbers were adequately large, the findings reached statistical significance. For patients with schizophrenia and their siblings representing a markedly younger population, only a trend was observed. The authors interpreted the obtained results in the terms of a genetic hypothesis that suggests the presence of a gene(s) with the dual effect of reducing the cancer risk and simultaneously disrupting neurodevelopment that, in turn, has been considered a plausible cause of the schizophrenia.

Catts and colleagues [65] performed a meta-analysis on SIRs of cancer in patients with schizophrenia and first-degree relatives and compared with general population samples. They revealed that the aggregated overall cancer incidence in patients was not significantly increased. Although lung cancer incidence was slightly increased (by 31%), it was reduced after adjusting for smoking prevalence. At the same time, the incidence of several cancers unrelated to smoking was reduced. However, breast cancer rates were significantly increased in female patients. The pooled overall cancer incidence in siblings and parents was significantly reduced. A metaregression detected a significant relationship between cancer risk in the general population and relative risk in patients. The authors concluded that a discrepancy between cancer risk exposure and cancer incidence in schizophrenia suggests a protective effect.

A lower risk of morbidity for cancer in both the index cases and their blood-related relatives points to genetic influence: if patients can be less exposed to chemical carcinogenic compounds as they are generally unemployed, and may benefit from some yet unknown protective action provided by antipsychotic drugs, such mechanisms cannot account for the reduced risk in their blood kin [66].

Despite several methodological issues and heterogeneous results, the epidemiological studies of the relationships between schizophrenia and cancer detected a reduced incidence of cancer observed in patients with schizophrenia compared with the general population [40, 67, 68]. It is intriguing that two rigorous population-based studies found a significantly lower risk of lung and prostate cancer in people with schizophrenia and their first-degree relatives compared with people without schizophrenia after adjustment for confounder variables [44, 64]. More recently, the first meta-analysis of cancer incidence rates in patients with schizophrenia, their parents and siblings has been published [65] and reported a discrepancy between cancer risk exposure and cancer incidence in schizophrenia, consistent with a possible genetic protective effect. Although other possible explanations may be

involved such as, epidemiological bias, cancer-protective effect of classical antipsychotic medications, obstetric complications and lifestyle differences, [55, 61, 66] the authors propose the explanatory hypothesis that the genetic predisposition toward schizophrenia confers genetically reduced susceptibility to cancer.

Cancer in Bipolar and Schizoaffective Disorders

In contrast with schizophrenia, few studies have explored the cancer rates in patients with depressive symptoms, bipolar disorders or schizoaffective disorders. Despite the presence of similar factors among patients with bipolar disorder that might affect the risk for cancer (diet, smoking and medications), several studies found a nonsignificant statistical risk for cancer (reviewed by Carney and Jones [69]). The authors conducted a review of health claims for over 3,500 individuals with bipolar disorder and described a significantly greater presence of multiple medical conditions. Compared with persons who had no claims for a mental illness, persons with bipolar disorder were more likely to have multiple comorbid and chronic medical conditions. Although an increased prevalence was found for conditions spanning all organ systems, hyperlipidemia, lymphoma, and metastatic cancer were the only conditions less likely to occur in persons with bipolar disorder than in the general population.

More recently, Barchana et al. [70], using linkage analysis based on the psychiatric and the cancer national databanks in Israel, found an enhanced risk for aggregated cancer sites among patients with bipolar disorders. However, the risk for breast cancer was not significantly higher than in the general female population that does preclude drawing firm conclusions.

The same research group, [71] using the same methodological approach to explore risk for cancer among schizoaffective disorders, revealed no significant increase or decrease in the risk in these patients compared with the Israeli general population. The authors disposed conditionally these results between the schizophrenia findings that in general show a reduced risk for cancer and the bipolar disorder findings that show generally an increased risk.

Another study [72] examined association of depressive symptoms with prospective incidence of colorectal cancer and distal colorectal adenomas in 81,612 women without prior cancer from the Nurses' Health Study; 400 cases of colorectal cancer and 680 distal colorectal adenomas. The study found that women with the highest levels of depressive symptoms had an elevated risk of incident colorectal cancer compared with women with the lowest levels of symptoms and this association appeared stronger in overweight women. However, depressive symptoms were unrelated to risk of colorectal adenomas. The associations were interpreted as consistent with a possible role in late promotion of the disease.

In contrast, one of few studies that have addressed the problem of depression and breast cancer risk using population-based cohorts and prospective designs, [73] found that women with clinically significant depressive symptoms had a lower risk of breast cancer during a 2–5 year period following their screening. Family

history of breast cancer, hypothyroidism and unilateral oophorectomy were found to be significant predictors of breast cancer development. The findings suggest that depressive symptoms may be associated with a protective factor involved in the development of breast cancer.

Finally, a resent population-based, nested, case-control study using data from a general practice database, explored the risk of 6 common cancers (breast, colon, rectal, gastroesophageal, prostate, and respiratory) in patients with schizophrenia or bipolar disorder [54]. This study showed that patients with schizophrenia had a significantly higher risk of colon cancer and a lower risk of respiratory cancer compared with patients without schizophrenia. In contrast, the risks of cancer in patients with and without bipolar disorder were similar. The authors emphasized the fact that risk of colon cancer was threefold increased in patients with schizophrenia who take antipsychotic medications.

Cancer Mortality

Similar to inconsistent findings regarding cancer incidence, there are conflicting results on the relationship between cancer incidence and mortality in psychiatric patients. Osborn et al. [74] in the UK found that the rates of cancer-related deaths, other than those directly attributable to smoking, were not increased. Most studies, however, suggest that cancer mortality is increased, even if cancer incidence is no different from that in the general population. Different methodologies and outcomes may account for the inconsistency of the results. Recently, Kisely and associates [75] explored the association between mental illness and cancer incidence, first admission rates, and mortality in Nova Scotia, Australia, using a population-based record-linkage data on 247,344 patients in contact with primary care or specialist mental health services, which were linked with cancer registrations and death records. Their analysis showed that cancer mortality was 72% higher in males and 59% higher in females among patients in contact with mental health services that reflected similarly elevated first admission rates. Evidence for increased cancer incidence was weaker and less consistent. For several cancer sites, such as melanoma, prostate, bladder, and colorectal cancers in males incidence rate ratios were lower than might be expected given the mortality and first admission rate ratios, and no higher than that of the general population. The researchers concluded people with mental illness in Nova Scotia have increased mortality from cancer, which cannot always be explained by increased cancer incidence. Possible explanations, requiring further study, included delays in detection or initial presentation leading to more advanced staging at diagnosis, and difficulties in communication or access to health care.

Rouillon et al. [76] reported an 11-year prospective cohort study of mortality in patients with schizophrenia in Reims, France. Their mortality rate was nearly fourfold higher than in the general population. Cancer was the second most frequent cause of mortality, with a global standardized mortality ratio (SMR) of 1.5. For men, lung cancer was the most frequent localization, with an SMR of 2.2. For women,

breast cancer was the most frequent localization, with an SMR of 2.8. The two baseline predictors of death by lung cancer in that study were duration of smoking and age older than 38 years.

Capasso et al. [77] compared the mortality in a large cohort of patients with schizophrenia and schizoaffective disorders to the general US population and found that there was excess of cancer mortality: 19% deaths of patients with the mental disorders was caused by lung cancer and other 17% by other respiratory diseases. These results suggest that the survival gap in schizophrenia/schizoaffective disorder appears to be increasing over the last three decades, particularly in light of continued improvements in the general population's lifespan.

In order to explain excessive mortality and shortened longevity of patients with schizophrenia, Kirkpatrick and colleagues [78] proposed the hypothesis that schizophrenia is a syndrome of accelerated aging. The biological plausibility of the hypothesis is supported by the existence of established syndromes of accelerated aging and by the sharing of risk factors between schizophrenia and other age-related conditions (e.g., cancer). Reduced cancer incidence among patients with schizophrenia that contradicts their hypothesis the authors attempt to explain by the assumption that patients with schizophrenia may not live long enough to show an increase in cancer deaths because of their very high rates of suicide and cardiovascular diseases.

Cellular and Molecular Explanations

Defects in genetic and developmental processes are thought to contribute susceptibility to schizophrenia [79, 80]. Due to etiological complexity identifying susceptibility genes and abnormalities in the development has been difficult; however the importance of genes within chromosomal 8p region for neuropsychiatric disorders and cancer is well established [81].

It is biologically plausible that specific tumor-suppressor genes on 8p, that are down-regulated in lung and prostate cancer, could be up-regulated in schizophrenia. This phenomenon has been considered for various tumor-suppressor genes, such as TP53 on 17p13, [82] APC or adenomatous polyposis coli on 5q21–22 [83] and TGFBR2 or transforming growth factor-b receptor on 3p22, however in this last case with negative association for 10 single-nucleotide polymorphisms in the Japanese population [84].

The tumor-suppressor TP53 gene has been identified as the most commonly mutated gene in human neoplasms [85]. The p53 tumor-suppressor protein regulates the cell cycle, checkpoint control, repair of DNA damage and apoptosis, [86, 87] and several developmental processes, including cerebral vascularisation, [88] neurogenesis and neural crest migration [89]. Independent genetic evidence for TP53 as a schizophrenia susceptibility gene is strong, with five of six studies reporting significant association [90–94]. Genotype and allele frequencies at MspI polymorphisms of TP53 are likewise significantly different between Korean schizophrenia

and lung cancer subjects [82]. TP53 activates the transcription of PTEN (tumorsuppressor phosphatase with tensin homology), and therefore functions as a negative regulator of the entire phosphatidylinositol-3-kinase (PI3K)-AKT signaling pathway that drives tumorigenesis [95] and many critical signaling systems involved in neural development, survival and plasticity [96]. The inappropriate inhibition of PI3K-AKT pathway has been associated with diseases as diverse as diabetes and schizophrenia [97, 98]. It is noted that the NQO1 enzyme protects against oxidative stress and carcinogenesis, including stabilization of TP53 [99]. NQO1*2 is a missense variant (NP_000894:p.187P > S) that predicts poor survival among women with breast cancer mediated, in part, by TP53-linked roles of NQO1 [100].

Defects in tumor-suppressor APC gene, which is associated with colon and other cancers [101, 102] are also associated with susceptibility to schizophrenia; furthermore, APC is up-regulated in patients with schizophrenia [83].

It is possible that the same genetic factors located in the chromosomal region 8p might induce cancer in the general population, but have also a possible protective effect for lung and prostate cancer in individuals with schizophrenia and their relatives. In this respect, 8p may represent a landmark for the identification and cloning of genes involved in cancer and schizophrenia.

Recently, *MET* proto-oncogene (*MET*) was identified as a candidate gene for schizophrenia [103]. If the *MET*-schizophrenia association is true, one would expect over-transmission of cancer-*protecting* variants to patients with schizophrenia, a hypothesis that is likely to require a much larger sample size to test with adequate power [104].

Signal Transduction Explanations

The role of phosphatidylinositide 3-kinase (PI3K) and protein kinase B (PKB) pathway in schizophrenia and its potential role in cancerogenesis were recently reviewed by Kalkman [105]. Since the PI3K-PKB pathway is involved in cellular growth and proliferation, [106, 107] reduced activity of this cascade in schizophrenia could at least partly explain the neuronal dystrophy reported in neuroanatomical studies of brains from schizophrenic patients [108, 109]. It is known that risk factors for schizophrenia, such as corticosteroids and cannabis, suppress the activity of the PI3K–PKB pathway, [110] and conversely, estrogen and vitamin D2 factors, that exhibit a moderate protective activity in schizophrenia, electroconvulsive therapy, and chronic antipsychotic treatment stimulate this pathway [111–114]. Likewise, reduced activity of the PI3K–PKB pathway makes the brain more susceptible to virus infections, anoxia, and obstetric complications -recognized risk factors for schizophrenia, [115, 116] whereas a reduction of growth factor levels towards the end of puberty could contribute to the emergence of schizophrenia symptoms around that age [117, 118]. On the other hand, constitutive overactivation of the PI3K–PKB pathway increases cancer risk and facilitate the growth of colon, ovarium, uterus, breast, prostate, gastric cancers, melanoma and other cancers [119, 120]. Therefore,

the presumed hypoactivity of the PI3K–PKB cascade might provide a partial explanation for the epidemiological finding of a reduced cancer rate in schizophrenic patients [105]. Recognition of the role of a dysfunctional PI3K–PKB pathway in schizophrenia might help in the discovery of hitherto undetected causative gene mutations and could also lead to novel therapeutic approaches. However, a major challenge that remains to be solved is how the PI3K–PKB pathway can be activated without increasing the risk of cancer.

Apoptosis

Another explanation for reduced cancer risk in schizophrenia involves apoptotic mechanisms closely related with both the synaptic pathology of schizophrenia [121] and controlling cellular growth and proliferation. Apoptosis is a highly regulated form of cell death that is often likened to cellular suicide [122, 123]. Apoptosis is morphologically and molecularly distinct from necrosis, the other principal form of cell death [124]. Cytomorphological features of apoptosis include cell shrinkage, membrane blebbing, chromatin condensation, DNA fragmentation, and cellular disintegration via phagocytosis [125]. Apoptosis occurs without inflammation and generally requires the formation of new gene products to proceed [126]. Significant apoptotic cell death occurs during early development of the nervous system with over half of all developing neurons dying by apoptosis [127]. This process has been referred as to neuronal pruning or sculpturing neurons [128, 129] impaired in schizophrenia [121]. Apoptosis also serves to eliminate injured or diseased neurons throughout life and it has been implicated in a number of neurodegenerative disorders [130, 131].

Apoptotic activity can be triggered by a broad array of stimuli including oxidative stress (e.g., ischemia, hypoxia), pro-inflammatory cytokines, excitotoxicity, neurotrophin withdrawal, mitochondrial dysfunction, and abnormal intracellular calcium concentrations [124]. A number of these stimuli can alter Bcl-2 family protein expression via potent regulatory genes such as p53 on 8p region [132] and par-4 [133] in order to promote cytochrome C release and induce caspase-3 activation.

Oxidative insults are well established triggers of apoptosis [124] and several lines of evidence implicate oxidative stress in the pathogenesis of schizophrenia, especially perinatally [134]. Oxidative stress occurs when the levels of reactive oxygen species (including hydroxyl and superoxide radicals) exceed the antioxidant capacity of a given cell or system.

Patients with first-episode and chronic schizophrenia have lower than normal levels of antioxidant defense enzymes including superoxide dismutase (SOD) activity in red blood cells which suggests an increased vulnerability to oxidative insults [135]. Several lines of investigation also indicate that membrane phospholipid turnover is increased in schizophrenia including increased peripheral activity of the phospholipase A2 system [136–138] as well as increased cortical phosphodiester levels in first episode psychosis by 31P MRS [139].

Psychotropic Drugs Effects

Antipsychotics

Another possible explanation for reduced cancer risk in schizophrenia is the cancer protective effect of antipsychotic medications. Csatary [140] observed an antitumor effect for chlorpromazine; subsequent studies confirmed this effect for other antipsychotic agents in cell culture and mouse models [141–146]. Carrillo and Benítez [147] speculated that the antitumor effect is "related to the modulation by antipsychotic drugs of CYP enzymes involved in mutagen activation and also elimination."

Another possible mechanism whereby antipsychotic drugs could decrease the incidence of hormonally-dependent cancers (e.g., prostate cancer) is by decreasing testosterone. Many antipsychotic agents are known to stimulate the production of prolactin, and galactorrhea is a frequent side effect. Increased prolactin levels are known to suppress luteinizing hormone, follicle-stimulating hormone, and testosterone levels. In support of this, Mortensen, [19] using a case-control cohort, reported that patients with schizophrenia who received a cumulative lifetime dose of 15 g or more of chlorpromazine "had an incidence of prostate cancer approximately one third the incidence".

Laboratory studies [148] have enabled the possibility that some centrally acting dopamine antagonists used for treating psychotic disorders may increase the risk of breast malignancies. Likewise, in clinical studies it is well established that at therapeutic dosages, some of these drugs cause dose-dependent increases in serum prolactin levels, with significantly greater increases in women than in men [149]. In animals, increased prolactin levels can cause malignant transformation of breast tissue [150]. Elevated prolactin levels also promote tumor growth in rodents with induced mammary malignancies [151–153].

Finally, Wang et al. [154] in a retrospective cohort study including 52 819 women exposed and 55 289 not exposed to dopamine antagonists, aged 20 years or older, and initially free of breast cancer, found that the use of antipsychotic dopamine antagonists was associated with a 16% increase in the risk of breast cancer, with a dose-response relationship: the larger cumulative dosages the greater risk. The increased risk was also noted in women who used prolactin-elevating antiemetic dopamine antagonists despite having different breast cancer risk profiles compared with antipsychotic dopamine antagonist users.

Interestingly, dopamine antagonist use was not associated with risk of colon cancer, ie a control condition unrelated to elevated prolactin levels.

Antidepressants

Studies that explored risk for cancer in the use of antidepressants yield inconsistent findings and such information has created considerable confusion, especially in cancer patients [155]. For instance, two clinical studies reported that women

taking the selective serotonin reuptake inhibitor (SSRI) paroxetine had a sevenfold increased risk of breast cancer; those taking the older tricyclic antidepressants, that increase levels of both serotonin and norepinephrine, as well as antagonize histamine-1 receptors, had a twofold higher risk [156]. However, in a subsequent report within that year, the same authors announced that paroxetine was associated with an increased risk of only 70%, instead of the sevenfold reported previously [157].

Antidepressants had previously been reported to promote the growth of some tumors in laboratory tests [158, 159] along with certain antihistamines [160]. In those reports, amitriptyline and fluoxetine, along with the histamine-1 receptor antagonists loratadine, astemizole only in low doses and hydroxyzine, increased melanoma growth in mice; however, high doses did not [161, 162]. Other studies suggested that tricyclic antidepressants (e.g., amitriptyline and desipramine) may increase the risk of breast cancer [163–165]. Yet, there is an unexplained paradox in that many publications report opposite results. For instance, hydroxyzine was shown to be cytotoxic against human breast cancer cells [166] and other histamine-1 receptor antagonists were protective against tumor cell proliferation [167]. Moreover, fluoxetine, imipramine, sertraline, paroxetine and citalopram demonstrated antineoplastic properties, [168–171] elsewhere amitriptyline inhibited the growth of renal cell adenocarcinoma [172]. In fact, amitriptyline, fluoxetine and paroxetine were all found to protect neurons from the damaging effects of stress [173].

Histamine has been reported to promote cancer by stimulating cell division and activating suppressor T-cells [174, 175]. Drugs with histamine-1 receptor antagonist actions have been reported to augment the therapeutic effect of anticancer agents [176]. These drugs bind to an intracellular antiestrogen “histamine receptor” [166, 177] that affects cell growth. This binding site may also explain the antiproliferative effects of the antiestrogen tamoxifen [178] and may be involved in the anticancer effects of select flavonoids [179] with unique structural requirements [180]. Results using an “intracellular histamine antagonist” showed that low doses accelerate tumor growth in rodents, while high concentrations are cytotoxic to many human tumors [162]. To confuse the matter further, *in vivo* human studies with this molecule were suggestive of augmentation of the beneficial effect of chemotherapy [162] and possibly enhancement of the response to cyclophosphamide in advanced hormonally unresponsive prostate cancer [181].

Later studies reported that patients receiving fluoxetine and amitriptyline have increased incidence of cutaneous pseudolymphomas [182] and that drugs with antihistaminic properties contribute to atypical cutaneous lymphoid hyperplasia [183]. However, a careful review of these results showed that the most of patients studied were receiving polypharmacy treatment, of which only tricyclic antidepressants and phenothiazines had histamine-1 receptor antagonist properties, whereas others were SSRIs and benzodiazepines without antihistamine effect [183]. Thus, even though the authors referred to “antihistamines”, it was impossible to clearly conclude what type of drug may have been associated with these benign lesions.

Ascertainment Bias

Because most epidemiological studies reviewed here have been carried out by using official registers, ascertainment bias could be responsible for the findings of reduced cancer risks among mentally ill people [61]. First, because patients with schizophrenia are known to be less compliant with medical advice and care [184] and it increases the chance that they are not detected or are lost at followup following initial screening. Second, because they are also less likely to be undergoing to autopsy in the case of their death, [19] another cause of missing cancer diagnosis in official repertories [61]. However, Catts et al. [65] discount diagnostic ascertainment bias as a reason for their findings, because in many types of cancer the symptoms are very impairing and or painful and are unlikely to go undetected when they had their onset, and because the same reduced risk observed in patients is seen among their relatives, who are less likely to be exposed to ascertainment bias [44, 64, 185].

Conclusion and Future Directions

There are relatively lower rates of some cancers in schizophrenia patients despite their heavy smoking [185] and unhealthy diet and life-style. It is possible that genes responsible for cellular differentiation, proliferation, growth, migration, signal transduction, adhesion [186], metabolism, survival, protection and apoptosis play a role in both schizophrenia and cancer.

Research on the molecular relationships between schizophrenia spectrum disorders and cancer could be relevant to both pathophysiology of schizophrenia and malignancy. The presence of the same genes can increase the risk for schizophrenia but lower the risk for cancer. The identification of the cellular pathways that lead to the neurodevelopmental insults involved in schizophrenia, could contribute to the development of new antipsychotics, as well, the designing of novel therapeutic agents for those types of cancer, whose incidence is indeed reduced in schizophrenia.

Further studies are required to explore the topic in depth. As noted in this review, patients with schizophrenia are not completely immune to cancer, and when they develop such a malignant disease, the course is often critical, due to their noncompliance to therapy and medical follow-up [9, 184].

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Afterword

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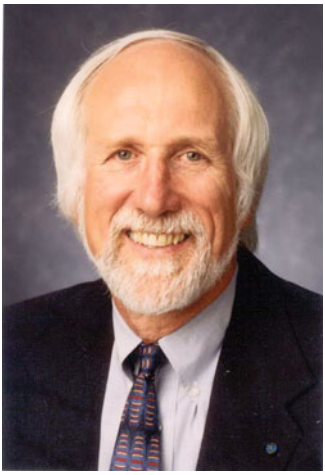

The Future of the Schizophrenia Construct and Acquisition of New Knowledge

Professor Ritsner has presented three volumes containing the accumulated knowledge and wisdom developed in the schizophrenia field. Current knowledge is broad and deep, but fundamental challenges remain. Some are as old as Kraepelin's dementia praecox and Bleuler's group of schizophrenias. "What is schizophrenia?" is still a critical question. The construct used to develop new insights and guide clinical therapeutics has a profound effect on study designs, research questions,

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and etiological and therapeutic discovery. In this Afterword I will briefly comment on the current paradigm and speculate on a shift that will substantially change the construct and the methods of acquiring knowledge.

Is the Kraepelinian dichotomy dead? The porous boundaries observed between schizophrenia and bipolar disorders, as presently defined, suggest the answer is yes. However, it is important to appreciate how much the definition of schizophrenia has changed since he proposed a disease entity based on the co-morbidity of avolition and dissociative pathology. Bleuler's postulate that the dissociative pathology was fundamental and primary in all cases, if true, suggested a psychopathological process uniting the various clinical presentations in a single disease concept. However, seemingly without comment, this idea radically changed as Schneider's symptoms of first rank and Langfeldt's true versus pseudo schizophrenia became influential. Movement in the direction of emphasis on ego boundary impairment and reality distortion symptoms became almost universal with the criteria-based DSM-III. Its revolutionary diagnostic standardization required only a single first rank symptom to meet criteria A for schizophrenia and excluded consideration of avolitional pathology as a diagnostic criteria. Described in more detail elsewhere [1] this movement minimized attention to cognitive pathology and negative symptoms. The porous boundary with bipolar disorder observed in genetic and environmental risk factors, neuroimaging, cognition, and response to anti-psychotic drugs is not a test of Kraepelin's concept. Rather, it may represent, at least in part, the heterogeneity of a syndrome based on psychotic features rather than avolition and dissociative pathology. Investigators at the Maryland Psychiatric Research Center have demonstrated substantial differences between schizophrenia patients with the negative symptom pathology compared to schizophrenia patients without primary negative symptoms [2].

It is essential that we recognize the syndrome status of the psychotic disorders including schizophrenia. Doing so immediately raises the challenge of heterogeneity reduction. Does the overlap between syndromes suggest an artificial distinction, or is it indicative of a proportion of patients in each syndrome manifesting similar pathology? For example, depression pathology will be found in almost all bipolar patients, but also in many patients with schizophrenia. A biomarker for depression would be expected to distinguish both groups from non-depressed controls, but may be more robust in bipolar cases. However, including only depressed schizophrenia patients in the schizophrenia cohort could make the difference disappear. This does not suggest that schizophrenia and bipolar are the same disorder. Rather, it suggests that depressive pathology, found in many different diagnostic groups, may be a domain of pathology that merits investigation across diagnostic classes. It would be surprising if, for example, genes associated with vulnerability to depression were not similar in depressed patients from several diagnostic classes. Rather than a genetic marker for a single diagnostic class, this genetic profile could be viewed as marking vulnerability for depression in several discrete disorders and perhaps in the general population as well.

A paradigm shift is essential to maximize progress in the study of schizophrenia. When we recognize schizophrenia as a syndrome, we realize that attempts to define

specific disease entities within the syndrome have not worked with traditional subtypes, but have had some success based on the presence of deficit pathology [2]. Attempts to define dimensions of pathology have been successful. The challenge, then, is to advance the most heuristic approach to deconstructing pathologies associated with syndromes. In the context of the IPSS we put forward a proposal for six pathology domains in 1974 [3] with substantial overlap with the eloquent analysis by Cuesta and Peralta [4] defining eight pathology domains. In the current DSM-V process (I serve as chair of the psychosis workgroup) a series of pathology domains are being considered in addition to diagnostic class. Schizophrenia and other psychotic syndromes would be deconstructed into relevant dimensions representing the pathologies that vary among patients in the diagnostic class and require specific assessment and therapeutic attention. In drug discovery, for example, the paradigm moves away from developing a drug for schizophrenia. Sixty years of producing similar anti-psychotic drugs without discovery for other key domains of pathology illustrates the limited utility of a clinical syndrome. The shift to a deconstruction paradigm defines multiple and separable targets for drug discovery. Therapies for a pathology domain may thereby be effective in multiple diagnostic classes. If this hypothesis is valid, it will transform the developmental pathway for therapeutic discovery. Just as we now have dopamine antagonists with efficacy for psychosis across diagnostic classes, we may come to have a compound or behavioral treatment approved for cognition, avolition, depression, anxiety, and other pathology domains that cross diagnostic boundaries.

DSM-V development is in progress. In addition to the usual diagnostic classes for psychotic disorders, dimensions for anxiety, depression, mania, restricted affect, avolition, cognition, disorganization of thought, delusions, and hallucinations are being field tested. Thus clinical assessments will more closely fit the individual patient's actual pathology and will position the clinician closer to the issues addressed in personalized clinical care. It may also impact future research designs. Rather than genome-wide association study (GWAS) analyses for genes associated with heterogeneous syndromes, the genetics of specific pathological processes will be addressed. Neuroimaging studies may define the structure, function and chemistry associated with specific pathology domains rather than attempting to define biomarkers for syndromes.

This shift in paradigm is relevant for the future study of pathophysiology. The NIMH is developing research diagnostic criteria (http://www.nimh.nih.gov/research-funding/rdoc.shtml) based on neural circuit concepts of symptom expression. For example, a variety of anxiety and mood disorders may relate to pathology in the fear circuitry involving the amygdala and associated structures. NIMH will encourage investigators to investigate neural circuits related to the symptom or impairment of interest, consider phenotype assessment in animal models and recruit patient subjects from the several diagnostic groups associated with the symptom complex of interest. It is hoped that translational science will be advanced by more clearly assessing genotype/phenotype relationships at the level of brain dysfunction where the neuroanatomy and physiology can be "mapped-on" between human and animal models. This involves explicit recognition of the syndrome status of many

psychiatric disorders where deconstruction into component pathologies is essential, and that patients within each syndrome may vary in the domains of pathology with which they are afflicted.

The impact of this paradigm shift will be substantial. Consider the following examples:

- Instead of searching for genes of heterogeneous syndromes, study designs will seek association of genes with neural circuits, phenotypes and specific domains of pathology.
- Drug discovery will target domains of pathology seeking novel compounds for unmet treatment needs such as cognition and negative symptoms associated with some forms of schizophrenia. Efficacy for a specific domain may be relevant to cases in several diagnostic classes where patients manifest the pathology in question.
- Neuroimaging will focus on anatomy, function and chemistry at the intersection of neural circuit and pathology domain rather than the clinical syndrome level.
- Psychosocial treatments will be directed at pathology that cuts across diagnostic boundaries. Instead of broad-based cognitive remediation for schizophrenia, interventions will be tested with subjects who manifest the target impairment. Thus, tailored CBT will address domains such as depressed affect, avolition, or reality distortion rather than major depressive disorder or schizophrenia.

These three volumes speak to the power and the limitations of the dominant model. A paradigm shift, already reflected in some recent studies, promises a new and more robust approach to understand psychopathology and to more specifically addressing the needs of our patients.

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