Michael S. Ritsner *Editor*

Handbook of Schizophrenia Spectrum Disorders

Volume I

Conceptual Issues and Neurobiological Advances

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

- *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 Michael S. Ritsner
March, 2011

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Chapter 1
The Schizophrenia Construct After 100 Years of Challenges

Michael S. Ritsner and Irving I. Gottesman

Abstract The concept of schizophrenia (SZ) (nee dementia praecox) has been widely used in medicine for the last 100 years. However, major controversies concerning the construct have yet to be resolved. The traditional categorical nosology of functional psychoses is challenged by observations that SZ, schizoaffective disorder (SAD), major depression (MDD) and bipolar disorder (BPD) share clinical presentations, endophenotypes and several genes. The present overview presents various theoretical frameworks for categorical and dimensional models, and specifically their applicability to the fields of epidemiology, genetic epidemiology, genetics and endophenotype studies. It should be noted that clinical dimensions, candidate genes and endophenotypes have not been found to be specific to any one type of functional psychosis. Clinical syndromes, including depression, anxiety, and substance use disorders, co-occur with SZ, SAD, MDD and BPD at appreciable rates. Genetic linkage studies have primarily focused on the phenotype of functional psychoses (SZ, SAD, MDD, and BPD) susceptibility. To date, however, relatively limited work has been conducted to identify the genetic variants associated with symptom dimensions. While the potential advantages of an endophenotype based approach are widely appreciated in the investigation of the genetics of functional psychoses, there is no consensus for achieving this goal. Overlapping endophenotype processes include physiological or electrophysiological anomalies, psychological or neurocognitive deficits and biochemical alterations. Specific challenges need to be addressed in the future if we hope to move forward in our goal to reach meaningful and applicable clinical results. We conclude that we need: (a) a new concept for functional psychoses in order to develop a new classification for research purposes, (b) new and improved clinical assessment tools, (c) to target persons with functional psychoses; and (d) to conduct molecular genetic studies using a number of candidate genes and endophenotypes with measured symptom dimensions and patterns.

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Keywords Functional psychoses · Schizophrenia · Classification · Categorical models · Dimensional models · Genes · Endophenotypes

Abbreviations

BPD	Bipolar disorder
BPRS	Brief psychiatric rating scale
CAPON	carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase
COMT	Catechol-ortho-methyl transferase
CNS	Central nervous system
DAO	d-amino acid oxidase gene
DAOA	d-amino-acid oxidase activator (formerly known as G72)
DAT1	Dopamine transporter 1
DISC1	Disrupted-in-schizophrenia-1
DSM-IV	Diagnostic and statistical manual of mental disorders – 4^{th} edition
DTNBP1	Dysbindin
FP	Functional psychoses
GRIN1, GRIN2	NMDA subtypes of glutamate receptors
GRM3	Glutamate receptor 3 gene
GWAS	Genome-wide association study
HOPA (12 bp)	Mediator of RNA polymerase II transcription (subunit 12 homolog)
5-HTTLPR	The long serotonin transporter promoter region
5-HT_{2C} and 5-HT_{2A}	Serotonin receptor
ICD-10	International classification of diseases and related health problems. 10^{th} Revision.
KCNN3	Potassium conductance calcium-activated channel
MAO_A	Monoamine oxidase A
MDD	Major depressive disorder
MTHFR	Methylenetetrahydrofolate reductase
NRG1	Neuregulin 1
OCD	Obsessive-compulsive disorder
OCS	Obsessive-compulsive symptoms
OPCRIT	Operational criteria checklist of psychotic illness
PANSS	Positive and negative syndrome scale
PPP3CC	Calcineurin
RGS4	Regulator of G protein signaling 4
SAD	Schizoaffective disorder
SANS	Scale for the assessment of negative symptoms
SNPs	Single nucleotide polymorphisms
SPD	Schizotypal personality disorder
SZ	Schizophrenia

The Schizophrenia Construct

Schizophrenia (SZ) is one of the most devastating functional psychoses (FP). It affects about 1% of the world's population, and remains a major challenge for clinical and biological psychiatry. Given the fact that debates about the concept and classification of psychotic disorders have continued throughout the last century, it might be expected that most of the main controversies ought to have been resolved by now (see e.g. [1–10]). But they have not, as is apparent from the contrasting positions presented in this textbook. Mounting evidence indicates that main challenges have focused primarily on the following: diagnostic criteria and their stability over time, validation of categorical models, integration of dimensional approaches to diagnosis, genetic epidemiology, molecular genetics, endophenotypes and identification of persons at early risk [11–26]. Three main concepts or models attempt to account for the symptom polymorphism of functional psychoses: *unitary, categorical, and dimensional*.

A Unitary Concept

'Unitary psychosis' is the collective name for a set of disparate doctrines whose common denominator is the view that there is only one form of psychosis and that its diverse clinical presentations can be explained in terms of endogenous and exogenous factors [27]. Unitary psychosis connotes an absence of psychopathologically ascertainable nosological entities and points rather to a wide variety of disease variations that converge. The idea of a unitary psychosis is thus contrary to the concept of natural nosological entities or multiple and distinguishable psychoses which show individual symptomatology, etiology, and course [27, 28]. There are insufficient data to confirm or refute the unitary concept at present.

Categorical Models

The historical development of these models has been repeatedly described (e.g. [5–8, 26, 29]) (Fig. 1.1). Briefly, Kahlbaum [30] proposed a classification based on *symptoms, course and bad vs. good outcomes*. Later, in the year 1878, Emil Kraepelin [31, 32] based on *bad vs. good outcomes* presented *dementia praecox* (emotional dullness, lack of interest and apathy) and *manic-depressive disorder* as two naturally-occurring disease entities. Eugen Bleuler [1] gave *dementia praecox* its current name '*schizophrenia*' (SZ) based on the loosening of associations, which preceded both fundamental (*affective and thought disturbances, ambivalence and autism*) and accessory (*hallucinations, delusions and catatonic symptoms*) symptoms. He wrote: "I call dementia praecox 'schizophrenia' because (as I hope to demonstrate) the 'splitting' of the different psychic functions is one of its most

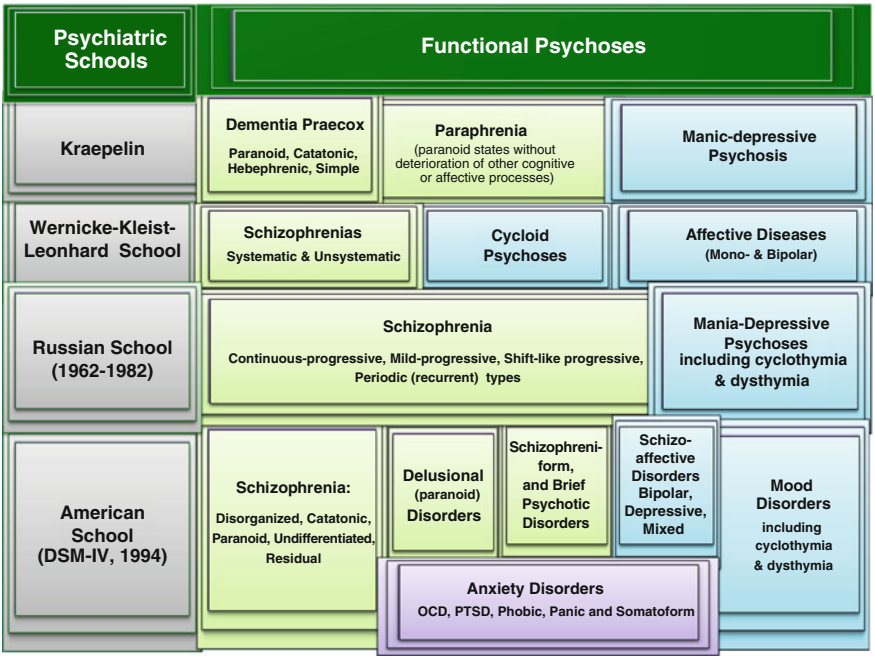

Fig. 1.1 A suggested typology of the functional psychoses. © M.S. Ritsner & I.I. Gottesman (2011) and used by permission

important characteristics. For the sake of convenience, I use the word in the singular although it is apparent that the group includes several diseases" (p 8). Later, Langfeldt [33] divided schizophrenia into nuclear SZ with poor prognosis, and schizophreniform psychoses, with an acute onset and good prognosis.

The *German model*, of the Wernicke-Kleist-Leonhard school, is based on sophisticated clinical descriptions and hierarchical symptom patterns that occur during the long-term course of psychiatric disorders [34]. Psychoses exhibiting "schizophrenic symptoms" need to be divided into three distinct clinical subgroups: *unsystematic and systematic schizophrenias, and cycloid psychoses* [35, 36].

The *Russian-Soviet model* [37–39] of the classification of schizophrenia developed at the Institute of Psychiatry of the Academy of Medical Sciences of the USSR, the criterion for differentiation within the group of schizophrenias is the course of the illness. Three main forms are distinguished depending on whether the course is continuous, recurrent, or "mixed"; and these are thought to differ from each other in terms of symptoms, development, response to treatment, and pathogenesis. The subtypes of continuous schizophrenia are (a) "sluggish," (b) "moderately progressive (paranoid)," and (c) "malignant juvenile." Several operational criteria have been developed to establish the diagnosis of SZ, making it obvious that there are no precise diagnostic boundaries. For example, sluggish SZ is viewed not as an initial

(prodromal) stage of SZ, but rather as an independent diagnostic category characterized by a slow progressive course, subclinical manifestations in the latent period, overt psychopathological symptoms in the active period, and then by a gradual reduction of positive symptoms, with negative symptoms predominating the clinical picture during patient stabilization [40]. Unfortunately, the "sluggish" ("latent") form of schizophrenia has been used for *political purposes in the Soviet Union*. Clearly, the use of diagnoses such as sluggish schizophrenia exposes fundamental deficiencies in the reliable and valid definition and classification of psychiatric disorders.

The *American model* requires the presence of psychotic features, established chronicity, evidence of deterioration, and the exclusion of affective and organic features [41]. The diagnostic criteria for SZ in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [42] are based on the premise that it is a discrete illness entity, in particular, distinct from the affective psychoses. A variety of psychotic syndromes has been described which have features in common with the so-called schizophrenic psychoses (DSM-IV): schizophrenia (295.x), schizophreniform disorder (295.4), schizoaffective disorder (295.7), delusional disorder (297.1), brief psychotic disorder (298.8), shared psychotic disorder (297.3), psychotic disorder due to (specify medical condition, 293.x), substance-induced psychotic disorders (293.x), delusional disorder (297.1), psychotic disorder NOS (298.9). The validity of schizophreniform disorder (295.4), brief psychotic disorder (298.8), and shared psychotic disorder (297.3) remains controversial and their diagnosis has limited clinical utility. For instance, findings from prior research suggests that cases of schizophreniform disorder may be: (1) atypical cases of affective disorders, (2) cases of schizophrenia in early course, or (3) a heterogeneous group of disorders including a subgroup with benign course and outcome that maintains this diagnosis for less than 6 months.

The International Classification of Diseases and related Health Problems (Tenth Revision; ICD-10) [43] classifies SZ together with schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders, induced delusional disorder and schizoaffective disorder. This classification avoids criteria based on social and occupational dysfunction for the diagnosis of SZ on the grounds that it is difficult to compare these criteria across different cultures.

Thus, in the current categorical classifications of diseases (DSM-IV and ICD-10), SZ, as well as other disorders, are seen as a categorical entity that includes both clinical (symptoms) and outcome (duration) items. However, because the definition of SZ requires only a certain number of items without any preference, it is not uncommon for two patients with the same diagnosis to have almost totally different symptomatology, while outcomes within the SZ diagnosis vary considerably [29]. The diagnostic criteria for SZ are based on the premise that it is a discrete illness entity, in particular, distinct from the affective psychoses. This assumption has persisted for more than a century, even though patients with a diagnosis of schizophrenia show a wide diversity of symptoms and outcomes, and no biological or psychological feature has been found to be pathognomonic of the disorder [26, 44–46].

The Concept of Schizoaffective Disorder. The clear-cut distinction between SZ and BPD rapidly began to lose strength in the concept of schizoaffective psychoses [47]. The term schizoaffective disorder (SAD) reflects the acceptance of intermediary states, in which the symptoms of SZ and BPD mingle [6, 48]. The concept of SAD covers favorable as well as unfavorable forms of FP that do not contribute to nosological classification [49]. Schizoaffective disorder has been shown to cluster with both SZ and BPD in families [50, 51]. Many follow-up investigations demonstrated that SAD patients can manifest, over their lifetime, manic, depressive, catatonic, hebephrenic and other psychotic syndromes, the course and outcome of which take an intermediate position between SZ and BPD [52]. Heckers [53] highlights the difficulty of the longitudinal diagnosis due to the lack of reliable information and the doubtful accuracy of self-report, especially from a patient with psychosis. Distinctions of SAD compared to SZ and BPD disorder are not clearly defined by findings from neuropsychological, neuroimaging, molecular neurobiology, or genetic epidemiology studies [54, 55].

Despite its uncertain nature, SAD is widely diagnosed: between 5.7 [56] and 8% [57] of psychotic patients met the criteria for SAD. There are a few alternative models that account for individuals presenting with mixed psychotic and affective symptoms: (a) SAD is a comorbid set of symptoms that occur as a by-product of two separate disorders (SZ and BPD) or, that (b) SAD exists as the mid-point on a continuum between SZ and BPD, such that the incorporation of these two disorders onto one dimension may be a suitable alternative [54]; and that (c) SAD is simply a more severe form of affective disorder; a third type of psychosis or a variation of SZ.

Since the reliability of the diagnosis is equivocal [58], it has been suggested that SAD should be eliminated from the diagnostic nomenclature (e.g. [59]). However, recent reviewers have continued to recommend a diagnostic separation along the continuum from psychosis to mood disorder [54, 60–62].

Dimensional Models

These models postulate *a continuum of psychosis* ranging from self-reported psychotic symptoms in the general population, to schizotypal traits, to schizotypal personality disorder, and finally to full-blown psychosis resulting in a diagnosable primary psychotic disorder. It would appear that psychotic symptoms, whether perceptual or involving thought processes, are fairly common occurrences within a general population not necessarily diagnosed with a psychotic disorder in accordance with the categorical model, be it DSM or ICD. Indeed, the incidence of positive psychotic experiences in the general population is approximately 100 times greater than traditional estimates of the incidence of psychotic disorder such as SZ [63]. Hallucinations, delusional ideas and other more subtle reflections of psychotic thought processes might occur in ordinary mental life [64–66]. Approximately 21% of children, 11–12 years old, experience hallucinations [67]. Consequently, these

psychotic incidents can be looked upon as part of a dimensional continuum that are magnified as a result of various genetic and environmental factors rather than as rigid diagnostic criteria for disorders [68]. Thus, we have at least three axes of the continuum: (a) within affected persons (SZ, SAD, MDD, BPD), (b) from affected persons to non-affected persons in the general population, and (c) among relatives of probands with FP.

Psychotic symptoms such as hallucinations and delusions, disorganized speech and behavior, and negative symptoms are distributed along a continuum that extends from SZ to psychotic mood disorders [69–71]. Regarding the number of putative symptom dimensions, there is some consensus that there are 3–6 symptom dimensions underlying the latent structure of FP (Table 1.1). Repeat examinations of patients revealed results that further support the validity, internal consistency and inter-rater reliability of the PANSS factor models of SZ psychopathology [72–78]. In addition, poor insight [79, 80], elevated emotional distress [81, 82], cognitive [83–85] and quality of life impairments [86], disruption of everyday functioning [87–90] should be added to phenotypic characteristics of functional psychoses.

Table 1.1 Syndrome dimensions underlying functional psychosis

Syndrome dimensions	References
Type I consisted of positive symptoms such as delusions and hallucinations.	Crow [227, 228]
The type II syndrome is more or less chronic and is characterized by negative symptoms, such as flattening of affect, poverty of speech and loss of drive; these symptoms are related to poor outcome, poor response to neuroleptic drugs, and structural pathology in the central nervous system.	
Positive and negative symptoms	Andreasen and Olsen [229]
Positive, negative, and general psychopathological scales	Kay et al. [230]
Positive, negative, excited and depressed, cognitive dysfunction, suspiciousness and stereotypic thinking	Kay, Sevy [231]
Anergia, thought, activation, paranoid, and depression factors	Kay [232]
Psychomotor poverty, disorganization, and reality distortion	Liddle [72]; Peralta, Cuesta [73]; Keefe et al. [74]
Negative, psychoticism, disorganization	Arndt et al. [233, 234]; Andreasen et al. [235]
Negative, positive, excited, cognitive, anxious/ depressive	Lindström, Von Knorring [236]; Lindenmayer et al. [237]
Negative, positive, activation, dysphoric mood and autistic preoccupation factors	White et al. [75]
Negative, positive, cognitive, excitement and depression components	Lindenmayer et al. [237]; Lançon et al. [76]

Moreover, there is clearly an increased prevalence of *anxiety, depressive, and substance abuse disorders* in patients with SZ than in the general population [91–93]: 15% for panic disorder, 29% for posttraumatic stress disorder, and 23% for obsessive-compulsive disorder (OCD); 47% of patients also have a lifetime diagnosis of comorbid substance abuse [94]; anxiety symptoms could occur in 60% of patients with chronic psychotic disorder [93]. Cunill et al. [95] reviewed 23 studies, (18 articles provided usable data for the meta-analysis). The presence of obsessive-compulsive symptoms (OCS) or obsessive-compulsive disorder (OCD) is common in patients with SZ. The presence of OCS was significantly associated with greater severity of global psychotic symptoms (standardized mean difference, 0.39), positive symptoms (0.28), and negative symptoms (0.36). A meta-analysis revealed that the presence of OCS in SZ is associated with higher global, positive, and negative symptoms. This association was not found when a categorical definition of OCD was used. Regarding depressive symptoms, it is estimated that comorbid depression occurs in up to 40% of patients with chronic psychotic disorder [93]. For each of these comorbidities, their presence is generally associated with more severe psychopathology and with poorer outcomes.

Overall, current data indicate that the functional psychoses are best understood not only categorically but with some provision for dimensionality [16, 96, 97] since setting the boundaries for psychosis is not a limiting problem in dimensional models as it is in categorical models. Converging evidence from critical studies comparing categorical and dimensional models of functional psychoses demonstrated that symptoms and life time course, risk factors, endophenotypes, and putative neurobiological underpinnings are better explained in terms of continuous distributions [98]. A promising and useful line of research for assessing the validity of competing definitions or continuum models in FP is to establish a strategy that combines multidimensional and polydiagnostic approaches to define clinical markers or phenotypes [99]. Nevertheless, two problems arise when including the dimensional approach to diagnosis in an official nomenclature: (a)there is no widely tested and accepted system of dimensional diagnosis, and (b) clinicians find the added work of rating dimensions burdensome [100].

For the diagnosis of neuropsychiatric disorders, a categorical classification system is often utilized as a simple way for conceptualizing an often complex clinical picture. This approach provides an unsatisfactory model of mental illness, since in practice patients do not conform to these prototypical diagnostic categories. Deo et al. [101] introduced an analytic framework to dissect the phenotypic heterogeneity present in complex psychiatric disorders based on the conceptual paradigm of a continuum of psychosis. The approach identifies subgroups of behavioral symptoms that are likely to be phenotypically and genetically homogenous. The authors have applied this approach to a psychiatric dataset of a genome scan for schizophrenia that includes extensive behavioral information and that has identified significant evidence for linkage among depressed individuals with two distinct symptom profiles.

Genetic Epidemiology

Family, twin and adoption studies have demonstrated a high heritability of SZ and BPD disorder [102–106]. Early estimations of the load of SZ in families show high rates compared to population estimates. Figure 1.2 presents data compiled from 40 family and twin studies in European populations from 1920 to 1987. However, the registration of probands at a psychiatric hospital (conventional sampling method) leads to over-estimation of the number of persons affected in their families.

For example, the ascertainment of probands according to place of residence in the community has enabled the sampling to be representative of whole subpopulations of patients in the Tomsk region (Russia) [107–111]. Probands from psychiatric hospitals ($n = 452$, "clinical sample") are characterized by biased prevalence of SZ among the first degree relatives ($R_I = 6.29\%$) compared to relatives of a community-based ("epidemiological") sample of 229 probands ($R_I = 2.88\%$) (Table 1.2). Table 1.3 gives estimated lifetime prevalence rates (over 15 years, PR) and lifetime morbid risks (MR) of schizophrenia among 26,449 first-degree relatives of SZ probands of a large number of family studies (data and references see [103]). The lifetime PR = MR for groups of siblings and offspring, and the estimate PR>MR only among parents ($10.5 > 5.7\%$, $p < 0.001$). Therefore, the lifetime MR estimate for first degree relatives is on average lower (8.3%) as compared with the lifetime PR (10.5%, $p < 0.001$). Thus, values for lifetime PR for parents, siblings, and offspring are just the same (corresponding to the proportion of the genes shared with the proband), but values for lifetime MR for parents are significantly lower ($p < 0.01$) than MR for siblings and offspring.

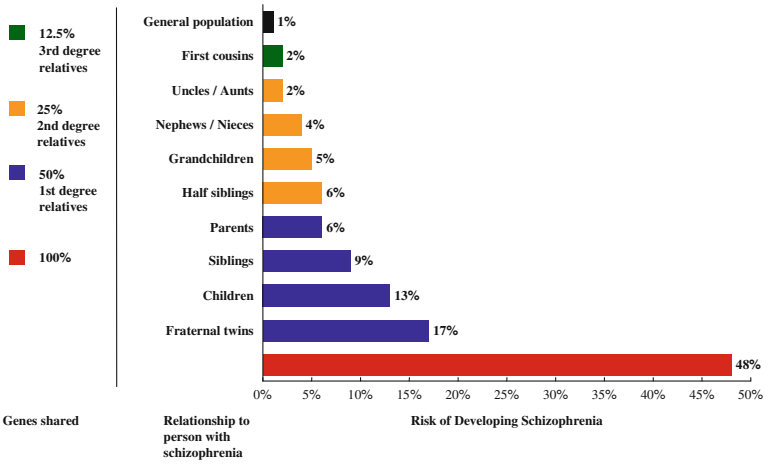

Fig. 1.2 Lifetime age-adjusted, averaged risks for the development of schizophrenia-related psychoses of relatives differing in their degree of genetic relatedness [369]. Note. Compiled from the 40 family and twin studies in European populations from 1920 to 1987. © I.I. Gottesman (2004) and used by permission

Table 1.2 Prevalence of schizophrenia (ICD-9) among relatives of probands (findings from the Tomsk Genetic Epidemiological Study of Schizophrenia [109])

Category of relatives	Epidemiological sample (n=452 probands)			Clinical sample (n=229 probands)		
	Number of relatives	Schizophrenia		Number of relatives	Schizophrenia	
		N	%		N	%
Parents	819	25	3.05**	439	26	5.92**
Siblings	1,005	28	2.79**	383	26	6.79**
Offspring	303	8	2.64**	52	3	5.77**
First degree (R_I)	2,127	61	2.88**	874	55	6.29**
Half sibling	116	0	–	67	1	1.49
Grandparents	790	5	0.63	541	3	0.55
Uncles, aunts	1,532	18	1.17	908	15	1.65
Grandchildren	28	0	–	2	0	–
Nephews, nieces	700	5	0.71	207	2	0.97
Second degree (R_{II})	3,166	28	0.88**	1,725	21	1.22**
Third degree (R_{III})	1,528	14	0.92*	815	4	0.49

Comparison with population frequency: *p < 0.01; **p < 0.001.

Table 1.3 Lifetime morbid risks and lifetime prevalence of schizophrenia among relatives of probands (compiled data) [103, 109]

Category of relatives	Age-corrected values	Number of relatives	Affected		Significance p
			N	Percent ± SE	
Parents	MR	8,919	512	5.7 ± 0.2	<0.001
	PR	2,520	264	10.5 ± 0.6	
Siblings	MR	10,463	1036	9.9 ± 0.3	>0.05
	PR	2,815	295	10.5 ± 0.6	
Offspring	MR	1,247	167	13.4 ± 1.0	>0.05
	PR	485	52	10.7 ± 1.4	
First degree	MR	20,629	1715	8.3 ± 0.2	<0.001
	PR	5,820	611	10.5 ± 0.4	

MR – lifetime morbid risk.
PR – lifetime prevalence data (over 15 years).
SE – standard error.

According to the data of a large number of family studies, SZ lifetime prevalence rates and morbid risks among first–degree relatives of patients run 5–14% [103], which corresponds to the lifetime prevalence date (6.29%) in the "clinical sample". The lifetime morbid risk estimates for nonselected groups of patients are 2–3 times lower, constitute 2–4% [112], and resemble lifetime prevalence data in the epidemiological sample (2.88%). Thus, the ascertainment of probands according to place of residence provides important results which appear to contradict those produced by conventional sampling methods.

Family studies of mood disorders have consistently demonstrated that first degree relatives (R_I) of BPD-I probands are 8–18 times more likely than are the R_I of healthy subjects to have BPD-I and 2–10 times more likely to have major depressive disorder (MDD). Prior literature provides evidence that SZ, SAD, MDD and BPD can occur in the families of either of the disorders [102]. Recently, Laursen et al. [113] investigated the magnitude of the overlap between the clinical diagnoses of SZ, SAD and BPD over a 35-year period based on the entire Danish population. The authors found a large comorbidity index between SZ and SAD, as well as a large index between BPD and SAD. Furthermore, a substantial comorbidity index between BPD and SZ was present.

Van Snellenberg, de Candia [114] systematically reviewed family studies of probands with SZ and BPD published from January 1, 1980, to December 31, 2006. Of the original 2,326 studies identified through the database search, 38 studies were used to investigate rates of BPD in R_I of probands with SZ, while 39 studies were used to examine rates of SZ in R_I of BPD probands. The R_I of probands with SZ showed significantly increased rates of BPD relative to control R_I (odds ratio [OR] = 2.08). The R_I of probands with BPD showed marginally ($p = 0.06$) increased rates of SZ relative to control R_I (OR = 2.10); this analysis was significant ($p = 0.02$) when studies that did not report morbid risk estimates were excluded (in this case, OR = 3.49). *This meta-analysis provides direct evidence for familial coaggregation of SZ and BPD, a finding that argues against the view that these disorders are entirely discrete diagnostic entities*.

Lichtenstein et al. [115] linked the multi-generation register, which contains information about all children and their parents in Sweden, and the hospital discharge register. The analysis, which included more than 9 million individuals from more than 2 million families over a 30-year period between 1973 and 2004, individuals with either SZ or BPD. In particular, authors found that siblings of probands with SZ had a significantly increased risk for SZ and BPD than the general population. When relatives of BPD probands were analyzed, there was an increased risk for SZ for all relationships, including adopted children to biological parents with BPD. Heritability for SZ and BPD was 64% and 59%, respectively. The comorbidity between disorders was mainly due to additive genetic effects common to both disorders. *These results challenge the current nosological view that SZ and BPD are separate and distinct conditions*.

Gottesman and his collaborators [116] in Denmark tapped an enviable database; it contained national registry data on the over 2.6 million people alive in Denmark in 1968 or later and whose both biological parents had been identified in the same registry. Among the SZ * SZ parent couples 27.3% of 270 children had been discharged with a SZ diagnosis by age 52. When only one parent had been treated for schizophrenia (SZ*N, non-affected), 7% of 13,878 offspring had also received this diagnosis. In contrast, the incidence dropped to 0.86% in the children of couples (N * N) in which neither member had received any diagnosis during the study. When the phenotype included schizophrenia-related disorders (schizoid personality disorder, paranoid disorders, SAD, and various psychoses other than BPD), the percentage of offspring with related disorders rose to 39.2% among the SZ * SZ

couples. Similar findings emerged for BPD: among the BPD*BPD couples 24.9% of their 146 offspring had BPD. When one parent had bipolar disorder and the other no psychiatric history (BPD ∗ N), the percentage of treated children fell to 4.4%. In comparison, only 0.48% of children born of two parents never receiving any diagnosis(N * N) received treatment for it themselves. Couples with one parent SZ and the other BPD resulted in offspring with a cumulative incidence of 15.6% for SZ and 11.7% for BPD. Statistically, their risk did not differ from that of subjects who owed their start in life to one diagnosed parent and an apparently healthy one, but the researchers ascribe that to small group sizes.

Thus, these genetic epidemiological studies support the existence of an overlap between SZ, SAD, MDD and BPD thus challenging the strict categorical approach used in the current classification systems.

The Concept of Schizophrenia Spectrum Disorders. This concept explains a high frequency of persons with personality disorders, pseudoneurotic schizophrenia, schizotypal personality disorder, borderline and latent schizophrenia among relatives of probands with SZ [53, 117–122]. The current version of the DSM-IV-TR recognizes SZ, SAD, MDD, BPD schizophreniform and brief psychotic disorders, delusional disorder and shared psychotic disorder, personality disorders (i.e., schizotypal, paranoid, and schizoid personality disorder).

Investigation of the prevalence of mental illness among the biological and adoptive relatives of schizophrenic adoptees showed a significant concentration of chronic SZ (5.6%) and latent schizophrenia (14.8%) in the biological relatives (first and second degree relatives) of SZ adoptees [123]. Lenzenweger and Loranger [124] examined the morbid risk of SZ, MDD, and BPD in the first-degree relatives of 101 nonpsychotic psychiatric probands who were classified as schizotypy (+) or schizotypy (-) using the Perceptual Aberration Scale. The relatives of schizotypy(+) probands were significantly more likely to have been treated for SZ than the relatives of schizotypy (-) probands.

There is a specific familial association between schizophrenia-related personality disorders, and clinically diagnosed schizotypal personality disorder (SPD) patients [125]. Possible relatedness of SPD to SZ was analyzed by coefficient genetic correlation (r_g) between liability to SZ and liability to SPD, and by multifactorial threshold model (MTF) using two pedigree samples: 357 probands with SZ and 168 probands with SPD [111]. A high rate of SZ was found in relatives of both samples, but any excess of SPD was found only in relatives of the SPD sample (Table 1.4). Based on these data, the hypotheses assuming a single liability with two thresholds and different liability for both disorders were rejected ($r_g = 0.61$). This result demonstrates the existence of both different and common genetic factors for SZ and SPD or the interaction between these factors.

Furthermore, Table 1.5 provides estimates of the liability of SPD and SZ reached by using the MTF model. As can be seen, this model shows very modest specificity differences for any of these disorders. Thus, this study suggests that SZ and SPD are separate states and that some of the factors that contribute to susceptibility for SPD influence the development of SZ, but not vice versa. Several studies show similarities between SPD and SZ with respect to structural neuroimaging studies

Table 1.4 Coefficient genetic correlation (r_g) between liability to schizophrenia and liability to schizotypal personality disorder [111][a]

	First degree relatives						
		Schizophrenia		Schizotypal personality disorder			
Probands' diagnosis (N)	N	N	%	N	%	χ^2	r_g
Schizophrenia (n=357)	1761	42	3.38	8	0.45	3.2	0.61
Schizotypal personality disorder (SPD; n=168)	626	16	2.56	9	1.44		

[a]Prevalence rate of schizophrenia = 0.29%, and schizotypal personality disorder = 0.14%.

Table 1.5 Multifactorial Threshold (MTF) Model liability to schizophrenia and to schizotypal personality disorder [111]

Relatives	Affected (%)	Correlation in liability r_R (± SD)	Components of variance[a], % (± SD)
Phenotype: Schizophrenia			
Parents, children	2.06	0.25 (0.03)	$G_A = 49.2$ (8.9)
Siblings	2.75	0.30 (0.03)	$E_u = 7.0$ (2.8)
Second degree	0.87	0.13 (0.02)	$E_w = 43.8$
Third degree	1.00	0.15 (0.04)	
Phenotype: Schizotypal personality disorder			
Parents, children	2.01	0.37 (0.05)	$G_A = 59.3$ (11.5)
Siblings	0.72	0.23 (0.08)	$E_w = 40.7$
Second degree	0.16	0.07 (0.06)	
Third degree	0.17	0.07 (0.09)	

[a]The decomposition of phenotypic variance included the following components: additive autosomal (G_A), systematic environmental of "single generation" (E_u), and residual environmental (E_w).

[126–129]. They differ, however, in that both do not show psychotic symptoms (see reviews [130, 131]).

Thus, the concept of schizophrenia spectrum disorders is the result of a categorical diagnostic system and has resulted in the idea that schizophrenia may be one extreme of a continuum, which is a phenotypic representation of a liability to functional psychoses.

Familiality of Schizophrenia

Studies which have investigated the familiality of SZ phenotypic variability have consistently shown a substantially earlier illness onset [132–134], higher severity of negative symptoms [135–137], poorer outcome and higher rehospitalization rate [138, 139] among patients with than without a family history of SZ. Particularly,

Malaspina et al. [137] assessed family history and the deficit syndrome in 99 patients with DSM-III-R-diagnosed schizophrenia who were assessed during clinical treatment. The authors found that (a) patients with a family history of schizophrenia had greater and more treatment-resistant negative symptoms than those without a family history, and (b) the group with a family history had more severe negative symptoms related to psychosocial function. Wickham and associates [134] reported that premorbid functioning, mode of onset, and course of schizophrenia are familial.

Studies that investigated both a genetic association with phenotypic variability and the familiality of clinical polymorphism have at least two serious limitations. First, previous research has focused on the cross-sectional measures of symptoms in schizophrenia though it may not be stable at different phases of the illness, and dimensions of psychopathology show different patterns of exacerbation and remission during the course of illness [140, 141]. Second, severity of symptoms also associated with poor insight [142] and side effect [143] domains were omitted in the above-mentioned studies. In order to address these limitations, Ritsner and associates [144] examined stability associations between family history and variability of PANSS dimensions repeatedly examined during a naturalistic 16-month follow-up study of 69 patients with familial and 79 patients with sporadic schizophrenia, at hospital admission and at stabilization stage. Analysis showed that schizophrenia patients with positive family history have significantly higher PANSS dysphoric, activation and negative factor scores. However, familiality of PANSS activation and negative factors were dependent on additional variables such as age of onset (both factors), baseline ratings, insight, and side effects (negative factor). No significant association of family history with intensity of PANSS positive and autistic preoccupation factors was found. Thus, familial schizophrenia is characterized by higher *severity of dysphoric mood factors* including PANSS items of anxiety, tension, guilt, depression and somatic concern that may represent impaired emotional reactivity.

Finally, Simonsen et al. [145] asked whether neurocognitive dysfunction in schizophrenia spectrum disorders depends more on history of psychosis than diagnostic category or subtype. Neurocognitive function was measured among persons with SZ (n = 102), SAD (n = 27), and BPD (I or II) with history of psychosis (n = 75) and without history of psychosis (n = 61) and healthy controls (n = 280). Obtained findings suggest that neurocognitive dysfunction in BPD and SZ spectrum disorders is determined more by history of psychosis than by DSM-IV diagnostic category or subtype, supporting a more dimensional approach in future diagnostic systems.

Candidate Genes

Many putative susceptibility genes are being identified weekly, arising both from positional cloning and candidate gene approaches. Despite intensive research and spectacular advances in molecular biology, however, no single gene variation has been consistently associated with a greater likelihood of developing FP. Molecular genetic studies have implicated genes related to dopaminergic, serotonergic and

glutamatergic neurotransmissions, GABA, and candidate genes with other mechanisms. Genetic linkage studies in schizophrenia have primarily focused on the phenotype of disorder susceptibility. There is evidence for significant associations between SZ and specific genes: neuregulin 1 (*NRG1*), dysbindin (*DTNBP1*), disrupted-In-Schizophrenia-1 (*DISC1*), the catechol-*O*-methyl transferase gene (*COMT*), d-amino-acid oxidase activator (DAOA, formerly known as G72), regulator of G protein signaling 4 (*RGS4*), *NOGO receptor 1*, calcineurin (*PPP3CC*) and the carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase (*CAPON*) [146–160]; see also web-resources: http://www.polygenicpathways.co.uk, and http://bioinfo.mc.vanderbilt.edu/SZGR.

To date, however, relatively limited work has been conducted to identify the genetic variants associated with symptom dimensions. For example, Wilcox et al. [161] conducted a genome-wide linkage scan of symptoms measured by the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms in schizophrenia, in a study of 51 families (n = 136). These analyses revealed suggestive linkage to chromosomes 6, 9, and 20 for the *disorganized symptoms* and to chromosome 12 for the *negative symptoms*. DeRosse et al. [55] reported that lifetime severity of positive symptoms was significantly associated with single-nucleotide polymorphisms (SNPs) within the origin recognition complex subunit 3-like (ORC3L) gene, a gene implicated in synaptic plasticity. The level of *disorganized symptoms* was significantly associated with 2 SNPs within the brain-specific angiogenesis inhibitor 3 (BAI3) gene, which is highly expressed in the brain during development. These data point toward specific candidate genes located within previously implicated linkage peaks for clinical symptomatology.

Figure 1.3 summarizes significant associations of specific genes with the symptom dimensions of SZ (see review [160]). As can be seen, there is overlap in associations between symptom dimensions and candidate genes. For example, significant relationships have been identified between the DISC1, HOPA, KCNN3, RGS4 and MTHFP genes and the severity of positive and negative symptoms in patients with SZ, as well as between DTNBP1, 5-HT, CYP206, DAOA and 5-HTTPLR and negative symptoms. In addition, DAOA, 5-HTTPLR and COMT genes are associated with severity of depressive symptom dimensions, while the COMT gene showed significant association with positive and mania symptom dimensions. Based on these data, it seems likely that susceptibility genes may influence the clinical presentation of the illness.

According to recent knowledge there are probably many multiple susceptibility genes (e.g. COMT, BDNF, 5-HTT, NRG1, DISC1, BDNF, DTNBP1, DGKH, CACNA1C, ANK3, DAOA) involved in the pathogenesis of both SZ and BPD, each of small effect, that challenge the current concepts of disease classification [157, 162–168]. Additional evidence appears weekly in the major neuroscience journals.

1. Vesicular monoamine transporters (VMATs) are involved in the presynaptic packaging of monoaminergic neurotransmitters into storage granules. The gene encoding VMAT1 is located on chromosome 8p21, a region implicated in linkage studies of SZ, BPD, and anxiety-related phenotypes [169].

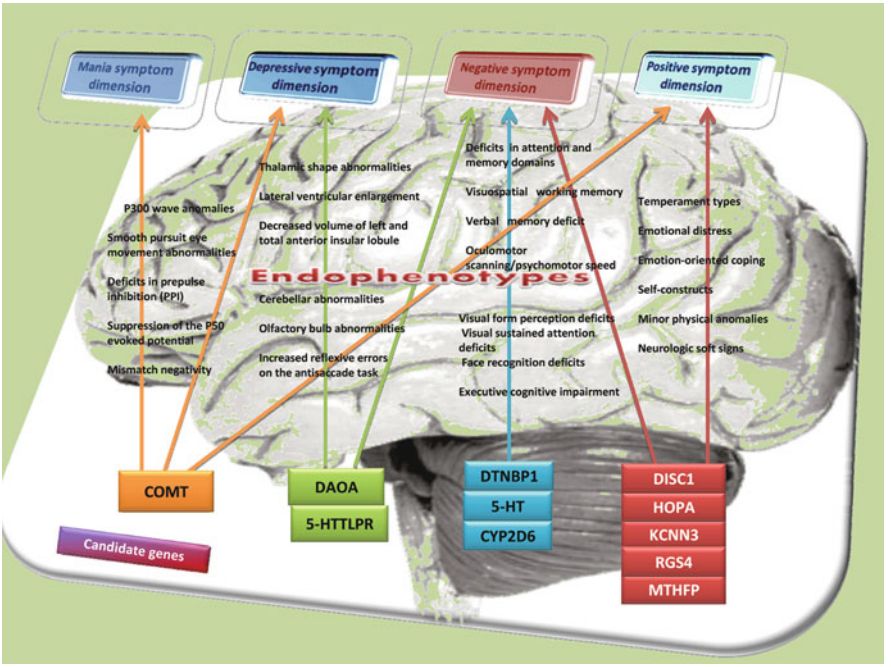

Fig. 1.3 From genes through endophenotypes to clinical dimensions. Associations between genetic polymorphism and symptom dimensions in schizophrenia measured with PANSS; BPRS; SANS; and OPCRIT (the Operational Criteria Checklist of Psychotic Illness). *Negative symptoms*: 5-HTTLPR [346, 347], 5-HT_{2C} [348], 5-HT_{2A} [349], DAOA [350], KCNN3 [351, 352], MTHFR [353], DTNBP1 [354–356], DAT1 [357], HOPA (12bp) [358], DISC1 [359]. *Positive symptoms*: COMT [360], MTHFR [353], HOPA [361], DISC1 [359], DISC1 [362], RGS4 [363], NRG1 [364], 5-HTTLPR [347], KCNN3 [352]. *General psychopathology*: 5-HTTLPR [346], 5-HT_{2C} [348], RGS4 [365]. *Depression factor*: DAO/DAOA [350, 366], 5-HTTLPR [367], COMT [368]. © M.S. Ritsner & I.I. Gottesman (2011) and used by permission

2. Candidate-gene based population and family association studies have implicated some ionotrophic glutamate receptor genes (GRIN1, GRIN2A, GRIN2B and GRIK3), metabotropic glutamate receptor genes (such as GRM3) and GABAergic genes (e.g. GAD1 and GABRB2) in both SZ and BPD to varying degrees, but further replication studies are needed to validate these results (for review see [170]).
3. Angiotensin-converting enzyme (ACE) insertion/deletion polymorphism was associated with SZ and BPD: DD genotype and D allele distributions in BPD patients and their first-degree relatives were significantly higher than those of SZ patients, their relatives, and controls. SZ and BPD characterized by similar or different gene variant in ACE could be a useful marker for these psychiatric disorders [171].
4. A cytogenetic abnormality and rare coding variants identify the lipid transporter gene ABCA13 as a candidate gene in SZ, MDD, and BPD [172]. Published

studies suggest associations between circadian gene polymorphisms and BPD-I, SAD and SZ [173].

5. YWHAH (22q12.3) is a positional and functional candidate gene for both SZ and BPD [174].
6. Mitochondria are intracellular organelles crucial in the production of cellular energy. A growing body of evidence suggests that mitochondrial dysfunction is important in patients with SZ, MDD and BPD [175].
7. Molecular genetics and developmental studies have identified 21 genes (ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, DPYSL2, EGR3, FGF17, FGF20, FGFR1, FZD3, LDL, NAT2, NEF3, NRG1, PCM1, PLAT, PPP3CC, SFRP1 and VMAT1/SLC18A1) that are most likely to contribute to neuropsychiatric disorders (SZ, BPD, MDD, autism, Parkinson's and Alzheimer's disease) and cancer (for review see [176]).
8. Chromosome 13q13-q14 locus overlaps SZ and BPD [177].
9. Most of the genomic DNA sequence differences between any two people are common (frequency >5%) single nucleotide polymorphisms (SNPs). For psychiatric disorders, there are initial significant findings for common SNPs and for rare copy number variants, and many other studies are in progress. Genome-wide association (GWAS) studies of SZ and BPD have implicated some chromosomal regions in common; this is consistent with the presence of shared susceptibility genes [178, 179]. This has lead to the assumption that SZ is not only a genetically defined static disorder but also a dynamic process leading to dysregulation of multiple pathways [106].
10. The Psychiatric GWAS Consortium is conducting GWAS meta-analyses for SZ, MDD, BPD, autism, and attention deficit hyperactivity disorder [180]. A number of GWAS of SZ and BPD have produced stronger evidence for association to specific risk loci than have earlier studies, specifically for the zinc finger binding protein 804A (ZNF804A) locus in SZ and for the calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C) and ankyrin 3, node of Ranvier (ANK3) loci in BPD. The ZNF804A and CACNA1C loci appear to influence the risk for both disorders, a finding that supports the hypothesis that schizophrenia and BPD are not completely etiologically distinct [181]. Moskvina et al. [182] have undertaken gene-wide analysis of two GWAS data sets: SZ and BPD. The authors found that association signals are enriched in and around genes, and that large numbers of genes contribute to both disorders. Another GWAS analysis [183] showed a common genetic component which contributes to the risk of SZ and BPD, but not to several non-psychiatric diseases. Thus, systematic GWAS and follow-up studies have reported genome-wide significant association findings of common variants for SZ and BPD [184], they also allow us to narrow the boundaries on the models of genetic architecture that are consistent with the observed data [185].

There is little clear indication which of the categorical models is valid for genetic and other biological research. Nevertheless, GWAS analysis, which has successfully identified susceptibility genes for a variety of complex disorders, has begun to

implicate specific genes for BPD (DGKH, CACNA1C, ANK3). The polygenicity of the disorder means that very large samples will be needed to detect the modest effect of loci that likely contribute to BPD [164]. Recently, single nucleotide polymorphisms (SNPs) of the tetraspanin gene TSPAN8 were found among the best ranked markers of genome wide association studies on BPD (rs1705236) and type-2 diabetes, but functional consequences remained largely unknown. Scholz et al. [186] reported the results, which argue for a differential promoter activity specific to the variant associated with BPD, but impaired protein functionality in SZ. This suggests that TSPAN8 contributes to both diseases, yet with different underlying mechanisms: regulatory versus structural.

As stated above, the majority of these studies have proceeded under the assumption that SZ, SAD, MDD, and BPD are distinct entities with separate underlying disease processes. A large number of linkage and association studies have been conducted and have produced a large number of findings often not replicated or even partially replicated.

Endophenotype Model Challenges

The clinical heterogeneity of SZ and it's phenotypic and genetic overlap with SAD, MDD, and BPD have raised questions about the optimal phenotype definition for genetic studies. Endophenotype strategy was originally proposed by Gottesman and Shields [187], Gottesman and Gould [188, 189] in order to reduce the heterogeneity and complexity of research into common, multifactorial, genetically-influenced disorders. The term *endophenotype* refers to a set of quantitative, heritable, trait-related deficits typically assessed by biochemical, endocrine, neuroanatomical, neurophysiological, neuropsychological, imaging and other methods. There is a growing consensus that an endophenotype approach may be utilized to overcome the difficulties regarding the ambiguities inherent in phenotypic description and to facilitate the identification of the susceptibility or protective genes of a wide spectrum of neuropsychiatric disorders (for review see [25, 190–192]). Indeed, this approach is being applied to SZ, SAD, MDD, and BPD [193–200], attention-deficit hyperactivity disorder [201], autism [202], alcohol dependence [203], and other complex conditions (for further reading see elsewhere in these volumes as well as an earlier 4 volume Handbook [10]). *While the potential advantages of an endophenotype based approach are widely appreciated for the genetics of multifactorial disorders, there is no consensus on how to achieve this goal in FP.*

Table 1.6 presents a sample of investigated traits, which have been discussed as candidates for endophenotypes for functional psychoses. As can be seen, potential candidate endophenotypes have been suggested for SZ, including a variety of structural brain pathologies, minor physical anomalies, neurocognitive deficits, various event-related potentials measured by electroencephalography (EEG), and olfactory identification deficits, neurocognitive deficits, including impairments in executive functioning, attention and memory domains, several electrophysiologic

Table 1.6 Selected candidates for endophenotypes in schizophrenia and in mood disorders

Endophenotypes	Schizophrenia	Bipolar and/or major depression disorders
Neuroanatomical or neuroimaging traits	Thalamic shape abnormalities [238], lateral ventricular enlargement [239, 240], decreased volume of left and total anterior insular lobule [241], cerebellar abnormalities [242], olfactory bulb abnormalities [243, 244], frontal white matter integrity [207], abnormal prefrontal cortical activity and connectivity [245]	Subcortical gray matter volume abnormalities [246], hippocampal glutamate concentrations [247], abnormal medial temporal structures [248]
Neurodevelopmental signs, physiological or electrophysiological anomalies	Minor physical anomalies [249], neurological soft signs [250], anomalies P300 wave anomalies [251], smooth pursuit eye movement abnormalities [252, 253, 254, 255, 256, 257, 258], sensory-motor gating deficits (e.g. deficits in pre-pulse inhibition, PPI) [259, 260, 261], deficits in inhibitory functions of sensory gating measured via suppression of the P50 evoked potential [262], mismatch negativity [263, 264], oculomotor measures regarding saccades and antisaccades [265], increased reflexive errors on the antisaccade task [266], a weighted combination of mismatch negativity, P50, P300, and antisaccades [267], aggregability of red blood cells [268], phenylthiocarbamide perception [269], early visual processing deficits, as measured by clear amplitude reductions in the occipital P1 component of the visual event-related potential [270], suppression of P50 auditory evoked responses, P50 sensory gating ratio, inhibition of leading saccades during smooth pursuit eye movements, and cancellation of reflexive saccades in the antisaccade eye movement task [271, 272, 273, 274, 275, 276, 277], auditory P300 [278]	Fronto-temporal alterations within the first 200 ms during an attentional task [279], increased REM density [280], pupillary reactivity [281], auditory P300 [282], suppression of P50 auditory evoked responses, P50 sensory gating ratio, inhibition of leading saccades during smooth pursuit eye movements, and cancellation of reflexive saccades in the antisaccade eye movement task [271, 272, 273, 274, 275, 276, 277], auditory P300 [278]

Table 1.6 (continued)

Endophenotypes	Schizophrenia	Bipolar and/or major depression disorders
Biochemical or immunological alterations	Decreased expression of reelin receptor VLDLR in peripheral lymphocytes [283], ceruloplasmin, C3 and C4 blood levels [284], elevation of serum levels of C-reactive protein [285], serum soluble L-selectin [286], niacin skin test [287, 288, 289], plasma homovanillic acid [290], peripheral-type benzodiazepine receptors [291], platelet 5-HT2A binding [292], BDNF and nerve growth factors [293, 294], serum cortisol to dehydroepiandrosterone molar ratio [295, 296, 297, 298]	The fluorescence intensity of the membrane potential [299], melatonin [300], N-terminal pro-B-type natriuretic peptide [301], response to corticotropin-releasing hormone [302], increased waking salivary cortisol levels [303], HPA activity [304], 42 amino-acid form of beta-amyloid (Abeta42), cerebrospinal fluid [305], platelet imipramine binding, 5-HT1A receptor expression, soluble interleukin-2 receptor and interleukin-6 in serum, BDNF in serum, blood folate levels, suppression of the dexamethasone suppression test [306], platelet adenylyl cyclase activity [307], dexamethasone/corticotropin releasing hormone test [308], lower mRNA BDNF expression in lymphocytes [309], serum cortisol to dehydroepiandrosterone molar ratio [295, 296, 297, 298]
Psychological or neurocognitive deficits	Face recognition deficits ratio [310, 311, 312], visual form perception deficits [313], visual sustained attention deficits [314, 315], deficits in prepulse inhibition [244], executive cognitive impairment [316], impairments in attention and memory domains [317, 318], visuospatial working memory, verbal memory, language, oculomotor scanning/psychomotor speed, and general intelligence [319, 320, 321, 322], intellectual asymmetry with a relative superiority of verbal skills to spatial skills [323], temperament types, emotional distress, emotion-oriented coping and self-constructs [324], a source monitoring deficit [325], an auditory processing abnormality [326], inhibition of the P50 cerebral evoked response to repeated auditory stimuli [327], impaired performance on the Rapid Visual Information Processing task [328], facial emotion recognition [329], learned irrelevance and associative learning [330], processing speed, working memory, and declarative (facial) memory [331]	Cognitive impairment and an isolated facial emotion processing deficit [332], sustained attention [333], the melancholic type of personality [334], impairment of executive function [335], executive functioning [336], cyclothymic personality traits [337], impairment in facial emotion recognition [338], verbal recall deficits [339], a virtual reality spatial memory navigation task [340], visual sensory processing deficits [341], disrupted auditory attention [342], subclinical anxiety [343], emotional hyper-reactivity [344], nonspecific deficits in face-emotion recognition [345], processing speed, working memory, and declarative (facial) memory [331]

findings, such as sensory-motor gating deficits, and smooth pursuit eye-tracking abnormalities (reduced gain during smooth pursuit and increased saccade frequency), and biochemical alterations. Endophenotypes for MDD and BPD under current investigation also include neuroanatomical (e.g. subcortical gray matter volume abnormalities), neurophysiological (e.g. fronto-temporal alterations within the first 200 ms during an attentional task), biochemical (e.g. impaired response to corticotropin-releasing hormone), psychological (e.g. cyclothymic personality traits), and others.

However important differences also emerged. Jabben et al. [204] assessed neurocognition, psychopathology, and psychosocial functioning in samples of patients with a SZ spectrum disorder (n = 345) and BPD (n = 76) that met DSM-IV criteria, first-degree relatives of both patient groups (n = 331 and n = 37, respectively), and healthy controls (n = 260 and n = 61, respectively). They found that cognitive deficits were more severe and more generalized in patients with a SZ spectrum disorder compared to patients with BPD; cognitive alterations were present in relatives of patients with SZ spectrum disorders but not in relatives of BPD patients. The association between neurocognitive dysfunction and psychosocial functioning was more generalized in SZ spectrum disorders than in BPD; for both disorders, associations were only partly mediated by symptoms. The evidence for cognitive dysfunction as a marker of familial vulnerability was stronger for schizophrenia than for bipolar disorder. Although the presence of multiple cognitive deficits was shared by the 2 groups, the severity of cognitive deficits and its consequences appeared to somewhat different between schizophrenia and bipolar disorder, which is in line with a model that implies the specific presence of a neurodevelopmental impairment in the former but not in the latter.

It should be noted that endophenotypes may not be specific to the disorder and are shared across different conditions from mood disorders to schizoaffective disorders and schizophrenia. Indeed, overlapping endophenotypic processes included physiological or electrophysiological anomalies, psychological or neurocognitive deficits and biochemical alterations as the following suggest:

Physiological or electrophysiological anomalies:

- suppression of P50 auditory evoked responses;
- P50 sensory gating ratio;
- inhibition of leading saccades during smooth pursuit eye movements;
- suppression of P50 auditory evoked responses.
- Delayed P300 latency is a promising candidate endophenotype for psychotic BPD, as well as SZ, and may reflect the impact of shared susceptibility genes for both types of psychosis [205].

Psychological or neurocognitive deficits:

- processing speed, working memory, and declarative (facial) memory;
- facial emotion deficits.

Biochemical alterations:

- serum cortisol to dehydroepiandrosterone molar ratio.

In addition, neurocognitive and neurophysiological impairments [83], brain morphometric alterations [206], anatomical connectivity and its abnormalities [207] appear largely to meet the criteria for endophenotypes in psychotic and mood disorders. These and other conditions may have some common biological basis, including SNPs or genes, that are reflected in common markers and/or endophenotypes. The ability to discern commonalities and differences in the neurobiology of *functional psychoses* is limited by different methodologies applied in various studies and the putative neurodevelopmental trajectories for each disorder. Definitive clarification of what SZ, SAD, MDD and BPD have in common and in what ways they are distinct, if at all, will only be derived from studies that examine *all functional psychoses* using the same study design and methodology.

A considerable body of literature exists concerning the relationship between cognitive impairment and schizophrenia, but there is less data concerning cognition in BPD. However, there are some notable similarities between data observed in SZ and BPD [70]. Many domains of cognition are disrupted in SZ with varying degrees of deficit. Regarding mood disorders, cognitive dysfunction could be considered as a state marker. Globally some studies indicate that, compared with schizophrenia, those with bipolar disorder display a similar but less severe neuropsychological pattern of impairment. It is only recently that cognitive dysfunction has been recognized as a primary and enduring core deficit in schizophrenia and further studies in BPD are needed.

Neurocognitive impairment is common to several neuropsychiatric disorders. The growing use of cognitive impairment as an endophenotype in psychiatry raises the issue of whether global measures of cognition, such as IQ, or assays of more specific cognitive domains, such as working memory, will best serve to enhance power in detecting susceptibility loci in molecular genetic studies. Burdick et al. [208] reviewed the research on general intelligence in SZ and BPD and evaluated its strengths and weaknesses as a candidate intermediate phenotype, concluding that global measures of cognition represent good endophenotypes in SZ; current research does not support the use of global measures of cognition as endophenotypes for BPD. Neuropsychological data do not provide evidence for categorical differences between schizophrenia and other diagnoses. However, a subgroup of individuals with SZ who have more severe negative symptoms may be cognitively more impaired than those with affective psychosis or SAD disorder [83].

Genetic linkage and endophenotype studies are challenged by focusing on the categorical phenotype of functional psychoses, the lack of measures of symptom dimensions, and by overlapping candidate genes and endophenotypes between SZ, SAD, MDD, and BPD including physiological or electrophysiological anomalies, psychological or neurocognitive deficits and biochemical alterations. Specific challenges need to be addressed in the future if we hope to move forward in our goal to reach meaningful and applicable clinical results.

Current Challenges

Functional psychoses are relatively common psychiatric syndromes, affecting virtually all brain functions, and yet have eluded explanation for more than 100 years. Whether by developmental and/or degenerative processes, abnormalities of neurons and their synaptic connections have been the recent focus of attention [209]. The categorical models have continued to be the focus of much criticism for many years [11–15, 17–22, 24, 160]. In spite of the rich body of work that validates categorical and dimensional models of FP, challenges remain because none of the group of FP, or of the individual psychoses included within them, has been clearly demonstrated to be a disease entity.

However, *the categorical models pose several distinct advantages* [23]:

1. Categorical reasoning arises naturally from the medical model and uses the familiar concept of disease.
2. Current categorical nosology of the functional psychoses meet the needs of clinical practice since a categorical diagnosis can be communicated with ease to patients, clinicians, and third parties.
3. This lends itself naturally to traditional linear methods of defining a clinical syndrome, elucidating the underlying pathophysiology, and ultimately identifying etiology.
4. For obvious practical reasons, the important and influential diagnostic and statistical manuals (ICD, DSM) develop slowly, call for discrete diagnostic classes and need to be conservative [8].
5. There are data that do not contradict categorical models since SZ is a more chronic affliction and BPD presents with a more cyclic pathology [70].

Kraepelin's dichotomy formed the foundation of our current categorical nosology of the functional psychoses, before treatment response was introduced into the nosology, that has radically changed over time [24, 210]:

- The concepts of manic depression, which included manic, circular, as well as recurrent depressive conditions, was changed to clearly differentiate bipolar from major depressive disorders [19].
- Avolitional and dissociative symptoms that were described as distinctive manifestations of dementia praecox, as well as further nuclear manifestations of SZ, were de-emphasized in favor of Schneiderian first-rank symptoms [4, 20], which were widely accepted in Europe [211]. However, these symptoms may be found in non-schizophrenic conditions, and therefore, they are not specific or diagnostic for schizophrenia [212].
- Multiple studies subsequently confirmed the existence of a group of conditions, which were named SAD, between SZ, MDD and BPD.
- Clinical syndromes, including depression, anxiety, and substance use disorders, co-occur with SZ at significant rates [213].

Next, *the categorical models do not take into account several central concerns* [160]:

1. Many of the mental disorders are in fact part of a dimensional spectrum such as an affective spectrum, an obsessional spectrum and in our case the psychotic spectrum.
2. Each of these disorders is in fact constructed from several discrete dimensions such as a cognitive dimension, an impulsivity dimension, dimensions of positive and negative symptoms and so on.
3. As such, by utilizing a dimensional approach we would be treating the particular pathological dimensional symptoms or syndromes and not an entire categorical disease entity.
4. Moreover, the validity of the categorical approach is further questioned by the vast heterogeneity of the diagnosis – the "x symptoms out of y" approach employed by the DSM-IV or ICD-10 leads to numerous different clinical combinations with little in common apart from the diagnosis.
5. There is contradictory evidence from a long-term longitudinal study that supports Kraepelin's original hypothesis [214], and is consistent with the existence of an individual and a familial overlap between SZ and BPD (see e.g. [70, 116]). Longitudinal studies demonstrated the existence of cases beginning as BPD and later turning into SZ, as well as, vice versa [215, 216]. At 5-year follow-up, 63.6% of 55 subjects, aged 12–20 years, consecutively hospitalized for a manic or mixed episode still had a diagnosis of BPD; 14.5% changed life-time diagnosis for SAD disorder and 20% for SZ [217].
6. The clinical boundaries of SZ remain indistinct blending at one extreme with BPD and at the other with schizotypal personality disorder [218].
7. Schizophrenia does not represent a "real" construct in nature, therefore, it will not delineate the true pathology and causal mechanisms underlying psychosis; it will obfuscate etiology [219]. A century of work has been based on designs that conceptualize SZ as a single disease entity, despite recognition that SZ must have scientific status of a syndrome in the absence of proof of a single disease process [14]. Independent of the clinical picture, we have no criteria such as a laboratory test for diagnosing schizophrenia or its subtypes. Etiological heterogeneity, complex patterns of gene-gene and gene-environment interaction, the existence of phenocopies and the presence of low disease penetrance and inadequately elucidated SZ pathophysiology are among the explanations invoked to explain our inadequate understanding of the etiopathogenesis of schizophrenia [158, 220].
8. Reexamination of patterns or chronicity within psychosis, i.e., Kraepelin's "poor outcome" principle of SZ, led many authors to also identify chronic deterioration in the course of bipolar disorders [59]. A large subset of patients diagnosed with SZ seemed to recover or significantly improve over the long term.
9. The heterogeneity of patients that receive this diagnosis is substantial; causal and neuropathological findings valid for some patients will not be found in others.

Furthermore, there is modest similarity between SZ and BPD relating to risk factors, neural substrates, cognition and endophenotypes, but key differences are noted [221]:

- There is greater support for a spectrum relationship of SZ and SPD.
- Antecedent temperament, an important validator for other groupings, needs more empirical study in the various psychotic disorders.
- The DSM-IV-TR grouping of psychotic disorders is supported by tradition and shared psychopathology, but little data exists across these diagnoses relating to the spectrum criteria.

Currently, many fields of clinical and endophenotype assessments, neuroscience, proteomics, gene expression analysis and genetics operate largely independently of each other. Once the functional pathways that are involved in psychiatric disorders and their associated traits of interest are identified, statistically sound combined *analysis of genetics with gene expression and pathway analysis* will be needed. Merging different data types from *separate fields* into a common analysis that results in a joint statistical probability is a bioinformatic and statistical challenge [222]. (p. 537). *The prospective strategy of overcoming the boundaries that separate these fields, may be a triangular design* (Fig. 1.4). This design may include a combination of multi-candidate genes with multi-candidate endophenotypes and symptom measures in the framework of dimensional models of FP (see Chapter 3 in this volume). This type of design may lead us to define common clusters that must be present in all individuals diagnosed with the FP and discrete, non-overlapping psychopathological endophenotype domain groups of patients.

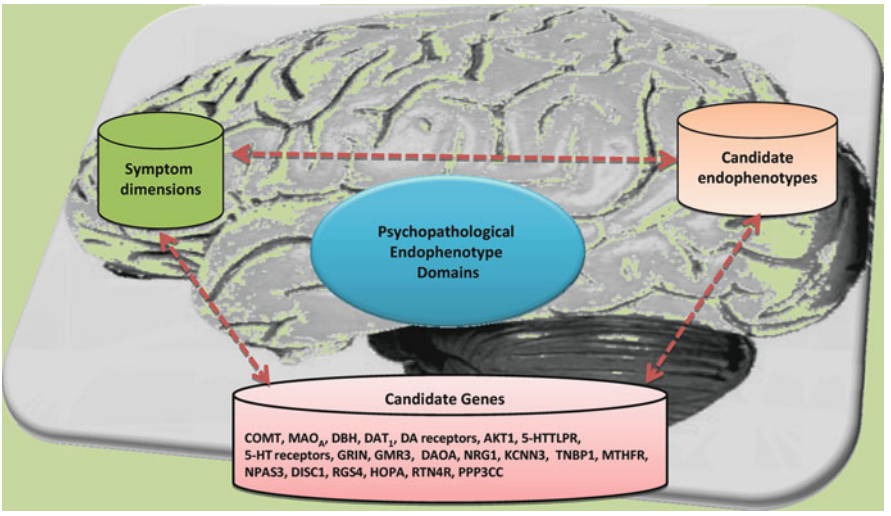

Fig. 1.4 A triangular design for genetic and endophenotype researches and looking for psychopathological endophenotype domains. © M.S. Ritsner & I.I. Gottesman (2011) and used by permission

Conclusions and Future Directions

In this chapter we have attempted to review past and current challenges to the schizophrenia construct within the framework of the functional psychoses spanning unitary, categorical and dimensional models using previous and contemporary research in the field of GWAS polymorphisms, epidemiology, genetic epidemiology, longitudinal studies, candidate genes and endophenotypes.

The study of functional psychoses is difficult and can be frustrating. Specific challenges need to be addressed by cross-disciplinary teams in the future if we hope to move forward in our goal of reaching meaningful and applicable clinical results.

- *We need a new concept of functional psychoses.* Our inability to fathom the pathophysiology of SZ forces us to challenge our theoretical models and beliefs [209]. The unitary concept of psychosis ("Einheitspsychose") has been discussed in controversial terms for a long time [223, 224]. The validity of the categorical models of FP have been increasingly challenged by emerging data from many fields of psychiatric research. Therefore, from consideration of the available evidence it is suggested that the SZ, SAD, MDD, and BPD syndromes are non-specific or fuzzy clinical domains of functional psychoses. As a result it is not clear where the boundaries should be drawn. Current classification systems, such as the DSM and ICD, are concerned with "diagnoses" but not with "disorders", they are intended more for achieving face than for neurobiological research [225].
- *We need new and improved clinical assessment tools*. There are various arguments for the dimensional models of FP. Current data indicate that psychotic disorders are best understood with provisions for categories, dimensions, and thresholds in a context informed by epigenetic regulatory systems. The challenge is to devise diagnostic dimensions that have heuristic value for neuroscientific research and that can also guide clinical understanding and intervention [226]. Moving to a spectrum concept (be it with categories or dimensions) with recognition of overlapping pathogenetic factors and varying expression dependent upon genetic risk, epigenetic regulation, and environmental exposure would allow a confident and clear diagnosis to be offered.
- *We need to target persons with functional psychoses instead of persons with current categorical diagnoses.* This rationale is less extreme than it sounds – as stated above, symptom dimensions, candidate genes and endophenotypes show overlapping between SZ, SAD, MDD and BPD.
- *We need to apply a triangle design for future genetic and endophenotype studies*. This design suggests combining multiple-candidate genes with multiple-endophenotype and symptom measures in the framework of a dimensional model of FP (see Fig. 1.4). Despite the enormous effort to find a linkage between SZ and one or more loci, the results are far from conclusive. Molecular genetic studies have primarily focused on phenotypes (SZ, SAD, MDD, and BPD). To date, however, relatively limited work has been conducted to identify the genetic variants associated with symptom dimensions. To understand etiological factors, genetic

studies will shift from the genetics of SZ, SAD, MDD, and BPD as syndromes to the genetics of clinical symptom-endophenotype multidimensional measures and domains.

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Chapter 2
Diagnosis and Classification of the Schizophrenia Spectrum Disorders

Daniel Mamah and Deanna M. Barch

Abstract The classification of schizophrenia related disorders have been evolving with advances in psychiatric research. In 1893 Emil Kraepelin distinguished dementia praecox from manic-depression, heralding the diagnosis of schizophrenia as a separate entity, but this distinction has since been challenged by data from genetic epidemiology. Over the past century, two major classification systems emerged: the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD), of which new editions are expected to be soon published. The latter criteria are typically used in European countries, while the DSM criteria are used in the United States and the rest of the world, as well as prevailing in research studies. As with other psychiatric disorders, some have suggested that the diagnosis of psychotic disorders would be better addressed as individual dimensions of psychotic experiences (e.g. hallucinations and delusions) along which everyone varies, such that there is a spectrum or continuum rather than a cut-off between disorders and normality. Some disorders in the schizophrenia spectrum, such as schizoaffective disorder and schizotypal personality disorder have also been criticized for a relatively low interrater reliability, in part due to the difficulty of establishing fine grained timecourse information and to identifying subtle, sub-threshold psychotic type phenomena. This chapter discusses past and present diagnostic classifications of schizophrenia spectrum disorders, and research considerations for further improving our nosological system.

Keywords Diagnosis · Classification · Schizophrenia · Schizoaffective disorder · Schizotypal personality disorder · Psychosis · DSM · ICD

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Abbreviations

CCMD	Chinese classification of mental disorders
CHR	Clinical high-risk criteria (*for Developing a Psychotic Disorder*)
COMT	Catechol-O-methy transferase
DSM	Diagnostic and statistical manual (of Mental Disorders)
DSM-IV-TR	Fourth edition (Text Revision) of the DSM
fMRI	Functional magnetic resonance imaging
GAF	Global assessment of functioning
ICD	International classification of diseases
ICD-10-CM	Tenth edition (Clinically Modified) of the ICD
OCD	Obsessive-compulsive disorder
PCA	Principal components analysis
PDD	Pervasive developmental disorder
RDC	Research diagnostic criteria
RDoC	Research domain criteria
UHR	Ultra high-risk criteria (*for Developing a Psychotic Disorder*)

Introduction

The *schizophrenia spectrum disorders* are a group of psychiatric conditions, with a distinct set of diagnostic criteria, which share similarity on clinical grounds or at the level of disease mechanism or etiology. Typically, these disorders have clinical features in common with schizophrenia, involving some degree of reality distortion [1]. Together with schizophrenia, the diagnoses most commonly mentioned in the spectrum are schizoaffective disorder and schizotypal personality disorder. However, results from family and genetic studies have suggested that other conditions may also be included, such as affective psychotic states [2, 3]. Schizophrenia, while considered an identifiable diagnostic construct, is characterized by significant heterogeneity of signs and symptoms, disease course and outcome. This gives rise to various clinical subtypes and to variants defined by a shorter duration of illness, and outcomes ranging from full remission to long-term disability.

Disorders in the schizophrenia spectrum are diagnosed using various standardized criteria. *The Diagnostic and Statistical Manual of Mental Disorders (DSM)*, published by the American Psychiatric Association and in its fourth text revised edition (DSM-IV-TR) [4], provides a common language and standardized criteria for the classification of mental disorders, and is used in the United States and in varying degrees around the world. The *International Statistical Classification of Diseases and Related Health Problems (ICD)* is published by the World Health Organization and is used worldwide for morbidity statistics, reimbursement systems and automated decision support in medicine. Now in its tenth revision (ICD-10), this text classifies "Mental and Behavioral Disorders" in its Chapter V [5]. Both the DSM and ICD Chapter V have converged disorder codes so that the manuals are often broadly comparable, although some differences remain. Other classification schemes may be used more locally, for example, the *Chinese Classification*

of Mental Disorders (CCMD) [6]. The CCMD includes schizophrenia, as well as potentially related psychoses more specific to Chinese and Asian culture, such as mental disorder due to Qigong, superstition or witchcraft, and traveling psychosis [7].

Due to the more extensive of the DSM and ICD worldwide, compared to other diagnostic manuals, this chapter will focus on diagnosis and classification based on the criteria in these systems.

Historical Aspects of Classification

In the 1890s, Emil Kraepelin's organization of psychopathology, including dementia praecox and manic-depression, became the foundation for future classification systems. Krapelin argued strongly for a categorical distinction between schizophrenia and psychotic bipolar disorder. The question of the boundaries of schizophrenia became more controversial when Eugen Bleuler [8] observed that certain "fundamental" features of Kraepelin's dementia praecox [9] could be found in "latent" form. After Kety and colleagues [10] in 1968 introduced the term "schizophrenia spectrum" to refer to all disorders that are "to some extent genetically transmitted" with schizophrenia, the identification of which disorders should be under this genetic umbrella became a focus of investigation.

The initial impetus for developing a classification of mental disorders in the United States was the need to collect statistical information about the prevalence of mental illness. The 1880 census distinguished among seven categories of mental disorders. These consisted of *monomania* – paranoia involving only one idea or type of idea – in addition to mania, melancholia, paresis, dementia, dipsomania and epilepsy. The American Psychiatric Association, in 1952, published the *Diagnostic and Statistical Manual of Mental Disorders* (now referred to as *DSM-I*) [11], as an effort to develop a version of the ICD section on mental disorders specifically for use in the United States [12]. DSM-I used the term "*Schizophrenic Reactions*", which was described as *"a group of psychotic disorders characterized by fundamental disturbances in reality relationships and concept formations, with affective, behavioral, and intellectual disturbances in varying degrees and mixtures. The disorders are marked by strong tendency to retreat from reality, by emotional disharmony, unpredictable disturbances in stream of thought, regressive behavior, and in some, a tendency to 'deterioration'"*. In DSM-II, which was first published in 1968, the term "reactions" was no longer used, and the prototypic psychotic disorder was referred to as "schizophrenia" [13]. New subtypes of schizophrenia were also added by subdividing old categories. For example, the "schizoaffective type of schizophrenia" was further divided into *excited* and *depressed* subtypes. Among the personality disorders in DSM-II, paranoid and schizoid personalities were listed, but not schizotypal personality. Both DSM-I and DSM-II reflected the predominant psychodynamic psychiatry of the time [14], and symptoms were not specified in detail for specific disorders. Sociological and biological knowledge was incorporated, in a model that did not emphasize a clear boundary between normality and abnormality [15].

Robins and Guze [16] enunciated the proximate intellectual underpinning of DSM-III [17]. Using schizophrenia as their example, Robins and Guze argued that reliable and valid diagnoses would follow from observation in five domains: (a) clinical description, (b) laboratory studies, (c) delineation of one disorder from another, (d) follow-up studies, and (e) family studies [16]. Their work motivated the development of two sets of diagnostic criteria intended for the identification of homogenous populations for research, the *Feighner criteria* [18] and the *Research Diagnostic Criteria* (RDC) [19]. In addition to these, a number of other competing operational diagnostic systems were proposed since the 1960s in an attempt to improve the reliability of psychiatric diagnosis for research purposes. These included Taylor's, Schneider's, Langfeldt's, Spitzer's, Carpenter's, Astrachan's, two from Forrest & Hay, and the Present State Examination – CATEGO system [20]. While internally reliable, the various competing diagnostic systems showed wide disparity in reliability, concordance and prediction of outcome [21, 22]. For example, the systems varied by as much as sevenfold in their rates of diagnosing schizophrenia [23]. DSM-III, published in 1980, was the first DSM to feature operationalized criteria for each mental disorder, and thus marked a significant change from previous diagnostic manuals. The criteria adopted in DSM-III for many of the mental disorders were taken from the RDC and Feighner criteria. Efforts to develop operational definitions of latent schizophrenia led to development of the criteria for DSM-III schizotypal personality disorder. In DSM-III, cluster A, or the "odd cluster", or presumptively schizophrenia-related, nonpsychotic personality disorders included schizotypal, schizoid, and paranoid personality disorders. DSM-III also included a vast increase in the background information about each disorder, including course, prevalence, differential diagnosis, family patterns and cultural and gender features. A revised version DSM-III-R was published in 1987 and a new edition – DSM-IV – in 1994. DSM-IV shifted the emphasis on which psychotic symptoms were required for a diagnosis of schizophrenia, in that patients without either delusions or hallucinations could receive the diagnosis. In these cases, however, other characteristic psychotic symptoms were required, namely, gross disorganization of speech and/or behavior. The diagnostic importance of Schneiderian symptoms was also reemphasized, as hallucinations could satisfy a criterion if they involved one or more voices engaging in running commentary or ongoing conversation and delusions could count if they are bizarre [24]. The most recent manual did not involve major criteria modifications but involved only a text revision (DSM-IV-TR) [4].

The first International Classification of Disease (ICD) effort was in 1893, and it has been revised periodically since. The sixth revision, ICD-6, published in 1949 was the first to contain a section on mental disorders [25]. The ICD section classifying "Mental and Behavioral Disorders" has developed alongside the DSM, and the two manuals seek to use the same diagnostic codes. There are some differences that exist in the diagnostic criteria of certain disorders, and the ICD includes personality disorders on the same axis as other mental disorders, unlike the DSM. Work on the latest major ICD revision – ICD-10 – was completed in 1992. Adoption was relatively swift in most of the world. In the United States, the ICD-10 was adopted for reporting mortality but ICD-9-CM (clinical modification)

was still used for morbidity. Under the current proposal, the ICD-9-CM code sets would be replaced with ICD-10-CM code sets in the United States, effective October 1, 2013.

Nosological Overview of the Schizophrenia Spectrum Disorders

Many studies have proposed (and in some cases rejected) schizophrenia spectrum status for at least six psychotic disorders other than schizophrenia – schizoaffective disorder [3], schizophreniform disorder [26], delusional disorder [3, 27, 28], psychotic disorder not otherwise specified [3, 24], and bipolar and depressive disorders with psychotic features [26, 29, 30]. In addition, the cluster A or the "odd cluster" of presumptively schizophrenia-related nonpsychotic personality disorders included schizotypal [31], schizoid [32], and paranoid [3, 33] personality disorders. However, identification of the specific nonpsychotic and psychotic disorders that belong within the genetic boundary of the "schizophrenic spectrum" is acknowledged in DSM-IV-TR to be an "unresolved problem". The following section discusses mental disorders which have been considered part of this spectrum, including key diagnostic criteria in the most recent editions of the DSM and ICD were applicable.

Schizophrenia

Schizophrenia is the prototypic disorder within the spectrum, and overwhelmingly the one most studied clinically and in the research literature. No single symptom is pathognomonic of schizophrenia; the diagnosis involves the recognition of a constellation of signs and symptoms associated with impaired occupational or social functioning. DSM-IV-TR [4] describes the essential features of schizophrenia to be a mixture of two or more characteristic "Criterion A" symptoms (i.e. delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms) that have been present for a significant portion of time during a 1-month period (or for shorter time if successfully treated), with some signs of the disorder persisting for at least 6 months. Only one Criterion A symptom is required for diagnosis if delusions are "bizarre" or Schneiderian first-rank hallucinations [34, 35] (i.e. a *voice keeping up a running commentary on the person's behavior or thoughts*, or *two or more voices conversing with each other*) exist. Symptoms are associated with marked social or occupational dysfunction, and are not due to schizoaffective disorder, a psychotic mood disorder, substance use or a general medical condition. DSM-IV-TR also recognizes five subtypes of schizophrenia: (1) paranoid, (2) disorganized, (3) catatonic, (4) undifferentiated, and (5) residual, based on the predominant symptomatology at the time of evaluation.

The ICD-10 diagnostic criteria for schizophrenia requires only a duration of more than 1 month of symptoms, and does not require social and occupational dysfunction

as part of the clinical picture. Its criteria put more emphasis on Schneiderian first-rank symptoms [34], although in practice, agreement between schizophrenia diagnosis in DSM and ICD is high [36]. Characteristic symptoms required in ICD-10 are either: (1) one or more of symptoms that include thought echo, insertion, withdrawal or broadcasting; delusions of control, influence of passivity or delusional perception; hallucinatory voices giving a running commentary or discussing patient between themselves; and persistent bizarre delusions; or (2) two or more of symptoms that include persistent hallucinations accompanied by delusions or overvalued ideas, disorganized speech, catatonic behavior, or negative symptoms. Exclusionary criteria also are present in ICD-10, similar to that in DSM-IV-TR. ICD-10 lists 8 subgroups of schizophrenia: (1) paranoid, (2) hebephrenic, (3) catatonic, (4) undifferentiated, (5) residual, (6) simple, (7) other, and (8) unspecified. An additional "subgroup" listed is *post-schizophrenic depression*.

Brief Psychotic Disorders

DSM-IV-TR recognizes two forms of "schizophrenia" with shorter duration, i.e. *schizophreniform disorder* and *brief psychotic disorder*. Symptoms of schizophreniform disorder are identical to that of schizophrenia except for two differences: (1) the total duration of the illness is at least 1 month but less than 6 months, and (2) impaired social or occupational functioning during some part of the illness is not required. It is estimated that up to two-thirds of those who receive an initial diagnosis will progress to a diagnosis of schizophrenia or schizoaffective disorder [4, 37, 38]. "Brief psychotic disorder" involves the sudden onset of positive, disorganized or catatonic symptoms, which lasts at least 1 day but less than 1 month. Cases of brief psychotic disorder are rarely seen in clinical settings in the United States and other developed countries [39, 40].

ICD-10 lists a category of "Acute and Transient Psychotic Disorders", which requires that the time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder to not exceed 2 weeks. This category includes two disorders, named: (1) *acute polymorphic psychotic disorder without symptoms of schizophrenia*, and (2) *acute polymorphic psychotic disorder with symptoms of schizophrenia*. The former requires the total disorder duration not to exceed 3 months. The latter requires that "schizophrenia symptoms" not exceed 1 month.

Schizoaffective Disorder

The diagnosis of schizoaffective disorder lives in the borderland between schizophrenia and mood disorder. Kasanin [41] introduced the diagnosis to capture a milder form of schizophrenia, associated with better outcome. However, the current version of the DSM conceptualizes it as schizophrenia with prominent mood symptoms, with no a priori distinction of disease course or outcome.

Despite the low reliability of the diagnosis due to disagreements on estimates of affective relative to psychotic symptoms [42], many researchers have compared the genetics and neurobiology of schizophrenia and schizoaffective disorder. Cardno et al. [43] for example, reported that the genetic liability for schizoaffective disorder was entirely shared with schizophrenia and affective disorders. Reviews of the neurobiological literature literature [44–47] have nevertheless questioned the validity of the schizoaffective disorder diagnosis, but continued to recommend a diagnostic separation along the continuum from psychosis to mood disorder.

According to DSM-IV-TR, the fundamental clinical presentation in schizoaffective disorder is an uninterrupted period of illness during which at some point there is a major mood episode (i.e. depressive, manic, or mixed) concurrent with symptoms that meet Criterion A symptoms of schizophrenia (i.e. delusions, hallucinations, disorganized speech, grossly disorganized/catatonic behavior, and negative symptoms). In addition, there must have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms (Criterion B). Criterion C requires that symptoms meet criteria for a mood episode for a substantial portion of the total duration of the active and residual periods of the illness.

ICD-10 requires that symptoms meet criteria for a mood disorder to a moderate or severe degree, as well as at least one schizophrenia-symptom for at least 2 weeks. It also requires that these two general criteria be met within the same episode of the disorder, and concurrently for at least some time of the episode. Thus, unlike DSM, ICD-10 does not require a period of psychotic symptoms in the absence of mood symptoms.

Personality Disorders

Personality disorders are categorized separately from other mental disorders as they are thought to involve patterns of symptoms that are inflexible and pervasive across a broad range of personal and social situations, as compared to the putatively episodic nature of many other disorders. Considered integral to an individual's personality, the characteristic patterns of symptoms are generally stable, and their onset can be traced back at least to adolescence or early adulthood. In the current DSM diagnostic system, by convention personality disorders are coded separately, on Axis II in its multiaxial system, which does not exist in ICD.

DSM-IV-TR includes three personality disorders with features that resemble schizophrenia: schizotypal, schizoid and paranoid personality disorder. These personality disorders are classified as *Cluster A Personality Disorders*, characterized by "odd" or "eccentric" behaviors. Avoidant personality disorder has been proposed as an addition to this group [48, 49], although studies generally show that this disorder closely linked to other schizophrenia spectrum disorders [2, 50]. ICD-10 categorizes schizoid personality disorder and paranoid personality disorder under the section: *"Personality Disorders",* but schizotypal disorder under: *"Schizophrenia, Schizotypal and Delusional Disorders"*.

Schizotypal

The vast majority of genetic, epidemiologic or neurobiological studies of schizophrenia spectrum disorders involve schizotypal personality disorder [51, 52]. This may partly be due to the fact that schizotypal personality disorder is more closely related to schizophrenia than other personality disorders. Tienari et al. [2] for example, reported that in adoptees of biological mothers with schizophrenia spectrum disorders, among cluster A personality disorders, schizotypal personality disorder clearly stood out as more prevalent compared to those adoptees at genetic low risk.

Schizotypal personality disorder involves cognitive or perceptual distortions, eccentricities of behavior, and acute discomfort in close relationships [4]. For a diagnosis, DSM-IV-TR requires at least five symptoms from among: (1) ideas of reference, (2) odd beliefs or magical thinking, (3) unusual perceptual experiences, (4) odd thinking and speech, (5) suspiciousness or paranoid ideation, (6) inappropriate or constricted affect, (7) odd or eccentric behavior, (8) lack of close friends, and (9) excessive social anxiety. The ICD-10 lists this disorder as "schizotypal disorder" and as a mental disorder associated with schizophrenia, rather than a personality disorder as in DSM. For diagnosis in ICD, schizotypal disorder requires at least four of nine symptoms, which are similar to that in DSM. One notable difference, an optional symptom in ICD, is "occasional transient quasi-psychotic episodes with illusions, auditory or other hallucinations and delusion-like ideas, usually occurring without external provocation", which is not present in the DSM criteria for schizotypal personality disorder.

Schizoid

Schizoid personality disorder appears to be intermediate between schizotypal and paranoid personality disorders with regards to its genetic relationship to schizophrenia [2, 48]. Its characteristic symptoms are a pattern of detachment from social relationships and a restricted range of emotional expression. DSM-IV-TR requires at least four symptoms among: (1) no desire or enjoyment of close relationships, (2) usual choice of solitary activities, (3) little interest in sexual experience with others, (4) little pleasure derived from activities, (5) lack of close friends, (6) indifference to others' praises/criticisms, and (7) emotional coldness, detachment or flattened affect. ICD-10 also lists this diagnosis among the personality disorders, and the diagnostic criteria are largely identical to that in DSM.

Paranoid

Compared to schizotypal personality disorder, there is substantial but less consistent evidence for a familial relationship between paranoid personality disorder and schizophrenia [2, 48, 53]. Tienari et al. [2] reported that in adoptees of biological mothers with schizophrenia spectrum disorders, among cluster A personality disorders, paranoid personality disorder was the least closely linked to the rest of the

putative schizophrenia spectrum. Comorbidity with, and a higher familial relationship with affective disorders [52, 54] and delusional disorder [55, 56] have been reported for paranoid personality disorder.

Paranoid personality disorder is a pattern of distrust and suspiciousness such that others' motives are interpreted as malevolent. For a diagnosis in DSM-IV-TR, there must be four or more of the following symptoms: (1) suspiciousness that others are exploiting/harming/deceiving, (2) preoccupation with doubts about others' trustworthiness, (3) reluctance to confide in others, (4) reading hidden meaning into benign remarks/events, (5) persistent grudges, (6) perceiving attacks on character or reputation, and (7) recurrent suspicions regarding fidelity of partner. The diagnostic criteria in ICD-10 are largely identical to DSM.

Other Disorders

The following disorders have sometimes been included as part of the schizophrenia spectrum, although less commonly mentioned as such compared with schizophrenia, schizoaffective disorder or schizotypal personality disorder.

Bipolar Disorder with Psychotic Features

The status of the affective psychoses in relation to the schizophrenia spectrum is controversial, although they are usually excluded from the schizophrenia spectrum [57]. Family co-aggregation of bipolar disorder with schizophrenia has been noted by some [58–61], but not all authors [2]. Several risk genes, originally identified in schizophrenia cohorts, have also been linked to an increased risk for bipolar disorder [60–65]. However Segurado et al. [66] did not find overlap in the highest-ranking genes for each disorder. There also do not appear to be significant similarities in brain abnormalities in bipolar disorder and schizophrenia. A recent meta-analysis of structural imaging studies in bipolar disorder concluded that brain volume changes are less significant and less localized when compared to studies of subjects with schizophrenia [67]. There has also been some debate about whether bipolar disorder with a history of psychotic symptoms may represent a different pathophysiological subtype compared to those without psychotic symptoms, as the former is more closely linked to schizophrenia clinically [68–71] and genetically [69, 72–74].

The essential feature of Bipolar Disorder is a clinical course that is characterized by the occurrence of one or more *manic, mixed*, or *hypomanic episodes*. In the DSM nomenclature, Bipolar I Disorder requires a history of one or more manic episodes or mixed episodes. Depressive episodes, while common in bipolar I disorder, is not required for diagnosis. Bipolar II Disorder consists of hypomanic episodes as well as a least one major depressive episode. The ICD system uses a more general germ, "Bipolar Affective Disorder", and specifies the current episode as manic, hypomanic, mixed or depressed. At least 50% of individuals with bipolar disorder are estimated to have experienced psychosis in their lifetime [68, 75].

Major Depressive Disorder with Psychotic Features

Research generally suggests that there is relatively little genetic relationship between schizophrenia and major depressive disorder, with or without psychotic features [2, 76, 77]. Tienari et al. [2] reported that among several putative schizophrenia spectrum disorders studied in adoptees, major depression with psychotic features was the least closely related to schizophrenia spectrum diagnoses in biological mothers. A significant genetic relationship between schizophrenia and major depression has however been reported [78].

To be diagnosed with major depressive disorder in DSM-IV-TR, there must be a history of a *major depressive episode* comprised of five (or more) characteristic symptoms including low mood or anhedonia, during a 2-week period. The counterparts of major depressive disorder in the ICD-10 are termed "Depressive Episode" or "Recurrent Depressive Disorder" depending on if there is a history of one or more depressive episodes. Psychosis in major depressive disorder can occur with all depression severities, and be both mood-congruent and mood-incongruent [79].

Delusional Disorder

Delusional disorder is characterized by significant *non-bizarre* delusions, as the major symptom. Thus, symptoms of auditory or visual hallucinations, disorganized behaviors or speech, or negative symptoms (as may additionally occur in schizophrenia), are not present. Nevertheless, clinical similarities between schizophrenia and delusional disorder have led some to argue for potentially common etiology and inclusion into a common spectrum [80] Individuals with delusional disorder do not appear to have an increased familial risk of schizophrenia spectrum disorders or vice versa [27, 81, 82]. The diagnostic stability over time of delusional disorder is also not as strong as for the major psychotic disorders, with diagnosis shifting in a substantial number of patients to a schizophrenia spectrum disorder [83, 84].

Obsessive Compulsive Disorder

It has been suggested that obsessive-compulsive disorder (OCD) might overlap phenomenologically with schizophrenia [85]. Obsessive-compuslive symptoms have been widely observed in schizophrenia [86–88], and psychotic symptoms may occur during the course of OCD [89, 90]. These disorders have also been noted to share similar cognitive characteristics [91]. Particularly in OCD patients *with poor insight*, there appears to be a higher genetic risk for schizophrenia as well as a higher comorbidity with schizotpal personality disorder [92]. In both DSM-IV-TR and ICD-10, obsessive-compulsive disorder is listed among the *Anxiety Disorders*.

Pervasive Developmental Disorders

Pervasive developmental disorders (PDD) involve *Autistic Disorder, Asperger's Disorder*, and other related disorders characterized by severe and pervasive

impairment in social interaction skills, communications skills, or the presence of stereotyped behavior, interests, and activities. Due to disorganized or odd behaviors and speech, adults with pervasive developmental disorders are sometimes diagnosed with schizophrenia [93]. There is also a significant symptomatic overlap between schizotypal and schizoid personality disorders and Asperger's Dsiorder [94]. Similarities in genetic abnormality in pervasive developmental disorders and schizophrenia [95, 96] as well as familial diagnostic overlap [97], may be present indicating potentially shared biological pathways. Significant comorbidity between pervasive developmental disorders and schizophrenia or other psychoses have also been reported [98–100].

Psychosis-Risk Syndromes

A clinical or sub-clinical risk syndrome for psychosis has been considered part of the schizophrenia spectrum [101], and often precedes the onset of a full-blown psychotic disorder. While no official diagnosis exists currently, an at-risk syndrome is being reviewed for inclusion in the next revision of the American Psychiatric Association's diagnostic manual, DSM-5 [102, 103]. The proposed criteria are derived from the prodromal or *Clinical High Risk criteria* (CHR) [104] and the *Ultra High Risk criteria* (UHR), and consist of subthreshold or attenuated positive psychotic symptoms with operationalized recency and frequency criteria. The rationale behind the proposed inclusion is that some studies indicate that these criteria can predict the conversion to a psychotic disorder with a 20–50% probability within up to two and a half years [105–109], which can guide preventative treatment strategies. As non-conversions to psychotic disorder generally outnumber conversions, the validity of the psychosis-risk syndrome is still unclear [103, 110].

Currently, diagnostic criteria on psychosis-risk has been mainly used in the evaluation of individuals for research, with symptom severity measured using research diagnostic instruments, such as the *Scale of Psychosis-Risk Symptoms* [111–113] or the *Comprehensive Assessment of At-Risk Mental States* [114]. The CHR criteria, differentiate at-risk patients with moderate to severe attenuated positive symptoms, referred to as CHR+, from at-risk patients that exhibit only nonspecific, attenuated negative symptoms, such as social isolation and deterioration of functioning, referred to as CHR- [104, 115, 116]. The CHR- would often precede the CHR+ state before the eventual onset of psychotic disorder [104]. A past or present episode of positive psychotic symptom would exclude a diagnosis of CHR.

Other groups define the psychosis-risk syndrome using the Ultra-High Risk (UHR) criteria [111, 113, 117]. The UHR state can present in one (or more) of three clinical forms: (1) brief intermittent psychotic syndrome, (2) attenuated positive symptom syndrome, and (3) genetic risk and deterioration syndrome. Patients with *brief intermittent psychotic syndrome* have experienced positive psychotic symptoms only infrequently (unlike in schizophrenia), but at least once a month. The *attenuated positive symptom syndrome* mirrors the CHR+ criteria in requiring only a reduced intensity of positive symptoms. Symptoms must occur at that intensity on

average at least weekly. The *genetic risk and deterioration syndrome* is defined by a combined genetic risk for schizophrenia (or other psychotic disorder) and functional deterioration. The genetic risk criterion can be met if the patient has a first-degree relative with any psychotic disorder and/or the patient meets criteria for schizotypal personality disorder. In addition, there must be overall functional deterioration defined as a 30% or greater drop in *Global Assessment of Functioning* (GAF) score during the last month, compared to 12 months ago [111, 112].

The presence of *basic symptoms* has also been studied as potentially complementary to the UHR criteria, and have been suggested by some authors as a set of criteria that would allow for an earlier detection of psychosis-risk [118–120]. Basic symptoms may involve a range of subjective cognitive and perceptual disturbances [118, 121], and are commonly assessed using the *Bonn Scale for the Assessment of Basic Symptoms* [118].

Critiques of Current Nosology

The next major psychiatric manual revision will be the DSM-5, expected to be published in May 2013. For this reason, and since the DSM generally guides psychiatric research worldwide [122], critiques will mainly focus on those relevant to the DSM classification system.

Differences Across Psychiatric Manuals

As discussed previously, the use of psychiatric diagnostic manuals are not uniform throughout the world. The two most commonly used are that proposed by the World Health Organization, the Mental and Behavior Disorders (Chapter V) of the ICD-10, and that published by the American Psychiatric Association, the DSM-IV [4]. These manuals are reasonably similar in terms of basic content as they are both largely based upon the same body of literature, however some differences exist in diagnostic criteria of individual disorders (including those included in the schizophrenia spectrum, as previously discussed). The DSM for example, requires 6 months of continuous illness at some point in a person's life to make a diagnosis of schizophrenia. There is no empirical basis for selecting 6 months as a cutoff, but it gives a kind of precision, and a putative increase in reliability, to the diagnosis of schizophrenia that it would lack if the definitions simply asked that symptoms be "chronic" [123]. The ICD-10 requires only that one of the cardinal symptoms be present for 1 month or more. Both manuals have the same intentions, but such arbitrary differences in operationalization influence measurements of prevalence across cultures and the selection of subjects for research and treatment.

Much of the differences that exist are of considerable educational interest since they are based upon opinions and clinical traditions, and not necessarily robust evidence. The DSM has been said to have a decidedly American outlook, meaning that

differing disorders or concepts of illness from other cultures (including personalistic rather than naturalistic explanations) may be neglected or misrepresented, while Western cultural phenomena may be taken as universal [124]. Culture-bound syndromes are those hypothesized to be specific to certain cultures (typically taken to mean non-Western cultures). While some of these syndromes are listed in the appendix of DSM-IV, they are not detailed and there remain open questions about the relationship between Western and non-Western diagnostic categories and sociocultural factors.

Validity of Existing Diagnostic Constructs

It has become increasingly recognized that the current nosological framework represented by the DSM-IV, originally developed to promote reliability in making diagnoses, exhibits serious shortcomings with respect to validity [125]. These include extensive comorbidity among diagnoses, overspecification of categories, and the proliferation of "Not Otherwise Specified" diagnoses [126]. Diagnostic manuals provide an operational definition of schizophrenia presenting the disorder as a condition qualitatively different from health and qualitatively different from the other diagnosis. This clear criterion-based definition of mental disorders in the current diagnostic manuals facilitates diagnostic agreement and communication among clinicians [127, 128]. It has high clinical utility, providing information about course, outcome and likely treatment response [129, 130]. Clinical utility, however, does not provide information about the fundamental nature and structure of schizophrenia. If our definition of schizophrenia does not represent a "real" construct in nature, then it will not delineate the true pathology and etiology underlying psychosis.

Mounting evidence suggests that there are no discrete breaks in the distribution of psychotic symptom. Delusions and hallucinations seem to have a continuous distribution in the general population [131–141]. Prevalence estimates of psychotic symptoms in nonclinical samples range from 4% to 17.5 [131, 139] (with methodological differences likely to explain much of this variability) and results from a longitudinal study using the British National Psychiatric Morbidity Survey data found that 4.4% of the general population reported incident symptoms at 18-month follow-up [141]. This skewed continuum of positive psychotic symptoms may be an artifact caused by measurement error, but is more likely indicative of a latent continuous pathology in the general population. This is consistent with the prevailing view that schizophrenia has a multifactorial etiology where many different genes, which interact with each other and with environmental risk factors to cause the disorder, along with different combinations of risk factors resulting in a gradation of exposure and associated range of presentations.

These findings challenge the assumption that schizophrenia exists as a discrete disease entity (categorical latent variable). The requisite population-based studies, using appropriate structural statistical analyses, e.g. finite mixture modeling (and its derivatives) [142, 143] or coherent cut kinetic methods [144] have not been

carried out, so it is conceivable that a dichotomous latent construct could underlie the skewed distribution of psychosis indicators [145, 146]. Although there are significant shortcomings to the definitions that exist in diagnostic manuals, the major disorders contained therein, such as schizophrenia, pick out highly replicable features of psychopathology [123]. The evidence includes the stability of symptom clusters and clinical course across historical time [147] and across cultures [148]. In addition many of the major disorders exhibit a high degree of family aggregation [149].

The commonly used diagnostic categories, created over a generation ago when brain science was in its infancy, do not represent current knowledge about genetics, neural circuits and neurotransmitters, or behavior [125]. In response to this situation, the National Institute of Mental Health (NIMH) of the United States included in its new Strategic plan a specific aim to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" [150]. This goal is being implemented with a new initiative dubbed the Research Domain Criteria (RDoC) project. The intent is to create a framework for creating research classifications that reflect functional dimensions stemming from translational research on genes, circuits, and behavior. Examples of such domains might include executive functioning, fear circuitry, and reward circuitry.

Reliability

The lack of objective tests for mental disorders makes achieving excellent diagnostic reliability, i.e. diagnostic agreement between clinicians, a difficult problem. Given the early state of the science, psychiatric diagnostic manuals rely on phenomenology: symptoms, signs, and course of illness as the basis for diagnosis. Interrater reliability based on phenomenology varies greatly across diagnostic categories in the schizophrenia spectrum, with schizophrenia reported to have good reliability unlike schizoaffective disorder [151]. While it is conceivable that modifying current criteria sets based on empirical evidence could further improve diagnostic reliability, it is unclear if this would be of significant benefit. Some have argued that there is little to be gained and much to be lost in frequently and arbitrarily changing the system [152–154], unless a more fundamental and explanatory understanding of causality is attained. A seemingly small change can sometimes result in a different definition of caseness that may have a dramatic and totally unexpected impact on the reported rates of a disorder [155]. For example, although many other factors were certainly involved, the sudden increase in the diagnosis of autistic, attention-deficit/hyperactivity, and bipolar disorders may in part reflect changes made in the DSM-IV definitions [152].

Phenomenologically based diagnostic systems cannot fully solve the reliability problem. In clinical encounters, information must be elicited from patients who may lack insight into their symptoms as a result of their illness or who may have complex motives ranging from shame to paranoid ideation to drug-seeking that influence

reporting of symptoms. Moreover, it can prove quite difficult to interpret the diagnostic significance of some symptoms, e.g. whether a particularly highly overvalued idea represents an obsession or a psychotic delusion. Ultimately, a more objective system will be required in order to make additional substantial improvements in reliability.

Distinction of Disorders Within the Psychotic Spectrum

The symptoms comprising the schizophrenia diagnosis are also found commonly in the other categories of psychosis. In reality, psychosis is specific neither to schizophrenia nor even to psychiatric disorders. It occurs, for example, in neurological disease (e.g. Alzheimer's disease, Huntington's disease, schizophrenia-like psychosis of epilepsy, and traumatic brain injury) and can be caused by a range of toxic substances or impaired metabolic states. Even Schneiderian first-rank symptoms, which have played such a prominent role in defining the nature of psychotic symptoms in modern diagnostic systems, are not specific to schizophrenia [156]. Similarly, several factor-analytic studies showed that measures of psychosis in schizophrenia do not differentiate psychosis from other forms of psychopathology [157, 158]. Thus, while diagnostic manuals delineate psychotic disorders (e.g. schizophrenia, schizoaffective disorder and delusional disorder) based on specified criteria, the true latent structure of psychosis psychopathology remains to be clarified. The factor solutions across studies have been broadly consistent, demonstrating a 5-factor solution for psychosis – manic, depression, disorganized, positive and negative symptoms [159]. Latent class analyses have shown similar indicator profiles to those from exploratory factor analysis [160, 161]. However, the overlapping co-occurrence of these symptom domains may be indicative of underlying shared risk factors, which are quantitatively rather than qualitatively distinct and continuously expressed. The ambiguous schizoaffective disorder construct, for example, may be the result of trying to demarcate where in reality no latent discontinuity exists. Several molecular genetic studies have also failed to show linkage to schizophrenia on the basis of DSM diagnosis, finding instead stronger evidence for linkage when the phenotype was broadened to include additional psychotic disorders [162, 163].

Organization of the Meta-Structure of Psychotic Disorders

The DSM-IV classifies schizophrenia under the section "Psychotic Disorders", along with disorders such as schizoaffective disorder, schizophreniform disorder, brief psychotic disorder and delusional disorder, which all have in common the presence of some form of reality distortion (i.e. delusions and/or hallucinations). There is a phenomenological similarity where schizotypal pathology can be viewed on a continuum with psychosis. Comparing psychopathology of bipolar disorder and schizophrenia however may support separateness. Much of the manifest

pathology of bipolar disorder is mood disturbance, and reality distortion is not always present. Cognitive impairments are often noted in schizophrenia, bipolar disorder and schizotypal personality disorder [164]. In general, the pattern of cognitive deficits in bipolar disorder is similar to the cognitive profile of schizophrenia, although impairment may be somewhat less severe and in some cases more state dependent [165, 166].

Are-organization of the current meta-structure of psychotic disorders could alternatively reflect familial and genetic risk factors of schizophrenia, in addition to clinical manifestations [102]. In the current version of the ICD, schizotypal (personality) disorder is listed with the psychotic disorders in a common class of disorders, although like DSM, bipolar disorder is classified with "Mood Disorders" due to the predominance of affective symptoms. Among the research findings with some support for a common meta-structure are family and twin studies, which have shown that familial risks are partly shared among schizophrenia and schizotypal personality disorder, and to a lesser extent bipolar disorder [167]. These findings are further corroborated by several large population-based studies, which showed that risk of bipolar disorder is associated with a history of schizophrenia or schizoaffective disorder in parents and siblings [168, 169]. Meta-analyses have generally suggested there are shared candidate genes and chromosomal locations in schizophrenia and bipolar disorder [170–173], although these conclusions have been questioned [174]. Other authors failed to find overlap in the highest-ranking genes for each disorder [173].

Findings from the neuroimaging and neurophysiology literature appear to indicate only weak similarities among the disorders considered for inclusion among the psychotic disorders. Meta-analyses document a 3–4% whole brain volume reduction in schizophrenic probands compared to controls [175–177], that is not consistent with the pattern of loss in Bipolar Disorder [178] or schizotypal personality disorder [179] where brain volume reductions are not commonly seen. In both schizophrenia and bipolar disorder, volume reductions are most consistently reported in cortical gray matter, particularly in frontotemporal regions. Temporal, but not frontal, cortical volume decreases is often found in schizotypal patients [179]. The volumes of deeper lying gray matter regions are generally different in schizophrenia and bipolar disorder. For instance, little (increased amygdala size) or no abnormalities are usually found in bipolar patients, while decreased volumes (e.g. hippocampus, thalamus or basal ganglia) are often noted in schizophrenia patients [180, 181]. While the size of the medial temporal lobe structures (such as hippocampus) are not generally found to be decreased in schizotypal personality disorder, that of other gray matter structures have been variably reported [179]. There have been several reports of reduced white matter integrity in schizophrenia in a variety of regions [182], but there are fewer reports regarding bipolar disorder or schizotypal personality disorder, which are inconsistent [183, 184].

In functional magnetic resonance imaging (fMRI) of schizophrenia and bipolar disorder patients, both similarities [185, 186] and differences [185, 187, 188] in brain activation have been reported depending on task requirement. Very few functional imaging studies have been done in individuals with schizotypal

personality disorder, however abnormalities have been reported when compared to controls [189, 190]. Both differences [191, 192] and similarities [192] to abnormal brain region activity in schizophrenia has been reported in schizotypal individuals.

Bipolar disorder and schizophrenia also show similarities in saccadic eye movement abnormalities [193], reduced prepulse inhibition [194–196], and reduced P300 amplitude and increased latency [197]. Schizophrenia and bipolar disorder probands with a lifetime history of psychosis also show muted inhibition as measured by P50 responses to a paired click paradigm [195]. Saccadic eye movement abnormalities in individuals with schizotypal personality disorder appear to be more similar to that of controls than patients with schizophrenia [197, 198]. Reduced sensorimotor gating measured by prepulse inhibition and P50 responses have been found in schizotypal personality disorder [199]. Compared to controls, both significant [200] and trend level [201] P300 amplitude decreases have also been reported in schizotypal personality disorder.

In summary, there is significant familial and genetic overlap between schizophrenia and schizotypal disorder, and to a lesser degree bipolar disorder, which provides some support for classifying these disorders under a common meta-structure. Both similarities and differences between schizophrenia and the other two disorders exist phenomenologically and in neuroimaging and neurophysiological findings.

Refining Schizophrenia Subtypes

In the current version of the DSM, schizophrenia subtypes are based on the predominant symptomatology at the time of the evaluation of the patient's experiences. There are five subtypes listed in the manual: paranoid, disorganized, catatonic, undifferentiated and residual types. DSM-IV however acknowledges that there is limited value of these schizophrenia subtypes in clinical and research settings (e.g. prediction of course, treatment response, correlates of illness). Alternative subtyping schemes are being investigated, including those derived from dimensional descriptors of schizophrenia psychopathology (e.g., psychotic, disorganized and negative) [4, 202]. The clinical heterogeneity of DSM-IV schizophrenia could be reduced by refinement of the current definition, narrowing the concept to describe more homogenous symptoms clusters or subgroups [203, 204]. One putative categorical subtype is the "deficit syndrome", characterized by enduring primary negative symptoms [205]. Association studies support the clinical usefulness of this subgroup [206–212] but give little information on construct validity. A latent level discontinuity in negative symptoms within (chronic) schizophrenia has been suggested, with an estimated base rate of (28–36%) [213]. Further support for a possible discrete negative subcategory of schizophrenia comes from a study, which used principal components analysis (PCA) to identify dimensions of psychopathology and found the negative factor scores were bimodally distributed in people with a diagnosis of schizophrenia [130]. If the PCA factor does represent a latent dimensional construct then this suggests a quantitative discontinuity in the negative dimension.

Dimensional Representations

The limitations of a purely categorical approach to diagnostic classification are widely documented [214]. A major problem with the categorical approach is that for many disorders in the DSM-IV, there is no evidence for discontinuities in symptom profiles (zones of rarity) and often evidence for the opposite. A diagnostic reliability study of DSM-IV disorders [215] found that for many categories, diagnostic disagreements less often involved boundary issues with other formal disorders but were primarily due to problems in defining and applying a categorical threshold on the number, severity and duration of symptoms. In addition to introducing measurement error, imposing categories on dimensional phenomena leads to a substantial loss of potentially valuable clinical information. The DSM does not provide adequate coverage for clinically significant symptom presentations that fail to meet criteria for formal diagnostic categories [216], and does not provide a sufficient mechanism to record the severity of disorders. Analyses comparing dimensional representations with the traditional categorical diagnostic constructs show the dimensions to be more useful at predicting clinical course and treatment needs, though the different in the discriminative power may be rather small [217, 218]. Thus, dimensions seem to add to the information contained within the diagnostic systems, providing assessments that are more detailed and likely to be important particularly in clinical research.

Usually 4 or 5 different factors or dimensions in schizophrenia have been extracted (depressive, manic, positive, negative, and/or disorganization symptoms), which have been consistent between studies of different patient cohorts [219–223]. These symptom dimensions have been shown to explain more about disease characteristics (e.g. premorbid impairment, the existence of stressors before disease onset, poor remissions or no recovery between episodes and exacerbations, response to neuroleptics, and deterioration) than diagnoses, which add substantial information to diagnostic categories [130].

The current positioning of the clinical significance criterion in many disorder definitions of the DSM-IV illogically confounds a severity measure with a symptom list [224]. Empirically grounded, graded diagnostic thresholds, as exist for hypertension, would require a separation of symptoms and signs from severity measures even for categorical disorders. It nevertheless does not appear ideal to propose a purely dimensional DSM. Indeed, clinical utility is a compelling argument for retaining categorical distinctions in nosology. The question is how and at what level should dimensional elements be incorporated in the DSM. The least drastic option would be to introduce dimensional severity ratings to the existent diagnostic categories and/or the constituent symptom criteria. This alternative would also be the most practical because the categorical system would remain intact and the dimensional rating system could be regarded as optional in settings where its implementation is less feasible (e.g. primary care). Because dimensional ratings would simply be added to the current diagnostic categories, this approach would have several other advantages, including (a) its basis on preexisting and widely studied set of constructs, and (b) the ability to retain functional analytic and temporal (duration) aspects of

diagnosis that are difficult to capture in a purely psychometric approach. Moreover, adding severity ratings to existing categories would provide a standardized assessment system that fosters across-site comparability in the study of dimensional models of psychopathology.

However, simply adding a dimensional approach to existing categories would not resolve many of the key problems in current classification, such as poor reliability and high comorbidity. For instance, "difference in patient report" is a very common source of diagnostic unreliability [212] that would be equally germane to dimensional clinical assessment. The fact that quantitative rating systems already present in the DSM (Axis V Global Assessment of Functioning [GAF] ratings) have been found to be rather unreliable may not bode well for an expanded dimensional classification system [225, 226].

A dimensional view of schizophrenia is more consistent (compared with a categorical one) with polygenic models of inheritance, which account the best for familial transmission of schizophrenia. People with increased risk genes and environmental risk factors are at high risk for schizophrenia, whereas those with moderate risk factors may have related conditions such as schizotypal personality disorder, negative symptoms, neuropsychological impairment, or other neurobiological manifestations of the predisposition to schizophrenia [227]. As has been the case for new diagnostic categories, the introduction of broader trait constructs in the DSM would result in a proliferation of empirical inquiry in this domain (e.g. development of interventions directly targeting these higher order features).

The development, where appropriate, of quantitative scales, that are both scientifically justified and clinically useful for the diagnosis and treatment of mental disorders will be a challenging process, proceeding over years. Undoubtedly, this process will begin with clinical ascertainable scales, but will eventually involve cognitive measures and, in the more distant future, perhaps structural or functional brain imaging and other technologically based measures [123]. A criticism of introducing dimensional measures has been that busy clinicians do not have the time, training, or inclination use dimensional ratings [152]. Indeed, the dimensional components already built into the DSM system (i.e. severity ratings of mild, moderate and severe or every disorder, and the Axis V Global Assessment of Functioning scale) are very often ignored. Including an adhoc, untested, and complex dimensional system in an official nomenclature is premature and will likely lead to similar neglect and confusion [228].

Use of More Proximal Indicators of Disorders

The current definitions of schizophrenia and related conditions depend heavily on symptoms and signs that are probably somewhat distal to the underlying pathoetiology. Integration of defining characteristics, more proximal to the pathological process underlying schizophrenia may occur at some point in the future, although it is unlikely to occur in the next edition of the DSM. Potentially

informative, alternative indicators of psychopathology are the development of standardized and validated functional clinical tests for psychological dysfunction [229].

Mounting evidence suggests that psychosis may be the "fever" of severe mental illness, and is a nonspecific indicator [230]. Psychosis appears to be an end-state condition that, in comparison with other indicators, is a relatively distant consequence of schizophrenia's causes and pathophysiology. These conclusions provide support for an alternative conceptualization of schizophrenic illness, one based on the notion of *schizotaxia* [230]. Meehl [231] introduced the term "schizotaxia" to describe the unexpressed genetic predisposition to schizophrenia, and suggested that individuals with schizotaxia develop either schizotypy or schizophrenia, depending on the protection or liability afforded by environmental circumstances. Faraone and colleagues [232] proposed the use of the term schizotaxia to indicate the premorbid, neurobiological substrate of schizophrenia. If this conceptualization is correct, it may be a more specific expression of this predisposition to schizophrenia than is the DSM-IV diagnosis of schizophrenia. Unlike schizophrenia, schizotaxia is not masked by the florid clinical symptoms and possible neurotoxic consequences of psychosis that are seen in so many other conditions. The criteria would presumably reflect the biological and clinical alterations that occur *before* the advent of psychosis. If these new criteria were used, the diagnosis of schizophrenia could comprise two categories: schizotaxia and schizotaxia with psychosis (schizophrenia) [230]. Tsuang and colleagues [233] operationalized schizotaxia criteria based on the combination of negative symptom and neuropsychological deficits, which are two of the most robust findings in first-degree relatives of patients with schizophrenia. Even if the syndrome is validated, much work will be needed to establish adequate levels of sensitivity and specificity. Further, there will be questions about the degree to which one should diagnosis schizotaxia in the potential absence of symptoms that cause personal distress or functional disability.

Etiology Related Classification

Current diagnostic criteria are based on a categorical approach where diagnostic entities share common phenomenological features. Implicitly, each of these categories is probably produced by one or different specific etiological factors [234]. Based on the complex nature of psychiatric disorders and the current knowledge about disorder etiology, however, it will likely be many years or decades before diagnostic criteria will incorporate biological measures reflecting disorder etiology, such as risk genes or markers [235]. There is nevertheless evidence that one or several of the same genes impact on the risk for developing different disorders, and it may be possible in the future to subtype based on the presence of specific genetic or biological findings. In addition, different trials show that only the combination of a genetic subtype with specific events at a certain point of time during development of an individual creates a risk factor for developing a disorder. Patients with a diagnosis may present with different genetic/environmental combinations. When such

combinations are scientifically well established and are relevant for treatment or prevention strategies it would be important to also consider such gene/environment interactions as a potential subtype scheme within the frame of a broader diagnosis (e.g., individuals with some premorbid features of schizophrenia, the COMT subtype and an important consumption of cannabis) [234].

Cognition in Psychotic Disorders

It is estimated that at least 85% of patients with schizophrenia suffer from a cognitive deficit [236, 237]. These deficits (executive function, working memory, verbal memory, attention) are a better predictor of social functioning than even positive symptoms [238–240], and may be more likely to be associated with biological findings and therapeutic interventions [241]. Cognition may also be more reliably determined than psychotic symptoms, the absence of which can be easily feigned. The DSM-IV makes no mention of the cognitive symptoms of schizophrenia because the criteria were based on older conceptions that focused largely on positive symptoms and noncognitive treatments.

The question of how to incorporate conceptions of cognitive impairment into existing diagnostic criteria for schizophrenia and/or other psychotic disorders raises a challenging set of issues. Including cognitive dysfunction as one of the "criterion A" symptoms for schizophrenia in the DSM-5 would be problematic from a differential diagnostic viewpoint" [242]. A critical question in this regard is whether cognitive impairment as currently determined will facilitate the specificity and/or positive predictive power in identifying those individuals with schizophrenia. Current cognitive methods are unlikely to create a sufficient "point of rarity" with other disorders that would be the sole justification for the inclusion of a cognitive criterion in the diagnosis of schizophrenia [243, 244]. Recent meta-analyses and reviews have demonstrated that the profile of cognitive impairment is similar across schizophrenia, schizoaffective disorder, psychotic bipolar disorder, and even psychotic major depression, though the level of impairment is greater in schizophrenia [245–247].

If included in diagnosis, it is unclear how many different domains of cognition would need to be assessed in order to generate sufficient information about cognitive function in patients. Assessment of multiple domains of cognition (e.g. working memory, episodic memory, processing speed etc) may be impractical for diagnosis, or require specialize training to carry out. One important consideration is whether there may be measures available for use in schizophrenia that, by themselves, can account for a large amount of the variation captured by full neuropsychological assessment. Dickinson and colleagues [248] have shown that impairments on digit symbol-type tasks have the largest effect sizes among many different measures for characterizing cognitive impairment in schizophrenia, as they appear to tap into many different cognitive abilities simultaneously (e.g. working memory, episodic memory, attention, processing speed, etc). Thus, assessment with such measures may provide a useful tool for estimating cognitive dysfunction in psychosis in a

practical and efficient manner when the resources for more extensive evaluations are not available.

Characterizing the longitudinal course of cognitive function may have more utility as a diagnostic tool than cross-sectional assessments of psychopathology. Cognitive dysfunction in individuals with schizophrenia has been demonstrated to be more stable and less dependent on symptom severity than cognitive dysfunction in individuals with other psychotic disorders [247]. Furthermore, in many individuals who develop schizophrenia, cognitive impairments occur very early in life and often precede the onset of any clear clinical indicators of psychosis [249, 250]. The question of whether longitudinal assessments of cognitive function have more predictive utility awaits further research that prospectively compares the stability of cognitive function across psychotic disorders at different stages of illness [251].

Characterizing the Risk Syndrome for Psychosis

Over the years, various groups have argued that minor psychotic symptoms occur in the general population [139, 141, 233] and that psychosis is best conceived as a dimension like hypertension or hypercholesterolemia rather than a distinct category [128]. There is ample evidence that psychosis is "brewing" long before its manifestation as a diagnosable illness [137] and that identifiable signs and symptoms preceding the development of frank psychotic symptoms are evident [252, 253]. DSM-III identified 9 symptoms considered to be "prodromal" for schizophrenia and included them as diagnostic contributors, however these symptoms are not specific to schizophrenia and do not have high positive predictive values for the disorder [253]. In one study, Yung and colleagues [254] reported that for those ultra-high risk individuals who subsequently developed psychosis, diagnoses ranged from schizophrenia, through schizoaffective disorder, brief psychotic disorder, bipolar disorder to major depression.

When biological, psychological and clinical features indicate the existence of an important risk for developing a disorder, a corresponding nosological entity can be beneficial as it can foster more effective earlier interventions and improve outcome [255–257]. Prevention and/or postponing the onset of some disorders such as schizophrenia have been studied as relevant strategies with pharmaceutical and cognitive treatments [258–260]. In research models of psychosis risk syndromes [107], attenuated symptoms of schizophrenia are present which, in some cases, may lead to later florid onset of psychosis. This belief has some validity, which is currently being further tested, but there are negative consequences of such a diagnosis for those concerned, particularly issues of stigma [152–154, 260]. Potential therapeutic interventions in an individual with a "disorder" who may never experience full-blown disorder may expose these individuals to long-term health risks that have not been fully tested. Diagnosis of psychosis risk syndrome in an individual has been likened to telling ten people with the common cold that they are "at risk for pneumonia syndrome" when only one is likely to get the disorder [261]. As well as the distress that may be experienced by the diagnosed individuals and their families, the

logic entailed by a psychosis-risk syndrome might also divert attention away from understanding causes of schizophrenia. Rather than including as official disorders, these subthreshold conditions have been proposed to be included in an appendix of suggested disorders that require more research and testing.

Culture and Ethnicity

Much of the research on psychotic conditions from developing countries – where the vast majority of individuals with psychotic conditions live – is unknown or tend to be dismissed as methodologically flawed by nosologists from developed countries [262]. The substantial differences in the onset, course, and treatment response of psychotic symptoms between developed and less developed countries identified in the international pilot study on schizophrenia [263] have had little effect on the dominant theories of psychosis, which have all been developed in Western countries and based on data from developed countries. Furthermore, studies that identify acute remitting psychosis [264] in developing countries have been largely disregarded by western nosologists. Little attention has been paid to the fact that experience and understanding of psychotic symptoms are embedded in a network of local meanings that vary from nation to nation, within different subcultural groups in a single nation, and over time (as communities undergo sociocultural changes). Culture influences an individual's perception of the world, the content of their thoughts, and therefore the form and quality of psychotic symptoms.

Difficulties in diagnosing mental illness among ethnic minority groups highlight the need for a universal classification system that can be effectively applied. However, the difference in rates of psychotic illness between countries and among different ethnic groups within a country also suggest that viewing culture and ethnicity as confounding variables in the conceptualization of mental illness is misguided. Rather, culture and ethnicity ought to be seen as fundamental elements driving its expression and interpretation.

Whether diagnoses are based on symptom dimensions or diagnostic categories, the instruments for rating symptoms have typically been developed by selecting a subset of useful items from a large preliminary pool of items based on the results of a series of studies involving subjects in Western countries. If the entire process was repeated in a non-Western country, it would almost inevitably result in a very different instrument with different items and a different factor structure [261]. Commonly used structured diagnostic instruments also often do not allow the interviewer to revise the question based on the educational and cultural background of the respondent. In China for example, the huge sociocultural differences between urban and rural residents make it necessary to employ multiple probes to capture the different methods of experiencing and describing specific psychological symptoms [265]. Thus if our system of classifying psychosis is to be relevant to patients in the developing world, then instruments aimed at either making diagnoses or rating symptoms have to be subject to much more sophisticated field studies in non-Western countries.

Future Directions

Current versions of the DSM and ICD have facilitated reliable clinical diagnosis and research, however diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics [266, 267]. The boundaries of categories have not been predictive of treatment response, and may not capture fundamental underlying mechanisms of dysfunction. Given the extraordinary challenges that lie ahead to gain understanding of the etiologies and pathologic processes underlying mental disorders, phenomenology will continue to play the dominant role in the next DSM and ICD [123].

Publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5, will be in May, 2013, during the American Psychiatric Association's annual meeting. ICD-11, is expected to be published in 2014. There have been significant efforts to improve the diagnostic consistency across the two diagnostic manuals. Recommendations for the new manual will continue to be guided by research evidence, with an effort to maintain continuity with the previous revision. DSM-5 is planned to be a living document, which would allow for more frequent revisions, to advance with research developments, as opposed to the traditionally long period between major DSM revisions. In early 2010, the DSM-5 Task Force released the proposed criteria for DSM-5 for public review, some of which are listed below. These suggested changes are considered preliminary, and will likely be further influenced by ongoing research including the DSM5 field trials.

Schizophrenia

Since the publication of DSM-IV, additional data about the relationship between different symptoms of schizophrenia have been generated and dimensions of schizophrenia psychopathology have been further clarified. In view of the minimal utility and diagnostic stability of schizophrenia subtypes (i.e. paranoid, disorganized, catatonic, undifferentiated, and residual), it was recommended that subtypes be eliminated and instead dimensional measures be utilized. Dimensions would be assessed on a 0–4 scale cross-sectionally, with severity assessment based on the past month. Proposed dimensional measures recommended for psychotic disorders include psychopathologic domains of hallucinations, delusions, disorganization, abnormal psychomotor behavior, restricted emotional expression, avolition, impaired cognition, depression, and mania.

Minor revisions to criterion A of schizophrenia were recommended, some of which are stated here. First, there would be a requirement that at least one of the characteristic symptoms be delusions, hallucinations, or disorganized speech, which are the most pathognomic symptoms of schizophrenia. Second, the requirement that only 1 characteristic symptom need be present to meet criteria if that is a bizarre delusion or a Schneiderian first-rank symptom hallucination would be dropped. This was recommended as no unique diagnostic specificity for these characteristic symptoms in comparison to others has been identified. Third,

disorganized behavior would be removed from the symptom option "grossly disorganized and catatonic behavior", leaving only catatonic symptoms. The rationale for this was that disorganized behavior and catatonic cluster separately, the former with general disorganization (both behavior and speech) and the latter in the psychomotor domain of schizophrenia. Fourth, in the negative symptom option, flat affect would be changed to *restricted affect*, which better describe the range of affective experience and expression in schizophrenia.

Schizoaffective Disorder

The current DSM-IV-TR diagnosis schizoaffective disorder is unreliable [42, 268] and has poor temporal stability [38, 269]. Suggested changes for DSM-V are meant to increase the reliability. The diagnosis of schizoaffective disorder requires longitudinal data, to assess temporal overlap of psychotic and affective symptoms (criterion B) and relative distribution over time (criterion C). Clinical settings however, do not usually allow for the direct observation of the required pattern of symptoms over time. Therefore most diagnoses of schizoaffective disorder have to rely on accurate autobiographic memory of the patient, collateral information, or access to health records.

In DSM-IV-TR, Criterion B states "During the same period of illness, there have been delusions or hallucinations for at least 2 weeks *in the absence of prominent mood symptoms*". In DSM-5, suggested changes include changing the latter part of the criterion to "*in the absence of symptoms meeting criteria for a major mood episode*". As mood symptoms are defined more precisely, it is expected to improve the reliability and possibly limit the frequency with which it is used clinically. It would also likely more clearly demarcate this diagnosis from bipolar disorder with psychotic features.

Another aspect of the diagnosis considered for change is Criterion C, which defines the temporal distribution of the illness, and may have the lowest reliability among the schizoaffective disorder criteria [267]. Currently Criterion C states "Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness". Suggested changes would include changing the term "substantial portion" to "substantial portion (over 30%)", also to improve reliability.

Attenuated Psychotic Symptoms Syndrome

Among the more controversial proposals for DSM-5 is a *Psychosis Risk Syndrome*, later renamed *Attenuated Psychotic Symptoms Syndrome*. Still being examined is whether its inclusion is merited in the main DSM-5 manual or in its "Appendix for Further Research". Tentative diagnostic criteria would include "one or more of characteristic symptoms (i.e. delusions, hallucinations or disorganized speech) in attenuated form with intact reality testing, but of sufficient severity and/or frequency

that is not discounted or ignored." Further, these symptoms would have begun in or significantly worsened in the past year, and must be present in the past month and occur on average at least once weekly.

Personality Disorders

Among the three Cluster A personality disorders in DSM-IV-TR, only schizotypal personality disorder is recommended for inclusion into DSM5, albeit with suggested changes. It is recommended that paranoid and schizoid personality disorders be represented and diagnosed by a combination of core impairment in personality functioning and specific pathological personality traits, rather than as a specific personality disorder type. Reasons for reducing the overall number of personality disorders include excessive co-occurrence among personality disorders diagnosed using the categorical system of the DSM [270, 271], and arbitrary diagnostic thresholds for existing personality disorders (i.e. the number of criteria necessary for diagnosis). There is also a significant reformulation of the approach recommended to the assessment and diagnosis of personality psychopathology, including the provision for clinicians to rate dimensions of personality traits and the overall severity of personality dysfunction.

Consideration has also been given to including Schizotypal (personality) disorder among the general category of "Psychotic Disorders", rather than "Personality Disorders" where it is currently located [102]. Classifying schizotypal disorder together with other psychotic disorders like schizophrenia (as is currently done in ICD-10) would reflect research evidence showing their genetic relationship. At the time of publication however, this was not among the recommendations released publically by the DSM-5 task force. The main reservation relates to failure of cases to manifest psychotic symptoms and the fact that antipsychotic drugs are not frontline therapy [102].

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Chapter 3
Toward a Multidimensional Continuum Model of Functional Psychoses for Research Purposes

Michael S. Ritsner

Abstract Schizophrenia (SZ), schizoaffective disorder (SA), major depressive disorder (MDD) and bipolar disorder (BPD) are clinically heterogeneous conditions called "functional psychoses" (FP). The paradigm, underlying the current model of FP, was based on Kraepelinian dichotomy and was a practical starting point for the categorical classification of FP. Nevertheless, the concept is increasingly challenged by emerging data from modern research in the field of clinical, genetic epidemiology, molecular genetics, neuroscience and neurobiological studies. The literature suggests that, despite intensive efforts and progress towards more reliability in classification, no definite and causally relevant biological abnormalities have been identified to date. Because the underlying disease mechanisms are poorly understood it is difficult to define a biologically plausible classification of functional psychoses. Recent research findings support a multidimensional model for FP. This chapter describes proof-of-concept for the Multidimensional Continuum Model (MDC model) of functional psychoses for research purposes. It is based on *multi-dimensional parameterization* of the clinical-endophenotype-genetic domains with a *three-axis continuum* (distribution) of psychopathological and behavior patterns among FP-affected persons, their relatives and the general population, on a *hypothesis-free approach*, and on an *endophenotype strategy*. The MDC model provides a framework for research purposes, in particular, for the study of the interactions between clinical, neurocognitive, behavioral, brain imaging and other neurobiological representations of functional psychoses. Postulated common to functional psychoses etiological and pathogenetic mechanisms include at least four interactive hits: a genetic load hit ("genetic vulnerability"), a neurodevelopmental hit ("neuronal vulnerability"), a stress sensitization hit ("life stress vulnerability"), and a neurodegeneration hit. These hits were presented as a Multi-Hits Vulnerability Model of functional psychoses. Implications for future researches in this field are discussed.

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Keywords Functional psychoses · Schizophrenia · Schizoaffective · Major depressive disorder · Bipolar disorder · Classification · Categorical models · Dimensional models

Abbreviations

BPD	Bipolar disorder
BPRS	Brief psychiatric rating scale
CGI-S	Clinical Global Impression Severity scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. Fourth edition
FP	Functional psychoses
HPA axis	Hypothalamic-pituitary-adrenal axis
HRQL	Health related quality of life
ICD-10	International Classification of Diseases and Related Health Problems. Tenth revision.
MDC model	Multidimensional continuum model of functional psychoses for research purposes
MDD	Major depressive disorder
MHV model	Multi-Hits vulnerability model of functional psychoses
PANSS	Positive and negative syndrome scale
SAD	Schizoaffective disorder
SZ	Schizophrenia

Statement of Conundrum

Functional psychoses (FP) or schizophrenia (SZ), schizoaffective (SAD), major depressive disorder (MDD) and bipolar disorder (BPD) vary widely in clinical presentation and course (onset, remission and relapse), genetic epidemiology and molecular genetics, neuroimaging and neurobiological findings. Indeed, the symptoms of FP are remarkably heterogeneous to the extent that two patients with the same diagnosis (SZ, or SAD, MDD and BPD) can display completely different symptom patterns. Standard guideline criteria of categorical classifications of functional psychoses (DSM-IV [1] and ICD-10 [2]) are widely accepted and have several distinct advantages [3]. Discrimination between FP cannot be soundly based on the phenomenology of psychosis or symptom clusters [4, 5]. Overall, the categorical approach continues to be the focus of much criticism; in particular, research based on the presumption of a single disease has produced weak findings that frequently fail confirmation in replication studies [6–17]. Indeed, many investigators have attempted to dissect the phenotype into homogeneous subtypes using molecular genetics and endophenotype approaches, but these attempts had limited success in

relating the categorical subtypes to biological markers, genetic factors, or treatment response (see reviews [18]).

Converging evidence from critical studies comparing categorical and dimensional models of psychosis demonstrated that symptoms and disease course, risk factors, endophenotypes, and putative neurobiological underpinnings are better explained in terms of continuous distributions [19] (*see review and more specific criticism in Chapter 1 in this volume and other chapters of this book*). It is clear that standard nomenclatures do not represent disease entities with separate etiologies or rather different facets of the same disease. However, a recently published draft of the DSM-V is based on the same categorical model of functional psychoses (http://www.dsm5.org/Pages/Default.aspx).

Thus, other conceptualizations of FP for research purposes are warranted. A promising and useful line of research for assessing the validity of competing definitions or continuum models in psychotic disorders is to establish a strategy that combines multidimensional and polydiagnostic approaches to define clinical markers or phenotypes [20]. As an initial step in this endeavor, Brown and Barlow [21] suggest introducing dimensional severity ratings to the existent diagnostic categories and criteria sets. Therefore, the most useful approach to classification seems to be the complementary use of categorical and dimensional representations of functional psychoses [22, 23]. Dutta and colleagues [24] consider that at present the best option is to implement a hybrid of a categorical-dimensional approach in DSM-V. This would introduce the benefit of increased explanatory power of clinical characteristics, without completely dismissing the traditional paradigm of the Kraepelinian dichotomy. The dimensional approach to classification of functional psychoses is not intended to substitute categorical organization but rather to complement it in clinical practice and to challenge the exclusivity of the categorical approach in research settings. Current data indicate that psychotic disorders are best understood dimensionally rather than categorically [25–27]. Setting the boundaries for psychosis is not a limiting problem in dimensional models as in categorical models, but whether or not there is a continuum from normality to psychosis is controversial. Current discussions about dimensional and categorical approaches, which both have value, and limitations, are presented [28]. *Nevertheless, no proposals have been offered for introducing dimensional classification in the diagnostic system in a valid and feasible manner*.

Recently, the National Institute of Mental Health (NIMH) included in its new Strategic Plan a specific aim to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" [29]. This goal is being implemented with a new initiative dubbed the Research Domain Criteria project. The intent is to create a framework for research classifications that reflect functional dimensions stemming from translational research on genes, circuits, and behavior (http://www.nimh.nih.gov/research-funding/newsletter/2009-july-inside-nimh.html#message-from-the-nimh-director). Examples of such domains might include executive functioning, fear circuitry, and reward circuitry [30].

Proof-of-Concept for a Multidimensional Continuum Model

Basic principles applied to the conceptualization of a *Multidimensional Continuum Model* (MDC model) [31] of functional psychoses for research purposes include (see Fig. 3.1):

1. Recognizing a *three-axis continuum* that precedes the distribution of phenotypic dimensions of functional psychoses: *one axis* represents a phenotypic continuum among *FP-affected persons, second axis* – among *relatives of probands with* functional psychoses, and *third axis* – in the *general population* (Fig. 3.2). Variation within each continuum of psychotic experience has been recently discussed [32].
2. Using a *multidimensional approach* that allows us to assess all phenotypic expressions of functional psychoses such as psychopathological symptoms, aggressive and suicidal behaviors, insight, cognitive functioning, and health related quality of life, general functioning, side effects, neurobiological and other characteristics.
3. Using a *hypothesis-free (empirical) approach* for parameterization and classification of the phenotypic expressions of functional psychoses.

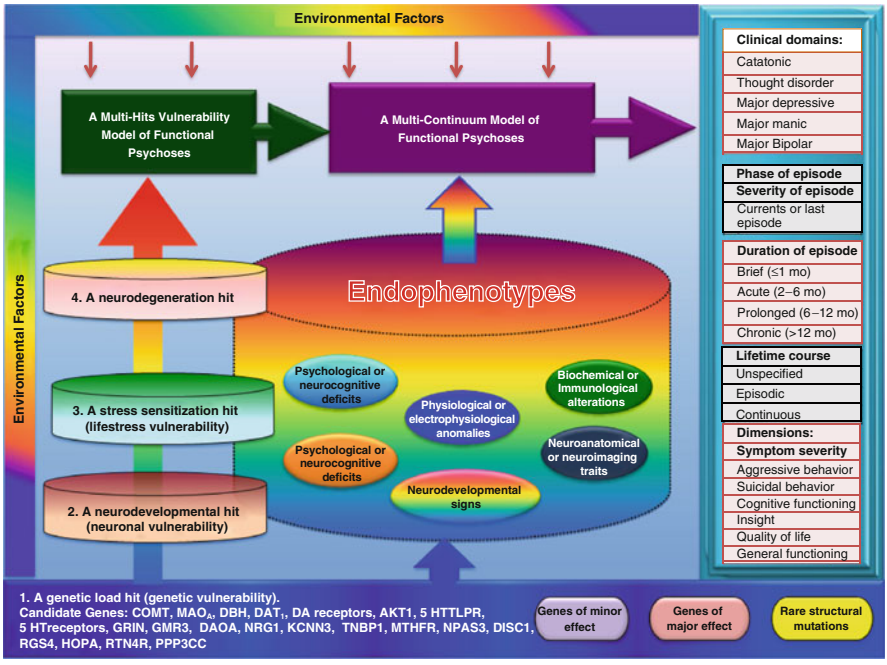


Fig. 3.1 Multidimensional continuum model of functional psychoses for research purposes (version 1.1). © M.S. Ritsner 2011 and used by permission

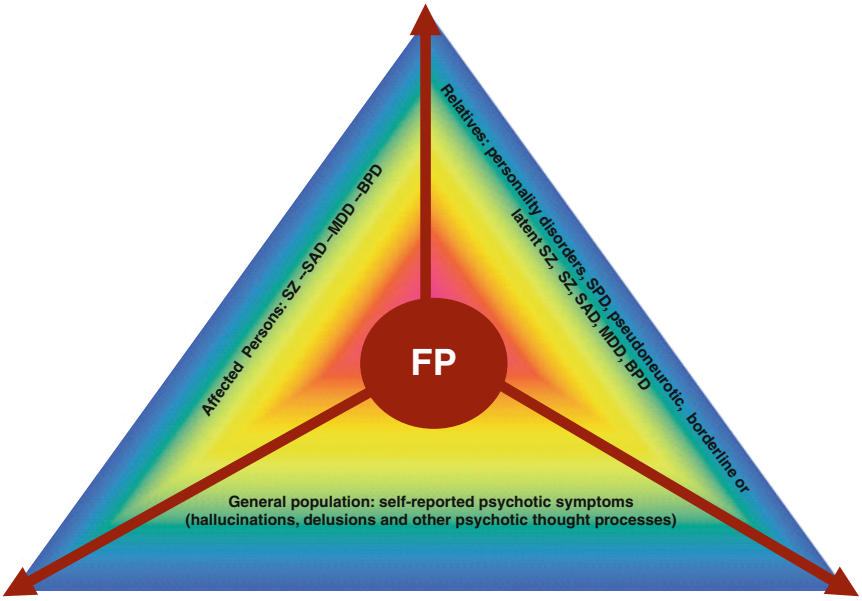


Fig. 3.2 A Three-axis continuum model of functional psychoses (FP). © M.S. Ritsner 2011 and used by permission

4. Using the *endophenotype approach* [33] for investigating gene-phenotypic relationships in order to define future typology of functional psychoses based on etiological and pathophysiological (neurobiological) mechanisms.
5. Recognizing *unitary etiological and pathogenetic components* underlying functional psychoses.

According to the MDC model each patient with functional psychoses may be characterized by the following parameters (Table 3.1):

(a) phase of episode,
(b) severity of episode,
(c) current or last episode,
(d) duration of episode,
(e) lifetime course, and
(f) phenotypic domains.

The dimensions of the phenotypic expression of current mental health state are assessed using psychiatric rating scales, a cognitive test battery and self-reported inventories: catatonic, positive and negative symptoms, aggressive and suicidal behaviors, depressive, anxiety, and mania symptoms, emotional and somatic distress, insight, cognitive functioning, health related quality of life (HRQL), general

Table 3.1 Measuring severity of phenotypic dimensions of functional psychoses

Parameters of phenotypic expression	Domains of functional psychoses				
	Catatonic domain	Thought disorder domain	Major depressive domain	Major manic domain	Major bipolar domain
Phase of episode	Acute (relapse), full (asymptomatic) or partial (asymptomatic) remission; unspecified. PANSS remission items may be considered according to their factor loadings [51, 122, 123]. Remission in SZ may be measured either by improvements in overall psychopathology from baseline (as measured by statistically significant percentage reductions in all thirty PANSS) items or by reduction below specific threshold levels (e.g.: scores of less than 3 in all thirty PANSS items) [124, 125]				
Severity of episode	Clinical Global Impressions Scale [126]. Based on work by Leucht and others [127–129], being considered "mildly ill" according to the CGI approximately corresponded to a PANSS total score of 58, "moderately ill" to a PANSS of 75, "markedly ill" to a PANSS of 95 and severely ill to a PANSS of 116. To be "minimally improved" according to the CGI score was associated with a mean percentage PANSS reduction of 19, 23, 26 and 28% at weeks 1, 2, 4 and 6, respectively. The corresponding figures for a CGI rating "much improved" were 40, 45, 51 and 53%				
Current or last episode	A prodromal episode, a single (or first) episode, a recurrent episode (number of episode)				
Duration of episode	Weeks or months				
Life time course	Unspecified, continuous, episodic				
Severity of symptoms	Bush-Francis catatonia rating scale [130]; Brief psychiatric rating scale [34], Positive and negative syndromes scale [35], Scale for the assessment of negative symptoms [131], Calgary scale for depression in schizophrenia [132], Hamilton depression scale [133]; Hamilton anxiety scale [126]; Bech-Rafaelsen mania rating scale [134], Clinician-administered rating scale for Mania [135]; Overt aggression scale [136], Life history of aggression scale [137]				
Insight (awareness)	Insight and treatment attitudes questionnaire [138], Scale to assess unawareness of mental disorder [139–141]				
Cognitive functioning	Cambridge automated neuropsychological test battery [142], Measurement and treatment research to improve cognition in schizophrenia [143], Mindstreams computerized cognitive test battery [144]				
Quality of life	Quality of life enjoyment and life satisfaction questionnaire [145], Heinrichs-carpenter quality of life scale [146], World Health Organization quality of life-bref scale [147, 148]				
General functioning	Global assessment of functioning scale [126]				
Side effects	Extrapyramidal symptom rating scale [149, 150], Barnes akathisia scale [151], Simpson-angus scale [152], abnormal involuntary movements scale, Distress scale for adverse symptoms [63]				

functioning and side effects. Some interview-based scales have been developed to measure the full range of psychiatric symptoms, such as the Brief Psychiatric Rating Scale (BPRS) [34] and the Positive and Negative Syndrome Scale (PANSS) [35], whereas other interview-based scales have been designed to tap specific dimensions, such as the Scale for the Assessment of Negative Symptoms (SANS) [36]. The same classification holds true for self-report scales. A battery of standardized psychometric scales should be administered to measure all these dimensions (Table 3.1). These and other (well-known or new) instruments should be validated, if possible, shortened and divided to 2–3 sets according to needs of different research purposes.

Phenotypic domains: There is wide agreement among psychiatrists and biological researchers that functional psychoses are a multi-dimensional spectrum of broadly heterogeneous disorders, but there is less consensus concerning the number and types of disorders. My research and clinical experience of treating patients with functional psychoses over the last 30 years suggests that the functional psychoses continuum may be currently divided into five *phenotypic (clinical) domains:*

(a) catatonic,
(b) thought disorder,
(c) major depressive,
(d) major manic, and
(e) major bipolar.

At this stage, researchers may use some DSM-IV clinical criteria (Table 3.2) for domain representations in order to search for FP domains that will be based on *phenotypic dimensional-endophenotype-gene associations*.

Detailed discussion about each FP-domain is beyond the scope of this chapter; the reader is advised to refer to the other relevant chapters, however I do have a few comments.

- *Catatonia* is a motor dysregulation syndrome described by Karl Kahlbaum in 1874 who considered it an independent disease. Emil Kraepelin made it a linchpin of his concept of dementia praecox [37]. Catatonia is a distinct neuropsychiatric syndrome (non-malignant, malignant, a dream-like stupor) that is increasingly recognized both clinically and in ongoing research [38]. The DSM-IV recognizes catatonia as a distinct diagnostic category (catatonia due to organic mental disorder), a subtype of SZ, as an episode of MDD and BPD and in the framework of neuroleptic malignant syndrome. Catatonia was found in 10–38% of psychiatric populations. Fink [39] asked to divorce catatonia from SZ and to recognize catatonia as an independent diagnostic class in the forthcoming DSM-V. Clinicians developed rating scales to identify the catatonia syndrome and applied the immediate relief afforded by a barbiturate or a benzodiazepine as a diagnostic test, the lorazepam test. Heckers and colleagues [40] mentioned three compelling reasons to change the classification of catatonia in the next edition of

Table 3.2 Definition of functional psychoses domains in the terms of DSM-IV [1]

FP-domains	Included (DSM-IV codes)	Excluded
Catatonic domain	Schizophrenia, catatonic type (295.20)	Catatonic disorder due to general medical condition (293.89); catatonia in framework of neuroleptic malignant syndrome
Thought disorder domain	Schizophrenia (295.1, 295.3, 295.6, 295.9), schizophreniform disorder (295.4), schizoaffective disorder (295.7), delusional disorder (297.1), brief psychotic disorder (298.8), shared psychotic disorder (297.3); MDD and BPD with mood-incongruent psychotic features.	Schizophrenia, catatonic type (295.20); alcohol-induced psychotic disorder with hallucinations (291.3) and with delusions (291.5); substance-induced psychotic disorder with delusions (292.11) and with hallucinations (292.12); psychotic disorder due to general medical condition with delusions (293.81) and with hallucinations (293.82)
Major depressive domain	Major depressive disorder, single episode (296.2x) and recurrent episode (296.3x); bipolar II disorder (296.89)	Major depressive episode with mood-incongruent psychotic features; dysthymic disorder (300.4); alcohol-induced mood disorder (291.8); substance-induced mood disorder (292.84); mood disorder due to general medical condition (293.83); bipolar I disorder with most recent episode hypomanic (296.40) and unspecified (296.7)
Major manic domain	Bipolar I disorder with manic episode (296.0x)	Manic episode with mood-incongruent psychotic features; alcohol-induced mood disorder (291.8); substance-induced mood disorder (292.84); mood disorder due to general medical condition (293.83); bipolar I disorder with most recent episode hypomanic (296.40) and unspecified (296.7); cyclothymic disorder (301.13); bipolar II disorder (296.89)
Major bipolar domain	Bipolar I disorder with most recent episode manic (296.4x), mixed (296.6x) and depressed (296.5x) At least two episodes (one manic and other depressive) should be documented.	Major depressive, manic, and mixed episodes with mood-incongruent psychotic features; bipolar II disorder (296.89); alcohol-induced mood disorder (291.8); substance-induced mood disorder (292.84); mood disorder due to general medical condition (293.83); bipolar I disorder with most recent episode hypomanic (296.40) and unspecified (296.7); cyclothymic disorder (301.13)

the DSM: (1) catatonia is often not recognized, (2) a better recognition of catatonia would facilitate proper treatment, and (3) a better recognition of catatonia as a diagnostic entity would catalyze the dormant research of the neural and genetic mechanisms of catatonia. Authors claim that removing catatonic symptoms as a diagnostic feature of schizophrenia from the DSM would affect the classic phenotype of SZ. However, "the classic phenotype of SZ" has already been affected by many clinical, epidemiological, genetic and neurobiological studies [7–17, 41–43].

- The *thought disorder domain* exhibits widely diffuse positive symptoms (marked delusions with or without hallucinations) with disturbances of emotion and a broad range of negative symptoms, cognitive decline, HRQL and functional impairments with personality deterioration. Following Jaspers' hierarchical principle stating that "schizophrenic" symptoms have diagnostic prominence over "mood" symptoms for diagnostic and prognostic purposes [44] the MDC model suggests including in this domain patients with depressive and manic episodes with *mood-incongruent psychotic features*. Accordingly, such patients should be excluded from the major depressive domain, the major manic domain and from the major bipolar domain.
- Furthermore, the presence of a *mania episode* in the absence of depressive episodes is insufficient for a diagnosis in the *major bipolar domain*. Lastly, dysthymic and cyclothymic disorders should be removed from FP since they are characterized by chronic, *non-psychotic mild signs and symptoms*.

Thus, preliminarily, a "diagnosis" for research purposes of a person with functional psychosis could be characterized by clinical domain (*catatonic, thought disorder, major depressive, major manic or major bipolar*) domain, phase of episode, severity of episode, current or last episode, duration of episode, life time course, and specific measures of the phenotypic expressions (Table 3.1).

Symptom Dimensions

The emerging dimensional approach to classification and treatment of psychiatric disorders calls for better understanding of diagnosis-related variations in psychiatric syndromes and for proper validation of psychometric scales used for the evaluation of those syndromes. The PANSS is a well-established rating scale used in the research of schizophrenia and related disorders. Findings from this rating scale are usually presented as mean scores (total and/or sub-scales), nevertheless, raw scores include much more information such as symptom severity, factor structure, symptom frequency and patterns. Psychotic symptoms such as hallucinations and delusions, disorganized speech and behavior, and negative symptoms are distributed along a continuum that extends from SZ to psychotic mood disorders with increasing levels of severity [45]. For the translation of research results into practice, understanding of the PANSS scores from a clinical perspective is essential.

Factor Structure: The study of symptom structure serves two main purposes in the field of psychopathology research. First, the identification of consistent patterns of symptom clusters may help identify homogeneous subgroups of patients and provide validation for diagnostic concepts. Second, distinct clusters may hypothetically reflect distinct pathophysiologies within the schizophrenic disorder [46, 47]. The symptoms of FP aggregate in factors. Different factor structures with solutions have been found using exploratory factor analyses on the PANSS. Regarding the number of putative dimensions underlying psychosis, there is some consensus that there are 3–7 factors underlying the latent structure of psychosis: reality distortion, disorganization, negative symptoms, catatonia, mania, and depression. Several symptom dimension models were constructed for SZ from the 30 PANSS items:

1. a three-factor model was established with positive, negative, and general psychopathological scale scores [48].
2. five-factor models with (a) anergia, thought, activation, paranoid, and depression factors or clusters [48]; (b) negative, positive, cognitive, excitement and depression components [49, 50]; and (c) negative factor, positive factor, activation, dysphoric mood and autistic preoccupation [51].
3. Van den Oord et al. [52] revisited the factor structure and external validity of the PANSS in a sample of 500 participants with DSM IV diagnoses of schizophrenia. They found that five factors corresponded closely to those typically derived in other studies: Negative, Positive, Excited/Activation, Anxious-Depressed/Dysphoric, and Disorganized/Autistic preoccupation, while the sixth factor seemed to have face validity and was labeled Withdrawn. With the exception of Anxious-Depressed/Dysphoric, Cronbach's Alpha ranged from 0.70 to 0.85 suggesting an acceptable internal consistency.
4. Six- and seven factor solutions have also been reported [51, 53].

There is evidence based on the use of exploratory factor analysis of the PANSS in heterogeneous populations of patients with FP. Purnine and associates [54] examined the reliability and validity of PANSS among outpatients with schizophrenia (N = 75) and mood disorders (N = 61). Four of five factors were similar to those reported among inpatients with schizophrenia. Daneluzzo and collegues [55] compared the clinical characteristics of manic patients with those of SZ patients evaluated with PANSS. The clinical symptoms of 148 BPD patients and 86 SZ patients hospitalized for an index psychotic episode were assessed. Schizophrenic patients showed more positive and cognitive symptoms than BPD. The factor analysis of the two PANSS scores showed a three-factor solution with "positive", "negative" and "mixed" depressive-activated factors for BPD and "positive", "negative" and "depressive" factors for SZ. Factor analysis in a large sample (N = 1,294) of patients diagnosed with DSM-IV schizophrenia (n = 460), BPD (n = 726) and delusional disorder (n = 108) subjects indicated that the symptomatology of major psychoses is composed of the following five factors: mania, positive symptoms, disorganization, depression and negative symptoms [56]. Eisenberg and associates [57] administered the PANSS to subjects with SZ (n = 305), organic brain disease

(n = 66) and major depressive disorder (MDD, n = 75). The results of this study indicate diagnosis-related variations in the negative and depressive syndrome dimensions in schizophrenia, organic brain disease and MDD. These results also validate limited use of the PANSS for evaluation of negative and depressive syndromes in disorders other than schizophrenia. Overall, this data suggested that positive, negative, and disorganization factors are not specific to SZ; this is consistent with a dimensional view of psychopathology in FP [58]. Finally, Rietkerk et al. [59] investigated whether the symptom dimensions "reality distortion", "psychomotor poverty" and "disorganization" are heritable phenotypes. Data from twin and affected sibling studies are consistent with a genetic contribution to the disorganization dimension. These data suggest that only the disorganization symptom dimension may provide a useful alternative phenotype for genetic research. Additional research is necessary to reach definitive conclusions.

Symptom Frequency, Numbers and Patterns (Fig. 3.3): PANSS item raw scores are not particularly helpful for norm-referenced interpretation. *A raw score of 3 and more for each PANSS item may be used as a cutoff for a clinically relevant symptom*. Thus, we can progress from symptom (item) severity to symptom frequency, numbers and patterns that may lead us to categorical clinical presentation of mental health state of patient.

For instance, Fig. 3.4 shows the frequency of PANSS symptoms (defined as 3 and more raw scores) for 579 inpatients and outpatients with various severities

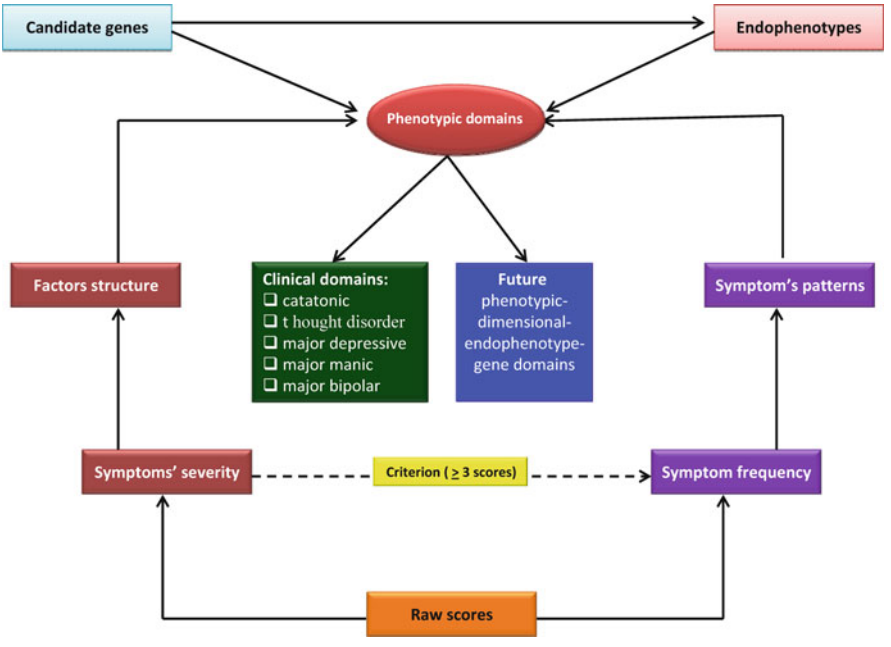


Fig. 3.3 Analysis of dimensional and categorical parameters are based on PANSS raw scores. © M.S. Ritsner 2011 and used by permission

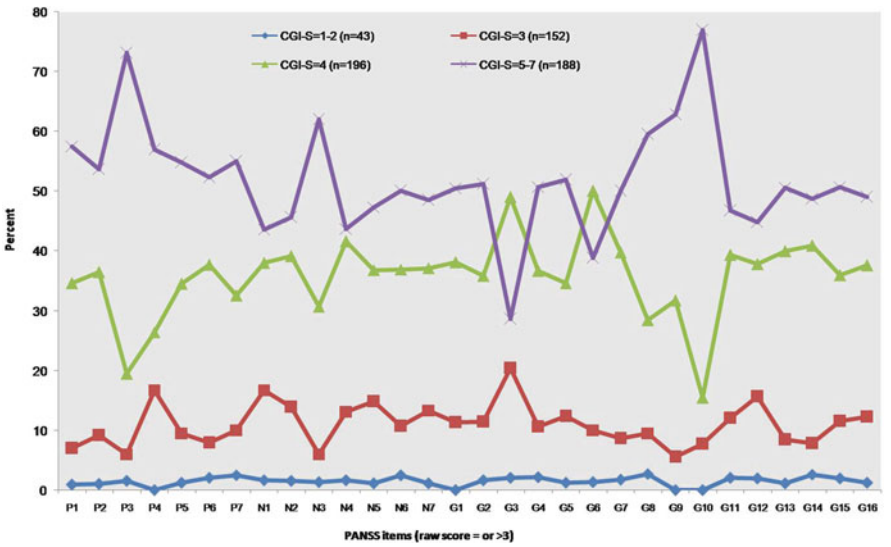


Fig. 3.4 Frequency of PANSS symptoms (defined as 3 and more row scores) among persons with various severities of functional psychoses measured by CGI-S

Table 3.3 Mean number of PANSS symptoms and DSM-IV diagnoses of 579 patients with functional psychoses

Severity of illness	Number of PANSS symptoms		Distribution of patients by DSM-IV diagnoses (codes)						
	Mean	SD	295.1	295.3	295.6	295.7	295.9	296	Total
CGI-S (1–2 scores)	1.6	4.2	0	29	10	1	0	3	43
CGI-S (3 score)	3.7	4.9	1	91	33	14	8	5	152
CGI-S (4 score)	8.9	5.4	7	100	28	35	8	18	196
CGI-S (5–7 scores)	12.7	5.0	13	120	21	20	8	6	188
Total	–	–	21	340	92	70	24	32	579

CGI-S – Clinical Global Impressions Scale: 0 = Not Assessed; 1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients

of functional psychoses as measured by CGI-S (Table 3.3). As can be seen, the higher the CGI-S scores the higher the frequency and the most PANSS symptoms. In addition, these findings might be presented as the "number of PANSS symptoms" (Fig. 3.5), and as individual patterns of symptoms (Fig. 3.6). These individual patterns look different than mean scores of five symptom factors (Fig. 3.7).

Temporal Stability: One potential challenge of the dimensional approach is the assumption that FP patients experience drastic symptom changes over time. For a

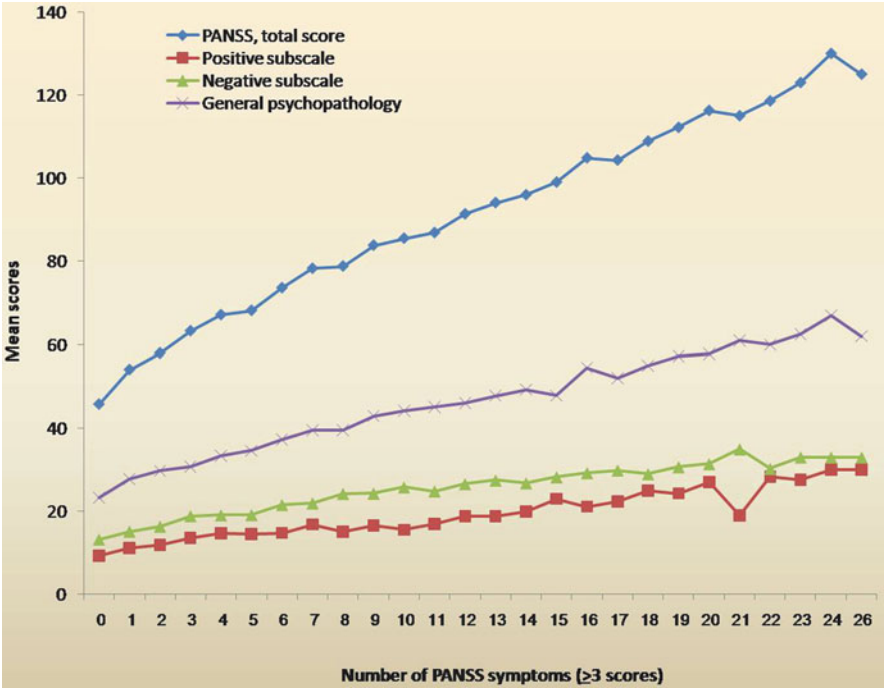


Fig. 3.5 PANSS positive, negative, general and total mean scores by number of symptoms among 579 patients with functional psychoses

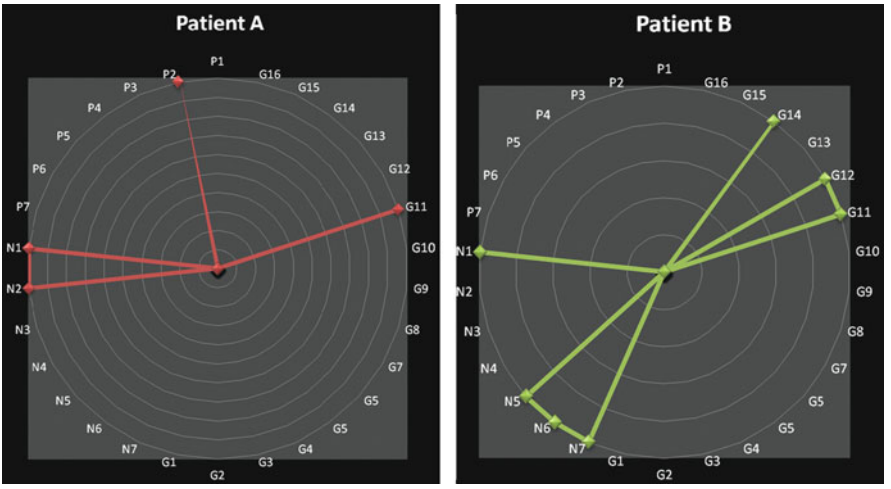
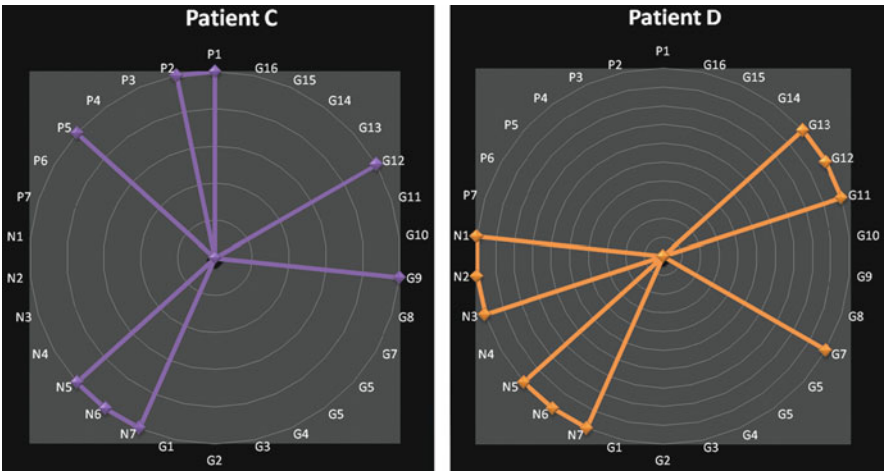
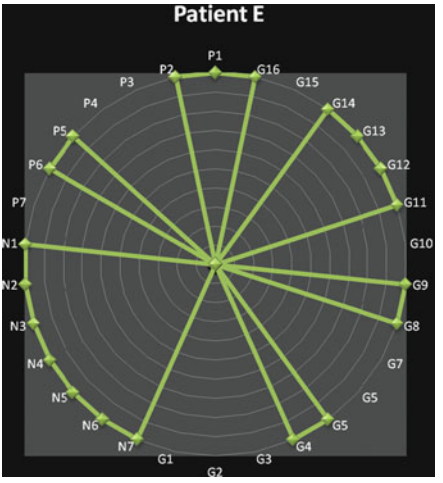


Fig. 3.6 Individual patterns of PANSS symptoms among persons with functional psychoses. PANSS items: positive: P_1–P_7, negative: N_1–N_7, and general psychopathology: G_1–G_{15}





Patients	Sex	Age (yr.)	DSM-IV	Illness duration (yr.)	CGI-S, score	PANSS, score	Number of symptoms
A	Men	37	295.3	9	3	72	4
B	Men	42	295.6	17	4	82	7
C	Men	23	295.3	6	4	83	8
D	Women	29	295.3	10	3	92	10
E	Men	22	295.3	5	4	112	20

Fig. 3.6 (continued)

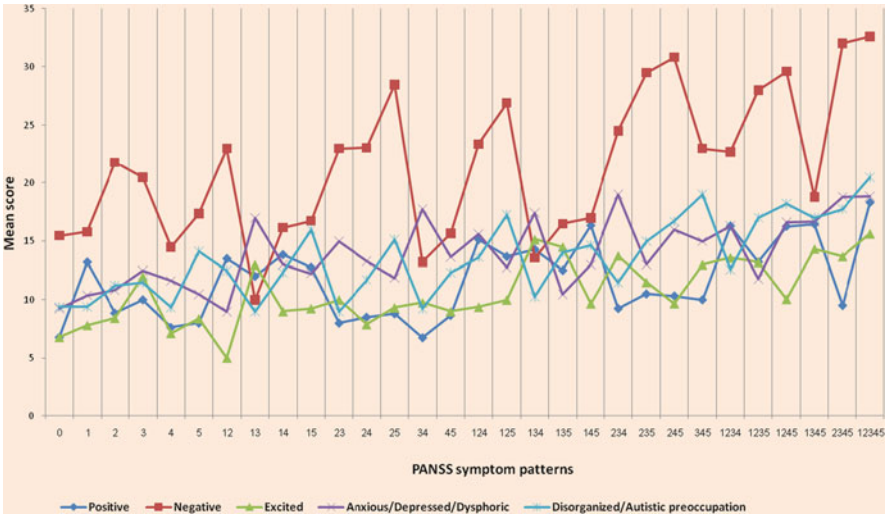


Fig. 3.7 Mean scores of PANSS factors by symptom patterns among 579 patients with functional psychoses. *Factor structure*: Positive factor (P_1, P_2, P_5, P_6, G_9), Negative factor (N_1:N_4, N_6, G_5, G_7, G_{13}, G_{16}), Excited or activation factor (P_4, P_7, G_4, G_8, G_{14}), Mood (anxious depressed/dysphoric) factor (G_1:G_3, G_6, G_{12}, G_{15}), Disorganized or autistic preoccupation factor (P_3, N_5, N_7, G_{10}, G_{11}, G_{13}). *Symptom patters*: 0 = all PANSS items ≤3 scores; 1 = Positive factor symptoms (at least one from P_1, P_2, P_5, P_6, G_9 items > 3 scores); 2 = Negative factor symptoms (at least one from N_1:N_4, N_6, G_5, G_7, G_{13}, G_{16} items > 3 scores); 3 = Excited factor symptoms (at least one from P_4, P_7, G_4, G_8, G_{14} items > 3 scores); 4 = Mood factor symptoms (at least one from G_1:G_3, G_6, G_{12}, G_{15} items > 3 scores); and 5 = Disorganized factor symptoms (at least one from P_3, N_5, N_7, G_{10}, G_{11}, G_{13} items > 3 scores). Consequently, for instance, pattern 12 includes Positive and Negative symptoms; pattern 235 means Negative-Excited-Disorganized symptom pattern, and ctr

dimensional approach to be useful, some degree of symptom stability would be expected, but few longitudinal studies examined the evolution of symptoms per se. In a longitudinal study of symptoms, Arndt et al. [60] found that the negative symptoms were already prominent during the patients' first episode and remained relatively stable throughout the 2 years of follow-up. The positive symptoms of disorganization and psychoticism were found to be prominent at intake and declined over the course of the follow-up period. Repeat examinations of patients revealed results that further support the validity, internal consistency and inter-rater reliability of the five-factor models of SZ psychopathology as measured by the PANSS [50, 61, 62]. Reichenberg et al. [47] examined the stability of symptoms of SZ over time, focusing on the stability of symptom structure. Symptoms were assessed with the PANSS of 215 chronic patients followed up for as long as 4 years. The results demonstrate that despite changes in the severity of symptoms in individual patients with SZ, the factor structure and interrelatedness of symptoms have considerable stability over time.

The results long-term study [63, 64] of 108 patients that met DSM-IV criteria for SZ or SAD for 10-year period demonstrate a reduction in PANSS total scores

Table 3.4 Frequency of PANSS symptoms (scores ≥3) among 108 patients with schizophrenia and schizoaffective disorders at initial assessment and over 10-year follow up

		Initial assessment		10-year follow up assessment			
	Variables	*n*	%	*n*	%	χ^2 test	*p*
P1	Delusions	41	38.0	28	25.9	3.6	0.058
P2	Conceptual disorganization	50	46.3	35	32.4	4.4	0.036
P3	Hallucinatory behavior	16	14.8	13	12.0	0.4	0.55
P4	Excitement	17	15.7	12	11.1	1.0	0.32
P5	Grandiosity	15	13.9	16	14.8	0.04	0.85
P6	Suspiciousness	37	34.3	28	25.9	1.8	0.18
P7	Hostility	11	10.2	1	0.9	8.8	0.003
N1	Blunted affect	60	55.6	84	77.8	12.0	0.0005
N2	Emotional withdrawal	57	52.8	46	42.6	2.2	0.13
N3	Poor rapport	33	30.6	17	15.7	6.7	0.009
N4	Passive/apathetic	44	40.7	42	38.9	0.1	0.78
N5	Difficulty in abstract thinking	63	58.3	68	63.0	0.5	0.49
N6	Lack of spontaneity	45	41.7	31	28.7	4.0	0.046
N7	Stereotyped thinking	65	60.2	48	44.4	5.4	0.020
G1	Somatic concern	16	14.8	22	20.4	1.1	0.28
G2	Anxiety	29	26.9	7	6.5	16.1	0.0001
G3	Guilt feelings	.7	6.5	11	10.2	1.0	0.32
G4	Tension	34	31.5	4	3.7	28.7	0.0001
G5	Mannerism and posturing	27	25.0	5	4.6	17.8	0.0001
G6	Depression	14	13.0	16	14.8	0.2	0.69
G7	Motor retardation	10	9.3	7	6.5	0.6	0.45
G8	Uncooperativeness	13	12.0	5	4.6	3.9	0.049
G9	Unusual thought content	33	30.6	17	15.7	6.7	0.009
G10	Disorientation	4	3.7	3	2.8	0.2	0.70
G11	Poor attention	37	34.3	21	19.4	6.0	0.014
G12	Lack of judgment and insight	64	59.3	55	50.9	1.5	0.22
G13	Disturbance of volition	52	48.1	19	17.6	22.8	0.0001
G14	Poor impulse control	22	20.4	19	17.6	0.3	0.60
G15	Preoccupation	39	36.1	18	16.7	10.5	0.001
G16	Active social avoidance	56	51.9	22	20.4	23.2	0.0001

(p=0.044), and general psychopathology (p=0.008). Ratings of negative and positive symptoms did not change significantly during the follow-up period. When frequency of PANSS items (scored ≥3) was analyzed, two groups of symptoms were found (Table 3.4):

- *Groups of patients with stable frequency of symptoms* [delusions (P_1), hallucinatory behavior (P_3), excitement (P_4), grandiosity (P_5), suspiciousness (P_6), emotional withdrawal (N_2), passive/apathetic (N [4]), difficulty in abstract thinking (N_5), somatic concern (G_1), guilt feelings (G_3), depression (G_6), motor

retardation (G_7), disorientation (G_{10}), lack of judgment and insight (G_{12}), poor impulse control (G_{14}), active social avoidance (G_{16})]; and

- *Groups of patients with decreased frequency of symptoms* [conceptual disorganization (P_2, $p = 0.036$), hostility (P_7, $p = 0.003$), poor rapport (N_3, $p = 0.009$), lack of spontaneity (N_6, $p = 0.046$), stereotyped thinking (N_7, $p = 0.020$), anxiety (G_2, $p<0.001$), tension (G_4, $p<0.001$), mannerism and posturing (G_5, $p<0.001$), uncooperativeness (G_8, $p = 0.049$), unusual thought content (G_9, $p = 0.009$), poor attention (G_{11}, $p = 0.014$), disturbance of volition (G_{13}, $p<0.001$) and preoccupation (G_{15}, $p = 0.001$)]. Only frequency of blunted affect (N_1) was increased from 55.6% at initial assessment to 77.8% after 10-year period ($p = 0.0005$).

Thus, these dimensions have considerable validity and temporal stability. Longitudinal studies that followed patients from childhood to adulthood are needed to further understand the course of FP symptoms over longer periods of time.

Subtyping FP into mutually exclusive entities could be an endless process and would have the same limitations as some of the categorical approaches. A dimensional continuum model of FP provides researchers with a more complete picture. Because monosymptomatic patients are rare, dividing FP into mutually exclusive DSM-IV illnesses is unreasonable and impractical. From a dimensional perspective, each patient can score in one or more symptom dimensions. The focus is on symptom severity, frequency, profile or patterns. FP research should concentrate on identifying the general and specific etiological factors that contribute to the development of phenotypic domains. A dimensional approach assumes that FP symptoms are normally distributed in the general population. Future genetic endophenotype oriented studies involving patients from across a broad spectrum of FP or involving population-based samples may be particularly informative if phenotypic dimensions are stable traits.

Toward a Unitary Pathogenetic Mechanism

The etiology of FP is a topic of controversial debate, while researchers strive to achieve a common objective. The goal is to identify the cause(s) of FP to understand the complex interplay between environment and gene regulation. A conclusive identification of specific etiological factors or pathogenic processes in the FP has remained elusive, although recent studies have shown that several neurobiological alterations in domains of brain structure, physiology and neurochemistry may reflect diverse pathophysiological pathways from the "genome to the phenome" (see reviews [18, 65, 66]). The stress-vulnerability models of FP have dominated etiology theories for over three decades [67, 68]. For instance, the *neural diathesis – stress model* proposes that the constitutional diathesis for schizophrenia depends on neuroendocrine pathways through which stress exposure, specifically cortisol release mediated by the hypothalamic-pituitary-adrenal (HPA) axis, influences dopamine transmission [67, 69]. "Multiple hit" models suggested the importance of additive and interactive effects of environmental risk factors against a background

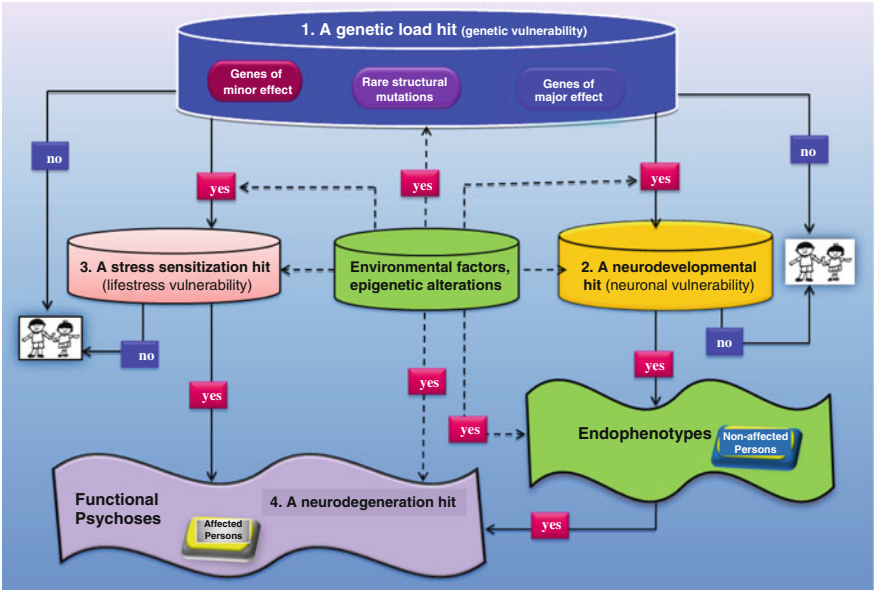


Fig. 3.8 A Multi-Hits Vulnerability Model of functional psychoses. © M.S. Ritsner 2011 and used by permission

of genetic predisposition [70–75]. Figure 3.8 presents the *Multi-Hits Vulnerability Model (MHV model)*, which based on interaction between four main hits:

(a) a genetic load hit ("genetic vulnerability"),
(b) a neurodevelopmental hit ("neuronal vulnerability"),
(c) a stress sensitization hit ("life stress vulnerability"), and
(d) a neurodegeneration hit.

A genetic load hit: For more than 40 years, researchers worldwide have sought to reveal the genetic basis of FP. Linkage and candidate gene association study results have led to a range of hypotheses concerning the pathogenesis of the disorders, but overall genetic findings have been inconsistent and not a single functional risk causing variant has been identified. Advances and challenges in molecular and genetic studies of FP were recently reviewed [18, 76–81]. Although linkage and association studies have identified a series of chromosomal regions likely to contain susceptibility genes, progress in identifying causative genes has been largely disappointing. However, rapid technological advances are beginning to lead to new insights. Systematic genome-wide association and follow-up studies have reported genome-wide significant association findings of common variants for schizophrenia and bipolar disorder. There is emerging evidence that some cases of FP (in particular, SZ) might be due to rare genetic structural variations, though the majority of cases are putatively due to a cumulative effect of common variations in multiple

genes, which in combination with environmental stressors may lead to the development of schizophrenia [82, 83]. The aggregate data provide support for polygenic inheritance and for genetic overlap in FP [79].

A neurodevelopmental hit: Owing to several advances, principally developments in neuroimaging, electrophysiological and neuropathological approaches, in the last two decades FP have been increasingly viewed as neurodevelopmental disorders [84–88]. Human epidemiological studies have provided compelling evidence that the risk of developing schizophrenia is significantly increased following prenatal and/or perinatal exposure to various environmental insults, including maternal exposure to stress, infection and/or immune activation, nutritional deficiencies and obstetric complications [89]. Pathways associated with genes that regulate neuronal migration by influencing the function of microtubules in the developing fetal brain may be interfered with as part of the "first-hit" of SZ [90]. There is evidence from brain pathology (enlargement of the cerebroventricular system, changes in gray and white matters, and abnormal laminar organization), genetics (changes in the normal expression of proteins that are involved in early migration of neurons and glia, cell proliferation, axonal outgrowth, synaptogenesis, and apoptosis), environmental factors (increased frequency of obstetric complications and increased rates of schizophrenic births due to prenatal viral or bacterial infections), minor physical anomalies, and gene-environmental interactions, which support of the neurodevelopmental model [18, 91–94]. In addition, findings from both cross-sectional studies of first-episode patients and longitudinal studies in childhood-onset and adolescent onset schizophrenia support the concept of early-onset schizophrenia as a progressive neurodevelopmental disorder with both early and late developmental abnormalities [95].

A stress sensitization hit: Psychosocial stress, such as life events, childhood trauma, or discriminatory experiences powerfully affect the brain and body and last throughout the entire life span, influencing brain function, behavior, and the risk for a number of systemic and mental disorders [96, 97]. There is evidence that environmental factors, which interact with multiple genes, and epigenetic factors, psychological or physiological alterations, induce persistent sensitization to stress [98, 99]. Stress sensitization may be critical in the development or relapse of FP. The neurobiological substrate of stress sensitization involves dysregulation of dopaminergic and noradrenergic systems.

Glutamatergic regulation activates HPA axis in stress response [67, 100]. The HPA axis is one of the primary neural systems triggered by stress exposure, in the expression of vulnerability for schizophrenia. The results indicate that psychotic disorders are associated with elevated baseline and challenge-induced HPA activity; that antipsychotic medications reduce HPA activation, and that agents that augment the stress hormone (cortisol) exacerbate psychotic symptoms (see review [68]). A fundamental question in the neuroendocrinology of stress-related psychopathology is why some individuals flourish and others perish under similarly adverse conditions. The data suggest that mineralocorticorticoid and glucocorticoid receptors contribute to individual differences in resilience and vulnerability to stressors [101]. Although many of the physiological effects of corticosteroid stress hormones on

neuronal function are well recognized, the underlying genomic mechanisms are only beginning to be elucidated [102]. Brain regions such as the hippocampus, amygdala, and prefrontal cortex respond to acute and chronic stress by undergoing structural remodeling, which alters behavioral and physiological responses. Lyons et al. [103] suggest that small hippocampi reflect an inherited characteristic of the brain of monkeys. It has been reported that volume reductions in the amygdala, hippocampus, superior temporal gyrus, and anterior parietal cortex common to both patient groups may represent vulnerability to schizophrenia, while volume loss of the prefrontal cortex, posterior parietal cortex, cingulate, insula, and fusiform cortex preferentially observed in schizophrenia may be critical for overt manifestation of psychosis [99]. Genetically informed clinical studies should assess whether inherited variation in hippocampal morphology contributes to excessive stress levels of cortisol through diminished neuroendocrine regulation. In humans with mood and anxiety disorders, small hippocampal volumes have been considered evidence that excessive stress levels of cortisol induce hippocampal volume loss. Translational studies in humans with structural and functional imaging reveal smaller hippocampal volume in stress-related conditions [104], and major depressive illness [105]. Laruelle [106] proposed that, in schizophrenia, neurodevelopmental abnormalities of prefrontal dopaminergic systems might result in a state of enhanced vulnerability to sensitization during late adolescence and early adulthood. It is also proposed that dopamine D_2 receptor blockade, if sustained, might allow for an extinction of this sensitization process, with possible re-emergence upon treatment discontinuation. Changes of protein expressions in the amygdala in the categories of synaptic, cytoskeletal, oxidative stress, apoptosis, and mitochondria related proteins could be associated with mechanisms underlying behavioral sensitization [107]. Behavioral sensitization to daily life (environmental) stress may therefore be a vulnerability marker for schizophrenia, reflecting dopaminergic hyper-responsivity in response to environmental stimuli [108]. There is evidence that emotional reactivity to daily life stress may be related to a familial liability to develop schizophrenia [109]. Stress sensitization is most often *unspecific for FP*, since its can trigger high blood pressure, diabetes, ulcers, asthma and digestive and lung ailments among others.

A neurodegenerative hit: has postulated that FP underlie progressive pathophysiological processes that occur in the brains of patients (see review [110]). The question of whether this key characteristic of the disorder means that schizophrenia is a degenerative disorder has been discussed for over 100 years [111]. Investigation of the long-term course of schizophrenia with progression to different residual syndromes has inferred that schizophrenia is not a neurodegenerative process in the usual sense, but may be uniquely neuroregressive in most cases [112]. The following findings support this assumption: 78% of SZ patients do not show full remitting courses; progression occurs only 5–10 years after onset; chronic defect psychoses can remit even after decades to non-psychotic pure deficiency syndromes; that approximately 15% progress even after years and decades of a remitting course and, finally, that altogether there is no correlation between the duration of course and outcome. There are associations between brain imaging and psychopathological

findings and also between the progression revealed in neuroimaging and psychopathological changes. Progressive MRI changes in longitudinal studies were revealed in childhood-onset SZ [113], before and after transition to psychosis [114], and in the course of early psychosis [115]. Progressive MRI changes were seen in subgroups of patients with chronic schizophrenia [116–118]. Some, though not all studies revealed more pronounced progressive brain changes in patients that are associated with poor outcome, more negative symptoms, and a decline in neuropsychological performance [119, 120]. Brain imaging studies documented progressive increases in ventricular size, accelerated loss of brain tissue, progressive delays in treatment response, and neurochemical (magnetic resonance spectroscopy) and neurophysiological (P300) indices, all of which are consistent with ongoing cerebral degeneration in a significant subgroup of schizophrenia patients [121].

Conclusions and Future Directions

Although emerging data from many fields of psychiatric research have increasingly challenged the validity of the DSM-IV and ICD-10 classifications, the categorical nosology of the functional psychoses needs further clarification for use in clinical practice. Since the current categorical nosology of functional psychoses challenges neurobiological studies, a new model and classification of FP for research purposes is needed.

This chapter describes proof-of-concept for the Multidimensional Continuum Model (MDC model) of FP for research purposes, that is based on multidimensional parameterization of the three-axis continuum of the phenotypic (clinical)-endophenotype-genetic domains, on a hypothesis-free approach, and on the endophenotype strategy. The complex clinical presentation of FP can be summarized with a few consistent, temporally stable symptom dimensions and factor structures. Although the factor structure of FP symptoms is imperfect, this quantitative approach to phenotypic traits has the potential to advance our understanding of FP and may aid in the identification of more robust endophenotypes. The Multidimensional Continuum Model is proposed for validation and further development. In particular, the first step towards this goal should be cross-sectional and longitudinal measures of phenotypic expressions of FP. Suggested observer-rated and self-report scales should be shortened and divided into 2–3 sets as per the various research purposes. Using a few consistent and temporally stable symptom dimensions, factors and patterns can summarize the complex clinical presentation of FP. A dimensional approach may advance our understanding of FP while symptom structure is far from definitive and is still subject to revision. Obviously, the FP domains mentioned above (catatonic, thought disorder, major depressive, major manic, and major bipolar) have been delineated to help elaborate future typology of FP that should be based on multidimensional measures of phenotypic expressions, endophenotypes and candidate genes. A further step would be to elaborate, for instance, a symptom profile of each FP-domain using raw scores of rating scales.

Multi-dimensional presentations of FP might stem from the interaction between four hits (a genetic load hit, a neurodevelopmental hit, a stress sensitization hit, and a neurodegeneration hit) as presented by the Multi-Hits Vulnerability Model. Further research is needed to determine common and distinct mechanisms for FP-domains. If supported, this model may have important implications for future classification of FP and much more effective treatment and rehabilitation. Ultimately such a classification should be based on an understanding of the etiology and pathogenesis of FP. Research on the common and distinct genetic and neural substrates of the various dimensions has already begun and is likely to develop even further.

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Chapter 4
Irving Gottesman and the Schizophrenia Spectrum

Aksel Bertelsen

Abstract Our knowledge of the genetics of schizophrenia and its borderlands is heavily indebted to the research and writings of Irving Gottesman. In a twin study of personality assessment in adolescents with the Minnesota Multiphasic Personality Inventory (MMPI) begun in 1957 he demonstrated that certain traits were under appreciable genetic influences. In a major twin study of schizophrenia with Shields begun in 1962, using audio-taped interviews, including MMPI, and diagnosed by

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a cross-national panel of blinded judges, he demonstrated a strong genetic factor, suggesting a polygenic contribution to a multifactorial liability to the disorder. In a study on the offspring of discordant twins he demonstrated that the genetic risk was passed on from non-schizophrenic as well as from schizophrenic identical twins. Super-high-risk studies on the offspring of two schizophrenic parents (2010) showed 4 times increased risk of schizophrenia compared to offspring of only one schizophrenic parent and suggested some kind of genetic overlap with bipolar disorder. In molecular genetics his concept of endophenotypes as interforms between the genotype and its phenotypical manifestations, influenced by epigenetic and environmental factors, have inspired a large number of research studies.

Keywords Schizophrenia · Schizophrenia spectrum · Schizoidia · Schizotypal disorder · Twin-studies · Twin-offspring studies · Dual mating studies · Endophenotypes

Abbreviations

MMPI	Minnesota multiphasic personality inventory
ICD-10	International classification of diseases, 10th revision
DSM-IV	Diagnostic and statistical manual of mental disorders, fourth revision

Le hazard ne favorise que les esprits préparés (Louis Pasteur, 1822–1895)

Schizophrenia and the Schizophrenia Spectrum, including Schizotypal Disorder (ICD-10) or Schizotypal Personality Disorder (DSM-IV), Schizo-affective Disorder and Schizoid and Paranoid personality Disorder have, for the last century, been among the main topics of research in psychiatric genetics, and Irving Gottesman one of the persons who through the last half century has contributed significantly to our knowledge in this field.

Early Career

Following graduate education [1], Gottesman 1956 began his training as clinical psychologist at the University of Minnesota, which he selected because the training program was oriented towards biology, genetics and objective assessment of personality, being the home of the Minnesota Multiphasic Personality Inventory, MMPI [2]. For his dissertation he conducted a twin study of personality traits, using the MMPI in adolescent MZ and DZ twins who were school children in the area.

Heritability of Personality

The Ph.D. dissertation: “The psychogenetics of personality”, 1960, was published as a monograph: Heritability of Personality: a demonstration [3], but first in 1963, after it had been rejected by the same journal as irrelevant to psychology. The twin study

demonstrated significant hereditary components of variance for several MMPI personality dimension scales, particularly for the introversion and schizophrenia scales. This indicated that psychopathology of the psychoses had a substantial genetic component and that the MMPI might provide dimensional measures of traits observed in patients with schizophrenia and in some of their near relatives, called "schizoids" in early German genetic research. The work received considerable attention and resulted in a travel grant to the Second International Congress on Human Genetics in 1961 in Rome [1]. In Rome Gottesman was introduced to Franz Kallmann from New York and Eliot Slater from London who both had performed major twin studies on Schizophrenia [4, 5]. To Slater he happened to suggest the possibility of coming to London as a postdoctoral fellow at Slater's institute, which was met with encouragement.

The Maudsley Twin Study on Schizophrenia

In 1963 Gottesman came to Slater's Unit in Psychiatric Genetics – the "hut" – at the Medical Research Council Institute of Psychiatry on a fulltime fellowship abroad from the United State Public Health Service. He wanted to do a new twin study on Schizophrenia, based upon the Maudsley twin register, systematically ascertained in an unbiased manner from consecutive admissions to in- and outpatient services in the Maudsley, Bethlem Royal and nearby hospitals. Slater arranged that Gottesman came to work with James Shields, known from his renowned study on identical twins reared apart [6]. Gottesman wanted to improve the methodology by using the MMPI to get indicators of psychopathology and assess whether schizophrenic personality traits or schizoidia were on a continuous dimension with schizophrenia. He tape-recorded extensive semistructured interviews with the twins and presented case summaries, MMPI profiles and verbatim transcripts of the interviews to a cross-national panel of 6 diagnostic experts, leaving out information about zygosity and proband/co-twin status to get diagnostic assessments in a blindfolded way. He was in London for 1 year, came back the following year for 3 months and then every year for 2–3 weeks to work with James Shields on the analysis and the writing of papers and a book, which was published in 1972: Schizophrenia and Genetics: A Twin Study Vantage Point [7].

Apart from probandwise concordance of 58% (15/26) in MZ and 12% (4/34) in DZ twins of consensus among the 6 judges on a diagnosis of certain or probable schizophrenia, the MMPI questionnaires, obtained from the majority of the twins, showed presence of schizophrenia-like profiles in the concordant MZ and, to a lesser degree, DZ twins confirming the diagnosis. In the discordant co-twins, however, schizophrenia-like profile-scores were seen in only 3 DZ and in no MZ co-twins, disappointing the hope of finding evidence of schizoid personality traits in the discordant twins. More support was forthcoming from the blindfolded evaluation by another judge, not part of the 6 judge panel, Erik Essen-Möller from Sweden, known for his Swedish twin-study of schizophrenia [8, 9] and for his special interest in personality theory and the concept of schizoidia [10]. He coded 12 MZ probands and 7 of their co-twins as "true schizophrenia", further 2 co-twins as "possible

schizophrenia", and every one of the remaining co-twins as having characterological abnormalities of a schizoid kind. In the DZ twins he coded 19 probands and 2 co-twins as schizophrenia and further one co-twin with a schizophrenia-related personality.

The findings from the Maudsley twin study led Gottesman and Shields to genetic theorizing. Inspired by Douglas Falconer's multifactorial polygenic threshold model for diabetes and other common diseases [11], they improved the model into a diathesis-stress model with a "multifactorial" liability to schizophrenia, considered to be a continuously distributed variable determined by both genes and environment such that only those individuals whose liability exceeds a certain threshold value will manifest the disorder. Just below the threshold they expected to find a zone of schizophrenia spectrum disorders but with unknown lower border, if any, towards normality [7]. Theodore Reich and his colleagues [12] have extended the model to include two or more thresholds, for milder and more severe forms. Later, together with Peter McGuffin and Ann Farmer, Gottesman analyzed subdivisions of the twin data to look for quantitative and also qualitative differences, not finding evidence for the latter [13].

The Schizoidia Concept

Through the following years the schizoidia-related findings from the twin-study were analyzed in articles [14–16], discussing the concept of schizoidia, together with Shields and Leonard Heston, who also had been to Slater's institute in London and had performed the first adoption study in schizophrenia on adopted away children of schizophrenic mothers [17]. They discussed whether the concept implied a phenotypic resemblance and a genotypic connection to schizophrenia.

For semantic clarification they listed four uses of the term "schizoid": (1) Resembling schizophrenia, but not implying genetic connection to it, as used in "schizoid personality", meaning shy, sensitive, aloof or eccentric, shading into the normal, possibly extended to include paranoid personality and maybe also high MMPI scores on the schizophrenia scale. (2) For any disorders occurring in co-twins and other relatives of schizophrenics, whether resembling schizophrenia or not and whether occurring more frequently in families of schizophrenics than of controls. No genetic connection to schizophrenia is implied. (3) For disorders belonging to a class found more often among relatives of schizophrenics than of controls, whether occurring among relatives of schizophrenics or not. (4) For a diagnosis or behavioral traits genotypically related to schizophrenia to indicate a probable carrier of a high-risk genotype.

Disorders broadly resembling schizophrenia, schizoids and other spectrum disorders, occurring in co-twins and other relatives of schizophrenics and found more often among relatives of schizophrenics than of controls were suggested to be the most probable candidates for carriers of a schizophrenia genotype. Future twin and family studies on the relatives of probands with such disorders could possibly confirm their candidature.

Applied to the findings in the Maudsley twin study [14–16], they tried to stepwise add co-twins with other disorders resembling schizophrenia, Essen-Möller's schizoid characters, and those with high MMPI schizoid profiles, to the concordant co-twins. This, however, by each step raised both the MZ and DZ concordance rates and diminished the ratio of the rates as an indicator of "biological specificity". These co-twins therefore probably were not carriers of the genotype.

In Denmark 1972–1973: The Twin Study on Criminality

In 1972 Irving Gottesman won a Guggenheim Fellowship and went to Denmark for 1 year as a guest researcher at the Psychological Institute at Kommunehospitalet in Copenhagen [1]. Here Sarnoff Mednick and Fini Schulsinger and their team worked on high risk studies in children and on adoption studies with Seymour Kety and David Rosenthal, defining Schizotypal Disorder [18] and redefining the schizophrenia spectrum [19]. Denmark was an ideal country for epidemiological genetic research because of the existence of effective national registers, such as the Central Person Register with individual person-numbers for every inhabitant, the Central Psychiatric Register going back to 1920 [20], the Danish Twin Register, the Danish Adoption Register, the Police Register, and the Register of Causes of Death. At the institute Gottesman came to work with a Danish criminologist, Karl Otto Christiansen, on a twin study of criminality, which they did not finish because of Christiansen's death, so that only part of it has been published [21].

The Danish Dual Mating Study

During this visit he initiated a dual mating study of mental disorders in the offspring of parents who both had been psychiatric inpatients, together with Margit Fischer at the Institute of Psychiatric Demography in Århus. He had met her at a previous visit to Erik Strömgren in Århus, where she was working at a Danish twin study of schizophrenia [22]. Over the following decade Margit Fischer sorted out data from the cards in the central psychiatric register containing information about admissions of spouses, children and other relatives, and she obtained and scrutinized their hospital records for diagnostic information. After her untimely death in 1983 the author of this chapter was asked to take over her part of the project. A sample of 139 parent couples with a total of 378 children were identified. Various diagnostic parent combinations produced subgroups with offspring for evaluation of morbidity risk of same or similar disorders, but numbers were too low for statistical analysis [23].

There were no offspring of parent couples with one or both parents with schizoid or paranoid personalities. Of interest for schizophrenia spectrum disorders were the offspring of parents with reactive psychosis. According to the Scandinavian concept of psychogenic psychoses they were psychoses with acute onset as a reaction to a traumatic event, good prognosis and affective, confusional, paranoid or

schizophrenia-like symptomatology. Among the four children of two parent-couples both with reactive psychosis there were no mental disorders. Among 14 children of 5 couples with reactive psychosis versus schizophrenia was one child with probable schizophrenia resulting in a morbidity risk of 10%, which is no higher than found in children of one schizophrenic parent, suggesting that reactive psychoses did not contribute genetic liability factors to schizophrenia [23].

The Professorships and the Books

Gottesman returned to Minneapolis in 1973, where he had worked since 1966 at the University of Minnesota as professor at the Departments of Psychology, Psychiatry and Genetics and director of the Behavioral Genetics Center. From 1980 to 1985 he served at Washington University School of Medicine in St. Louis as Professor of Psychiatric Genetics at the Departments of Psychiatry, and of Genetics and Cell Biology. From 1985 he worked as professor of psychology and of clinical pediatrics (medical genetics) at the University of Virginia in Charlottesville. Following his retirement in 2001 he moved back to Minneapolis, where he took up semiretired work as Bernstein Professor in Adult Psychiatry and as Senior Fellow in Psychology at the University of Minnesota. As professor he mentored 36 doctoral students through their dissertations and 7 postdoctoral students. He was consultant on the New York high-risk prospective projects on children of schizophrenic parents, led by Erlenmeyer-Kimling and her group [24] and to a study on environmental and biological factors in identical twins by Fuller Torrey [25], in which no evidence of spectrum sub-threshold schizophrenia was revealed by a personality questionnaire in 22 non-schizophrenic co-twins. Gottesman authored or coauthored quite a number of articles and book chapters and with about 10 years interval he produced or co-produced three books of major importance: In 1982 together with Shields: “Schizophrenia. The Epigenetic Puzzle” which has become the source- and handbook of schizophrenia genetics [26]. In 1991 “Schizophrenia Genesis. The Origins of Madness”, with updated information and written for a wider audience [27], and in 2002 (updated in 2004) “Psychiatric Genetics and Genomics” together with Peter McGuffin and Michael Owen [28], the successor to the classic Slater and Cowie book on psychiatric genetics [29]. Through all these years he traveled abroad to meetings and conferences, also paying annual visits to London and Denmark.

The Discordant Twins’ Offspring Study

In the mid-1980s Gottesman took the initiative to do a follow-up study of the morbidity risk in the offspring of the discordant twins in the late Margit Fischer’s Danish twin study on Schizophrenia, assisted by the present author as his Danish partner. She had provided morbidity risk figures for the MZ schizophrenic and

non-schizophrenic twins of about the same size, but not for the DZ twins [30]. Now 18 years later it was possible to include the DZ twins in a register- and record-based follow up study, with a proper statistical evaluation of the observed difference between the risks in the offspring of the non-schizophrenic MZ and DZ twins. The morbidity risk of ICD-8/9 schizophrenia and schizophrenia-like disorders in the offspring of the schizophrenic and the non-schizophrenic MZ twins were of the same magnitude, 16.8 and 17.1%, respectively, and the same as in the offspring of the schizophrenic DZ twins of 17.4%. This is about the same as usually found in children with one schizophrenic parent. The risk in the offspring of the non-schizophrenic DZ twins was only 2.1%, significantly different from the 17.1% in the offspring of the non-schizophrenic MZ twins, and on a level expected in second-degree relatives of schizophrenics, which they actually are being nephews or nieces of the schizophrenic twins. The results confirmed that unexpressed genotypes may be transmitted to the next generation and further demonstrated that schizophrenia non-genetic phenocopies did not occur to a substantial degree to discourage molecular genetics research. The paper was published in 1989 [31] and was awarded by the Kurt Schneider Prize, first time given to other than German scientists.

The New Dual Mating Study

During the last 20–30 years it has been increasingly difficult to do studies based on personal interviews because of diminished willingness in the population to take part and changed attitudes to medical science and registration, threatening the use and even the existence of registers, particularly the psychiatric registers, which in some countries had to close down. In Denmark they survived because of their obvious utility for medical statistics and research, although reduced to person identification data and more or less reliable or valid coded diagnoses for in-patient, and from 1995, also out-patient admissions. It became easier to cross-check the registers again in a way that did not reveal person-identifiable data and this opened the possibility for register-based studies. In collaboration with professor Preben Bo Mortensen at the National Centre for Register-based Research at the University of Århus, Denmark, Irving Gottesman in 2005 took up a new register-based Dual Mating study [32] on a population-based cohort of 2.7 million persons. The study was limited to the most reliable register diagnoses of Schizophrenia and Bipolar Affective Disorder in parents and offspring, for the offspring also of schizophrenia-related disorders to cover the schizophrenia spectrum and of Unipolar Affective Disorder. The schizophrenia-related disorder diagnoses included ICD-10 Schizotypal Disorder, Delusional Disorder, Acute and Transient psychotic Disorders, Schizoaffective Disorders, Schizoid and Paranoid Personality Disorders, and their corresponding diagnoses in ICD-8. The risk in the offspring was calculated as cumulative incidence up to age 52, that is, differently from the way morbidity risk was calculated in the earlier literature and only roughly comparable after arithmetical conversion. The results were published in 2010. The risk of

admission with a diagnosis of schizophrenia in 270 offspring of 196 parent couples with both parents admitted with a diagnosis of schizophrenia was 27%, increasing to 39% when schizophrenia-related disorders in offspring were included. For comparison we also calculated corresponding risks in offspring of couples with only one and with no parent ever admitted, with cumulated incidences of 7 and 0.86%, respectively. For Bipolar Disorder the corresponding incidences were 25% in 146 offspring of 83 parent couples with Bipolar Disorder diagnosis, increasing to 36% when Unipolar Disorder diagnosis in offspring was included. With only one and with no parent ever admitted the figures were 4.4 and 0.48%, respectively. Converted to morbidity risk figures they are of about the *same magnitude* as earlier results from literature [21]. The incidences of Schizophrenia and Bipolar Disorder in offspring of couples with one parent with schizophrenia and the other parent with bipolar disorder were 16 and 12%, respectively, suggesting a genetic relationship of some kind between the two disorders.

A diagnosis of Schizophrenia is thus seen to also predispose to schizophrenia-related disorders. It would have been of interest to see if and to which degree schizophrenia-related disorders predisposed to a diagnosis of schizophrenia. Here, however, we left the results unpublished because of inconclusive findings. Even if the incidence of schizophrenia was modestly raised in offspring of couples with only one parent ever admitted with a diagnosis of schizophrenia-related disorders compared to no parents ever admitted, it did not separate out markedly from corresponding figures in offspring with only one parent ever admitted with a diagnosis from almost any other diagnostic group, thus more or less drowning in the "noise" from less reliable diagnoses.

Endophenotypes

The failure to identify schizoid or other spectrum disorders as carriers of the genotype in the non-schizophrenic twins in the Maudsley twin study motivated Gottesman and Shields to introduce the concept of endophenotypes into psychiatry [7], adapted from insect biology in a paper by John and Lewis from 1966 [33], as a distinction between the externally visible exophenotype and the internal endophenotype, not visible to the naked eye without aid. The term was introduced to specify intermediate or intervening variables mediating the chain of events in the complex pathway between the genes and the psychiatric symptoms under epigenetic, environmental and stochastic influences. The identification of endophenotypes conferring vulnerability to psychiatric illness may point to etiological or pathogenetic models important for focused treatment. Along with the growing number of molecular-genetic investigations there has been an increased interest in research on endophenotypes, epigenetic and environmental factors, a research mixture in which Gottesman has been active, visionary and inspiring, coauthoring papers and reviews on the topic with the aim of resolving etiological questions particularly of schizophrenia and the schizophrenia spectrum [34–37].

Recognition

For more than 50 years Irving Gottesman has been a leading figure in psychiatric, especially schizophrenia genetics. He is an Honorary Fellow of the Royal College of Psychiatrists (London) and for his achievements he has received a number of well-deserved awards, including the Stanley Dean Research Award for Contributions to Schizophrenia Research 1988; the International Society for Psychiatric Genetics "Lifetime Achievement Award in Psychiatric genetics" 1997; the Society for Research in Psychopathology "Joseph Zubin Award, Lifetime contributions to psychopathology" 2001; and more recently the American Psychological Foundation Gold Medal for Life Achievement in the Science of Psychology 2007 and the NARSAD Lieber Prize for Outstanding Achievement in Schizophrenia Research 2008. The author of these lines gratefully appreciates the good luck and happy fortune to have had the privilege to have Irving as his mentor and friend for the last more than 30 years.

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Chapter 5
Schizotypy: Reflections on the Bridge to Schizophrenia and Obstacles on the Road Ahead to Etiology and Pathogenesis

Mark F. Lenzenweger

Abstract Abundant empirical data, drawn from a variety of methodologies and at different levels of analysis, support a robust connection between schizotypic psychopathology and the underlying liability for schizophrenia. This liability is termed schizotypy and represents a unifying latent construct that gives rise to both psychopathologies. Schizotypy can manifest itself in a variety of forms ranging from flagrant schizophrenia through less conspicuous schizotypic conditions to nearly silent manifestations known as endophenotypes, which can be detected only with properly sensitive technologies. Therein lies the power and research potential of the study of schizotypic psychopathology, namely it offers a window on schizophrenia liability (schizotypy). This window is particularly useful as it provides a view of liability uncontaminated by factors such as deterioration, medication sequelae, and institutionalization effects. However, the major stumbling block in the road ahead for schizotypy research, at all levels of analysis, is the problem of heterogeneity. Heterogeneity is observed across symptom pictures, performance patterns on laboratory tasks, longitudinal course, and, probably, at the level of genetic inputs as well. In order to advance our understanding of schizophrenia, schizotypic psychopathology, and all manner of endophenotypes the issue of heterogeneity must be confronted and resolved in a principled manner. A cautionary discussion of neuroimaging and its utility for advancing our understanding of the etiology and pathogenesis of schizophrenia and related pathologies provides a vantage point from which to view the promise of any one method in terms of resolving power. Finally, a discussion of the highly problematic, yet age-old, problem of *rating* approaches to measurement in psychopathology research and the value of the counting, ratio-scale approach is highlighted.

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Keywords Schizotypy · Schizotype · Schizophrenia · Endophenotype · Heterogeneity · Neuroimaging · Measurement · Rating · Counting

Abbreviations

DTI	Diffusion tensor imaging
*f*MRI	functional magnetic resonance imaging
MEG	Magnetoencephalography
MMPI	Minnesota multiphasic personality inventory
PET	Positron emission tomography
SPECT	Single photon emission computed tomography

Schizotypy research is entering its second century, building steadily upon the early observations of Kraepelin [1] and Bleuler [2], the prescient clinical observations of Rado [3], the seminal theoretical model of Meehl [4, 5] (see also [6]), and the emergence of the powerful endophenotype model of Gottesman [7, 8], which emerged from the genetic approach to schizophrenia (see [9] for extensive discussion). Advances in schizotypy research have largely been fostered by the experimental psychopathology approach, pioneered by Maher [10, 11] (see also [12, 13]) and exemplified in the work of many research psychopathologists, that seeks to bring the powerful methods of the experimental psychology laboratory to bear upon questions of etiology and pathogenesis in psychopathology [9].

Abundant empirical data, drawn from a variety of methodologies and at different levels of analysis, support a robust connection between schizotypic psychopathology and the underlying liability for schizophrenia [9, 12, 14, 15]. This liability is termed *schizotypy* and represents a unifying latent construct that gives rise to both schizophrenia-related psychopathologies and deviance on selected laboratory measures of neurocognitive and personality functioning. Thus, schizotypy can manifest itself in a variety of forms ranging from flagrant schizophrenia through less conspicuous schizotypic conditions to nearly silent manifestations known as endophenotypes [7], which can be detected only with properly sensitive technologies. Therein lies the power and research potential of the study of schizotypic psychopathology, namely it offers a window on schizophrenia liability (schizotypy). This window is particularly useful as it provides a view of liability uncontaminated by factors such as deterioration, medication sequelae, and institutionalization effects.

Despite the progress made and the evident scientific value of the schizotypy model as well as the power of the experimental laboratory, many challenging conceptual and methodological issues have been with us for some time in the study of schizotypy and schizophrenia – most notably the issues of heterogeneity, measurement scaling – and we are confronted with considerations of the best way to use new, emerging research technologies – such as neuroimaging. The age-old dilemmas of heterogeneity and measurement questions in concert with questions over new methods and the leverage they offer (or do not offer) conspire to limit the rate of progress in schizotypy and schizophrenia research. Critically, these challenges

are not going to go away any time soon. These substantive and methodological challenges will need to be confronted and surmounted to move our scientific understanding of schizotypy and schizophrenia forward. In this chapter, drawing upon my earlier discussion [9], in this chapter I share my reflections on several selected issues in the experimental psychopathology study of schizotypy and schizophrenia and, more importantly, the road ahead.

Where are we in schizotypy research? Where are we going in the experimental psychopathology of schizotypy? Much of this literature strongly suggests a connection between schizotypic psychopathology, schizophrenia and, importantly, the genetic liability for schizophrenia [9]. However, two questions frequently arise, either explicity or implicitly when one considers the road ahead for schizotypy research. First, will research into the fundamental nature of schizotypy become the purview for geneticists only? The short answer is, of course, No. This is so simply because the methodological and conceptual framework that will profitably link the liability for schizophrenia to measureable entities will rely heavily on laboratory methods for the study of neurocognition, social information processing, and other biobehavioral processes within an endophenotype model [7–9, 16]. Will the study of schizotypy, schizophrenia spectrum disorders, and schizophrenia proper it become the purview of neuroimagers only? Clearly, the answer is also, No. This is so because neuroimaging itself, as a research method, is hobbled by noteworthy limitations that will constrain the inferences that can be drawn from data gathered using these techniques and, most importantly, the best neuroimaging work will require the development of creative psychological and neuropsychological tasks within an interactive neurocircuitry model. Perhaps the most important thing for a contemporary student or aspiring psychopathologist interested in the study of schizotypy and schizotypic psychopathology to keep in mind is that *no single method is going to take us home to the discovery of what has caused schizotypy, schizotypic psychopathology, and schizophrenia.* It might be helpful to re-read the prior sentence. I say this as each of many research methods are discussed in this volume as well as many other recent works in this area has many enthusiastic proponents, each with one or two vibrant proponents hoping to mount the podium in Stockholm to claim their prize. Thus, the discovery process in illuminating the etiology and pathogenesis of schizotypy and schizophrenia will not be found *solely* in genomics, neuroimaging, psychophysiology, or advanced statistical analyses. To solve this scientific problem we will need to break down boundaries, work together, and share our methods and our different talents with one another. The role to be played by experimental psychopathology in this ongoing scientific saga will be substantial. One sees evidence of the critical role for the experimental psychopathologist already as geneticists and neuroimagers seek to incorporate the probes, tasks, and protocols developed in the experimental psychology and psychopathology laboratory into their research. To wit, observe the number of research projects that now include neurocognitive endophenotypes, which have been developed in the experimental psychopathology laboratory, particularly in the study of schizotypy, schizotypic psychopathology, schizophrenia spectrum conditions, and schizophrenia.

Reactions

Schizotypic Pathology/Schizophrenia Connection: Considering the "Damn Strange Coincidence" Argument

Some years ago I gave a colloquium on schizotypy at a reputable research institution. I presented a detailed overview of a number of studies from my laboratory, some of which are discussed in this book, and arrayed the final set of findings across a wide domain for schizotypic psychopathology (as an indication of schizotypy) next to findings for schizophrenia in the same domains. I pointed out that we had found deficits in the following areas – sustained attention, abstraction ability, working memory, attentional inhibition, smooth pursuit eye movement, antisaccade performance, thought disorder, MMPI Personality/Psychopathology, motor performance, somatosensory processing – for schizotypes and the same pattern had been found among schizophrenia patients [9, 12]. I argued that these empirical planks, *in toto*, built a compelling bridge between schizotypic deviance and schizophrenia deviance in the same domains, pointing to a possible common underlying liability (i.e., schizotypy). To my surprise, one member of the audience – a seemingly earnest fellow – asked me "couldn't the consistency of your findings for schizotypy and schizophrenia all be a big coincidence?" I thought for a moment and responded, "Are you advocating that the schizotypy model – the theoretical infrastructure underlying this program of work – has no truth value?" He responded, "Well, maybe, I'm not sure, actually, I am thinking, couldn't it be a coincidence?" I wondered out loud "Sort of like, the possibility that the NASA *Apollo 11* crew had no real idea where they were going and the systems heaped together in the *Saturn V* command-service modules were really not assembled in a manner so as to actually function efficiently and in an integrated fashion, but they got to the moon just the same?" He responded, "Well, maybe, I guess that is possible." "That would be a damn strange coincidence don't you think," I asked.[1]

Wesley C. Salmon, the late University of Pittsburgh philosopher of science and student of philosopher Hans Reichenbach, argued that if a theory, model, or proposal has no truth value, nothing going for it, or low to no *verisimilitude*,[2] then a set of results that array themselves in such a manner as consistent with what a theory predicts is what he termed a "damn strange coincidence" [17] (see also [5]). Bringing this down to earth, if schizotypic psychopathology has nothing to do with schizophrenia and the theoretical argument suggesting the latent construct "schizotypy" underlies both domains of psychopathology is essentially bogus, then how else can we explain the remarkable congruence between research findings for

[1] This question was posed in an earnest manner by the audience member. This moment during a research presentation puts me in mind of how I have felt when some people at clinical presentations still wonder if schizophrenia is "just a label," or "a myth," or "a sane reaction to an insane world."

[2] The degree of truth value or verisimilitude possessed by a theory or model can vary in a quantitative fashion, it need not be regarded as an "all-or-none" proposition.

schizotypic pathology and schizophrenia other than consider it a "damn strange coincidence." If the theory has low validity, then the array of findings we have discovered across schizotypic pathology and schizophrenia would be antecedently improbable – which means not likely from the get-go – and we would have no way of explaining the patterning of results, other than to throw up our hands and say it was a "damn strange coincidence." As scientists, we generally do not subscribe to the damn strange coincidence [17] (see also [5]) model of scientific explanation. That the notion of a latent construct of schizotypy (aka schizophrenia liability) has something going for it and helps to explain the congruence of findings across a diverse set of domains for schizotypic psychopathology/personality and schizophrenia strikes me as well supported at this point in experimental psychopathology. Did the astronauts on the *Apollo 11* mission make it to the moon by virtue of a big coincidence – probably not.

Leverage Gained with the Schizotypy Model

It is reasonable question to ask is "what leverage is gained on schizophrenia by working within the schizotypy model as proposed here?" The leverage provided is considerable. First, empirical research has now built enough bridges between the schizotypic psychopathology/personality phenotype and schizophrenia to view the former as an alternative expression of a common underlying schizophrenia liability. I argued this theoretical position explicitly in 1998 [12] and I believe the data continue to grow to support the validity of both the bridges and the alternative expression assumption [9]. Secondly, given that the schizotype – as a unit of analysis – genuinely has rarely come to the attention of clinicians and, therefore, conventional treatments of any sort,[3] the schizotype does indeed represent a relatively pure culture case of expressed schizophrenia liability, albeit in dilute form. Thus, if one wants to study basic neurocognitive processes, neural circuitry, and so forth *uncontaminated by clinical illness, medication, and deterioration*, the schizotype truly represents an elegant window for such exploration. Thirdly, inclusion of the schizotype as a schizophrenia-related phenotype in contemporary genetic and genomic investigations clearly increases the statistical power of such investigations. On this theme, it probably also provides a more accurately devised net, by which one can find polymorphisms of interest – in other words, an expanded phenotype (which includes schizotypic psychopathology) probably has greater construct validity. Finally, but by no means least important, the use of the schizotypy model to

[3] This is not to say that some schizotypes, like others, have not sought out alternative "new age" therapies (e.g., Integrated Energy Therapy, Rebirthing Therapy) outside the bounds of conventional clinical psychology and psychiatry. I raise this point as, on occasion, clinicians (myself) included will learn from schizotypes during the course of an evaluation that they have tried any number of alternative approaches to dealing with their intense ambivalence, diminished hedonic capacity, interpersonal aversiveness, and transient cognitive confusion before seeking out more traditional help.

organize research in the area of schizophrenia liability, genetics, and so forth is helpful [9, 14]. By placing bets, guided by a model, we are in a better position to create testable and, hopefully, falsifiable conjectures in our scientific work and be able to allow our search for consistencies in results to be reasonably circumscribed.

Reflections

Neuroimaging and Schizotypy/Schizophrenia: Selling Bridges v. Building Them. Where Are We, Are You Sure?[4]

We are now in a most fortunate position in psychological science generally, and in experimental psychopathology in particular, with respect to the tools at our disposal. Foremost among the newly developed tools are the various neuroimaging methodologies (PET, SPECT, *f*MRI, MEG, DTI) for use in imaging the structure and functioning living and active brain. Neuroimaging has come to occupy the energies and interests of any number of experimental psychopathologists (as well as absorbed untold grant funding dollars). However, at the end of the day as of 2011, the insights gained from neuroimaging in schizophrenia and schizotypy can be described as modest without denying their importance in a few specific areas (e.g., illumination of the actively hallucinating brain [18]). This view is based on two major considerations (a) we are not appreciably much closer to understanding the origins and development of schizophrenia now as compared to the pre-neuroimaging period[5] and (b) neuroimaging, in the opinion of some, has contributed little to the diagnosis and treatment of schizophrenia. Admittedly, the latter point is a tall order to fill in schizophrenia no matter how one slices the pie as one could level this criticism at many laboratory explorations of schizotypy and schizophrenia. However, one hears this criticism at a higher volume for imaging work, probably due, in part, to the considerable resources expended.

Today's students often display a rather knee-jerk proclivity to ask "has anyone done an imaging study of that?" This tendency typically diminishes over the semester as that question is normally met with a counter-question posed by yours truly of "Why would you want to do that?" followed simply by "and therefore?" My students have usually learned (or, at least, I hope they have learned) that neuroimaging is a new *tool* – and a rather glitzy one at that – but it does not represent the key

[4] Lest I be accused of castrative intent *vis a vis* neuroimaging, I would like to go on record as being generally supportive of the enterprise. I have been part of exciting research projects where neuroimaging has played an important role and seen the methodology complement existing research approaches.

[5] Advances in the neurobiology of the illness have been made. Consider the elegant model development of on the tonic and phasic components of the dopaminergic aspects of the pathology. Consider also the fruitful work on glutamatergic-mediated systems in relation to schizophrenia symptomatology.

to the psychological science knowledge kingdom.[6] Encouraging students to adopt a critical attitude toward neuroimaging is challenging at times, especially when they are bombarded by reports in the lay media (e.g., *The New Yorker*, *The New York Times*) regarding this and that new finding – "where jealousy or virtue lives in the brain" or "what men's brains want from women." Imaging is even being sold as a tool in political consulting ("here's a Republican's brain, now there's a Democrat's brain"). The presence of colorful depictions of statistical comparisons of changes in blood flow activation are also appealing to many as they can create, for some, the illusion of certainty in understanding neuronal activity.[7]

There are several forms of neuroimaging (PET, fMRI, DTI, MEG, and so on), none can claim to be superior to the other in all cases, yet all seek to characterize behavior (e.g., psychopathology) from what is essentially a biological (within the person) level of analysis. Will we explain schizotypy or schizophrenia from one level of analysis – I think not. *Albeit something of a truism, it is important to remember that complicated phenomena such as schizotypy, schizophrenia, or, generally, psychopathology will not be illuminated or understood from one model, theoretical perspective, methodological technique, disposition, or level of analysis* [9, 19–22].

To be clear neuroimaging methodology is very impressive and, in the right hands, can be used to begin to gain leverage on some important questions, within constraints related to speed and resolution. There is also no doubt that neuroimaging "sells." Ask any member of an NIMH Study Section where grant proposal applications undergo "peer review" if the presence or absence of neuroimaging makes a difference in how an application is viewed. It is not uncommon for reviewers to suggest (almost insist) that investigators consider adding a neuroimaging component to their applications upon revision. Why is this? Consider the following experiments

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[6] Some long-time and sophisticated observers of scientific psychopathology research, who have watched new technologies come and go, view neuroimaging with considerable caution as to its ultimate value in resolving important questions in schizophrenia and schizotypy. While I do not align myself with this view, one of my colleagues describes neuroimaging as the "new phrenology." Phrenology, which emerged in the nineteenth century, describes a (pseudoscientific) view, advocated by Franz Gall (1758–1828), that the contours, bumps, and shapes on someone's skull provided tell-tale signs regarding personality and psychopathology, ostensibly enabling one to make important clinical predictions for a person. Needless to say, phrenology faded from the scene due to its lack of validity. Phrenology argued (indirectly) that the brain (in the head) had meaningful connections to thought, emotion, and behavior, but it left the tracks in a major way when the bumps on the head told the story. Only time will tell if neuroimaging technology genuinely advances our understanding of schizophrenia and schizotypy. We may (or may not) move beyond neuroimaging methods only to look back and see all of it as something of a distraction.

[7] The view on the attractive colorful images is not simply my own. Consider the following, by recognized experts, "Despite the language used to discuss them, the brain images display in scientific publications and in the popular press are not representations of changes in brain neuronal activity or areas of "activation," or even the magnitude of the BOLD signal. Rather, the images are computer-generated, color-coded "maps" of statistically significant comparisons. It is important to stress that the finding of statistically significant differences and a measured change in the actual magnitude of the signal acquired are not necessarily interchangeable ([24], p. 807)." To be sure, numbers and data can fool us as well if we are not alert to their impact on our decisions.

done recently by a Yale psychology graduate student Deena Skolnick Weisberg and her colleagues that appeared in the distinguished *Journal of Cognitive Neuroscience* titled "The seductive allure of neuroscience explanations" [23]. In the first of a clever triad of experiments, she found that scientific explanations that contained neuroscience information (i.e., neuroimaging-based information) were rated as significantly more satisfying than the same basic explanation without such information by novice subjects without a neuroscience background. In the second experiment, Weisberg et al. [23] found that even students in a neuroscience course, where critical evaluation skills were being taught, rated neuroscience-laden explanations as more satisfying than those without such information. Finally, in a third experiment, she [23] found that neuroscience experts were *not* unduly swayed in their views of scientific explanations whether or not neuroscience information was contained therein. These latter data are both somewhat comforting and discomforting. It is comforting that neuroscience experts should be able to read explanations of scientific results in a manner that is appropriately appreciative of what neuroscience information adds (or does not add) to such explanations. These results are discomforting in that the vast majority of the people in psychological science are not neuroscience experts, which includes the vast majority of members of study section review panels and ad hoc reviewers of journal manuscripts.[8]

In pondering neuroimaging and what it can (and cannot) tell us I think we should consider four basic questions. The first, in simple terms, where and how quickly does the interesting stuff happen in the brain? Answer: It happens at the levels of inter- and intra-cellular transmission and it occurs at very high speeds. Those researchers that conduct single cell recordings are well aware of the high speed at which information is moved through neural pathways (events occur quickly in the brain, typically within milliseconds). This raises the question – to what extent can neuroimaging capture the events we want to see? Is it fast enough to capture events as they happen? Given that events happen at the level of single cells and networks of cells, one must ask is neuroimaging fine-grained enough to capture the picture we want to capture (or, perhaps, is it too coarse). Are the temporal resolution and spatial resolution of the methods sensitive enough for the study of in vivo brain-based psychological processes? Consider the following analogy: If the brain process or event we want to see represents a pea in magnitude or activity level, yet neuroimaging can only resolve to an expanse of a six-lane highway, will we see the pea? Moreover, if it can only generate results for what happened six exits ago (the hemodynamic response that follows the neuronal event by 2,000 ms) on the highway as the pea-sized car (i.e., the signal) travels along at very high speeds, does it capture the pea when we really want to image it (i.e., in real time)? We must confront the issue of speed and resolution in neuroimaging *vis a vis* what we really want to see (or understand).

[8] Another caveat to prudent interpretation concerns the rather large correlations between variables that are often reported in neuroimaging studies. Correlations of a magnitude rarely seen in scientific psychology (e.g., *r*'s >0.70 or 0.80) and, so large, that some refer to them as "voodoo correlations."

The second question is "what does the cognitive neuroscientist *really* see when he/she considers what the *f*MRI signal taps into?" A useful perspective is provided by Fitzpatrick and Rothman [24]:

> Cognitive neuroscientists, particularly those not actively engaged in fMRI research, when asked the question "what does the fMRI signal measure?" often answer (in decreasing order of frequency and increasing order of accuracy): regional neuronal activity, then incremental changes in regional neuronal activity, and finally, incremental changes in regional cerebral blood flow. None of these descriptions is completely accurate. An MR physicist would describe the most popular fMRI method, blood oxygen level-dependent (BOLD) imaging, as measure the change in the intensity of the nuclear MR signal due to changes in the transverse relaxation time of the protons of water molecules in the blood and brain tissue as a result of changes in hemoglobin oxygenation and blood volume. The difference signal is referred to as having BOLD contrast (p. 806).

Therefore, it is essential to understand the fMRI is a method that measures changes in hemodynamic events in the brain – it does not measure neuronal activity in a *direct* manner. Rather it is only by *inference* that a neuroimager can make states linking changes in such hemodynamic events and nearby brain tissue (areas). The operative word in the prior sentence is *inference*. Thus, bringing psychological meaning to the statistical comparisons conducted in the analysis of the neuroimaging data is no mean task. This chore, however, is not unique to brain imaging. For example, when a child is asked to wait for an adult to return to a room in order to get a special treat vs. summoning the adult back to the room and receiving a lesser quality treat, one child will oblige and wait for the adult to return whereas another will summon the adult to return. We could measure the amount of time it takes until any given summons an adult (or does not summon). This dependent variable – the amount of time – then needs to be understood psychologically. What this means is that we have to *infer* what it means. Does it mean "delay of gratification" and "good ego control" (one possible interpretation, see Mischel et al. [25]) or does it merely correspond to how obedient some children are as opposed to others (another interpretation, see [26])? We "assign" the psychological meaning to what is measured, which was time to behavior in this example. The same is true, in essence, when trying to "bring meaning" – by inference – to data concerning changes in hemodynamic events and nearby brain tissue in neuroimaging studies. We "infer" what is happening in the brain.

The third basic question I believe we should ask ourselves when we consider neuroimaging research findings is "what is the question?" As discussed in Lenzenweger [27], the early period of neuroimaging research consisted of relatively unfocused use of the technology and there was often no real theoretical question at stake. The reality of this state-of-affairs stimulated Stephen Kosslyn, the Harvard psychologist and neuroscientist, to write his powerful 1999 paper entitled, "If neuroimaging is the answer, then what is the question?" [28] clearly one needs to have a question in mind before undertaking a neuroimaging study, there should be a model in place, and there should be some clear sense of what one is trying to do in conducting such an experiment. I would add that the level of *post hoc* speculation – i.e., coming up

with a "story" – after the data are in should be kept to a minimum. Let us consider the following comments and ponder them (Table 5.1):

Table 5.1 What is the student in psychological science to do with neuroimaging as a tool for understanding mind-brain-behavior relations?

We are duly warned by a leading neuroimager in 1999:
If neuroimaging is the answer, what is the question?
– Stephen M. Kosslyn, PhD [28]
But 10 years on in 2008, we still hear the following regarding neuroimaging:
The key is to not go on fishing expeditions. Have specific, testable hypotheses. That's not currently happening; 98% of brain imaging is just blindly groping in the dark.
– Vilayanur S. Ramachandran, MD, PhD (APA Monitor on Psychology, June 2008).

Finally, the fourth question I raise regards the wish of many to run to neuroimaging as a method in the hopes that it will, in and of itself, resolve the etiology of schizotypy and, therefore, schizotypic psychopathology and schizophrenia. In the rush to embrace the technology of neuroimaging, some research basics were overlooked (and still are in some settings) and have only come in for scrutiny once scientists realized that somehow they had missed a step, so to speak. In the spirit of considering those tools necessary for the experimental psychopathologist – let us ponder a research basic staple, namely reliability, in relation to neuroimaging. Let us consider the issue of reliability. If an investigator is running a cognitive neuroscience protocol on a magnet in New York City, will her results match those obtained by a different investigator who is running the same protocol in San Francisco? One would hope so – a hope that assumes reliability – this issue is very basic. Imagine if one wanted to analyze data hailing from a new psychometric measure, yet did not have reliability established for the psychometric instrument. How would the instrument and collected data be regarded? The reliability of neuroimaging is no different in that, simply stated, it must show evidence of reliability across sites and comparable technical setups. Reliability assessments for neuroimaging has been explored on a very limited scale and there are reasons to be both comfortable as well as uncomfortable with the level of reliability achieved across sites in neuroimaging research [29–31].

Major Impediments to Our Future Progress in Our Understanding Schizotypy and Schizophrenia

The Problem of Heterogeneity

It would be relatively easy to reel off a dozen or so candidates for potential conceptual impediments to our future progress in understanding schizotypy and schizophrenia. However, this is not the place for such an extended list. What are

the two biggest impediments that we face on the road ahead? First, and foremost, in order of importance is the issue of *heterogeneity.* By this I mean heterogeneity at several levels of analysis. For example, heterogeneity is present in the actual phenotype of schizophrenia and the schizotype in cross-section as well as over time (i.e., growth trajectories). Heterogeneity occurs within the laboratory data that we collect for EVERY endophenotype of interest, whether assessed with paper and pencil or with highly sophisticated psychophysiology or neuroimaging apparatuses. Heterogeneity probably even exists at the level of genetic factors in relation to what we term schizotypy and schizophrenia. I like very nearly all others in our field often work with the assumption that schizophrenia represents a disease construct that is characterized by some degree of homogeneity. This allows us to assemble patient samples for study, schizotypy samples for study, and so forth. The assumption of *homogeneity* (even if lip service is given to the reality of heterogeneity) is likely problematic. Simply stated, we need to continue to move forward with a more engaged theoretical and methodological approach *vis a vis* heterogeneity – we need to embrace it. We need to embrace it in our theory development, models, and, importantly, statistical analytic strategies [32, 33]. Failure to fully grasp the challenge posed by heterogeneity will only serve to thwart even the most thoughtful and clever approaches to research in this area.

The issue of heterogeneity is intimately and profoundly connected with the notion of schizophrenia as a complex disease and the related genetic/genomic research strategies. First of all, heterogeneity will be present, through and through, in the various indicators we seek to use to tap schizotypy, whether they be signs, symptoms, endophenotypes, or any other feature. It is a complex phenotype, in part I would argue, because of heterogeneity. Secondly, the search for genes or susceptibility loci of relevance to schizotypy (schizophrenia liability) must more fully embrace the possibility that the fact that multiple genes seem to be in play with schizophrenia is because there may well be more than one form/type of the illness. That schizophrenia represents a unitary illness with an associated, but still unknown, common polygenic genetic architecture remains, most certainly, an open question.

How does this concern about heterogeneity of illness and, likely, associated heterogeneity among causal genetic factors play itself out? One frequently hears at psychopathology research meetings, "we know that one gene does not cause schizophrenia, there are multiple genes, presumably of small effect at work in the illness." This sort of statement is normally offered as an objection to simple, single major locus models as well as an objection to mixed models (such as Meehl's). The simple SML models (single gene, no variation in expressivity, complete penetrance) clearly do not fit schizophrenia and this has been long known. The mixed model proposed by Meehl does fit data when assessed in model fitting exercises, however it does assume a gene of relatively powerful effect (his so-called schizogene), but the jury is out on the existence of such a gene. The statement – that schizophrenia must be the result of numerous small effect genes – however, is often implicitly founded on the assumption that schizophrenia is a *unitary, homogeneous* illness that possesses a consistent, homogeneous genetic architecture across all cases. The idea that schizophrenia may be a unitary, reasonably homogeneous disorder may simply

not be true (see [9] for extended discussion). Thus, our future efforts, both substantive and methodological, need to take heterogeneity head-on. We need to view it as a major problem of scientific interest, not merely a nuisance. *Simply stated, heterogeneity represents, perhaps, the single greatest obstacle to progress in schizophrenia research, including genetic research on the disorder. Heterogeneity is probably the Achilles' heel of all schizophrenia research. If schizophrenia research is to advance appreciably, heterogeneity within phenotype and, most likely, the genotype must be resolved. I would go so far as to predict that we do not solve the schizophrenia puzzle, until we resolve the heterogeneity issue.*

The Problem of Rating in Schizotypy and Schizophrenia Research

The second major conceptual impediment to our progress in understanding schizotypy and schizophrenia is that there is still far too much *rating*, as used in our varying methods of data collection, going on in our laboratories and not enough *counting*. In other words, embedded in nearly all the types of data collected and metrics used in psychopathology research, we find (and must confront) a major methodological problem. Although experimental psychopathology, unlike clinical psychiatry, relies in many instances on experimental tasks that are completed by subjects, this is by no means true for most data collected in psychopathology research. In fact, it is safe to assume that many of the most basic data collected in psychopathology still rely upon *self-rating* and *observer-rating* techniques. For example, the diagnosis of a patient (e.g., schizophrenia vs. panic disorder vs. depression) is still made on the basis of a patient's self-report (symptoms) and the observations of a diagnostician (signs). It represents a *rating*. When a researcher assesses the level of thought disorder in a patient's speech, a *rating* is made. When a symptom of schizotypic personality disorder is diagnosed (e.g., Does the patient have an odd or eccentric appearance?), a *rating* is made. When a patient completes an inventory regarding personality traits such as extraversion or neuroticism, a self-*rating* is made. The picture should be clear at this point – the process of *rating* plays a major role in psychopathology research, even in the day of experimental paradigms and laboratory science. This is not a new problem or a novel insight, it has long been known in personality science and the proponents of experimental psychopathology have attempted to draw attention to this issue for decades [10, 11]. Nonetheless, although this cautionary song has been sung for some time, researchers continue to rely upon the rating methodology for some of the most important data collected in psychopathology studies. The problematic nature of ratings has not gone noticed only in personality. For many years, this problem of rating in psychopathology has been a focal issue for Brendan A. Maher [10, 11], one of the principal architects of experimental psychopathology. Maher has advocated, what is essentially a mantra for the psychopathologist, namely, "*don't rate, count*." In counting, one should pursue ratio-scale measurement. Another way to think about this issue is provided by an anecdote provided by Paul Meehl to illustrate the concern and preferred position on this matter:

> When you checkout at a supermarket, you don't eyeball the heap of purchases and say to the clerk, "Well it looks to me as it it's about $17.00 worth; what do you think?" The clerk adds it up ([34], p. 372).

We need not revisit the relative merits of counting and ratio-scale measurement versus the rating (ordinal-scaling at best) approach (see [9]). While we clearly must view phenomenology and the value of careful diagnosis and classification with high regard, I think that for our field to move forward we need to consistently seek to development *counting* based approaches for our laboratory probes, tasks, and measures. The diagnosis of schizophrenia – over 100 years after Kraepelin and Bleuler – is still fundamentally at rating-based exercise. The loss in precision that comes from reliance on a rating approach to psychopathology (vs. a counting approach) cannot be estimated easily, though I suspect it is one of the issues that continues to hold back research progress. *Don't rate, count!*

Conclusions and Future Directions

The schizotypy model, which holds that a genetically-influenced liability is critical for the development of schizophrenia, schizotypic disorders, and deviance on many putative endophenotypes, offers considerable promise for future research on those factors responsible for the etiology and pathogenesis of schizophrenia. The schizotypy model provides, in the view of the author and others, a particularly clean window on schizophrenia liability and is, therefore, ideal for an organizing strategy with implications not only for the questions asked by research studies, but also the selection of research subjects for such studies. Methodological issues, however, will continue to slow progress in this research arena unless they are addressed head-on. Two of the most vexing issues are heterogeneity in performance patterns and clinical symptoms as well as ongoing misguided preference by some for rating approaches to measurement as opposed to the superior counting-based approach with ratio-scale properties. Finally, cautionary caveats are provided insofar as the promise of neuroimaging is concerned for advancing our search for the causes of schizotypy, schizotypic psychopathology, and schizophrenia.

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Chapter 6
Autistic Spectrum Disorders and Schizophrenia

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Abstract Autism spectrum disorders are a group of complex neurodevelopmental disorders that primarily present with deficits in social interactions, communication, and repetitive behaviors. With a progressive evolution in understanding this unique group of disorders, a variety of phenotypes have been postulated, with variability in both biological features and response to treatment. Etiologically, autism is believed to involve a genetic predisposition that may be triggered by environmental factors. While there is no known cure for autism, many treatment approaches are available that potentially improve certain core and associated symptoms. In the past decade, research in the etiology and treatment of these disorders has grown tremendously, as evident by the increasing number of publications in this area. This chapter will review some of the recent advances in the current understanding of these disorders. In addition, a historical background regarding the clinical diagnosis of autism spectrum disorders, including the development of diagnostic concepts and definitions, will be reviewed. Clinical features of autism, its course, prognosis, interventions, including psychosocial and educational interventions, and pharmacological treatments, will also be highlighted. This will be followed by an outline of standard clinical assessment of individuals with a suspected diagnosis of autism. Furthermore, epidemiological data along with recent advances in the understanding of autism's etiology and pathogenesis, including genetic influences, neuropsychological research, and neurobiological mechanisms, will also be briefly discussed. Finally, although autism can be separated from early onset psychosis and recent data suggest that individuals with autism are probably not at higher risk for developing schizophrenia, it is striking that children with childhood onset schizophrenia show high rates of early social, language and motor developmental abnormalities, with premorbid social impairment being the most common feature. Beginning with Kanner's use of the term autism that suggested a similarity to schizophrenia, the question of comorbid association or phenotypic variations between autism and schizophrenia has been frequently asked. This chapter will also aim to clarify

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the similarities and differences in presentation between autism and childhood onset schizophrenia.

Keywords Autism · Childhood onset schizophrenia

Abbreviations

PDD	Pervasive developmental disorder
ASD	Autism spectrum disorder
ADI-R	Autism diagnostic interview revised
ADOS	Autism diagnostic observation schedule
CDC	Center for disease control and prevention
ADDM	Autism and developmental disabilities monitoring
AS	Asperger's syndrome
PDD-NOS	Pervasive developmental disorder not otherwise specified
DSM	Diagnostic and statistical manual
IQ	Intelligence quotient
CDD	Childhood disintegrative disorder
IDEA	Individuals with disabilities act
BAP	Broad autism phenotype
CMA	Chromosomal microarray
NLGN4X	Neuroligin 4
NLGN3	Neuroligin 3
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
FFA	Fusiform face area
MCP	Macrophage chemoattractant protein
MMR	Measles mumps rubella
ASQ	Autism screening questionnaire
SCQ	Social communication questionnaire
CARS	Childhood autism rating scale
ABC	Autism behavior checklist
CHAT	Checklist for autism in toddlers
M-CHAT	Modified checklist for autism in toddlers
PDDST	Pervasive developmental disorder screening test
ABA	Applied behavior analysis
EIBI	Early intensive behavioral interventions
OT	Occupational therapy
SLP	Speech and language pathologist
FDA	Food and drug administration
ADHD	Attention deficit hyperactivity disorder
SSRI	Selective serotonin reuptake inhibitor
NIH	National institutes of health
CAM	Complementary and alternative medicine

COS	Childhood onset schizophrenia
MCDD	Multiple complex developmental disorders
ARMS	At risk mental state

Introduction

Autism is a complex neuropsychiatric syndrome characterized by a spectrum of abnormal behaviors that include: (a) marked impairment of social reciprocity, (b) verbal and non-verbal communication deficits, and (c) a pattern of restricted, repetitive and stereotyped behaviors and interests [1]. Since Kannner's classic description of the syndrome of infantile autism in 1943 [2], significant advances have been made in understanding this disorder, particularly in the past decade. Though initially considered nosologically related to schizophrenia with emotional disturbance resulting from early attachment experiences [3], autism was later accepted as a disorder distinct from childhood schizophrenia [4]. As the diagnoses of autism and related conditions become increasingly standardized [5], our conceptualization of these disorders has become broader [6]. In this chapter, the terms autism, autistic disorder and childhood autism are used interchangeably. The terms pervasive developmental disorder (PDD) and autism spectrum disorder (ASD) are used in the same way.

The development of validated standardized instruments such as the Autism Diagnostic Interview Revised (ADI-R) [7] and Autism Diagnostic Observation Schedule (ADOS) [8] makes it more reliable to compare research findings. Recent research has indicated a dramatic surge in the prevalence of ASD [9, 10]. In addition, the Center for Disease Control and Prevention's (CDC) most recent Autism and Developmental Disabilities Monitoring (ADDM) data show an estimated prevalence of ASD of about 1% [11]. With the development of clearer diagnostic guidelines, enhanced monitoring efforts, and increased public awareness, autism is now recognized as a broader spectrum disorder of prenatal and postnatal brain development [12].

Autistic Spectrum Disorders: Diagnosis and Sub-types and Phenomenology

The term autistic spectrum refers to strictly defined autistic disorder, Asperger's syndrome (AS), and pervasive developmental disorder not otherwise specified (PDD-NOS). Although there tends to be excellent agreement on the clinical diagnosis of autism, the situation for AS and PDD-NOS is much more complicated [4]. PDD-NOS was referred to as atypical autism in the DSM-III, and considered to be a subthreshold condition that affects the majority of persons with ASD. Several aspects of Asperger's including social and interpersonal impairments

suggest an overlap with autism; however, there are equally important distinctions for Asperger's such as preserved language, family history of similar difficulties, and in some cases, fact based special interests. Although Asperger's is included as a separate diagnosis in the DSM-IV, the distinction between Asperger's and high functioning (high IQ) autism has been debated [4, 13]. ASD affect boys more frequently than girls, with an average male to female ratio from 4.3:1 to 5.5:1 in individuals with normal intelligence, and 2:1 in individuals with mental retardation [10].

In the current DSM-IV-TR diagnostic classification, there are two more disorders within PDD – childhood disintegrative disorder (CDD) and Rett's disorder. While rare and not typical of ASD, both are characterized by regressive phenomena. Moreover, much can be learned from their clinical presentations and the known genetic etiology of Rett's disorder. Rett's disorder is a progressive neurodevelopmental disorder and one of the most common causes of mental retardation in females, with an incidence of 1 in 10,000−15,000 [14]. Patients with classic Rett's appear to develop normally until 6−18 months of age, then, they gradually lose speech and purposeful hand use, with microcephaly, seizures, autism, ataxia, intermittent hyperventilation and stereotypic hand movements [15]. After initial regression, the condition stabilizes and patients usually survive into adulthood.

Despite the fact that longitudinal data show Rett's disorder is not a variant of autism, it was included in the DSM due to concerns that it might be confused with ASD, especially in early childhood [4]. Meanwhile, with the discovery of X-linked methyl CpG binding protein 2 (MECP2) gene mutation in 80% of affected girls [16], interest in Rett's genetics as it relates to ASD has increased. It is yet unclear if the behavioral similarities that Rett's shares with autism reflect a shared mechanism (as in the case of fragile-X).

CDD resembles autism in a variety of respects. It has been classically noted as having a regressive period after years of typical development with little improvement or deterioration thereafter. The basic genetics and epigenetic mechanisms of this rare disorder would potentially be informative with regards to the developmental regression seen in some cases of autism [4]. DSM-IV-TR criteria for the diagnosis of CDD include having a period of normal development up to the age of two, with marked regression thereafter. Interestingly, approximately 25% of parents of children with classic autism report a period of regression [17]. The significance of this finding is not certain, especially since such regression is not clearly defined in children who already have a history of prior developmental delays [4].

Epidemiology

While the prevalence of autism was estimated at 5 per 10,000 in the 1960s and 1970s, and 10 per 10,000 in the 1980s [10], recent surveys suggest ASD in total occur in 60–70 persons per 10,000 [9]. The most recent CDC-ADDM data found that between 1 in 80 and 1 in 240 children have ASD, an estimated prevalence of about 1% [11]. Prevalence of autistic disorder per se is estimated at 13–20 per 10,000, PDD NOS around 30 per 10,000, Asperger's syndrome at approximately 3

per 10,000, and the more rare childhood disintegrative disorder at the rate of only 0.2 per 10,000 [9, 18]. These new findings identify ASD as one of most frequent of all childhood neurodevelopmental disorders. This raises the question whether an autism epidemic exists. To examine this question, it is important to distinguish between prevalence (the proportion of individuals in a population who suffer from a defined disorder) and incidence (the number of new cases occurring in a population over a period of time). The increase in numbers of children referred to specialist services and special education services cannot be used as evidence for an increase in the incidence of autism, without consideration of confounding factors or secular effects, such as referral patterns, availability of services, heightened public awareness, decreased age at diagnosis, and changes overtime in diagnostic concepts and practices [9]. There is also evidence of "diagnostic switching", suggesting that children once diagnosed with mental retardation and specific language disorders are now identified as having ASD [19–22]. Therefore it is hard to draw conclusions from referral statistics without conducting further and more robust epidemiologic studies.

In both the United Kingdom and the United States, recent surveys conducted at similar times and within similar age groups showed a sixfold variation in UK prevalence, and a 14-fold variation in the US. Prevalence rates were higher when intense population based screening techniques were used [18]. Repeated surveys of the same methodology in the same geographical area conducted at different time points can provide potentially useful information on time trends. However, other factors such as improved detection and increase in local services may also account for fluctuations. Studies of successive birth cohorts that report an increase in the incidence of autism should also be interpreted cautiously. For example, the increase in numbers of US children diagnosed with ASD by the school systems in the 1990s coincided closely with the inclusion of ASD in the federal Individuals with Disabilities Act (IDEA) [9].

As it stands, recent upward trends in estimates of prevalence cannot directly be attributed to an increase in incidence of the disorder because changes in diagnostic criteria, diagnostic substitution, policy changes and increased availability in services could also explain the increased prevalence rates. Still, even as available epidemiologic data are not clearly valid and reliable, a true increase in the incidence of autism is certainly possible.

Etiology

The spectrum range of ASD symptoms could be explained by multiple etiologies resulting in overlapping patterns of deficit. In about 10% of children with autism, specific genetic, neurologic, or metabolic disorders can be identified as etiological factors. Many other symptoms or disorders are commonly reported in children with autism: seizures [23, 24], immune system dysregulation [25], gastrointestinal symptom [26], feeding difficulties, and sleep disruption [10, 27]. The autism phenotype is the result of complex interactions of genetic and non-genetic factors throughout development [4], many of which are detailed below.

Genetics

Autism is among the most familial of all psychiatric disorders, with heritability estimated at approximately 90% amongst identical twins [28]. Epidemiologic data supporting the heritability of autism include modest sized studies of twins [29, 30], and stronger evidence via prevalence rates of ASD in siblings of persons with autism, that range from 2 to 6% [31], and with estimates as high as 14% in siblings of females with autism [32]. Family studies have shown approximately 20% of siblings of individuals with autism exhibit more subtle variants of ASD, which include a varied phenotype of social, communication, and/or behavioral difficulties referred to as broad autism phenotype (BAP) [33]. Advances made in conceptualizing and narrowly defining the deficits domain of autistic disorder has made it possible to identify BAP and advance research concerning the transmission of ASD [6].

Before 2003, the field of autism genetics was guided almost entirely by the common disease – common variant model, presuming many genes frequently identified in the general population affect the phenotype from a small to moderate degree [34–36]. Though linkage and association studies have identified a few common variants as possible candidate genes, many have not been replicated in successive studies, underscoring difficulties inherent in attempts to identify common causes for a heterogeneous disorder [37]. However, the first large scale genome-wide association study has identified a common variant of statistical significance – an intergenic region between cadherin 9 and 10, i.e., two genes that encode neuronal cell-adhesion molecules. These results were replicated in two independent cohorts, and implicate neuronal cell-adhesion molecules in the pathogenesis of ASD, representing the first demonstration of genome-wide significant association of common variants with susceptibility to ASD [38].

The discovery of variations in the gene copy-number as a risk factor is another promising development [39]. Copy-number variation is a structural variation in the genome in which material is either duplicated or deleted, and can be de novo or inherited [36]. Rare microscopic chromosomal abnormalities occur at a mean rate of up to 7.4% in autism versus less than 1% in the general population [40]. The most common chromosomal abnormalities in autism are maternally inherited duplications at 15q11–13, which are found in as many as 1–3% of patients diagnosed with idiopathic autism [41, 42]. In a study comparing diagnostic yield of clinically significant genetic changes in patients with ASD, 933 patients received clinical genetic testing including G-banded karyotype, fragile X testing, and chromosomal microarray (CMA) to test for submicroscopic genomic deletions and duplications. With the exception of recurrent deletion and duplication of chromosome 16p11.2 and 15q13.2q13.3, most copy-number changes were unique or identified in only a small subset of patients. CMA had the highest detection rate among clinically available genetic tests for patients with ASD, suggesting that it should be considered as part of the initial diagnostic evaluation of patients with ASD [43].

The study of known monogenic syndromes associated with ASD may advance the field of autism genetics and enable creation of animal models. While ASD may be diagnosed in 30% of males with Fragile X Syndrome, Fragile X mutations may

be found in as many as 7–8% of individuals with idiopathic ASD [44]. Mutations in MECP2, the Rett's disorder gene [16], have been found in cases of idiopathic autism without the Rett's phenotype [45]. This is interesting, as functions of the genes underlying fragile X (FMR1) and Rett's syndrome (MECP2) implicate synaptic dysfunction in cause and pathogenesis [36, 46]. More evidence for synaptic dysfunction as a unifying etiology has come from findings of rare mutations in neural cell adhesion and synaptic molecules such as x-linked neuroligin 4 (NLGN4X) and neuroligin 3 (NLGN3) [36, 47]. Similarly, individuals with autism have a 100-fold increased risk for neurofibromatosis, as well as an increased risk for tuberous sclerosis and Joubert syndrome. Patients with these disorders also have an increased risk for having autism [34, 48, 49].

Endophenotypes

The study of endophenotypes (intermediate phenotypes) has been increasingly used in the study of genetically complex psychiatric disorders, including schizophrenia [50, 51]. Intermediate phenotypes are heritable sub-clinical markers of disease, which may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature. Endophenotypes may provide more clues to the genetic underpinnings of a disease than the syndrome itself, resulting, hopefully, in successful-genetic analysis [52, 53].

Family studies of autism repeatedly find subclinical language and cognitive features among relatives, a finding referred to as broad autism phenotype (BAP). Those features resemble autism symptom domains but are subtle and not typically associated with clinical impairment [54]. However, these features may decouple and segregate independently in relatives without autism, and do not correlate with neurotypical populations. Therefore, studies of relatives with BAP may help identify component traits more amenable to neurocognitive and genetic dissection. Studies suggest that measures of social cognition may best differentiate individuals with ASD and parents with BAP from controls [54, 55]. By contrast, measures of executive function and central coherence (such as impairments in planning and cognitive flexibility) do not differentiate the groups as clearly [54, 56]. Language difficulties, including phonological processing as measured by a non-word repetition task, have been implicated to be part of BAP in first-degree relatives of individuals with autism [57].

Neuropathology and Brain Imaging

In ASD, a non-static complex pattern of brain growth abnormalities is found in the cerebellum, cerebrum, amygdala and possibly the hippocampus [12]. There appear to be age related differences in specific areas of brain growth. While at birth the average brain circumference in infants with ASD is close to normal, by age 3–4 years brain size exceeds normal by 5–10%, by age 6–7 years brain size in only

slightly increased, and then by older age there is approximately a 5% increase [12]. This brain enlargement represents both increased cerebral gray and white matter, especially white matter immediately underlying the cortex, and possibly increased cerebellar gray and white matter. There is also evidence for altered molecular markers: regional decreases in neuron-related molecules like N-acetyl aspartate, creatine and myoinositol, which could reflect changes in the numbers and sizes of neurons and glia; the elaboration of axons, dendrites and synapses; axodendritic pruning; programmed cell death; production of cortical columns; or myelination. An inflammatory response has been described in frontal cortex and cerebellar regions [12]. The most consistent abnormalities reported in neuropathological studies are decreased cerebellar Purkinje neurons and cerebral cortex dysgenesis, which may represent alterations in primary developmental processes [12].

Although ASD affects language, attention, communication and social interactions, until recently, functional magnetic resonance imaging (fMRI) studies tended to focus only on social functioning. More recent work has examined the perception of facial expression, joint attention, empathy and social cognition, with reduced neuronal activity in specific function domain regions [12]. For example, when compared to neurotypical individuals, autistic patients lack of modulation of the superior temporal sulcus region by gaze shifts that convey different intentions [58], activation of the fronto-temporal regions but not the amygdala when deriving socially relevant information from visual stimuli [59], and a pattern of individual-specific, scattered activation seen in autistic patients in contrast to the highly consistent fusiform gyrus activation seen in neuro-typical individuals [60]. Mirror neurons (i.e., motor neurons that fire when a person watches the actions of others) are dysfunctional in children with ASD while observing others and attempting to imitate their emotional expressions. Although able to perform those tasks well, children with autism showed no mirror neuron activity in the inferior frontal gyrus (pars opercularis). Notably, activity in this area was inversely related to symptom severity in the social domain, suggesting that a dysfunctional 'mirror neuron system' may underlie social deficits observed in autism [61]. Positron emission tomography (PET) studies of a previously identified 'mentalizing network' (medial prefrontal cortex, superior temporal sulcus at the temporo-parietal junction and temporal poles), found that autistic patients showed less activation than did the neurotypical group in all but one brain region. Curiously, the extrastriate cortex, which was highly active when watching animations that elicited mentalizing, showed the same amount of increased activation in both groups [62]. Although deficits in ASD are varied, at this juncture hypoactivation of the fusiform face area (FFA) appears to be the best replicated fMRI abnormality [12].

Infection and Immune Dysfunction

Cerebral spinal fluid and peripheral blood from older children with autism often show atypical levels of autoantibodies to neural antigens, immunoglobulins, inflammatory cytokines, and other markers that may signal dysregulation and/or

dysmaturation of both adaptive and innate immune systems [10, 63–65]. A chronic inflammatory process (activation of microglia and astroglia, macrophage chemoattractant protein 1 (MCP-1) and tumor growth factor-beta1, derived from neuroglia, were the most prevalent cytokines) is seen in postmortem central nervous tissue from individuals with autism, especially in the cerebellum [10, 66]. This suggests that localized brain inflammation and autoimmune disorder may be involved in the pathogenesis of ASD.

An epidemiological study in Montreal, Canada, evaluated the prevalence of ASD among 27,749 children born from 1987 to 1998 attending 55 schools [67]. Prevalence was more specifically assessed in relation to exposure to ethylmercury (thimerosal) and trends in measles-mumps-rubella (MMR) vaccination use. This study found that thimerosal exposure was unrelated to the increasing trend in PDD prevalence. No relationship was found between ASD rates and 1- or 2-dose MMR immunization schedule [67]. In 2004, the US Immunization Safety Review Committee published their eighth and final report examining the hypothesis that vaccines, specifically the MMR vaccine and thimerosal-containing vaccines, are causally associated with autism. After reviewing published and unpublished epidemiological studies regarding causality and potential biologic mechanisms by which these immunizations might cause autism, the committee concluded that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism, as well as rejection of a causal relationship between thimerosal-containing vaccines and autism [68].

Early Recognition

Early recognition and diagnosis of ASD in children lays the foundation for prompt and early initiation of interventions that may modify disease progression and improve outcomes. Although diagnosis before the age of four is becoming more frequent, many children still receive a formal diagnosis years after parents initially raise concerns with providers and systems of care. As a result, attention has been given to unique characteristics in the early presentation of ASD. Research supports the conclusions that observant clinicians can both reliably diagnose as young as 24 months [69, 70], and also observe many behavioral markers of autism well before 24 months [6, 71, 72]. Although the ADOS and ADI-R are the most reliable assessment tools, each requires extensive training and certification, and is generally reserved for research. Other assessments that may be used include the Autism Screening Questionnaire (ASQ), Social Communication Questionnaire (SCQ), Childhood Autism Rating Scale (CARS), Autism Behavior Checklist (ABC), Checklist for Autism in Toddlers (CHAT), Modified Checklist for Autism in Toddlers (M-CHAT), and Pervasive Developmental Disorder Screening Test (PDDST) [73, 74]. Most of the work aimed at identifying early signs of ASD has been retrospective, focusing on prior behavioral evidence of the disorder in children who have received a diagnosis. The most common methods used to gather information about earlier behaviors are retrospective reports from parents and analysis of early home videotapes [75].

In a shift of diagnostic paradigm for a disorder Kanner deemed to be congenital, Zwaigenbaum and colleagues (2007) outlined the theoretical advantages and general feasibility of prospective studies of infants and young children at high-risk for ASD. Such prospective research into the early development of ASD in high-risk infants may answer questions regarding early recognition and diagnosis more systematically, while avoiding biases associated with retrospective designs [75]. Some research suggests very early emergence of significant differences in social information processes [76]. Although the clinical diagnosis of autism at the age 2 years is stable over time, specific aspects of the disorder do change, especially in younger and more developmentally delayed children. Lord evaluated 30 two year-old children referred for possible autism (who were reassessed within a year) and divided them into three distinct groups: (1) those who exhibited all features by age two; (2) those who showed some features (usually social/communication deficits) by three, but not other features (usually restricted interests); and (3) a small number of children who had all the features of autism before the age of three, but not when reassessed. There was an increased differentiation between the ages of two and three, with the development of clearly recognizable repetitive behaviors in the autistic children, compared to significant improvements in basic social skills in the children judged not to be autistic [69]. The chronological age of three and the cognitive and mental age of 18 months appear to be a diagnostic watershed after which the diagnosis of autism is easier to make, with specific developmental markers and potential physiological ones [77, 78]. Age at diagnosis and levels of cognitive function and communicative speech remain the strongest predictors of outcome [10, 74, 79, 80].

Interventions

Early recognition and interventions are linked with better outcomes [36]. Although the core features of autism may not change, interventions can significantly improve adaptive skills and are the most effective when implemented concurrently [74]. Many interventions address core deficits such as socialization, communication and behavior, and associated developmental, psychiatric and medical conditions. For most children, the main source of interventions is their family and educational system [36]. A brief synopsis of some such interventions follows:

Psychosocial and Educational Interventions

Intervention programs applying principles of applied behavior analysis (ABA) have been widely studied. ABA has 30 years of evidence basis to support its use in children on the spectrum and as a result interventions based upon ABA principles are the treatment of choice. ABA functionally assesses the relationship between a targeted behavior and the environment, in order to change that behavior. Some

interventions are designed as comprehensive programs to broadly address all developmental areas of need, whereas others focus on specific skills or are directed toward specific sets of goals. Both approaches for children with ASD effectively improve communication, social skills, and management of problem behaviors [81]. Recently, Howlin and colleagues (2009) conducted a systematic review of controlled studies of early intensive behavioral interventions (EIBI) for young children with autism. Like ABA, EIBI programs are one-on-one behaviorally based intervention programs conducted in home or school, and may include up to 40 hours of weekly intervention. Overall, eleven studies have been reported including two randomized controlled trials. Although there is considerable variability in the outcome of these studies, taken together, EIBI result in improved outcomes (primarily measured by IQ) [82]. A variety of other approaches are aimed at reducing parental stress to help parents meet their children's needs more effectively, notably parental training and ongoing psychological support. Other means of intervention include occupational therapy (OT) to address sensory integration and self regulation, as well as regular sessions with a speech and language pathologist (SLP), and the use of diverse assistive technologies that concentrate on language and communication delays [36, 74].

The National Standards Project published a report reviewing a broad range of treatments for ASD, including 775 research studies [83]. Significant findings include 11 "established treatments" that are known to produce beneficial outcomes and are effective. Twenty two treatments were found to be "emerging" – treatments that have some evidence of effectiveness, and 5 treatments were found to be "unestablished" – treatments for which there are no sound evidence for effectiveness. More information can be found at the National Autism Center website [83].

Pharmacological Interventions

To date, there are no pharmacologic interventions that target the core deficits seen in ASD. However, individuals with ASD often suffer from other challenging behaviors that not only interfere profoundly with relationships and physical health, but also may impede various non-medical interventions, whether behavioral, educational, or rehabilitative. Among associated behaviors or symptoms are aggression, irritability, inattention, hyperactivity, and mood or anxiety symptoms. Self-injurious behaviors, tantrums, and aggression can be severely impairing and disrupt treatment of patients with ASDs. Pharmacological therapies are often used to facilitate non-pharmacological interventions. A variety of psychotropic medications have been used to treat patients with ASD including antipsychotics, psychostimulants, antidepressants, and, to a lesser degree, antihypertensives and mood stabilizers [84].

In October 2006, risperidone became the first drug approved by the United States US Food and Drug Administration (FDA) to treat irritability associated with autism. Multiple open-label reports and case series, as well as double-blind placebo-controlled trials described beneficial effects of risperidone on aggression

and irritability in youth with ASD [85]. Aripiprazole has been shown to be effective in an open-label study as well as a double-blind placebo-controlled trial [86, 87], and was also approved by the FDA in November 2009 for use for the treatment of irritability associated with autistic disorder in pediatric patients. Open-label studies of clozapine, olanzapine, quetiapine, and ziprasidone have also shown some promise in treating aggression and irritability [88].

Attention Deficit Hyperactivity Disorder (ADHD) symptoms can be treated with stimulants and evidence suggests that although children with ASD respond to treatment with methylphenidate, their response is less robust than that of children with ADHD alone; furthermore, those with lower IQ tend to experience more adverse events [89]. There is some evidence that clonidine treatment modestly benefits overactivity in children with autism [90].

Selective Serotonin Reuptake Inhibitors (SSRIs) have been studied in autism spectrum disorders, demonstrating significant improvement in global functioning and in symptoms associated with anxiety and repetitive behaviors. While side effects were generally considered to be mild, increased activation and agitation occurred in some subjects [91]. In a placebo controlled cross over trial, fluoxetine was found to significantly decrease repetitive behavior with no overall difference in side effects between the research groups [92]. In a double blind placebo controlled trial fluvoxamine was found to significantly decrease repetitive behaviors and aggression in adults with ASD, with reported side effects of nausea and sedation [93]. The results were largely negative in a US National Institutes of Health (NIH) sponsored randomized controlled trial, examining effectiveness of citalopram for the treatment of repetitive behavior in children and adolescents with ASD. In addition, use of citalopram was associated with more adverse events, including increased energy levels, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin/pruritus [94].

Attention has also been paid to the use of antiepileptic drugs in patients with ASD, as is plausible given the frequent comorbid occurrence of seizure disorders. Topiramate and divalproex sodium have been shown to have some benefit in the treatment of irritability in patients with ASD [95–97]. A randomized, double-blind, placebo-controlled trial of lamotrigine for the treatment of ASD did not find any significant observed differences in improvements between lamotrigine or placebo groups, although parents reported marked improvement [98].

Recently, interest has turned to oxytocin for social deficits and repetitive behaviors. Oxytocin is a peptide synthesized in the hypothalamus that plays an important role in facilitating uterine contractions during parturition, milk let-down, and regulation of repetitive and affiliative behaviors including mother-infant and adult-adult pair-bond formation and sexual behavior. Since social deficits and repetitive behaviors are key features of autism, it is hypothesized that oxytocin may play a role in autism and, if so, may be an effective treatment strategy for these symptoms [99]. Furthermore, a genetic variation in the OXTR gene might be etiologically relevant in autism [100]. A recent study showed that oxytocin nasal spray improves emotion recognition in young people diagnosed with ASD, suggesting a potential treatment to improve social communication and interaction in ASD [101].

Complementary and alternative medicine (CAM) treatments are commonly used for children with ASD. While some CAM, such as secretin, have evidence to reject their use, others, such as melatonin, have emerging evidence to support their use. Most CAM treatments have not been adequately studied [102].

Autism and Schizophrenia: Co-morbid Association and Phenotypic Variations

Finally, although autism has long been reliably separated from early onset psychosis [103, 104] and data shows individuals with ASD are probably not at higher risk for developing schizophrenia [105], it is striking that children with childhood onset schizophrenia (COS) show high rates of early social, language and motor developmental abnormalities, with premorbid social impairment being the most common feature [106]. Beginning with Kanner's use of the term autism that suggested a similarity to schizophrenia, the question of comorbid association or phenotypic variations between autism and schizophrenia has been asked repeatedly. As the present volume focuses on schizophrenia spectrum disorders, this section of the chapter aims to clarify similarities and differences in presentation of ASD and COS.

COS is defined as the onset of psychosis before the age of 13, and is considered a rare and severe form of schizophrenia. Systematic studies of COS show high co-morbidity between COS and ASD [107]. Kolvin and colleagues were the first to describe the severity and frequency of prepsychotic developmental disorders in COS, an observation that had been replicated in multiple other studies [103]. Such developmental abnormalities include deficits in communication, motor abnormalities, and abnormalities in social relatedness. Alaghband-Rad and colleagues described transient motor stereotypies, delayed and disordered premorbid language development, learning disorders, and disruptive behavior disorders in children with COS. The authors suggested the presence of prepsychotic language difficulties indicate early temporal and frontal lobe development abnormalities, and that early transient motor stereotypies indicate developmental abnormalities of the basal ganglia [108]. A number of studies examining developmental abnormalities predating the onset of psychosis in children with COS replicate Kolvin and colleagues' observations, finding a rate of symptoms consistent with PDD-NOS in 28–55% of children [106, 107, 109]. Among other considerations, it is important to note the overlap of symptom presentation may complicate the use of research instruments such as ADOS and ADI-R as a tool to help distinguish between ASD and COS. In such cases, a clinical diagnosis should be the final one [110].

In an effort to account for some of this complex psychiatric co-morbidity and mixed developmental psychopathology, a sub-group of ASD termed multiple complex developmental disorders (MCDD), was proposed in the Netherlands. Criteria for MCDD include: impairment in social relatedness, affect regulation, and thought disorders. Although these children meet criteria for PDD-NOS, they also exhibit psychotic thinking [111, 112]. Sprong and colleagues compared high-risk traits and

symptoms in two populations at risk for psychosis: (1) help-seeking adolescents presenting with prodromal symptoms meeting the criteria for 'At Risk Mental State' (ARMS), and (2) adolescents with MCDD. Although the two groups clearly differed in early developmental and treatment histories, they did not differ with regard to schizotypal traits, disorganization, and prodromal symptoms. Interestingly, 78% of the adolescents with MCDD met criteria for ARMS, thus suggesting that children diagnosed with MCDD are at high risk for developing psychosis later in life, and supporting the notion that there are different developmental pathways to psychosis [113].

There is a large set of direct and indirect genetic evidence linking schizophrenia and autism. A comprehensive review of this literature is beyond the scope of this chapter and can be found elsewhere [114]. Individuals with velocardiofacial syndrome (chromosome 22q11) have higher rates of ASD and psychosis [115]. Similarly, 16p11.2 microdeletions or microduplications are reported in 1% of cases of autism and found in 2% of NIMH COS cohort [43, 116, 117]. Furthermore, variants at the neurexin 1 locus likely predispose individuals to autism, schizophrenia, or both [107]. At this point, the only conclusions that can be drawn from these interesting genetic links is that many rare genetic abnormalities affect common epigenetic pathways, which in turn affect neurodevelopment, and the emergence of clinical phenotypes.

Conclusions and Future Directions

In the past 10 years, much progress has been made in the identification, diagnosis and treatment of ASD. The validity of Asperger's syndrome in the DSM-IV field trials for autistic disorders has been controversial [13], and the DSM-5 [118] proposes to include both PDD-NOS and AS under a new category of ASD. The rationale for this proposed change is that while ASD are reliably and validly differentiated from typical development and other "non-spectrum" disorders, distinctions among disorders have been found to be inconsistent over time, to vary across sites and to be associated with severity, language level or intelligence rather than features of the disorder. The DSM-5 work group assigned to reviewing PDD has suggested autism best be represented as a single diagnostic category that is adapted to the individual's clinical presentation via inclusion of clinical specifiers (e.g., severity, verbal abilities and others) and associated features (e.g., known genetic disorders, epilepsy, intellectual disability and others). It is further argued that a single spectrum disorder is a better reflection of the state of knowledge concerning etiopathology and clinical presentation. In DSM-5, the three symptom domains become two: (1) social/communication deficits, and (2) fixated interests and repetitive behaviors [118].

There is evidence both that detection of ASD is possible as early as infancy, and that earlier interventions may alter the course of this neurodevelopmental disorder. There have been significant advances in the understanding of the neurobiology and

genetics of autism and related disorders; however, there are no immediate clinically profound implications from these findings. Lastly, the complex clinical and genetic link between ASD and COS warrant close attention to the overlapping clinical presentations of the autistic spectrum and schizophrenia spectrum disorders.

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Chapter 7
One Hundred Years of Insanity: Genomic, Psychological, and Evolutionary Models of Autism in Relation to Schizophrenia

Bernard J. Crespi

Abstract The Swiss psychiatrist Eugen Bleuler coined the terms "schizophrenia", for the splitting of psychic functions, and "autism", for withdrawal from external reality in patients with schizophrenia, almost exactly a century ago. Ever since 1943 when Leo Kanner co-opted "autism" to refer to a new condition involving "disturbance of affective contact" manifested in children, the relationship between schizophrenia and Kanner's autism has remained unclear. In this article I draw on data from studies of genomics, neurodevelopment, psychology, psychiatry and evolutionary biology to develop and evaluate alternative hypotheses for the relationship between autism and schizophrenia spectrum conditions. These data provide evidence for two hypotheses: partially-overlapping etiology of autism with schizophrenia mediated by common risk factors, and diametric causes of autism and schizophrenia mediated by genes underlying under-development versus dysregulated over-development of human social-brain phenotypes. The primary practical implications of these results are that: (1) false-positive diagnoses of premorbidity to schizophrenia-spectrum conditions as autistic spectrum conditions may be common, and may indicate a structural flaw in current diagnostic, nosological frameworks; (2) schizophrenia may be due in part to losses of function in negative regulators of social cognition and affect, rather than "deficits" in brain development; (3) the development of new pharmacological treatments for autism and schizophrenia can benefit directly from models of how autistic spectrum and schizophrenia spectrum conditions are etiologically related; and (4) future studies of autism, schizophrenia, and their relationship to one another must increasingly seek to integrate across analytic levels, from genes to neurodevelopment, neurological function, neuroanatomy, cognition, and evolutionary biology of the social brain, in the context of subtyping the substantial genetic and clinical heterogeneity found in each set of conditions.

Keywords Schizophrenia · Autism · Genomics · Nosology · Evolution · Social brain

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Abbreviations

DSM-IV	Diagnostic and statistical manual of mental disorders
PDD-NOS	Pervasive developmental disorder not otherwise specified

Introduction

The great Colombian author Gabriel García Márquez reified the cyclical nature of history in his Nobel Prize-winning 1967 book, *One Hundred Years of Solitude*. Eugen Bleuler's less-famous book *Dementia Præcox or the Group of Schizophrenias* [1], originally published in 1911, saw first use of the term "autism", a form of solitude manifest by Bleuler as withdrawal from reality in schizophrenia. This neologism, about to celebrate its centenary, epitomizes an astonishing cycle of reification and change in nosology, a cycle only now coming into clear view as molecular-genetic data confronts the traditional, age-old categories of psychiatric classification.

The purpose of this article is to review and evaluate the relationship of schizophrenia with autism, to help illuminate the causes of both conditions. To do so, I integrate data from recent studies of genomics, neurodevelopment, psychology, and psychiatry, in the context of alternative hypotheses for how schizophrenia and autism are related to one another, genetically, developmentally, psychologically, and with regard to the evolution of social-cognitive and social-affective phenotypes in humans.

I first provide a brief history of the term "autism", in the context of schizophrenia, Kanner's autism, and diagnostic methods. This background is necessary for understanding how "autism" and "autistic" are currently conceived and applied in the literature.

Second, I review evidence regarding the phenotypes and phenotypic structure of autism, and schizophrenia, and how they relate to diagnostic classifications. I introduce the concept of "positive" symptoms as manifestations of autism, to help in contrasting autism with schizophrenia psychiatrically, psychologically, and with regard to underlying neurodevelopment, physiology, and brain morphology and function.

Third, I describe alternative models for how schizophrenia-spectrum conditions and autism are related to one another psychologically, developmentally, neurologically, and with regard to evolution of the human social brain. Each of these models makes specific predictions that can be tested in a strong-inference framework, using data on causes, correlates and consequences of variation in neurodevelopment.

Finally, I discuss the primary implications of this review for practical applications, including pharmacological therapy, strategies for uncovering genetic risk factors, integration of etiological studies across causal levels from genes to psychiatric phenotypes, and conceptualization of psychiatric conditions in relation to normative development.

"Autism" from Bleuler to the DSM

> One of the most important symptoms of schizophrenia is the preponderance of inner life with an active turning-away from the external world. The most severe cases withdraw completely and live in a dream world; the milder cases withdraw to a lesser degree. I call this symptom "autism." [1, p. 397]
>
> The outstanding, "pathognomonic", fundamental disorder is the children's inability to relate themselves in the ordinary way to people and situations from the beginning of life. . . . This is not, as in schizophrenic children or adults, a departure from an initially present relationship; it is not a "withdrawal" from formerly existing participation. From the start there is an extreme autistic aloneness. [2]

Kanner [2] struggled to establish "autism" as a condition separate from schizophrenia, especially given the tendency among psychiatrists to consider schizophrenia as some function of Bleuler's "four As" of autism, association, affect, and ambivalence [3]. Kanner's attempts to conceptually-extract autism from schizophrenia initially failed, and throughout much of the 1950s, 1960s and 1970s, autism was considered as a manifestation or subtype of schizophrenia in children ("childhood-onset" schizophrenia) [4, 5]. Eventually, documentation by Kolvin [6] of a bimodal onset or diagnosis of autism (in early childhood) and schizophrenia (in adolescence), and comprehensive reviews by Rutter [7–9] contrasting the correlates and phenotypes of autism and schizophrenia, validated autism as a separate and distinct condition. This condition was formalized by DSM-III in the context of "infantile autism" as a subgroup of "pervasive developmental disorder" [10]. The initial diagnostic criteria for "infantile autism" included: (1) lack of responsiveness to others, (2) language absence or abnormalities, (3) resistance to change or attachment to objects, (4) the absence of schizophrenic features, and (5) onset before 30 months. A more-flexible DSM-III-R, based in large part on work by Rutter [9], saw the first formalization, in "autistic disorder", of the familiar triad of impairments: (1) reciprocal social interaction; (2) verbal and non-verbal communication; (3) restricted repertoire of activities and interests; with diagnostic thresholds based on minimum numbers of specific behaviors in each category, and overall.

DSM-IV was fundamentally similar to DSM-III, but with the addition, among other diagnoses, of PDD-NOS (pervasive developmental disorder not otherwise specified). PDD-NOS is defined as "severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interests, and activities are present", when the full criteria are not met for autistic disorder or other conditions (including schizophrenia and schizotypal personality disorder), due to late age of "onset" (after age 3), or atypical or sub-threshold symptoms.

Finally, nascent DSM-V simplifies diagnostics by subsuming the full set of closely-related idiopathic autism spectrum conditions (autistic disorder, Asperger's syndrome, and PDD-NOS) under a single category, "autistic disorder", with three criteria: (1) persistent deficits in social communication, reciprocity, and peer interactions, (2) restricted, repetitive patterns of behavior, interests and activities, and (3) symptoms present in early childhood but possibly "not fully manifest until social demands exceed limited capacities".

Most modern research on autism spectrum conditions, and their relationship to schizophrenia, has been conducted under the rubrics of DSM-IV, which was published in 1994. Under these criteria, PDD-NOS, considered as an autism spectrum condition, applies to any child with social-behavorial impairments salient but sub-threshold to autistic disorder. The PDD-NOS category has been applied very extensively, with diagnostic prevalence comparable of that of autism and Asperger's syndrome combined in some populations (e.g. [11]), probably due in part to its lack of specificity [12]. About half of PDD-NOS cases involve clinical social and communication deficits, but sub-threshold impairments in repetitive behavior and restricted interests [13].

With regard to diagnostic accuracy, and conceptualization of how autism is related to schizophrenia from a neurodevelopmental perspective, two key questions follow from work conducted under DSM-IV: how often premorbidity to schizophrenia is sufficiently severe to result in autism spectrum diagnoses during childhood, and how often schizophrenia that lacks prominent positive symptoms has been diagnosed as autism spectrum or considered "autistic". These questions will be addressed below, in the contexts of information on manifestations of premorbidity to schizophrenia, and genetic data on the causes of schizophrenia and autism.

Despite the clear separation of schizophrenia from autism provided by all versions of the DSM, Bleuler's concept of "autistic" deficits in schizophrenia has persisted in the literature, probably due to the prominent impairments in social reciprocity, language, and theory of mind found in most schizophrenic individuals [14–18]. Such impairments are, moreover, frequently combined with elements of obsessive or compulsive behaviors [19], as is autism [20]. These phenotypes of schizophrenia correspond closely, of course, with the tried of traits used to describe and diagnose autism. Conflation of schizophrenia with autism can usually be avoided by the frequent presence of prominent "positive" symptoms, such as hallucinations, delusions, and thought disorder, characteristic of schizophrenia and exclusionary of autism in the DSM. However, such positive symptoms are also highly variable and episodic, and patients with schizophrenia or schizotypy typified by predominantly negative and disorganized symptoms overlap in their profiles of psychological and behavioral symptoms with some autistics [21–25]; such individuals are also, like autistics, most-commonly male [26].

These considerations suggest that many schizophrenics and individuals with schizotypal personality disorder are likely to score in the "autism" or "autism spectrum" (including PDD-NOS) ranges on DSM-based or other metrics of "autistic" symptoms, as demonstrated by several studies (e.g., [22, 27, 28]). Of such metrics, the most inclusive is represented by the "broad autism phenotype" [29], a set of language and personality traits that are similar to, but milder than, those found in autism. Comparison of the broad autism phenotype questionnaire [29] to its equivalent in the study of schizophrenia, the schizotypal personality questionnaire [30–32], indicates considerable similarity between measures of the broad autism phenotype and the interpersonal and disorganized dimensions of schizotypy. Such resemblances are validated by scores above the broad autism phenotype cutoff for schizophrenic and schizotypal individuals in one study [33], and supported by

similarities between questionnaire measures of Asperger's syndrome and schizotypy [23]. These similarities and possible "false-positive" diagnoses apparently reflect the central roles of deficits in social cognition and behavior, and unusual patterns of interests and compulsions, among both the autism and schizophrenia spectra, regardless of their underlying causes.

Deficits in sociality and language, and the presence of repetitive behavior and restricted interests, usually remain idiopathic, but are also not uncommon in a variety of neurogenetic conditions, such as Velocardiofacial syndrome, Klinefelter syndrome and Prader-Willi syndrome, that involve neurological phenotypes of schizophrenia in a large subset of individuals, and a high incidence of schizophrenia and schizotypy in adults [34–45]. Individuals with such syndromes – which are usually recognized in childhood – have often been diagnosed as "autistic" if they meet all three autism criteria, or "autism spectrum" (usually PDD-NOS) if the fit between phenotypes and criteria is less complete. "Autism spectrum" diagnoses are thus usually applied, in both idiopathic and syndromic cases, to children who are under the usual age (in the late teens) at which schizophrenia is expressed. As a result, individuals who are "premorbid" for schizophrenia are not diagnosed as such (due to a lack of specific, predictive criteria for later development of schizophrenia), but are categorized as "autism spectrum" if their social, language, and/or repetitive-behavioral restricted-interest impairments are sufficiently severe. Social, language, and other developmental deficits and delays are indeed common among children – especially boys – who later develop schizophrenia [27, 46–54]. How often do such phenotypes motivate childhood diagnoses of "autism spectrum"?

The frequency of "false-positive" autism spectrum diagnoses [55] among pre-schizophrenic or schizotypal children remains unclear, especially for individuals without identified genetic or genomic risk factors. However, the tendencies for genomic copy number variants to exert severe effects on diverse aspects of early neurodevelopment [56], and for schizophrenia of earlier onset to exhibit a higher male sex-ratio bias and a stronger tendency to be associated with copy-number variants rather than other factors [5, 57] suggests a substantial risk for false-positive diagnoses of autistic spectrum conditions [4, 28, 33, 49, 55] at least for individuals with genomic or genetic risk factors of high penetrance. The most direct evidence for diagnostic conflation of the autism spectrum with premorbidity to schizophrenia, schizotypy, or other schizophrenia-spectrum conditions comes from diagnoses of autism spectrum conditions in children with deletions at 15q11.2, 15q13.3, and 22q11.21, and duplications of 16p11.2, copy number variants for which schizophrenia risk has been well-established from studies of adults [36, 49, 58, 59, 60–62]. By contrast, autism-associated copy number variants, such as deletions at 16p11.2 [63], or duplications at 22q11.21 [64] have seldom also been reported in individuals diagnosed with schizophrenia and have not been established as risk factors.

Differentiating autism spectrum conditions from false-positive diagnoses of premorbidity to schizophrenia requires judicious use of intermediate, biologically-based phenotypes including "positive" symptoms of autism (as described below), adoption of relatively-new diagnostic categories such as Multiple Complex Developmental Disorder [65, 66], and use of data from genomic risk factors in

developmental, longitudinal perspectives. In particular, children with diagnoses of autism spectrum conditions who harbour deletions at 15q11.2, 15q13.3, or 22q11.21, duplications at 16p11.2, supernumary X chromosomes (Klinefelter syndrome in males), paternal deletions of 15q11–13 or maternal uniparental disomy for chromosome 15 (Prader-Willi syndrome), or other well-validated schizophrenia-spectrum genomic risk factors, might usefully be monitored for the development of schizophrenia spectrum conditions after the onset of adolescence, and studied for the presence of biologically-based schizophrenia-spectrum phenotypes (e.g., [43, 67]; see also [44, 62]). To the degree that false-positive diagnoses of autism spectrum conditions in childhood are not uncommon, and autism and schizophrenia are underlain by different genetically-based risk factors, inclusion of children premorbid for schizophrenia in studies to uncover novel genetic or genomic risk factors for autism will dilute the probability of detecting significant results.

Consideration of autism from the general perspective of impaired social interaction, due to some combination of deficits in reciprocity and language, and repetitive, restrictive interests and behavior, cycles us back to Blueler's original incarnation. The extensive cognitive-affective and behavioral variation among children with Kanner's autism has motivated, justifiably, a wide diagnostic net – but such a net, especially when structured mainly by the presence of deficits, may capture individuals with impairments due to highly diverse causes. Ultimately, the diagnostic bases of autism and schizophrenia should presumably be founded on models of causation, models that can subsume the diversity of developmental, physiological, morphological, behavioral and psychological phenotypes found in each condition under a relatively small set of convergent frameworks. Only in this way can the diagnostic categorizations of autism and schizophrenia each be reconciled with their genetic and neurodevelopmental foundations, and nosology be connected with proximate and ultimate causes [68]. These are fundamentally important issues because, as described below, many researchers consider autism and schizophrenia to be similar conditions based on the centrality of social deficits in both, while others consider them to be separate and independent (as in the DSM), or diametric.

Phenotypic Structure of Autism and Schizophrenia Spectrum

Reification of autism and schizophrenia as "real" categories, rather than pragmatic human constructs, may be a natural consequence of their fundamental, long-term historical role in structuring 100 years of thought and research into causes of human psychiatric conditions. The usefulness to society of these constructs has been extensively demonstrated, but evaluation of their status as dimensional versus categorical, and causally divisible into components versus unitary, has required data on the genetic bases of the conditions, their sets of diagnostic criteria, and the relationships between their component phenotypes. Such information has become available and begun to solidify mainly within the past few years, allowing the first explicit comparisons between the phenotypic structures of schizophrenia and autism.

First, schizophrenia (and related conditions) and autism each encompass sets of dissociable but more or less related phenotypes. Schizophrenia is not clearly separable from bipolar disorder and major depression; these conditions overlap broadly in core phenotypes, exhibit joint familial aggregation even when underlain by single, segregating penetrant risk factors such as DISC1 loss of function, and are mediated by genetic risk factors that may influence liability to pairs or trios of the conditions, or specific symptoms such as aspects of psychosis (e.g., [69–72]). Considered together, these conditions are thus referred to as the "schizophrenia spectrum", or "psychotic-affective spectrum", and considered as a set of genetically and phenotypically related conditions comprising a mosaic of partially-overlapping but dissociable psychotic, manic, affective and other symptoms. Any given individual can be conceptualized as occupying a zone in three-dimensional space defined by degree of expression of psychotic (including positive, negative and disorganized), manic and affective phenotypes, or, more specifically by a multidimensional space that comprises the constellation of phenotypes found in schizophrenia, bipolar disorder, and major depression. Van Os [73] provides a useful depiction of such a space, in the context of "salience syndrome" as a unified framework for understanding phenotypes associated with psychosis. Phenotypes of the schizophrenia spectrum are dissociable, in that specific symptoms can and do occur in isolation, and components are relatively independent genetically (e.g., [74, 75]) – but they often occur together, presumably due to pleiotropy and shared neurodevelopmental causes. However, the relationship of psychotic, manic, affective, and other schizophrenia-spectrum symptoms to one another remains poorly understood.

The trio of phenotypes diagnostic of idiopathic autism has been demonstrated to be partially if not largely dissociable, in that the phenotypic and genetic correlations between measures of impairments in social reciprocity, language, and restrictive, repetitive behavior and interests are modest [12, 76, 77]. Autism can thus be considered as a set of social and behavioral traits that are genetically and phenotypically related in that they occur together somewhat more often than expected by chance, or interact additively or in synergy to produce a recognizable pattern, but are also separable, in that any specific component of the three can and does occur in isolation. Any given individual can thus be conceptualized as occupying some area in a multidimensional space with axes defined by the diagnostic triad and their severities [12]. The relationship of social with non-social phenotypes remains poorly understood [78], and the degree to which the three core components of autism would emerge from factor analysis of a much wider range of childhood behavioral phenotypes than previously included (e.g., [77]) has yet to be ascertained.

Unlike the schizophrenia spectrum, the autistic spectrum is defined predominantly by the presence of deficits and impairments, rather than by "positive" symptoms that represent novel patterns of behavior, cognition and affect that are reasonably specific to the condition or its subtypes. A suite of "positive" symptoms can be described for autism (Table 7.1), although each of them applies more or less strongly across subsets of autistic individuals. The primary usefulness of "positive" autistic phenotypes rests in their use for deliniation of discrete sets of causes

Table 7.1 Psychological, behavioral, neurological and physiological traits that can be considered as "positive" symptoms of autism

Trait	Studies
Enhanced local information processing, visual-spatial skills	Soulieres et al. [79]; Russell-Smith et al. [80]
Savant skills, islets of ability	Mottron et al. [81]; Happé and Vital [82]
Hyperlexia	Newman et al. [83]
High fluid intelligence	Dawson et al. [84]; Hayashi et al. [85]
Insistence on sameness	Kanner [2]; Prior et al. [86]
Self-stimulatory behaviors	Cunningham and Schreibman [87]; Goldman et al. [88]
Enhanced perceptual functions	Bonnel et al. [89]; Ashwin et al. [90]; Mottron et al. [91]
High serotonin levels	Scott and Deneris [92]; Whitaker-Azmitia [93]
Large head, brain size	Mraz et al. [94]; Redcay and Courchesne [95]
Increased white matter	Herbert et al. [96]; Bigler et al. [97]

that convergently mediate autism, and in their ability to facilitate differential diagnosis of autism from other conditions characterized by social and communicative impairments, such as relatively-severe premorbidity to schizophrenia.

Second, studies of the genetic basis of schizophrenia in relation to schizotypy, the prevalence of autistic and schizotypal traits in non-clinial populations, familial aggregation of phenotypes considered as autistic or schizotypal, quantitative-genetic studies of autistic phenotypes, and studies of genetic variation in specific genes subject to either large-scale or small-scale alterations, provide convergent evidence that schizophrenia-spectrum traits, and autistic-spectrum traits, each grades more or less smoothly from severe impairment into normality [98–100]. In accordance with such continuity, autism and schizophrenia have each been demonstrated to be strongly mediated by effects from de novo and segregating genetic variation of small and large effects, with high heritabilities, but also with high levels of genetic heterogeneity, such that a large number of genetic risk factors, separately and/or in combination, convergently mediates the risk of each condition [101–103]. A primary implication of the continuity between these clinical disorders and normality is that the phenotypes characteristic of schizophrenia and autism spectrum conditions can each be considered as extreme manifestations of normal human variation in cognitive and affective phenotypes (e.g., [73, 104, 105]) rather that pathology disembodied from human adaptation.

For both the schizophrenia and autism spectrum, the neurocognitive adaptations most relevant to the disorders are components of the human "social brain" – the integrated, distributed set of neural systems that subserves the acquisition, processing and deployment of social information [44, 106–108] (Fig. 7.1). To the extent that these psychiatric conditions are mediated by dysregulated development and function of the social brain, understanding the ontogeny, modularity, integrated ultimate and proximate functions, and genetic bases of social-brain components becomes fundamental to dissecting the etiologies of autism and schizophrenia, and ultimately, to defining disorders of human development based on biological criteria.

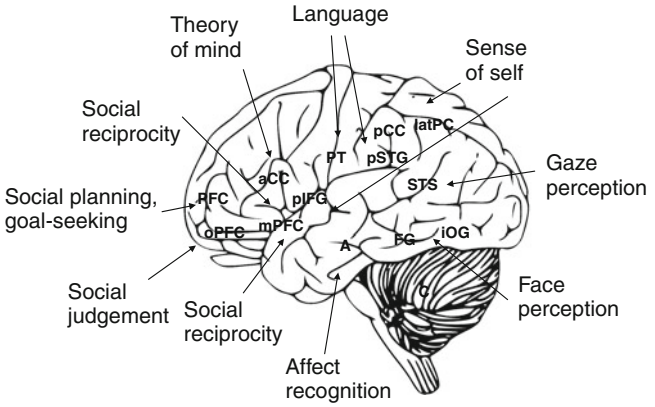

Fig. 7.1 Functional partitioning of components of the human "social brain", mainly from imaging and lesion studies. A = amygdala; aCC = anterior cingulate cortex; FG = fusiform gyrus; iOG = inferior orbital gyrus; latPC = lateral parietal cortex; mPFC = medial prefrontal cortex; oPFC = orbital prefrontal cortex; pCC = posterior cingulate cortex; pIFG = posterior inferior frontal gyrus; pSTG = posterior superior temporal gyrus; PT = planum temporale; STS = superior temporal sulcus. The cerebellum ("C") also plays important roles in social-brain cognition and affect. Neuroanatomical positions are approximate

A simple, testable model for conceptualizing the adaptive significance of social-brain phenotypes, in relation to their maladaptive dysregulation in schizophrenia spectrum conditions, is provided in Fig. 7.2. This model can be tested and refined by evaluating the normal adaptive functions of specific cognitive-affective phenotypes (e.g., [109]) in relation to their forms of dysregulation in more or less severe

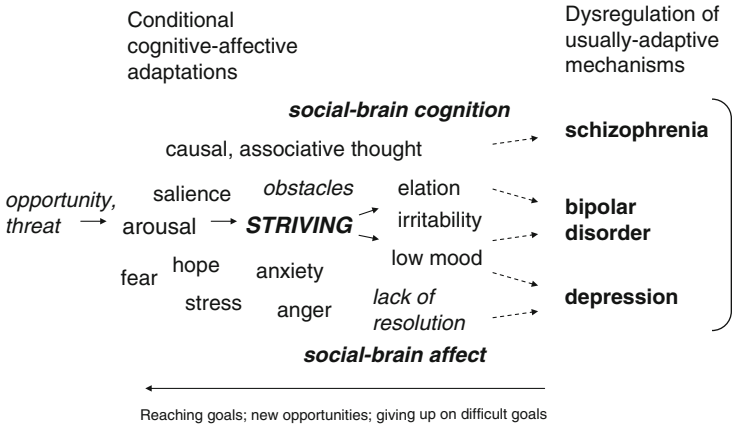

Fig. 7.2 The social, cognitive-affective context of schizophrenia spectrum phenotypes, considered as dysregulated manifestations of neurological-psychological traits that are conditionally adaptive

psychiatric conditions, and by systematically elucidating the cognitive-affective correlates of validated schizophrenia or autism "risk" alleles in non-clinical populations (e.g., [110, 111]).

Despite the continuity of the autism spectrum and the schizophrenia spectrum with normality, the multidimensional distributions of autistic and schizophrenic-spectrum phenotypes in populations of clinical and non-clinical individuals considered together remain unclear, in part because they are some function of the spectrum of salient genetic and environmental variation present in populations. Thus, if the bulk of variation in such phenotypes is mediated by relatively common, segregating alleles each of small effect, normal distributions are expected – as for any polygenic trait. By contrast, rare, commonly de novo mutations of large effect, such as highly-penetrant copy number variants and monogenic causes of autism, should tend to produce discontinuities, with "spikes" in the distributions at the clinical ends of the spectra and their components. Each type of genetic risk factor has now been well documented, especially for schizophrenia, but the spectrum of effect sizes, and risk allele frequencies, remain to be fully elucidated, with much of the heritability for each set of conditions yet to be discovered [112].

The confrontation of genetic and genomic data with data on diagnosis-related phenotypes represents one of the most important ongoing developments in understanding the etiologies of autism and schizophrenia. A useful set of models relating genes to psychiatric conditions and their diagnostic phenotypes is described by Fanous and Kendler [70]: allelic variation may affect risk of the condition itself, risk of some subset of clinical features of the condition, or expression of clinical features but not risk. Genes "for" autism or schizophrenia [68] have thus far been evaluated in genome-wide association, copy number variant, and deep-sequencing studies predominantly under models of causation that involve genetic factors mediating risk of the full diagnoses as threshold traits, rather than mediating phenotypic expression, qualitative or quantitative, of the component phenotypes. To the extent that diagnostic phenotypes are genetically as well as phenotypically dissociable, and to the extent that neurodevelopmental disorders are mediated by sets of distinct genetic causes that convergently yield particular diagnostic phenotypes, this approach will be notably inefficient. Much of the heritability of schizophrenia and autism may thus be presently "missing" due to the phenotypic and genetic structures of the disorders, and not the limitations of genomic technology. Despite such considerations, the observation of a proportion of cases of autism or schizophrenia that appears attributable to losses of function or dosage alterations in single genes (e.g. AUTS2, FMR1, DISC1, and NRXN1, among others) indicates that single genes may pleiotropically mediate expression of the full suite of symptoms sufficient for diagnosis, perhaps due to extensive pleiotropy (e.g., [113]). Such data provide evidence for coherence of autism and schizophrenia as biologically-based conditions, with shared causal linkages between their components.

The primary question that follows from these considerations is whether or not the phenotypic and genetic structures of the autism and schizophrenia spectra – their partially-dissociable phenotypes, continuity with normality, highly-heritable nature, and notable clinical and genetic heterogeneity – can be reconciled such that

the two conditions are causally and functionally related in some manner that can be evaluated statistically. If so, then the criteria for defining the two sets of conditions can, in principle, be grounded within a common non-arbitrary, biologically-based, non-historical, yet pragmatic causal framework. Addressing this question involves consideration of explicit alternative models for how the schizophrenia spectrum and autism spectrum are related to one another, and how strong inference can be used to evaluate which model or models best fits the available data.

Alternative Models for the Relationship of Schizophrenia with Autism

Differentiating between alternative models for the relationships of major human psychiatric conditions with one another has important implications for diagnoses, pharmacological and psychological treatment, and strategies for dissection of etiology at all levels from genes to psychology. Recent studies [114–117] have demonstrated how genetic data can be deployed to evaluate explicit alternative hypotheses for the relationship of schizophrenia with bipolar disorder, originally described as a dichotomy in work that followed from the pioneering studies of Emil Kraepelin but now viewed in terms of partial overlap, based on the presence of shared genetic risk factors mediating shared phenotypes. Such analyses have only recently become feasible with the discovery of robustly replicated genetic risk factors, and they allow objective criteria to be applied to nosological frameworks that have thus far been difficult to evaluate rigorously.

Studies by Craddock and colleagues [114–117] have provided strong evidence for continuity between schizophrenia and bipolar disorder, because specific genetic risk factors – both highly-penetrant alterations and common polymorphisms of small effect – predispose to either one or both of the conditions. As a result, despite the common presence of patients with “pure” psychotic or mood symptoms, schizophrenia and bipolar disorder grade together phenotypically, apparently due to a continuum of shared and separate genetic risk factors. Such structure should, eventually, allow clinical heterogeneity to be connected with, and mapped onto, genetic heterogeneity, in the additional context of environmentally-based risk.

The relationship of schizophrenia with autism remains much less clear [44, 62, 118–120]. For some years, Kanner [121] considered autism as a distinct, early-expressed subtype of schizophrenia, similar in general form to negative-symptom schizophrenia. As noted above, this viewpoint persisted for several decades in the context of autism as a manifestation of childhood-onset schizophrenia, and as a disorder characterized predominantly by social deficits similar to those found in negative-symptom schizophrenics [122]. Under this model (Fig. 7.3a), autism should be mediated by a subset of negative-symptom schizophrenia genetic-risk factors – presumably those with early onset or high severity.

Kanner [123] later renounced the idea of autism as a subtype of schizophrenia, in favor of a view, also supported by Rutter [7, 8], with the conditions as distinct, separate and unrelated to one another (Fig. 7.3b). By this model, autism and

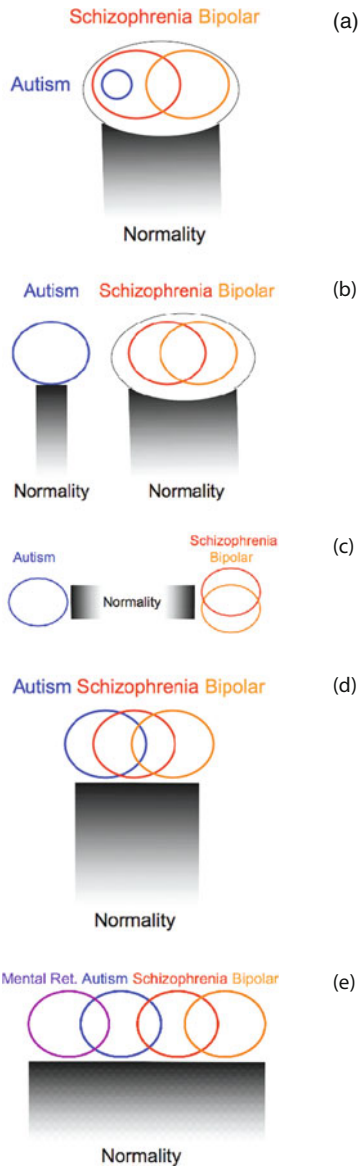

Fig. 7.3 Alternative models for the relationship of autism with schizophrenia and bipolar disorder, in comparison to normality. (**a**) Subsumed [121, 122], (**b**) Separate [123, 7–9; DSM III–V]; (**c**) Diametric [44, 62]; (**d**) Overlapping I [129]; (**e**) Overlapping II [117]

schizophrenia should not overlap in genetic risk factors, unless some risk alleles are sufficiently general to underlie a broad swath of cognitive-affective dysfunctions.

Under each of these two hypotheses, autism and schizophrenia each grades independently into normality. Under a third model (Fig. 7.3c), schizophrenia and autism have been considered as diametric (opposite) sets of conditions along a spectrum of social-brain phenotypes, from hypo-development in autism, to normality, to hyper-development in schizophrenia [44, 124]. The idea of diametric disorders is novel

to psychiatric classification, but can be conceptualized as analogous to neurodevelopmental pathways that can be perturbed in two opposite directions, or signaling pathways can become under- versus over-activated. Schizophrenia spectrum conditions may thus develop in part due to losses of function in negative, homeostatic regulators of social-cognitive-affective phenotypes (phenotypes that in autism never matured), which leads to differential deficits in social skills that may appear similar to those in autism but develop by fundamentally-different means (Fig. 7.4). Examples of such losses in negative regulation may include over-activity of the midbrain dopaminergic systems leading to inappropriate assignment of motivational salience to irrelevant objects, people and actions [125], "jumping to conclusions" as a risk factor for the formation of delusions [126] and impairments of corollary discharge systems mediating aspects of hallucinations and passivity phenomenon (e.g., [127, 128]). In a developmental context, social skills are impaired during childhood in autistics due to hypo-development of social brain phenotypes, and, in some cases, childhood social skills are also reduced in individuals premorbid for schizophrenia, though for other reasons.

Diametric etiology of the autism and psychotic-affective spectra, in the context of the normally-developing social brain, takes account of their fractionable natures in that corresponding hypo- and hyper-developed social-brain phenotypes can be described for the two conditions, each of which may be underlain by some subset of the genetic risk factors that underly the full spectra. Each phenotype of the

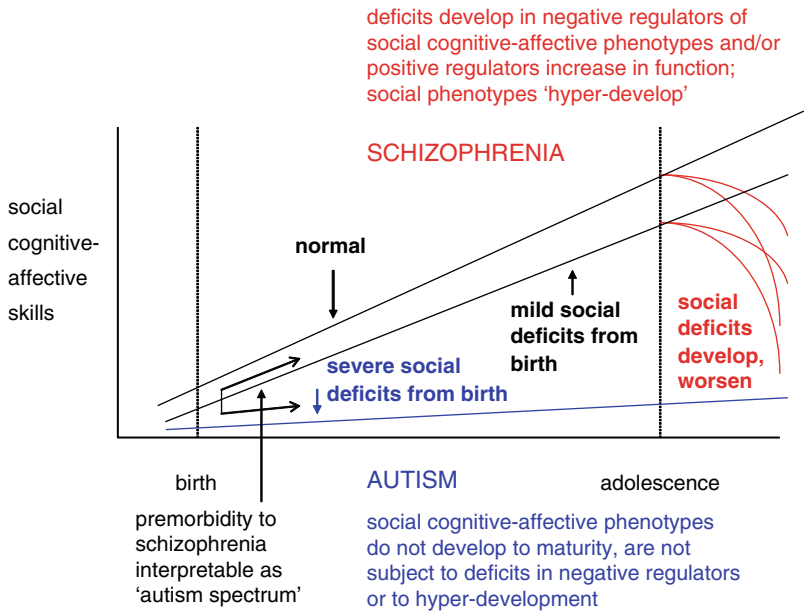

Fig. 7.4 The development of autism and schizophrenia, with regard to the timing, causes and expression of social-cognitive-affective impairments

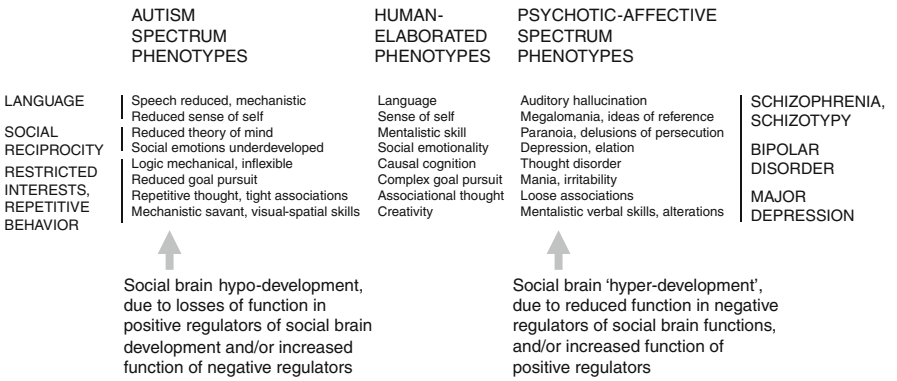

Fig. 7.5 The relationships of autism spectrum and psychotic-affective spectrum phenotypes to social-behavioral-cognitive phenotypes that have become highly developed and elaborated along the human lineage

autism and psychotic-affective spectra can also be directly related to normal social-brain functions that became highly-developed along the human lineage (Fig. 7.5), such that expression of these psychiatric phenotypes becomes explicable in terms of the recent expansion and elaboration of the human social brain [44, 107, 108]. By contrast, other models of autism in relation to the psychotic-affective spectrum remain disconnected from human evolution and the cognitive-affective adaptations that characterize our lineage.

By a fourth model, autism overlaps broadly yet partially with schizophrenia, sharing some risk factors and phenotypes but not others (Fig. 7.3d). This model has been motivated by recent genetic evidence for shared loci and pathways mediating both autism and schizophrenia risk (e.g. [129, 130]), as well as by work describing social deficits as central to both Kanner's autism and the "autistic" symptoms of Blueler's schizophrenia, as described above. Under this hypothesis, autism and schizophrenia are expected to share a subset of risk alleles, which underlie shared social-deficit phenotypes, but each condition should also be mediated by unshared risk alleles that mediate unique phenotypes.

Finally, Craddock and Owen [117] have proposed a variant of the overlapping model, under which schizophrenia overlaps partially with autism along a spectrum of increasing cognitive impairment, with autism grading into mental retardation (Fig. 7.3e). By this hypothesis, autism and schizophrenia should be mediated by a partially-overlapping set of genetic risk factors, with autism the result of more-severe alterations to the genetic bases of neurodevelopment. This model can help to explain evidence for: (1) high comorbidity of autism with intellectual disability; (2) the presence of cognitive impairments but not mood-disorder symptoms in schizophrenia, autism and intellectual disability; and (3) data showing overlap of risk loci between schizophrenia and autism, as well as between autism and intellectual disability [62, 73, 131, 132].

The primary assumptions involved in using strong inference to evaluate the predictions of these alternative hypotheses include: (1) the absence of ascertainment biases, which have been proposed to explain reports of relatively low IQ in autism spectrum conditions, given that lower-IQ individuals are more likely to be brought to the attention of clinicians ([133]; see also [84, 85]); (2) accuracy of diagnoses, especially with regard to "false positive" diagnoses of relatively-severe premorbidity to schizophrenia as autism spectrum, as described above; (3) validity of the associations between genetic risk factors and diagnosed conditions, especially for autism, which has been subject to considerably less well-replicated, large-sample genetic study than schizophrenia; and (4) the possibility that the hypotheses are not mutually exclusive, due to the presence of genetic variants and polymorphisms that increase risk of any psychiatric condition non-specifically, or due to relationships between autism and schizophrenia that are more complex than the models depicted here. These assumptions are unlikely to be met, but each can be addressed with regard to future studies and the nature of the potential biases and inaccuracies that they introduce.

Crespi et al. [62] used copy number variant and genetic association data to evaluate the former four hypotheses described above. They reported evidence of statistically significant increased sharing of risk genes, from genetic association studies, between autism and schizophrenia. This sharing of risk genes was generated by two patterns in the relationships of alleles and genotypes to the conditions: (a) for some loci, the same allele mediated risk of both conditions; and (b) for other loci, autism was associated with one allele or genotype and schizophrenia was associated with the other; other loci could not be directly compared due to heterogeneity of markers or complexity of the findings.

For copy number variant data, Crespi et al. [62] found diametric patterns at three (16p11.2, 22q11.2, 22q13.3) of the seven copy number variant loci with sufficient data for analysis: deletions were statistically associated with one condition from case-control studies, and duplications were statistically associated with the other. By contrast, one of the loci (16p13.1) showed duplications associated with both conditions, and for 1q21.1, deletions were associated with both autism and schizophrenia (though with only two autism cases reported, compared to 15 cases for schizophrenia), whereas duplications were associated only with autism.

Taken together, these results from genetic-association and copy-number variant data can be interpreted as apparent falsification of the hypotheses that autism is subsumed within schizophrenia (Fig. 7.3a), or that schizophrenia and autism are genetically independent of one another (Fig. 7.3b). The findings of diametric patterns for several copy number variant loci, and some genetic-association loci, are compatible with the diametric model (Fig. 7.3c) but the presence of some unambiguously-shared risk factors support a model of partially-shared risk and some degree of overlap, or a substantial degree of false-positive diagnoses of premorbidity to schizophrenia as autism (or negative-symptom schizophrenia and schizotypy as autism). These questions require further, focused study in hypothesis-testing frameworks, to assess the prevalence of false positives, and jointly evaluate the genetic

underpinnings of autism and schizophrenia using genome-wide approaches with the same suites of markers.

One possible reconciliation of diametric and overlap models is that some set of loci exerts diametric genetic effects, while at other loci, some alleles mediate mild impairments of social cognition that increase risk of both autism and schizophrenia. For example, in autism such alleles may contribute to hypo-development of social brain phenotypes, whereas in schizophrenia they increase the likelihood of social-brain dysregulation by other means such as deficits in theory of mind, after the social brain has developed to maturity. Alleles with relatively general effects on social-cognitive development, which would be analogous to intellectual-disability genes but differentially affect social cognition, should also contribute to premorbid phenotypes of schizophrenia involving impairments in sociality and language.

Ultimately, robust evaluation of alternative hypotheses for the relationship of autism with schizophrenia will require in-depth analyses of the neurodevelopmental and neuronal-function effects of different alterations to the genes that mediate social-brain function and dysfunction, and integrative data from diverse disciplines other than genetics, especially the neurosciences and psychology.

The primary impediments to further testing of the models are likely to be reified conceptualizations of autism and the schizophrenia spectrum divorced from social brain adaptations, and perspectives from psychology that focus on deficits rather than their causes. Indeed, substantive progress in understanding these neurodevelopmental conditions is especially likely to come from analyses that span and connect levels of analysis, from genes to intermediate neurological and behavioral phenotypes, and from such phenotypes to psychiatric conditions [117, 134–137]. Head size provides a paradigmatic case in point, as relatively large head size or brain size have been reported in idiopathic autism, syndromic autism, and autism associated with specific copy number variants, and causes of large head size in autism have been ascertained in terms of growth-signaling pathway dysregulation (reviewed in [44, 62]). Large head size has also been demonstrated to mediate enhanced local compared to global information processing [138], a phenotype characteristic of autism that may connect directly to social and non-social impairments as well as explain enhancements of some sensory and cognitive skills [81].

An important practical implication of understanding the relationship between schizophrenia and autism is its potential usefulness in developing pharmacological therapies based on similar, independent, or diametric alterations to neurological systems. For example, antagonists of mGLUR5 signaling have recently been deployed for treatment of the autistic syndrome Fragile X [139], while agonists of this pathway are under development for schizophrenia [140]; similar considerations may apply to treatments for autism and schizophrenia that target the cholinergic system [141, 142]. The presence and nature of similarities and differences between autism and schizophrenia may thus reciprocally illuminate the causes and potential treatments for both conditions, and motivate psychiatric classifications and associated therapies based on biology rather than symptoms [143].

Conclusions and Future Directions

Recent accelerating progress in genetics, molecular biology, and neuroscience have brought psychiatry into a new era, facing the first realistic hopes of comprehensively characterizing the genetic underpinnings of autism and schizophrenia spectrum conditions and developing rational therapies based on alterations to sets of specific biological pathways [144]. Psychiatric classification, and psychological methods based on categorizing and correlating deficits, have lagged behind such advances, and indeed may impede progress to the extent that they conflate disparate conditions, combine individuals across highly-fractionable DSM diagnoses, deny the reality and effects of false-positive diagnoses, ignore the adaptive significance of the cognitive-affective mechanisms disrupted by autism and schizophrenia spectrum phenotypes, and echo Blueler's century-old conceptualization of autism. Indeed, until interdisciplinary studies that integrate across levels from genes to neurodevelopment to psychological phenotypes are systematically deployed, in hypothesis-testing frameworks that use strong inference [62, 145], we should expect to remain, as penned by García Márquez, in "permanent alternation between excitement and disappointment, doubt and revelation, to such an extreme that no one knows for certain where the limits of reality lay" – for yet another 100 years.

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Chapter 8
Quantifying the Dynamics of Central Systemic Degeneration in Schizophrenia

Anca R. Rădulescu

Abstract Schizophrenia is a mental condition defined by widespread, complex and inspecific symptoms. This complexity prevented many attempts to provide a simple explanation, a reliable cure or even a neurobiology-based diagnosis. Statistics has been so far the preferred method used in psychiatric research in conjunction with clinical data. However, regression-based analyses are generally limited by reliance upon their linear and static nature and emphasized (depending on the study) either unusually high or unusually low levels of one variable at a time (brain activation, cortisol, dopamine etc). Relatively little research has been conducted to reconcile these discrepancies. We review a recent stress/vulnerability hypothesis of systemic degeneration in schizophrenia. Based on the biophysics of the stress cascade, schizophrenic symptoms are viewed as an end-stage of a cyclic process: prefrontal-limbic systemic degeneration is triggered by environmental stress acting on a pre-existing vulnerability, so that the prefrontal-limbic system can be considered a quantifiable dynamical system evolving under external perturbations. We propose that a nonlinear systems analysis could best address the complex mechanisms of the disease. While dynamics has already successfully addressed regulation of various somatic systems, psychiatry has only started using similar methods to understand mental disorders as complex nonlinear systems. Recent imaging and bioengineering technologies are promoting a fresh research trend, and concepts of nonlinear dynamics (chaos, fractality or bifurcation theory) are now considered a suitable framework for describing the temporal architecture of the brain. We review some of our dynamical approaches to prefrontal-limbic degeneration in schizophrenia, including theoretical modeling and collaborative work with imaging time series from schizophrenia patients. We describe how a latent predisposition can remain dormant until a triggering event activates a threshold in the dynamics of the system (with each individual's vulnerability setting the threshold level) moving it into an unstable regime. Pharmacological

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treatment can be used to provide external inhibitory control over the system, but the intrinsic dynamics quite possibly remains in the unstable regime and is more prone to relapses. We finally discuss this work's overreaching goal: developing a neurophysiology-based quantitative chart of brain architecture profiling, usable by clinicians to complement the current behavior-based DSM diagnostic methods.

Keywords Limbic dysregulation · Critical state · Complex systems · Nonlinear dynamics · Mathematical modeling · Functional imaging

Background and Significance

Schizophrenia – A Complex Unsolved Problem

Schizophrenia is a severe mental disorder with a devastating impact on social functioning (having been associated with significantly increased risk for homelessness [1], suicide [2], unemployment [3], and substance abuse [4]). It is a relatively common illness, affecting annually 1.1% of the population, over 65 million people worldwide and 2.2 million in the United States alone [5]. Studies over the past two decades have found it to be a neurodegenerative disease [6, 7], affecting not only the structure and function of various cortical and subcortical regions involved in cognitive, emotional and motivational aspects of behavior [8, 9], but also the autonomic [10, 11] and endocrine [12] systems.

There are three primary types of clinical manifestations: "negative symptoms" (poverty of quantity or content of speech, flatness of affect, disturbances of volition, catatonia), "positive symptoms" (hallucinations and delusions, disorganized thinking and behavior, agitation) [13, 14] and cognitive disruption. It has been argued that all types of symptoms could be primary to the disease process [15], yet they have different development of and prognoses [16], and are not mutually exclusive (many, but not all patients have components of each).

This clinical, pathophysiological and etiological heterogeneity has helped schizophrenia resist many attempts to provide a simple explanation, or establish a disease etiology. The diagnostic criteria, periodically revised in the Diagnostic Statistical Manual [17], are consensually based upon statistically common behavioral symptoms. Establishing precisely the meaning and severity of these symptoms is not ideal for clinical decisions, since they are often compatible with other diagnoses (e.g., bipolar mania, delusional disorder or psychotic depression). In addition, symptom-based decisions cannot be made until such symptoms develop, which may already be too late for optimal intervention [18]. The treatment, typically combining medication and therapy, relies on these diagnoses and is often trial-and-error. At present, there is no generically sustainable cure for schizophrenia; despite pharmacological progress, the drugs that are being used may only treat the symptoms of the disease rather than its cause.

For all these reasons and more, a neurobiologically-based, quantitative instrument is crucially needed. The gold-standard for medical diagnoses is to provide an objective physiological test that provides unambiguous results while minimizing the need for either the patient's or the clinician's subjective interpretation of symptoms.

A variety of theories, not always mutually consistent, have evolved across scientific fields, aiming to address the cause for schizophrenia's symptom complexity, respectively in the context of risk increasing genes, of environmental stress factors, of receptor dynamics pharmacology or of neurodevelopmental deficits in early brain circuitry. A few corresponding research paths have developed over the past few decades, each with its advantages and limitations. A main direction has been recently approaching schizophrenia with *genetic sequencing* [19]. This approach seems the most promising as far as finding the small error(s) responsible for a person eventually developing schizophrenic symptoms. However, it has a few major draw-backs, and no immediate answer in sight. Obstacles include the very probable non-uniqueness of a schizophrenia-causing gene, the difficulty of finding such responsible genes with the error rate of current micro-array methods, the large number of spurious (non-genetically based) cases and the high costs of sequencing one person (making it almost impossible at this stage to sequence enough people to permit appropriate comparisons). While *structural studies* [20, 21] of the human brain have successfully identified a variety of neuroanatomical abnormalities in schizophrenia, they have not provided any meaningful explanation of their possible cause.

Functional imaging studies in humans (fMRI, PET, EEG, MEG, NIRS) seemed at first better suited, since they can approach the function of different brain areas, and their inter-connectivity [22]. In fact, since the advent of fMRI as a technology, schizophrenia has been one of the illnesses that has been perhaps most extensively imaged (a PubMed search with key words *fMRI* and *schizophrenia* yielded nearly 3,000 articles over the past 25 years). Yet in spite of early promise and enormous effort in addressing the goal of exploiting fMRI as a diagnostic instrument for schizophrenia, this approach has met with a surprisingly small degree of success in identifying clear and consistent biomarkers for the disease across studies, even for homogeneous clusters of patients with similar symptoms.

A possibility raised previously [23] is that traditional analytical techniques associated with neural imaging data are looking at the wrong features of the brain's response, mainly by localizing it to a temporally static reading and to a particular area of the brain. Recently, however, increasing attention has focused on the possibility of exploiting the *dynamic components* of physiological time-series over a network of brain locations, to explore neural functional connectivity, neural dynamic patterns and their evolution in time.

Phenomena such as neural burst activity, or channel dynamics (considered crucial in understanding pathophysiology, and well addressed by *electrode recordings* in behaving animals [24, 25] or in vitro preps [26]) provide an indispensable mechanistic perspective on network firing rates, and good insights into the network stability and kinetics. Basic experiments, however, have been normally too small-scale to be directly relatable to human behavior, not to mention that brain function and

pathways have not yet been mapped across species. Much research effort has been invested, in the context of neural functioning, into understanding how the microscopic laws of cell and receptor dynamics come together both structurally and functionally.

While cellular and computational neuroscientists often speak anecdotally about brain imaging, there exists the exciting and largely unexplored possibility of using dynamical systems modeling techniques, to bridge the basic and clinical ends into one picture, unify some of the existing conflicting approaches, complement their advantages and minimize their individual draw-backs.

A Diseased Complex System?

Embracing this systems perspective, the brain can be viewed as a complex ensemble, organized at multiple temporal and spatial scales, whose levels interact both within and between one another [27]. Our general working hypothesis is that there are seemingly ubiquitous optimization algorithms, used by the brain in a similar fashion at each of its structural and functional levels, thus suggesting a certain self-similarity (or *fractality*) of the brain's nature. This theory fits within the large body of historical mathematical work on fractals: Mandelbrot showed that many of nature's complexities could be described by certain ubiquitous mathematical laws [28], and in depth analyses of phase transitions showed how scale invariant phenomena such as fractals and power laws emerged at the critical point between phases [29].

Optimization is a common problem faced by biological systems, over the full course of their development and at all levels of organizational complexity. In order to maintain the creativity required for successful evolution, biological systems need to maintain a dynamic range that provides sensitivity to a variety of different inputs – and will thus self-organize as complex systems, functioning far from equilibrium, at *the boundary of chaos* [30], where things are much looser and more fluid. Taking this concept one step further, it has been hypothesized that an improper optimization code could lead to an overall dysregulated system – performing in a too stiff or too chaotic behavior range [31]. Over the past few decades, the preference for the boundary of chaos has been witnessed – derived by theory and confirmed by experiments – in various networks, such as the cardiac [32], endocrine [33] and central nervous [34, 35] systems, as well as at microscopic levels – in mitochondria [36] and in synaptic dynamics [37].

The brain, like most other live systems, is believed to function close to the boundary between order and chaos [35, 38], and is likely to use the same optimizing algorithms in more than one context. It is then plausible that schizophrenia may represent a temporary or permanent escape towards/into a more chaotic regime. *Nonlinear dynamic* methods used in conjunction with clinical data may be able to detect precisely this escape towards disorder, may thus lead to connectivity-based models, and possibly, in the future, to extremely useful clinical options for establishing a more precise psychiatric instrument (see section "Conclusions: The Future of This Approach").

Systems-based quantitative diagnoses and classification theories have already started to emerge in medical literature, and even in psychiatric literature [39]. In this light, schizophrenia can be placed in the same category with other diseases of dysregulation (e.g., conditions like type I diabetes, or Cushing's disease), for which taking an explicitly systems-based approach (rather than simply asking which areas are hyper or hypo-active in any given population) is key in understanding the behavior of the system, in developing reliable biomarkers and even in establishing prognosis and treatment.

Diabetes, for example, illustrates how a simple imbalance between excitatory and inhibitory components of a system can have far-reaching and diverse symptomatology that at first glance appear to be completely unrelated and random. Type I diabetes is a chronic disease that occurs when the pancreas produces too little insulin to regulate blood sugar levels appropriately. The exact cause of diabetes is not known, but, just as schizophrenia, it manifests itself with diverse and seemingly unrelated signs and symptoms (e.g., increased hunger and thirst, weight loss, fatigue, nausea, vomiting, blurred vision). Within 5–10 years after diagnosis, this dysregulation leads to complete destruction of the insulin-producing beta cells of the pancreas. The diagnosis for diabetes is not made by simply measuring glucose or insulin levels and asking whether they are higher or lower than those found in the healthy population. Instead, the diagnostic/illness severity tests (intravenous insulin-tolerance test and oral glucose-tolerance test) slightly "perturb the system" by giving a bolus of insulin or glucose and then observe the dynamic interplay between excitatory (glucose) and inhibitory (insulin) components in regaining homeostasis. These tests are brief and safe [40–42], reproducible, inexpensive, easy to perform, suitable for screening diabetes and other insulin resistant abnormalities in a general population.

Schizophrenia as a Degenerative Systemic Dysregulation

Clinically, a systems approach can be placed in light of novel theories of schizophrenia, which suggest that symptoms are only an epiphenomenon, and constitute an end-stage of a cyclic process of prefrontal-limbic systemic degeneration triggered by stress (hence the often delayed onset [43]). Such *stress/vulnerability* hypotheses [44–46] base schizophrenia on a hereditary predisposition ("vulnerability") that reduces the individual's psychological threshold towards stimuli [47], to the point where even minor environmental stressors will directly trigger overt psychotic experiences [48]. In this context, it is perhaps not surprising that, as a systemic disease governed by complex central interactions, schizophrenia has remained hard to understand.

Advances in understanding the neurobiology of the stress cascade [49, 50] have involved the neurotoxic effects of stress-induced hypercortisolemia on the hippocampus [51, 52], involving cell genesis [53] and synaptic remodeling [54, 55], and leading to dysregulated excitatory/inhibitory feedback. Prefrontal-limbic areas control regulation of emotional arousal, contain key structures and perform

key functions responsible for reward, motivation and addiction. These areas and these functions have been repeatedly associated with the physiology and respectively the cognitive deficits of schizophrenia [24, 43]. The dominant regulatory components of the prefrontal-limbic system have, by now, been relatively well mapped out in the animal literature [24], suggesting dynamic regulation between these regions as an ideal candidate for systems modeling (see Fig. 8.6 for a schematic representation of the known representative circuitry). In addition, a few imaging studies in schizophrenia patients versus healthy controls have measured coupling between excitatory (from amygdala) and inhibitory (from prefrontal cortex and hippocampus) control of the limbic system during fear extinction, and have found a weaker coupling in patients – which supports a limbic dysregulation hypothesis.

A dynamical systems analysis of prefrontal-limbic circuitry not only is a promising approach for establishing a theoretical framework and potential explanation for the many symptoms and complexities of schizophrenia, but may also hold a crucial practical value, allowing the study of schizophrenia's unknown physiology over time and under perturbation starting from clinical data. In fact, the underlying hypothesis to this approach – the evolution of the physiology and symptoms in schizophrenia may not be random, but be in fact the expression of dysregulation in a complex system – suggests two clinically crucial applications: (i) that the evolution of the disease can be studied, better understood, classified and predicted, and (ii) that its behavior can be altered by proper tuning of parameters through medication or therapy. It appears thus increasingly possible that the study of dynamics could be a very promising path towards understanding the underpinnings of the disease process, and that risk, diagnosis and severity of the illness could be assessed and standardized by capturing these dynamics through a collection of quantifiers computable from clinical data.

Psychiatric neuroscience has only recently started using mathematical concepts to understand mental disorders [56–58], by identifying the temporal architecture of these disorders as a complex, nonlinear system – rather than embracing standard statistics as the preferred quantitative method for analyzing between-group differences. While regression-based analyses are valuable in delineating differences between groups (patients versus controls) on particular variables, and in addressing the strength of relationships between variables, they are generally limited by their reliance upon linearity and are not designed to address systems biology. This may be why, in the context of researching schizophrenia, standard statistical methods have not been able to provide conclusive results, but only disparate observations. They emphasized either unusually high or unusually low levels of the coordinate being measured, be it cortisol [50, 53], dopamine [59] or glutamate [60], skin conductance [61] or heart rate variability [11]. If schizophrenia is indeed a systems-based dysregulation, reliance upon these methods would be a significant limitation. In contrast, modeling dysregulation requires analytical techniques for the nonlinear components of a self interacting system, quantifying excitatory and inhibitory elements of feedback loops and their effects over time and under perturbation.

Theoretical Remarks

In order to illustrate this idea, and support a dynamical systems approach, the author constructed a simplified theoretical model (a system of equations) of the feedback relationships among hippocampus, prefrontal cortex (PFC) and dopamine (DA) [62]. Specifically, this feedback was represented schematically as a balance between the two components of a feed-back loop: (i) the top-down control provided by the cortical systems over subcortical areas involved in emotion and (ii) the control of neuromodulatory systems that in turn affect the cortex. For example, one possible view involves the ability of the hippocampus and prefrontal cortex to contextualize and inhibit activation of the amygdala, which in turn drives the dopaminergic system [63]. Outputs of the dopamine system modulate processing in the hippocampus and PFC, thus closing the feed-back cycle. Although this amygdalar modulation is a plausible and documented set-up [63], anatomical details are not generally critical for our model, and other neural circuits or mechanisms (such as nucleus accumbens imbalances) may exhibit similar dynamics relevant to the disease (see Fig. 8.1). Finally, even though there could also be inhibitory effects, as captured in the gain hypothesis of dopamine function [64, 65], dopaminergic influence on cortical control is net excitatory.

The model delivers a concise and formal account of the most salient features of schizophrenia: a latent predisposition (e.g., caused by a combination of genetic and environmental factors during early development) can remain dormant until a triggering event (e.g., major life stress) "activates a *bifurcation*" [66] (i.e., a sudden qualitative change) in the dynamics of the system, moving it into a regime of

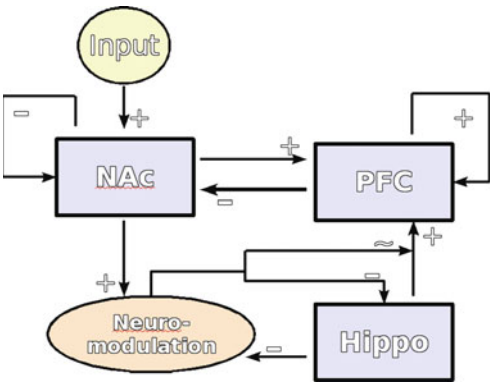


Fig. 8.1 The subset of prefrontal-limbic interactions and modulations captured by our simplified model. Interactions assumed to be overall excitatory are marked with (+), and overall inhibitory, with (–). The building blocks are the modules known to participate in mechanisms of fear conditioning and extinction. The predominant view is that the amygdala is excitatory and the hippocampus and prefrontal cortex are inhibitory (see [62], or Fig. 8.6). More precisely, the activity of the prefrontal cortex integrates external and internal information (including inputs from amygdala, hippocampus and within its own layers) to modulate amygdalar fear reaction to a stressor

increasing instability. Simulated medical treatments can help restore functional stability to the overall system's behavior. However, this form of stability is less robust than the one in effect prior to this regime or than the one intrinsic to the "normal" model (without the latent susceptibility). Hence, the system is more prone to relapses in this latter state.

When the model operates in the normal behavior regime, the strength of the feedback inhibition to the amygdala is sufficient to control arousal levels. As shown in Fig. 8.2, the strong inhibitory feedback always insures the existence of either a stable equilibrium or a stable oscillation, so that the time evolutions of all neighbouring states evolve asymptotically towards the respective stable state.

Transition from "mentally normal" to the "high risk" locus is represented in our model by a Hopf bifurcation [67]. The susceptibility for schizophrenia is associated with a weakening of the hippocampus inhibitory feedback control. This is consistent with considerable data suggesting a critical role for early hippocampal impairment in schizophrenia [68–71]. However, for most ordinary dynamic ranges of activation, the system does have a stable state, just as a normal system.

When a high risk system is subjected to a significant stressor or to some other triggering event that takes it out of the ordinary activation range, it crosses over a threshold and enters an unstable regime characterized by net positive feedback dynamics instead of net negative (Fig. 8.3a). This corresponds to first outbreak symptoms, with neuromodulatory systems and overall network activity functioning outside of the normal range and without inherent inhibitory control to return to a stable state.

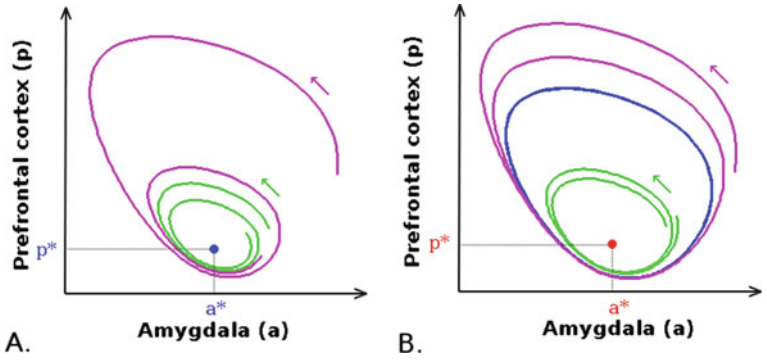


Fig. 8.2 Temporal trajectories of the two-dimensional system formed by the excitatory limbic component a (e.g., amygdala) and the inhibitory feedback p (e.g., prefrontal cortex), portrayed in the (a, p) phase plane (a is represented along the abscissa, and p along the ordinate axis). Each panel illustrates a system functioning in the "normal" regime of brain interactions, characterized as outward behavior by asymptotic convergence to either a stable equilibrium (a*, p*) (panel **A**, *blue dot*) or to a stable oscillation around the equilibrium (panel **B**, *blue cycle*). Each *panel* shows the long-term trajectories for two different initial states in the form of *two curves* parametrized chronologically by time, colored in *pink* and *green*, respectively. The corresponding *arrows point* in chronological direction along the *curves* (in this case, counter-clockwise) (see [62] for the equations and for a more detailed analysis of the dynamic behavior)

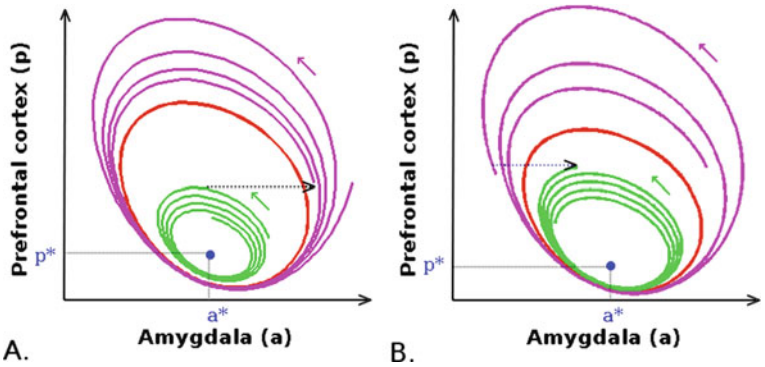


Fig. 8.3 **a** A system functioning in a dysregulated regime of brain interactions may successfully converge towards a stable state until a stress boost elevates arousal (i.e., amygdalar activation) beyond a threshold-cycle into an unstable range, preventing the system from stabilizing. The escaped trajectories will develop in time increasingly larger oscillations, eventuating in a symptomatic range, with wild emotional swings. **b** A dysregulated system functioning in the unstable range above the threshold-cycle can be forced in our model to return to the stable range by applying a small boost in arousal at a carefully chosen time

The more vulnerable the person is, the easier it is for the threshold to be crossed, hence more likely for an even small stressor to make the system's evolution unstable. Medications can be used to provide external inhibitory control over the system, but the intrinsic dynamics quite possibly remains in the unstable regime, as suggested by the high patient relapse rate when interrupting antipsychotic treatment.

An important counter-intuitive prediction from this system is that activation of the system at a particular point in the phase space can actually boost it out of the unstable state (Fig. 8.3b). This would correspond to properly-timed activation, not suppression as one would more intuitively assume, of the limbic excitatory component. A similar dynamic occurs in the Hodgkin-Huxley equations for the spiking behavior of an individual neuron, and this same kind of prediction was actually tested and confirmed in that system [72].

This simplified mathematical analysis captures many of the most central features of schizophrenia, in a way that can be informed by underlying neurobiological research and effects of pharmacological treatments. Clearly, much more detailed biological models would be necessary to encompass in any useful way the complexity and nonlinear behavior of the system, but this abstract model could serve as a preliminary means of capturing schematic system dynamics; this can then be further and more thoroughly analyzed and understood through more mechanistic or data-driven models (it is notable, however, that a too-elaborate model, even when faithful, may turn out being mathematically intractable). The theoretical predictions this phenomenological model generates can be explored initially by validating with actual data the underlying dynamics of the model (see "Theoretical Remarks"). Searching for a match of theoretical behavior with realistic physiology may require iterative

corrections of the model to agree with data, and fine tuning of parameters (see this section's last paragraph).

In an attempt to get closer to the biophysics of schizophrenia's neural dysregulation, and to investigate its mechanisms, we extended the construction in a subsequent paper [73] to a higher-dimensional model of the prefrontal-limbic-dopamine system. There, the dynamical trajectories and stability depend on an entire set of physiological parameters, representing synaptic strengths, vulnerability to stress-induced cortisol, dopamine regulation and autoimmunity. The model thus illustrates how seemingly similar signs of dysregulation could correspond to malfunction of different parameters, i.e., they could be manifestations of different types of physiological impairment. The conclusions agreed with the hypothesis of an *etiologically heterogeneous* schizophrenia, and may explain some of the diagnosing difficulties. The analysis confirmed and extended the prior results. While lack of proper amygdalar self-inhibition (e.g., high trait anxiety) causes a less efficient return to baseline after a stressor, a dysregulation in the external feedback inhibition of arousal (e.g., defective prefrontal-hippocampal inhibition resulting from exposure to high stress cortisol of an already existent hippocampal vulnerability) may cause time evolutions to never converge, thus leading to ranges of brain activations compatible with psychotic behavior. The model predicted that the feedback dysregulation could be compensated by decreasing dopamine responsiveness (i.e., simulating the pharmacology of dopamine-agonist based antipsychotics). To emphasize the importance of individualized pharmacological treatments, we considered (per our model) two psychiatric cases with clearly different causes: the first, of psychosis primary to autoimmunity, and the second, of stress-vulnerability schizophrenia. Simulated corticosteroids (immunosuppressants) alleviated symptoms when administered *correctly* in the autoimmune dysregulation (although over-medication produced psychosis secondary to hypercortisolemia); yet they exacerbated symptoms in a system with a cortisol vulnerability. Conversely, antipsychotics cannot be regarded as a substitute or alternative to immunosuppressants in the case of an autoimmune disorder. Hence misdiagnosing stress-vulnerability as an autoimmune condition would have serious consequences, even though the outward psychotic symptoms may be indistinguishable. We concluded that teasing apart the different mechanisms underlying psychosis is crucial for customizing the choice, dose and timing of medication to target the particular malfunction.

New biophysical theories (derived from basic experimental evidence) further hypothesize that the limbic dysregulation found in schizophrenia might in fact correspond to an exacerbated ventral subicular firing. Via one of the distinct indirect afferent pathways whose interactions control tonic and phasic activity in midbrain neurons (MDN) [25, 74], this may induce abnormal firing in the ventral tegmental area (VTA) dopamine neurons, which has been related to schizophrenia in a behaving rodent model [63, 75, 76]. Although translation of results from animal research into the dynamics of the human brain has been difficult, neural regulatory pathways and even dynamic rhythms have been found in animal neural populations which correspond precisely to those observed in humans [77–79]. Biophysical phenomena

such as excitability, or burst firing in neural populations, experimentally observed in intact animals and in vitro and correlated to animal behavior, have been extended to hypotheses about human mental health.

An ideal quantitative model, aiming to address the clinical and physiological diversity of schizophrenia, would embrace a *translational* approach, and incorporate this basic level of mechanistic detail, but in such a fashion so as to not lose the connections with the macroscopic scale, the behavior and outward symptoms. This is not easy, since most biophysical models of neural dynamics, exhaustively discussed in existing literature, are membrane-potential models of single cell activity (excitability, oscillations or bursting). This creates a problem of excessive dimensionality if attempting to construct a network model from single cells (e.g., membrane-potential models of bursting have been shown to involve minimally three equations [80, 81]). Modeling collective behavior of region of interest (ROI) networks using such building blocks would involve tens of thousands of equations and would be too expensive computationally. Network dimension reductions may be obtained by using *population* biophysical models, in which a building block is a mean field model, e.g., a neural population capable of showing a variety of representative behaviors (such as isolated firing, synchronized oscillations, bursting) depending on the external inputs and on the modulation received from other similar populations. Such at model could be viewed at two spacial scales (neural populations/brain regions) and two temporal scales (population excitability/mean amplitude fluctuations across whole brain regions) – one compatible with existing results from in vivo rodent electrode recordings, the other with region of interest based human imaging data. This would attain the desired biophysical detail, while staying in touch with the neuropsychiatric aspect and potential clinical applications.

In the end, a theoretical model is only useful if validated by experimental evidence (ideally both biophysical and clinical), in this case if the theoretically predicted trajectories of the system should match the behavior predicted based on physiological data (e.g., neural electrode recording, brain imaging, autonomic, cardiac or other appropriate physiological time series). The results of the data-driven analysis should be used to estimate the theoretical model. Practical measures of systemic complexity and long-term dynamics (such as entropy, largest Lyapunov exponent, attractor dimension) can be used to compare a theoretical model with real, data-driven dynamics, and thus fine tune the model (adjust any unknown free parameters within their biological ranges) until these behaviors coincide qualitatively, and live in the same quantitative range. Once this is obtained, a model can help generate testable predictions. Such a translational model may finally deliver a formal framework for studying specific prefrontal-limbic and dopamine inhibitory/excitatory feedback pathways which, although no longer only speculative, have a poorly understood functional influence on neural activity. Before addressing directly and practically any clinical questions (a more ambitious goal), a realistic short-term general attribute of a data-validated biophysical model is the potential to verify or suggest theoretical alternatives to existing hypotheses about dynamics in these networks.

Quantifying Schizophrenia from Physiological Time Series

Nonlinear Analysis Methods and Physiological Data

In light of these facts, it appears quite clear that a key part of a clinically useful quantitative approach to study the system dysregulation in schizophrenia is finding a way to represent and decode the temporal architecture of the prefrontal-limbic system based on dynamic clinical data. This data generally comes in the form of finite, discrete measurements (time series).

Dynamical system modeling has already been employed successfully in quantifying regulation of physiological systems such as complex cardiac-circulatory interactions [82], or motor performance [83]. Based on their success, it is a natural continuation to attempt to use them in a similar fashion to address the dynamics of mental illnesses, such as schizophrenia [23]. Over the past few decades, new mathematical fields have appeared (e.g., the study of chaotic dynamics is a relatively new area whose major development in the 1960s was triggered by observations of natural phenomena [84]). New quantitative methods, more suitable as a framework for the experimental and clinical observations, have subsequently developed (e.g., time-delay embedding techniques [85] were initiated in the early 1980s). However, mathematical approaches have had a paradoxically slow advance in psychiatry, for reasons which include the notorious unfamiliarity of mathematicians and clinicians with each others' technical language, the difficulty of recording neural measures reliably enough to use for a dynamical systems analysis, as well as the focus on observations at the microscopic level (receptor/synapse). Fortunately, science is now evolving towards emphasizing interdisciplinary initiatives, and new imaging technologies are addressing large-scale processes, while simultaneously increasing their spacial and temporal resolution and accuracy. These advances are promoting a fresh trend in psychiatric research, based on novel quantitative techniques and models.

It has now been accepted that some tools of nonlinear dynamics and chaos theory are well-suited for biological data analysis, and these tools have finally started to be applied to modeling work on schizophrenia [23, 86–88], including our own [89–91]. Most of the quantitative methods that are being applied in conjunction with physiological measures (such as brain activation, or heart rate variability time series) are most appropriate when the data shows strong and consistent nonlinear deterministic signatures. Physiological time series (obtained via recording techniques such as fMRI, EEG or ECG) are finite, discrete representations of continuous processes and reflect simultaneously nonlinear responses and effectively stochastic components; they may lack stationarity and involve a mixture of noise fluctuations produced by the system, its environment and recording techniques. Too much additive noise may break the scaling behavior and limit predictability. One has to carefully select the appropriate tools to correctly interpret the dynamics of a system based on time-series. Pure determinism and chaos, even when low-dimensional, are hard to detect, and should not be assumed a priori; nor should the quality (e.g., length) of the

data-set be assumed sufficient without theoretical back-up [92]. Hence theoretical nonlinear methods, while potentially powerful, need to be applied with caution to clinical data. Complexity tools have been applied to physiological time series with skeptically-regarded and non-replicable results, and such inaccuracies have slowed down progress in this direction of work and have shed skepticism over the entire approach [92].

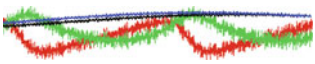
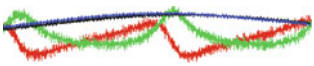
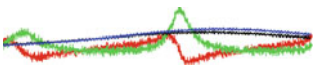
Due to this initial questionable start, dynamic methods for studying physiological systems have been thought inappropriate, and have been somewhat temporarily abandoned by a large part of the scientific community. However, over the past decade, a better founded machinery of nonlinear methods has been steadily developing. A few software packages of such methods (e.g., TISEAN 3.0.1 [93], TSTOOL [94]) offer appropriate analytical alternatives to support a nonlinearity assumption with statistical evidence [94, 96], to investigate stationarity [97–99] and apply appropriate noise reduction filters to the data stream [100, 101]. These preprocessing stages prepare the data-set for further, more elaborate analyses, informing on the methods which are best suited to address its particular aspects and problems.

Beyond this preprocessing stage and when investigating further the dynamics of a physiological system based on measured time series, an informative study will typically adopt both reconstructive (bottom-up) techniques and estimative (top-down) methods. This combination provides a thorough approach to the dynamics, and could facilitate – when this is the case – estimation and validation of a theoretical hypothesis, or model, regarding the nonlinear behavior. Furthermore, while techniques of state space reconstruction from time series offer good descriptions of individual and statistical patterns, for clinical purposes it is not mathematically desirable or necessary to reconstruct the entire state space. Dynamic invariants may be better measures of the complexity and chaos in the system as a whole [58], while maintaining the ability to characterize these by only a few numerical values – a key feature for diagnostic and classification based on physiological dynamics (see Table 8.1).

Over the past 6 years, the author has conducted a significant amount of joint work[1] dedicated to dynamical analyses of clinical data. Initial analyses performed at LSEC [11] had considered identifying the limbic system dysregulation in schizophrenia by looking indirectly at the complex dynamics of heart rate variability (HRV) as an autonomic measure, with conveniently clean associated time series, and commonly used as a psychiatric biomarker. However, one of the critical limitations of cardiac data in that capacity is its non-specificity. Indeed, lowered heart rate variability has been observed not only for schizophrenia, but also for other illnesses with clearly distinct clinical manifestations, such as anxiety [102], depression [102] and panic disorder [103].

[1] All recruitment, data collection, methods development and analyses are collaborative work with Lilianne Mujica-Parodi, Ph.D., director of the Laboratory for the Study of Emotion and Cognition (LSEC) at Stony Brook University, NY. See our published work for details [89, 90].

Table 8.1 Profiling three hypothetical subjects X, Y and Z. The data was computer generated based on an underlying system of equations, as signal+noise, to simulate two types of recordings: (i) a limbic regions fMRI scan, performed in conjunction with emotional stimulation, and (ii) a number of higher temporal resolution (NIRS or EEG) recordings of the same prefrontal region. Connectivity parameters are "computed" from the fMRI data (amygdala and prefrontal activation are plotted in red and green) then used to estimate the linear and nonlinear parameters τ and respectively σ. The longer, higher resolution time series (shown in blue and black), are used to estimate the sensitivity of the system (the degree of separation attained in time by two initially very close trajectories), by computing the largest Lyapunov exponent $\mathcal{L}$. Although the first two subjects have seemingly indistinguishable data, their nonlinearities σ tease apart their fundamentally different situations (a high state anxiety become symptomatic versus an early stage of schizophrenia). For the third patient, the severity of the illness is revealed by the Lyapunov exponent $\mathcal{L}_Z > 1$, which suggests that even minute perturbations in mental state may produce a dramatic change in the evolution of arousal and subsequent behaviour

Data	Invariants	Interpretation	Decision
	$\sigma x = -0.557 < 0$ $\tau x = -0.1 < 0$ $\mathcal{L} x = 0.5 < 1$	Schizophrenia risk: none Trait anxiety: low State anxiety: moderate	Short vacation and rest
	$\sigma y = 0.588 > 0$ $\tau y = -0.1 < 0$ $\mathcal{L} x = 0.2 < 1$	Schizophrenia risk: moderate Vulnerability: low Stage: presymptomatic	Intense preventive therapy
	$\sigma z = 0.680 > 0$ $\tau z = -0.01 < 0$ $\mathcal{L} x = 1.35 > 1$	Schizophrenia risk: high Vulnerability: high Stage: late prodromal	Immediate medication plan

We saw potential advantages in measuring neural dysregulation more directly, as opposed to its presumed effects downstream in the autonomic nervous system, especially since brain imaging techniques provide added spacial degrees of freedom (instead of just one recording of a cardiac channel), and therefore a greater likelihood of identifying disorder-discriminating characteristics. Along these lines, most of our joint work has been focused on imaging the limbic system: beginning with extensive validation of technical parameters designed to minimize signal loss in limbic areas and maximize computational power, and continuing with a systematic search for the nonlinear methods best applicable to such data. Some information on the experimental design and stimuli, acquisition and preprocessing parameters etc, is included in Fig. 8.7, and further details can be found in our published and current work [89–91, 104]. The following section reviews some of the results we obtained applying nonlinear dynamic methods to fMRI time series. The author's joint work with LSEC is currently extending to encompass analyses of other dynamic neural measures, such as EEG and NIRS.

Our Existing Nonlinear Analysis Results

We investigated neural regulation of emotional arousal using fMRI. By presenting human subjects during scanning with affect-valent facial stimuli (blocks of angry,

fearful, happy and neutral faces, interposed with rest blocks), we activated neural regions associated with the emotional arousal response. Identification of activated regions led to extraction of time series for a subsystem of six prefrontal-limbic regions of interest (ROI): bilateral amygdala and hippocampus (established a priori, based on existing knowledge of their function and connectivity) and two prefrontal regions (Brodmann Areas 9 and 45, found thorough a random-effects analysis). The posthoc identification of prefrontal regions was not surprising in light of the known prefrontal contributions to emotional circuits (already discussed in previous sections); however, the particular prefrontal areas found by our GLM analysis, BA9 and 45, are newer to schizophrenia literature than Brodmann Areas 10 [105] or 46 [106] in humans, or than medial prelimbic and infralimbic areas in animal models [107, 108].

We hypothesized that the interactions between these regions and possibly with other regions determine their activation trajectories and are potential key components underlying the differences between healthy individuals and those with schizophrenia. The results of our analyses supported this hypothesis. To begin with a relatively standard approach, we analyzed our data over all contrasts (Anger–Neutral, Anger–Rest, Fear–Neutral etc). While standard statistics of peak and mean amplitudes failed to capture any significant differences between the patients and the healthy controls, we found (using *cross-correlation coefficients* to capture the mutual coupling dynamics between ROI time series) significant differences in signal dynamics, specifically between the right amygdala and Brodmann Area 9 (BA9), when viewing angry facial expressions ($p = 0.002$). Further analyses over the entire time-series found in patients significantly lower BA9 activation during the beginning of the response ($0.000 \leq p \leq 0.021$) and significantly higher BA9 activation towards the end of the response ($0.008 \leq p \leq 0.025$) [89]. This suggested that patients show longer time-lags between the excitatory response and the inhibitory activation that modulates it.

While these first results supported our excitatory/inhibitory feedback dysregulation hypothesis of the illness, cross-correlations constrained us a priori to relationships between node-pairs. Understanding the overall network dynamics required a higher-dimensional approach to the data. To address this, we developed in a subsequent paper [90] a *Principal Component* approach to the same six-dimensional system of prefrontal-limbic ROIs found by our initial random-effects analysis. We showed that all subjects' trajectories were almost embedded in two-dimensional subspaces, suggesting that the meaningful dynamics of the system may be contained in a plane (see Fig. 8.4a, b). The positions of these subspaces differentiated between the control and patient populations (patients showed a predominantly excitatory response, expressed by higher amygdalar contributions to the first principal component). This result agreed with our theoretical paradigm (see section "Quantifying Schizophrenia from Physiological Time Series") in that it suggested distinct attractor positions and geometry for the patients and controls. The intrinsic differences in the trajectories that distinguished between the two populations were best represented not by the evolution of any particular region, but rather by combinations of regions. Hence a systemic approach to estimating the system (e.g., computation of degree of regularity, or of a global dynamic invariant, such

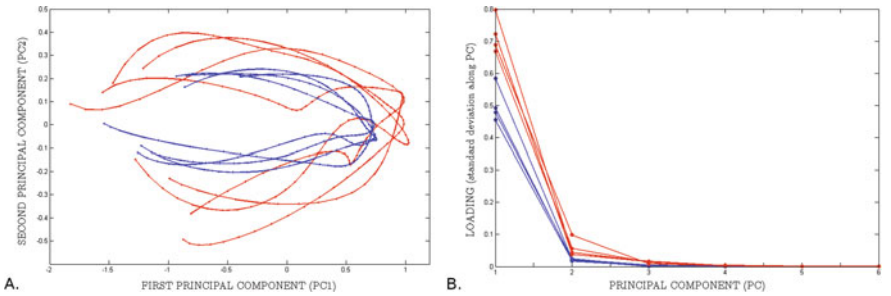


Fig. 8.4 Principal components of a six-dimensional prefrontal-limbic network (comprised of amygdala, hippocampus and prefrontal regions) [90]. In both *panels*, control subjects are shown in *blue*, and patients in *red*. **a** Group average trajectories, illustrated here separately for each of the four Arousal–Rest contrasts provided by the scan. The trajectories are each projected in the plane defined by their corresponding first two principal components (PC1 and PC2), which contains the significant dynamics. For simplicity of the illustration, we collapsed all PC1-PC2 planes to one, although their positions differed significantly between subject groups (not shown). Even ignoring this effect, as well as the temporal sequence, it is notable that the patients' *curves* are consistently more widespread than the ones for controls. **b** Group average loadings (standard deviations along the directions of the six principal components)

as dimension of an asymptotic attractor) may be preferable to direct observation of any one variable in time. Part of our following work concentrated on finding the best, simplest possible representation of the system's key dynamics (e.g., overall degree of complexity/regularity of temporal trajectories, or position and geometry of potential attractors).

In order to approach these tasks in a more thorough and conservative way, we developed, independently of our first results and of other existing hypotheses, an *exploratory analysis* that made no a priori assumptions of the neural regions involved in the circuits relevant to schizophrenia. We believed such an approach to be particularly advisable when computing regularity invariants, which may not behave well under averaging over large brain areas, with somewhat arbitrary anatomical boundary. Moreover, while these areas may have similar function, they may still assemble very heterogeneous voxel-wise rhythms and patterns, which would be lost through a poorly chosen mean field approach. We therefore continued by performing an exploratory voxel-wise analyses of time series regularity, including whole brain scans and carefully accounting for the large number of voxels ($53 \times 63 \times 46$) by using statistical methods which compensated for the large number of comparisons. Since each regularity measure may be best at encoding particular dynamic properties, we calculated two different invariants to estimate the variability of each voxel-wise time series (one in the time, and the other in the frequency domain), using computational methods tailored specifically to address the issues characteristic to biological data. The time courses we used for this analysis were entire, undivided time-series, rather than specific conditions or contrasts, since regularity analyses optimally require a large number of data points. We then investigated whether any 3-dimensional patterns appeared to form consistently across the brain.

First, we attempted to quantify voxel-wise time series variability in the time (i.e., amplitude) domain, using *approximate entropy* (ApEn) – a regularity invariant frequently used in the context of physiological data. This measure, conceptually derived from the theoretical Kolmogorov entropy, was introduced in data analysis in 1991 [109] as a model-independent measure of complexity which can successfully handle the noisy and short data-streams from biological measurements [109, 110]. It has been used successfully in quantifying heart rate [111–114] and respiration [115] variability of endocrine activity in dysregulatory conditions (Cushing disease [116], diabetes [117]). Used for EEG time-series, ApEn had effectively graded the depth of anesthesia [118, 119] and predicted epileptic seisures [120]. It has been applied to cognition and motor control in patients with Parkinson's disease or mental retardation [121, 122]. In conjunction with behavioral data (e.g., self-reported mood) it was used to analyze bipolar [123, 124], depressive and schizophrenic courses [56, 125, 126]. In our case, however, the voxel-wise results did not reliably differentiate between the healthy and patient populations as well as one might have expected in light of the known differences. The results rather appeared to be merely driven by noise, and ApEn was not robust under averaging of time series over voxel clusters, even when these were only slightly unsynchronized and exhibited comparable regularity (i.e., entropy values). One potential cause for this may be insufficiently high quality (length and temporal resolution) of the data, allowing inaccuracies in the computation that would strongly reflect in the between group statistics. Our current data collection is centered around improving these characteristics to increase computational power (section "Work in Progress").

In contrast, the frequency domain measure that we chose to use (*power spectral scale invariance*) proved to be effective and robust, and revealed very interesting results [91]. We used the Fourier spectrum to capture the irregularity, or "deterministic noise" of network oscillations by the power spectral density (PSD) of the signal. We found that the PSDs were to a large degree "scale-invariant" (i.e., had no preferred temporal scale), and thus followed the power law: $S(f) \sim f^{\beta}$. Power spectral scale invariance (PSSI) has been interpreted within the theory of self-organized criticality (SOC) [127–129], in which even a minor perturbation of the system is able to produce a large reaction. The hypothesis of SOC in neural systems, supported by other existing experimental research, is in line with our view of the brain as a fractal-like complex system (as presented in section "A Diseased Complex System?"), reiterating similar structure at different temporal and special scales.

For each individual voxel, we determined the scaling parameter β (which estimates whether the data are a pure random walk or have underlying trends), by plotting the power spectrum of linearly detrended time series on a log-log scale and estimating the slope of the linear fit to the data in the 0.06–0.2 Hz range (upper limit determined by sampling rate, lower limit chosen empirically). The voxel clusters with β-values significantly different between the patient and control groups were localized in Brodmann Area 10 (BA10), a prefrontal inhibitory component of the control circuit regulating emotional arousal [130, 131] (see Fig. 8.5a). Within these specific clusters, as shown in Fig. 8.5b, the control subjects had signals β in [−2,−1] (i.e., what in SOC literature is called pink to brown noise, which represents

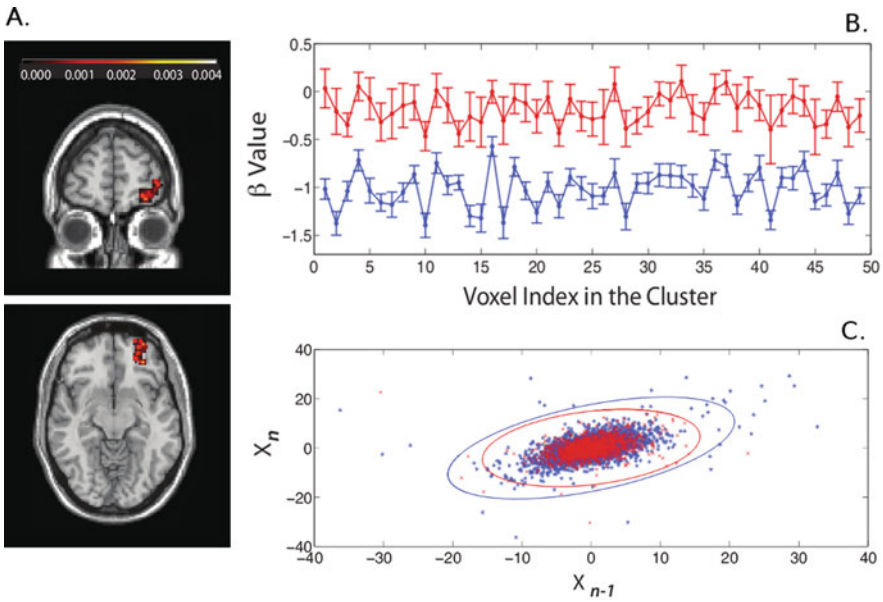


Fig. 8.5 Characterization of the larger prefrontal cluster found by our PSSI analysis to significantly differentiate between subject groups. **a** The 3-dimensional position of the cluster. Talairach coordinates of its most significant voxel: x = 27, y = 46, z = –12. **b** Distribution of voxel-computed β over the cluster, for patients (in *red*) and controls (in *blue*), shown with the group error bars. For patients, cluster mean(β) = –0.18 (S.E. = 0.2). For healthy controls, cluster mean(β) = –1.02 (S.E. = 0.12). **c** The lag one Poincaré plots had different geometry (e.g., different distributions of radii and different aspect ratios) between patients and controls. The plots are shown in *blue* for control subjects and in *red* for schizophrenia patients; the illustration includes, for better visualization of the group differences, the *ellipses* with radii equal to the standard deviations along the principal components of the Poincaré group distributions [91]

an ideal range of functioning, close to the critical "edge of chaos," more orderly and short-term predictable). In contrast, the patient group had β values close to 0 (i.e., close to the white noise range, denoting increased complexity and lower predictability). Power laws corresponding to pink to brown noise had been observed before at multiple levels in the normal function of the brain, from the context of behavior [132] to activation of brain regions (recoded through EEG [133, 134], MEG [134, 135] or MRI [104]), to neural population activity [136, 137], to the dynamics of the nerve cell membrane [138, 139]. Our results supported therefore the idea that the systemic malfunction underlying schizophrenic pathology produces an inclination towards increased chaos (i.e., higher complexity and harder predictability) in schizophrenia.

Since our time series were too short for an in-depth reconstruction analysis, we used lag one *Poincaré plots* to investigate whether the frequency-domain features of cluster-wise dynamics obtained with PSSI reflected into the time-domain. The

lag one Poincaré map illustrates variability within the time series in a different way than ApEn, by plotting activation at each time X_n as a function of its predecessor X_{n-1}, in the context of nonlinear dynamics, it is a two dimensional reconstruction of the time series phase space. The use of Poincaré maps has been successful in quantifying variability of heart rate R-R time series [140–142] and of other clinical measures [143]. In our case, we found significant differences between groups in the distribution of the Poincaré scatter points (see Fig. 8.5c), in particular in their aspect ratio and average diameter [91] (which are thought to be indicators of the balance between long and short-term variability). An extensive analysis considering all lags (e.g., time-delay embedding methods [85], which compute and use an optimal lag) are expected to better contextualize this result and would provide a more complete picture of the dynamics.

Work in Progress

Our current work is following along the lines of an extensive search for appropriate imaging techniques which, in conjunction with such large scale computational algorithms, could best be used to (1) estimate the strengths of the functional neural connections between prefrontal-limbic regions (effective connectivity), and to (2) reconstruct asymptotic prefrontal-limbic dynamics from the time-series (time-delay embedding methods).

One of the most commonly used programs intended specifically to assist with estimating *effective connectivity* within the brain is Dynamic Causal Modeling (DCM) [144]. Developed as a method that uses a Bayesian framework, DCM is capable of integrating fMRI responses to experimentally designed deterministic inputs, and then inferring nonlinear coupling among brain regions. Effective connectivity parameters obtained from observed data using DCM have been tested to behave well under different levels of noise. Since its first bilinear set-up, a number of developments have improved and extended the DCMs [145], including refined hemodynamic [146], nonlinear neuronal [147] and stochastic [148] models. We are working on finding the appropriate imaging design and regions of interest, and the appropriate DCM algorithm, looking for evidence of nonlinear coupling within the prefrontal-limbic system. We have chosen this framework instead of other statistical models of effective connectivity (such as Bayesian networks, Structural Equation Modeling (SEM) [149], or Granger causality [150]), because DCM makes fewer assumptions on the data (unlike Granger causality, it does not assumes serially uncorrelated random fluctuations), allows causal cycles (unlike Bayesian networks) and has been shown to be more effective than SEM in fMRI analyses similar to ours [151]. We are expecting to obtain, for each subject, connectivity parameters that may further be used, perhaps in conjunction with a theoretical model, to understand differences in coupling that may underlie differences in systemic dynamics.

Time delay embedding theorems, initiated by Takens [85] in the early 1980s, and later continued by Sauer [152] and others, showed that it is mathematically possible

to use discrete information to predict long term nonlinear behavior (e.g., determine dimension of a chaotic attractor), with no other a priori knowledge of the system. Time delay embedding has been used by itself and in conjunction with other nonlinear methods on fMRI time series (e.g., such methods were used to support the claim that BOLD fluctuations in resting states may be an inherent model of basal neural activation of human brain [153]). Our preliminary results suggested a low dimensional attractor in the PLD system, with variations in position and geometry marking differences in the system's homeostatic regulation; however, principal components and lag one Poincaré plots were not sufficient to reach a definitive conclusion. Time-delay embedding methods, in conjunction with an improved data-set, may deliver a more exhaustive reconstruction of the dynamics. This reconstruction requires a few educated choices: although solved in theory, choosing the correct embedding parameters (embedding dimension [154] and lag [155]) is not immediate [156], especially for data-driven models (a reasonable choice of parameters gains importance through the fact that a finite amount of noisy data prevents access to infinitesimal length scales [157, 158]). Mutual information and false nearest neighbor methods are generally used to compute the optimal embedding dimension and lag for such time series. More recent studies suggest that an "optimal" embedding should only be defined relative to a specific purpose, and that, even so, it is safer to draw thorough conclusions by integrating and interpreting results for more than one choice of these parameters [92, 156].

The time-series length and temporal resolution are in this context factors crucial to the computational accuracy (in the sense that longer and higher resolution time series lead to more relevant results and safer conclusions). For example, estimates for numbers of data-points necessary to safely perform time delay reconstruction were first given by Sprott ($10^{\{2+0.4D\}}$ data-points to accurately reconstruct an attractor of dimension D [159]), and later optimized by others [160, 161]. In this light, we are currently considering using additional imaging measures, such as EEG, or Near Infrared Spectroscopy (NIRS), which (i) may be more convenient and less costly to obtain with adequate lengths (10–20,000 data points per run) and (ii) have better temporal (although not necessarily spacial) resolution than even state of the art fMRI data. Used in conjunction with a stimulus pattern that does not emphasize particular frequencies or introduces periodicity, they may deliver more informative results than the ones presented here.

Conclusions: The Future of This Approach

Clearly, the first goals of a quantitative approach to schizophrenia are identifying the system of neural and other physiological modules involved in the mechanisms of the illness, and understanding the physiological dynamics of this system and its relationship with the observed outward behavior. A consequential attribute of the approach is the potential to verify existing experimental hypotheses (both basic and clinical) which are still only speculative at this point, and suggest theoretical alternatives to these hypotheses.

In the long term, a neurobiology-driven, temporal architectural model of the brain networks involved in schizophrenia could lead to clinically usable quantitative assessments of the illness. *Brain profiling* [39, 73], as a strategy of replacing subjective clinical assessments of patient-reported symptoms with objective biomarkers, could complement, or perhaps in time even replace, the current diagnostic approach. The dynamical profile of a particular patient or high risk individual could be created – from a set of clinically measurable parameters, describing the underlying system (including, for example, strengths of neural interactions, or sanguine cortisol levels in response to a controlled stress). The individual profile could then be compared against a multidimensional, continuous profile chart, constructed based on common statistics. This would place the person in the correct locus of risk/vulnerability, would facilitate predictions and would help assign appropriate individualized treatment. A naive, perhaps very premature, but hopefully conceptually illustrative example of such an application is the classification rendered by our first phenomenological model (shown in Table 8.1). In this case the invariants used were τ (describing the local linear stability of the equilibrium state) and σ (the degree of nonlinearity of the system around this equilibrium).

Addressing schizophrenia as an illness of systemic dysregulation, by analogy with the systemic approaches taken to diabetes and Cushing's disease, may eventually prove equally helpful, and efficiently applicable clinically. Considering the possibility of brain profiling-based diagnoses as an over-reaching research goal could thus initiate important pioneering work towards a more biologically-based psychiatry. This extremely novel view may provide a coherent framework for integrating the variety of seemingly unrelated abnormalities commonly found in schizophrenia, and may offer new ways of using the rapidly developing neuroimaging technology for medical research applications. Evaluation of an individual's symptoms and prognosis based on a reliable neurobiological quantification would clearly increase the potential for early and optimal treatment, and could avoid much suffering.

Appendix 1: Simplified Schema of the Brain Circuitry Implicated in Schizophrenia Dysregulation

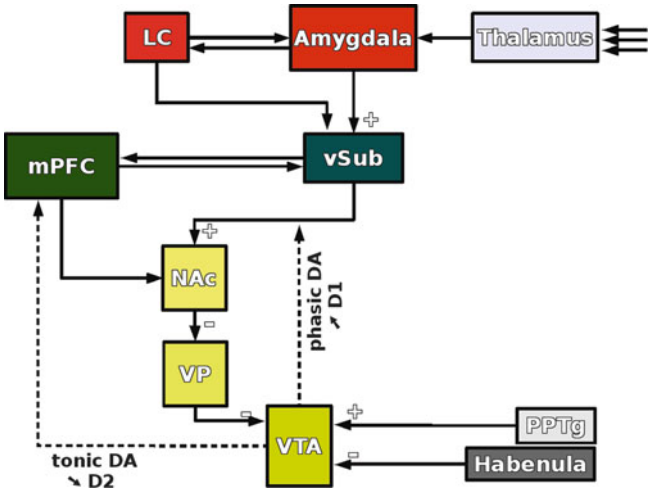


Fig. 8.6 mPFC = medial prefrontal cortex; vSub = ventral subiculum; VP = ventral pallidum; VTA = ventral tegmentum; NAc = nucleus accumbens; LC = locus coeruleus; PPTg = pedunculopontine tegmentum. Some of the known pathways within the PLD system. The amygdala (main excitatory component of the arousal response [162]) receives inputs via thalamic pathways, and feedback inhibition from the PFC [163, 162]; it provides excitatory outputs to the mPFC [163]. The basal lateral amygdala receives a stress-responsive DA projection from the VTA [74], and controls the DA response in the NAc [164]. Bidirectional projections between the mPFC to the VTA [165] comprise the mesocortical circuit [166, 167]. The hippocampus directly inhibits activation of the amygdala, reinforces activity in the PFC (supporting the process of memory formation and centralization) and contributes to the modulation of the DA system [25, 168, 75]. The Figure presents these connections, and those associated with the habenula [169], LC [170] and PPTg [25]. Not shown: limbic outputs from the amygdala, through the hypothalamo-pituitary axis, control the endocrine and autonomic nervous systems (e.g., stress cortisol production, heart rate)

Appendix 2: Neural Complexity Layers that May Exhibit Suboptimal Dynamics in Schizophrenia

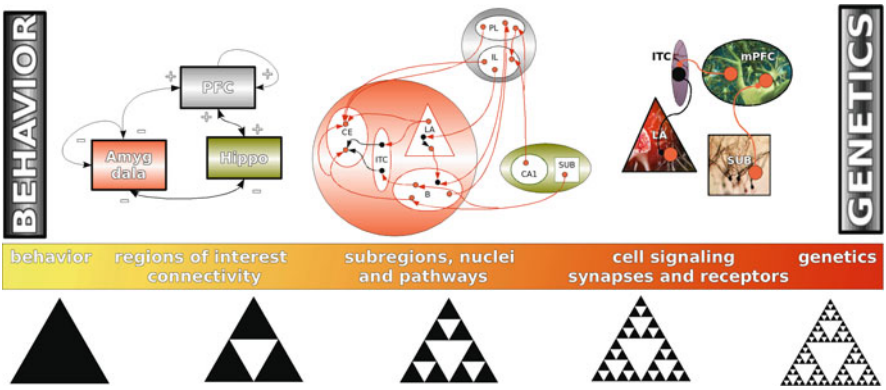


Fig. 8.7 We view the brain as a self-organized, fractal-like complex system, which exhibits a large degree of self-similarity between the organization and behavior of its complexity layers (*bottom*). This similarity may be based on recycling, within different layers, of typical neural algorithms that maintain the function at an optimal (critical) stage, close to the boundary of chaos. Disturbance of these optimization codes may lead to dysregulation of the system and to symptoms of mental illness. We hypothesize that schizophrenia is such a systemic condition, affecting neural mechanisms at a variety of these anatomical/physiological complexity levels

Appendix 3: Subject Recruitment and Data Collection

We investigated neural regulation of emotional arousal using fMRI. By presenting human subjects with affect-valent facial stimuli during scanning, we activated neural regions associated with the emotional arousal response. The study was approved by the Stony Brook University Institutional Review Board.

Participants. We tested N = 76 adult human subjects. Of these, N = 11 were medicated patients diagnosed with DSM-IV schizophrenia recruited from the Stony Brook University Hospital's Psychiatric Adult Inpatient, Outpatient, and Day Units. As controls, we tested N = 65 healthy adult subjects, recruited from the general community (a subgroup of N = 11 were age and gender matched with the patients). Exclusion criteria included fMRI safety criteria, substance abuse and, for patients only, medication with known affects on arousal (e.g., benzodiazepines). All subjects provided informed consent. Subjects' screening prior to participation included a medical history and physical exam, conducted by study physicians, and a diagnosis confirmation interview using the SCID-I [47]. Patients had an additional capacity evaluation signed by their treating psychiatrists, and a symptom severity assessment [171].

Study design, task and stimuli. While in the MRI scanner, subjects passively viewed block stimuli consisting of black and white pictures of faces depicting angry, fearful, happy and neutral emotions [172], which are known to reliably activate the limbic system [173, 174]. The stimuli blocks (each consisting of 9 different faces of the same emotion type, displayed for 2.2 s each for total block duration of 20 s) alternated with 20 s fixation cross blocks. Each run lasted for 5 min and 40 s and included twice each emotion type.

Image acquisition and preprocessing. Subjects were scanned on a 1.5T Philips Intera MRI scanner at the Stony Brook Hospital using a SENSE head coil. These were acquired using two blocks (one for each fMRI run) of 136 T2*-weighted echo-planar single-shot images covering the frontal and limbic areas of the brain, with TR = 2500 ms, SENSE factor = 2, TE = 45 ms, Flip angle = 90° Matrix = 64×64, 3.9×3.9×4 mm^3 voxels, and 30 contiguous oblique coronal slices. In addition to the functional scan, an anatomical scan to match the slice orientation of the functional scan was obtained and used to generate a customized EPI template for normalization of our EPI scans. The fMRI data pre-processing was performed using the Statistical Parametric Mapping software, running under Matlab 6.5. The raw functional BOLD images were realigned, corrected for movement, then spatially normalized using a customized template created using the data for the first 12 subjects. After skull-stripping, images were registered and normalized to each other, then the average image was smoothed with a Gaussian kernel of 8 mm full-width half maximum.

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Chapter 9
Schizophrenia Has a High Heritability, but Where Are the Genes?

Patrick P. McDonald and Shiva M. Singh

Abstract Schizophrenia is a debilitating psychiatric disorder affecting 1% of the world's population. The diagnostic criteria (DSM IV) are broad and characterized by positive and negative symptoms which vary from patient to patient and over the course of the illness. The disease is known to have a genetic component, a reported heritability estimate of 80% and a concordance rate of ~50% in monozygotic twins. Most research on the disease has concentrated on the search for genes using traditional approaches. This includes cytogenetics, linkage, association, gene expression and whole genome scans. Although this extensive research has identified a number of genomic regions of interest and some candidate genes, it has not produced any confirmed causations. Yet, identification of the cause(s) of this disease will be required in order to develop effective preventive management and corrective strategies. Considering the decades of research in the field, one obvious question arises: where are the genes that cause schizophrenia? This forms the focus of the chapter. During the course of this discussion, we will argue that there are two main reasons as to why traditional genetic approaches have met with little success in schizophrenia. First is the diagnosis of the clinical phenotype. There are no biological markers of this disease and the diagnosis is based on interviews and self-reporting of the patient. Also, the DSM-IV diagnostic criteria are broad enough that two individuals with schizophrenia may have very few symptoms in common. This leads to a highly heterogeneous sample, which is not optimal in traditional genetic research, or research on complex disorders. The second issue deals with the genetic hypothesis being tested. Here the assumption is that a number of genetic variants of small to moderate effect interact with environmental factors leading to a predisposition for schizophrenia. What is not fully appreciated is the actual number of potential gene variants involved, the heterogeneous mechanism and timing of their occurrence and recurrence and any understanding of their interaction with the environment. These issues recognize that there is a long pathophysiological chain that extends from

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genes, through proteins, neurons, cognition, behaviour, symptoms, and finally to the DSM-IV construct of schizophrenia.

Keywords Schizophrenia · Genetics · GWAS

Abbreviations

CDCV	Common disease common variant
CDRV	Common disease rare variant
CNV	Copy-number variation
DSM-IV	Diagnostic and statistics manual of mental disorders
GWAS	Genome-wide association study
ISC	International schizophrenia consortium
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
RR	Relative risk
SNP	Single nucleotide polymorphism
VCFS	Velo-cardio facial syndrome

Introduction

Schizophrenia is a severe and debilitating neuropsychiatric disorder with a worldwide lifetime risk of 0.7% [1]. The symptoms are broadly characterized as positive (delusions, hallucinations, disorganized speech and behaviour) or negative (flattening of affect, alogia, avolition) and are often accompanied by significant social and occupational dysfunction [2]. Treatment may include any number of antipsychotic medications (and combinations thereof), but there is no cure with more than half of patients having lasting impairments from their psychotic episodes or symptoms which continue to worsen [3]. As such, prognosis for recovery and course of illness are very difficult to predict. Sadly, it often ends in suicide, the rate of which is 15–25 times higher in patients than in the general population [4]. Schizophrenia is one of the top 10 causes of long-term disability [5] and represents a major societal and economic burden. Given its high frequency in the population and its potential for long lasting impairment, finding effective drugs and treatments for the disease is a high priority. This has been hindered in large part due to a lack of understanding of the underlying etiology of schizophrenia. Thus, determining the underlying biological nature of the disease is of paramount importance and must come before effective treatments are developed.

Family, twin and adoption studies have demonstrated that there is a genetic susceptibility to schizophrenia. Siblings and di-zygotic twins show proband concordance rates as high as 28% while monozygotic twins range from 41 to 65% concordance [6]. The heritability is estimated (the percentage of phenotypic variation attributable to genetic variation within a population) at 81% [7]. While concordance rates among relatives and a high heritability estimate convincingly

demonstrate an underlying genetic component, they also provide evidence that non-genetic (environmental) factors play a significant role as well. Despite this clear evidence of predisposing genetic factors, researchers have (thus far) been largely unsuccessful in identifying them. A PubMed search using the keywords "schizophrenia" and "genetics" identifies 11,622 articles, suggesting that the lack of findings is not due to a lack of research. Within the last year, the largest Genome Wide Association Studies (GWAS) and meta-analyses ever conducted in schizophrenia offered surprisingly little insight into this genetic mystery [8–10]. The reasons for this lack of success can be generalized to two areas: the materials and the method.

The materials are the various biological samples collected from schizophrenia patients and matched controls or family members. The problem lies not in the collection of samples, but in the diagnosis of the individuals those samples are collected from. Since there is no biological marker which is definitive enough to use as a test, diagnosis is based on the self report of the patient during a structured clinical interview. The symptoms (from positive to negative) are wide-ranging and of varying severities in different patients. Thus two individuals diagnosed with schizophrenia may have few (if any) symptoms in common and has led some to postulate that schizophrenia is not single entity, but rather a collection of discrete syndromes lumped together under the schizophrenia umbrella [11]. Whether this is the case or not, it does illustrate the main problem when using these individuals in genetic research – heterogeneity.

The methods which have proven effective in identifying genes for mendelian disorders (single gene) are not as effective for complex disorders (multiple genes) like schizophrenia. Traditionally, families with a high incidence of a disease are analyzed for co-segregation of the disease phenotype with genetic markers spaced throughout the genome. This is called linkage analysis and its use in schizophrenia has produced positive associations to 21 out of 23 chromosomes [12]. Some genes identified by this method including dysbindin (*DTNBP1*) [13], neuregulin (*NRG1*) [14] and D-amino acid oxidase activator (*DAOA*) [15] still remain among the best candidates for the disease. Despite the noted successes, linkage studies have suffered from a lack of reproducibility. This is demonstrated by a meta-analysis of 20 such linkage studies (1,208 pedigrees, 2,945 affected individuals) where Lewis et al. [16] identified only one region on chromosome 2 (2p12-q22.1) which achieved genome-wide significance. More recently this same group performed another meta-analysis, this time utilizing 32 scans with 3,255 pedigrees and 7,413 affected individuals [17]. This study confirmed the major finding of their previous work by demonstrating genome-wide evidence for linkage on chromosome 2q. Based on aggregate significance, chromosomes 1, 3q, 4q, 5q, 8p and 10q were also implicated as harbouring predisposing genetic factors. Linkage analysis has been the typical starting place in a search for genes involved in diseases. When applied to schizophrenia, however, the results have been disappointing and difficult to replicate. Thus, despite some initial success, there have been few notable linkage studies of schizophrenia in more recent years and it seems less and less likely that this technique will identify the underlying genetic susceptibility.

Table 9.1 Genes with the top "A" ranking for association to schizophrenia as determined by SGene database

Gene symbol	Gene name	Location	SNP	Protein function
PGBD1	Piggybac transposable element derived 1	6p22.1	rs13211507	Piggyback family transposase
NRGN	Neurogranin	11q24	rs12807809	Postsynaptic protein kinase substrate
NOTCH4	Notch 4	6p21.3	rs3131296	Regulation of CNS development (control of cell fate decisions)
PDE4B	Phosphodiesterase 4B	1p31	rs910694	Regulate cellular concentration of cyclic nucleotiedes (signal transduction)
TCF4	Transcription factor 4	18q21.1	rs9960767	E-box recognizing transcription factor
DAOA	D-amino acid oxidase activator	13q33.2	rs778293	Activates D-amino oxidase
TPH1	Tryptophan hydroxylase 1	11p15.3-p14	rs1800532	Catalyzes rate limiting step in biosynthesis of serotonin
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	13q14-q21	rs6311	Serotonin receptor
RELN	Reelin	7q22	rs7341475	Neuronal migration
MDGA1	MAM domain containing glycosyl-phosphatidylinositol anchor 1	6p21	rs11759115	Cell adhesion
CCKAR	Cholecystokinin A receptor	4p15.1-p15.2	rs1800857	Regulates the release of beta-endorphin and dopamine
DRD4	Dopamine receptor D4	11p15.5	rs1800955	Dopamine receptor
DRD1	Dopamine receptor D1	5q35.1	rs4532	Dopamine receptor (regulates neuronal growth and development)
APOE	Apolipoprotein E	19q13.2	APOE_e2/3/4	Catabolism of triglyceride-rich lipoprotein constituents

Within the genomic locations identified by linkage analysis are thousands of genes which may play a role in the etiology of schizophrenia. Candidates are typically chosen from this pool based on the function of the protein and its potential role in susceptibility to the disease. Thus, candidates become candidates based on location and function. These genes can then be examined in population or family based studies for association to the disease. Any genetic difference could be implicated from large scale genomic rearrangements down to single nucleotide polymorphisms (SNPs). Given the relative ease with which a SNPs can be detected, they have become the primary focus in schizophrenia association studies. This type of research flourished after the publication of the human genome in 2001 [18,19] and the subsequent haplotype map in 2005 [20]. Researchers were able to pick their favourite candidate gene from under one of the linkage peaks, identify a number of SNPs of interest from the published genome sequence or HapMap and perform association analysis on families or population-based samples. These studies generated massive amounts of data but much like previous linkage studies, positive associations in one sample were often difficult to replicate in another.

In 2008 this association data became much easier to navigate with the introduction of the SchizophreniaGene (SZGene) database (http://www.schizophreniaforum.org/res/sczgene) as a centralized up-to-date repository of the association study findings in schizophrenia. It currently contains data from 1,619 studies involving 958 genes and 8,374 polymorphisms. Additional meta-analyses are performed on all genes where sufficient data is available, providing a ranking system of candidates across all studies to date [21]. This ranking system (described on the website and in [21]) evaluates and assigns a letter grade to each gene. Currently, there are 14 genes which are listed with an "A" (highest ranking) grade (Table 9.1). How they are involved in the predisposition to schizophrenia is still unknown; however, these genes remain the strongest association-based candidates.

Likely Causes for Failure of Traditional Linkage/Candidate Gene Studies

Linkage and candidate gene studies have provided compelling evidence for the involvement of a number of genes in schizophrenia, but the number of studies that have been conducted far exceeds the amount of solid evidence scientists expected to produce. This is largely due to the complex nature of schizophrenia where multiple genes and chromosomal regions [22] along with environmental factors [23] are thought to interact leading to a predisposition to the disease. From a strictly genetic perspective, there are three main factors which confound analysis: genetic heterogeneity, pleiotropy and incomplete penetrance.

When multiple genetic factors can lead to the same phenotype, that phenotype is said to exhibit genetic heterogeneity. This is almost certainly the case in schizophrenia, where multiple mutations of small effect are thought to interact together or in concert with rare mutations of greater effect resulting in predisposition to the disease. Furthermore, the specific factors involved in one population

or family may be entirely different from those involved in another. This is likely the cause for replication difficulties in traditional linkage and association study findings. Given the known genetic heterogeneity involved in schizophrenia, a high degree of failure in replication should realistically be considered an expected outcome.

Pleiotropy defines a single genetic factor which can influence multiple phenotypic traits. Schizophrenia is a disease with multiple phenotypic traits from hallucinations and delusions to negative effects and social dysfunction. Take for example any number of neurotransmitter or neurotransmitter receptor genes which have been implicated in schizophrenia. A mutation or SNP in such a pleiotropic gene may affect any number of positive or negative symptoms depending on which allele is present. Along with other genetic factors, however, the phenotypic outcome (schizophrenia) is the same. Thus, it may not be surprising when studies disagree about which allele of a SNP is causal in the disease. These findings may not actually be contradictory, but rather another piece of the genetic puzzle.

The final confounding factor is incomplete penetrance, or the proportion of individuals with the genetic factor which also show the phenotype. As a polygenic disease, it is known that several or many genes of small to larger effect are involved in predisposition. Thus an individual may be carrying a susceptibility allele but without other predisposing factors will not develop the disease. Furthermore, genes which are more penetrant in some populations may be less penetrant in others depending on the other genetic and environmental factors involved. With all of the issues outlined above, determining the underlying genetic basis of schizophrenia represents a monumental challenge. The traditional approaches of linkage and candidate gene analysis have provided researchers with a solid starting point, and a number of candidate genes of interest. More importantly, it demonstrated that complex diseases like schizophrenia need to be investigated by non-traditional methods.

The Genome-Wide Association Approach

Alternative approaches are often driven by technological advances and recent microarray technologies have offered schizophrenia researchers new insights into the genetic basis of the disease. The failure of linkage and association studies has demonstrated that the disease was not likely caused by rare, highly penetrant mutations. It seems far more likely that schizophrenia was caused by dozens, perhaps hundreds of common variants each with small effect acting in concert. The only way to find variants of such small effect is to drastically increase the power of the study. Enter the microarray. Never before has it been so affordable to gather so much data in a single study. Current commercially available chips can assay millions of SNPs simultaneously and provides the opportunity for “hypothesis-free” research designs. Furthermore, the use of the same or similar microarray platforms in different research groups has allowed for an unprecedented level of data

sharing and collaboration. This has led to recent publications with analysis and meta-analyses of ten of thousands of affected and control individuals, the largest ever studies of their kind.

In August 2009 the results of the largest of these GWAS were published in Nature. The International Schizophrenia Consortium (ISC) group assayed 3,322 affected and 3,587 control individuals of European origin [8]. They determined that only one (imputed) SNP reached genome-wide significance. This SNP is located in the Major Histocompatibility Complex (MHC) on chromosome 6p, only 7 kilobases (kb) from the *NOTCH4* gene which has previously demonstrated association to schizophrenia [24]. Despite not reaching genome-wide significance, association was also observed to a SNP in the first intron of Myosin XVIIIB on chromosome 22 as well as a large region on chromosome 6p (comprising more than 450 SNP's) within the MHC. Two other large GWAS were published along with the ISC study in the same issue of Nature. Stefansson et al. [9] assayed 2,663 affected and 13,498 controls from eight European locations, while Shi et al. [10] examined a sample with European (2,681 cases, 2,653 controls) and African–American (1,286 cases, 973 controls) ancestry. No SNP's in either study reached genome-wide significance. Thus, the three largest GWAS ever conducted on schizophrenia generated only a single (imputed) genome-wide significant finding. Meta-analysis did add further evidence for the MHC region on chromosome 6p but it could be argued that the results as a whole fell well short of expectations.

Copy Number Variation in Schizophrenia

In recent years mircroarray data has also been used to assess Copy Number Variation (CNV) in addition to its traditional use in SNP analysis. Copy number variation refers to insertions, deletions and duplications that range in size from 1,000 bp to multiple megabases. The notion that this type of chromosomal rearrangement may be involved in schizophrenia is not a new one. Velo-Cardio-Facial Syndrome (VCFS) is caused by a deletion at chromosome 22q11.2 and is characterized by congenital heart disease, palate defects, learning disability and neuromuscular problems [25]. Interestingly, affected individuals also have a ~30-fold increase in the incidence of psychotic disorders [26] which is most likely due to haploinsufficiency of one or any number of genes found within this large region. The region itself is 3 MB in size (in some cases 1.5 MB) and can be observed using traditional cytogenetic chromosome banding techniques. Current microarray technologies are an extension of these cytogenetic techniques as they allow for the scanning of an entire genome for deleted or duplicated DNA in a single experiment. Microarrays allow us to see these insertions and deletions at a much higher resolution, with the most recent chips having a median marker spacing of less than 700 base pairs.

Several GAWS have been published over the last 3 years which implicate CNV in the predisposition to neuropsychiatric conditions including schizophrenia. Some of the most compelling evidence comes from two large studies published in 2008 [27, 28]. These studies identified three recurrent CNVs at 15q11.2, 1q21.1 and

15q13.3 with the latter two regions being replicated in both study samples. All three CNVs represent rare genetic rearrangements occurring in only ~0.1–0.5% of patients but at a 5–10 fold increase over control individuals from the same sample [29]. Perhaps more important than the identification of any particular genomic region, is that the ISC study confirmed previously published results by Walsh et al. [30] which indicated that there was an increase in rare genomic rearrangements in schizophrenia. Interestingly, genes involved in brain developmental pathways including NRG signalling, integrin signalling and axonal guidance were significantly over-represented. Like SNPs, CNV is considered rare when it occurs in less than 1% of individuals. Walsh et al. [30] demonstrated a threefold increase in these CNVs in schizophrenia when compared to controls. In the much larger ISC study [27], rare variation was found 1.16 times more often in cases than controls and this number was increased to 1.45 when only the rarest (singleton) events were considered. Thus, it seems plausible that rare genomic variation plays a role in the neurodevelopmental abnormalities which occur in schizophrenia. What is not known is the exact mode of action or the relative timing of these events.

Family-based studies (trios with an affected child) have also reported an increase in de-novo CNV in affected individuals [31]. This finding simply takes the notion of rare CNV one step farther as de-novo events would be entirely unique to that individual. Xu et al. [31] addressed both familial (positive disease history in a first or second degree relative) and sporadic (no disease history in any first or second degree relative) cases of schizophrenia in this study. The sporadic cases showed an eightfold increase in the number of de-novo CNVs when compared to their unaffected family members. A similar increase was not found in their familial cohort suggesting a possible difference in etiology between sporadic and familial cases of schizophrenia.

Common Disease, Common Variant or Rare Variant?

From the early linkage analysis and candidate gene studies to the more modern GWAS approaches, no single genetic marker has emerged as causative for schizophrenia. However, these studies do shed some light on the underlying genetic architecture involved in predisposition to the disease. Currently, there is some debate between conflicting models of this genetic architecture. The non-mendelian inheritance pattern observed in the disease has always suggested a polygenic model with several genes of varying influence acting in concert, leading to predisposition to the disease [32]. While this is not under debate, the relative contribution of these genetic factors is where the discrepancy lies. The common disease common variant model (CDCV) postulates that common variants (SNPs, CNV etc. present in >1% of individuals) having small to moderate effect act together (additively, multiplicative or epistatically) leading to a predisposition to schizophrenia [33]. This model has inspired the recent trend towards large-scale SNP association studies which assess almost every common SNP in the genome. The rationale behind this type of study is that by using increasingly large sample sizes that it will be possible to identify those genetic variants which contribute only a small increase in risk.

Contrary to the CDCV model, the common disease rare variant model (CDRV) suggests that fewer rare variants (present in <1% of individuals) of greater effect act together leading to a predisposition to the disease [34]. This model has recently been inspired by CNV studies which have demonstrated the involvement of rare genomic variants in schizophrenia. As evidence continues to accrue supporting and refuting each model in turn, it seems increasingly likely that both have merit and that a model intermediate between the two may be more appropriate. An integrative model would suggest that schizophrenia is caused by numerous variants of small effect along with fewer variants of larger effect acting additively, multiplicatively or epistatically leading to a predisposition to the disease.

The Dilemma of the Heterogeneous Sample

One of the major difficulties in schizophrenia research is the lack of any reliable biomarker for the disease. Until one is found, the ambiguity surrounding diagnosis may be the single most difficult obstacle to overcome. A heterogenous sample will always lead to spurious results. Given this fact, research is highly reliant on the clinician who diagnoses the patients. Having a single clinician who makes all of the diagnoses is the obvious best solution although it is not always possible, especially in the case of some of the large-scale GWAS studies published recently. With the selection of samples largely out of researchers' hands, the question is simply how to work best with what we have.

Reducing Genetic Heterogeneity Through Endophenotypes

As mentioned previously, genetic heterogeneity refers to multiple genetic factors all leading to the same phenotypic outcome. That phenotypic outcome in this case is schizophrenia, a diagnosis which involves a large number of highly varied symptoms. Thus, it seems plausible that while some genetic factors may affect the phenotype as a whole, still others may affect particular characteristics of the phenotype. For example, a gene which contributes to the predisposition to hallucinations would also contribute to the predisposition to schizophrenia. This is the concept of the endophenotype where complex behavioural symptoms can be classified into subgroups where it becomes more likely that a specific genetic connection can be made. Classifying based on an endophenotype theoretically reduces the genetic heterogeneity as it is thought that the endophenotype is more closely associated to the genetic variation than are the clinical symptoms of the disease. Schizophrenia can then be though of as the product of the interactions of multiple genetically determined endophenotypes and the environment [11]. Thus, it may be beneficial to search for genes for psychosis or hallucinations (as an example) rather than searching for genes for schizophrenia itself.

While some studies have had success in identifying genetic factors associated to specific clinical subtypes [35, 36], this research suffers from the same problem that schizophrenia research as a whole does, the lack of a measureable

characteristic or biomarker. While the search for a truly predictive biomarker continues, a number of experimentally measurable endophenotypes have shown association to schizophrenia. As outlined by Gottesman and Gould [37], viable endophenotypes should share certain characteristics: (1) it is associated with illness in the population, (2) it is heritable, (3) it is primarily state-independent (present whether or not the illness is active), (4) within families, it co-segregates with the illness and (5) it is found in unaffected family members at a higher rate than in the general population. Following these guidelines, structural, information processing, neuromotor and neuropsychological endophenotypes have been identified [38].

Perhaps most notable of these endophenotypes is the marked reduction in grey matter volume in affected individuals when compared to their matched controls [39]. A recent meta-analysis of 42 magnetic resonance imaging (MRI) studies (including 2,058 affected individuals) confirms the volume reduction in previously reported brain regions [40]. Based on a sum-rank analysis, two regions were identified; the first and largest includes the insula bilaterally (extending into the dorsolateral prefrontal cortex and superior temporal cortex and bilateral hippocampal-amygdala region), thalamus, cortex and bilateral hippocampal-amygdala region. The second region is the posterior cingulate. Interestingly, these brain structural differences have also been observed in first-episode drug-naive patients [41] suggesting that they are causative rather than being a result of the disease. Furthermore, differences have also been observed in high-risk individuals (offspring and relatives of schizophrenia patients) and may be predictive of which subsequently transition to schizophrenia [42]. Thus, identifying the genetic factors responsible for brain structure alterations would be a large step towards identifying the genetic factors involved in schizophrenia.

Brain volume reduction is not the only experimentally demonstrated endophenotype in schizophrenia. Neuromotor abnormalities, sensory processing abnormalities, event-related potential measures and physiological abnormalities among others have all been documented [38]. Once again, identifying the genes responsible for these associated endophenotypes could potentially identify genes responsible for schizophrenia itself. It should be noted that these endophenotypes are no doubt complex traits themselves, but the thought is that they are less complex than the disease they contribute to. As of yet, however, no causative genetic factors have been identified.

Shared Genetic Susceptibility with Autism and Bipolar Disorder

When breaking a disease entity into smaller endophenotypes it becomes increasingly obvious that the endophenotypes in question are often shared among other neuropsychiatric conditions. Genes which cause psychosis in schizophrenia may be the very same genes that cause psychosis in other disorders. This is not a new concept as there is a plethora of evidence that neuropsychiatric conditions such as schizophrenia, affective disorder and autism all have predisposing factors in common [43].

In 2009 a landmark study was published which assessed over 9 million individuals in more than 2 million nuclear families from Sweden's multi-generation register [44]. This included information about all children and their parents as well as all public psychiatric inpatient admissions, the largest study of its kind. The results clearly demonstrate that first-degree relatives of probands with schizophrenia (n = 35,858) have an increased relative risk (RR) of developing bipolar disorder which decreases as the degree of genetic relatedness to that individual decreases (siblings RR = 3.7, maternal half-sibs RR = 1.2, paternal half-sibs RR = 2.2). Similarly, first degree relatives of probands with bipolar disorder (n = 40,487) had an increased risk of schizophrenia (siblings RR = 3.9, maternal half-sibs RR = 1.4, paternal half-sibs RR = 1.6). This extremely large family study of schizophrenia and bipolar disorder clearly demonstrates that there are genetic factors which are common to both diseases.

The *CACNA1C* gene which encodes the α-1C subunit of the L-type voltage-gated calcium channel is one example of a gene which has shown association to both bipolar disorder [45] and schizophrenia [46]. GWAS approaches have also demonstrated that the aggregate polygenic contribution alleles of small effect overlap between the two diseases [8]. Furthermore, there is also an overlap in genes which show genewide association signals between schizophrenia and bipolar disorder [47]. Finally, it is also important to note that these studies provide clear evidence that there are still other genetic factors which contribute specifically to one disease or the other [8].

Like bipolar disorder, autism also shows overlap in genetic susceptibility factors which predispose to schizophrenia. The *CNTNAP2* gene in particular (a member of the neurexin family) has shown association to autism by linkage, family-based association studies [48], expression analysis [49] and CNV [50]. Copy number variation associated with schizophrenia has also been observed at the *CNTNAP2* locus [51] as well as other loci common to autism including 1q21.1 [52] and 15q13.3 [53]. Furthermore, the 22q11 deletion which is associated with an ~30× increased risk of schizophrenia has also shown association to autism [54]. Taken together, these results suggest that rare genomic rearrangements may be a common to both schizophrenia and autism. Contrast this with bipolar disorder where the overlap was mainly found in common genetic polymorphisms. Genetic factors common between schizophrenia, autism and bipolar disorder could be essential tools in determining the phenotypes in common between these diseases. As of yet, no common causal genetic determinants have been identified.

Schizophrenia Research: Novel Approaches

In the last 20 years, research into the genetic basis of schizophrenia has come a long way from its start with linkage analysis and single gene association studies to its current state with GWAS of SNP and CNV assessing tens of thousands of individuals. Yet despite the progress, no causative genetic factors have yet been identified. This is not uncommon in the study of complex genetic disorders and has led Manolio et al. [55] to coin the term "missing heritability". It is used to refer to

highly heritable complex disorders where only a small portion of that heritability has been explained. Where then is this missing heritability in schizophrenia? Thus far, traditional and GWAS approaches have been unable to answer this question, leading some researchers to consider alternative approaches to the problem.

Micro RNAs

One of the more interesting approaches in recent years examines the possible involvement of micro RNAs (miRNA) in the etiology of schizophrenia. Micro RNAs are a class of small (~22 nucleotide) non-protein coding RNAs which function by binding to mRNA resulting in degradation or repression of translation. In doing so, miRNA plays a critical role in the post-trancriptional regulation of numerous genes. In fact, each individual miRNA has been predicted to have an average of 400 different mRNA targets suggesting that >60% of protein coding genes are influenced by miRNA regulation [56]. It is this ability to modify the expression of multiple genes in multiple different systems which makes miRNAs of particular interest in schizophrenia genetics.

Altered miRNA expression levels have been observed in the prefrontal cortex [57] as well as the superior temporal gyrus and dorsolateral prefrontal cortex [58] of schizophrenia patients when compared to normal controls. Several groups have also reported association between specific miRNA SNPs and the disease including miR-206, miR-198 [59] and miR-30e [60] as well as 8 miRNAs on the X chromosome [61]. Furthermore, the schizophrenia associated CNV "hot spot" at chromosome 8p21-p23 contains 6 miRNAs [62].

Perhaps the most compelling evidence comes from a mouse model of the 22q11 deletion in humans. Stark et al. [63] engineered the mouse to carry the equivalent of the 1.5 MB 22q11.2 deletion. This is a syntenic region containing all orthologs of human genes including the *Dgcr8* gene which is involved in miRNA biogenesis. The engineered mice showed a 20–70% reduction of a particular subset of miRNAs and, when the *Dgcr8* locus was specifically deleted, Stark et al. [63] demonstrated both behavioural and cognitive defects in the knockout mice. Furthermore, these mice also showed impaired dendritic tree and dendritic spine development. Taken together, this mouse model suggests that miRNA is involved in the development of neuronal connectivity leading to the behavioural and cognitive defects observed in the 22q11 deletion syndrome and schizophrenia. Although in its infancy, studies of miRNA involvement in schizophrenia are generating some interesting results.

Cytosine Methylation

The majority of studies attempting to identify the underlying genetic basis of schizophrenia have focused on DNA sequence variations. As outlined in the preceding sections, some progress has been made in identifying variations associated to the disease. However, the lack of any causal genetic element has led some

researchers to consider that the genetic heritability may not be confined to the sequence itself. Furthermore, they suggest that heritable modifications of an epigenetic nature (such as cytosine methylation) may be responsible for the underlying genetic predisposition to schizophrenia.

Cytosine methylation is simply a methyl group (CH_3) covalently attached to the 5-carbon position of the cytosine residue. It is a heritable but reversible modification catalyzed by a group of enzymes called DNA methyltransferases [64]. In humans cytosine methylation occurs at CpG dinucleotides (5′-CG-3′) and is often found in clusters (called CpG islands) in the promoter region of genes. Methylation of cytosines within this promoter region is closely associated to decreased expression or silencing of that gene [65]. This is caused by directly blocking transcription factor binding or by recruiting chromatin remodelling proteins which are involved in the formation of transcriptionally silent heterochromatin [66]. Dysregulation of this system is known to play a role in several neurodevelopmental disorders including Rett syndrome [67] and Fragile X syndrome [68].

Having seen a role for DNA methylation in other neurodevelopmental disorders, researchers are considering the potential role of methylation in schizophrenia. Previously, discordance for schizophrenia between monozygotic twins had been attributed to non-shared environmental effects. Cytosine methylation provides an explanation as to why two genetically identical individuals could show discordance for a heritable phenotype [69]. It also provides a mechanism by which environmental factors can directly affect gene expression [70]. Furthermore, cytosine methylation has been shown to be a dynamic process which changes over the lifetime of an individual even between monozygotic twins [71]. These differences must occur during mitosis and would accumulate through adolescence and adulthood. The relative timing, the gene(s) involved and the tissue where these methylation differences arise will determine what (if any) phenotypic outcome results. If neurodevelopmental gene(s) are involved, an alteration of expression may lead to errors in development, ultimately resulting in a psychiatric phenotype. These incidental neurodevelopmental episodes could result in one twin developing schizophrenia while the other remains phenotypically normal [72].

Methylation differences have been reported between monozygotic twins for the schizophrenia candidate genes *DRD2* [73] and *COMT* [74]. Further evidence is also accumulating which suggests that it plays a role in the GABAergic neuron dysfunction in the disease [75]. A number of genes in the GABAergic system have been shown to be downregulated in the brain of schizophrenia patients when compared to healthy controls [76]. The most consistent findings involve GAD67 [77] and Reelin [78]. GAD67 catalyzes the decarboxylation of glutamate to form GABA and is thought to play a role in working memory deficits in schizophrenia [79]. Reelin is secreted by GABAergic neurons and controls neuronal migration as well as layer formation during brain development [80]. Both genes have a CpG island in the promoter region making them particularly susceptible to transcriptional regulation by methylation. Reelin, in particular, has shown a decrease in expression associated with a methylated promoter region in cultured neuronal precursor cells

[81]. Furthermore, DNA methyltransferase 1 (which is selectively expressed in GABAergic neurons) has been shown to be upregulated in schizophrenia [82].

As of yet, the methylation hypothesis of schizophrenia has not been proven. However, the accumulation of evidence does suggest that methylation and methylation in the GABAergic system, in particular, may play a role in schizophrenia.

Conclusion and Future Directions

Schizophrenia research has come a long way since it was first recognized as a complex genetic disorder. Countless studies, study designs, samples and theories have been tested over the years, and, while progress has certainly been made, we are still far from understanding the underlying genetic etiology of the disease. While some researchers point to the progress that has been made, still others feel that the potential has not been realized. The question which now must be answered is how to proceed going forward.

The last 5 years of schizophrenia research has been dominated by the GWAS. Whether assessing SNPs or CNV, the GWAS design provides a plethora of data for a relatively inexpensive price. Perhaps more importantly, they allow for "hypothesis free" research design. The microarray platforms currently in use allow us to assess virtually every common SNP in the genome while simultaneously screening for CNV. As technology continues to advance, microarray platforms will be able to assess an increasing number of markers on a single chip. More markers result in an increase in resolution, giving more information from each individual experiment. The recent trend in schizophrenia GWAS has been bigger is better. The rationale is simply that larger sample sizes are necessary to identify genetic contributors of small effect. It could be argued that the largest GWASs on schizophrenia have added relatively little that was not already known. This has led some to suggest that even more numbers are needed while still others believe that the money would be better spent elsewhere. Taken together, however, the GWAS method is currently our best approach and perhaps now is the time to use this technology to explore novel hypotheses like miRNA and methylation on a much larger scale.

Advances in microarray technology have been directed towards fitting more densely spaced markers on to a single chip. The more information that can be gathered in an experiment the better. However, even with advances in microarray technology, it is unlikely it will ever give us a complete picture of the genome. The only thing that can (of course) is whole genome sequencing. Advancements in technology have continued to decrease the price of sequencing an entire genome, but large case-control sequencing studies are still far out on the horizon. In the meantime, sequencing projects like the 1,000 genomes project (http://www.1000genomes.org) will add an unprecedented amount of data about human sequence variation into the public domain. Ultimately, however, we may need case-control sequencing studies of the same magnitude as the current GWAS studies before the underlying genetic etiology of schizophrenia is completely revealed.

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Chapter 10
Changes in Gene Expression in Subjects with Schizophrenia Associated with Disease Progression

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Abstract Schizophrenia is increasingly recognised as a progressive disorder because the central nervous system (CNS) structure, symptom profile and drug requirements vary with the duration of illness. Changes in gene expression and subsequent levels of CNS protein are likely to underlie the progressive changes in CNS function in schizophrenia. This chapter will review evidence that supports the notion that differential changes in gene expression with duration of illness does occur in the CNS of subjects with schizophrenia. Moreover, the temporal nature of these changes suggests that they may contribute to changes in drug treatment that occurs in the middle years of the disorder. It will be argued that some of the changes in gene expression in the CNS of subjects with schizophrenia may be associated with a differential aging/maturation processes and, that there are fewer differences in gene expression in subjects with schizophrenia of long duration compared to age-sex matched controls than are apparent between subjects with schizophrenia of short duration and their age-sex matched controls. Schizophrenia is a complex disorder and a further understanding of how temporal changes in gene expression contribute to the pathophysiology of the illness is likely to underpin a better understanding of the changes in CNS structure, symptom profile and treatment regimes that have been associated with the disorder.

Keywords Schizophrenia · Dorsolateral prefrontal cortex · Duration of illness · Microarray Brodmann's area 46 · Postmortem

Abbreviations

BA	Brodmann's area
CDC42BPB	Cell division cycle 42 binding protein kinase β (DMPK-like)
CNS	Central nervous system

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DLPFC	Dorsolateral prefrontal cortex
DSC2	Desmocollin 2
LRP	Low density lipoprotein receptor-related protein
MBNL1	Muscleblind protein 1
NCAM1	Neural cell adhesion molecule 1
PCDH17	Protocadherin 17
PTPRE	Protein tyrosine phosphatase receptor type E
RFDD	Restrictive fragment differential display
RGS4	Regulator of G protein signaling 4

It has been postulated that the underlying pathophysiology of schizophrenia is, at least in part, a progressive process [1]. This hypothesis is gaining credibility from a growing number of neuroimaging studies showing progressive structural changes in the CNS of subjects with the disorder [2]. There is also an acceptance that schizophrenia develops in individuals with a genetic susceptibility for the disorder, after they have encountered as yet unknown environmental insults [3]. Extending this latter hypothesis, it would be predicted that complex gene x environment interactions come into play to alter gene expression in the central nervous system (CNS) of subjects with schizophrenia that precipitate the onset of the frank disorder. This premise has lead to the use of technologies that can probe the transcriptome in postmortem CNS from subjects with schizophrenia in an attempt to identify changes in gene expression that are associated with the pathophysiology of the disorder.

Studies on the Human CNS Transcriptome: The First Indication of Progressive Changes in Gene Expression in Schizophrenia

The first indication that changes in gene expression could be link to a progressive pathophysiology associated with schizophrenia arose from a study that used restrictive fragment differential display (RFDD) to measure levels of 12,500 transcripts in Brodmann's area (BA) 46 from subjects with the disorder [4]. The overall data on gene expression obtained using RFDD suggested that the expression of genes associated with cell adhesion, signal transduction, development, transcription, energy and metabolism, cell structure/matrix, DNA/RNA binding proteins, membrane transport and receptors were particularly affected by the pathophysiology of schizophrenia; findings consistent with the types of genes identified using microarrays [5]. Taken on face value, these data indicated that there are complex changes in gene expression present in the dorsolateral prefrontal cortex (DLPFC) from subjects with schizophrenia, a CNS region that has long been implicated in the pathophysiology of the disorder [6].

All high-throughput approaches to identifying changes in the human CNS transcriptome require verification. It was verification of the data from the RFDD study that first indicated that there were progressive changes in gene expression in the cortex from subjects with schizophrenia [4]. Thus, using polymerase chain reaction to measure levels of individual transcripts, it was confirmed that mRNA for two

genes identified as having increased expression by RFDD [muscleblind protein 1 (MBNL1) and protocadherin 17 (PCDH17)] were increased in BA 46 from subjects with schizophrenia. A level of diagnostic specificity was conferred on the finding as mRNA for the two genes were not altered in BA 46 from subjects with bipolar disorder. Equally importantly, in a further analysis it was shown that mRNA for both genes were increased in BA 46 from subjects who had had schizophrenia for <7 years and not altered in the same region from subjects with schizophrenia who had had schizophrenia for >22 years. These data suggested that there could be more pronounced changes in gene expression in the CNS from subjects with schizophrenia of short duration compared to that in the CNS of subjects who had had the disorder for many years.

The finding of changes in gene expression with increasing duration of illness was significant given that duration of illness is also associated with changes in symptom profile [7], a deterioration in olfactory identification [8], an accelerated loss of verbal fluency [9] and changes in the structure of the frontal cortex [10, 11]. Hence, findings from the validation studies of RFDD supported the hypothesis that changes in CNS gene expression could underlie changes in CNS structure and function and hence symptom profile in schizophrenia. One cautionary observation from the RFDD study was that changes in MBNL1 mRNA were not associated with changes in levels of that protein in BA 46 from subjects with schizophrenia, whether they had had the illness for a short or long period [4]. Thus, interpreting changes in levels of mRNA with regards to functional outcomes must be done with some reservations.

Studies on the Human CNS Transcriptome: Outcomes from the Use of Microarrays

It is now apparent that microarray technologies allowed for more effective studies of the transcriptome in human CNS [12]. This technology was utilized to study gene expression in BA 46 from cohorts of subjects with schizophrenia of short (<4 years), intermediate (7–18 years) and long (>28 years) duration [13]. There were a number of outcomes from this study; firstly levels of 1,306 transcripts were found to be significantly different in the cortex of subjects with schizophrenia of short duration compared to their age and sex matched controls. By contrast, levels of only 487 and 279 transcripts were altered in BA 46 from subjects with intermediate and long duration schizophrenia, respectively. These data could argue that gene expression in the cortex of subjects with schizophrenia of long duration is most like that observed in relevant age and sex matched control subjects. This postulate marries with the observation that some changes in CNS structure that are detectable in subjects with schizophrenia of short duration cannot be distinguished in older subjects with the disorder [14]. The intriguing question that arrives from these observations is whether changes in gene expression that disappear with duration of illness underpin the changes in CNS structure that also become less apparent as the duration of illness progresses.

Whilst the microarray data from subjects with schizophrenia at different duration of illness suggested a progression in changes in the human transcriptome, the expression levels of 4 genes were identified as being altered in each of the phases of the illness [13]. These 4 genes were SAM domain, SH3 domain and nuclear localization signals 1 (SAMSN1), cell division cycle 42 binding protein kinase β (DMPK-like) (CDC42BPB), desmocollin 2 (DSC2) and protein tyrosine phosphatase receptor type E (PTPRE). The SAMSN1 gene encodes an adaptor protein that appears to be important in immune response with expression in the periphery being up-regulated by various cytokines [15]. Studies using the SAMSN1 knockout mouse suggest the gene plays a role in immunosuppressive pathways [16] but its role within the CNS remains unclear. CDC42BPB is a member of the serine/threonine protein kinase family and has been suggested to play a role in neuronal outgrowth [17]. DSC2 is a member of the desmocollin subfamily of the cadherin superfamily [18] that does not have a well established function in the mammalian CNS. Finally, PTPRE is a member of the protein tyrosine phosphatase family which have been suggested to be important in neuro-modulation in the CNS [19]. Therefore, at present it is not clear what contribution the 4 genes that are altered throughout all phases of schizophrenia might make to the pathophysiology of the disorder but even currently available data would suggest changes in the expression of these proteins would have a significant effect on CNS function.

The power of exploring changes in the human transcriptome in disease states comes from the analysis of gene expression in a way that provides information on pathways that might be particularly affected by the pathophysiology of a disorder [20]. Using such analyses, it has become clear that different pathways and processes are altered in the cortex from subjects with schizophrenia as duration of illness progresses [13] (Table 10.1). Despite the relatively low overlap of differentially expressed gene from each cohort, comprehensive pathways analyses revealed that different stages of illness do have common dysfunction in certain systems. For example, all stages of illness were associated with signal transduction mechanisms, lipid metabolism and protein transport/metabolism (see figure 2 from [13]). However, pathways analysis also disclosed major differences in dysfunctional systems depending on duration of illness, with a short duration of illness being particularly associated with disruptions in pathways involved in gene expression, metal ion binding, RNA processing and vesicle-mediated transport. By contrast, after a long duration of illness pathways involved with infection, inflammation, glycosylation, apoptosis and immune functions were particularly prominent.

It is now widely accepted that identifying the networks that encompass genes that have altered expression in a disease state informs on the functional consequences arising from the complex patterns of changes in the human transcriptome. Thus it is of interest that drug metabolism, molecular transport and small molecule biochemistry are key networks affected in the cortex of subjects with schizophrenia of intermediate duration [13]. Such changes in gene expression would be expected to be associated with changes in drug-responsiveness and therefore it may be more than coincidental that antipsychotic drug doses increase in subjects with schizophrenia through the third decade of life and then begin to decrease in the fifth decade

Table 10.1 The top 10 gene ontology terms that were identified has been associated with schizophrenia of short, intermediate or long duration based on gene expression changes in Brodmann's area 46 ranked according to increasingly significant probability

Schizophrenia of short duration			Schizophrenia of intermediate duration			Schizophrenia of long duration		
Gene ontology term	No. of genes	p	Gene ontology term	No. of genes	p	Gene ontology term	No. of genes	p
Vesicle-mediated transport	48	1.65E-6	Biopolymer glycosylation	9	0.0051	Immune response	29	3.31E–4
Secretory pathway	31	1.97E-6	Cell organisation and biogenesis	46	0.0115	Response to pathogen	18	6.11E–4
Secretion	34	1.29E-5	Endocytosis	9	0.129	Response to other organisms	18	0.0011
Transport	219	1.41E-4	Calcium-mediated signalling	4	0.0161	Inflammatory response	10	0.0012
Localisation	235	1.93E-4	Detection of stimulus	5	0.0302	Defence response	29	0.0015
Intracellular signalling cascade	100	2.08E-4	Receptor mediated endocytosis	4	0.0353	Response to biotic stimulus	29	0.0028
Protein transport	57	2.93E-4	Regulation of apoptosis	14	0.0364	Organismal process	46	0.0034
Cell organisation and biogenesis	128	3.39E-4	Cell death	20	0.0368	Response to wounding	13	0.0037
Protein localisation	59	4.69E-4	Death	20	0.0391	Signal transduction	56	0.0043
Cellular localization	60	6.56E-4	Detection of external stimulus	4	0.0436	Response to external stimulus	15	0.0048

of life [21]. This changing drug requirement may be driven by changing levels of CNS gene expression affecting drug sensitivity in the middle phases of the illness. In addition, it is intriguing to postulate whether the emergence of movement disorders such as orofacial dyskinesia late in schizophrenia [22] might be linked to changes in the expression of genes associated with connective tissue development and function, muscular system development and function that are notably altered in the cortex of long duration schizophrenia. Finally, the networks that are particularly affected in short duration schizophrenia involve genes involved in neurological and psychological disorders. This may support the notion that schizophrenia has a genesis early in development [23] and the signals from the embryonic abnormalities underlying the initial pathophysiological processes dissipates as the illness progresses.

The initial analysis of data from the study of gene expression was analysed with duration of illness and diagnoses as the significant variables [13] where subjects with different duration of illness were grouped into cohorts making this variable non-continuous. An alternative analyses has since been completed where diagnosis and the continual variable of age were taken as the major variables [24]. This analysis found that the expression of 2.5% of the genes studied correlated with age in both cohorts of subjects and that there may be a differential change in gene expression associated with aging occurring in the CNS of subjects with schizophrenia. This is perhaps best typified by the finding that 34% of the genes showing a change in expression with age were also identified as been differentially expressed in the cortex of subjects with schizophrenia of short duration. Moreover, the direction of these changes in expression was in the direction that would be expected comparing expression in the cortex of older versus younger control subjects. These data therefore support the hypothesis that part of the pathophysiology of schizophrenia in some way involves accelerated aging [25]. Notably, in the schizophrenia cohort evidence of accelerated aging involved genes that affect synaptic function, cell/cycle DNA damage and apoptosis. There is certainly strong evidence to support the hypothesis that synaptic function is altered by the pathophysiology of schizophrenia [26]. Significantly, recent genetic findings [27] and studies on peripheral tissue [28] have argued a role for apoptosis in the pathophysiology, however the failure to show significant cell loss in the cortex [29] and other CNS regions [30] from subjects with schizophrenia tends to argue that apoptosis may not be a major factor in the pathophysiology of the disorder. Finally, there is some suggestion that problems with DNA integrity and resistance to damage may be involved in the pathophysiology of the disorder [31, 32], although this is not a universally accepted finding [33].

One significant finding from examining changes in gene expression with age in the cortex from subjects with schizophrenia and controls subjects was that the expression of regulator of G protein signaling 4 (RGS4) decreased with age in the control subjects, but not the subjects with schizophrenia [24]. Significantly, an early microarray study found that the levels of expression of RGS4 were decreased in the CNS from subjects with schizophrenia and had validated this finding with in situ hybridization [34]. These findings took on greater significance when it was suggested that RGS4 could be a susceptibility gene for schizophrenia [35–37] and

further studies confirmed the expression of the gene was altered in a number of CNS regions [38, 39]. However, in the study of gene expression at different durations of illness, at no point did the differential age-related changes in RGS4 expression in the cortex of subjects with schizophrenia and control subjects result in significant differences in levels of RGS4 mRNA between schizophrenia and age/sex match controls [13]. This finding was confirmed by a more extensive study in BA 9 and BA 40 that failed to show changes in either RGS4 mRNA or protein in subjects with the disorder [40]. These data, plus other data suggesting RGS4 expression is not altered in the CNS of subjects with schizophrenia [41] and may not increase susceptibility for the disorder [42–44], make it less clear that changes in RGS4 plays a role in the pathophysiology of any phase of the illness.

Studies on the Human CNS Transcriptome: Outcomes from Pooling Microarray Sets

New strategies are being developed to allow the pooling of microarray data to obtain bigger disease cohort sizes and hence more power to detect changes in gene expression. Embracing this approach the data from the microarray array study on gene expression in the cortex from subjects with schizophrenia at different durations has been pooled with data from a microarray study using tissue from the Harvard Brain Bank [45]. The major outcome from the analyses of these data was that genes with altered expression in the cortex from subjects with schizophrenia cluster into networks that are primarily associated with neuronal function. Moreover, the analysis showed that the normal age-related decline in expression of some genes associated with neurite outgrowth, neuronal differentiation and dopamine-related signaling were absent in subjects with schizophrenia. Clearly, these findings do not tend to support the notion that schizophrenia is a disease of accelerated aging [25], rather certain normal aging functions do not occur in the CNS of subjects with the disorder. The finding on neuronal outgrowth would seem to support the conclusion from a study of the human proteome in the cortex from subjects with schizophrenia which also suggested this process was likely altered because of changes in levels of proteins associated with these pathways [46]. In addition, it is noteworthy that DISC1, a candidate gene for schizophrenia, has been shown to be important in the control of neuronal differentiation [47]. It will therefore be interesting to determine if DISC1 has any role in the absence of an age-related decline in neuronal differentiation in schizophrenia. Finally, dopaminergic systems have long been known to be affected by the pathophysiology of schizophrenia [48] however, it may be that the role of this neurotransmitter system in the pathophysiology of the disorder has a temporal dimension. Given it has being recognised that age-related changes in dopaminergic systems are important in modulating CNS function [49], it would seem likely that a derangement of such age-related processes could form the basis of ongoing and evolving symptoms in subjects with schizophrenia. This could easily include the negative symptoms associated with schizophrenia which become more dominant with aging [50].

The notion that age-related changes in gene expression may be important in understanding the pathophysiology of schizophrenia gains credibility from studies that are showing age-related changes in the expression of genes, regarded as schizophrenia susceptibility genes, in the cortex of control subjects [51]. Such findings suggest a link between a genetic disposition and a temporally modulated impact on gene expression and hence CNS function, perhaps the ultimate gene x environment interaction. Moreover, it is becoming apparent that CNS DNA methylation is a dynamic process that shows significant variation with aging [52] and that DNA methylation is a key component of the epigenetics by which environment can regulate gene expression [53]. Given that complex gene x environment interactions are postulated to contribute to the pathophysiology of schizophrenia [3], it would seem logical that some age-related changes in gene expression may reflect gene x environment interactions and could be contributing to the evolving symptoms and CNS structural changes thought to be present in subjects with the disorder.

Studies on the Human CNS Transcriptome: Moving Beyond Microarray Studies

The encompassing and holistic nature of microarray studies has expanded notions on the possible mechanism underlying the pathophysiology of schizophrenia. Some of these new hypotheses growing from microarrays studies are being tested using alternative technologies, such as quantitative PCR (qPCR) or in situ hybridization. Thus, preliminary qPCR data generated to validate microarray data from subjects with schizophrenia of short duration confirmed the direction of gene expression change for protein phosphatase E1, REST co-repressor 3, neuropeptide Y, solute carrier family 29 (member 2), sulfatase 1 and F-box protein 31 found in the data from the microarray. These data give strong face-validity to the subsequent gene ontology and pathway analysis completed using the microarray data.

The next phase in beginning to fully understand the impact on changes in gene expression in the CNS from subjects with schizophrenia is to complete studies in larger cohorts in multiple CNS regions and, where appropriate, attempt try to identify isoforms specific changes in gene expression. Thus, the finding that the expression of neural cell adhesion molecule 1 (NCAM1) was increased in BA 46 from subjects with schizophrenia [13] prompted a study to measure levels of mRNA for the NCAM 180 isoform in BA46, BA 10 and BA 17 from 15 subjects with schizophrenia of short duration (<7 years) and 15 age-sex matched controls [54]. This study confirmed increased levels of NCAM 180 mRNA in BA 46 from subjects with schizophrenia but failed to find any evidence for change in levels of expression in the other two regions of the cortex. These data showed that changes in gene expression can have regional-specificity, which means caution must be applied in extrapolating microarray studies across CNS regions. In addition to caution in extrapolating data from microarray studies between CNS-regions, as mentioned with regards to the data from RFDD, further caution must be applied in

extrapolating changed level of mRNA to changes in levels of proteins. With this regard, a study in BA 46, BA 10 and BA 40 failed to identify any changes in levels of NCAM 180 protein in those CNS regions from subjects with schizophrenia or bipolar disorder [55]. There was a change in NCAM 180/140 ratio in BA 10 which could indicate some complex remodelling of synaptic function given the role of NCAMs in maintaining synaptic structure [56].

When examining the effects of gene expression over a lifespan it is also critical to be aware of changes in the expression of a family of proteins as this may have important consequences for CNS function. Thus, it has been shown that the level of expression of polysialylated NCAM (NCAM PSA) change during life and that NCAM PSA has important roles in neurodevelopment up to adolescence [57]. This makes the finding that NCAM PSA levels are altered in the CNS of subjects with schizophrenia of particular significance [58] as these data could be suggesting a failure of CNS maturation is occurring very early in the disease process and may not be apparent in the CNS from older subjects who have the frank disorder.

The microarray study on gene expression across different duration of illness also provided data to suggest that there were changes in mRNA for low density lipoprotein receptor-related proteins (LRP) in the cortex of subjects with schizophrenia of short duration [13]. This finding was significant in that some LRPs act as receptors for apolipoprotein E [59] and Reelin [60], both of which have been reported as being altered in the CNS of subjects with schizophrenia [61–63]. To further investigate the potential role of LRPs in the pathophysiology of schizophrenia, qPCR was used to measure the levels of LRP2, LRP4, LRP6, LRP8, LRP10 and LRP12 mRNA in Brodmann's area (BA) 46 from 15 subjects with schizophrenia of short duration and 15 age-sex matched controls; levels of apolipoprotein E protein was also measured to confirm previous findings that levels of that protein are increased in the cortex of subjects with schizophrenia [64]. These studies showed that there were increased levels of LRP10 mRNA, decreased levels of LRP12 mRNA and increased levels of apolipoprotein E in BA 46 from subjects with short duration schizophrenia. Significantly, it is known that apolipoprotein-enriched very low density lipoprotein signals through LRP10 and there are strong structural homologies between LRP10 and LRP12 suggesting common agonist binding properties [65]. Together, these data may indicate that apolipoprotein E signalling is affected by the pathophysiology of schizophrenia of short duration. In humans, genotype dictates whether an individual has one or two forms of the three forms of apolipoprotein E (apolipoprotein E2, E3 or E4) [66], this is significant because different forms of apolipoprotein E have different effects in the human CNS [67]. Thus, further studies will be required to fully understand the likely role of altered apolipoprotein E signalling in the CNS of subjects with schizophrenia of short duration.

Conclusions and Future Directions

Neuroimaging studies suggest that there are progressive changes in gray [68, 69] and white matter [68, 70], ventricular size [71], the cortex [69, 72, 73], the hippocampus [74, 75] and deep brain nuclei [76] in subjects with schizophrenia. Data also

suggests these progressive changes are in train at the onset of the disorder [69, 75, 77] and are a feature of childhood onset schizophrenia [78, 79]. Moreover, there is some evidence to suggest that the magnitude of progressive CNS changes is associated with symptom severity [73] and that early treatment with antipsychotic drugs may help ameliorate the progressive changes in CNS structure [77].

The finding that the changes in gene expression in the cortex from subjects with schizophrenia also changes with duration of illness [13], and presumably disease progression, raises the possibility that changes in gene expression underpin the progressive changes in CNS structure and function [80] as well as the changing symptom profile with time [50, 81]. Given that changes in gene expression in the CNS from subjects with schizophrenia show clear regional-specificity [54], there would be an argument to explore changes in the human transcriptome in regions of the CNS thought to be affected by the pathophysiology of schizophrenia, such as the anterior cingulate [82], hippocampus [83] and basal ganglia [84], at different duration of illness. Such studies would inform as to whether different pathways and/or genes contribute to the progression of the disorder in different CNS regions.

In the case of the dorsolateral prefrontal cortex, where progressive changes in gene expression have already been reported [13], microarray data needs to be validated at the level of protein, as without a change in protein levels it is difficult to postulate how changes in gene expression can have a physiological outcome. However, it is now clear that factors such as microRNA can act to change levels of proteins when levels of mRNA are not altered [85] and thus studies of the transcriptome may be blind to the effect of microRNAs. Hence a study using technologies that are able to explore significant proportions of the human CNS proteome [86] in cortex from subjects with schizophrenia at different duration of illness would also be valuable in understanding the true progressive nature of the disorder.

Finally, it is becoming increasingly recognised that schizophrenia is a syndrome of disorders rather than a single disease entity with a common pathophysiology [87]. Hence it is feasible that only select component disorders within the syndrome of schizophrenia may show a progressive pathophysiology that is associated with changes in CNS gene expression. The notion that different forms of schizophrenia may, or may not, be a progressive illness is again supported by neuroimaging findings that show varying degrees of changes in different individuals with the disorder ranging from no apparent structural change, to significant levels of progressive changes [71]. The advent of biomarkers, such as a marked loss of cortical muscarinic receptors [88], which allow the separation of subjects with schizophrenia into more biologically homologous populations, is opening up the possibility of exploring the extent to which a progressive pathophysiology contributes to the different forms of schizophrenia.

Finally, it is clear that there are age related changes in gene expression that are independent of disease processes [51] which are presumably contributing to changes in CNS function with aging. These data add to others which clearly shows that the structure of the CNS is changing during normal aging from the level of gross anatomy [89] to that of cellular architecture [90]. Hence a fuller understanding of age-related changes in all levels of CNS structure/function should ideally be

elucidated to allow a better identification of disorder-specific changes in age-related CNS development in subjects with schizophrenia.

In conclusion, there is now evidence to show that changes in gene expression, like other measures in schizophrenia, evolve with the progression of the disorder. Understanding the full extent and functional consequences of these changes will be critical in gaining greater insight into the pathophysiology of schizophrenia.

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Chapter 11
Amino Acids in Schizophrenia – Glycine, Serine and Arginine

Glen B. Baker, Jaime E.C. Hallak, Alexandria F. Dilullo, Lisa Burback, and Serdar M. Dursun

Abstract In recent years, there has been increased interest in the possible role of amino acids in the etiology and pharmacotherapy of schizophrenia. Much of this research has focused on glutamate and γ-aminobutyric acid (GABA), and these are the subjects of other chapters in this book. However, there have also been interesting findings reported with glycine, serine (particularly D-serine) and arginine, and this chapter provides a brief overview of those findings. Glycine and D-serine are coagonists at the NMDA glutamate receptor and lower plasma levels of these two amino acids have been reported in schizophrenia compared to controls. Combinations of glycine with antipsychotics or glycine transport inhibitors have been reported to be useful in treatment of schizophrenia, and increased glycine serum levels have been reported in schizophrenia patients responsive to antipsychotics. Behavioural studies in mutant mice in which D-serine levels are altered by manipulating catabolic or anabolic enzymes suggest that inhibitors of D-amino acid oxidase (DAO), particularly in combination with D-serine, may represent a useful future therapeutic approach to the treatment of schizophrenia. Arginine, a precursor to nitric oxide (NO) is also of interest in schizophrenia, although at present there is evidence for both hypo- and hyperfunction of this amino acid in schizophrenia and further clarification is required.

Keywords Glycine · Serine · Arginine · Glutamate · Schizophrenia · Antipsychotics · Transport inhibitors

Abbreviations

DA	Dopamine
DAO	D-amino acid oxidase

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fMRI	functional magnetic resonance imaging
GABA	γ-Aminobutyric acid
GTI	Glycine transport inhibitor
HPLC	High performance liquid chromatography
5-HT	5-Hydroxytryptamine
L-NAME	Nitro-L-arginine methyl ester
MWM	Morris water maze
NMDA	N-methyl-D-aspartic acid
NMDAR	NMDA receptor
NO	Nitric oxide
PCP	Phencyclidine
PFC	Prefrontal cortex
PLP	Pyridoxal 5-phosphate
PPI	Pre-pulse inhibition

Introduction

Despite more than a half decade of intensive searching, the biochemical basis of schizophrenia remains uncertain. For over 30 years, the catecholamine dopamine (DA) has been studied extensively [1–4]. The dopamine hypothesis, which suggests that there is dopaminergic hyperfunction in the mesolimbic system and dopaminergic hypofunction in the mesocortical system, has certainly contributed to our understanding of the functions of DA in the brain and has been useful for screening potential new antipsychotic drugs. Several of the "atypical" or "second generation" antipsychotics are also relatively potent 5-HT_2 receptor antagonists, suggesting that 5-hydroxytryptamine (5-HT serotonin) may also play an important role in the etiology of schizophrenia. Despite advances made in schizophrenia research and drug development based on our knowledge of DA and 5-HT, the currently available drugs for this disorder are disappointing with regard to the speed of action, their overall efficacy and their adverse side effect profile, all of which contribute to decreased medication adherence by patients. It seems obvious that other neurochemical systems must be contributing to the symptoms and that we must have an increased knowledge of the effects of these other neurochemicals if we are to advance in the treatment of this devastating disorder.

In recent years, there has been a great deal of interest in the possible involvement of amino acids in the etiology and pharmacotherapy of schizophrenia. The focus of this research has been on the excitatory amino acid glutamate [5–10] and, to a lesser extent, the inhibitory amino acid γ-aminobutyric acid (GABA) [11–13]. Comprehensive reviews of the literature on these two amino acids are provided in other chapters in this book, but several other amino acids are also of interest in this regard (glycine, serine and arginine; Fig. 11.1), and they will be the topics of this chapter.

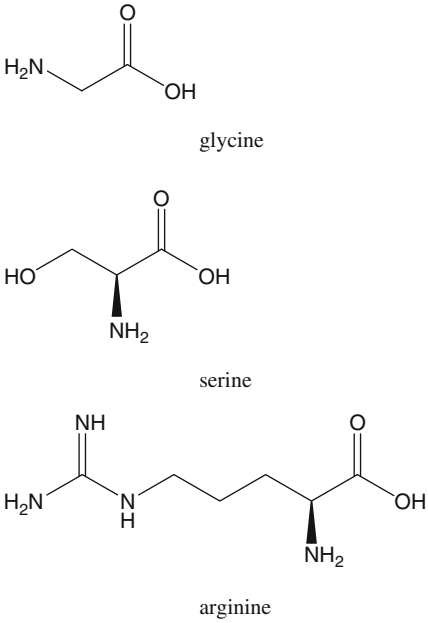

Fig. 11.1 Structures of the amino acids that are the topic of this chapter

Glycine

Glycine is an amino acid that has inhibitory effects in the spinal cord and lower parts of the brain but acts as a coagonist at the glutamate NMDA receptor (NMDAR) in some other parts of the brain. Given the interest in glutamatergic dysfunction in schizophrenia, the possible involvement of glycine in the etiology and/or pharmacotherapy of schizophrenia has been the subject of considerable research interest in recent years. Genetic and pharmacologically-induced deficiencies in glycine binding in mice produce behavioural changes which appear to model the negative and cognitive symptoms of schizophrenia [14].

Reduced plasma levels of glycine have been reported in schizophrenia patients, and these reduced levels seem to correlate with severity of negative symptoms [15–17] and response to clozapine [18]. Hones et al. [17] found the lower serum levels of glycine to be associated with an increased intensity of negative symptoms but to have no relationship with positive or cognitive symptoms in schizophrenic patients. In a study comparing treatment-responsive and non-responsive schizophrenia patients to healthy controls, Cunha et al. [19] found increased serum levels of glycine in the responsive group and increased serum glutamate in the treatment resistant patients.

Several studies have tested the effects of combining glycine with certain antipsychotics or using glycine transport inhibitors (alone or in combination with glycine) as possible treatment approaches for schizophrenia and obtained promising results

[20–26]. Glycine transport inhibitors (GTIs) indirectly activate the glycine modulatory sites on NMDA receptors, increasing their functional capacity, and also prevent glycine from being removed from the synaptic cleft, thereby elevating glycine levels [26, 27]. When glycine is administered concurrently with GTIs, lower drug doses of glycine are required [27].

In conclusion, there is evidence supporting the administration of glycine and GTIs in order to enhance NMDA receptor-mediated neurotransmission for treatment in schizophrenia. However, further research is still needed since study results are inconsistent [27]. Further testing is also necessary to identify the level of glycine reuptake inhibition needed to produce effective results in treating schizophrenic patients [27].

D-Serine

Although currently prescribed antipsychotics successfully alleviate the positive symptoms of schizophrenia, they either do not or only mildly improve negative symptoms and cognitive deficits, and it is necessary to develop effective treatments with greater symptom coverage for this disease. In recent years, D-serine, a potent co-agonist at the NMDA receptor site, has been receiving a great deal of attention in research studies. For NMDA receptor channels to open, glutamate must bind to one receptor site (NR2), and either D-serine or glycine must activate the other (NR1) [27]. D-Serine has a high affinity for the glycine receptor site and is more permeable to the blood-brain barrier than glycine. Therefore, in comparison to each other as treatment approaches, a smaller dose of D-serine should be more effective than an equal amount of glycine [27]. According to current literature, D-serine is the main NMDA receptor co-agonist and it potentiates NMDA receptor function [27]. Increased activation of the hippocampus has been observed using functional magnetic resonance imaging (fMRI) following D-serine administration [28]; improvements in learning processes, enhancement of long term potentiation, and an increase in field potential occurred as a result [28].

Waziri et al. [29, 30] reported increased levels of serine in the blood and brains of schizophrenics and Macciardi et al. [31] also reported increased serum levels of serine in schizophrenics. Neither of these groups separated the D- and L-serine, but their studies probably represent changes in levels of L-serine since it is much more abundant in blood and brain than D-serine. The literature about L-serine continues to be confusing since several groups have reported abnormal serine levels in schizophrenia [16, 18, 31–34] while others have reported no differences from control values [19, 35, 36]. Using high performance liquid chromatography (HPLC), Hashimoto et al. [36] found lower serum levels of D-serine in schizophrenia patients than controls. These results suggest that the enzymatic activity of serine racemase, which converts L-serine to D-serine in the presence of a pyridoxal 5-phosphate (PLP) co-factor, could be reduced in individuals with schizophrenia or that there could be overactivity of D-amino acid oxidase, the enzyme that catalyzes catabolism of D-serine. Ohnuma et al. [37] reported that D-serine levels and the D-/L-serine ratio increased markedly in schizophrenia patients as clinical symptoms

improved. Loss of serine racemase in mutant mice dramatically reduces brain levels of D-serine, and these mice display schizophrenia-related behaviours (impairments in prepulse inhibition, sociability and spatial discrimination) [38].

Daily administration of large quantities of glycine or D-serine alone or use of either as an adjunct to atypical antipsychotics has been reported to result in improvement of schizophrenic symptoms [25 for review]. Duffy et al. [39] reported that administration of D-serine to mice resulted in augmented cognitive flexibility. Heresco-Levy et al. [40] reported that D-serine added to risperidone or olanzapine resulted in improvements in negative, positive, cognitive and depressive symptoms in treatment-refractory schizophrenics. Lane et al. [41] found that the GTI sarcosine was a more effective add-on treatment than D-serine in acute exacerbation of schizophrenia. Tsai et al. [42] reported that when D-serine was given with clozapine, neither positive, negative, nor cognitive symptoms improved.

D-Serine is metabolized by D-amino acid oxidase (DAO) and inactivation of DAO in mice has been reported to improve behavioral deficits which are similar to the negative and cognitive symptoms in schizophrenic patients as well as improve sociability deficits, special recognition impairments, and long-term special memory disruption [43]. Since DAO breaks down D-serine, DAO inhibitors may have therapeutic potential for treatment of the disorder. There have been recent efforts to identify and characterize small molecule DAO inhibitors [44]. Some of the molecules currently under study include AS057278, CBIO, and Compound 8 [44, 45]. AS057278 is orally bioavailable, it increases D-serine in the midbrain and cortex of rats, normalizes PPI when administered acutely and chronically, and also normalizes phencyclidine (PCP)-induced hyperlocomotion when administered chronically [45]. In a recent study the coadministration of CBIO with D-serine increased the bioavailability of D-serine when administered orally, enhanced the effects D-serine had on PPI deficits, and increased D-serine extracellular concentrations in the frontal cortex [46]. This combination therapy also allowed for the administration of a lower dose of D-serine to patients in treatment [44]. Thus, treatment using DAO inhibitors, particularly in combination with D-serine, is a novel therapeutic approach worthy of further investigation.

The antipsychotic drugs chlorpromazine and risperidone have been reported to inhibit DAO [47, 48] although the contribution of this inhibition to the therapeutic efficacy of these drugs has been disputed [49]. Interestingly, the distribution of D-serine levels does not correlate well with DAO activity in adult brain, but there is a high correlation between D-serine levels and concentration of NMDA receptors in brain [50]. It has been postulated that increases in cerebellar D-serine levels by inhibition of DAO may result in antipsychotic activity through an augmentation of D-serine mediated facilitation of NMDA receptors in that brain region [49].

Arginine

In recent years, there has been considerable interest in the involvement of amino acid L-arginine, the precursor of nitric oxide (NO), in both schizophrenia and depression. Although the literature in this area is very interesting, there is evidence

suggesting both increased and decreased synthesis of NO in schizophrenia [51–53] Phencyclidine (PCP), a non-competitive antagonist of the NMDA receptor, induces very similar symptoms (including positive and negative symptoms and cognitive deficits) in humans to schizophrenia [54]. PCP mimics NMDA receptor hypofunction, and therefore, a knowledge of PCP's affects may be useful in discovering treatments for schizophrenia [54, 55]. Interfering with nitric oxide (NO) production in rodents has been reported to reverse PCP-induced effects [54]. NO is a gas synthesized in a two-step oxidation process from the amino acid L-arginine and oxygen [55]. In the prefrontal cortex, NO is also known to affect the storage, uptake, and/or release of certain neurotransmitters including glutamate, GABA, and dopamine [51]. Other evidence suggests that NO may have a role in learning and memory formation. Using a NO-sensitive microelectrocemical sensor, NO levels in awake, freely moving animals have been reported to be raised in the brain after PCP administration [54]. Pretreatment with nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor, counteracted PCP's behavioral effects and NO levels were reduced [54]. According to the findings mentioned above, the cognitive dysfunctions seen in schizophrenia may be relieved using NOS inhibitors as a therapeutic treatment approach [56].

NMDA receptor hypofunction causes learning and memory deficits, and experimentation involving the Morris water maze (MWM) model can be used to test the PCP model of schizophrenia and how spatial memory is impacted by the administration of NMDA receptor antagonists including PCP and others [55, 57]. NOS inhibition has been shown to decrease the effects of PCP during a MWM swim test [55]. It has also been reported that the NO system is over-active in schizophrenia patients, and that NOS inhibitors block the behavioral and biochemical effects of PCP and block the disruption of PPI [52, 56].

However, there is also evidence from animal studies with PCP that underproduction of NO may be linked to schizophrenia. Some preclinical studies suggest that NO donors such as sodium nitroprusside and molsidomine can block the behavioral effects of PCP [58, 59] and improve cognitive deficits induced in animals by MK-801 [60]. A decrease in NOS activity has been reported in prefrontal cortex of brains from patients with schizophrenia [61].

Conclusions and Future Directions

In summary, although there are certainly some contradictions in the literature, it appears that the amino acids glycine, serine and arginine may play important roles in the etiology and pharmacotherapy of schizophrenia. Given the rather disappointing therapeutic efficacy and the disturbing side effect profile of currently available drugs, the possibility of new therapeutic agents based on actions on these amino acids is a promising area for continued research. It now appears that other glutamate receptors in addition to NMDA receptors may play a role in the etiology

of schizophrenia, and these receptors also appear to be involved in the actions of D-serine; these interactions and the involvement of D-serine and other amino acids should be investigated further. It is now known that glial cells play a much more important functional role in the central nervous system than was orginally thought. Given the knowledge that astrocytes and microglia can affect transport of D-serine and glycine as well as glutamate, the role of glia in schizophrenia warrants further attention. In addition, there has been increased interest in recent years in the involvement of the immune system in various psychiatric disorders, including schizophrenia, and microglia appear to be major players here. The effects of activated microglia on amino acids in the brain is an area that is underexplored. With regard to the controversy about arginine/NO hyper- or hypofunction in schizophrenia, presumably neurochemical/molecular biological studies in more areas of the brain and more comprehensive behavioural studies with drugs that affect levels of arginine and/or NO should provide clarification.

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Chapter 12
Developmental Consequences of Prenatal Exposure to Maternal Immune Activation

Stefanie L. Bronson and Neil M. Richtand

Abstract Schizophrenia is a developmental disorder which likely comprises a heterogeneous collection of pathophysiologies converging upon a common end-stage. For example, prenatal exposure to maternal infection increases schizophrenia risk; preclinical studies suggest risk elevation is mediated through the maternal inflammatory response to infection. Prenatal immune activation therefore provides an opportunity to identify mechanisms underlying altered neurodevelopment in offspring following exposure to maternal inflammatory response. Significantly, previous studies have demonstrated behavioral, cognitive, and neurochemical abnormalities of relevance to schizophrenia in adult offspring following prenatal immune activation. Hypotheses of schizophrenia etiology suggest pathophysiologies in glutamatergic and GABAergic neurotransmission may precede and underlie dopaminergic dysfunction. Here we discuss evidence in support of these hypotheses, and detail studies evaluating support of this model following prenatal immune activation, a known schizophrenia risk factor. Finally, we highlight the potential for this model to inform future studies of schizophrenia evaluation, prevention, and treatment. Three areas of particular promise include an improved understanding of gene x environment interactions; identification of novel pharmacological targets for prevention; and development of therapeutic interventions targeting specific stages of illness. For example, new treatments may target GABAergic and glutamatergic systems early in development, in contrast to all current FDA-approved treatments targeting dopaminergic systems in later stages of illness.

Keywords Schizophrenia · Psychosis · Prodromal · Antipsychotic · Neuroleptic · Psychotic disorder · Animal model · Poly I:C · LPS · Influenza

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Abbrevations

AIS	Axon initial segment
ASST	Attentional set-shifting task
GABA	γ-Aminobutryic acid
GAD67	Glutamic acid decarboxylase, 67 kDa isoform
GD	Gestational day
IL	Interleukin
LI	Latent inhibition
LPS	Lipopolysaccharide
MK-801	(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate (dizocilpine)
MWM	Morris water maze
NMDA	*N*-methyl-D-aspartate
NORT	Novel object recognition test
PD	Postnatal day
Poly I:C	Polyinosinic:polycytidylic acid
PPI	Prepulse inhibition
RAM	Radial arm maze
TH	Tyrosine hydroxylase
TLR	Toll like receptor
TNF	Tumor necrosis factors
WAIS	Wechsler adult intelligence scale
WSCT	Wisconsin card-sorting test

Introduction

Schizophrenia is a neurodevelopmental disorder resulting from a heterogeneous collection of genetic and environmental risk factors. In spite of the widely recognized impact of this condition's disease burden, significant gaps in treatment efficacy remain unmet, and prevention remains an unattainable goal. These unmet needs stem from the fact that specific neurobiological mechanisms underlying schizophrenia remain incompletely characterized. Thus, while schizophrenia likely results from an interaction between multiple genetic and environmental causes, the initial step of selecting a single suspected cause and elucidating the underlying neurobiology, a necessary first step in identifying mechanism-based prevention and treatment, has not been fully achieved.

Epidemiological studies suggest elevated risk for schizophrenia in offspring exposed to maternal infection during pregnancy, and preclinical research has characterized a range of behavioral, neurochemical, and neuroanatomical abnormalities following prenatal immune activation. Schizophrenia is a developmental disorder, with different characteristic stages of cognitive and behavioral deficits throughout the life course. Subtle impairments in social, organizational, and cognitive function in the late teenage years are associated with the later appearance of psychotic

symptoms of schizophrenia [1]. In contrast, the prominent emergence of positive symptoms of psychosis typically become manifest several years later [2], and continued cognitive decline may persist into the later stages of illness [3]. Here we review literature suggesting the developmental life course of rodents following prenatal immune activation follows a similar pattern, recapitulating the progression of abnormalities observed during the developmental life course of individuals with schizophrenia. Elucidation of neurobiological mechanisms underlying the progression of behavioral and cognitive abnormalities in rodents could identify novel developmentally based interventions for prevention and treatment of symptoms of schizophrenia. The prenatal immune activation animal model therefore provides the potential to progress from tertiary treatment to primary prevention of disorders for which prenatal inflammation represents an important environmental risk factor.

Epidemiologic Overview

Epidemiological studies beginning in the 1970s identified significant correlations between winter/early spring births and elevated incidence of schizophrenia, with increased risk ranging from 5 to 15% [4, 5]. Although seasonal correlations are open to alternative explanations, one conceivable explanation is the higher occurrence of infectious disease in winter months [6]. In order to determine the involvement of infectious disease, Mednick and colleagues [7] used a Finnish cohort to study the prevalence of patients with schizophrenia that were in utero during the 1957 influenza epidemic. They identified an increased risk of schizophrenia (approx. 50%) for those in the second trimester during the epidemic. As reviewed extensively [5, 8, 9], many subsequent studies have attempted to replicate and extend these findings, more recently utilizing serological evidence of maternal infection exposure. To date, gestational exposure to multiple bacterial and viral infections is associated with elevated schizophrenia risk. Associated exposures include influenza virus, toxoplasmosis, herpes simplex virus, rubella, and cytomegalovirus, as well as serologically confirmed elevations in maternal pro-inflammatory cytokine expression [9].

Collective findings from the above studies suggest that prenatal exposure to a variety of infectious agents accounts for as many as one-third of schizophrenia cases [9]. While it is possible that pathogen-specific processes mediate the adverse effects of these diverse infections, a more parsimonious theory posits that one or more factor(s) common to the maternal immune response disrupt fetal development [9, 10].

Modeling Maternal Immune Activation

While numerous epidemiological investigations have provided evidence linking maternal infection during pregnancy with increased risk of schizophrenia spectrum disorders in offspring, preclinical animal models are necessary to determine whether

these prenatal exposures can indeed *cause* alterations in neurodevelopment and to identify underlying pathogenic mechanisms. A number of animal models of maternal immune activation have been developed based on the epidemiologic evidence reviewed above. In general, inflammatory agents are administered systemically to pregnant laboratory rodents to stimulate the maternal immune response during specific periods of gestation. Inflammatory agents utilized to date include live pathogens, pathogen-free bacterial and viral mimics, and immune mediators. These models have supported a causal relationship between the maternal immune response and the development of behavioral, neurochemical, and neuroanatomical abnormalities in offspring. Because various immune-activating agents have been utilized, preclinical models continue to clarify the relative contributions of specific pathogens and mediators of the acute phase immune response to central nervous system maldevelopment.

Live Pathogens

Maternal immune activation models in which live pathogens are used as the challenge agent have been almost exclusively limited to influenza virus [11]. A viral strain is typically administered to pregnant, anesthetized rodents intranasally at doses sufficient to induce sublethal lung and upper respiratory infection and sickness behaviors lasting for several days [12, 13]. Although offspring exhibit no gross abnormalities or indications of viral infection at birth, neurodevelopmental alterations are detectable in neonates, and ultimately, behavioral, and pharmacological abnormalities related to those observed in patients with schizophrenia and autism occur in adult offspring [12–16].

To date, it is unclear to what degree changes in offspring of virus-infected mothers are due to direct infection of the fetus or indirect effects of the maternal immune response, and there are conflicting data regarding possible transplacental passage of the influenza virus. Aronsson et al. [17] detected viral RNA and nucleoprotein in fetal brains and postnatal offspring following intranasal viral infusion of pregnant mice. In contrast, Shi and others [18] did not detect viral RNA in fetal brains. The authors suggest that differences in tissue handling, sensitivity of detection protocols, or viral strain variability may account for these incongruent findings [18]. It is also conceivable that the infection itself may alter transplacental passage or that placental permeability may change during the course of embryonic development, thus requiring consideration of gestational day of infection. Despite the discrepant evidence of direct fetal infection, maternal influenza continues to be implicated in the abnormal behavior and neuropathology of prenatally-exposed offspring. Notably, similar behavioral outcomes were observed in offspring of dams infected with influenza virus and dams administered a pathogen-free viral mimic. These seminal findings indicate that activation of the maternal immune response, in the absence of live a pathogen, is sufficient to alter offspring behavior [13].

Pathogen-Free Inflammatory Agents

In order to delineate the contribution of maternal inflammation, pathogen-free agents have been used to elicit viral-like and bacterial-like responses. In contrast to live infectious agents, pathogen-free viral and bacterial mimics induce non-specific acute phase immune reactions that can be limited to a precise time course and immunogen dose [19–22]. The duration and intensity of the inflammatory response is both predictable and reproducible, typically lasting from 24 to 48 h depending on dose [23, 24]. Thus, these agents are advantageous in studies requiring precise exposure windows, including investigations of critical vulnerability periods during fetal development. Activation of the innate maternal immune response is achieved via subcutaneous, intraperitoneal, or intravenous administration while eliminating potential confounds introduced by any direct effects of a pathogen. Following administration of these agents, alterations in cytokines are detectable in the maternal circulation. Changes in cytokine message and protein in the fetus and maternal-fetal interface are complex, and may occur in the placenta, amniotic fluid, fetus, and fetal brain depending on gestational stage at exposure, dose, and sampling interval (see [25]).

The bacterial endotoxin lipopolysaccharide (LPS) is a well-characterized model of bacterial infection frequently utilized in investigations of maternal immune activation. LPS is a component of the outer membrane of gram-negative bacteria and is released when these bacteria multiply or die, and is recognized by toll-like receptors (TLR) TLR2 and TLR4 [26]. LPS administration alone is sufficient to produce an immune response similar to that of whole bacteria, including potent stimulation of pro-inflammatory cytokine expression, corticosterone elevation, fever, and sickness behavior [19, 26, 27]. Because LPS does not enter fetal tissues, it is possible to infer that effects on the fetus are indirect and due to the maternal response rather than the agent itself [22, 28, 29].

Polyriboinosinic:polyribocytidilic acid (poly I:C) is a synthetic analogue of double stranded RNA that mimics acute phase viral infection and activates the innate immune system upon systemic administration [20]. Poly I:C stimulates pro-inflammatory cytokine synthesis and release via TLR3 [30]. Like LPS, poly I:C is used to investigate the consequences of prenatal immune activation due to its induction of a transient nonspecific immune response that can be limited to a precise timepoint. Fortier et al. [20] demonstrated the transient nature of poly I:C immune activation through measures of body temperature, food intake and plasma profiles of pro-inflammatory cytokines. Fever was detected within 2 h of injection, with body temperature returning to baseline by 8 h post injection. Decreased food intake normalized by 24 h, while elevated plasma levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α peaked at 2 h and normalized by 4 h post injection. Notably, poly I:C administration also results in increased plasma corticosterone levels [31]. The above results suggest immune activation by poly I:C is limited to approximately 24 h after exposure, thus providing the opportunity to elucidate its impact at precise developmental stages.

Pro-inflammatory Cytokines

Finally, the hypothesized involvement of pro-inflammatory cytokines in the maldevelopment of prenatally-immune challenged offspring has been examined directly in models utilizing exogenous cytokine administration (see [10]). In these models, pregnant rodents receive systemic injections of specific pro-inflammatory cytokines. For example, intraperitoneal IL-6 injection results in a transient increase in maternal plasma corticosterone and ACTH (at 4 h); however acute IL-6 administration does not alter dam behavior [32]. A single maternal IL-6 exposure on GD 12.5 is sufficient to cause behavioral abnormalities of relevance to schizophrenia [impairment of prepulse inhibition (PPI) of the startle response and latent inhibition (LI) 33]. Furthermore, Smith and colleagues report that these effects are specific to IL-6, as behavior was unaltered following gestational exposure to IL-1α, TNF-α, and interferon (IFN)-γ. In addition to direct cytokine administration, cytokine-blocking antibodies have been administered together with inflammatory agents to further delineate the role of specific cytokines [33]. These studies have revealed the critical role of IL-6 in the adverse effects of prenatal immune activation.

Summary of Preclinical Models

These and other approaches have demonstrated that prenatal exposure to maternal immune activation does indeed cause alterations in pre- and postnatal development, neurochemistry, and behavior. In addition to the models described above, other approaches include neonatal immunogen treatment in rodents, direct fetal immunogen administration, and use of alternative species (see [25]). Models vary by route of immunogen administration, use of anesthesia, frequency of administration (acute, subchronic, chronic), and gestational timing of exposure. Notably, consideration of the differences between human and rodent fetal development is essential when interpreting vulnerability at precise gestational stages. According to a mathematical model developed by Clancy et al. [34], mouse gestational days (GD) 1–15 (rat GDs 1–17) roughly correspond to the first trimester in humans. The human second trimester is estimated to occur from GD 16 in mouse (GD 18 in rat) and into postnatal development. Thus brain development in the human late second and third trimesters is occurring postnatally in rodents.

Behavioral Consequences of Prenatal Immune Activation

Rodent models of maternal immune activation share a similar etiological mechanism with as many as one-third of schizophrenia cases [9], thereby providing etiological validity to this animal model. There has been considerable interest in determining the extent to which offspring exhibit behaviors similar to characteristics of the human disease. Assessing the relevance of rodent phenotypes to schizophrenia and other neuropsychiatric disorders presents unique challenges, as these

disorders lack definitive biomarkers and remain behaviorally defined. Additionally, it is unlikely that all aspects of these complex disorders can be reproduced in a single animal model. Despite these limitations, many well-characterized rodent behavioral assays are available to evaluate the relevance of these models to positive, cognitive, and negative symptoms of schizophrenia [11, 35, 36]. These assays are based on parallels between rodent behavior and deficits in patients, or behaviors that are mediated by neurocircuitry implicated in schizophrenia [35].

Relevance to Positive Symptoms

Positive symptoms of schizophrenia including hallucinations, delusions, and disorganized behavior are thought to result from elevated mesolimbic dopamine function [37, 38]. Sensitivity to psychotomimetic drugs, including dopamine receptor agonists and NMDA receptor antagonists, has been assessed frequently in offspring exposed to maternal immune activation based on the observation that these drugs (1) cause psychosis in healthy individuals [39–41], and (2) exacerbate psychotic symptoms in schizophrenia patients [42]. Rodents respond behaviorally to systemically administered psychotomimetic agents such as amphetamine and MK-801 with increased locomotor activity and/or stereotyped movements [43, 44]. Potentiation of the locomotor-stimulating effects of psychotomimetics in rodents is thought to reflect neurochemical changes similar to the pathology in schizophrenia. In addition to their impact on locomotor activity, psychotomimetic drugs have measurable effects on other rodent behavioral paradigms of relevance to schizophrenia. Elevated behavioral responses to the effects of these agents are therefore interpreted as relevant to psychosis susceptibility [35].

The locomotor response to the indirect dopamine receptor agonist, amphetamine, is mediated by mesoaccumbens dopaminergic projections [45], circuitry believed to underlie psychotic symptoms [37, 38]. In general, rat and mouse models of maternal immune activation have demonstrated heightened locomotor sensitivity of adult offspring to low doses of systemic psychostimulants, including amphetamine and methamphetamine (see [25, 46]). Although elevated amphetamine sensitivity in adult offspring occurs independently of the gestational timing of immune challenge [47], the response of peripubertal offspring appears to be dependent on gestational stage at exposure [48]. Prenatal poly I:C challenge during middle – late gestation (GD 12–17) resulted in increased psychostimulant sensitivity in adult offspring, but the response was unaltered in peripubertal rats (PD 40, amphetamine) and mice (PD 35, methamphetamine) [49, 50]. In contrast, modestly elevated amphetamine sensitivity has been reported in peripubertal offspring exposed to poly I:C earlier in gestation; however, other dopaminergic abnormalities were dependent on postnatal maturational stage as discussed in detail below [48, 51]. Together, these findings indicate that adult offspring prenatally exposed to maternal immune activation exhibit heightened behavioral responses to psychostimulants. Such findings are consistent with the enhanced sensitivity observed in patients with schizophrenia. Additionally, the apparent post-pubertal onset of these abnormalities parallels the

illness course of schizophrenia, as psychotic symptoms in patients emerge following maturational delay [2].

Fewer studies have investigated the sensitivity of prenatally immune-challenged offspring to NMDA receptor antagonists such as MK-801, ketamine, and phencyclidine (PCP). These drugs elicit a behavioral response in humans resembling both the positive and negative symptoms of illness [40, 41]. Similar to that of amphetamine, low-dose NMDA receptor antagonists stimulate locomotor activity in rodents [43]. The locomotor-enhancing effects have been attributed to mesoaccumbens dopaminergic hyperactivity based on the ability of these agents to activate dopamine neurotransmission; however, the involvement of dopamine in the locomotor-stimulating effects of NMDA receptor antagonism is unclear [52, 53].

Behavioral studies report elevated locomotor response to MK-801 in adult rats [54] and adult mice [47, 51, 55] following prenatal immune activation. These findings have been attributed to a hyper-response dopamine system in adult offspring. In contrast, the locomotor response to MK-801 was not affected by prenatal immune activation in periadolescent mice [51], or adult mice following early/mid-gestational (GD 9) poly I:C exposure [47]. Together these data suggest that, in contrast to amphetamine, sensitivity to the locomotor-activating effects of MK-801 is dependent on *both* the gestational stage of prenatal exposure as well as the age of offspring at testing. Of interest, our laboratory recently identified attenuated MK-801 sensitivity in pubertal rats (PD 56) following late gestation poly I:C (GD 14; Bronson, unpublished observations). We hypothesize that the neurochemical mechanism(s) underlying this finding may be related to hypofunction of the NMDA receptor. This hypothesis is further supported by in vivo microdialysis data demonstrating attenuated MK-801 stimulated prefrontal cortical extracellular glutamate in these offspring [56]. These data suggest a developmentally early glutamatergic dysfunction in prenatally immune-challenged offspring precedes the post-pubertal emergence of amphetamine sensitivity described above. Such findings are highly relevant to the NMDA receptor hypofunction model of schizophrenia pathogenesis [40, 41, 57], and therefore could link a known schizophrenia risk factor, prenatal immune activation, with alterations in NMDA receptor function. Future studies may investigate the degree to which altered behavioral responses to NMDA receptor antagonism are mediated by cortical glutamate or subcortical dopamine neurotransmission.

Relevance to Cognitive Symptoms

Cognitive deficits are core features of schizophrenia and are highly predictive of functional outcome of patients [58, 59]. Impairments have been identified in multiple aspects of cognition, including working memory, attention/vigilance, learning and memory, problem solving, and speed of processing [60]. Despite the enormous clinical significance of these deficits, there is currently a lack of effective interventions to address cognitive symptoms of schizophrenia [61, 62]. Development

of preclinical models with predictive validity is essential for investigating the efficacy of novel therapeutic interventions. Investigations of cognition in prenatally immune-challenged offspring have been limited to those cognitive domains that are readily testable in rodents. Table 12.1 provides an overview of cognitive assays utilized in models of prenatal immune activation. These and additional rodent behavior paradigms of relevance to cognitive impairments in schizophrenia have been reviewed extensively [36, 63].

Attention/Vigilance. Of these behavioral assays, prepulse inhibition (PPI) of the acoustic startle response has been utilized frequently to examine a behavioral deficit of relevance to schizophrenia in rodent offspring exposed to maternal immune challenge. PPI, defined as the reduction of the startle reflex when it is preceded by a weak stimulus or prepulse, is an operational measure of sensorimotor gating that can be tested in both humans and animals [64, 73, 74]. Patients with schizophrenia, schizophrenia spectrum disorders, and their first-degree unaffected relatives exhibit impaired prepulse inhibition of the startle response [74–77]. An overwhelming majority of studies investigating the consequences of prenatal immune activation have reported reductions in PPI in adult offspring, including rats and mice prenatally exposed to influenza virus, LPS, poly I:C, and IL-6 at varying gestational stages (see [25]). Additionally, PPI deficits appear to emerge following a maturational delay [49, 78]. These impairments may be dependent on gestational stage at exposure, as a recent study identified reduced PPI in adult mice exposed to maternal poly I:C on GD 9 but not GD 17 [47]. These data suggest that there may be differences in vulnerability of the neural circuitry underlying PPI during different stages of gestation in mice, and provide an opportunity to identify mechanisms.

Table 12.1 Summary of rodent behavioral tasks used to assess cognitive function after prenatal immune activation

Cognitive domain	Behavioral paradigm	Measured construct	References
Attention/vigilance	Prepulse inhibition	Sensorimotor gating	[64]
	Latent inhibition	Pre-attention	[65]
Learning & memory	Novel object recognition	Recognition memory	[66]
	Morris water maze (MWM)	Spatial reference memory	[67]
	Radial arm maze (RAM)	Spatial reference memory	[68]
Working memory	Radial arm maze (RAM)	Spatial working memory	[68]
	Morris water maze (MWM): Match-to-sample task	Spatial working memory	[69]
Reasoning/problem solving	Attentional set-shifting task	Discrimination, reversal, intra- & extra-dimensional shifting	[70, 71]
	Reversal learning trials in MWM, RAM, Y-Maze, T-Maze	Rule reversal	[63, 72]

Based on the preponderance of PPI deficits across multiple models, it is clear that prenatal immune activation impairs PPI in a manner that is dependent on aspect(s) of the acute phase response rather than a specific pathogen. However, the processes and brain regions mediating PPI impairment following prenatal immune challenge by different immunogens and at different gestational stages may be diverse. As discussed in detail [79], the neural circuitry mediating PPI is complex and species dependent, thereby emphasizing the potential contribution of multiple pathogenic mechanisms. PPI deficits are not unique to schizophrenia, as they are also observed in first-degree relatives and patients with other neurological and psychiatric disorders (see [75]); however, the normalization of PPI by antipsychotic treatment following prenatal immune activation illustrates an example of the predictive validity of these models [80, 81].

Latent inhibition (LI) is another behavioral paradigm used to probe the pre-cognitive status of prenatally immune-challenged offspring. LI is the ability to ignore stimuli that are known to be irrelevant based on past experience, and is therefore related to attention and salience [82, 83]. In other words, reduced LI results in the assignment of excess salience to stimuli, a process that has been proposed to contribute to psychosis [84]. LI, which is also directly testable in humans, is impaired in patients with schizophrenia [84]. LI has been tested less frequently in models of maternal immune activation, likely due to the complexity of the behavioral task. Despite this disadvantage, evidence suggests LI is impaired in adult offspring exposed to poly I:C and IL-6 during gestation [32, 33, 50, 85, 86]. Furthermore, these deficits emerge following a maturational delay [50, 85], and LI is also reinstated by antipsychotic treatment [50].

Learning & memory. In addition to these pre-cognitive deficits, learning and memory, specifically long-term explicit or declarative memory, is impaired in patients with schizophrenia [60, 87]. The learning and memory abilities of prenatally immune-challenged rodent offspring have been studied using a variety of rodent behavioral tests including the Morris water maze (MWM) [67], 8-arm radial maze (RAM) [68], and the novel object recognition test (NORT) [66]. As indicated in Table 12.1, these paradigms are most frequently used to measure spatial and recognition memory, respectively.

Analysis of these behaviors after prenatal immune activation have been studied in multiple laboratories, and to date alterations in learning and memory have been identified after prenatal exposure to LPS, poly I:C, and IL-6. Spatial learning in the MWM was impaired in pre-pubertal mice after LPS on GD 19 [88, 89], in adult rats after prenatal subchronic IL-6 [32], and in adult poly I:C-exposed mice and rats [47, 49]. Of interest, a similar effect was absent in adult mice following late gestation LPS (GD 17) [90]. Additionally, decreased spatial learning and retention in the RAM was identified in adult mice exposed to repeated LPS in middle – late gestation (GD 8–15) [91]. Recognition memory performance in the NORT following prenatal immune activation is inconsistent and appears to be dependent on the challenge agent (see [25]).

Working memory. Impairments in working memory are consistently observed in patients with schizophrenia [92]. Working memory function in rodents can be

measured using delayed or spontaneous alternation in the Y- or T-maze, as well as by task variants of the MWM and RAM procedures (Table 12.1). These tasks typically require rodents to rapidly acquire memory for unique events and/or stimuli, and to transiently retain this information for a given inter-trial delay (seconds to hours) prior to retention testing [35]. To date, there are few reports of working memory function in prenatally immune-challenged offspring. Poly I:C exposure on GD 9 significantly impaired working memory of adult mice in a match-to-sample task variant of the MWM (see [93]), as evidenced by failure to improve escape latency between trials 1 and 2 [24]. In a subsequent study using smaller inter-trial intervals (i.e., lower demand), the working memory performance of these offspring was intact [47]. Additionally, impaired working memory performance was observed in adult mice after late gestational poly I:C exposure (GD 17) [47]. These data suggest that impairments in working memory may be more prominent in adult offspring following late gestation immune insult.

Reasoning & problem solving. Impairments in abstract reasoning, problem solving, discrimination learning, and attentional set-shifting are also frequently observed in schizophrenia. These deficits are evidenced by impaired performance on tests of executive function such as the Wisconsin Card-Sorting Test (WCST) and Wechsler Adult Intelligence Scale (WAIS)-III Block Design [36]. Set-shifting refers to the ability to suppress a previously rewarded (learned) response based on one aspect of a stimulus (such as shape) and shift responding to a previously irrelevant aspect of the same stimulus (color) [72]. In rodents, attentional set-shifting is assessed in the Attentional Set-Shifting Task (ASST) designed by Birrell and Brown [70] and modified for mice by Colacicco et al. [71] based on the WCST. To date, there are no published studies reporting ASST performance after prenatal immune challenge. Future investigations will be of great interest, as prenatally immune-challenged offspring exhibit impairments in reversal learning [94], a similar form of cognitive flexibility involving only intra-dimensional rule shifting [72]. These reversal learning impairments are consistent with impaired reversal learning in patients [95, 96], and suggest cognitive flexibility is altered by prenatal immune challenge.

Processing speed. Lastly, reductions in processing speed are observed in schizophrenia. This aspect of cognition is assessed in patients by pencil and paper tasks including Trails A and the Symbol-coding subtest of WAIS-III. These tests measure speed at which target stimuli can be located and digit/symbol pairings made [36]. Rodent behavioral tests of processing speed are available (see [36]); however, the impact of prenatal immune activation on processing speed has not been previously reported.

Summary of Behavioral Consequences

Taken together, the data described above demonstrate that prenatal immune challenge produces changes in behavior and cognition of relevance to schizophrenia. Prenatal immune activation in rodents causes behaviors of relevance to positive symptoms of psychosis that emerge following a maturational delay. Furthermore,

multiple domains of cognition impaired in schizophrenia are also altered in offspring exposed to maternal immune activation, including attention, learning and memory, working memory, and cognitive flexibility. In addition, although not discussed here, prenatal immune activation causes deficits in social interaction [33], thereby also reproducing some negative schizophrenia symptoms.

Neurochemical Consequences of Prenatal Immune Activation

Dopamine

Dopamine neurotransmission, specifically an imbalance of mesolimbic and mesocortical activity, has long been implicated in the pathophysiology of schizophrenia [38, 97]. While mesolimbic hyperactivity is thought to underlie psychosis, hypoactivity of mesocortical projections may be involved in cognitive and negative symptoms. Although recent hypotheses propose substantial involvement of additional neurotransmitter systems, dopamine dysregulation is generally believed to be a "final common pathway" of symptoms of schizophrenia [38]. It is thus not surprising that much attention has been devoted to investigating the consequences of prenatal immune activation on dopaminergic development, neurochemistry, and dopamine-mediated behavior. As discussed above, psychostimulant-induced locomotor activity is altered in prenatally immune-challenged offspring; however, the response to these agents is an indirect indicator of dopaminergic function. Alterations in the locomotor-activating effects of psychostimulants may result from numerous changes in the mesolimbic system, including altered (1) expression and/or function of dopamine receptors; (2) dopamine synthesis; (3) dopamine neuron cell number; (4) dopamine release and reuptake; and (5) dopamine metabolism. Additionally, these changes may be primary or compensatory in nature. Further molecular and neurochemical characterization of offspring has provided extensive evidence that prenatal immune activation disrupts dopaminergic development and function.

Prenatally immune-challenged offspring exhibit a complex pattern of dopaminergic disruption that is highly dependent on the challenge agent, dose, brain region, and developmental stage. Abnormalities have been reported in numbers of dopamine cells, density of dopaminergic innervation, tissue and extracellular dopamine levels, as well as expression of dopamine receptors and the dopamine transporter (See [25, 98]). Notably, evidence from recent longitudinal investigations suggests dopaminergic maldevelopment in poly I:C- and LPS-exposed offspring begins as early as the fetal stage and continues throughout adulthood; however, the direction and magnitude of the observed abnormalities differ between fetal, peripubertal, and adult stages [48, 78]. Furthermore, dopaminergic function is generally increased in adulthood in the poly I:C model, whereas LPS-exposed adult offspring exhibit some indicators of decreased function as well (see [25]).

For example, increased basal dopamine levels have been detected in the nucleus accumbens of adult offspring following chronic LPS exposure during gestation

[78, 80]. In contrast, following identical prenatal LPS exposure, dopamine levels were actually *decreased* in peripubertal offspring (PD 39) and unchanged in juveniles (PD 21) and young adults (PD 70) [78]. Parallel increases in immunoreactivity for tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine synthesis and a marker for dopamine neurons, have been reported in adult offspring [80]. Of interest, in some models of acute and subchronic LPS administration, reductions in TH immunoreactivity and dopamine concentration have been reported in adult offspring [99–101]. Gestational timing of immune challenge and postnatal age at testing also significantly influence dopaminergic development after prenatal poly I:C. Acute treatment with poly I:C in early/middle gestation (GD 9) increases TH immunoreactivity in the nucleus accumbens of adult offspring, while TH expression is reduced in peripubertal offspring [48]. In addition, acute poly I:C administration leads to age-dependent changes in dopamine D1, D2, and transporter expression [48]. These molecular alterations typically correspond with abnormalities in dopamine-mediated behavior [48, 78].

Although the impact of prenatal immune challenge on the dopaminergic system is complex, it is clear that maternal immune activation results in dopamine maldevelopment. Furthermore, these adverse effects are mediated by the maternal inflammatory response. The specific component(s) of the acute phase response underlying this altered development, however, have yet to be determined. These data suggest the potential that compensatory mechanisms may underlie the transition from dopaminergic hypofunction in young offspring to hyperfunction in adulthood.

Glutamate

Considerable attention has been devoted to glutamatergic and GABAergic pathophysiology in schizophrenia. The glutamate hypothesis of schizophrenia is based in part on the observed effects of glutamate receptor antagonists in both human and animal studies. According to the hypothesis, hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor subtype, underlies the psychotic, cognitive, and negative symptoms of schizophrenia. The hypothesis is supported by evidence that acute NMDA receptor antagonism by drugs such as PCP and ketamine elicit both psychotic and cognitive characteristics of schizophrenia in healthy individuals, and exacerbate these symptoms in patients [40]. The NMDA hypofunction schizophrenia model posits that lessened NMDA-subtype glutamate receptor activity in schizophrenia results in decreased stimulation of GABAergic inhibitory neurons in the cortex and hippocampus. The loss of GABAergic activity thereby releases glutamatergic efferent neurons from inhibition, resulting in elevated glutamate release [Fig. 12.1 below 40, 41, 57]. Ultimately, elevated glutamate release may result in dysregulation of dopamine neurotransmission [57]. Thus, the glutamate hypothesis provides a unified explanation for the observed pathophysiologies in the GABA, glutamate, and dopamine neurotransmitter systems.

As discussed earlier, the locomotor-activating effects of NMDA receptor antagonists are altered in some models of maternal immune activation, depending on

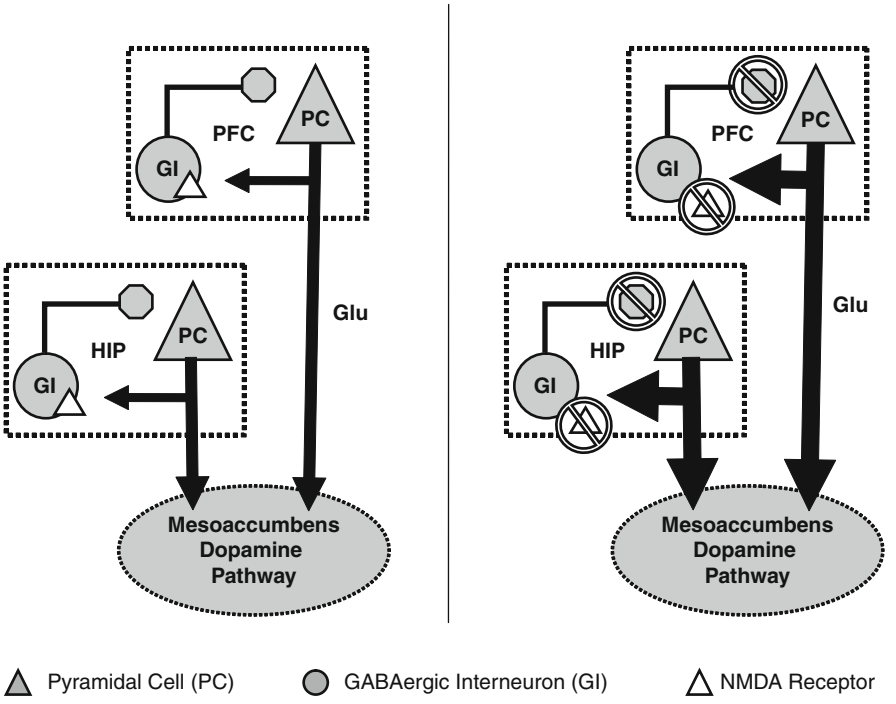

Fig. 12.1 Simplified circuit for NMDA receptor hypofunction. *Left*, normal: NMDA receptor stimulation of GABAergic inhibitory neurons provides negative feedback to glutamatergic pyramidal neurons in hippocampus and prefrontal cortex. *Right*, NMDA hypofunction: Decreased NMDA receptor function results in deficient GABAergic inhibition of glutamatergic pyramidal neurons. Elevated glutamatergic output from pyramidal neurons increases local glutamate release in hippocampus and cortex, and elevates outflow to mesoaccumbens dopaminergic system. Glu = glutamte; HIP = hippocampus; PFC = prefrontal cortex

immunogen, gestational stage at exposure, and postnatal age. Notably, in contrast to previous reports, behavioral data from our laboratory suggest hypofunction of the NMDA receptor in adolescent offspring. One possible underlying mechanism is a change in the function and/or expression of the NMDA receptor. Assays of NMDA receptor expression following prenatal immune activation have produced variable results. These investigations have been limited to quantification of message and/or protein expression of the obligatory NMDA receptor subunit NR1. Although NR1 immunoreactivity was decreased in the dorsal hippocampus of adult mice following late gestation (GD 17) prenatal immune activation, a similar effect was absent following early/middle gestation (GD 9) prenatal immune activation [47]. Additionally, maternal IL-6 treatment during pregnancy increased adult hippocampal NR1 subunit mRNA expression [32]. To date, expression of other NMDA receptor subunits modulating receptor activity have not been reported following prenatal immune activation.

Few studies have determined prenatal immune activation effects on glutamate levels. Basal extracellular glutamate is elevated in the hippocampus following *neonatal* immune activation, as measured by microdialysis in awake adult offspring [102]. Consistent with this finding, a recent microdialaysis study conducted by our research group identified elevated basal prefrontal cortical extracellular glutamate together with a blunted glutamate response to MK-801 following late gestation (GD 14) prenatal immune activation [56]. Notably, the blunted glutamate response to MK-801 paralleled our observation of attenuated locomotor response to MK-801 in these offspring (Bronson, unpublished observations). In contrast, basal tissue glutamate levels assayed in homogenized cerebellum [16] or dissected brain regions [103] were not altered by prenatal immune activation. These data suggest additional microdialysis studies to directly measure extracellular glutamate following prenatal immune challenge may allow clarification of the effects of prenatal immune activation upon glutamatergic systems in brain regions of interest.

GABA

Converging clinical and pre-clinical evidence has implicated GABAergic interneurons in schizophrenia pathophysiology [104]. Analyses of mRNA and protein expression in postmortem brains of patients with schizophrenia consistently reveal abnormalities in a subset of interneurons that express the calcium-binding protein parvalbumin. Specifically, the number of cells expressing the 67 kDa isoform of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD67) is reduced in the prefrontal cortex and hippocampi of patients relative to controls [105–108]. The GAD67 isoform is responsible for greater than 90% of GABA synthesis, and is the predominant GAD isoform in these cells [109, 110]. The reduction in GAD67 immunoreactive cells suggests a functional deficit in GABA synthesis, and ultimately impulse-dependent release. Correspondingly, post-synaptic GABA receptors are upregulated in the same brain regions, suggesting a compensatory mechanism [111]. GABAergic deficiencies, specifically those occurring in the prefrontal cortex, have been widely replicated. In addition, impairments in cognition are likely to arise from these deficiencies [104].

Similar GABAergic deficiencies occur in prenatally immune-challenged offspring; however, to our knowledge, alterations in GAD67 expression have not been reported to date. As summarized in Fig. 12.2, gestational immune challenge produces changes in GABAergic cell-type markers including reelin and parvalbumin. Numbers of cells immunoreactive for these markers are decreased in the prefrontal cortex and hippocampi of mice exposed to poly I:C in early gestation (GD 9) [47, 94], late gestation (GD 17) [47], to influenza [12]. In addition, early gestation poly I:C exposure (GD 9) upregulates expression of the $GABA_A$ α2 subunit of the $GABA_A$ receptor, specifically on the axon initial segments (AIS) of pyramdial cells in the hippocampus [112]. Notably, $GABA_A$ α2 upregulation is consistently

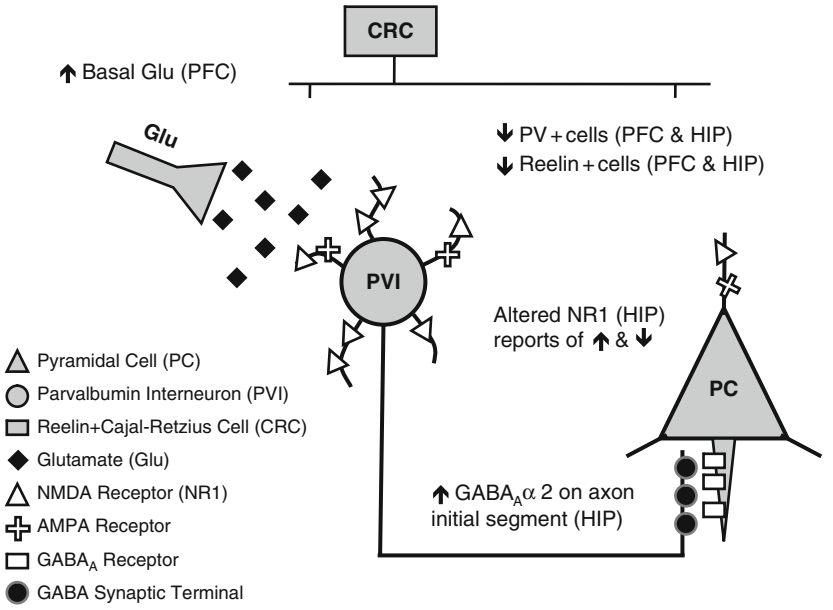

Fig. 12.2 Schematic summary of alterations in glutamate and GABA circuits following prenatal immune activation. Prenatal exposure to maternal immune activation leads to alterations in glutamatergic and GABAergic systems that are similar to those observed in schizophrenia. Reduced numbers of parvalbumin immunoreactive interneurons (PVI) and Reelin immunoreactive Cajal-Retzius cells (CRC) have been identified in the prefrontal cortex (PFC) and hippocampus (HIP) of prenatally immune-challenged offspring. These cells types regulate, in part, the activity of pyramidal cells (PC). Elevated basal prefrontal cortical glutamate (Glu) and alterations in the NMDA receptor obligatory subunit NR1 are also observed. The significant increase in expression of the α2 subunit of the GABAA receptor, specifically on the axon initial segment of pyramidal cells, is consistent with findings in patients

observed in post-mortem tissue; and changes in parvalbumin interneuron – pyramidal cell circuits, including at the AIS, are hypothesized to underlie schizophrenia symptoms (see [104]).

Overall Impact on Neurotransmitter Systems

Converging behavioral and molecular evidence suggests that prenatal exposure to maternal immune activation alters neurotransmitter system development. Of particular interest, abnormalities in dopaminergic, glutamatergic, and GABAergic systems may be similar to those observed in patients with schizophrenia. These changes are observed as early as the fetal stage and continue throughout adulthood. Notably, the degree and direction of the observed neurochemical alterations are frequently dependent on gestational timing of exposure and postnatal age examined.

Conclusions & Future Directions

The information described above suggests three areas where future studies using the prenatal immune activation model may be of particular benefit in developing new approaches to schizophrenia treatment: gene x environment interactions; identification of novel pharmacological targets for prevention; and development of therapeutic interventions targeting specific stages of illness.

Schizophrenia is believed to result from an interaction between genetic vulnerability and environmental factors. As has been reviewed elsewhere [9], lack of information regarding environmental exposure compromises the likelihood of identifying contributing genetic loci for disorders such as schizophrenia in which gene-environment interactions provide a significant contribution to disease etiology and development. Prenatal immune activation studies could help to overcome this obstacle in two ways. First, animal studies may identify translational biomarkers related to prenatal immune activation which might be defined in both human and animal subjects. Thus, biomarkers such as neuroimaging abnormalities, cytokine markers, and early cognitive deficits could, in combination, provide clearer identification of elevated environmental risk for schizophrenia to be utilized for human studies. Second, quantitative trait-loci mapping studies using genetically inbred mouse strains may help to elucidate genetic loci interacting with prenatal immune activation to influence behavioral abnormalities. In combination, these approaches may serve to develop new hypotheses for schizophrenia risk which could then be tested in human populations.

Second, prenatal immune activation may provide a useful model for identification of novel pharmacological targets for prevention of schizophrenia symptoms. Studies using animal models allow for the screening of more diverse compounds than is feasible in human subjects. Additionally, medication compliance in long-term studies of adolescents and young adults at high risk for schizophrenia is typically poor, a confounding variable which increases the likelihood of failing to detect beneficial effects of preventive treatment. Third, rather than preventing the development of psychotic symptoms, treatment interventions may merely delay the appearance of abnormal behavior. Adequately addressing this question requires following a large number of subjects over an extended length of time, a study design which is exceedingly difficult to accomplish in an adolescent or young adult human sample, but can be directly studied in animals. Studies using prenatal immune activation animal models may thereby circumvent each of these obstacles impeding the development of preventive interventions for first-episode psychosis and other symptoms of schizophrenia.

A third area of future studies for prenatal immune activation involves development of therapeutic interventions targeting specific stages of illness. Current pharmacological treatments for schizophrenia rely on medications developed for tertiary prevention, targeting psychotic symptoms of the illness after they have already become manifest. In contrast, current theories of schizophrenia pathophysiology suggest schizophrenia is a developmental disorder with abnormalities in cellular programming and connectivity, as well as social and cognitive deficits, which

precede onset of psychotic symptoms [2]. At the cellular level, dysfunction of specific subsets of GABAergic interneurons [113, 114], and lessened NMDA-subtype glutamate receptor activity [40, 41, 57] may precede sensitization of dopaminergic systems [115]. In combination, these observations suggest that future studies utilizing the prenatal immune activation model could determine whether interventions targeting GABAergic and glutamatergic systems early in development might prevent dysfunction of dopaminergic systems in later stages of development. These studies could thereby inform new intervention strategies which might address unmet needs of schizophrenia patients by improving treatment outcomes for psychotic symptoms as well as cognitive dysfunction and drug dependence problems.

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Chapter 13
Glutamatergic Neurotransmission Abnormalities and Schizophrenia

Yogesh Dwivedi and Ghanshyam N. Pandey

Abstract Schizophrenia affects approximately 1% of the adult population worldwide and requires lifelong therapy. Hyperfunction of the dopaminergic system has long been hypothesized as the underlying cause of schizophrenia. However, this hypothesis explains mostly the positive symptoms associated with schizophrenia. Several lines of evidence point to the glutamatergic system and suggest that abnormalities in this system may play a crucial role in the pathophysiological features of schizophrenia. Most prominently, *N*-methyl-D-aspartate receptor hypofunction has been associated with the positive, negative, and cognitive symptoms of schizophrenia. In this chapter, we describe the evidence showing that *N*-methyl-D-aspartate receptor hypofunction may be crucial in the pathophysiological features of this disorder. Although a plethora of evidence is available from preclinical studies, this chapter is focused mainly on the findings from patients with schizophrenia. In addition to *N*-methyl-D-aspartate receptors, we also describe the findings of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate/kainate receptors and glutamate transporters in patients with schizophrenia. Overall, these findings suggest that therapeutic agents directed toward glutamatergic systems may be helpful in the treatment of positive and negative symptoms and cognitive deficits associated with schizophrenia.

Keywords Schizophrenia · NMDA receptors · Kainate receptors · AMPA receptors · Glutamate · Glutamate transporter

Abbreviations

NMDA	*N*-methyl-D-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
PCP	Phenylcyclidine
GluR	Glutamate receptor
PSD	Postsynaptic density

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MRS	Magnetic resonance spectroscopy
NAAAG	N-acetyl-L-aspartyl-L-glutamate
mGluR	Metabotropic glutamate receptor
GlyT	Glycine transporter
GLAT	Glutamate transporter

Introduction

Schizophrenia affects approximately 1% of the adult population worldwide [1]. With the onset in early adulthood, schizophrenia is a severe psychotic disorder and is one of the leading causes of long-term disability. Schizophrenia is characterized by positive symptoms (e.g., hallucinations, delusions, and paranoia), negative symptoms (e.g., anhedonia, impaired attention, and social withdrawal), and cognitive symptoms [2]. Despite many years of research, the pathogenic mechanisms of schizophrenia are still unknown. The most widely accepted theory suggests that dopamine hyperfunction is the primary cause of some of the schizophrenia symptoms. In fact, chlorpromazine was the first drug introduced that alleviated some symptoms of schizophrenia. In 1963, Carlson and Lindquist [3] suggested that functional dopamine receptor blockade was necessary for the action of phenothiazine and butyrophenone. Later, it was found that blockade of dopamine D2 was the essential feature of all antipsychotic drugs [4–6]. This paved the way to introducing the dopaminergic hypothesis of schizophrenia, which is still the most acceptable theory in schizophrenia pathogenesis [7]. Even the recently developed second-generation antipsychotic agents target the dopamine D2 receptors [8].

Despite the fact that antipsychotic agents act at the level of dopamine D2 receptors and that hyperfunctionality of the dopaminergic system may be involved in schizophrenia, many lines of evidence indicate that this theory does not explain all of the aspects of schizophrenia. The most prominent finding is that many patients with schizophrenia do not respond to antipsychotic drugs and, more important, most antipsychotic drugs are partially effective in negative cognitive impairment associated with schizophrenia. In some cases, antipsychotic drugs are ineffective in the treatment of negative symptoms of schizophrenia; also, there are core negative symptoms that never respond to antipsychotic drugs [9, 10]. Moreover, there are inconsistencies in the report showing altered levels of dopamine or dopamine receptors in the postmortem brain of patients with schizophrenia [11]. It has since been proposed that the hyperfunctionality of the dopaminergic system may be secondary to primary changes in other neurotransmitter systems [12]. A primary dysfunction of glutamatergic neurotransmission may affect the dopaminergic system at the downstream level, which could account for explaining the positive, negative, and cognitive symptoms in schizophrenic patients.

The fact that *N*-methyl-D-aspartate (NMDA) glutamate receptor (GluR) antagonists, such as ketamine and phenylcyclidine (PCP) reproduce the full range of positive and negative symptoms of schizophrenia prompted examining the role of

the glutamatergic system in the pathophysiological features of this disorder [13–16]. There is strong evidence that hypofunctional NMDA receptor (NMDAR) function may contribute to schizophrenia symptoms. In this chapter, we will focus on the evidence demonstrating the role of the glutamatergic system in the pathophysiological features of schizophrenia.

Glutamatergic Neurotransmission

Glutamate is the major excitatory neurotransmitter in the brain, which is involved in many physiological functions, including cognition, memory, and perception [17]. Glutamate is synthesized in the brain from glutamine, which is transported across the blood-brain barrier with a high affinity and present at high concentrations in extracellular brain fluids and cerebrospinal fluid. After release, glutamate is reabsorbed by both neuronal and glial glutamate transporters (reviewed in Javitt [18]). These transporters release glutamate into the synaptic cleft [19, 20]. Once released, glutamate exerts its effects via GluRs located on the presynaptic and postsynaptic neurons and on astrocytes [21]. Based on molecular cloning, electrophysiological properties, and pharmacological antagonism, glutamate receptors are divided into two major families: ionotropic (gated cation channels) and metabotropic (G protein – coupled channels). Based on their selective antagonists, the ionotropic GluRs are further divided into three major groups: *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainate receptors. These ionotropic receptors cause the opening of cation channels permeable to Na^+ to Ca^{2+}, thereby depolarizing the neurons. In addition to the recognition site for glutamate, NMDARs also contain glycine and D-serine binding sites that act as allosteric modulators in the presence of the glutamate agonist. The binding of these amino acids is controlled by amino acid transporters that are colocalized with NMDARs. In addition to glycine, NMDARs bind to Mg^{2+} and PCP. At resting membrane potential, the NMDARs are blocked by. On depolarization via activation of AMPA/kainate receptors, Mg^{2+} block is removed, resulting in an opening of the NMDA channel. Once open, the NMDAR ion channel is permeable to Ca^{2+}, which acts as a second messenger, inducing gene expression and recruiting AMPA receptors that contribute to long-term potentiation (reviewed in [22]). Thus, the NMDAR is both ligand gated and voltage dependent in function. Phenylcyclidine, dizocilpine (MK-801) and ketamine are noncompetitive antagonists that can block the NMDA channel and prevent long-term potentiation and learning [23]. The NMDARs are crucial for synaptic plasticity because Ca^{2+} signaling is conducive to neuronal plasticity and, if present in an excessive amount, can cause excitotoxicity [24], leading to oxidative stress and neuronal death. Molecular cloning experiments have revealed that the NMDAR family is composed of two subunits (NR1 and NR2) and an additional inhibitory subunit (NR3) [25–28]. There are four subunits of NR2 (NR2A, NR2B, NR2C, and NR2D) and two subunits of NR3 (NR3A and NR3B). Both the NR1 and NR2 subunits are required for the formation of a functionally active receptor-channel complex; however, the molecular and functional diversities arise in

the formation of heterodimers with selective splicing of the NR1 subunit and differential expression of the NR2 subunits. In contrast to the NMDA channel containing NR1 and NR2 (activated by both glycine and D-serine), NR3-containing NDMA channels are activated by glycine but are inhibited by D-serine [29].

The AMPA receptors are another class of inotropic receptors, which form a tetramer with four different subunits: GluR1, GluR2, GluR3, and GluR4 [30]. Each AMPA receptor has four glutamate binding sites, each on one subunit. The kainate receptors are also tetramers and may contain GluR5, GluR6, GluR7, KA1, and KA2 [17, 31]. Glutamate receptor GluR5, GluR6, and GluR7 can form homomers or heteromers, whereas KA1 and KA2 form heteromers in combination with GluR5, GluR6, or GluR7. The AMPA receptors are critical for unblocking NMDARs receptors and allowing Ca^{2+} entry. This, in turn, causes insertion of AMPA into the postsynaptic density (PSD). Thus, both AMPA and NMDARs are important for glutamatergic neurotransmission.

Astrocytes play a crucial role in glutamatergic neurotransmission. In addition to neurons, astrocytes are the major source of glutamine, a precursor for glutamate [32]. Also, astrocytes play a key role in regulating NMDAR functions. This occurs through glutamate transporters (EAAT1 and EAAT2) and a glycine transporter (GlyT-1), which are expressed in astrocytes [33, 34]. These transporters maintain the availability of glutamate and glycine in the synapse. The EAAT transporter inactivates synaptic glutamate, thus protecting excitotoxicity. The astrocytes also express glutamate carboxypeptidase II, which degrades *N*-acetyl-L-aspartyl-L-glutamate (NAAG) into NAA and glutamate [35]. Glutamate release is downregulated by presynaptic metabotropic GluR (mGluR) 3 via *N*-acetyl-L-aspartyl-L-glutamate [36].

Based on the primary structure, signaling mechanisms, and pharmacological profile, metabotropic glutamate receptors are classified into three groups: group I, II, and III. Group I contains mGluR1 and mGluR5; group II, mGluR2 and mGluR3; and group III, mGluR4, mGluR6, mGluR7, and mGluR8. Group I GluRs are coupled with G protein Gq/11 subunit and phospholipase C activation, and group II mGluRs are coupled with adenylyl cyclase cyclic adenosine monophosphate signaling in a negative fashion. Some of the mGluRs are coupled with G protein $\beta\gamma$ subunits and modulate ion channel activities. Group I mGluRs are typically expressed postsynaptically in the somatodendritic domain, whereas group II and II mGluRs are mostly presynaptic, regulating the release of neurotransmitters [37, 38].

Glutamate Neurotransmission and Schizophrenia

During the past several years, several lines of evidence have suggested that aberrant glutamatergic neurotransmission, particularly at the level of the NMDAR subtype, may play a critical role in the etiological and pathophysiological features of schizophrenia. These lines of evidence are based on studies using NMDAR

antagonists, brain imaging studies, human postmortem brain studies, and genetic studies. Schizophrenia is associated with a loss of NMDARs, particularly on the interneurons [15]. This loss of inhibition leads to secondary overstimulation in glutamatergic neurotransmission. The NMDAR hypofunction also leads to excessive release of glutamate in the cortical regions [16], which causes overstimulation of downstream excitatory neurons and further disinhibition through a lack of NMDAR excitation on interneurons. The net effect is a loss in overall network inhibition [39]. This complex disinhibitory syndrome leads to hyperstimulation in the primary corticolimbic network. These events are thought to contribute to the psychotic, cognitive, and perceptual disturbances of schizophrenia [40]. Based on the NMDAR hypofunction hypothesis of schizophrenia, compounds that enhance NMDAR function at the GABAergic interneurons are beneficial in schizophrenia symptoms. These compounds include positive modulators of NMDARs and those that can facilitate AMPA channel activity.

NMDAR Antagonist Administration

The NMDAR hypofunction hypothesis is based on the observations that administration of noncompetitive NMDAR antagonists PCP and ketamine lead to effects that mimic the positive, negative, and cognitive symptoms of schizophrenia [41]. Krystal et al. [41] showed that a subanesthetic dose of ketamine to healthy volunteers results in dose-dependent induction of both positive and negative symptoms of schizophrenia and worsening of cognitive functions relevant to prefrontal cortical activity. However, these subjects had normal Mini-Mental Status Examination results, suggesting that the effect of ketamine was not delirious and not due to an anesthetic effect but due to specific activity toward a subpopulation of sensitive NMDARs. The effect of ketamine, causing cognitive dysfunctions in healthy volunteers, was also confirmed by many investigators [42, 43]. A low dose of ketamine also induced thought disorder and caused behavioral disorganization, similar to symptoms observed in patients with schizophrenia [44, 45]; however, the positive symptoms induced by ketamine are not as severe as those observed in patients with schizophrenia after relapse. As with ketamine, PCP participates in schizophrenia-like symptoms in healthy individuals. The NMDA antagonists are known to cause a deficit in working memory [46, 47], procedural memory [47], and response inhibition [48]. Furthermore, deficits are observed in sensory processing as well. For example, ketamine administration inhibits the generation of mismatch negativity that reflects impaired information processing at the level of the auditory cortex [49]. In a similar fashion, NMDA antagonists produce a pattern of visual event – related potential deficits in rodents, similar to that observed in schizophrenia [50]. The ketamine challenge strategy also reproduces several physiological signs of schizophrenia. For example, ketamine infusion causes an impaired smooth pursuit eye movement, a physiological event that occurs in patients with schizophrenia and their first-degree relatives [43, 51, 52].

Imaging Studies and Glutamate Hypothesis of Schizophrenia

Lahti et al. [53] used a [15O] water positron emission tomographic study to examine cerebral blood flow after ketamine administration in patients with schizophrenia. They showed increased cerebral blood flow in the anterior cingulate cortex and decreased blood flow in the hippocampus and primary visual cortex. These abnormalities were associated with an exacerbation in psychotic symptoms in schizophrenic patients. These findings were further confirmed in additional studies [54, 55]. Vollenweider et al. [56], using [18]flurodeoxyglucose, showed metabolic hyperfrontality in the ketamine model of psychosis.

Disruption of facial emotion perception occurs in schizophrenic patients, in whom the expression of emotion is dulled or blunted. It has been suggested that, in the clinical context of emotional blunting, there is a shift in the relative contribution of brain regions subserving cognitive and emotional processing. The noncompetitive GluR antagonist ketamine produces such emotional blunting in healthy subjects. Abel et al. [57] tested the hypothesis that, in healthy subjects, ketamine would elicit neural responses to emotional stimuli that mimic those reported in depersonalization disorder and schizophrenia. They predicted that ketamine would produce reduced activity in limbic and visual brain regions involved in emotion processing and increased activity in dorsal regions of the prefrontal cortex and cingulate gyrus, both associated with cognitive processing and, putatively, with emotion regulation. Measuring BOLD signal change in functional magnetic resonance images, they examined the neural correlates of ketamine-induced emotional blunting in eight young right-handed healthy men receiving an infusion of ketamine or saline placebo while viewing alternating 30-s blocks of faces displaying fear vs. neutral expressions. The normal pattern of neural response occurred in the limbic and visual cortex to fearful faces during the placebo infusion. Ketamine abolished this finding: significant BOLD signal change was demonstrated only in the left visual cortex. However, with ketamine, neural responses were demonstrated to neutral expressions in the visual cortex, cerebellum, and left posterior cingulate gyrus. These studies suggest that emotional blunting may be associated with reduced limbic responses to emotional stimuli and a relative increase in the visual cortical response to neutral stimuli. In another functional magnetic resonance imaging study, Honey et al. [58] characterized the effects of ketamine on frontal and hippocampal responses to memory encoding and retrieval in healthy volunteers using a double-blind, placebo-controlled, randomized, within-subject comparison of two doses of intravenous ketamine. They also determined the interaction of ketamine with the depth of processing that occurred at encoding. Their results suggest that left frontal activation is augmented by ketamine when elaborative semantic processing is required at encoding. In addition, successful encoding of ketamine is supplemented by additional nonverbal processing that is incidental to task demands. The effects of ketamine at retrieval are consistent with impaired access to accompanying contextual features of studied items. These findings show that, even when overt behavior is unimpaired, ketamine has an impact on the recruitment of key regions in episodic memory task performance. Recently, Northoff et al. [59] conducted a functional magnetic

resonance imaging study of the effect of ketamine in healthy human subjects during episodic memory retrieval, which is supposed to activate the posterior cingulate cortex. In the placebo group, they found that the BOLD signal was increased in the posterior and anterior cingulate cortex during retrieval. Signal increases were significantly lower in the ketamine group. Lower signal increases in the posterior cingulate cortex were correlated significantly with positive symptoms induced by ketamine. These studies demonstrate a relationship between NMDARs, the posterior cingulate cortex, and positive (i.e., psychosis-like) symptoms in humans; and the hypothesis of a pathophysiological role of NMDAR hypofunction in the posterior cingulate cortex in patients with schizophrenia.

The detection of glutamine and glutamate in the brain of living subjects is possible using magnetic resonance spectroscopy. To test whether NMDAR antagonism results in increased cortical glutamate activity, Rowland et al. [60] used 4-T hydrogen proton magnetic resonance spectroscopy to acquire in vivo spectra from the bilateral anterior cingulate cortex of 10 healthy subjects while they received a subanesthetic dose of either placebo or ketamine. They found a significant increased anterior cingulate cortex glutamine level, a putative marker of glutamate neurotransmitter release, with ketamine administration. This increase was not related to schizophrenia-like positive or negative symptoms but was marginally related to Stroop test performance. This study indicates that the acute hypofunctional NMDAR state is associated with increased glutamatergic activity in the anterior cingulate cortex. An elevated glutamine level in the anterior cingulate cortex and thalamus in patients experiencing first episodic schizophrenia was reported by Theberge et al. [61, 62] Increased glutamine and glutamate levels were reported in adolescents at high genetic risk for schizophrenia compared with low-risk offspring [63].

Postmortem Brain Studies of NMD/AMPA/Kainate Receptors in Schizophrenia

(**a**) **NMDA Receptors**

To examine whether NMDARs are involved in schizophrenia, Gao et al. [64] analyzed postmortem hippocampal tissue from individuals with schizophrenia and from healthy individuals. Ionotropic receptor binding for the NMDA, kainate, and AMPA receptors was quantified by using the usual radioligand techniques. In situ hybridization autoradiography was used to quantify messenger RNA (mRNA) for the NMDAR subunits NR1, NR2A, and NR2B. Ligand binding to the ionotropic GluRs (NMDA, kainate, and AMPA) did not differ significantly overall or in any subregion between the schizophrenic tissue and the healthy comparison tissue. The only exception was AMPA receptor binding in hippocampal subregion CA2, which was slightly but significantly less in schizophrenia. However, the level of mRNA for the NMDAR subunits NR1 and NR2B was significantly different between groups; in several hippocampal subregions, the level of NR1 mRNA was lower and the level of NR2B mRNA was

higher in schizophrenia. The researchers concluded that reduction of NR1 in the hippocampus in those with schizophrenia suggests a functional impairment in glutamatergic transmission at the NMDAR, resulting in reduced glutamatergic transmission within and possibly efferent from the hippocampus in patients with schizophrenia. This defect could underlie a hypoglutamatergic state in regions of the limbic cortex. In a similar fashion, Law and Deakin [65] reported reduced NMDAR1 mRNA levels compared with healthy controls. However, they found that reduced expression of NMDAR1 was more pronounced in the left hemisphere compared with the right hemisphere. In a comprehensive examination of all of the NMDA subunits in the prefrontal cortex, Akbarian et al. [66] found no differences in any of the NMDA subunits in schizophrenic patients; however, they noted that the contribution of NMDA2D to the total pool of NMDA2 transcripts was elevated. Because the thalamus is one of the critical brain areas for cognitive functions and it has been shown to be involved in schizophrenia, a number of studies have examined this brain area for NMDAR dysfunction. For example, Ibrahim et al. [67] reported reduced mRNA levels of NR1, NR2B, and NR2C in the thalamic nuclei. These reductions were associated with reduced [^{3}H]ifenprodil and [^{3}H]MDL105,519 binding to polyamine and glycine sites of the NMDAR. These changes were most prominent in nuclei with reciprocal projections to limbic regions. In a further study using in situ hybridization, Clinton et al. [68] examined the expression of the transcripts encoding NR1 isoforms containing exons 5, 21, or 22; and the NMDAR-related PSD proteins neurofilament-L, PSD93, PSD95, and SAP102. They found that reduced NR1 subunit transcript expression was restricted to exon 22 – containing isoforms. They also found increased expression of the NMDAR-associated PSD proteins NF-L, PSD95, and SAP102 in the thalamus of patients with schizophrenia. However, subsequent studies failed to show such changes in NR1 and NR2C subunits in schizophrenic patients [69–71]. In elderly patients with schizophrenia, increased protein expression levels of the NR2B receptor subunit and PSD95 in the dorsomedial thalamus have been reported [71].

A number of studies have attempted to examine PCP binding sites in brain specimens from patients with schizophrenia. By using [^{3}H]MK-801, Kornhuber et al. [72] studied the frontal cortex, hippocampus, putamen, entorhinal region, and amygdala. They found that [^{3}H]MK-801 binding levels were increased in all brain regions; however, a significant change was noted only in the putamen. In another study, Noga et al. [73], using the [^{3}H]CNQX ligand for AMPA receptors, found higher mean CNQX binding in the caudate nucleus of schizophrenic patients vs. healthy controls; the binding densities of [^{3}H]MK-801, KA, and D-aspartate were not significantly different in any of the striatal regions examined. The ion channel site has also been studied with the ligand [^{3}H]TCP. No changes in [^{3}H]TCP binding were found in various cortical areas, the putamen, or the cerebellum [74]. Another study also reported no change in the hippocampus, amygdala, or polar frontal cortex; however, [^{3}H]TCP binding was increased in the orbitofrontal cortex (Brodmann area 11) of patients with schizophrenia [75].

By using a single-photon emission tomographic radiotracer [^{123}I]CNS-1261, which binds to the PCP/MK-801 intrachannel site of the NMDAR, Bressan et al. [76] found no apparent difference in total volume of distribution of [^{123}I]CNS-1261 in drug-free patients with schizophrenia relative to healthy control subjects. A nonsignificant reduction in the total volume of distribution was observed in typical antipsychotic-treated patients. A significant decline in the total volume of distribution of [^{123}I]CNS-1261 was observed in all examined brain regions in the clozapine-treated patient group relative to healthy control subjects. These results suggest that clozapine treatment causes a global reduction in [^{123}I]CNS-1261 binding to the NMDAR intrachannel PCP/MK-801 site in vivo. By using a similar approach, Pilowsky et al. [77] found that NMDAR binding in the hippocampus relative to the whole cortex was significantly lower in drug-free schizophrenic patients compared with binding in the left hippocampus in healthy volunteers.

(**b**) **AMPA Receptors**

Because AMPA receptors play a crucial role in NMDA channel activity, expression levels of AMPA receptors have been studied in the postmortem brain of schizophrenia patients. Harrison et al. [78] found that mRNA expression of the GluR1 subunit was significantly decreased in hippocampal regions, most prominently in the CA3 region. In subsequent studies, Eastwood et al. [79] reported that expression of the GluR1 subunit was decreased in other hippocampal subfields, such as the dentate gyrus, CA3 and CA4, and the subiculum. On the other hand, they found that mRNA expression of the GluR2 subunit was decreased in the medial temporal lobe and that the GluR2 subunits are composed of more of the flip variant. In conclusion, they suggest that hippocampal AMPA receptors are impaired in schizophrenia by both an overall loss of GluR2 expression and the change in the flip to flop ratio [80]. In the cortical region, Breese et al. [81] and Healy et al. [82] did not find any significant differences in expression of any of the AMPA receptor subunits in patients with schizophrenia. On the other hand, Sokolov [83] reported decreased GluR1 mRNA in the superior frontal gyrus. Similarly, no changes were found regarding [^{3}H]AMPA binding in cortical areas in schizophrenia [84, 85].

(**c**) **Kainate Receptors**

Regarding kainate receptors, there have been some studies examining kainate receptor subunit expression and labeling of kainate receptors using [^{3}H]kainate in the postmortem brain of schizophrenia patients. Porter et al. [86] found decreased expression of GluR6 and KA2 mRNA in hippocampal brain regions. The expression of GluR6 mRNA was not altered in the cerebellar brain region. Decreased expression of KA2 subunit mRNA levels in the thalamus of schizophrenic patients has also been reported [67], without any change in the GluR5, GluR6, GluR7, or KA1 subunits [67, 69]. On the other hand, Sokolov [83] reported decreased expression of GluR7 and KA1 in the superior frontal gyrus in schizophrenic patients. At the protein level, Breese et al. [81] did not find a change in the level of GluR5 in the hippocampus of schizophrenic patients.

Kainate receptor binding has also been studied the postmortem brain of patients with schizophrenia. Although [^{3}H]kainite binding is not altered in the thalamus [67] or striatum [73], it is increased in cortical areas and decreased in the hippocampus and parahippocampal gyrus of schizophrenic patients [85, 87–89].

The primary agonist site for glutamate has also been studied, with [^{3}H]glutamate in the hippocampus. No differences have been noted in [^{3}H]glutamate-associated schizophrenia [89]. By using [^{3}H]glycine, Ishimaru et al. [90] reported increased binding in multiple cortical areas in schizophrenia. By using [^{3}H]L-689,560, Aparicio-Legarzaand et al. [91] also reported increased glycine binding sites in the putamen; however, they did not find any change in the caudate or accumbens of patients with schizophrenia.

(**d**) **Glutamate Transporter**

Recent studies suggest that transport of glutamate to synaptic vesicles may play a crucial role in schizophrenia. It is important to note that glutamate is recycled and overactivity of glutamate transporters may result in inadequate synaptic glutamate. The removal of excessive glutamate from the synapse via packing into vesicles is performed through two different types of glutamate transporters: (1) EAAT1 and EAAT2 and (2) VGLUT1 and VGLUT2. These two types of glutamate transporters differ from each other because EAATs require Na^+/K^+ ATPase as a source of energy. On the other hand, VGLUTs show much less affinity for L-glutamate and are chloride- dependent. In addition, they use hydrogen ion – dependent ATPase as a source of energy [92, 93]. Recently, Eastwood and Harrison [94] showed that vesicular mRNA expression of VGLUT1 is decreased in hippocampal formation and the dorsolateral prefrontal cortex of those with schizophrenia. These investigators concluded that, in the hippocampus, the loss of VGLUT1 mRNA supports data indicating that glutamatergic presynaptic deficits are prominent, whereas the pattern of results in the temporal and frontal cortices suggests that broadly similar changes may affect inhibitory and excitatory neurons. Interestingly, Smith et al. [95] reported an upregulation of VGLUT2 mRNA in the thalamus of schizophrenic patients. These investigators also found that the mRNA level of EAAT1 and EAAT2 is higher in the thalamus of those with schizophrenia [96]. Although the functional significance of this increase in EAATs is unclear, this could be associated with a compensatory response to decreased NR1 subunit expression in the thalamic nuclei of schizophrenic patients.

Neurodevelopmental Model of Schizophrenia and NMDAR Hypofunction

Schizophrenia has been considered a neurodevelopmental disorder [97–99], in which schizophrenia symptoms occur in the late teens or early 20 s. Several hypotheses have been proposed for this neurodevelopmental aspect of schizophrenia. One of them is based on preclinical findings that inhibition of NMDARs at the prenatal

or perinatal stage may lead to changes in the brain, which, in turn, may cause a manifestation of the schizophrenia symptoms in early adulthood. Olney et al. [100] proposed a hypothesis that "both genetic and nongenetic factors can contribute to the NMDAR hyofunction state and that this state is instilled in the brain early in life as a latent condition with the potential to erupt and trigger psychotic manifestations in adulthood but not usually in pre-adult life." They further propose that "it usually lacks the potential to produce psychotic symptoms in pre-adult life because certain maturational changes in the brain's circuitry have to occur before its pathological potential can be expressed. After these maturational changes have occurred, the NMDAR hyofunction state has the potential to trigger the full spectrum of schizophrenia-type symptoms and, in extreme cases, to cause ongoing structural pathology and clinical deterioration." In support of this hypothesis, it has been shown in rats that blockade of NMDARs by NMDAR antagonist MK-801 or PCP for only a few hours during late fetal or early neonatal life triggers apoptotic neurodegeneration in the developing rat brain. This suggests that glutamate, acting at NMDARs, controls neuronal survival [101]. This has been repeatedly shown in many other studies [102–104]. The interesting aspect is that this neurodegeneration occurs because of apoptotic mechanisms. On the other hand, NMDA antagonists administered in adulthood lead to necrosis [105]. Olney et al. [100] hypothesized that this could be due to the chain of neural connections involved in the psychotogenicity and neurotoxicity of NMDAR antagonism not being fully developed until late adolescence. In a recent study, Bubeníková-Valešová et al. [106] showed that the administration of *N*-acetyl-L-aspartyl-L-glutamate, an agonist of mGluR II and, at higher concentrations, NMDARs to 12-day-old rats causes an extensive death of neurons, particularly in the dentate gyrus of the hippocampus. This was accompanied by changes in grooming activity. These results show the neurotoxicity of *N*-acetyl-L-aspartyl-L-glutamate in the neonatal rat brain and implicate neonatally induced NMDAR-mediated neuronal loss in the development of abnormal behavior in young adult rats. Stefani and Moghaddam [104] showed that when rat pups were given the NMDA channel blocker MK-801 on postnatal days 7–10 (a period akin to the prenatal second trimester of primate development), impaired cognitive flexibility and working memory occur. These investigators conclude that impairment in cognitive flexibility is due to increased perseverative behavior and that a brief disruption of NMDARs during a sensitive period of cortical development is sufficient to produce selective cognitive deficits relevant to schizophrenia. Similar findings were reported by Wang et al. [102] and Sircar [107]. These results coincide with the fact that many people who develop schizophrenia exhibit deficits in cognitive and social function in childhood, long before psychotic illness emerges [108], and that a certain population of schizophrenic patients shows neurodegeneration, particularly those with cognitive deficits [109]. Sircar et al. [110] examined the effects of long-term neonatal exposure to PCP on [^{3}H]MK-801 binding and on gene expression of NMDAR subunits in juvenile male rats. Interestingly, they found that long-term PCP administration in postnatal rats produced a significant reduction in both [^{3}H]MK-801 binding and the mRNA level of the NR2B subunit in the cerebral cortex. Similarly, Harris et al. [111] reported that MK-801, administered

twice on postnatal day 7, caused reduced volume and neuronal number within the hippocampus and altered hippocampal NR1 expression during adulthood.

Conclusions and Future Studies

In this chapter, we have provided evidence that a dysfunctional glutamatergic system may play an important role in schizophrenia. This is based on evidence showing hypofunctional NMDARs in both preclinical models and imaging and in the results of postmortem brain studies in schizophrenic patients. The systemic administration of NMDAR antagonists causes inhibition of NMDAR function in cortical regions, leading to excessive glutamate release, which is excitotoxic. It has been suggested that excitotoxic loss of NMDARs on GABAergic neurons is crucial to NMDA hypofunction; this finding is supported by studies showing loss of GABAergic interneurons in the frontal cortex and in hippocampal formation [112, 113] and a reduced number of glutamic acid decarboxylase 67-expressing neurons that coexpress NR2A in the prefrontal cortex of schizophrenic patients [114]. In addition, the blockade of NMDARs leads to inhibition of thalamic GABAergic interneurons, which, in turn, may cause disinhibition of thalamocortical glutamatergic neurons and excess glutamate release [15, 115].

A growing body of evidence indicates that mGluRs may also be involved in the pathophysiological features of schizophrenia; groups I and group II mGluRs are the most studied (reviewed in Krivoy et al. [116]). Based on these studies, it appears that the group I mGluR5 agonist and the group II mGluR2 agonist may serve as modulators of the schizophrenia process [116].

Given that there is strong evidence of NMDAR hypofunction in schizophrenia, the development of drugs targeting the glutamatergic system will be highly important. Drugs that can enhance NMDAR function can be considered as clinically relevant; however, one of the limitations of developing a drug that stimulates NMDA function is exocytosis, which may affect GABAergic interneurons [12]. Alternatively, agents that can target glycine transport and glutamate transporters may also be effective in schizophrenia. Thus, agents are being developed, most prominently those targeting the glycine transporter, D-serine, and glycine uptake. In addition, agents that target mGluRs are also being considered as an adjunctive therapy of direct agonists of the NMDARs [117].

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Chapter 14
Mathematical Models in Schizophrenia

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Abstract Schizophrenia is a severe and complex mental disorder that causes an enormous societal and financial burden. Our current understanding of schizophrenia is very fragmented, and the disease is still regarded as an enigma even though its main features have been recognized for centuries. When the post-genomic era arrived, high-throughput instruments and methods ushered in an explosion in the generation of large datasets. This rich information began to facilitate the development of mathematical models, and these models are beginning to show the potential of propelling schizophrenia research onto a new, quantitative level. As schizophrenia is a complex disease that involves uncounted biological processes, there is no complete model which covers even the majority of aspects pertaining to schizophrenia. Instead, every currently available model focuses on a certain aspect of the disease. In this chapter, we review mathematical models of schizophrenia according to their mathematical foundation and structure, as well as the phenomenon they represent. Thus, an outline of mathematical modeling practices in schizophrenia is presented for biologists, psychiatrists, and clinicians. In the future, mathematical models may be expected to provide valuable guidance in the long-term investigation of complex diseases like schizophrenia.

Keywords Schizophrenia · Mathematical models · Systems biology

Abbreviations

ICD	International classification of diseases
DSM	Diagnostic and statistical manual of mental disorders

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Introduction

Schizophrenia is regarded as "the worst disease affecting mankind" and, with a lifetime prevalence of about 0.7%, is among the top ten causes of disease-related disability in the world [1–4]. The disease is clinically characterized by categorized symptoms, which are referred to as positive (e.g., delusions and auditory hallucinations), negative (e.g., blunted affect and emotion, alogia, and asociality), cognitive (e.g., disorganized thinking and poor memory), and mood related (e.g., depression). Every schizophrenic patient suffers from an admixture of symptoms, which changes in severity along with the disease course and varies widely among different individuals [5, 6]. Twin studies have shown that schizophrenia is highly heritable [7, 8]. Therefore, genetic factors are major contributors to schizophrenia. In addition, environmental factors such as social stress, prenatal exposure, and substance abuse are also known to contribute to schizophrenia [9–11]. Neurobiologically, there are morphological, structural, and/or functional changes in brains of schizophrenic patients [12–17]. Specially, several neurotransmitter systems show abnormalities, and these include the dopamine, glutamate, and GABA systems [18–21]. Because antagonists of dopamine D_2 receptor can alleviate some symptoms of schizophrenia, this receptor has been utilized as a target of medications for schizophrenia [22–24]. By contrast, dopamine agonists can exacerbate many of the symptoms of schizophrenia [18]. Unfortunately, antagonists of dopamine D_2 receptor such as clozapine are currently the only effective medication for schizophrenia and are mainly for the positive symptoms. However, there are inevitable adverse side effects.

Although the basic features of schizophrenia have actually been recognized for centuries and much information has been accumulated, our understanding of schizophrenia is rather fragmented, and schizophrenia is still regarded as an enigmatic brain disorder. Schizophrenia was first described in the middle of nineteenth century as a disease entity [25]. In late nineteenth century, Kraepelin described schizophrenia using the term *dementia praecox* and his description focused on the onset, course, and outcome of the disease [26]. In the early twentieth century, Bleuler coined the term *schizophrenia* and described the symptoms of the disease as the loosening of association, blunt affect, ambivalence, and autism (Bleuler's 4As), which are now regarded as the negative symptoms of schizophrenia [27]. In contrast, Schneider described 11 first-rank symptoms for schizophrenia, which are now considered as the positive symptoms of the disease [28]. Accompanying the conceptualization of schizophrenia, several sets of diagnostic criteria have been proposed (Table 14.1). Among these, the International Classification of Diseases (ICD series) of the World Health Organization has mainly been used in Europe, while the Diagnostic and Statistical Manual of Mental Disorders (DSM series) of the American Psychiatric Association are the criteria used in the US. These two sets of criteria were at first divergent, but later became much more similar [29].

Over the past decades, conceptual information and data about schizophrenia have been collected at an increasing speed. Especially when we entered the post genomic era, the generation of data accelerated explosively due to high-throughput instruments and methods like sequencing, microarray, mass spectrometry,

Table 14.1 Timeframe and concepts of schizophrenia

Timeframe	Concept/definition/diagnostic criterion
1850s	A distinct syndrome (Morel et al.)
1890s	*Dementia praecox* (Kraepelin)
1900s	Schizophrenia; "Bleuler's 4As" (Bleuler)
1950s	11 first-rank symptoms (Schneider), DSM I/ICD6-7
1960s	DSM II/ICD8
1970s	DSM III/ICD9
1980s, 1990s	DSM IIIR, DSM IV/ICD10
Twenty-first century	DSM V and beyond/ICD11 and beyond

NMR, and imaging for genomics, proteomics, metabolomics, and transcriptomics. Bioinformatics was created as a new tool for information retrieval, storage, sharing, and mining, primarily in the context of genomic data. More recently, systems biology emerged as a methodological framework for integrating, analyzing, and interpreting these high-throughput data and for making predictions on a systems level based on mathematical methods, modeling and simulation techniques, and computer-aided analyses. During these developments, not only qualitative information but also quantitative relationships became important and were found to be critical in biology, pharmacology, and the clinics, and approaches of systems biology and mathematical modeles emerged as a necessary and useful complement to traditional laboratory approaches. In the following, we will review the mathematical modeling efforts for schizophrenia and discuss some challenges and future directions.

Mathematical Models with Implications in Schizophrenia

Mathematical modeling has long been an important and useful approach in physics, chemistry, geology, engineering and other natural scientific fields. It was much later that its usefulness was also recognized in biology and the social sciences. Its applications in psychiatry are newer still. Systems biology is thus a rather new approach for studying diseases like schizophrenia [30, 31].

Schizophrenia is a very complex disease and involves numerous biological processes, with the consequence that there is no complete mathematical model which would cover every aspect of the disease. Instead, each of the currently available models focuses on a certain aspect of schizophrenia. The complexity of schizophrenia and heterogeneity between schizophrenic patients exist in the etiology, neurobiology, physiology, and phenomenology of the disease. Mathematical models of schizophrenia cover many of these aspects and components of the disease system, and it will be of great benefit for our understanding of schizophrenia if they are eventually integrated into a comprehensive systemic description of the disease. In the following, we review schizophrenia models according to their mathematical foundation and structure, as well as the aspects they model.

Conceptual Models

A conceptual model is a mapping of relationships between concepts instead of quantitative connections between quantifiable entities. Of course, the latter models are preferred in most cases, but they are not often achievable in biology because they require rich input data and parameter values that are usually difficult and expensive to obtain. A conceptual model can be used to verify concepts about a phenomenon.

Following the introduction of catastrophe theory by Thom [32], MacCulloch and Waddington applied this theory to schizophrenia, and especially to its psychosis, in recognition of the discontinuous nature of these phenomena [33]. Clinically, schizophrenia has characteristics of acute and discontinuous changes which could attribute to neurochemical, environmental, and psychosocial factors. For such discontinuous phenomena, catastrophe theory can explain sudden large changes in states of a system in response to small variations of controlling variables. Specifically, catastrophe theory assumes a folded topographic surface for the relationship between states and controlling variables of a system that allows steep jumps. Using catastrophe theory, the authors described how acute changes can occur following small changes in neurochemistry and environment. However, the descriptions are only qualitative and no quantitative information is provided. Also, the assumption of folded topographic surface has to be made, whose validity has to be tested against experimental and clinical observations.

Correlative Models

A correlative model resembles a black box that connects inputs with outputs in an entirely abstract fashion. This type of model is a natural and typical choice when the understanding of a phenomenon is limited. Since underlying mechanisms are unknown or ill characterized, statistical correlations between some factors and a phenomenon are the best one can do to draw inferences of potential associations. Indeed, such associations often offer the first clues regarding the mechanisms underlying the phenomenon.

Bromet and collaborators studied the relationship between symptoms of schizophrenic patients and the length of their hospitalization [34, 35]. They found a negative correlation between these two phenomena in a sense that a more severe symptom set at admission of a schizophrenic patient corresponded to a shorter-term prognosis. This observation is regarded as a paradox in the prognosis of schizophrenia. However, these authors also showed that there is a positive correlation between the premorbid functioning of a schizophrenic patient and the period of hospitalization. Following these studies, Branchey et al. formulated a statistical model including both severity of symptomatology and the level of premorbid functioning [36]. By separating schizophrenic patients into two groups, namely the hospitalized group and the non-hospitalized group determined one year after the admission to the

hospital, Branchey et al. compared the difference in the severity of symptomatology at admission between these two groups and showed that the paradox in the prognosis of schizophrenia does indeed exist under some conditions. The most valuable information from this study is the computation of some numerical configurations of the modeled system under which the apparent paradox is true.

Studies showed that the rehospitalization rate of chronic schizophrenics within a 2-year period post discharge is around 60%. Accordingly, Caton and coworkers carried out investigations on 119 chronic schizophrenics in New York City to study contributions of several factors to rehospitalization [37–39]. Data of hospital treatment, readiness for release, discharge planning, and social characteristics were gathered before patients were discharged from hospital, while patients' treatment compliance and living environment were assessed quarterly a year during the follow-up. The correlations between these factors and number and duration of rehospitalizations were analyzed. The results showed that discharge planning, treatment compliance after discharge, and some environmental factors were critical to rehospitalization. Thus, the study suggested early rehospitalization for schizophrenics and could predict their hospital time using assessment at discharge, the treatment compliance, and the community environment. This study could be helpful to improve patient care, better deliver services, and reduce societal and economical costs.

Also using a correlative model, Waldo et al. investigated the relationship between the P50 evoked potential in response to repeated auditory stimuli and schizophrenia in 82 individuals from six families [40]. The P50 potential, which as one of sensory gating is to suppress responses to repeated auditory stimuli, presents abnormality in both schizophrenics and some of their relatives. Statistically, disease status is relevant to the P50 potential that schizophrenics exhibit P50 ratios higher than those in their relatives, while these relatives of schizophrenic patients have higher P50 ratios than normal controls. Statistical analyses furthermore suggest a linear form of the relationship between the P50 ratio and the classification of disease status; however, a nonlinear relationship could not be ruled out by this study. Also focusing on the P50 auditory-evoked potential, Moxon et al. utilized a mechanistically based mathematical model to test hypotheses for abnormality of sensory gating in schizophrenia [41]. This study supported the hypothesis that nicotinic cholinergic input from septum to hippocampus and its stimulation of GABA release contributes to normal gating of repeated auditory stimuli.

The outcomes of a pharmacological study of the dose-response relationship of a schizophrenic treatment are influenced by the experimental design. Several factors mainly determine the dose-response relationships, including dose, pharmacokinetics, bioavailability, course moderators, the heterogeneity of the disease, and the selected response. As these factors are affected by random noise, and as noise may be differently transferred between factors in different experimental designs, Faraone et al. developed a statistical model for the effects of different experimental designs on the dose-response relationship of a schizophrenic treatment [42]. The authors assumed linear mechanisms for the dose-response relationship and normal distributions for the studied variables, and the relapse of schizophrenic outpatients

was selected as the response. The model showed that fixed dose designs have a better performance in the exploration of the correlation between bioavailability and disease stability than clinical dose designs. The model also provided recommendations regarding experimental designs for the easy detection and accurate measurement of the dose-response relationship, which can assist decision-making in psychopharmacologic research. A related work is the study by Wilson for the mathematical correlation between doses of risperidone and their active blood levels, which can aid clinicians in the selection of the optimal risperidone dose in situations of schizophrenic medications without empirical guidelines [43].

Other correlative models of schizophrenia include Allen's [44], Brown's [45], and Weinstein's studies [46]. Allen's model utilized data of the Wechsler Adult Intelligence Scale-Revised of 169 male schizophrenics and demonstrated small but significant correlations of social cognition with disorganization and negative symptoms of schizophrenia. Brown's model targeted the association of impaired working memory with schizophrenia and showed that this relationship does not exist in bipolar patients. Weinstein et al. showed there is a correlation between reduced grey matter volume in the left planum temporale, activation in the posterior temporal lobe, and severity of thought disorder under language tasks in schizophrenics.

Deterministic Models

A deterministic model is based on the assumption that mathematical representations of variables and relationships between them are deterministic, rather than probabilistic events or noise modeled with random variables and processes in stochastic models. With a deterministic model, thus, the same input settings always lead to the same output. Because no random effects are considered, which otherwise would require the specification of sampling procedures, choices of probability distributions, and the selection of confidence intervals, a deterministic model is much simpler than its corresponding stochastic counterpart. However, one must keep in mind that the validity of entirely deterministic systems may not be given in a case like schizophrenia.

Schizophrenic patients have abnormality of the eye-tracking system in target pursuit performance. Optimally, eyes can follow a moving target. However, when the eye-moving velocity is less than the velocity of target, the position error between the eyes and target accumulates, and the saccade system adjusts eyes position by the means of catch-up saccade. Thus, there seems to be interdependence between the velocity difference, the number of saccades, and the saccade amplitude. To test this alleged interdependence, Friedman et al. developed an equation of these factors based on some basic assumptions [47]. This model was tested against data from infrared oculographic measurements of eye-tracking performance of 37 schizophrenics and 45 controls. The model showed that schizophrenics have lower eye-tracking velocity and less duration than controls. Although schizophrenics exhibit more catch-up saccades, there is no statistical difference in saccade

amplitude between schizophrenics and controls. This study is helpful for addressing the relationship between the eye pursuit system and the saccade system in schizophrenia.

Mossman developed a deterministic model to help clinicians select doses of neuroleptics in schizophrenic medications [48]. A higher dose leads to a better response, however, it also increases the risk of side effects. Thus, a quantitative comparison was made to select an optimal dose of neuroleptics in consideration of a balance between benefits and risks. The model assumed a sigmoid curve for the dose-response relationship and a hyperbolic curve of the relationship between doses and side effects. A recommended dose was then suggested according to the policy of how to balance between benefits and risks chosen by a physician. One limitation of this model is that the variable accounting for side effects is a simple count of different types of side effects. A more natural and meaningful index would average the severity of different types of side effects with appropriate weights.

Stochastic Models

A stochastic model assumes that its variables and/or processes are subjected to random fluctuations and perturbations. The effects of this randomness can be studied with methods of statistics and all inferences are of a probabilistic nature. A pertinent example of a stochastic model in schizophrenia addresses genetic linkage analysis. This analysis is to locate schizophrenic genes, because schizophrenia is strongly heritable, as demonstrated by studies of pedigree, twins, and adoption. The main conclusion from this type of research is that schizophrenia has rather a complex profile of genetic predispositions than a single genetic cause [49–52]. However, various studies have not led to a consensus list of genetic loci of schizophrenia [53].

Another frequent application of stochastic models is classification between different groups, e.g. between schizophrenics and normal people, and between different subgroups of schizophrenics. Schurhoff et al. analyzed data of age at onset from 141 schizophrenics and found a mixture of two Gaussian distributions with a cutoff age at 28 [54]. The early-onset subgroup was dominated by males while the late-onset subgroup mainly consisted of females; other differences in symptoms and risk profiles existed as well between these two subgroups. Some frequently used classification techniques are clustering, principle component analysis, and discriminant analysis. In addition, artificial neural network is also often utilized for this purpose. Chen and Berrios applied some of these methods to categorize schizophrenia, depression, obsession, mania, and some other related diseases [55]. The study showed that these methods performed rather well. Compana et al. applied a backpropagation neural network to distinguish between schizophrenics and normal controls based on assumed differences in eye-tracking performance [56]. The model correctly classified cases with an accuracy of 80%, which strongly supports the alleged association of eye-tracking dysfunction with schizophrenia. Utilizing measurements of regional cerebral blood flow by functional brain imaging techniques, Berman performed discriminant analysis and compared cortical metabolism

under a resting state and cognitive tasks between chronic schizophrenic patients and normal subjects [57]. Cognitive tasks in this study included the Wisconsin card sort, a number matching task, and two visual continuous performance tasks. The greatest difference between two groups was found in the prefrontal cortex during the Wisconsin card sort task, which is used to retrospectively classify 85% of the subjects correctly. Möller et al. utilized time series data of mood alterations and showed that schizophrenics have stronger mood fluctuation in the later part of an inpatient stay than in the early part, which suggests different designs of treatment for mood improvement at different stages of the disease course [58, 59].

Artificial Neural Networks

Following the development of artificial intelligence and especially of artificial neural networks, and supported by huge advances in computer power, computational models have emerged that focus on the connectivity of neurons. These models are based on the concept of artificial neural networks that are composed of abstract interconnecting nodes that can mimic biological neurons. Basically, outputs are computed from inputs according to properties of nodes and connections between them. This type of model permits the study of biological neural networks and can solve problems of artificial intelligence. They can be divided into two broad categories according to their information flow: feedforward neural networks and feedback neural networks.

Some neural networks have been developed for the role of the neurotransmitter dopamine in enhancing signal transmittal and suppressing noise that has implications in information processing in the human brain. Cohen et al. constructed neural networks for a Continuous Performance Test in schizophrenics [60, 61]. The models showed that dopamine release increases discrimination of signals during human cognitive tasks through enhancing neuronal responsiveness to stimuli. They also demonstrated that reduced responsiveness of neurons induced cognitive deficits in schizophrenics. In a different line of research, Peled et al. developed a neural network for the Rorschach test [62], Moore et al. constructed a neural network for reasoning on the Beads task [63], while Amos' neural network model targeted the performance of schizophrenics on the Wisconsin Card Sorting Test [64]. These models suggest a role of dopamine in the dysfunction of schizophrenics. However, Moore's model investigates a positive symptom of schizophrenia – delusion, the Peled's model supports the alleged effect of dopamine on the signal-to-noise ratio and on disturbances of context, while Amos' model focuses on the maintenance of contextual information and its associations with dopamine imbalances. Moreover, Amos' model suggested a mechanism of working memory deficits in cortical-basal loops for schizophrenia, which is supported by a study by Mochi et al. [65]. Relevantly, Han et al. used a neural network of associative memory performance to show that chronic schizophrenics exhibit an overactivation of dominant patterns and underactivation of weak patterns [66]. Schmajuk et al. developed a neural network model of latent inhibition to simulate Sokolov's and Gray's hypotheses

that the behavioral inhibition system depends on novelty of stimuli and its control of information retrieval and storage [67]. Carter's model showed that schizophrenics are less accurate than controls on judgment of affect [68].

Building on the work by Cohen et al. about the role of dopamine in cognitive deficits, Jobe et al. used an artificial neural network to study how disturbances in the dopamine balance influence information processing in schizophrenics [69]. However, this study focused on cooperative interactions between neurons and modulators as well as among neurons, which were assumed as inhibitory, intermediate, and activating. A hypothesis was proposed that dopamine modulates neuronal responsiveness through regulation of conductance. The dopamine modulation is dependent on its concentration, its receptors, its binding to receptors, and a possible competition for receptors from other modulators. In consideration of these interactions, the neural network model can determine effects of modulators on the network activity. The results showed that cooperativity critically influences stimuli that are required to fire neurons in the network. Thus, various schizophrenic symptoms could be related to different neural networks or sub-networks that exhibit different degrees of cooperativity. Unfortunately, no empirical data were included in the study to test the validity of the proposed model.

Inspired by Stevens' hypothesis that changes in the hippocampus and projection sites of medial temporal neurons of many schizophrenics are relevant to the onset of schizophrenia, Ruppin et al. constructed a neural network model of the prefrontal neurons receiving inputs from temporal neurons in order to study the pathogenesis of schizophrenic delusions and hallucinations [70]. To investigate spontaneous and stimulated retrieval of memorized patterns, two scenarios were tested with model simulations: a stimulus dependent retrieval scenario and a spontaneous retrieval scenario. Model simulations showed that Hebbian-like activity-dependent synaptic changes in spontaneous retrieval lead to biased pattern formation, which could be the result of the inhomogeneous structure and connections of the neural network. Such spontaneous emergence of a pattern, when there are deficits in the projections from the temporal lobe, might have implications in delusions and hallucinations of schizophrenia, because these schizophrenic symptoms are related to some recurring cognitive and perceptual themes. Stimuli received from the temporal lobe generate more diverse retrieval of patterns. Overall, this study provided support to the Stevens' hypothesis of schizophrenia and has implications in the pathogenesis of schizophrenic symptoms.

A popular and powerful application of artificial intelligence is expert systems that may be of assistance for the diagnosis of schizophrenia, where multiple diagnostic criteria exist, such as the DSM series and the ICD series. The existence of multiple diagnostic criteria implies that a diagnosis of schizophrenia depends on the experience of a physician and the criterion he/she selects. Such diagnostic reasoning is critical to the diagnosis and treatment of schizophrenia, which an expert system intends to mimic. An expert system for disease diagnosis is based on theories of artificial intelligence, and its development consists of the defined steps of knowledge acquisition, knowledge selection and assessment, knowledge organization, computerized knowledge representation, modeling of diagnostic process, and

system evaluation. Some expert systems for schizophrenia diagnosis have been constructed and showed rather reliable performance [71, 72]. Expert systems of this type can not only assist with schizophrenia diagnoses, but also serve as valuable teaching tools for medical student training.

Mechanistically Based Models

A mechanistically based model requires known or hypothesized mechanisms for a phenomenon. This type of model is able to assemble known or alleged mechanisms into a testable structure and can sometimes provide details regarding the functioning of the system. The model can and shall make predictions which can be tested for the validity of the based underlying mechanisms. A mechanistic model is natural and very powerful, but it requires more data and is more complicated to construct.

Some mechanistically based mathematical models have been developed for selected aspects of schizophrenia. Examples include models for dopaminergic neurons of the substantia nigra and those for interneurons in the striatum in line with the dopamine hypothesis of schizophrenia [73–77]. The relationship between dopamine and the etiology of schizophrenia was first suggested by Van Rossum followed the designation of dopamine as a neurotransmitter and suggestions of effects of antipsychotic drugs on dopamine metabolism by Carlsson and his collaborators [78–81]. Later, Seeman et al. crystallized the dopamine hypothesis of schizophrenia by demonstrating that doses of antipsychotics, their affinities to the dopamine D_2 receptor, and the reduction of psychotic symptoms of schizophrenia were quantitatively correlated [22–24]. Especially for the psychotic aspect of schizophrenia, the dopamine hypothesis has become a primary guide.

Following the dopamine hypothesis of schizophrenia, Qi et al. developed a mathematical model of dopamine metabolism based on ordinary differential equations, which accounts for the processes of dopamine synthesis, degradation, compartmentalization, release, reuptake, and numerous regulating mechanisms [73]. The model was utilized to assess how dopamine homeostasis is affected by several factors that are implicated in schizophrenia, such as the enzyme catecholamine-O-methyltransferase. Because the model was mechanism-based and included various processes of the dopamine metabolism, it was used to simulate functions of drugs and showed that the model might assist in preliminary screening of potential drugs for schizophrenia aiming at presynaptic dopamine functions.

When dopamine signals are altered in the presynapse, its effects on postsynaptic neurons are changed correspondingly. To explore these effects, Lindskog et al., Fernandez et al., and Qi et al. developed different ordinary differential equation models to represent the processes with which dopamine and glutamate signals are transduced and to simulate their effects on phosphorylation profiles of striatal neurons, which regulate various physiological and behavioral functions of neurotransmitters [74–76, 82]. These models can serve as *in silico* platforms for exploratory studies of mechanisms of signal transduction relevant to schizophrenia.

At the individual neuron level, the Hodgkin-Huxley model is a great achievement which utilized physical analogs and ordinary differential equations to model ionic currents through a membrane [83]. In this type of model, the electrochemical gradients across a membrane are regarded as batteries. Voltage-gated ion channels and the lipid bilayer are treated as electrical conductances and a capacitance, respectively. Ion pumps and exchangers are modeled as current sources. Thus, ionic currents can be derived from formulae similar to Ohm's law. For schizophrenia, Wolf et al. developed a Hodgkin-Huxley type model to study the impact of the NMDA/AMPA ratio on state transitions and oscillations of neurons in the nucleus accumbens [84]. The study suggested that an altered NMDA current has implications in schizophrenia.

At the level of neural circuits, mechanistically based models often simulated neuronal projections of excitatory, inhibitory, or modulatory functions between different types of neurons, and investigated characteristics and properties of formed networks analogous to electronic circuits. For example, Schwegler simulated the nigro-striatal loop and focused on the stability of this circuit [85], while an der Heiden modeled inhibitory circuits in the cortex and a loop between thalamus, prefrontal cortex, and striatum with a focus on firing patterns and their bifurcations [86]. Wang developed a prefrontal microcircuit model for working memory and supported dopamine's suppression of distraction for memory maintenance [87]. Siekmeier et al. simulated the direct perforant pathway projected from entorhinal cortex to region CA1 of hippocampus and found that alterations of this input impair retrieval of organized memory which is implied in cognitive dysfunction of schizophrenia [88]. Tanaka's model showed dysfunctional GABAergic inhibition increases liability to psychosis of schizophrenia [89].

Other mechanistically based models addressed different aspects of schizophrenia. For example, Danziger and Elmergreen constructed an ordinary differential equation model for catatonic schizophrenia [90, 91], which consisted of three variables representing the thyroid, thyrotropin, and a hypothesized enzyme. The model was based on a correlation between rhythmic changes in metabolites and periodic symptoms. Their system showed that the concentrations of these variables could reach constant levels or oscillate, but are not periodic. Later, Cronin-Scanlon's analyses showed that the system could have a stable state, vary periodically, or vary in a bounded random manner [92]. These systemic behaviors depend on the mathematical configurations of the equations, including the eigenvalues that characterize the stability of the system. In correspondence with various solutions of the equations, Cronin-Scanlon claimed that a person could have no symptom or stable catatonia, periodic catatonia, or randomly varying symptoms.

Conclusions and Future Directions

Neuropsychiatric diseases like schizophrenia have caused human suffering throughout history. However, these diseases are complicated, and even after centuries of dealing with them, our understanding is still rather limited. This chapter reviewed

mathematical models of schizophrenia and described what knowledge and insights into schizophrenia these models have provided (Table 14.2). We showed that these models can be very different in structure and their ability to shed light onto the disease or to aid diagnostics and treatment. Therefore, different models should be developed and employed at different stages of disease research. For example, correlative models are most helpful in the identification of factors and mechanisms that critically affect a phenomenon of the disease. Conceptual models are useful for verification of concepts about a phenomenon that they could be critical at the very beginning of the disease research. Mechanistic models characterize the interdependence between processes underlying the disease, and they become possible when required detail information has been accumulated.

Along with the deepening of research, which accumulates more data and information, mathematical models of a disease will have more powers and to some extent are indispensable. The emergence of high-throughput technologies and the advent of the genome era have yielded huge amounts of data and information. These technologies of genome sequencing, transcriptomics, proteomics, microarrays, mass spectrometry, and genome-wide association study have begun to characterize many aspects of diseases like schizophrenia. Analysis and integration of these high-throughput data require advances in computer technology, such as high-performance and parallel computing. Also, relevant mathematical theories and methods have been developed.

On the other hand, psychiatric diseases like schizophrenia are very complex and involve multiple brain regions including the striatum, cortex, hippocampus, and thalamus, each of which contains millions of neurons that communicate through multiple neurotransmitters. However, the complexity that distinguishes healthy individuals and schizophrenics is not merely a matter of large numbers, but also of organization and dynamic change. For example, deficits in schizophrenia can be genetic, metabolic, physiological, and behavioral. Such complexities combined with huge amount of data described above determine the necessity of nontraditional approaches that can integrate various information into systemic descriptions and study a complex disease from a systemic point of view. Methods of modern systems biology have been developed for such a purpose. Using these methods, conceptual systems descriptions can be converted into mathematical models, and functional explanations, interpretations, and predictions can be made.

While mathematical models are very powerful, we must emphasize that they are not a replacement of clinical and biological investigations. The different approaches have their genuine advantages and limitations. Clinical and biological investigations can produce high-throughput data and information, and test predictions from mathematical models. Without them, mathematical models cannot progress very far. On the other hand, mathematical models can integrate data and information, and inspect them from a systemic point of view which has not been the philosophy of reductionistic approaches. It will be their seamless cooperation that will lead to the most significant advances in researches and treatments of a disease like schizophrenia.

Table 14.2 Mathematical models in schizophrenia

Modeled phenomenon	Model design	Model characteristics	Year	References
Discontinuous psychosis	Conceptual model	Uses the catastrophe theory	1979	[33]
Relationship between symptoms and hospitalization length	Correlative model	Negative correlation	1971, 1974	[34, 35]
Relationship between symptoms and hospitalization length	Correlative model	Positive correlation under some conditions	1977	[36]
Contributions of factors to rehospitalization	Correlative model	Discharge planning, treatment compliance after discharge, and some environmental factors are critical to rehospitalization	1971, 1977, 1985	[37, 38, 39]
Relationship between P50 evoked potential in response to repeated auditory stimuli and schizophrenia	Correlative model	A linear form of the relationship between the P50 ratio and the classification of disease status	1991	[40]
Effects of an experimental design on a dose-response relationship of a schizophrenic treatment in a pharmacological study	Correlative model	Provides recommendations of experimental designs for easy detection and accurate measurement of the dose-response relationship	1992	[42]
Correlation between doses of risperidone and their active blood levels	Correlative model	Aids clinicians to select risperidone dose in situations without empirical guidelines of medications	2004	[43]
Correlation between social cognition and schizophrenia	Correlative model	Confirmatory correlations	2007	[44]
Abnormality of eye-tracking system in target pursuit performance	Deterministic model	Supports that schizophrenics have lower eye-tracking velocity and less duration than controls	1991	[47]
Dose selection of neuroleptics	Deterministic model	Suggests a balance between benefits and risks of a selected dose of medication	1997	[48]
Screening of schizophrenic genes	Stochastic model	Supports the hypothesis of multiple genes association with schizophrenia	1984, 1990, 2000	[49, 50, 51, 52]
Classification of different stages of disease course	Stochastic model	Uses time series data of mood alterations	1987, 1988	[58, 59]

Table 14.2 (continued)

Modeled phenomenon	Model design	Model characteristics	Year	References
Classification of schizophrenia, depression, obsession, mania, and other diseases	Stochastic model	Reliable classification	1996	[55]
Classification of schizophrenics and normal controls	Stochastic model	Uses a backpropagation neural network of eye-tracking performance	1999	[56]
Classification of chronic schizophrenics and normal subjects	Stochastic model	Supports the usefulness of cerebral blood flow in the prefrontal cortex under Wisconsin card sorting task for classification	1999	[57]
Classification of different subgroups of schizophrenia	Stochastic model	Reliable classification	2004	[54]
Working memory deficits in schizophrenia	Stochastic model	Supports the association of impaired working memory with schizophrenia	2007	[45]
Dopamine's roles in information processing	Artificial neural network	Dopamine increases discrimination of signals during human cognitive tasks, using Continuous Performance Test	1993, 1999	[60, 61]
Dopamine's roles in information processing	Artificial neural network	Supports the hypothesis that dopamine modulates neuronal responsiveness through regulation of conductance	1994	[69]
Assisting diagnosis of schizophrenia	Artificial neural network	Expert systems	1995, 2006	[71, 72]
Latent inhibition abnormality	Artificial neural network	Supports the hypothesis that behavioral inhibition system depends on novelty of stimuli and its control of information retrieval and storage	1996	[67]
Roles of projections from the temporal lobe to the prefrontal cortex in delusions and hallucinations	Artificial neural network	Supports the hypothesis that changes in medial temporal neurons are relevant to the onset of schizophrenia	1996	[70]

Table 14.2 (continued)

Modeled phenomenon	Model design	Model characteristics	Year	References
Dopamine's roles in information processing	Artificial neural network	Dopamine's effects on disturbance of context during human cognitive tasks, using the Rorschach test	2000	[62]
Dopamine's roles in information processing	Artificial neural network	Effects of dopamine imbalance on maintenance of contextual information during human cognitive tasks, using Wisconsin Card Sorting Test	2000	[64]
Working memory deficits in cortical-basal loops	Artificial neural network	Supports working memory deficits in schizophrenia	2000	[65]
Associative memory dysfunction	Artificial neural network	Supports overactivation of dominant patterns and underactivation of weak patterns	2003	[66]
Dopamine's roles in information processing	Artificial neural network	Dopamine's roles in delusion, using the Beads task,	2006	[63]
Deficits of judgment of affect in schizophrenia	Artificial neural network	Supports that schizophrenics are less accurate than controls on judgment of affect	2007	[68]
Catatonic schizophrenia	Mechanistic model	Do not support periodic symptoms	1954, 1958	[90, 91]
Catatonic schizophrenia	Mechanistic model	Supports periodic symptoms	1974	[92]
Abnormality of sensory gating in schizophrenia	Mechanistic model	Suggests a mechanism that nicotinic cholinergic input from septum to hippocampus and its stimulation of GABA release	2003	[41]
Impact of NMDA/AMPA ratio on state transitions and oscillations of neurons in the nucleus accumbens	Mechanistic model	Hodgkin-Huxley type model	2005	[84]
Signal transduction of dopamine and glutamate signals	Mechanistic model	*In silico* platform for mechanistic studies of signal transduction	2006, 2008, 2010	[74, 75, 76, 77]
Stability of the nigro-striatal loop	Mechanistic model	Hodgkin-Huxley type model	2006	[85]

Table 14.2 (continued)

Modeled phenomenon	Model design	Model characteristics	Year	References
Firing patterns and their bifurcations of inhibitory circuits in the cortex and a loop between thalamus, prefrontal cortex, and striatum	Mechanistic model	Hodgkin-Huxley type model	2006	[86]
Working memory by a prefrontal microcircuit	Mechanistic model	Supports dopamine's suppression of distraction for memory maintenance	2006	[87]
The implications of NMDA receptor in cognitive dysfunction of schizophrenia	Mechanistic model	Supports the contribution of NMDA receptor to cognitive dysfunction	2007	[88]
Dopamine metabolism	Mechanistic model	Assists in preliminary screening of potential drugs for schizophrenia aimed at presynaptic dopamine functions	2008	[73]
Reduced GABAergic inhibition in schizophrenia	Mechanistic model	Reduced GABAergic inhibition increases vulnerability to psychosis of schizophrenia	2008	[89]

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Chapter 15
Methamphetamine-Associated Psychosis: A Model for Biomarker Discovery in Schizophrenia

Chad A. Bousman, Stephen J. Glatt, Ian P. Everall, and Ming T. Tsuang

Abstract Methamphetamine-associated psychosis (MAP) has been considered a pharmacological or environmental pathogen model of schizophrenia (SCZ) due in part to similarities in clinical presentation (i.e. paranoia, hallucinations, disorganized speech, and negative symptoms), response to treatment (e.g. neuroleptics), and pathologic mechanisms (e.g. central dopaminergic neurotransmission) of both conditions. In this chapter, we will provide an introduction to the typical clinical features and course of MAP as well as a review and discussion of the current putative genetic biomarkers for MAP. We will conclude with a discussion of the future directions and application of the MAP model with specific focus on how it may serve to elucidate further the complex neuromechanisms and discovery of viable biomarkers of SCZ.

Keywords Methamphetamine · Model of psychosis · Genetic · Biomarkers

Abbreviations

AMP	Amphetamine psychosis
DSM	Diagnostic statistical manual of mental disorders
ICD	International classification of diseases
MAP	Methamphetamine-associated psychosis
METH	Methamphetamine
MRS	Magnetic resonance spectroscopy
PCP	Phencyclidine
PET	Positron emission tomography
SCZ	Schizophrenia
SNP	Single nucleotide polymorphism
VNTR	Variable number tandem repeat

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Introduction

Schizophrenia (SCZ) affects approximately five of every 1,000 people and is considered one of the most severe and debilitating psychiatric disorders [1]. Unlike many heritable disorders such as cystic fibrosis, with known genetic etiology and blood, tissue or other confirmatory tests; complex disorders such as SCZ have proven difficult to categorize and currently have no objective diagnostic tools [2]. While genetic, neurobiological, and neuropsychological association studies have implicated many putative biomarkers in the etiology and/or course of SCZ, many have not been replicated and/or have withstood meta-analysis. Thus, the search for viable biomarkers continues and could be accelerated via examination of human models related to SCZ.

Methamphetamine-associated psychosis (MAP) has been considered a pharmacological and/or environmental pathogen model of SCZ due in part to similarities in clinical presentation (i.e. paranoia, hallucinations, disorganized speech, and negative symptoms), response to treatment (e.g. neuroleptics), and neuromechanisms (e.g. central dopaminergic neurotransmission) of both conditions [3–5]. Although other substances of abuse such as alcohol, cannabis, cocaine, phencyclidine (PCP), ketamine, and inhalants (i.e. toluene) have also been postulated as potential models for SCZ in animals and/or among human users [6–10], the proportion of methamphetamine (METH) users who experience psychosis has been estimated between 72 and 100% [11, 12] depending on the chronicity of use and is considerably higher than other prevalent psychosis-associated drugs (e.g. alcohol = 7% [13]; cannabis = 20–50% [14]; cocaine = 53–68% [9]). In addition, METH use is at epidemic levels in several regions of the world (e.g. Southeast Asia, North America, Australia, South Africa) and its global prevalence is estimated at 15–16 million people [15]. Thus, MAP as a model of SCZ in humans may be more salient and feasible at the global level. Yet, compared to the other psychosis-associated drugs mentioned above, there is a paucity of literature summarizing the potential role of MAP as a model for SCZ. Thus, in this chapter we will briefly summarize the MAP literature to date and focus on how investigations related to MAP may serve to elucidate further the complex antecedents and consequences of SCZ.

Epidemiology of Methamphetamine

Methamphetamine (METH) is a potent synthetic psychostimulant that can be injected, smoked, snorted, ingested or transrectally administered [16, 17]. Use of METH has been reported on every continent [15]. Although, the vast majority of METH users reside in East and Southeast Asia as well as North America, with isolated pockets of high usage [15] in parts of Europe such as the Czech Republic [15] and in South Africa. In China, the largest METH market in the world, prevalence of METH use among new drug users is estimated at 5.6%, which is surpassed only by heroin use among new users [18]. In neighboring Japan, 0.3% of the general population and 6.8% of juvenile offenders are METH users [19]. Furthermore, other countries in East and Southeast Asia, such as Cambodia, Indonesia, Laos, Myanmar,

Thailand, and the Philippines have also reported increased rates of METH use in recent years [20], and South Africa is currently battling an explosion of METH use in Cape Town [21]. In North America, Mexico has become the largest producer of METH as a result of restrictions on precursor chemicals in the US and Canada. However, the west coasts of the United States and Canada have been greatly impacted by METH use [22, 23]. The latest estimated annual prevalence rates in the general population for METH use in Canada were 0.8% in 2004, 1.4% in the United States in 2006, and 0.1% in Mexico in 2002 [22].

Acute and Chronic Effects of Methamphetamine

The acute and chronic effects of METH are dependent on several factors including the amount and length of time the drug is consumed, route of administration, and purity of the drug. The acute effects range from euphoria and increased energy to loss of appetite, insomnia, and irritability. Prolonged use of METH can result in the onset or exacerbation of a multitude of physical, psychological, emotional, motivational, behavioral, and psychiatric disorders (for review see [24]). Of particular concern are psychiatric morbidities that continue to rise in number and include a florid psychosis, which occurs at a rate 11 times higher than observed in the general population [25]. Longer and heavier periods of METH use have been shown to increase the probability of psychotic symptom manifestation [26, 27]. Likewise, route of METH administration, particularly intravenously injection, has been associated with higher rates of psychotic symptoms [26, 28].

MAP Clinical Features

Clinical features of MAP were first described in the late 1950s by groups in Japan during two independent METH epidemics (for review see Sato [29]). During the same period in London, Connell [30] characterized 42 cases of amphetamine psychosis (AMP). The consensus across these studies was that MAP and AMP typically resemble that of paranoid SCZ with ideas of reference and delusions of persecution, as well as auditory and visual hallucinations, in the context of clear consciousness. More recent studies examining MAP have echoed these clinical features and have expanded the clinical picture by suggesting MAP comprises a negative syndrome (e.g. flattened/incongruous affects) [11, 31], typically responds to neuroleptic treatment [32, 33], and often occurs in individuals with cluster A personality traits (i.e. schizotypy, schizoid, antisocial), and/or a family history of psychosis [34]; all of which are comparable to clinical features of SCZ without substance use [35].

MAP Clinical Course

Another key similarity between MAP and SCZ is MAP's clinical course with frequent relapses (recurrences) [36]. MAP's clinical course has been operationally defined in previous work [33, 37, 38] into two primary trajectories: transient and

prolonged. Both trajectories are classified based on the duration of the psychotic state after pharmacotherapy or suspension of METH use. Latency between onset of METH use and initial psychotic episode is typically greater than 1 year, although psychosis within 1 month of initial METH use has been reported [31, 38]. Usually, MAP will subside within 10 days or 1 month, at the longest, after the discontinuance of METH consumption and/or beginning of pharmacological therapy with antipsychotics (transient-type). However, it is known that, for some, the psychotic state is sustained for longer than 1 month despite detoxification from METH and treatment with antipsychotics (prolonged-type) (Fig. 15.1).

A third clinical course trajectory that is related to the transient-type course described above is spontaneous relapse. Spontaneous relapse is defined as the recurrence of psychotic symptoms (i.e. flashbacks), without the reuse of METH, in the context of a mild psychosocial stressor (e.g. non-physical confrontations with others) [36, 39] or alcohol ingestion [40]. Previous work has shown that relapse episodes are typically transient in course and closely resemble that of the initial psychosis associated with METH use [41]. During flashbacks, marked increases in plasma norepinephrine levels have also been reported and suggest a link between stress, the noradrenergic system, and susceptibility to spontaneous relapse

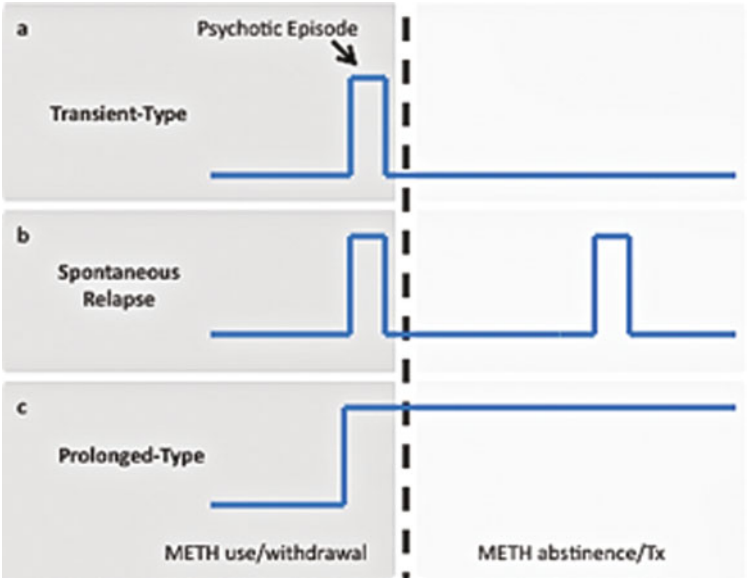

Fig. 15.1 Three main trajectories of methamphetamine-associated psychosis: **a** Following prolonged use of METH onset of psychotic episode which subsides within 1 month and no reoccurrence of psychosis is observed in abstinence (transient-type); **b** during abstinence a psychotic episode reoccurs during mild psychosocial stress (spontaneous relapse); and **c** psychotic symptoms are sustained for more than a month into abstinence and potentially while taking antipsychotics (prolonged-type). *METH* = methamphetamine; *Tx* = treatment

[42–45]. Given that stress has also been shown to precipitate the onset and relapse of SCZ [46], the MAP model may provide useful information for relapse prediction of SCZ [47].

MAP Diagnosis

MAP diagnosis is governed by two major classification systems: (1) the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) [48] and (2) the International Classification of Diseases version 10 (ICD-10) [49]. DSM-IV refers to MAP as amphetamine-induced psychotic disorder; whereas, ICD-10 uses stimulant psychotic disorder. These classification systems stem from similar scientific and conceptual roots, however disagreement on certain aspects and details do exist despite attempts to bring the two systems into accord. Divergence can be seen in the criteria related to the duration/persistence of psychotic symptoms (Table 15.1). The ICD-10 criteria for MAP are more stringent than the DSM-IV in that it requires an earlier onset of symptoms (2 weeks vs. 1 month) and minimum duration of symptoms (48 h vs. not specified). However, the ICD-10 permits a longer maximum duration of psychotic symptoms than the DSM-IV (6 months vs. 1 month) before a change in diagnosis is required. These differences can result in variations in participant recruitment and classification and deem comparisons across studies difficult. This issue is complicated further by the fact that criteria used to diagnosis MAP predates the METH epidemic resulting in difficulties in differentiating MAP from primary psychotic disorders in METH users [50]. As a result, studies of MAP often include clinical rating instruments such as the Brief Psychiatric Rating Scale [51] to capture sub-clinical psychotic symptoms and allow analysis of psychosis as a continuous rather than dichotomous phenomena.

Table 15.1 Comparison of ICD-10-DCR and DSM-IV phenotype criteria for Methamphetamine associated psychosis

	Classification type	
Criteria	ICD-10-DCR	DSM-IV
Onset of psychosis during/within		
2 weeks of use	X	
1 month of use		X
Persistence of psychotic symptoms:[a]		
Greater than 48 h	X	
Maximum duration of psychosis:		
6 months	X	
1 month		X

[a]DSM-IV does not specify criteria for persistence of psychotic symptoms.
ICD-10-DCR: International Classification of Disease, 10th revision, Diagnostic Criteria for Research; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

Biomarker Discovery

The search for and subsequent discovery of viable biomarkers for SCZ could have a profound effect on global public health. The MAP model could accelerate the discovery of antecedent (identifying the risk of disease development), screening (screening for sub-clinical disease), diagnostic (recognizing overt disease), staging (classifying disease severity) or prognostic (predicting future course of disease) biomarkers [52, 53]. Several approaches to biomarker discovery exist and include genetic, proteomic, transcriptomic, and metabolomic screens (for review see Bousman et al. [54]) as well as neuroimaging, neurocognitive, and neurophysiological assessments. However, many of these approaches are still developing and/or have yet to be widely applied to the study of MAP. Thus, in the following sections we will restrict our review of the literature to the putative genetic markers of MAP, though we include a brief discussion in the Future Directions section on research utilizing neuropsychological and neuroimaging approaches.

Genetic Biomarkers for MAP Susceptibility

To date, all significant genetic associations for MAP susceptibility (Table 15.2) have been indentified in Asian populations, primarily Japanese. In a recent review of the genetic association literature [55], MAP susceptibility was found to be associated with polymorphisms in four genes: dysbindin-1 (*DTNBP1)* [56]*, mu-opioid*

Table 15.2 Genetic biomarkers for MAP susceptibility

			Supporting evidence	
Gene	Location	Gene name	MAP	SCZ
ARRB2	17p13.2	Beta-arrestin 2	60	–
DAOA/G72	13q33.2	D-amino acid oxidase activator	61	74
DRD2	11q23.2	Dopamine receptor D2	62	74, 81
DTNBP1	6p22.3	Dystrobrevin-binding protien 1 (dysbindin)	56	74
ESR1	6q25.1	Estrogen receptor alpha	63	110
FZD3	8p21.1	Frizzled 3	64	111, 112
GLYT1	1p34.1	Glycine transporter 1	65	–
GRM2	3p21.2	Glutamate metabotropic receptor 2	113	–
GSTT1	22q11.23	Glutathione-related enzyme T1	66	114
HTR1A	5q12.2	5-hydroxytryptamine (serotonin) receptor 1A	75	115
OPRM1	6q25.2	Mu-opioid receptor 1	57	116
SNCA	4q22.1	Alpha-synuclein	58	–
SOD2	6q25.3	Superoxide dismutase	59	–

receptor (OPRM1) [57], alpha-synuclein (*SNCA)* [58], and superoxide dismutase 2 *(SOD2*) [59]. However, recently other putative polymorphisms for MAP susceptibility have been indentified in beta-arrestin 2 (*ARRB2*) [60], d-amino acid oxidase activator (*DAOA/G72*) [61], dopamine receptor D2 (*DRD2*) [62], estrogen receptor alpha gene (*ESR1*) [63], Frizzled 3 (*FZD3*) [64], glycine transporter 1 (GLYT1) [65], glutathione-related enzyme T1 (*GSTT1*) [66], and the serotonin 1a receptor (HTR1A) [67] genes. Many of the genes have also been implicated in SCZ (Table 15.2) and have subsequently supported the hypothesis of a common underlying genetic mechanism for susceptibility to MAP and SCZ.

A good exemplar of this common susceptibility hypothesis is the *DAOA/G72* gene. This gene encodes a potent activator of *N*-methyl-D-aspartate (NMDA) type glutamate receptors which has been shown in two meta-analyses to be associated with SCZ [68, 69] and has recently been linked to progression to first psychotic episode in prodromal subjects [70]. Consistent with these findings, Kotaka and colleagues [61] observed an association between this gene, specifically the G allele of the M22 (rs778293) polymorphism and MAP in a sample of 209 Japanese. Further supporting this hypothesis is *DTNBP1* or dysbindin-1 which encodes a coiled-coil containing protein that in brain is found primarily in axon bundles and mossy fiber synaptic terminals in the cerebellum and hippocampus [71, 72]. Currently, *DTNBP1* is one of the most promising candidate genes for SCZ [73, 74]. Thus, Kishimoto and colleagues [56] examined *DTNBP1* among 197 Japanese subjects with MAP and 243 controls. They identified two single nucleotide polymorphisms (SNPs) (rs2619538A>T and rs3213207A>G) that conferred an approximate 2.6- and 7.1-times greater odds of MAP, respectively. In addition, other genes for MAP susceptibility such as *ESR1* [63], *FZD3* [64], *GSTT1* [66], and *HTR1A* [75] have also been identified as putative susceptibility genes for SCZ (Table 15.1), albeit findings in SCZ have been inconsistent. Nevertheless, current knowledge suggests the underlying biological mechanisms that confer a risk of MAP may in part overlap with that of SCZ.

Genetic Biomarkers of MAP Clinical Course

Several genes have also been identified as predictors of the clinical course of MAP (Table 15.3). The monoamine oxidase A (*MAOA*) [76], dopamine transporter (*DAT*) [37], *DRD2* [62], dysbindin-1 (*DTNBP1)* [56], NRH-quinone oxidoreductase 2 (*NQO2*), and *SOD2* [59] genes have been associated with a prolonged-type clinical course. Whereas, the *DRD2* [62], catechol-o-methyltransferase (*COMT*) [77], protein interacting C kinase (*PICK1*) [78] and serotonin transporter (*SERT*) [79] genes were associated with spontaneous relapse. Interestingly, all but one (*SOD2*) of these genes has been implicated in SCZ (Table 15.3).

Of particular note are the *DRD2* and *DTNBP1* genes which have been implicated in MAP susceptibility and clinical course as well as SCZ. *DRD2* and other dopamine receptor genes were among the first to be studied in SCZ as a result of the dopamine hypothesis [73, 80]. A recent meta-analysis has showed strong evidence

Table 15.3 Genetic biomarkers for MAP clinical course

Gene	Location	Gene name	Supporting evidence	
			MAP	SCZ
DRD2	11q23.2	dopamine receptor D2	62	74
COMT	22q11.21	catechol-o-methyltransferase	77	74, 94
DAT	5p15.33	dopamine transporter	37	117
DTNBP1	6p22.3	dystrobrevin-binding protien 1 (dysbindin)	56	74
MAOA	Xp11.3	monoamine oxidase A	76	118
NQO2	6p25.2	NRH-quinone oxidoreductase 2	119	120
PICK1	22q13.1	protein interacting with C kinase	78	121, 122
SERT	17q11.2	serotonin transporter	79	74
SOD2	6q25.3	superoxide dismutase	59	–

for DRD2's association with SCZ, specifically two SNPs (rs1801028 and rs6277) [74], while Glatt and Jonsson [81] showed a significant effect of the Cys allele of the Ser311Cys polymorphism under both fixed-effects (odds ratio [OR] = 1.4; $P = 0.002$) and random-effects ($OR = 1.4$; P = 0.007) models. In Japanese MAP subjects, Ujike and colleagues [62] reported significant associations between the *TaqIA* polymorphism and prolonged psychosis as well as spontaneous relapse in which carriers of the AI/AI genotype were significantly less likely to have a prolonged-type (> 1 month) psychosis and spontaneously relapse. The *TaqIA* polymorphism has not been shown to be significantly associated with SCZ; although one family study has shown linkage with SCZ at this locus [82]. Thus, different variants of *DRD2* may be implicated in MAP and SCZ but *DRD2* appears to be a strong candidate gene for both MAP and SCZ. As discussed above *DTNBP1* is one of several promising candidate genes for SCZ and was significantly associated with MAP susceptibility by Kishimoto and colleagues [56]. In the same study, Kishimoto et al. [56] also showed a significant association between a functional SNP (rs3213207A>G) and prolonged psychosis. This specific SNP has been associated with SCZ among Japanese [83] and showed to be over-transmitted in an Irish population [84].

The *SERT* and *COMT* genes also merit discussion in that both have been identified by several studies and meta-analyses as putative candidates for SCZ [74] and have also been associated with MAP. The SERT gene encodes a transporter protein responsible for terminating the synaptic actions of serotonin by clearing it from the synapse into the presynaptic neuron. Within the SERT gene a variable number tandem repeat (VNTR) polymorphism has been widely studied. Meta-analysis of SCZ data identified a 12-repeat allele that conferred a greater risk for SCZ [74]. Whereas, the 14-repeat allele was associated with prolonged psychosis and spontaneous relapse among Japanese MAP subjects [79]. Although not consistent, these results do support a potential role of the serotonin transporter in MAP and SCZ.

The *COMT* gene encodes a major mammalian enzyme involved in the metabolic degradation of dopamine released in the brain. *COMT* has pleiotropic effects in that it has been linked to neurocognition [85–87], novelty seeking [88, 89], amphetamine response [90], and several psychiatric disorders [91–93] in addition to SCZ [74, 94]. In a sample of Han-Chinese with MAP, Suzuki and associates [77] showed that the Met allele of the common functional val158met polymorphism (rs4680) was associated with spontaneous relapse. Recent meta-analysis of the val158met polymorphism in SCZ has failed to show a significant association; although, two other SNPs (rs165599 and rs737865) in the *COMT* gene have been identified for SCZ [74].

Conclusions and Future Directions

The clinical presentation, course, and treatment of MAP are similar to that observed in SCZ and subsequently MAP has been hypothesized as a pharmacological or environmental pathogen model of SCZ. In this chapter, we have described the genetic and potential underlying biological overlap of these two conditions. Several of the candidate genes for MAP susceptibility and clinical course have also been identified as candidate genes for SCZ. However, it should be noted that other putative SCZ genes such as *AKT1* (v-akt murine thymoma viral oncogene homolog 1), *NRG1* (neuregulin 1), and *DRD4* (dopamine receptor D4) have not shown a significant association with MAP susceptibility or clinical course when they have been examined. Likewise, putative genetic variants for MAP such as *ARRB2*, *GLYT1, GRM2, SNCA*, and *SOD2* have not been replicated in studies of SCZ. As would be expected, discrepancies have and will continue to be uncovered between the two disorders but the degree of overlap demonstrated in the literature thus far appears to outweigh these discrepancies. Future research of MAP is therefore warranted and could provide additional insight into the underlying biological mechanisms of SCZ. However, several challenges, as mentioned above, in identifying and diagnosing MAP currently exist and will need to be addressed in future research efforts before the MAP model will be capable of contributing to the discovery of biomarkers of SCZ. Additional longitudinal studies are required to further explain the clinical course of MAP and the role various factors (e.g. stress, alcohol, culture) play. Finally, future research utilizing MAP as a model for SCZ will need to transcend disciplinary boundaries in order to capture a systems-based view of MAP and unlock its potential as a model for SCZ. Two disciplines for which integration of genetic biomarkers makes sense are neuropsychology and neuroimaging, albeit other genomic-related fields such as transcriptomics, proteomics, and metabolomics as well as the disciplines of immunology, pathology, and public health, to name a few, will also be required to create a systems view of SCZ.

Tests of neurocognitive performance have garnered significant attention among clinical and basic scientists as an approach to capture intermediate phenotypes or endophenotypes [95] that may serve to identify and/or differentiate the clinical course and/or functional outcomes of severe psychiatric disorders with more

precision than current psychiatric phenotyping approaches (e.g. DSM-IV) [96]. The notion is predicated on the theory that impairments in neurocognitive performance are more proximal to the underlying disease process, and thus screening for neurocognitive impairments will allow for early identification, treatment, and potential prevention of the negative impact that these disorders have on families and society [97]. Neurocognitive impairment among METH users and those with psychosis has been well documented with the largest deficits seen in executive functioning, learning, memory, speed of information processing, and emotion processing [98, 99]. To date only one study has examined neurocognitive performance in MAP [100]. In this study, 19 participants with MAP and 20 with paranoid SCZ were administered a 4-h neurocognitive battery. The authors reported impairments for both MAP and SCZ; however, no significant differences between the two groups were observed, suggesting neurocognitive impairment in MAP and SCZ are comparable. Future neurocognitive work in MAP, utilizing larger samples will be needed before MAP's potential to inform identification of clinical useful neurocognitive biomarkers for SCZ can be evaluated.

Neuroimaging has also recently received attention as an approach for identifying markers for identification and/or differentiation of a variety of psychiatric illnesses. Several neuroimaging techniques [e.g. Positron emission tomography (PET), Single photon emission computed tomography (SPECT), Magnetic resonance imaging (MRI), Magnetic Resonance Spectroscopy (MRS)] are available by which images of the structure and function of the brain can be ascertained. To date, several neuroimaging studies [101, 102] have been conducted related to METH abuse but only a few neuroimaging studies related to MAP have been published (for review see Iyo et al. [103]). Among those conducted for MAP, one used PET and the other a MRS approach. In the PET study [104], the density of dopamine transporters in the nucleus accumbens and caudate/putamen in MAP participants was significantly less compared with controls, and it was correlated with the length of use and severity of psychotic symptoms. This is in partial concordance with a SCZ study [105] which observed a lack of brain asymmetry in dopamine transporter ligand uptake (right > left) in neuroleptic-naive SCZ patients. In the MRS study [106], MAP participants showed a significantly reduced ratio of creatine plus phosphocreatine (Cr + PCr)/choline-containing compounds (Cho) in the brain compared with the healthy control participants. In addition, the reduction in the ratio of Cr + PCr/Cho was significantly correlated with the duration of METH use and with the severity of residual psychiatric symptoms. In SCZ participants, the ratio of Cr + PCr/Cho in the left temporal lobe has been shown to be lower than in control subjects, albeit not significant [107]. However, the Cr + PCr/Cho ratio was negatively correlated with the left temporal lobe gray matter and positively with left temporal lobe white matter [107].

Clearly, further research of MAP across several disciplines employing a variety of approaches, such as imaging genomics [90, 91, 108, 109], are required before MAP is fully adopted as a feasible model for biomarker discovery in SCZ. However, the current literature points to the potential of MAP as an adjunct approach to ongoing efforts aimed at discovery of biomarkers of SCZ susceptibility and

clinical course. This in addition to the advent of a variety of biomarker discovery approaches, transcending multiple disciplines, will move the field of psychiatry closer to identifying viable biomarkers of SCZ that could revolutionize public health. Achieving this vision will require that biomarker-discovery efforts continue pushing forward with innovative and sound methodological approaches, some of which were described in this chapter. Finally, collaborative, interdisciplinary, working groups will be needed to enable integration of knowledge generated from MAP investigations from diverse disciplines and will be paramount to our search for biomarkers in SCZ.

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Chapter 16
What Does Proteomics Tell Us About Schizophrenia?

Daniel Martins-de-Souza, Wagner F. Gattaz, and Emmanuel Dias-Neto

Abstract Schizophrenia is likely to be a consequence of serial alterations of a number of genes and proteins that, together with environmental factors, will lead to the establishment of the illness. The comparative proteomic analysis of human brain tissue from schizophrenia patients and healthy controls using methods as two-dimensional gel electrophoresis and shotgun mass spectrometry may lead to the identification of disease-related proteins that will help to understand the biochemical basis of this pathogenesis as well as indicate potential biomarkers candidates. Here we present and discuss the potential roles of proteins differentially expressed in distinct brain regions of post-mortem tissue from schizophrenia patients. Proteins involved in energy metabolism, oligodendrocyte-function and myelinization, calcium homeostasis and cytoskeleton have been recurrently found to be differentially regulated in distinct brain regions and are likely to be implicated in schizophrenia. Moreover, a combined analysis of these proteins might lead to a molecular signature of the patients, which might contribute for diagnostic and therapeutic ends.

Keywords Schizophrenia · Proteomics · Mass spectrometry · Two-dimensional gel electrophoresis · Energy metabolism · Oligodendrocytes · Myelin · Calcium · Cytoskeleton

Abbreviations

2D-DIGE	Two-dimensional difference gel electrophoresis
2-DE	Two-dimensional gel electrophoresis
ACC	Anterior cingulate cortex

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AD	Alzheimer's disease
ATL	Anterior temporal lobe
BPD	Bipolar disorder
CC	Corpus callosum
DLPFC	Dorsolateral prefrontal cortex
ELISA	Enzyme-linked immunoadsorbent assay
FC	Frontal cortex
LC-MS	Shotgun mass spectrometry
MRM	Multiple reaction monitoring
MS	Mass spectrometry
PFC	Prefrontal cortex
SCZ	Schizophrenia
WA	Wernicke's area
WB	Western blot

Schizophrenia

As a debilitating, psychotic mental disorder that affects about 0.5% of the population worldwide with a lifetime risk of 1% [1], schizophrenia (SCZ) is likely to be the result of multifactorial endogenous and exogenous interactions. The genetic components are probably the most important endogenous elements of this network: DNA alterations, which have already been described in SCZ, may lead to differential gene and protein expression. As consequence, physiological imbalances are driven that, combined with environmental factors such as viral and other infections [2], birth complications [3] and migration to urban centers [4] may trigger the disease.

Considering that all efforts to understand SCZ are still not enough to decipher such disorder and that the diagnosis of SCZ is essentially based in clinical symptoms, although this has been a changing matter, studies of protein expression in SCZ brain tissue may collaborate to fill up these gaps.

Proteomics

The word proteomics arose from the term proteome, originally defined as "the total set of expressed proteins by a cell, tissue or organism at a given time under a determined condition" [5]. Proteome analyses may also include studies of post-translational modifications, protein–protein interaction analysis and 3D structure determination. Quantitative proteomic technologies allowed the study of differentially expressed proteins that can usually be identified by comparing two or more samples, such as diseased and non-diseased tissues as well as samples submitted to distinct therapeutic regimens.

Methods for Differential Proteome Studies

The distinct proteomics approaches described in this chapter and presented in Fig. 16.1, have their intrinsic advantages and weaknesses. Thus, the combination of two or more of methods would be best to maximize proteome coverage, revealing to the most relevant molecular pathways.

Two-dimensional Gel Electrophoresis

Up to date, most proteomic analyses are performed using a combination of two-dimensional gel electrophoresis (2DE) for protein separation and mass spectrometry (MS) for protein identification. This combination of technologies allows the simultaneous separation of hundreds of proteins in a single experiment. Direct comparisons of 2DE profiles using computational software from different samples combined with unambiguous identification of the separated proteins by MS is the traditional approach used by most researchers. An alternative way for 2DE quantification is to label the protein samples with cyanine-derived fluorophores pre-electrophoresis,

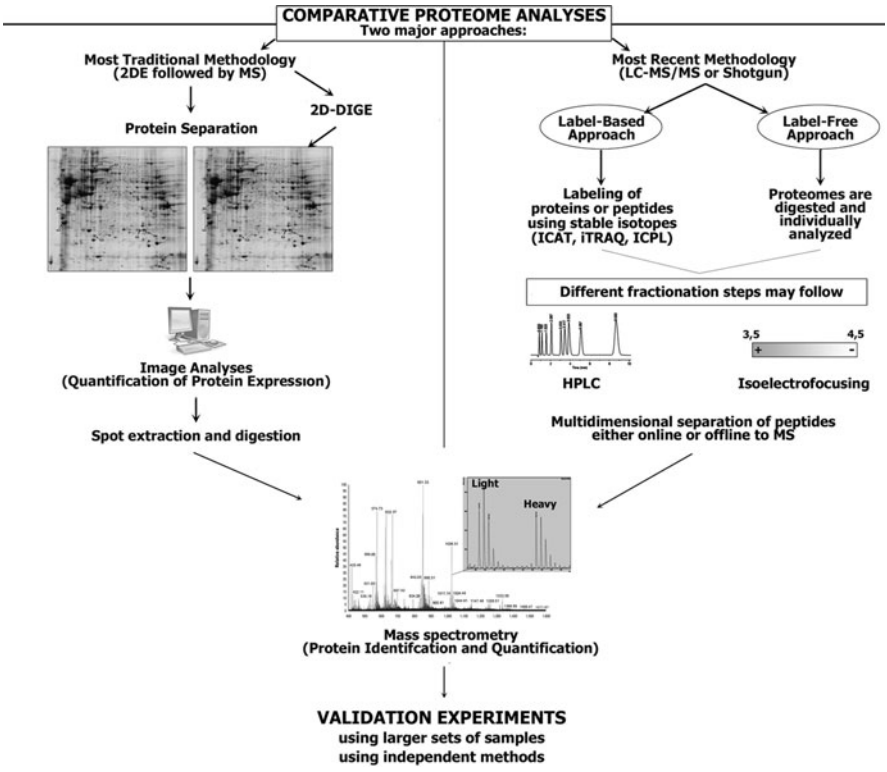

Fig. 16.1 Brief summary of proteomics methodologies

constituting the fluorescent two-dimensional difference gel electrophoresis (2D-DIGE). Beyond the higher quantitative power, reproducible proteome differences can be detected by using small amounts of sample (detection limit between 150 and 500 pg).

2DE and 2D-DIGE have been extensively and successfully used in studies of brain tissue of psychiatric disorders such as SCZ [6–9] and bipolar disorder (BPD) [10, 11] as well as in studies of neurodegenerative disorders such as Alzheimer's disease (AD) [12]. These studies have identified a number of proteins that could be involved in disease pathogenesis, increasing the understanding of such disorders.

Despite the analytical power of this approach, 2DE–MS-based proteomics presents some limitations such as a difficulty in detecting low-abundance, acidic or basic proteins as well as proteins with extremes of high or low molecular weight [13]. Such limitations have led researchers to pursue alternative ways for proteome characterization.

Shotgun Proteomics

Aiming to avoid the above mentioned drawbacks, Link et al. [14] have developed an alternative direct MS-based approach for proteome studies, generally known as "shotgun proteomics" which uses a combination of chromatographic steps prior to MS analyses in a high-throughput way. Protein quantitation of shotgun approaches, especially when stable-isotope methods such as iTRAQ (isobaric tag for relative and absolute quantitation) and ICPL (isotope-coded protein label) are used, is more accurate than the 2DE–MS approach. One potential drawback of shotgun approaches is that they are not capable of providing direct information on intact proteins, as is the case for 2DE. However, shotgun proteomics has been used in SCZ studies, revealing some differentially expressed proteins that have not be found by 2DE methods [15–17].

Validation Experiments

It is important to highlight that the global differences in protein expression of a given tissue generated from 2DE and shotgun experiments needs validation by other methods in order to demonstrate that the differences found in a certain set of samples can also be found in a broader universe of samples, considering factors such as age, gender, pharmacological treatment, disease endophenotypes and ethnical issues. Western blot (WB), enzyme-linked immunoadsorbent assay (ELISA), multiple reaction monitoring (MRM) mass spectrometry are the most used methods for this purpose.

Metabolomics

The comparative proteome analyses studies of human brain tissue directly lead to the identification of biochemical pathways and may consequently provide indication of the associated metabolites. The quantitation of metabolites using diverse

approaches can provide a more complete picture of brain activities which may be useful for comprehension of the biochemical processes as well as a means of providing a source of non-protein-based biomarkers. Energy metabolism metabolites such as pyruvate and NADPH have been quantified in SCZ thalamus using biochemical assays, confirming their different levels as suggested by the differential expression of glycolitic enzymes [17]. High-performance liquid chromatography (HPLC) has been used to quantify significant differences in the polyamines putrescine and spermidine in high anxiety-related behaviour (HAB) and low anxietyrelated behaviour (LAB) brain tissue extracts [18] and high-resolution proton nuclear magnetic resonance spectroscopy (1H-NMR) has been used to observe the effects of a number of psychotropic drugs on rat brain metabolites and significant differences were found regarding N-acetylaspartate (NAA) levels [19].

Proteomics of Schizophrenia Brain Tissue

Extensive proteome studies have been performed in tissues from SCZ patients such as brain, liver, and skin tissue as well as peripheral tissues such as cerebrospinal fluid (CSF), and serum using all sorts of proteomic methods. Those studies, conducted in distinct sample sets, have presented differentially expressed proteins, mainly converging to dysfunctions energy metabolism, cytoskeleton assembly, immune system, calcium buffering, phospholipids breakdown and oligodendrocyte metabolism. Moreover, some of the differentially expressed proteins revealed by proteomics studies have been used as disease biomarkers for diagnosis and may also generate potential biomarker candidates to therapeutic approaches and prognosis experiments.

As a disease of the brain, many efforts in proteomics have been devoted to studies of brain tissue. So far, there are 14 published articles on proteomics of SCZ brain tissue, investigating 9 distinct brain regions (Table 16.1), which consistently revealed the following pathways.

Cytoskeleton-Related Proteins

Cytoskeleton-related proteins (CPs) present particular expression patterns that are tissue specific and directly related to their function. Altered CP expression in brain tissues may influence developmental processes such as symmetrical shape, structural polarity, neuritogenesis, and neurotransmission. The involvement of CPs in neurodevelopment strongly supports the SCZ neurodevelopmental hypothesis [25].

Tubulins are CPs involved in multiple activities such as mitosis, cytokinesis, and vesicular transport [26]. Alterations of tubulin subunits have been documented in the PFC, DLPFC, ACC, CC, WA, ATL, and thalamus of SCZ patients. Denarier et al. [27] highlighted the possible roles of tubulin in SCZ. Moreover, by knocking out the stable tubulin-only polypeptide (STOP) gene, which is responsible for microtubule stabilization in neurons these authors were able to produce a SCZ mouse model so-called “STOP null mice”, which despite presenting a somewhat normal

Table 16.1 Proteome analyses of human brain tissue from schizophrenia patients

Article	Brain region	Sample subjects	Methodology
Johnston-Wilson et al. [20]	Frontal cortex (FC)	24 SCZ X 23 CTRL	2DE
Prabakaran et al. [6]	Prefrontal cortex (PFC)	54 SCZ X 50 CTRL	2D-DIGE
Clark et al. [21]	Anterior cingulate cortex (ACC)	10 SCZ X 10 CTRL	2DE
Beasley et al. [10]	Anterior cingulate cortex (ACC)	15 SCZ X 15 CTRL	2DE
Sivagnanasundaram et al. [22]	Corpus callosum (CC)	10 SCZ X 10 CTRL	2DE
Martins-de-Souza et al. [7]	Dorsolateral prefrontal cortex (DLPFC)	9 SCZ X 7 CTRL	Shotgun
Martins-de-Souza et al. [8]	Anterior Temporal Lobe (ATL)	5 SCZ X 4 CTRL	Shotgun
Martins-de-Souza et al. [15]	Dorsolateral prefrontal cortex (DLPFC)	9 SCZ X 7 CTRL	2DE
Martins-de-Souza et al. [16]	Wernicke's Area (WA)	9 SCZ X 6 CTRL	2DE
Behan et al. [23]	Dorsolateral prefrontal cortex (DLPFC)	10 SCZ X 10 CTRL	Shotgun and 2D-DIGE
English et al. [11]	Dorsolateral prefrontal cortex (DLPFC)	35 SCZ X 35 CTRL	2D-DIGE
Nesvaderani et al. [24]	Hippocampus	9 SCZ X 9 CTRL	2DE
Martins-de-Souza et al. [17]	Thalamus	11 SCZ X 8 CTRL	Shotgun and 2DE
Martins-de-Souza et al. [9]	Anterior cingulate cortex (ACC)	11 SCZ X 8 CTRL	2DE

brain anatomy, showed synaptic dysfunction, probably due to dysfunctional glutamatergic transmission [28], and exhibited a hyperdopaminergic state in the limbic system [29].

The glial fibrillary acidic protein (GFAP) is the major intermediate filament (IF) protein of mature astrocytes. Astrocytes play a role not only in the structural stability of brain tissue, but also in water and electrolyte homeostasis, provision of nutrients to neurons and other glial cells, neuronal migration, repair processes, modulation of the immune response and neurotransmitter release, and also have a role in controlling synapse formation [30]. Despite some controversial results, astrocytes have emerged as important players in the pathobiology of SCZ: the differential expression of proteins such as GFAP may play a key role in the synaptic metabolism of glutamate and monamines [31], compromising synaptic functioning and behavior [32]. The differential regulation of GFAP in the FC, PFC, DLPFC, ACC, CC, IC, WA, ATL and thalamus from SCZ patient specimens was reported in 9 of the 15 articles on SCZ global proteome analysis of brain tissue. GFAP has been previously associated to other neurological diseases such as multiple sclerosis [33], AD [34] and Schwann cell degeneration [35].

The neurofilaments M and L (NEFM and NEFL), whose genes are mapped to chromosomal hot spots for SCZ susceptibility, belong to the dopamine receptor interacting protein (DRIP) family of proteins, which play important roles in the

dopamine receptor signal transduction pathway [36]. NEFL, which is downregulated in the PFC, DLPFC, CC, and ATL, is directly associated with NMDA receptors [37]. The possible role of neurofilaments in SCZ has been shown by immunohistochemistry [38], in situ hybridization [39] and association studies [40, 41]; the association studies showed linkage disequilibrium of NEFM, which was found to be downregulated in PFC, ATL and CC. Alterations in NEFL were also described in brain tissue of patients with multiple sclerosis [42]. Neurofilaments were previously associated to neurodegeneration, a feature that may happen in SCZ brains [43] as discussed ahead.

Dynamin 1 (DNM1) was reported to be upregulated in the PFC, DLPFC and ACC from SCZ. DNM1 is a microtubule-binding protein that plays a central role as a mechanochemical enzyme in synapses promoting vesicle endocytosis [44, 45]. The internalization of the short form of the dopamine D2 receptor is DNM1 dependent, as is the internalization of the metabotropic glutamate receptors [46]. These findings are of interest because dysfunctions of both dopaminergic and glutamatergic receptors may be related to the biology of SCZ and to the effects of antipsychotic drugs.

Calcium Buffering

Ca2+ is considered a pivotal metabolite for the dopamine hypothesis in SCZ and plays a crucial role in the function of dopamine receptors D1 and D2 [36]. Most of the proteome analyses in SCZ brain tissue have revealed the differential expression of proteins related to Ca2+ homeostasis and metabolism such as calcineurin that among other functions regulates dopaminergic [47] and glutamatergic [48] neurotransmission, which are frequently compromised in SCZ [49, 50]. Dopaminergic hyperactivity in SCZ may result in altered N-methyl-D-aspartic acid (NMDA) receptor activation, which can lead to excitotoxicity and excess Ca2+ influxes through NMDA receptors [51]. Other differentially expressed proteins are calmodulin, which acts as an intracellular sensor of Ca2+, and PMCA-4 that is involved in the maintenance of Ca2+ homeostasis in the cell [52]. Both might interfere in phospholipase A2 (PLA2) activity and consequently in dopaminergic activity, as previously described [53, 54]. Moreover, demyelinization (to be discussed ahead) may occur as a result of differential Ca2+ buffering [55].

Oligodendrocyte Dysfunction

The main known function of oligodendrocytes, a type of neuroglia constituting approximately 51% of the cells around the soma of large neurons in the human cortex [56], is to insulate the axons in the central nervous system (CNS), wrapping it with myelin, providing an electrically-insulating phospholipid layer that facilitate axonal signal by increasing the speed at which the electrical impulses are propagated and by preventing the electrical current from leaving the axon. Other oligodendrocyte functions are trophic signaling among neurons, growth factor synthesis, neuronal survival and development and neurotransmission [57, 58]. Disturbances

in the myelin sheath could lead to ion leakage with reduced nerve impulse propagation, consequently compromising neuronal and glial functions. Convergent data from different research fields have described the dysfunction of oligodendrocytes as an important feature in SCZ pathogenesis because of their implication in brain connectivity. Recently, dysfunctions of oligodendrocyte metabolism have been often observed and suggested in SCZ studies of brain tissue [59].

Brain imaging studies have demonstrated the dysfunction of oligodendrocytes in SCZ. Decreased myelin integrity, as well as decreased axonal membranes has been observed in temporal and frontal lobes using magnetic transfer imaging [60, 61]. Moreover, levels of phosphatidylcholine, sphingomyelin and galactocerebroside – indispensable for oligodendrocyte metabolism – were found to be decreased in the post-mortem thalamus of patients with SCZ [62]. Also, abnormal distribution and decreased density of oligodendrocytes, apoptotic oligodendrocytes, damaged myelin sheaths and a decreased volume density of mitochondria were observed by electron microscopy studies in frontal regions of SCZ brains [63]. Epigenetic evidence and abnormal myelinization has also been discussed as potential issues of oligodendrocytes in SCZ [64–66]. Studies of neurodevelopment and synaptic circuits in several brain regions from SCZ patients have also found the dysfunction of oligodendrocytes in SCZ [67–69].

Right before proteomics, transcriptome studies – most of them using cDNA microarrays – in brain tissue has revealed oligodendrocyte dysfunction in SCZ [70–75]. The first proteome report about oligodendrocyte dysfunction in SCZ was published by Prabakaran et al. [6] and subsequent experiments were able to corroborate previous data and even present new SCZ oligodendrocyte candidates (Table 16.2).

All the transcriptome reports shown here (Table 16.2) have found the differential regulation of the myelin-associated glycoprotein (MAG), an indispensable membrane protein in the myelination process and post-natal neural development. However, it is interesting to observe that no proteome reports have found the differential expression of this protein, although it should be easily identifiable using available proteomics methods considering its theoretical isoelectric point (4.97) and a molecular weight (69,069). This suggest that a post-transcriptional regulatory could be acting, preventing altered mRNA concentrations to be translated into corresponding protein alterations. On the other hand, the mRNA concentration of this gene can still be a potential mRNA biomarker.

The 2′,3′-cyclic nucleotide 3′ phosphodiesterase protein (CNP) is a membrane-bound microtubule-associated protein which links tubulin to cellular membranes regulating the microtubule distribution in the cytoplasm [76] and in oligodendrocytes promotes microtubule assembly for process outgrowth [77]. It is a well-characterized marker of myelin-forming cells, playing an indispensable role in axonogenesis [78], RNA metabolic process [79], and synaptic transmission [80]. Genetic association studies have confirmed the relation of CNP in SCZ pathogenesis [81, 82]. CNP was found differentially expressed in 6 transcriptome analyses and 3 proteome analyses of SCZ brain tissue what might point it as a potential biomarker candidate for SCZ.

Table 16.2 Oligodendrocyte-related genes and proteins which are differentially expressed in schizophrenia brain tissue

Gene	Alteration in proteome level	Alteration in transcriptome level
MBP *Myelin Basic Protein*	Martins-de-Souza et al. [7, 16, 17]	Tkachev et al. [71]
CNP *2′,3′-cyclic nucleotide 3′ phosphodiesterase*	Prabakaran et al. [6] Martins-de-Souza et al. [15, 16]	Hakak et al. [70] Tkachev et al. [71] Aston et al. [72] Katsel et al. [73] Dracheva et al. [74]
MAG *Myelin-associated glycoprotein*	–	Hakak et al. [70] Tkachev et al. [71] Aston et al. [72] Katsel et al. [73] Dracheva et al. [74]
ERBB3 *v-erb-b2 erythroblastic leukemia viral oncogene*	–	Hakak et al. [70] Tkachev et al. [71] Aston et al. [72] Katsel et al. [73]
TF *Transferrin*	Prabakaran et al. [6] Clark et al. [21] Martins-de-Souza et al. [7, 17]	Hakak et al. [70] Tkachev et al. [71] Katsel et al. [73] Arion et al. [75]
GSN *Gelsolin*	Prabakaran et al. [6]	Hakak et al. [70] Katsel et al. [73]
MAL *T-lymphocyte maturation-associated protein*	–	Hakak et al. [70] Aston et al. [72] Katsel et al. [73]
CLDN11 *Claudin 11* *Oligodendrocyte specific protein*	–	Tkachev et al. [71] Katsel et al. [73] Dracheva et al. [74]
MOG *Myelin oligodendrocyte glycoprotein*	Martins-de-Souza et al. [15, 16, 17]	Tkachev et al. [71] Katsel et al. [73] Arion et al. [75]
PLP *Proteolipid protein*	–	Tkachev et al. [71] Aston et al. [72]
PLLP *Plasmolipin*	–	Aston et al. [72] Katsel et al. [73]

Beyond to the transport of iron ions, Transferrin (TF) has a pivotal role in oligodendrocytes during myelination [83]. TF was found to be differentially expressed in a number of transcriptome and proteome analyses. Deficiencies in iron concentration lead to higher levels of TF as previously demonstrated in rats [84]. More

recently, Insel et al. [85] suggested that maternal iron deficiency may be a risk factor for SCZ in the offspring.

Myelin basic protein (MBP) is the major constituent of the myelin sheath of oligodendrocytes and Schwann cells in the nervous system and its expression was found altered by transcriptome as well as by proteome studies [7, 16, 17, 71], suggesting disturbances in myelinization as previously observed. Myelin oligodendrocyte protein (MOG) is a membrane protein localized in the oligodendrocyte and myelin sheath surface which has active roles in CNS development and synaptic transmission. MOG differential expression was also found in RNA and protein levels in brain tissue (Table 16.2). MOG and MBP are known markers for neurodegenerative diseases such as Multiple Sclerosis (MS) and the altered levels of both proteins were found in the CSF of SCZ patients, suggesting them as potential biomarker candidates.

A number of other oligodendrocyte candidates such as gelsolin (GSN), myelin and lymphocyte protein (MAL), claudin 11 (CLDN11), proteolipid protein (PLP) and quaking protein (QK1) were found differentially expressed, suggesting an overall dysregulation of the oligodendrocyte metabolism and disturbed myelination (Table 16.2).

The differential expression of mRNA and proteins such as MBP, MOG, PLP and MAG in SCZ brain tissue, which are classic markers of multiple sclerosis, might support the hypothesis of neurodegeneration in SCZ [43, 86]. Patient's premorbid stage, the illness course, symptoms and cognitive function may keep up neurodegenerative events in SCZ. Recently, in vivo neuroimaging studies have suggested that SCZ patients display progressive losses of gray matter in the frontal and temporal brain cortices, probably due to abnormal apoptotic events [87]. Moreover, how calcium imbalance in SCZ, also observed in proteomics findings, might lead to degenerative processes, as a result of dysfunctions in intracellular calcium buffering, storage and influx is reviewed in Wojda et al. [88].

Energy Metabolism

In 1919, Kooy [89] published a report on the incidence of impaired energy metabolism in SCZ. In an extensive analysis of different psychiatric disorders, Kooy observed hyperglycemia in SCZ patients, similar to the effects seen in dementia praecox subjects and hypothesized that depression-like behavior influences the levels of blood sugar.

Alterations in glucose handling in the SCZ brain have been demonstrated by several studies such as: (a) imaging analyses showed reduced cerebral blood flow in the frontal cortex, which launched the term "hypofrontality" [90], lower metabolic rates in the frontal brain region before and even after the treatment with antipsychotics [91, 92] in SCZ patients; (b) lower rates of glucose metabolism in the hippocampus and the ACC of SCZ patients compared to controls [93]; (c) the administration of glucose to SCZ patients resulted in increased verbal declarative memory and attention [94]; (d) hyperglycemia, impaired glucose tolerance and/or insulin resistance in first onset, anti-psychotic naïve SCZ patients [95–97].

Impairments on glucose handling might lead to disturbed states of mitochondria which contain an intricate network of enzyme activities which are tightly regulated to optimize anabolic and catabolic processes. Perturbation in activity of one or more of these components could result in altered energy production through the impairment of citric acid cycle (or Krebs cycle), and oxidative phosphorylation (OXPHOS), which could lead to an increased production of damaging reactive oxygen species (ROS). Mitochondrial oxidative stress may lead to DNA damage, malfunction of energy production through protein inactivation, altered gene and protein expression and finally in apoptosis and cell death. These processes may impair neuronal plasticity, disturbing neurotransmission and increasing the vulnerability to biological stresses. Such processes may start during neurodevelopment in SCZ patients and coincide with manifestation of symptoms during early adulthood [98, 99]. Evidences such as morphological, volume and density alterations of mitochondria in SCZ [100] support this hypothesis.

Most of the differentially expressed proteins we found in SCZ brain tissue are energy-related (Table 16.3) and the largest group of these proteins is glycolitic enzymes. Glycolysis mainly processes intracellular glucose generating two molecules of pyruvate which in the mitochondria can be converted to acetyl-CoA and oxaloacetate to initiate the Krebs cycle. The most consistent differentially expressed enzyme is aldolase C (ALDOC), which has been found in 7 independent proteome reports of SCZ brain tissue. Enzymes as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and Hexokinase (HK1) were also consistently found differentially expressed. Aiming a functional validation, levels of pyruvate, the final product of glycolysis, was quantified in the thalamus of SCZ patients and found to be decreased in patients when compared to healthy controls [17].

The lower levels of pyruvate in SCZ brains may potentially lead to compromised function of the Krebs cycle, as also observed by proteomics for instance through the differential expression of pyruvate dehydrogenase E1 component alpha 1 (PDHA1), aconitase 2 (ACO2), and malate dehydrogenase 1 (MDH1). The role of Krebs cycle as producer of redox potential has been tested through quantitation of NADH and NADPH levels. Higher levels of NADH have been found in the thalamus of SCZ patients [17], indicating a disturbed production of ion donors, which might compromise OXPHOS.

Proteomic studies have also revealed that several components of the mitochondrial complex I and V are altered in SCZ. Complex I is located in the mitochondrial inner membrane and is composed of 45 subunits, being 5 of them found to be differentially expressed. This complex has NADH dehydrogenase and oxidoreductase activities. Complex V, formed by 16 subunits, is a general term for the enzymatic complex that synthesizes ATP.

As mentioned, the overall dysregulation of energy metabolism may raise hazardous ROS concentrations leading to oxidative stress events that have been identified by proteomic technologies. The peroxiredoxins (PRDXs), which are differentially expressed in SCZ brain tissue, reduce H_2O_2 to H_2O+O_2 and are regulated by phosphorylation and redox states that protect cells against oxidative injury. Interestingly, PRDXs may also act in phospholipid turnover, which is known to

Table 16.3 Energy-related proteins which are differentially expressed in schizophrenia brain tissue

Gene Name	Protein Name	Energy Metabolism Process	BA10 2DE [20]	BA9 2DE-DIGE [6]	BA24 2DE [21]	BA24 2DE [10]	CC 2DE [22]	BA9 2DE [23]	BA46 2DE [7]	BA38 Shotgun [16]	BA46 Shotgun [15]	BA22p 2DE [8]	Thalamus Shotgun 2DE [17]
ALDOC	Fructose bisphosphate; aldolase C	Glycolysis	↑	↓	↓				↑	↓		↓	
ENO2	Gamma enolase (2-phospho-D-glycerate hydro-lyase)	Glycolysis		↓			↓	↓				↑	
HK1	Hexokinase brain form	Glycolysis		↑						↑	↑		
PGAM1	Phosphoglycerate mutase 1	Glycolysis		↓								↑	↑
TPI1	Triosephosphate isomerase	Glycolysis		↓								↑	↑
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	Glycolysis		↓								↓	↑
PGK1	Phosphoglycerate kinase 1	Glycolysis							↑				
ACO2	Aconitate hydratase, mitochondrial precursor (Aconitase)	Krebs Cycle		↓		↑			↑			↑	
MDH1	Malate dehydrogenase 1, NAD (soluble)	Krebs Cycle		↓					↓				
PDHA1	Pyruvate dehydrogenase E1 component, alpha 1	(Pre) Krebs Cycle		↓									
DLD	Dihydrolipoyl dehydrogenase, mitochondrial precursor	(Pre) Krebs Cycle										↑	
ME3	Malic enzyme 3	(Pre) Krebs Cycle											↑
ATP5A1	ATP synthase alpha chain, mitochondrial precursor	OXPHOS							↑			↓	

Table 16.3 (continued)

Gene Name	Protein Name	Energy Metabolism Process	BA10 2DE [20]	BA9 2DE-DIGE [6]	BA24 2DE [21]	BA24 2DE [10]	CC 2DE [22]	BA9 2DE [23]	BA46 2DE [7]	BA38 Shotgun [16]	BA46 Shotgun [15]	BA22p 2DE [8]	Thalamus Shotgun 2DE [17]
ATP5H	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d isoform a	OXPHOS							↓				
COII	Cytochrome c oxidase subunit 2	OXPHOS											↓
NDUFB9	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9	OXPHOS											↑
NDUFS6	NADH-ubiquinone oxidoreductase 13 kDa-A subunit	OXPHOS								↓			
NDUFB5	NADH-ubiquinone oxidoreductase SGDH subunit	OXPHOS								↓			
NDUFS1	NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial precursor	OXPHOS										↓	
NDUFS3	NADH-ubiquinone oxidoreductase 30 kDa	OXPHOS								↓			
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2	OXPHOS								↓	↑		
PRDX1	Peroxiredoxin 1	Oxidative Stress		↓									

Table 16.3 (continued)

Gene Name	Protein Name	Energy Metabolism Process	BA10 2DE [20]	BA9 2DE-DIGE [6]	BA24 2DE [21]	BA24 2DE [10]	CC 2DE [22]	BA9 2DE [23]	BA46 2DE [7]	BA38 Shotgun [16]	BA46 Shotgun [15]	BA22p 2DE [8]	Thalamus Shotgun 2DE [17]
PRDX2	Peroxiredoxin 2	Oxidative Stress		↓							↑		
PRDX6	Peroxiredoxin 6	Oxidative Stress									↑	↑	
GSTM3	Glutathione-S-transferase M3 (brain)	Oxidative Stress		↓									
GSTTLp28	Glutathione transferase omega	Oxidative Stress		↓									
GSTP1	Glutathione S-transferase P	Oxidative Stress											↓
CBR1	Carbonyl reductase 1	Oxidative Stress		↓							↓		↑
CBR3	Carbonyl reductase 3	Oxidative Stress		↓									
QDPR	Quinoid dihydropteridine reductase	Oxidative Stress		↓								↑	↑
TKT	Transketolase	Penthose Phosphate Pathway							↑				↑
CNP	2′,3′-cyclic nucleotide 3′ phosphodiesterase	Oligodendrocyte metabolism		↓						↓	↓		
CA2	Carbonic anhydrase 2	Catalytic activity in energy pathways	↓		↑					↓			
CKB	Creatine kinase, B chain	Catalytic activity in energy pathways		↓	↑	↓	↓				↑	↑	
GLUL	Glutamate-ammonia ligase (glutamine synthase)	Transaminase activity in energy pathways		↓									↑
TF	Transferrin	Transport		↓	↓			↓	↓				
ATP6V1A	Vacuolar ATP synthase catalytic subunit A	Transport						↓	↑		↑	↑	

be altered in the pathogenesis of SCZ. Also differentially expressed are members of gluthatione transferases (GST) family, multifunctional enzymes which are involved in cellular detoxification, glutathione reduction and neutralization of ROS [101]. Moreover, the NADPH-dependent oxidoreductases carbonyl reductase 1 (CBR1), carbonyl reductase 3 (CBR3) and quinoid dihydropteridine reductase (QDPR) may be influenced by oxidative stress state in SCZ tissue. The imbalance of the NADP/NADPH ratio observed in SCZ thalamus may have an influence over their expression. In the presented context, oxidative stress seems to be a consequence of impaired metabolism. However, results from animal model studies suggest that oxidative stress may be a central feature of SCZ [102–104].

Other energy pathways were found involved in SCZ by proteomics through the differential expression of the following enzymes. Transketolase (TKT) is an enzyme of the pentose phosphate pathway (PPP) which main function is to generate redox potential for OXPHOS through the production of NADPH. NADPH plays a role in cell defense against ROS and was found in altered concentrations in SCZ thalamus [17]. Vacuolar ATP synthase catalytic subunit A (ATP6V1A) is a subunit of V-ATPase, an enzymatic complex that mediates acidification of eukaryotic intracellular organelles, necessary for synaptic vesicles function. Glutamine synthase (GLUL) catalyzes the synthesis of glutamine, which plays a role in cell proliferation, inhibition of apoptosis and cell signaling.

It should be mentioned that all SCZ proteome studies cited here have been performed using brain tissue from patients treated with antipsychotic drugs, so that for at least some findings a drug-derived artifact cannot be ruled out. However, this source of bias may be partially obviated by experimental evidence suggesting that the alterations of energy metabolism described in SCZ is a component of the disease itself and not an effect of antipsychotic drugs [99, 105].

Conclusions and Future Directions

Initially, the main idea of global expression studies in SCZ brain tissue was to reveal differentially expressed genes or proteins that might not only lead us to a better comprehension of the disease, but specially point out potential biomarkers for diagnosis, and secondary biomarkers for prognosis and disease monitoring. Instead, as data were generated and analyzed, it became very clear that complex disorder as SCZ, which involves the interaction of multiple genetic and environmental factors, wouldn't present a single or a couple of universal disease biomarkers, but a large set of them. Moreover, despite some encouraging results, most of the differences regarding protein expression in brain tissue couldn't be replicated in plasma or even CSF, pushing the dream of a diagnostic tool further while looking at the brain.

Analyses in peripheral tissues were the most well succeeded researches regarding diagnostic biomarkers. Studies such as carried on by Levin et al. [106] have led to a diagnostic test with approximately 85% efficiency that has been commercialized

since January/2010 by the companies Rules Based Medicine and Psynova. Results in SCZ CSF were also encouraging [17, 107–110] and present potential findings to be explored.

The SCZ proteome of tissues other than brain, such as liver and fibroblasts [111, 112], were also investigated and despite most of the differentially proteins weren't exactly the ones found in brain tissue, there were encouraging overlaps in terms of biochemical pathways, meaning that the SCZ does presents a pattern of protein differential expression.

If clinically relevant biomarkers couldn't be revealed from the proteome of brain tissue, on the other hand we are certainly ending up this cycle of brain studies with a much greater knowledge about SCZ, as shown in Fig. 16.2, which will be very useful for the next steps forward. Biological models, targeted treatments, and prognosis are some of these many steps to be walked. On this regard, we are certain that the data presented here will be definitely useful.

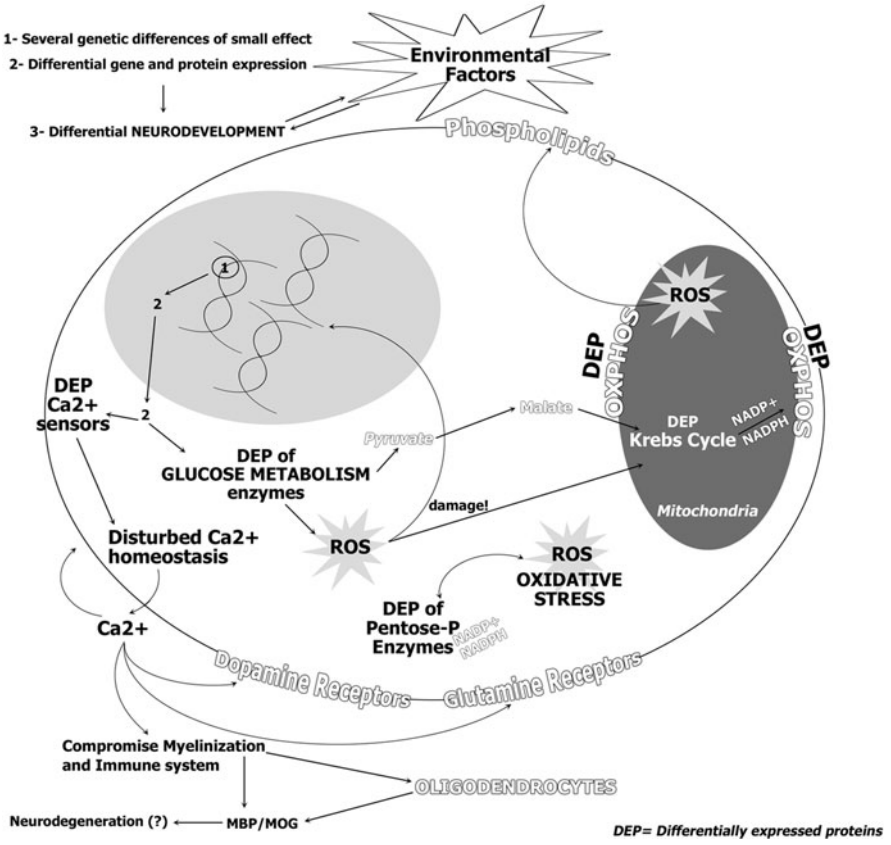

Fig. 16.2 Biochemical processes involved in schizophrenia revealed by proteome analyses of human brain tissue

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Chapter 17
The Role of 3α-Hydroxy-5α-Pregnan-20-One in Mediating the Development and/or Expression of Schizophrenia Spectrum Disorders: Findings in Rodents Models and Clinical Populations

Cheryl A. Frye and Danielle C. Llaneza

Abstract Neurosteroids, including 3α-hydroxy-5α-pregnan-20-one (3α,5α-THP), mediate stress-responding, and the function and development of the central nervous system. 3α,5α-THP can be produced in the brain or metabolized from peripheral sources, including the adrenals, gonads, and placenta. 3α,5α-THP has actions to dampen stress-responding and reinstate parasympathetic tone. There are sex differences in stress-responding, such that women are more stress-responsive than men. Further, there are sex differences in 3α,5α-THP, such that women have greater variations across the menstrual cycle and across the lifespan compared to men. Similar differences and variations in 3α,5α-THP are observed among rodent species, and elevated levels of 3α,5α-THP are associated with dampened stress-responding. These sex differences in stress-responding and neurosteroids may be related to sex differences in the incidence and/or expression of schizo-affective disorders. This chapter reviews findings in support of the hypothesis that 3α,5α-THP has a role in schizophrenia and/or affective disorders.

Keywords Neurosteroids · 3α,5α-THP · Allopregnanolone · Schizophrenia · Affective disorders · Cognition · Stress

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Abbreviations

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
3α,5α-THP	3α-hydroxy-5α-pregnan-20-one
3α-HSOR	3α-hydroxysteroid oxidoreductase
3β-HSD	3β-hydroxysteroid dehydrogenase
5α-R	5α-reductase
5α-RKO	5α-R knockout mice
ADX	Adrenalectomized
ACTH	Adrenocorticotropin
apoER2	Apolipoprotein E2 receptor
ADHD	Attention deficit hyperactivity disorder
CNS	Central nervous system
B	Corticosterone
CRH	Cortico-tropin-releasing hormone
P450scc	Cytochrome P450-dependent C27 side chain cleavage enzymes
DHP	Dihydroprogesterone
DA	Dopamine
D_1	DA-like type 1 receptors
DAT	DA transporters
DATKO	DA transporter knockout mice
ER	Endoplasmic reticulum
E	Estrogen
FST	Forced swim task
GBRs	$GABA_A$/benzodiazepine receptor complexes
GD	Gestational day
GAD	Glutamic acid decarboxylase
HPA	Hypothalamic pituitary adrenal
IL-1β	Interleukin-1β
METH	Methamphetamine
NMDARs	N-methyl-D-aspartate receptors
OVX	Ovariectomized
PFC	Prefrontal cortex
PMDD	Premenstrual dysphoric disorder
PNS	Prenatal stress
PPI	Prepulse inhibition
P	Progesterone
PR	Progestin receptor
PND	Post-natal days
RED	Reproductive Endocrine Dysfunction
StAR	Steroidogenic acute regulatory protein
TSPOs	Translocator proteins
USV	Ultrasonic vocalization
VTA	Ventral tegmental area
VLDLR	Very low-density lipoprotein receptor

Introduction

Neurosteroids, steroid hormones produced in the brain, such as 3α-hydroxy-5α-pregnan-20-one (3α,5α-THP), are important endogenous modulators of the hypothalamic pituitary adrenal (HPA) axis, and the function and/or development of the central nervous system (CNS). 3α,5α-THP can be produced in the brain in response to stress to dampen HPA-responding and reinstate parasympathetic tone (Diagram 17.1) [1, 2]. 3α,5α-THP can also be metabolized from progesterone (P) secreted by the adrenals, ovaries and/or placenta [3], where actions in the brain can also mitigate stress-responding. Thus, production of 3α,5α-THP mediates stress-responding.

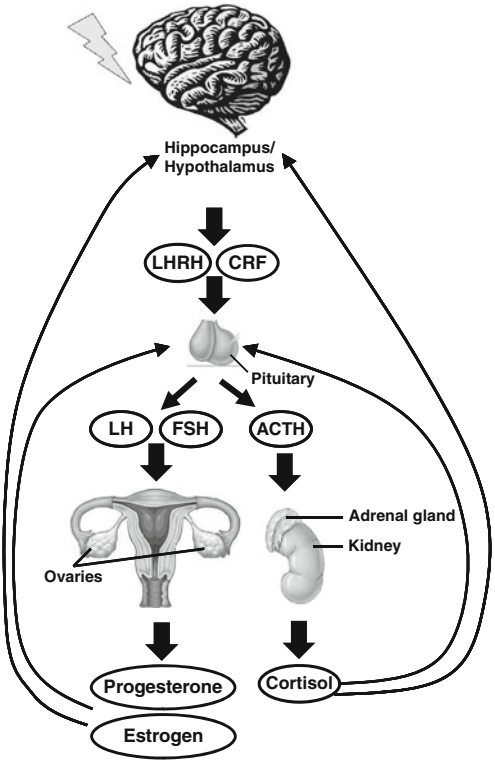

Diagram 17.1 The influence of endogenous hormones on the hypothalamic-pituitary-adrenal and the hypothalamic-pituitary-gonadal axes are depicted in this diagram

There are sex differences in stress-responding, such that women respond with greater HPA-reactivity and have higher cortisol (stress hormone) levels when presented with stressful stimuli, compared to men [4–6]. There are also sex differences in basal levels of 3α,5α-THP, such that women in the luteal phase and pregnancy have higher levels of 3α,5α-THP in plasma and hippocampus

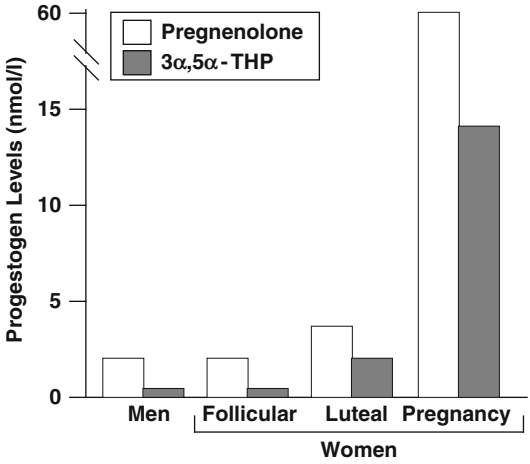

Fig. 17.1 There are sex differences in basal levels of 3α,5α-THP, such that women in the luteal phase and pregnancy have higher levels of 3α,5α-THP in plasma compared to men and women in the follicular phase

compared to men and women in the follicular phase (Fig. 17.1) [7, 8]. Sex differences in 3α,5α-THP coincide with sex differences in stress-responding, particularly during perimenstrual or post-partum 3α,5α-THP withdrawal [9, 10]. Thus, sex differences in stress-responding may be mediated by sex differences in 3α, 5α-THP.

Similar patterns of stress-responding and differences in 3α,5α-THP are observed among female and male rodents. Basal and stress-induced corticosterone (B) levels are higher among females during 3α,5α-THP decline compared to males [11– 13]. Further, stress-induced elevations in 3α,5α-THP are greater and occur more rapidly among female rats, particularly when gonadal sources of 3α,5α-THP are low [14, 15]. Administration of 3α,5α-THP to females and males attenuates the elevation of plasma adrenocorticotropin (ACTH) or serum B secretion produced by emotional and/or physical stress [2, 16]. Thus, enhanced levels of 3α,5α-THP dampens stress-responding in female and male rodents.

Sex differences in stress-responding and 3α,5α-THP may be related to sex differences in the incidence and/or expression of schizo-affective disorders among women and men. Women suffer from mood disorders and are uniquely at risk for affective disorders that are linked to hormonal status compared to men. Affective disorders that are typically diagnosed in women and are associated with precipitous decreases in 3α,5α-THP levels include premenstrual syndrome, post-partum depression, and associated psychoses [17–19]. This chapter reviews findings in support of the hypothesis that 3α,5α-THP has a role in schizophrenia and/or affective disorders. Basic research from our laboratory using various animal models of schizo-affective disorders (prenatal stress, social isolation, perinatal hippocampal lesion, dopamine transporter knockout mice, psychostimulants) will also be discussed to support the potential role of 3α,5α-THP in the development, etiology, and/or treatment of schizo-affective disorders.

Biosynthesis and Metabolism of 3α,5α-THP

The source of 3α,5α-THP can be central and/or peripheral. Central production is from biosynthesis, while peripheral production is from metabolism of hormones released from the adrenals, gonads and/or placenta. The enzymes necessary for neurosteroid biosynthesis and metabolism are expressed by the CNS, and are highest in the midbrain, limbic regions, cerebellum, tectum, pons, medulla, spinal cord, and pituitary. Further, this pattern of localization of these enzymes is conserved across species [20]. Biosynthesis of 3α,5α-THP starts with the expression of translocator proteins (TSPOs), which are high affinity cholesterol binding proteins that import cholesterol into the mitochondria and are highly expressed in steroidogenic tissues. The steroidogenic acute regulatory protein (StAR) and cytochrome P450-dependent C27 side chain cleavage enzymes (P450scc) are proteins that initiate steroidogenesis by oxidizing cholesterol to pregnenolone [21–23]. Following formation of pregnenolone, it is converted to P by 3β-hydroxysteroid dehydrogenase (3β-HSD). P, that is from biosynthesis previously described, or has been released from a peripheral source, is metabolized to dihydroprogesterone (DHP) by 5α-reductase (5α-R) and to 3α,5α-THP by 3α-hydroxysteroid oxidoreductase (3α-HSOR). Thus, biosynthesis and/or metabolism leads to the formation and potential actions of 3α,5α-THP.

Genes Implicated in 3α,5α-THP Dysregulation

A null mutation in a candidate gene that regulates biosynthesis of 3α,5α-THP and has been implicated in schizo-affective disorders disrupts the function of TSPO. This is found to be higher among schizophrenics, than in a control population [24]. As well, there is evidence for deficits in metabolic signaling in those diagnosed with schizo-affective disorders, mental retardation, Parkinson's Disease, Alzheimer's Disease, depression, brain development and ischemic stroke [25]. Thus, genes which regulate 3α,5α-THP biosynthesis may be important markers in the development, etiology, pathophysiology and vulnerability to dysregulation in stress-responding among schizo-affective patients.

Mechanisms of Action of 3α,5α-THP

3α,5α-THP has actions at several non-traditional steroid targets, including glutamate, norepinephrine, dopamine, serotonin, acetylcholine, and oxytocin receptors [26]. We will focus on actions of 3α,5α-THP through $GABA_A$, dopamine (DA), and N-methyl-D-aspartate receptors (NMDARs).

Actions of 3α,5α-THP at $GABA_A$/benzodiazepine receptor complexes (GBRs) have been investigated the most. At low concentrations, 3α,5α-THP alters the duration of GABA current by enhancing GABA influx [27–32]. This can occur through 3α,5α-THP enhancing GBR binding site number and/or affinity, and/or

increasing GABA synthesis, in neurons through glutamic acid decarboxylase [33]. However, at high concentrations, 3α,5α-THP exerts an intrinsic agonistic activity at GBRs in the absence of GABA [31]. In fact, 3α,5α-THP is the most potent naturally occurring ligand for GBRs such that its effects are ~600 times more potent than the most effective barbiturate, and ~60 times more potent than P itself [30]. Thus, 3α,5α-THP has actions involving $GABA_A$.

Actions of 3α,5α-THP at DA-like type 1 receptors (D_1) may be downstream of GBRs [34–36]. GABA neuron migration to the cerebral cortex is promoted by actions at D_1 during development. GABA neuron migration from the basal forebrain to the cerebral cortex can be altered by impairment of D_1 [37]. Thus, 3α,5α-THP can have actions at D_1 and/or GBRs to influence brain development.

Actions of 3α,5α-THP at NMDARs can enhance glutamate and cognitive performance in cortical tasks [33, 38, 39]. Enhancement in learning and memory is associated with actions at glutamatergic substrates, particularly in limbic regions [40, 41]. However, aberrant neural development can occur if there is glutamate overactivity and subsequent excitotoxicity [42]. Thus, GABAergic, DA-like, or glutamatergic targets that can be altered by 3α,5α-THP may influence the development and/or expression of aberrant behaviors, such as those observed in schizo-affective disorders.

Animal Models of Schizo-Affective Disorders and Alterations in 3α,5α-THP

Animal models are important in the investigation of the mechanisms underlying human disease and in designing new therapies. For example, these models may be used to test the plausibility of theories about the origin of schizophrenia; explore the mechanisms of schizophrenia-like phenomena; test the effects of confounding factors, such as medication and postmortem interval, or time since death; investigate therapeutic and adverse effects of the drugs used for the treatment of schizophrenia and develop potential new treatments [43]. It is important to reveal 3α,5α-THP's effects and mechanisms due to its potential role in the etiology and/or treatment of schizo-affective disorders and HPA responses. Few investigations to date have examined 3α,5α-THP's functional role; yet, those involving 3α,5α-THP and schizo-affective disorders, have primarily utilized men, despite more women being affected. Thus, understanding the role, source, and mechanisms of 3α,5α-THP in females is required to fill gaps in the current knowledge.

Stress-Responding and 3α,5α-THP

3α,5α-THP modulates the HPA axis and may serve to buffer stress-responding. P and 3α,5α-THP reduce levels of cortico-tropin-releasing hormone (CRH) in response to an acute stressor [44]. Acute increases in 3α,5α-THP, due to stress, enhances $GABA_A$ receptor function, and attenuates activation of HPA-responding,

which may help individuals return to a state of homeostasis following challenge [2, 16, 45–47]. Blocking 3α,5α-THP's actions at $GABA_A$ receptors prevents stress-induced glucocorticoid secretion and anti-anxiety behavior.

3α,5α-THP is present early in prenatal development at embryonic day 17 [48, 49]. As early as post-natal day 6, brain 3α,5α-THP concentrations increase in response to stressors, such as isolation from the nest, dam, and siblings [50, 51]. Neonatal stress also has more pervasive effects on females than males, such as greater weight loss in neonatally-stressed females compared to males in response to chronic restraint in adulthood [52]. Cold water-swim, and other stressors, increase brain 3α,5α-THP levels of female, more so than male, gonadectomized (GDX) and adrenalectomized (ADX) rats [3, 53, 54]. Increases in 3α,5α-THP produced by such acute stress experiences are conserved across species, and produce anxiolysis among avian, amphibian, and mammalian species in response to "fight-or-flight" stimuli [33, 55]. Thus, actions of 3α,5α-THP mediates stress-responding early in development.

Schizo-Affective Disorders and Stress-Responding

Diagnosis of schizophrenia is based upon both positive (hallucinations, delusions) and negative symptoms (avolution, alogia) [56]. There has been a recent emphasis on negative symptoms, which correlate with loss of social function [57] and plasma levels of stress hormones [58–60]. Notably, there is dysregulation of the HPA axis among people with schizophrenia or affective disorders [61–66]. Plasma levels of cortisol and/or ACTH of schizophrenics are higher than controls and correlate with their negative symptoms [59, 67–71]. How dysfunction of the HPA axis contributes to the pathophysiology of schizophrenia needs to be better-understood [72, 73]. Thus, the pathophysiology of stress-responding and other affective and cognitive disruptions associated with schizo-affective disorders may be related to actions of 3α,5α-THP.

Prenatal Stress and 3α,5α-THP

Stress during critical periods in development may influence stress responding in adulthood and vulnerability to psychiatric disorders. Women whose children were exposed to inordinate stress during pregnancy have an increased incidence of schizo-affective disorders [74–76]. Gestational stress activates the maternal HPA axis and can cause increases in placental CRH [77] and fetal hypoxia [78]. CRH secretion, as a result of prenatal and early life stress, may contribute to the development of stress-related mood and anxiety disorders in adulthood. An animal model of prenatal stress (PNS) has been used by our lab and others as a model of schizo-affective disorders. Methods of producing such a model using PNS vary, but common characteristics result from most models, including neuroendocrine, neuroanatomical, and behavioral sequelae similar to those observed in schizo-affective disorders. In

support, people or rodents respond to stressful stimuli in adulthood with higher and/or more prolonged elevation of ACTH and/or corticosteroids if exposed to PNS during development [79–83]. As well, rats exposed to PNS had adrenal hypertrophy, which may have resulted from chronic over-stimulation of the adrenal gland by ACTH [84]. Further, PNS exposure is associated with abnormal development of the hippocampus and the prefrontal cortex (PFC) in people and rodents [85–90]. Behavioral inhibitions, demonstrated by timidity and shyness in people [91], and reduced exploration in social and novel situations in animal models [92–96], are produced by PNS. Thus, PNS may be a useful model to examine the link between developmental exposure to stress and the expression of characteristics relevant for schizo-affective disorders.

Our laboratory has used several different models of PNS in rodents. The most simplistic model involved restraining dams under bright lights for 20 min on gestational day (GD) 18, when the hippocampus, PFC, and midbrain are developing [97]. Offspring of these dams had lower levels of 3α,5α-THP in hippocampus, but not plasma, when examined during adulthood [34]. Plasma B levels were significantly higher among PNS rats exposed to an acute stressor during adulthood, compared to basal levels of B and non-PNS controls [34]. The hippocampus of PNS rats had significantly fewer granule cells compared to non-PNS controls [98]. Behavioral inhibition was observed wherein PNS rats demonstrated more anxiety-like behavior and less sociability compared to controls. Thus, this model of PNS is related to changes in 3α,5α-THP and stress hormone levels, hippocampal integrity, and behavioral inhibition.

PNS alters behaviors related to inhibition, including affect, depression and stress-responding, suggesting that PNS may alter responses to gonadal hormones. For example, estrogen (E) is a gonadal hormone that mediates expression of depressive behavior in the forced swim task (FST) and enhances P metabolism to 3α,5α-THP [99, 100]. Data indicate that non-PNS and PNS rats administered E show less depressive behavior compared to non-PNS and PNS rats administered vehicle, respectively [101]. Response to an acute stressor is also altered in PNS rats and may be related to aberrant responding to gonadal hormones, such as E. Ovariectomized (OVX), E-administered, PNS rats exposed to 20 min of restraint stress immediately prior to exposure to a novel environment demonstrate more anxiety-like behavior compared to OVX, E-administered, non-PNS and OVX, vehicle-administered, PNS rats also given 20 min of restraint stress [102]. Together these data suggest that PNS can induce behavioral changes and that an acute stressor can amplify these effects on behavior and responsiveness to gonadal hormones. Thus, the effects of PNS on behavioral and neuroendocrine outcomes are of interest, particularly when examined across development and adulthood.

Effects of Prenatal Stress on Offspring Before Puberty

The effects of PNS on offspring before puberty is of interest, as this represents critical time points in development, and may provide insight of how alterations of

behavioral and neuroendocrine responses manifest in adulthood as a result of early developmental stress and challenge. As well, these changes that occur across development and into adulthood may predict vulnerability to etiology, expression and/or prognosis of schizo-affective disorders.

One model involved dams that were chronically-exposed to restraint stress for 45 min under a bright light, three times a day, on GDs 17–21, or not. PNS and control offspring were cross-fostered to non-manipulated dams in our colony and weaned at post-natal days (PND) 20–21. Offspring were tested for cognitive performance as juveniles at PND 28–30. Results indicate that PNS offspring showed reduced 5α-R of P and show decreased cognitive performance [103]. Further, although sex differences in cognitive performance were not observed, there were sex differences in anxiety-like responding such that PNS females demonstrated less anxiety-like behavior compared to controls, and no differences were observed among males (Fig. 17.2). Thus, sex differences in affective behavior are altered following chronic restraint stress during gestation.

Another model our lab used was immune challenge during gestational development by exposing dams to the cytokine interleukin-1β (IL-1β, 1 μg, IP) on GDs 17–20, and offspring were assessed for cognitive performance and affective behavior. Juvenile rats exposed to IL-1β demonstrate decreased cognitive performance compared to controls (Fig. 17.3). Further, anxiety-like behaviors of rats exposed to IL-1β are similar to rats exposed to PNS in that females demonstrate less anxiety-like behavior following gestational exposure to IL-1β (Fig. 17.3). These data imply the important role that physiological immune response of the dam may play on fetal development. However, the stress response to psychological aspects of these may encompass only one aspect of these effects.

The stress response of the dam may also account for much of these effects on offspring. When stressors are unpredictable, they can have even more salient effects on HPA function. We investigated the effects chronic unpredictable stressors (combinations of forced swim for 15 min, restraint for 60 min, cold exposure for 6 h, overnight fasting, lights on during the dark phase of the circadian light-cycle, social

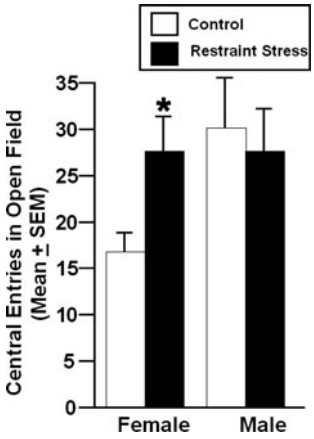

Fig. 17.2 PNS females demonstrate less anxiety-like behavior in the open field compared to controls, and no differences were observed among males

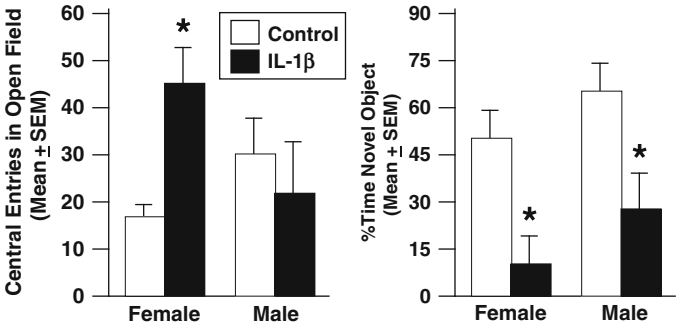

Fig. 17.3 Juvenile offspring of dams exposed to IL-1β during gestation demonstrate decreased cognitive performance in the object recognition task compared to controls. Offspring are similar to those exposed to PNS in that females exposed to IL-1β demonstrate less anxiety-like behavior in the open field

crowding) thrice daily to dams from GDs 17–21. Results indicate that variable stress-exposure reduces cognitive performance among juvenile rats compared to rats that were minimally handled [104]. Notably, females appeared more affected; however, significant sex differences were not observed as neither males, nor females, that were stressed demonstrated significantly different affective behavior. Thus, sex differences in behaviors are not observed among animals that experience variable stress, such that females may become more male-like in their behavioral phenotype.

To begin to assess mechanisms that may underlie offspring performance, HPA response to handling was examined in 28–30-day-old juvenile rats that were prenatally exposed to maternal injections of vehicle oil, finasteride (50 mg/kg, SC), or 3α,5α-THP (8 mg/kg, SC) on GDs 16–20. Plasma B levels in response to handling was significantly elevated in the finasteride-exposed group compared to vehicle- or

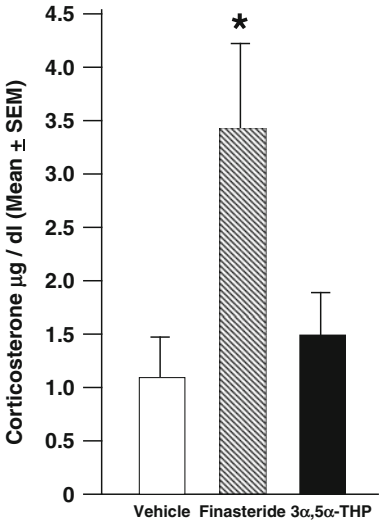

Fig. 17.4 Plasma B levels in response to handling was significantly elevated in the finasteride-exposed group compared to vehicle- or 3α,5α-THP-administered offspring

3α,5α-THP-administered offspring (Fig. 17.4). These data support the notion that developmental changes in HPA-responding of offspring can result when maternal 3α,5α-THP is perturbed during late pregnancy. These data provide proof-of-concept that exposure to psychological, physical, or immune stressors during late pregnancy can reduce cognitive performance among offspring. Further, disruption of maternal 3α,5α-THP alone can have commensurate negative impact of gestation and offspring cognitive development. These observations may be related to HPA dysfunction that results in prenatally-stressed offspring as data show that perturbing maternal 3α,5α-THP in late gestation can alter later neuroendocrine response to a mild stressor.

Sex Differences in 3α,5α-THP and Incidence and Symptom Manifestation of Schizophrenia

The incidence and/or expression of schizophrenia may be mediated by sex differences in biosynthesis and/or metabolism of 3α,5α-THP. Women, compared to men, typically have higher levels of 3α,5α-THP, are more likely to have schizophrenia with later onset, better prognosis, and therapeutic response to lower dosages of antipsychotics [105, 106]. More women than men suffer from mood disorders [107]. Women are uniquely at risk for affective disorders that are linked to hormonal status. First onset, or recurrence of psychotic episodes, are more likely and more negative symptoms are reported when 3α,5α-THP levels among women are low perimenstrually or post-menopausally [108–111]. Sex differences that favor women suggest that 3α,5α-THP may have a protective role in schizophrenia. Women with schizophrenia experience later age of onset, less debilitating psychiatric symptoms, fewer psychiatric hospitalizations, better pre- and post-functioning, and a more rapid and greater response to drug treatments than do men [112, 113]. Women who were diagnosed with schizo-affective disorder and were currently on a second-generation anti-psychotic medication received adjunctive pregnenolone treatment. These women had higher 3α,5α-THP levels and demonstrated improved performance in cognitive tasks than those who were on adjuctive placebo [114]. It should be noted that there is little evidence to suggest that women with psychopathologies, such as schizo-affective disorders, have different absolute levels of 3α,5α-THP, rather they may be more sensitive to changes in 3α,5α-THP [105] or more vulnerable to stress when levels change. Thus, 3α,5α-THP may play an important role in schizo-affective disorders.

Interactions of Therapeutics and Neurosteroids in Schizophrenia

Affective disorders associated with the onset of psychiatric disturbances with menstruation or parturition, when there are precipitous decreases in 3α,5α-THP, include premenstrual syndrome, postpartum depression, and associated psychoses [17, 107, 115]. 3α,5α-THP may underlie the pathophysiology and/or treatment of

schizo-affective disorders, as some anti-depressant and anti-psychotic treatments can increase 3α,5α-THP levels. Women who were diagnosed with severe premenstrual syndrome, also known as premenstrual dysphoric disorder (PMDD), were examined during the luteal phase for changes in severity of symptoms and changes in levels of 3α,5α-THP while on an anti-depressant (sertraline, desipramine, or placebo) for at least 2 months. Results indicate that women who demonstrated an increase in 3α,5α-THP levels reported improvements in symptom severity. Other women who had a decrease in serum 3α,5α-THP reported worsening of symptoms, compared to those that did not show changes in 3α,5α-THP (Fig. 17.5) [17]. Further, SSRI treatment with sertraline may be influenced by baseline levels of 3α,5α-THP in that women who demonstrated low levels of 3α,5α-THP had a significant increase in levels of 3α,5α-THP following SSRI treatment, while women with high baseline levels demonstrated a decrease following SSRI treatment. Those with low and mid baseline levels of 3α,5α-THP showed at least a 50% improvement in PMDD symptoms, while those with high baseline levels showed no change in symptoms (Fig. 17.6) [116]. Thus, changes in 3α,5α-THP levels following anti-depressant treatment may mediate symptoms associated with PMDD such that a greater change in levels are associated with a reduction in PMDD symptoms.

Men can also experience symptom improvement with changes in levels of 3α,5α-THP following treatment. Depressed men treated with an SSRI, fluoxetine, had increased 3α,5α-THP levels, but not P or DHP, similar to non-depressed controls in their cerebral spinal fluid, and concomitant with alleviation of their depressive symptomology [117, 118]. Due to this evidence that 3α,5α-THP may have a role in schizo-affective disorders, its effects in multiple animal models has been investigated. Findings from animal models suggest that 3α,5α-THP has anti-depressant effects [119, 120]. Male mice administered fluoxetine, 3α,5α-THP, or a drug that increases biosynthesis of 3α,5α-THP, show less depressive behavior

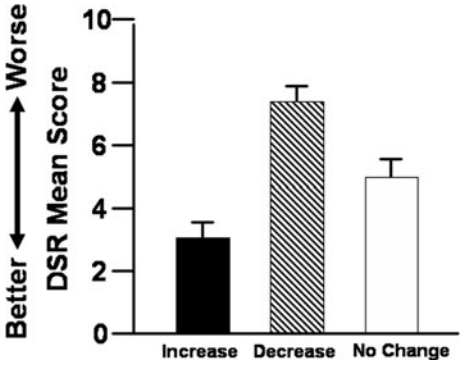

Fig. 17.5 Women diagnosed with PMDD were examined during the luteal phase for changes in severity of symptoms and changes in levels of 3α,5α-THP while being treated with an anti-depressant. Women that demonstrate an increase in 3α,5α-THP levels reported improvements in symptom severity. Women that demonstrate a decrease in 3α,5α-THP levels reported worsening of symptoms, compared to those that do not show changes in levels of 3α,5α-THP

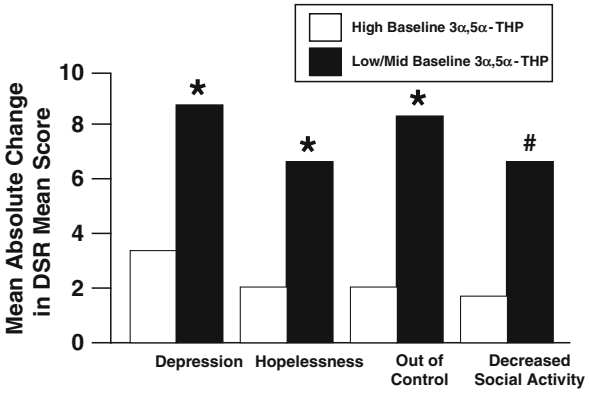

Fig. 17.6 Women diagnosed with PMDD treated with sertraline demonstrated an increase in 3α,5α-THP levels when levels prior to treatment were low, while women that had high baseline 3α,5α-THP demonstrated a decrease in 3α,5α-THP levels following treatment. Women with low and mid baseline levels of 3α,5α-THP showed at least a 50% improvement in symptoms, while those with high baseline levels of 3α,5α-THP showed no change in symptoms, following treatment

than vehicle-administered mice [121]. Thus, 3α,5α-THP may be involved in the pathophysiology and/or treatment of depression associated with schizo-affective disorders.

Anti-psychotics, Anti-depressants and 3α,5α-THP

Data from clinical reports suggest that olanzapine, a novel atypical anti-psychotic, may be as efficacious as traditional anti-psychotics at treating schizo-affective symptoms. Olanzapine reduces negative and positive symptoms, disorganized thoughts, impulsivity/hostility, and anxiety/depression [122, 123]. Notably, in contrast to traditional anti-psychotics, such as haloperidol, olanzapine's therapeutic effects occur with negligible extrapyramidal side effects or akathisia. Olanzapine can improve affect, cognition, interpersonal relationships, impulsivity, and agitation [124, 125]. Olanzapine can also reduce behavioral inhibition in animal models by attenuating fear and anxiety [126, 127]. As well, it increases positive affect and social interactions [128]. Although the mechanisms by which olanzapine may have its therapeutic effects are not known, administration of olanzapine to male or female rats increases central 3α,5α-THP levels compared to vehicle [129, 130]. Further, haloperidol, and the atypical anti-psychotic, clozapine (which alters biosynthesis of 3α,5α-THP), were administered to OVX, E-primed female rats. Haloperidol reduced motor behavior and did not improve sociability. However, clozapine or haloperidol enhanced affective behaviors (Fig. 17.7). Together, these data suggest that schizo-affective disorders may involve a reduced capacity to synthesize 3α,5α-THP in the brain, which may increase sensitivity to stress and expression of anxiety-like behaviors.

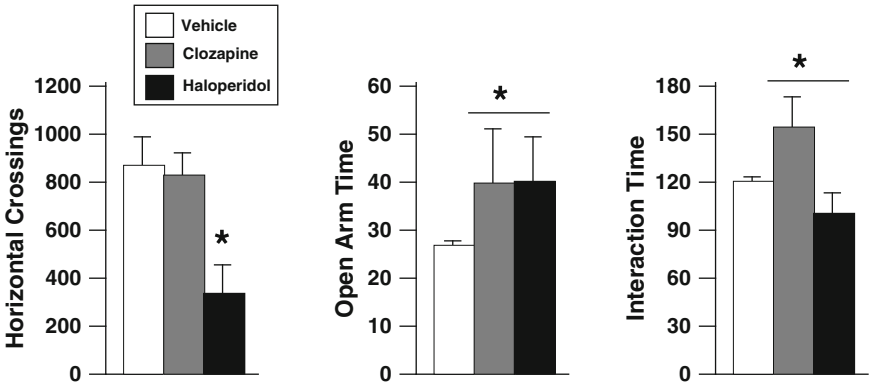

Fig. 17.7 OVX, E-primed female rats administered haloperidol demonstrated reduced motor behavior in the open field and no change in sociability in the social interaction task. Rats administered clozapine or haloperidol demonstrated enhanced affective behavior in the elevated plus maze

Another anti-depressant, mirtazapine, is an atypical anti-depressant that is a 5-HT2/alpha2-adrenoceptor antagonist devoid of affinity for 5-HT and NA reuptake sites [131]. Acute administration of mirtazapine enhances copulatory performance of male rats and strongly stimulates sexual motivation [132]. Chronic treatment with mirtazapine increases 3α-reduced neuroactive steroids by influencing 3α-HSD enzyme activity [133]. We investigated the effects mirtazapine may have on sexual receptivity in OVX, E- and P-primed female rats when administered with vehicle or 3α,5α-THP. Rats were tested for baseline sexual receptivity, and immediately following baseline assessment, rats were administered mirtazapine and assessed for sexual receptivity 20 min later. Results indicate that rats administered mirtazapine demonstrated a significant decrease in lordosis and a significant increase in aggression compared to baseline assessment (Fig. 17.8). Following the second assessment, rats were administered 3α,5α-THP or vehicle and tested for sexual behavior 20 min later. At 40 min following mirtazapine administration, rats continued to demonstrate a significant decrease in lordosis, propinquity and an increase in aggression compared to baseline assessment (Fig. 17.8). Administration of 3α,5α-THP attenuated the sexual side effects of mirtazapine, but this did not reach statistical significance (Fig. 17.8). These data from suggest that further investigation of 3α,5α-THP's involvement in the therapeutic action of anti-psychotic and anti-depressant drugs is warranted.

To begin to examine the mechanisms by which some anti-psychotic and anti-depressant drugs may have their therapeutic actions, olanzapine and fluoxetine were administered to the hippocampus of rats. Olanzapine administration to the hippocampus of OVX, E-primed rats increases affective behaviors compared to OVX, E-primed rats administered vehicle to the hippocampus (Fig. 17.9). Administration of fluoxetine to the ventral tegmental area (VTA) of OVX, E-primed rats enhances 3α,5α-THP-dependent sex behavior and increases central 3α,5α-THP [134]. Thus,

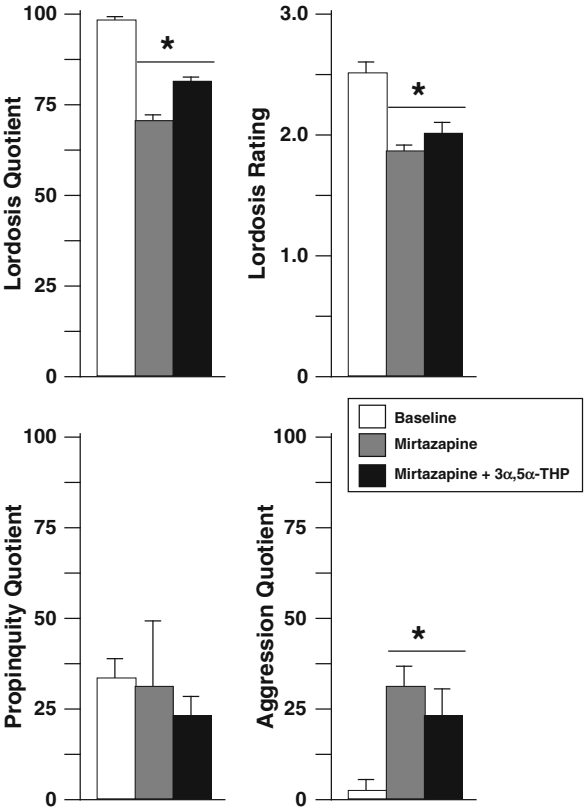

Fig. 17.8 OVX, E- and P-primed rats administered mirtazapine 20-min prior demonstrate a significant decrease in lordosis and a significant increase in aggression compared to baseline assessment. Rats administered 3α,5α-THP following mirtazapine assessment demonstrated attenuated sexual side effects

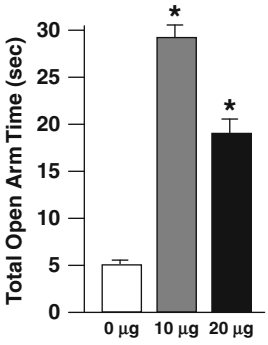

Fig. 17.9 OVX, E-primed rats administered olanzapine to the hippocampus demonstrate increases in affective behaviors in the elevated plus maze, compared to vehicle administered rats

administration of anti-psychotics and/or anti-depressants that increase levels of 3α,5α-THP, or co-administration of 3α,5α-THP, may mediate anxiety-like, reproductive, and social approach behaviors that may or may not be associated with side effects of treatment.

3α,5α-THP Actions in the PFC, Hippocampus, and/or VTA to Mediate Behaviors

In adulthood, 3α,5α-THP may influence the function of the PFC to mitigate negative symptoms of schizo-affective disorders. Schizo-affective disorders involve PFC hypofunction, poor social function, and disrupted working memory, and the PFC is integral to decisions made regarding social and cognitive function [135–137]. Notably, the PFC is sensitive to progestins such that systemic administration of precursors of 3α,5α-THP enhance working memory [138] and 3α,5α-THP enhances DA secretion in the PFC in response to stress [139]. Whether these effects are due to direct actions of progestins on the PFC or indirect actions of progestins on the hippocampus and/or VTA, which project to the PFC, has not been established. Progestins mediate social behavior, in part, through actions in the VTA. Administration of 3α,5α-THP to the VTA of rats increases sociability and blocking 3α,5α-THP formation in the VTA attenuates social behavior [140]. Progestins can also influence affective and cognitive processes through actions in the hippocampus. 3α,5α-THP is increased in the hippocampus concomitant with reduced anxiety-like behavior and enhanced cognitive performance [141, 142]. Blocking the formation of 3α,5α-THP in the hippocampus increases anxiety behaviors and impairs cognitive performance [142, 143]. Thus, 3α,5α-THP-enhanced social interactions and cognitive performance may be initiated in the VTA and/or hippocampus and involve projections to the PFC.

3α,5α-THP's Biosynthesis and Social Approach

A hallmark of schizo-affective disorders is Reproductive Endocrine Dysfunction (RED). In women with RED, differences in levels of progestogens may be absent, but there is evidence for HPA axis and/or response dysfunction. There are normal changes in progestogens, and people diagnosed with schizo-affective disorders experience these same changes, but they are different in their receptor mediated responses to fluctutations, such that they exhibit a dysregulatory response. Reproductive behaviors are linked to RED, as dysregulation in progestogens influences reproductive function and behaviors associated with reproductive success. The behaviors that are implicated in predicting reproductive success are also implicated in schizo-affective disorders, including stress responding, anxiety, depression, and social approach.

Environmental/behavioral stimuli may include social interactions with stimulus males and/or conspecifics, which may be particularly expressed during reproductive ventures when females are in proestrous. In the lab, we have used semi-natural mating situations, including larger mating arenas and/or enabling females to pace their sexual contacts with the male by escaping to a side of the chamber where the male is unable to follow ("pacing" chamber). In natural or semi-natural laboratory mating situations, female rats spontaneously exhibit social approach and avoidance behaviors (pacing behaviors), and other social solicitation behaviors (e.g. hopping,

darting, and ear-wiggling) toward males, which enable them to control the temporal pattern of mating and optimize their fertility and fecundity. These social approach and avoidance behaviors are readily observed and quantified in the lab using the pacing paradigm. Thus the pacing paradigm is a useful laboratory tool in assessment of the role of 3α,5α-THP in social approach and avoidance behaviors in a reproductive context.

3α,5α-THP has been demonstrated to mediate feedback of female sexual behaviors, including lordosis, social approach/avoidance, cognition, and reward, through actions in the VTA. The biosynthesis of, and metabolism to, 3α,5α-THP in the VTA is important for mediating lordosis, sociability and cognition. In our model, we have investigated how 3α,5α-THP mediates reproductive behaviors, social approach, and how actions in the VTA are linked to the hippocampus and PFC. Systemic administration of P or 3α,5α-THP to OVX E-primed rats similarly increases social solicitation behaviors [99, 140]. Co-administration of biosynthesis or metabolism inhibitors with P decreases P-facilitated solicitation behaviors and completely eliminates pacing behavior. Biosynthesis of 3α,5α-THP is enhanced by paced mating. Female rats that pace their sexual contacts have significantly higher whole brain and midbrain 3α,5α-THP levels than do females mated in standard arenas that cannot pace their sexual contacts or rats that are not mated. Solicitation and approach behaviors are attenuated in both standard and paced mating paradigms when biosynthesis or metabolism of 3α,5α-THP is blocked [33, 144, 145]. Thus, 3α,5α-THP may have an important role in mediating mating and solicitation behaviors.

Levels of P and 3α,5α-THP are increased coincidently with lordosis, and expression of lordosis is mediated by metabolism to 3α,5α-THP. Elucidating the source of 3α,5α-THP in the VTA for its behavioral effects is necessary to distinguish if such effects are via traditional endocrine/autocrine mechanisms (metabolism from P) and/or via paracrine effects (biosynthesis in glial cells). 3α,5α-THP biosynthesis occurs within seconds of environmental/behavioral events, whereas peripheral progestins are not as rapidly induced. Thus, dissociating the sources of 3α,5α-THP is important because central biosynthesis, and paracrine effects, may be an adaptive mechanism for mediating reproductive behaviors and social approach.

P, 3α,5α-THP and Social Approach/Avoidance Behaviors

P and/or 3α,5α-THP have been demonstrated to influence social approach/avoidance behaviors. Approach/avoidance behaviors are increased between sexual contacts in the paced mating paradigm when P or 3α,5α-THP are administered [144–146]. The social behaviors observed may be primarily mediated by 3α,5α-THP actions at $GABA_A$ and/or D_1 receptors in the VTA. Solicitation and approach behaviors of female rodents are significantly reduced when actions of progestins at $GABA_A$ or D_1 receptors in the VTA are blocked [33, 99, 145, 147, 148]. Thus, these behavioral effects on social approach/avoidance involved in reproductive behaviors are likely due to 3α,5α-THP's actions at $GABA_A$ and/or D_1 receptors in the VTA.

3α,5α-THP may also mediate social interactions in non-mating paradigms and is also of interest for schizo-affective disorders given that a hallmark of schizophrenia is that engaging in social interactions is less rewarding and willingness to approach novel conspecific stimuli may be attenuated. Two behavioral paradigms which assess this type of approach behavior, independent of mating, are the open field and elevated plus maze. Approach responses of female rodents in the open field are significantly decreased when formation of 3α,5α-THP is blocked systemically or in the hippocampus or amygdala [119, 120, 142]. Further, approach behaviors of 5α-R knockout mice (5α-RKO) are not increased following P administration compared to their wildtype counterparts [149]. Progestin receptor (PR) knockout mice administered P demonstrate increased approach behaviors in the open field similar to controls, which may be indicative of 3α,5α-THP's actions independent of intracellular PRs [147]. Our lab has also examined sex differences in rats in response to P in the open field, and results show that vehicle males demonstrate more approach behaviors than females. However, this is attenuated when males are administered P compared to males administered vehicle (Fig. 17.10). Thus, P and/or 3α,5α-THP's actions may mediate approach behaviors of rodents in an open arena.

The elevated plus maze consists of a dichotomous choice to approach, as indicated by increased open arm time, or avoid, as indicated by decreased open arm time. Results are similar to those of open field in that OVX decreases approach behaviors, but administration of P or 3α,5α-THP systemically or to the hippocampus or amygdala of rodents increases approach behaviors, independent of motor behavior [120, 145]. Approach behaviors are attenuated when metabolism of 3α,5α-THP is blocked pharmacologically or genetically [45, 149, 150]. As well, PR knockout

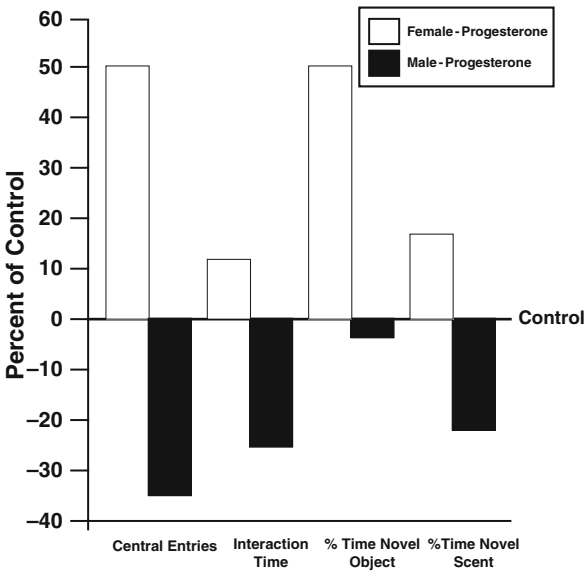

Fig. 17.10 Male rats administered vehicle show more approach behaviors compared to females, while males administered P show attenuated approach behaviors, in the open field, social interaction, object recognition, and social cognition tasks

mice administered P demonstrate approach behaviors similar to controls with PRs [151]. Thus, P or 3α,5α-THP may mediate approach behaviors of female rodents in the elevated plus maze task such that approach is more likely to be demonstrated when 3α,5α-THP can metabolize and have actions.

Social interactions also require approach behaviors to be expressed, and 3α,5α-THP may mediate social behaviors that involve conspecifics. When P and 3α,5α-THP levels are elevated, female rodents demonstrate more sociability with a conspecific, including sniffing, grooming, crawling over or under, and following. If metabolism of 3α,5α-THP is blocked, social approach and interaction is attenuated. There is a sex difference in sociability such that females typically demonstrate more pro-social behaviors, while males typically demonstrate more aggressive behaviors. Female mice administered P show decreased aggressive acts towards an intruder, but these behaviors are not altered by P administration in 5α-RKO mice. As well, administration of 3α,5α-THP to the VTA decreases aggressive behaviors of male hamsters in response to intruders [152]. Males administered P show less pro-social behaviors than males administered vehicle. As well, increased levels of P and 3α,5α-THP in plasma and hippocampus are associated with decreased sociability in male rats (Fig. 17.10). Thus, actions of P and/or 3α,5α-THP may play a role in mediating social interaction behaviors of female and male rodents.

P, 3α,5α-THP and Socially-Relevant Cognitive Performance

Social experiences may influence biosynthesis of 3α,5α-THP and, in turn, mediate cognitive processing. Biosynthesis of 3α,5α-THP is enhanced in response to social experience in the hippocampus and PFC. Cognitive processing is an important factor in socialization, and deficits in cognition may be related to deficits in sociability. In support, administration of P or 3α,5α-THP to OVX rodents increases cognitive processing and performance, similar to increases in sociability associated with P and 3α,5α-THP. Blocking metabolism of 3α,5α-THP attenuates these effects, also similar to changes in sociability. There are also sex differences in cognitive processing, such that women perform better in verbal tasks and men perform better in spatial tasks. Our lab has examined sex differences in response to P in cognitive processing, and there is a clear sex difference at baseline performance such that intact male rats outperform intact female rats. However, the performance of males is significantly decreased, while the performance of females is increased, following P administration. Further, increased hippocampal P and 3α,5α-THP levels are associated with increased cognitive performance of females, and decreased cognitive performance of males (Fig. 17.10). In another cognitive task wherein rodents must differentiate between a familiar and a novel scent, males outperform females at baseline, but P administration attenuates this effect in males (Fig. 17.10). Thus, actions of P and 3α,5α-THP may mediate sex differences in cognitive performance such that females outperform males when progestogen levels are elevated in both females and males.

Social Isolation and 3α,5α-THP

Separate reports indicate that social isolation, another animal model of schizo-affective disorders, produces differences in 3α,5α-THP concentrations, B levels, and behavioral inhibition. Social support minimizes stress and improves social functioning [153] and is used to manage schizo-affective disorders. Male mice that are socially-isolated have less 3α,5α-THP biosynthesis in the PFC and higher plasma B levels compared to group-housed control mice [154]. Social isolation is detrimental to social functioning in adult rats [155] and lack of social support can lead to marked behavioral changes, such as an increase in locomotor activity, anxiety, depression, and aggression, suggesting that lack of social support may be a stressor and these behaviors manifest as a result when it becomes chronic. As well, social isolation of male rats at weaning is associated with decreased levels of 3α,5α-THP in brain and increased anxiety-like behaviors during adulthood [156]. Social isolation can lead to reduced investigation of social odors when compared to group housed animals [157]. Together these data suggest that 3α,5α-THP may have an important role in schizo-affective disorders.

Data from our laboratory indicates that the presence of social isolation versus social support influences neuroendocrine responding, but not affective behaviors, following exposure to an unpredictable auditory stressor and environmental enrichment. These animals were exposed to an unpredictable stressor over 20 generations intermittently and were acutely exposed in either single- or group-housed conditions for the experiment conducted. During exposure to stressor, there were no significant sex differences or single- versus group-housed differences in corticosterone levels among rats. However, post-environmental enrichment results indicate that corticosterone levels were lower among female rats that were group-housed in comparison to male group-housed and female and male single-housed rats (Fig. 17.11). This may indicate that females may be more reliant on social support when experiencing an acute stressor, compared to males. Thus, these data suggest that social support in females can have beneficial effects on HPA responding, but males may not benefit from social support.

Maternal Separation Stress and 3α,5α-THP

Maternal separation is considered the ultimate social isolation as it occurs during a time when offspring are most dependent and can alter progestogen production. Perturbations during early post-natal development can have long last effects on offspring. In fact, those who are diagnosed with schizo-affective disorders commonly have a history of physical or psychological abuse beginning from an early age. Among offspring, stress-induced perturbations in progestogen-HPA homeostasis can be pervasive and persist throughout life [158]. In support, we have observed that acute perinatal stress via maternal separation and lithium chloride injection can alter 3α,5α-THP formation in circulation, whole brain and/or hippocampus, an important brain region for normative affective, cognitive, and ictal behavior, immediately

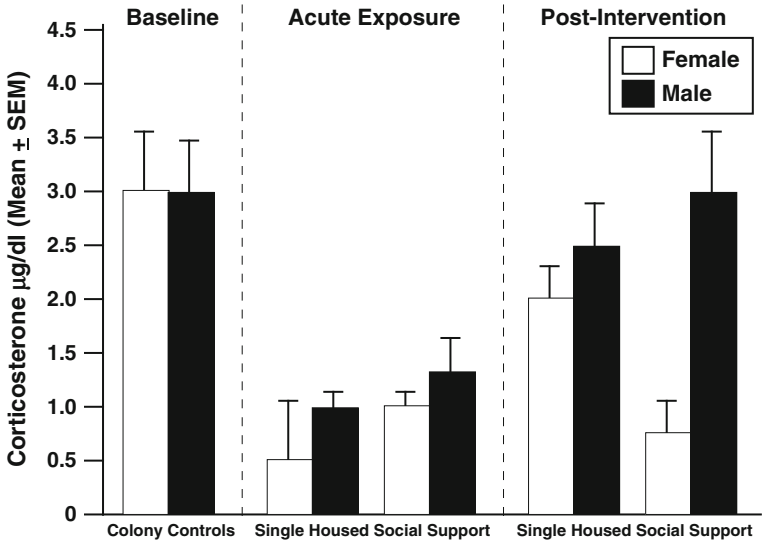

Fig. 17.11 Rats exposed to unpredictable stress over 20 generations intermittently, and acutely exposed to a stressor while single- or group-housed, did not demonstrate sex differences or plasma B levels. Post-environmental enrichment improved plasma B levels among females that were group-housed, compared to male group-housed and female and male single-housed rats

following isolation [50] and well into adulthood [47]. Neurodevelopmental and seizure disorders are commonly noted among premature children. Further, studies conducted in rhesus monkeys have demonstrated that infants who are subjected to maternal separation and social isolation develop behavioral and neurobiological profiles in which they are more likely to engage in drug and alcohol abuse [159]. Anxiety behaviors are altered in female and male rodents in adolescence after exposure to postnatal maternal separation, such that anxiety behavior is increased in the elevated plus maze in females and males, and in approach to a novel object latency is increased in females [160]. As well, female and male rats that were selectively bred to be low or high rates of ultrasonic vocalization (USV) following maternal separation were behaviorally tested. Results indicate that low responders show lower anxiety and depression behaviors compared to high responders. Further, levels of 3α,5α-THP were elevated among high responders compared to low responders (Table 17.1). Thus, early stress-exposure may underlie neurodevelopmental aberrations that persist throughout life and dysregulation in 3α,5α-THP formation may influence some of these observations.

Hippocampal Lesions and Schizo-Affective Behaviors

The hippocampus influences downstream HPA and HPG responding. Progestin receptors have been localized to the hippocampus [161, 162]. Excitability of hippocampal neurons is altered by P [161], and learning tasks involving the

hippocampus can be mediated by P [142, 163, 164]. The hippocampus is also vulnerable to stress [165, 166]. Glucocorticoid receptors have been localized to the hippocampus [167, 168] and neuronal firing in the hippocampus is altered by B, as is learning [169, 170]. Thus, the hippocampus may be altered following prolonged periods of stress, and this may be mediated by P.

There is evidence for an interaction between adrenal and gonadal hormones to influence hippocampal morphology. Extreme (low or high) levels of adrenal hormones produce cell death in the hippocampus [98, 171]. We examined if there are interactions between gonadal and stress hormones in the hippocampus to examine how 3α,5α-THP production mediates effects on behaviors. Previous data from our lab indicate that increasing biosynthesis of 3α,5α-THP in the hippocampus of male rats increases 3α,5α-THP levels in the hippocampus and concomitantly enhances affective behaviors [172]. Pre-treatment with PK 11195 to the hippocampus attenuated the effects of enhancement of 3α,5α-THP biosynthesis on behavioral inhibition and neurosteroidogenesis [172]. Although these data suggest that manipulating 3α,5α-THP production in the hippocampus of males can have salient effects on behavior, there has not yet been a systematic investigation of manipulating neurosteroidogenesis in the hippocampus of females to mediate behaviors related to schizo-affective disorders. Thus, gonadal hormones in the hippocampus may influence stress responding and expression of schizo-affective behaviors.

An animal model of schizo-affective disorders can be produced to examine the role of 3α,5α-THP in expression of symptoms associated with hippocampal function. A neonatal excitotoxic lesion of the ventral hippocampus during early development produces symptoms that parallel schizo-affective disorders, and indicate that early damage to the hippocampus may contribute to the prevalence [173]. Symptoms that indicate schizophrenic-like behaviors include: cognitive and

Table 17.1 Activity and 3α,5α-THP levels in Low versus High responding ultra-sonic vocalization rats

Activity	Low responders	High responders
Saline	3,000	3,000
Cocaine	8,000	6,000
Hippocampus levels of 3α,5α-THP	Low Responders	High Responders
Saline	6.5	4
Cocaine	2.5	7
Midbrain levels of 3α,5α-THP	Low Responders	High Responders
Saline	4.5	2.7
Cocaine	2.5	3.7
Cortex levels of 3α,5α-THP	Low Responders	High Responders
Saline	6	3.7
Cocaine	7	9.8
Amygdala levels of 3α,5α-THP	Low Responders	High Responders
Saline	4.7	3.5
Cocaine	3.7	6

social deficits, hyper-locomotion, enhanced sensitization to psycho-stimulants, and increased aggression [174]. Our lab conducted a study to determine the effects that neonatal ibotenic acid lesions to the ventral hippocampus of female rats on PND 7 would have on behavior and levels of 3α,5α-THP in adulthood. Results indicate that 40% of rats in the ibotenic acid group demonstrated abnormal cyclicity and proestrous rats showed decreased reproductive behaviors and increased aggressive behaviors compared to controls. Anxiety-like behavior of lesioned proestrous and diestrous animals was similar. However, there were differences in some cognitive performance due to cycle condition, but no differences due to cycle or lesion in working memory, spatial memory, or depressive tasks (Fig. 17.12). Thus,

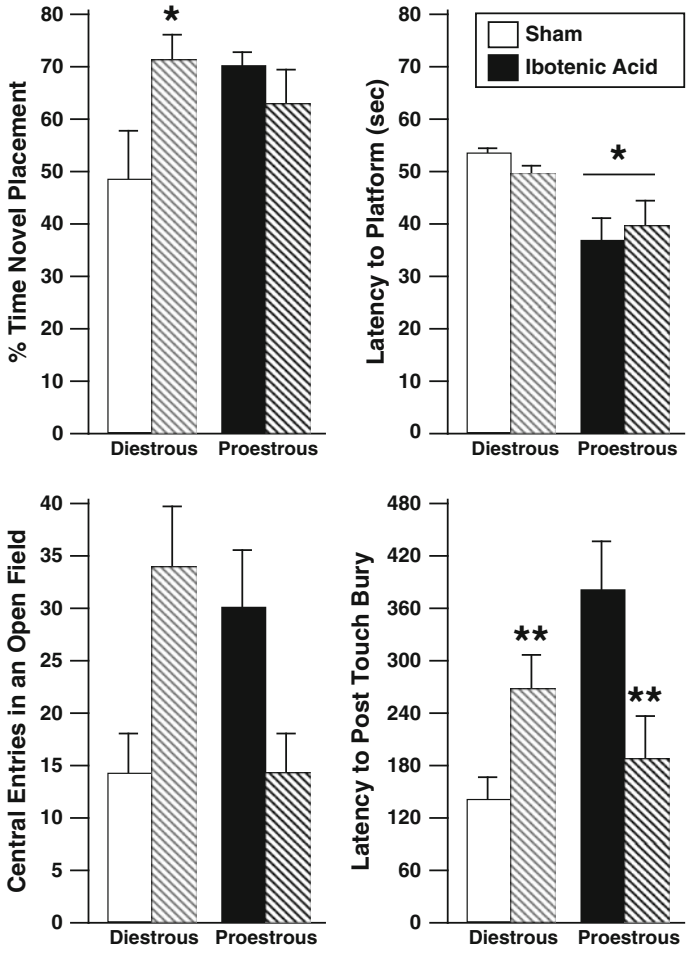

Fig. 17.12 Forty percent of female rats exposed to ibotenic acid demonstrated abnormal cyclicity and proestrous rats demonstrated decreased reproductive behaviors and increased aggressive behaviors compared to controls. Proestrous and diestrous females exposed to ibotenic acid did not demonstrate differences in anxiety-like behavior. There were no differences due to cycle or lesion in working memory, spatial memory, or depressive behavior

neonatal manipulations of the hippocampus can produce behavioral effects that persist into adulthood, and produce abnormal behaviors that appear to be related to changes in 3α,5α-THP due to abnormal cyclicity and changes in reproductive behaviors.

Another point of interest is whether insults in adulthood may produce similar long term effects in rodent models. Rats administered P then administered kainic acid or vehicle indicates that rats administered kainic acid show mild behavioral symptoms, such as low activity followed by periods of hyperactivity, head nodding, myoclonic jerks of forelimbs and jaws, wet dog shaking, and/or modest salivation [175]. Kainic acid administration produces neural insult in the hippocampus, increases plasma B levels, and decreases cognitive performance [175, 176]. Administration of P prior to kainic acid enhances cognitive performance in comparison to rats that were administered P following kainic acid [7]. Thus, these data suggest that P and/or 3α,5α-THP may be protective against a kainic acid-induced seizure model behavioral effects.

Dopamine in Schizo-Affective Disorders

Motivation and executive function can be mediated not only by 3α,5α-THP's actions, as evidence by its role in reward associated with social approach and reproduction. The DA and serotonin systems have been implicated in striatal dysfunction associated with schizophrenia and may also play a role in drug reward and abuse [177, 178]. As well, 3α,5α-THP has actions at D_2 receptors, in addition to actions at $GABA_A$ and NMDARs. DA initiates and maintains responses to salient stimuli such as drugs [179]. Changes in DA levels are of interest given how it may influence short- or long-term behavioral outcomes. Blockade of gluccocorticoids reduces release of DA. As we grow older we lose DA transporters (DAT) in our brain. As well, persons with attention deficit hyperactivity disorder (ADHD) have lower D_2 and D_3 receptors in the hypothalamus, ventral striatum, and mesencephalon. DA also regulates serotonin release in the forebrain, and there is a sex difference in DAT such that females have more than males. Social isolation just after birth alters levels of DA, B and 3α,5α-THP when examined during adolescence under stressful conditions [51]. Thus, DA and actions at D_2 receptors play a role in reward, motivation and executive functions, and this may be related to levels and/or actions of 3α,5α-THP in behaviors relevant for schizo-affective disorders.

Dopamine Transporter Knock-Out Mouse Model

Evidence that P may influence mood and/or arousal among some people with schizo-affective disorders led us to examine the effects of P on DA transporter knockout mice (DATKO), an animal model of schizo-affective disorders. The DAT

is a plasma membrane transport protein thought to control extracellular DA concentrations and is an important target for a variety of therapeutic agents [180]. DATKOs exhibit elevated interstitial levels of dopamine or serotonin and a range of behavioral alterations, including poor cognitive function [181], hyperactivity, and some stereotyped and/or preservative behavior [182] in the cliff avoidance reaction task. DATKO mice also have impaired prepulse inhibition (PPI), a model of sensorimotor gating in schizo-affective disorders [183]. As such, DATKO mice are known to be one of the animal models of schizo-affective disorders.

Our lab examined behavioral effects of P administration in DATKO mice and wildtype counterparts. Young adult, male and female DATKO and wildtype mice were subcutaneously administered P or vehicle 1 h prior to testing in the PPI, activity monitor, or open field. DATKO mice had impaired PPI compared to wildtype, but there was no effect of P. In the activity monitor, DATKO mice showed significantly greater distance traveled during the 60 min test compared to wildtype, and P decreased activity of DATKO mice. In the open field, DATKO mice made a significantly greater number of total, but fewer central, entries than did wildtype mice, and P decreased total entries of DATKO mice. P increased the number of central entries made by DATKO and wildtype mice [184]. Thus, P partially attenuated the hyper-active phenotype of DATKO mice, indicating that P and/or 3α,5α-THP may play a role in the behavioral phenotype of an animal model of schizophrenia.

Cocaine, Schizo-Affective Disorders and 3α,5α-THP

One drug of abuse that has been implicated for behaviors similar to schizo-affective disorders is cocaine, as it involves the DA reward system and influences levels of 3α,5α-THP. Cocaine can have developmental effects and activational effects when administered in adulthood. Rat strains have been bred to emit low versus high rates of USVs in response to maternal separation at 10 days of age. The High line demonstrates an "anxiety-like and depressive" behavioral phenotype. Notably, 3α,5α-THP levels in midbrain and plasma were significantly greater in High line compared to Low line rats. Further, these levels of 3α,5α-THP in the midbrain were found to correspond with differences in reproductive behaviors between the High and Low line females. Male High line rats had shorter latencies to initial intromission and shorter intervals between intromissions, but longer latencies to ejaculation and longer postejaculatory intervals than Low line rats. Female High line rats had higher lordosis quotients and lordosis ratings, were more likely to pace their sexual contacts, and typically stayed away from the male-associated side of the mating chamber longer than Low line rats. These data indicate that endogenous levels of 3α,5α-THP in the midbrain may be associated with individual differences in sexual behavior of rodents.

Low line and High line rats may demonstrate differences in activity when administered cocaine versus saline in adulthood, and this may be related to differences in levels of 3α,5α-THP. Activity levels differ such that Low line rats are more active

following saline administration and less active following cocaine administration, compared to High line rats (Table 17.1). A similar pattern is observed for levels of 3α,5α-THP in hippocampus, cortex, midbrain, and amygdala, such that Low line rats have higher 3α,5α-THP levels compared to High line rats when administered saline. As well, cocaine increases levels of 3α,5α-THP in High line rats, but not in Low line rats (Table 17.1). These data demonstrate that levels of 3α,5α-THP at baseline may predict activity and/or stress reactivity in response to cocaine administration. Thus, 3α,5α-THP levels may influence HPA-responding dependent on vulnerability to expression of stress responses.

Cocaine disrupts not only activity, but also normative reproductive function among all rats. This effect is such that reproductively active (proestrous) rats, exhibit significant decreases in reproductive function, concomitant with brain progestin levels. Of interest, males administered a high dose of cocaine (the dose at which we observed a motor response), show significant increases in brain progestogens (Fig. 17.13). These data indicate that levels of 3α,5α-THP and reproductive behaviors of female and male rats may be influenced by administration of cocaine, such that higher doses of cocaine negatively influence reproductive function. Thus,

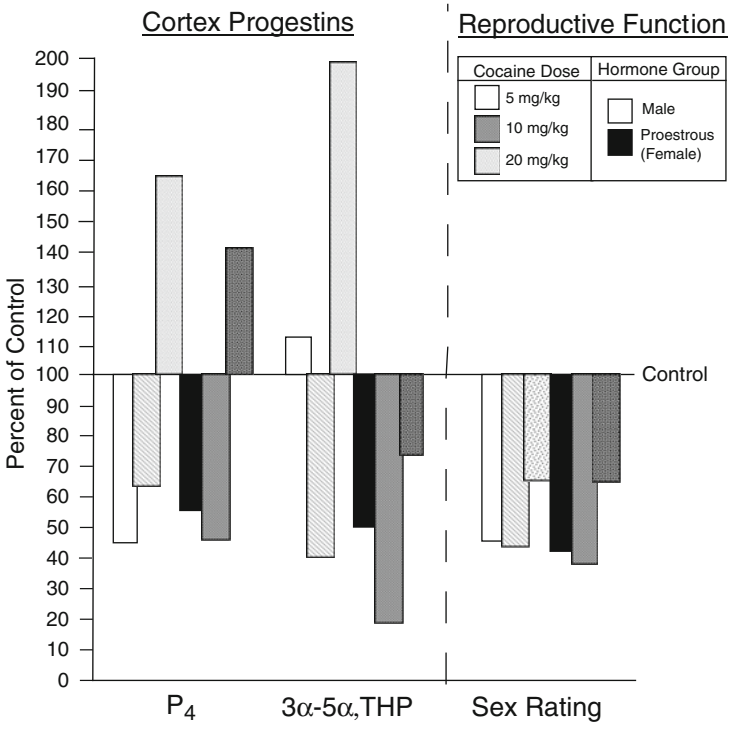

Fig. 17.13 Proestrous female rats administered cocaine demonstrate significant decreases in reproductive function, concomitant with brain progestin levels. Males administered a high dose of cocaine demonstrate significant increases in brain progestins

cocaine can impact reproductive behaviors through altering levels of 3α,5α-THP biosynthesis in females and males.

Methamphetamine, Endoplasmic Reticulum, and Schizo-Affective Disorders

Methamphetamine (METH), another drug of abuse, may be related to schizo-affective disorders, as it can negatively impact the endoplasmic reticulum (ER). The ER is an intracellular organelle which is involved in diverse arrays of cellular functions, is mediated by cholesterol signaling, and is affected by METH. The ER is very densely packed with enzymes that are involved in quality control of protein synthesis and post-translational modification including folding of proteins. Malfunctions in these processes result in misfolded and/or unfolded proteins that can accumulate in the ER, with consequent activation of compensatory reactions such as the unfolded protein response. If these compensatory mechanisms fail to restore cellular homeostasis, cell death ensues via activation of ER-dependent apoptosis [185]. The accumulated evidence supports the involvement of ER stress and related molecular events in neurodegenerative events including METH-induced neuronal apoptosis. METH addicts often use large quantities of the drug and can suffer from drug-induced psychosis similar to symptoms of schizo-affective disorders. Neuroimaging studies have also revealed a number of abnormalities in the brains of these patients, including loss of striatal DAT and of serotonin transporters and evidence of reactive microgliosis. Previous postmortem studies are in agreement with some of those results. Moreover, METH can cause degeneration of monoaminergic systems and neuronal apoptosis in various brain regions including the rodent striatum. METH-induced cell death is dependent, in part, on activation of ER-dependent death pathways. With protracted absence of METH, there can be partial recovery of brain DAT. Thus, ER activation is important for cellular functions that may be disrupted in schizo-affective disorders and/or as a result of drugs that induce schizo-affective-like behaviors.

There exists a clear sex difference in E, which clearly plays an important role in modulating the nigrostriatal dopaminergic system in response to neurotoxins. For example, male mice display greater function in response to neurotoxins. Moreover, administration of high doses of METH produces more severe striatal DA depletions in male compared to female Swiss-Webster mice without E treatment following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. In adolescence, socially stressed females show greater stereotypy to amphetamines than do males. Amphetamine has been demonstrated to be rewarding in that socially stressed females show greater conditioned place preference compared to males. Socially stressed females and males demonstrate long lasting deficits in object spatial location, but not object memory compared to controls. Socially stressed males show long lasting deficits in contextual, conditioned, and generalized fear compared to controls. Females demonstrate long lasting deficits in neurogenesis, and these deficits take a long period of time to emerge and lead to hippocampal deficits. Socially

stressed males demonstrate increased neurogenesis compared to controls. Thus, amphetamines can influence expression of psychosis-like phenotype as indicated by changes in stress reactivity, cognition, fear behaviors and levels of progestogens, and these changes may be related to differences in resilience, relationships and resources that mediate manifestation of this phenotype.

Other Genetic Mutations in Schizo-Affective Disorders

There are several candidate genes which have been implicated in schizo-affective disorders, including those which regulate 3α,5α-THP biosynthesis, neuronal migration in development, and influence plasticity. Mutations that have been identified are in RELN and DISC1 genes. RELN encodes reelin, which is an evolutionarily-conserved nonabundant extracellular glycoprotein that can exist in multiple isoforms. Reelin is important in the organization of the developing fetal brain and neuroplasticity in the adult brain [186]. If there are disruptions in reelin-signal transduction, this can lead to disruption of the cytoskeletal structure of neurons [187]. In relation to reelin-signaling is the very low-density lipoprotein receptor (VLDLR), and reelin-signal transduction is interfered with in a VLDLR-deficient knockout mouse [188]. There are functional impairments of reelin signaling as indicated by attenuated levels of VLDLR mRNA in those diagnosed with schizophrenia [189]. Further, expression of the apolipoprotein E2 receptor (apoER2) is important for reelin binding. Mice with mutations of both VLDLR and apoER2 demonstrate a phenotype similar to the reelin phenotype, with disruptions in reelin protein [188]. Thus, mutations which alter receptor expression may disrupt reelin-signal transduction, an important mediator of neuronal migration and subsequent brain structure.

DISC1 has also been implicated in schizophrenia, as it is related to functional anatomic and cognitive consequences due to alterations in the cortex and hippocampus of those diagnosed with schizophrenia [190]. Several genetic studies have found that the DISC locus is related to many psychiatric disorders and cognitive disruptions [191, 192]. Further, mouse models of mutations in DISC1 demonstrate impairments in neurite outgrowth in vitro, and disrupted development of the cerebral cortex and behavioral impairments in vivo [193–198]. As a result, DISC1 may be important for effects on the organization of brain structures which may lead to vulnerability to the development of schizophrenia. Further, DISC1 is implicated in neurogenesis, neural migration, and synaptogenesis, which may be related to early development of schizophrenia [199]. Thus, there are genetic implications for schizo-affective disorders, some of which may be in involved in development and/or 3α,5α-THP biosynthesis.

Conclusions and Future Directions

The neurobiology and pathology of schizoaffective disorders will not be understood by considering these disorders as they are defined in the DSM-IV-TR. Many

of the disorders classified as "schizo-affective" overlap with neurodevelopmental disorders such as autism, and this review will not be constrained to the DSM criteria because this is not a useful approach to understanding the mechanisms that may drive disorders with similarities. There are slightly different manifestations of common neurobiological factors that manifest in schizoaffective, as well as neurodevelopmental disorders. Due to the prevalence of schizophrenia and affective disorders in the population today and the aging population that may be more vulnerable to schizo-affective disorders due to hormonal changes, it is critical that all avenues of treatment, particularly hormones, are considered. While there has been interest in the ability of steroid hormones to mediate affective and depressive disorders, there has been little basic research done to characterize these effects and determine the mechanisms by which hormones may act to mediate these behaviors. Further understanding of neurosteroids is relevant for etiology, manifestation, and treatment options for people with affective and depressive disorders.

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Chapter 18
Neural Substrates of Emotion Dysfunctions in Patients with Schizophrenia Spectrum Disorders

Katharina D. Pauly and Ute Habel

Abstract Within the last decades brain imaging techniques improved our knowledge about most psychiatric disorders. This is especially true for schizophrenia spectrum disorders, which affect not only the cognitive domain, such as executive functions, but also encompass the core symptom complex of emotional impairments. Functional magnetic resonance imaging (fMRI) can help to understand the neural basis of such deficits as well as their mutual interactions. Emotional functions include several sub-processes such as emotional experience, emotion recognition, emotion regulation, empathy, the interaction of affective states with different cognitive functions, or the forming of an emotional self-concept. Each of these processes can be impaired in schizophrenia spectrum disorders, and such deficits can be based on different dysfunctional neural networks. An enhanced knowledge about the etiology of schizophrenia, the identification of biological risk markers and the integration of multimodal approaches including findings from neuroimaging, neuropsychological, and psychopathological data can improve early detection and intervention resulting in a preferably (neuroprotective) short duration of untreated psychosis. The identification of the endophenotypes of emotional dysfunctions constitutes one central aspect of this endeavor.

Keywords Schizophrenia · Schizophrenia spectrum disorders · Emotion · Mood induction · Emotion recognition · Emotion regulation · Emotion-cognition interactions · Emotional self-concept · Functional magnetic resonance imaging · Neuroimaging

Abbreviations

ACC	Anterior cingulate cortex
BOLD	Blood oxygen level dependency
CHR	Clinically at high risk (for psychosis)

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DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
MEG	Magnetoencephalography
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
STG	Superior temporal gyrus
VLPFC	Ventrolateral prefrontal cortex

Introduction

Explanatory approaches to the endophenotypes of schizophrenia spectrum disorders have to combine neurobiological and genetic mechanisms, environmental and stress factors as well as neuropsychological profiles. Moreover, schizophrenia spectrum disorders encompass heterogeneous clinical pictures. A comprehension of the neurofunctional basis of the disorder requires the decomposition of its distinct symptoms. Emotional deficits may not be amongst the most obvious dysfunctions in schizophrenia and schizophrenia spectrum disorders but they represent a very crucial and agonizing aspect of the illness. Noticeable emotional deficits in schizophrenia encompass negative symptoms, such as a flat affect, but also more bizarre features such as parathymia, i.e. emotional reactions which are not adequate in the context in which they appear, for example when a patient is laughing while telling a sad story. Measurable emotional performance deficits are of high clinical relevance and predictive value for social functioning, but nevertheless not taken into account in clinical diagnostics sufficiently, so far.

The development of brain imaging techniques allows us to enhance our knowledge about the neurobiological substrates of emotional dysfunctions in schizophrenia spectrum disorders. In clinical research, functional magnetic resonance imaging has two main advantages. First, the non-invasive character is especially advantageous for patients. Secondly, the high spatial resolution allows an exact localization of brain activation changes. However, fMRI gives an indirect insight into the neural activity of the brain. In contrast to positron emission tomography (PET), electroencephalography (EEG), or magnetoencephalography (MEG) fMRI neither measures biochemical changes at the synapses nor electrical activity nor the magnetic fields induced by it. fMRI reflects changes in brain activation on the basis of changes in the oxygenation level of the regional cerebral blood flow. The blood oxygen level dependency (BOLD) effect can work as a natural contrast agent. On the basis of the subtraction method the contrast of an experimental (e.g. emotional) task and a control (e.g. neutral) condition, which ideally only differs concerning the component of interest, is said to reflect the brain activation underlying the function under focus.

In this chapter we want to give an overview over imaging (mainly fMRI) studies characterizing the neural substrates of emotional dysfunctions in schizophrenia

spectrum disorders. Even if many emotional processes in everyday life seem to take place rather automatically or unconsciously they can be based on rather complex interactions of different sub-functions. Imaging paradigms need to simplify such complex processes to allow an experimental investigation of the basic compounds.

A model describing the underlying neural structures of emotion perception [1] and accordant dysfunctions in various mental disorders [2] was developed by Phillips and colleagues. It divides emotion perception into three sub-processes: (A) the appraisal of emotional significance to sensory input. This in turn evokes (B) a certain affective state, which finally (C) is regulated by a control system (Fig. 18.1). It is assumed that these processes depend on two main brain networks. The ventral system, including the amygdala, the insular gyri, the ventral striatum, and ventral regions of the prefrontal cortex (i.e. the orbitofrontal (OFC) and ventrolateral prefrontal cortex (VLPFC), and the ventral anterior cingulate cortex (ACC)), is said to underlie the first two stages of this emotion perception model. A dorsal system, on the other hand, is associated with emotion regulation and encompasses mainly the dorsolateral and dorsomedial prefrontal cortex (PFC) as well as the dorsal ACC

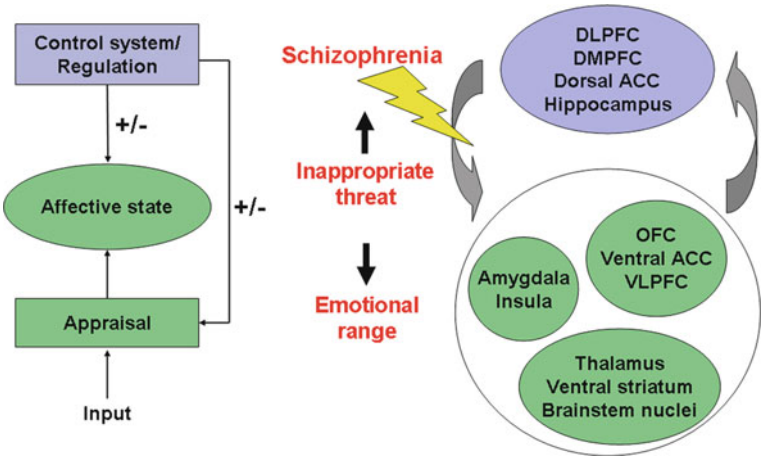

Fig. 18.1 Model after Phillips et al. [2] according to which a contextually appropriate emotion perception depends on three processes (*on the left*): (1) the identification and appraisal of emotional significance of the sensory input, which evokes (2) a certain affective state that (3) further may be modulated by a control system also capable to modify the appraisal system. Those three functions are related to two networks (*on the right*): a ventral system responsible for the identification of the emotional significance of the sensory input, evoking the affective state, as well as the regulation of the autonomic reactions (*green*). The dorsal system (*blue*) comprises a control system for the regulation and modulation of affective states. Both systems interact with each other reciprocally and may be dysfunctional in schizophrenia (*red*). Deficits in the ventral system may result in a limited range of emotions identifiable and subsequent affective states as well as a misinterpretation of neutral stimuli as negative or threatening. They may further interact with dysfunctions in the dorsal system, which impair the regulation of emotional responses (ACC = anterior cingulate gyrus; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; OFC = orbitofrontal cortex; VLPFC = ventrolateral prefrontal cortex)

and the hippocampus. A conscious or subconscious identification or appraisal of stimulus salience to sensory input is essential for emotional responses. The evoked affective state comprises autonomic, neuroendocrine, and somatomotor reactions reflected in mimic, gesture, prosody, and other behaviors which come along with a conscious feeling of emotion. On a higher processing level the control system is responsible for the context appropriate modulation or inhibition of the first two sub-processes.

This model may also be suitable for explaining symptoms in mental disorders such as schizophrenia, where patients reveal flat affect or have difficulties in interpreting social cues correctly. Structural and functional changes in regions of the ventral system may result in altered emotional experiences, a reduced range of emotions identifiable, and a limited range of subsequent affective states and behaviors. Furthermore, changes in the ventral system may be the reason for the misinterpretation of neutral stimuli as negative or threatening. This may be further perpetuated by deficits in the active control of emotions due to dysfunctions in the dorsal system, which, on the other hand, may result in dysfunctions in emotion regulation (Fig. 18.1) [2].

In the following we will describe a wide range of emotional functions impaired in schizophrenia spectrum disorders and their underlying neural correlates. We will present different imaging results from paradigms on emotion induction and emotion recognition using different sensory channels. Furthermore, we would like to illuminate the interaction of affective states with cognitive functions. Finally, we will focus on emotional dysfunctions and their effects on the emotional self-concept in schizophrenia.

A better understanding of the etiology of symptoms in schizophrenia spectrum disorders can ease the identification of endophenotypes and risk markers and give new impulses for pharmacological and psychotherapeutic treatment. This will hopefully also contribute to an early detection and intervention.

Emotion Induction

Visual Emotion Induction

Emotional tasks can be rather explicit or implicit based on automatic processing of emotional stimuli. Furthermore, the neural substrates of emotional functions may be influenced by the sensory modality in which the emotional process is evoked. However, there seem to be networks linked to emotion independent of the sensory system engaged. Comparing the effects of emotional visual, olfactory, and auditory stimuli (versus neutral material, respectively) an increase in activation in the orbitofrontal cortex, the left temporal pole, and the superior frontal gyrus was found for all three sensory modalities [3]. In addition to modality unspecific emotion-related activation there may be brain networks specific to the sensory system in which the emotional information is processed.

When asked to look at emotional faces with a happy or sad expression and to try to feel the respective emotion, healthy males revealed activation in the left

amygdala [4]. Although patients with schizophrenia reported a similar rating of experienced negative emotion (affirming a successful mood induction) the accordant neural correlates failed to demonstrate a corresponding activation in the amygdala [5]. Even the non-affected siblings of patients with schizophrenia revealed a similar dysfunctional amygdala activation pattern implying that this lack of amygdala activation represents a trait marker and endophenotype of schizophrenia. However, other regional activation differences in emotion-related areas were only found between patients with manifest schizophrenia and healthy subjects, such as in the orbitofrontal cortex and the posterior cingulate gyrus [6]. Hypoactivation in the amygdala and the medial frontal cortex were also found during processing of fearful faces (while judging the depicted gender), especially in patients with paranoia [7]. Interestingly when emotion is not actively self-induced but rather automatically elicited, e.g. by masking sad and happy faces by neutral faces, this kind of emotional priming yielded an *increase* in amygdala activation in patients with schizophrenia. This amygdala response correlated with negative symptoms [8]. A lack of amydala activation during the visual perception of aversive material but increased activation in response to ambiguous stimuli has been related to an altered activation threshold in schizophrenia patients in response to negative stimuli (for an overview: Kucharska-Pietura et al. [9]). Furthermore, increased activation in the hippocampus in response to emotional faces [10] may partly be related to a reduced habituation in the hippocampus, e.g. in response to fearful faces [11]. Similar findings were found for the amygdala during the initial processing of fearful or happy faces. Nevertheless, if compared to neutral faces as baseline no such group differences were discovered [10].

A meta-analysis of Cohen and Minor [12] analyzed the often reported finding that patients with schizophrenia in most studies do not differ from healthy subjects in emotional experience based on self-ratings in spite of obvious emotional symptoms of mostly decreased positive and increased negative emotions. This could be due to the fact that many clinical experimental studies dealt with comparably small sample sizes resulting in a rather small statistical power. However, the meta-analysis came to the same result: patients did not differ from healthy subjects when rating their hedonic reactions to the stimuli. Interestingly, in spite of a lack of hedonic deficits, patients as compared to healthy subjects reported experiencing stronger aversion to positive and neutral stimuli. Positive and neutral material could elicit both, positive but also negative emotions. Such a negative bias might reflect a cortico-limbic dysregulation underlying an impaired emotion modulation in schizophrenia spectrum disorders.

Also clinical characteristics may play a crucial role. An inverse relationship was found between negative symptoms and activation in the right prefrontal cortex when patients with schizophrenia watched sad (as compared to neutral) movie clips. However, data also reflected distinct gender influences with male patients additionally revealing a correlation between negative symptoms and an increase of temporal, caudate, and ACC activation (amongst others), while negative correlations were found in women between positive symptoms and hippocampal or occipital cortex activation [13]. The results of this interesting pilot study will need to be confirmed by further studies, in the future.

Dysfunctions in several emotion-related areas such as the orbitofrontal cortex, the ACC, and medial temporal areas including the hippocampus during the visual induction of sadness and happiness remained unaffected by psychopharmacological treatment (haloperidol and risperidone). However, therapy-related signal increases included inferior frontal and inferior temporal areas during the induction of sadness. The authors hypothesized that these activation increases might reflect an increased usage of autobiographical emotional memories as strategy for self-induced mood induction [14].

Olfactory Emotion Induction

An example for an alternative technique for mood induction is olfactory stimulation via a so-called olfactometer delivering pleasant and unpleasant odors (Fig. 18.2).

Especially in the context of brain imaging, it has the great advantage that emotion induction takes place rather automatically due to the close anatomical connections

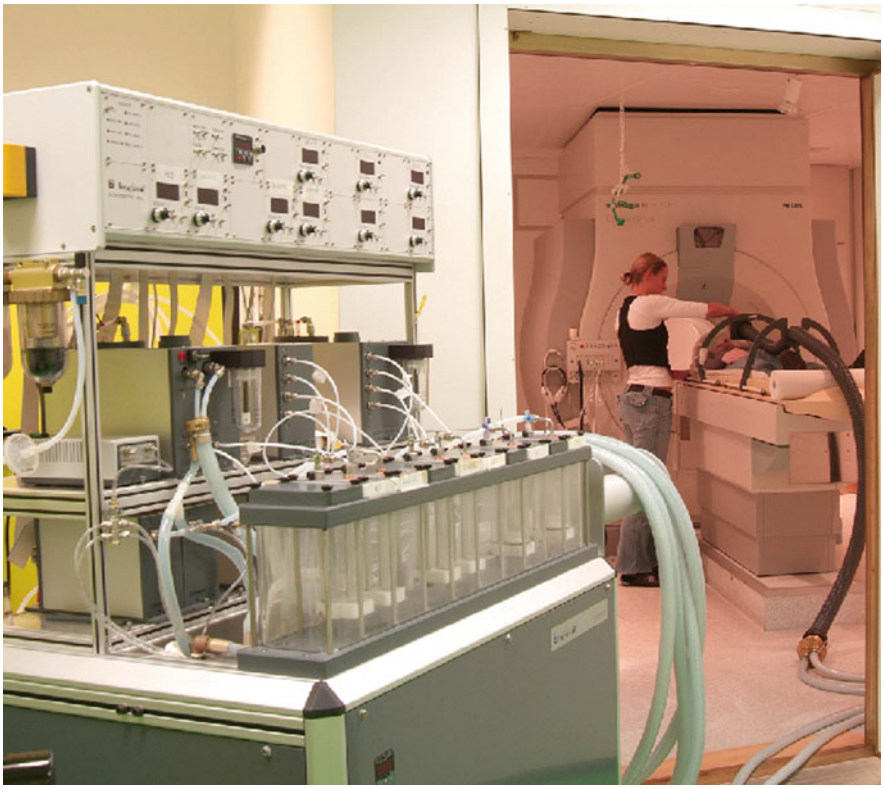

Fig. 18.2 Olfactometer – a technical device for positive or negative emotion induction in- or outside the scanner

between the olfactory and the limbic system with no need for conscious cognitive effort. Schneider and colleagues [15] induced positive emotion by the odor of vanilla and negative emotion by the smell of rotten yeast and compared both to neutral stimulation with ambient air. The standardized subjective emotion ratings revealed a successful mood induction with no significant differences between healthy subjects and a sample of patients with schizophrenia. Furthermore, the positive odor only decreased thalamus activation and this applied only to patients with manifest schizophrenia. However, during the negative emotion induction patients with schizophrenia revealed reduced activation in the right middle frontal and middle temporal cortex. A similar decreased activation in the frontal cortex was also found in their healthy brothers. Moreover, there was a trend for decreased activation in the right insula in patients with schizophrenia and their healthy siblings, a region known as key area of experiencing disgust [16]. The neural correlates of olfactory processing of negative stimuli might be especially suitable for the detection of genetic trait markers in schizophrenia spectrum disorders. However, in addition to decreased activations in patients, both emotions were also associated with hyperactivations, namely in the middle frontal and the anterior cingulate gyrus, both also present in patients' siblings (at least on a trend level).

Interestingly, temporo-limbic dysfunctions during negative olfactory emotion induction already became apparent in subjects clinically at high risk (CHR) for psychosis, too, i.e. in persons who for example show first attenuated psychotic or brief limited intermittent symptoms. Persons with CHR revealed decreased activation in the insula and the medial superior temporal gyrus, which is in good accordance to the idea of a continuum between healthy subjects, persons clinically at risk for psychosis and schizophrenia [17].

Further evidence points to prefrontal regions being especially affected in schizophrenia, such as the orbitofrontal, inferior, or medial frontal cortex, in addition to temporo-limbic areas including the insular cortex. Negative and positive odors (vs. air) [18] as well as unpleasant vs. pleasant olfactory stimulation [19] revealed a lack of limbic and paralimbic involvement (insular cortex, parahippocampal gyrus) in patients with schizophrenia as well as dysfunctions in the orbitofrontal gyrus. Compensatory activations were found in widespread frontal regions including dorsolateral as well as medial prefrontal regions but also the posterior cingulate cortex during odor pleasantness judgments [19]. The authors suggested that these prefrontal areas would normally rather be activated by positive stimuli but were "hijacked [in patients] for the more fundamental and evolutionary necessary task of recognizing unpleasant stimuli, as a compensation for the apparent failure of their paralimbic regions to recognize unpleasant stimuli as negative or dangerous".

Increased activation during negative emotion induction in prefrontal areas was also found in an adolescent sample of schizophrenia patients with early-onset [20]. An interesting aspect of investigating adolescent patients is the fact that they are still in a phase of brain development. Moreover, before the age of 15 years, the prevalence of schizophrenia is 50 times lower than for a later onset [21]. This clearly implies that early neurodevelopmental dysfunctions in schizophrenia (such as in the context of birth complications or viral infections of the mother during pregnancy)

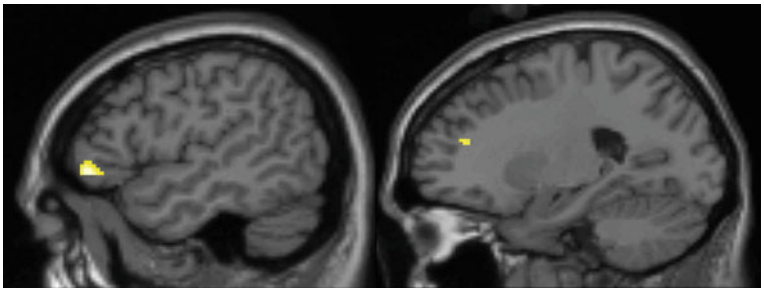

Fig. 18.3 Increased activation in the lateral orbitofrontal and the medial frontal gyrus in adolescent patients with schizophrenia during olfactory negative emotion induction (see also Pauly et al. [20])

interact with factors during the later development, such as an exaggerated synaptic pruning during the normal selective pruning during adolescence [22]. This dramatic disruption of the neurodevelopment often results in an especially severe form of the illness with a relatively bad outcome. Regions of dysfunctional increased activation during negative emotion processing encompassed the lateral orbitofrontal gyrus, which is known to be crucial not only for higher-order olfactory processing but also for related emotional reactions, the middle frontal gyrus as well as the medial frontal gyrus [20] (Fig. 18.3). The latter was found to be the brain area most reliably activated in emotional tasks independently of stimulus modality [23].

As it is the case with visual and acoustic emotional material (see below) subtle changes in emotion-related areas in reaction to olfactory stimuli may be influenced by subtle dysfunctions in the accordant sensory system. However, deficits in the olfactory system in schizophrenia mainly refer to difficulties in odor discrimination and an increased detection threshold [24, 25]. Others report preserved detection threshold sensitivity but deficits in odor identification and changes in odor familiarity ratings [18, 26]. Yet, emotion induction via clearly supra-threshold stimuli, on the other hand, seems to be rather unaffected on a subjective behavioral level.

Different studies reported dysfunctions in similar areas but with diverging results concerning the direction, i.e. hypo- and hyperfrontality. This to some extent might be related to the use of the positive odor condition. Results may differ depending on whether positive conditions are combined with negative odor stimulation phases, both are contrasted with each other, or are used as single experimental conditions compared with neutral stimulation. This may especially be true in the context of a negative bias found in patients with schizophrenia spectrum disorders and at-risk first-degree relatives in the judgment of neutral and positive material [18–20, 27–29]. Similar phenomena become also apparent in emotion recognition (see below).

In summary, on a subjective level the induction of affective states in patients with schizophrenia results in a hedonic emotion experience comparable to the subjective ratings of healthy controls, however, with more negative reactions to non-threatening (i.e. positive or neutral) stimuli. On a cerebral level, dysfunctions

in emotion-related networks are found. The amygdala plays a crucial role especially during visual emotion processing, but also dysfunctions in the hippocampus and other limbic areas were detected. Olfactory emotion induction, on the other hand, may be especially suitable to reflect dysfunctions of the insular cortex. On a higher processing level, medial prefrontal and orbitofrontal activation changes become apparent – independent of the mood induction technique or sensory system. They may therefore reflect more general disturbed evaluative and regulatory processes. The fact that brain activation changes partly are also found in individuals genetically or clinically at risk for psychosis implies trait characteristics of at least some structural or functional cerebral changes in this context.

Emotion Recognition

Recognizing Emotional Facial Expressions

While patients with schizophrenia spectrum disorders are capable of experiencing affective states induced experimentally, on average they reveal robust emotion recognition and emotion discrimination performance deficits [30, 31]. In a social context the incorrect interpretation of facial expressions in the surrounding world can considerably interfere with successful inter-personal interactions. Basic emotion perception distortions can therefore contribute to social problems patients with schizophrenia spectrum disorders often encounter [32].

While the recognition of facial emotion expressions normally becomes easier with increasing emotion intensity, chronic schizophrenia patients profit significantly less from this effect [29]. Moreover, emotion recognition deficits can further interact with demographic or clinical factors. Most studies found a correlation between the severity of negative and partly also of positive symptoms and emotion recognition performance. However, this alone could not explain the heterogeneity between different research results [31]. Furthermore, the effect sizes did not differ between samples with schizophrenia patients and mixed samples of patients suffering from schizophrenia and schizoaffective disorders. Patients with schizoaffective disorders seem, therefore, to show similar performance deficits in emotion recognition tasks but reveal, however, a slightly better performance in social theory of mind situations [33]. Finally, results in respect to the effects of illness duration are inconsistent, with some studies showing a significant correlation of emotion recognition deficits and illness duration [34], while others report no such association [31], or just a trend in this direction [30].

Interestingly, it seems to be less the ability to recognize a specific emotion which is impaired in patients with manifest schizophrenia spectrum disorders, i.e. the performance sensitivity, but rather the performance specificity. When patients with schizophrenia were asked whether the emotion presented reflects a certain basic emotional state they consistently revealed difficulties in rejecting an incorrect emotion (see Fig. 18.4), especially if dealing with negative affect.

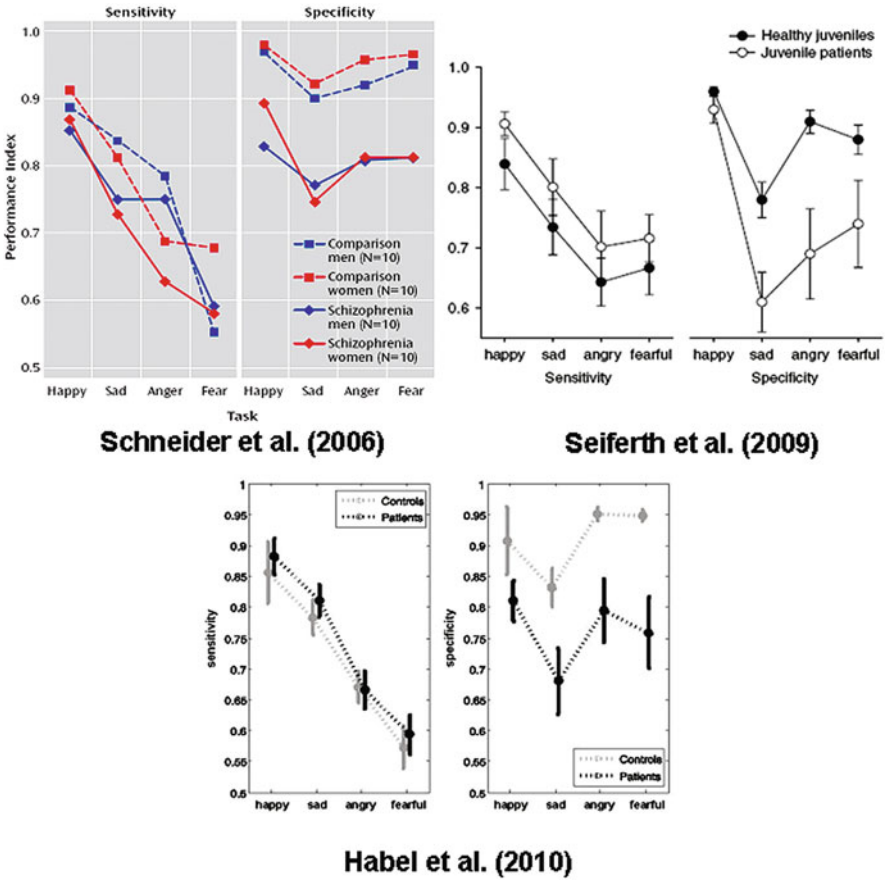

Fig. 18.4 Facial emotion discrimination specificity decreases in patients with schizophrenia with specificity being defined as the ratio of true negative answers and the sum of true negative and false positive responses (and sensitivity accordingly as true positives/[true positives + false negatives]). Replicated findings from Schneider et al. [35], Seiferth et al. [42], and Habel et al. [34]

Emotion recognition dysfunctions not only become obvious in patients with manifest schizophrenia [35]. Even healthy first-degree relatives of schizophrenia patients revealed subtle affect perception deficits [27, 36]. Thereby, the performance of siblings of patients with schizophrenia fell in the middle of a continuum between the performance of patients and unrelated healthy controls. However, only about 10% of the patients with first-episode psychosis report a positive family history [37] and subjects clinically at risk for psychosis were still able to perform normally in a visual emotion discrimination task [38]. Yet, as discussed below the latter might be the result of a compensatory increase of effort.

Emotion recognition deficits are reflected in altered brain activation patterns. Decreased activation in the fusiform "face" area (or occipitotemporal gyrus) has been found consistently during facial emotion discrimination in adult [34, 39,

40] and first-episode schizophrenia patients [41] as well as adolescent early-onset schizophrenia patients [42]. A seemingly successful compensatory increase of fusiform gyrus activation was found in subjects clinically at risk for psychosis [38]. The notion of hyperactivations as compensatory mechanisms is further affirmed by the fact that activation of the gyrus frontalis medialis during an emotion labelling task was not only increased in patients but also in healthy subjects during increasing task difficulty [43]. Interestingly, in individuals with CHR hyperactivations were not only associated with emotional faces. The decomposition of emotion by group interactions revealed that significant effects were mainly related to activation increases in response to neutral faces in putatively prodromal subjects, mainly in the left inferior and superior frontal gyrus and the thalamus [38]. This might be related to an emotional misinterpretation of neutral material and could represent a biological risk marker for psychosis. The same phenomenon is also found on a behavioral level in siblings and offspring of schizophrenia patients [27].

Although cerebral dysfunctions during the processing of emotional material may vary according to stimulus valence [34], dysfunctions in the fusiform gyrus during emotional as well as neutral facial discrimination conditions imply that patients with schizophrenia reveal already rather basic face processing deficits [44]. Accordant structural changes also reflect gray matter loss in the fusiform gyrus in chronic [45] and first-episode schizophrenia patients [46]. Moreover, in patients the volume of the anterior fusiform gyrus was significantly correlated with the performance on a delayed memory task for faces [45].

In addition, in response to happy, sad, angry, disgusted, neutral, and fearful or surprised faces during tasks of facial affect labelling [43] and emotion discrimination [47] patients with schizophrenia revealed hypoactivation in the amygdala-hippocampal complex (see also Li et al. [39] for a meta-analysis). The importance of the amygdala and the hippocampus for visual facial emotion processing was underlined by the fact that an overall increase in activation was found in both areas during emotion discrimination as compared to age discrimination [47]. Activation increases in patients with schizophrenia were found for some emotions, such as increased amygdala activation for happy faces [48]. A closer inspection of these activation changes suggests that deficits may become obvious over time [49]: during an emotional facial matching task patients with schizophrenia showed similar amygdala activation to healthy subjects for the first 21 s of a stimulation block. However, while healthy subjects showed increased activation across time, it decreased in patients (Fig. 18.5). Furthermore, at the beginning of the task patients revealed an increased cortical activity and connectivity with the medial frontal gyrus and the inferior parietal lobe. In the sustained phase (during the last 21 s of the block), however, activity in the superior temporal cortex increased, which was related to a greater connectivity with the inferior parietal cortex. The authors suggest that there is an initial automatic emotional response in patients after which they have to switch to conscious compensatory cognitive mechanisms to solve the task. These might include a closer feature analysis of the facial stimuli. Behaviorally this was reflected in lower performance of patients during the initial phase of the task and higher reaction times in the later part of the block.

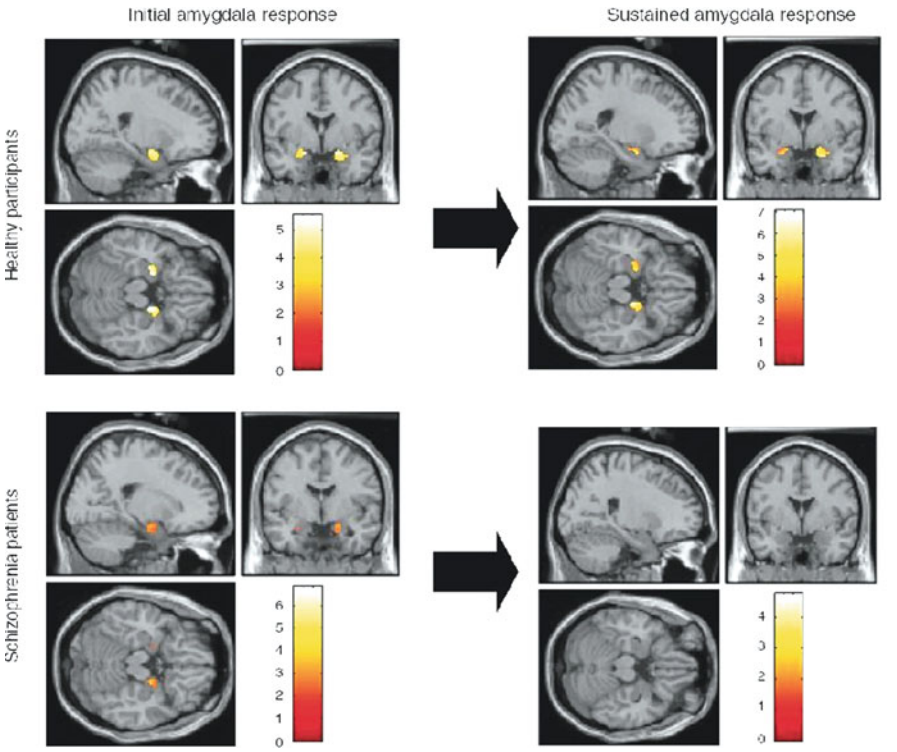

Fig. 18.5 Amygdala activation in the course of time during a facial emotion matching task with an initial (rather automatic) response in schizophrenia patients and healthy subjects (during the first 21 s of the emotional condition) but decreased amygdala activation in patients in the course of time (i.e. during the last 21 s of the task; Salgado-Pieda et al. [49])

Further reduced activations in patients during emotional face discrimination encompass the anterior cingulate gyrus and, depending on the emotion, also the inferior frontal gyrus [34, 41, 43]. Both areas are closely linked to other regions involved in emotion processing such as the amygdala and other medial temporal regions.

Preceding studies produced a plethora of divergent findings concerning the neural correlates and the dysfunctions in schizophrenia. Amongst others, this reflects a heterogeneity in general definitions of emotion recognition, emotion processing, and emotion discrimination, which may differ in their functional substrates but are not clearly separated from each other. The different sub-components of emotional processing discussed in literature may be impaired in schizophrenia spectrum disorders to a greater or lesser extent. The character of the tasks used may be a critical point accounting for some of the reported divergences in preceding results. For example, paradigms may vary in their implicit or explicit character. Most of the emotion recognition studies mentioned above investigated explicit facial emotion discrimination [34, 38, 41, 42, 47], or affect labelling [43]. Both kinds of tasks required

the explicit naming of (or choosing between) different emotions. In less conscious implicit tasks, such as emotion matching paradigms [49], on the other hand, subjects are never asked to explicitly recognize or classify displayed emotions. Such paradigms lack information as to whether subjects really knew that the two facial expressions they matched were actually happy, angry, or fearful.

Explicit emotion recognition is linked to our knowledge of and capacity for emotional and social interactions. Consequently, explicit and implicit tasks may not be comparable in terms of requirements and processing load and may partly rely on different brain networks. Accordingly, emotion recognition dysfunctions should be more obvious in explicit tasks. Indeed, an actual meta-analysis [39] yielded decreased activation in the fusiform gyrus in patients with schizophrenia only in explicit tasks. However, impaired activation in the amygdala and the parahippocampal gyrus bilaterally was found in both cases underlining the key role of both regions for emotion processing dysfunctions in schizophrenia.

Other methodological issues, which may be related to divergences in previous research results, encompass the baseline condition used (e.g. neutral faces, gender or age discrimination, or low-level baseline), and whether the compared baseline is used as activation mask, e.g. to avoid a subtraction of potential (negative) deactivations [48].

As it is the case with behavioral performance measures (see above), psychopathological measures may also play a crucial role regarding differences in brain activation patterns. For example, during the processing of fearful faces, schizophrenia patients with paranoia revealed decreased amygdala activation. However, patients without paranoia showed increased activation in the hippocampus [50] underlining psychopathology related specific dysfunctions and differentially affected networks comprising the amygdala and the hippocampus [7].

Deficits in visual affect recognition seem to be rather stable and unrelated to psychopharmacological therapy [31, 51]. However, specific emotion remediation might be beneficial [52–55]. Facial affect perception in schizophrenia could be improved by training facial feedback via imitation of the expressions of target faces, but also by means of monetary reward [54]. However, there is limited evidence for a generalization of these effects to general facial affect discrimination. Active affect decoding was practiced in a standardized performance dependent 12-session training involving restitution and compensation strategies via self-instruction, positive reinforcement, and principles of errorless learning [53, 55]. Patients gradually learned to identify, discriminate, and verbalize characteristic facial features and to integrate this information into an increasing holistic picture. In a last step, ambiguous non-prototypical emotional facial expressions, which can typically occur in everyday life, were integrated in a social and situational context. Indeed, after such training patients' emotion recognition performance approached the level of healthy subjects and was significantly better than the performance of patients after a cognitive remediation training or treatment as usual. In parallel to this behavioral improvement activation increases were found in the middle and superior occipital lobe, the right inferior, and superior parietal cortex, and the inferior and middle frontal cortex as compared to patients who had received treatment as usual [52]. This

underlines that specific trainings may be effective and should be further validated with respect to their contribution to social functioning in patients with schizophrenia spectrum disorders in addition to pharmacological treatment.

Interpreting Emotional Prosody

Emotion recognition usually relies on the integration of multimodal information. Hence, in addition to mimic information, prosody, i.e. the "speech melody", is especially crucial for emotion recognition and consequently for social interactions. Unfortunately patients with schizophrenia cannot completely rely on such information because they also suffer from deficits in prosody recognition. These dysfunctions show a large effect size (for a review and meta-analysis: Hoekert et al. [56]). For example, when differentiating between high and low clarity emotional prosody, paranoid patients with schizophrenia revealed worse performance than healthy subjects or patients with depression in the high clarity condition [57]. Hence, comparable to visual material, patients profit less from an increased intensity of the expressed emotion. The authors suggested this might be due to a reduced signal-to-noise ratio in the internal representations of schizophrenia patients. Interestingly, and in line with this idea, prosody identification was better predicted by the ability to identify emotional faces than by other illness-related factors.

In individuals with schizotypal personality disorder difficulties in prosody processing were too subtle to reach significance. Nevertheless, although healthy subjects and individuals with schizotypal personality disorder both activated the superior temporal sulci, healthy subjects revealed broader activated areas in the superior temporal gyrus (STG), especially on the right side of the brain, a key region of prosody processing. In healthy subjects the amount of hemodynamic response in the STG was further correlated with the accuracy of the response but not in persons with schizotypal personality disorder [58] (Fig. 18.6).

Just as for emotional facial expressions the processing of prosody has been related to deficits in basic sensory processes (e.g. estimation of rising tone intensities, tone matching, auditory attention, etc.; for an overview: Dickey et al. [58]). Accordingly, patients with schizotypal personality disorder also showed dysfunctional activation in the Heschl's gyrus when listening to tones differing in pitch and duration. However, here, the authors found an *increase* in activation in the STG in subjects with schizotypal personality disorder when detecting pitch and duration deviants [59].

In summary, the investigation of emotion recognition in schizophrenia spectrum disorders underlines the under-recruitment of an "emotional" and "social" brain network including medial temporal areas, such as the amygdala, as well as medial and ventral prefrontal regions. This indicates disrupted networks and disconnections in schizophrenia rather than dysfunctional single loci. However, some dysfunctions can also be characterized as rather modality specific, such as in the fusiform gyrus during the visual processing of emotional faces or in the STG during the processing of prosody.

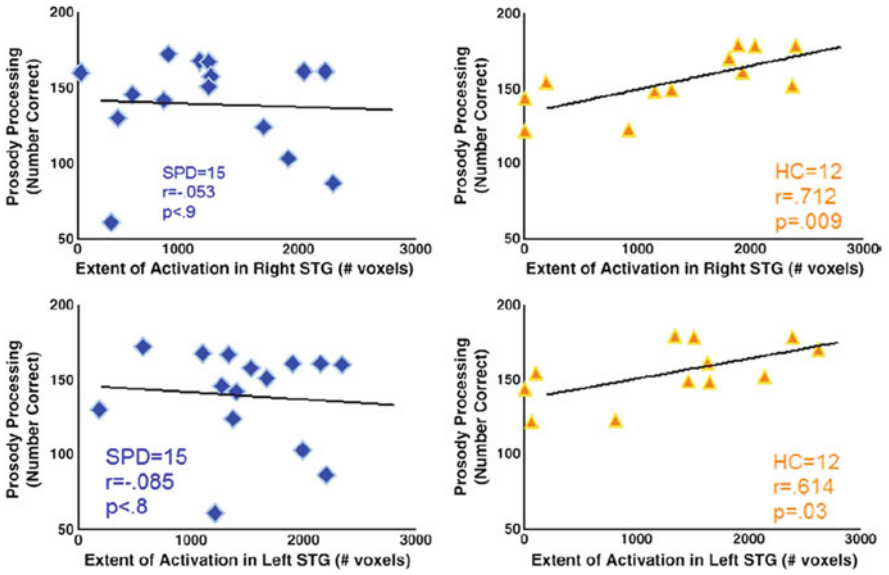

Fig. 18.6 Correlation between the ROI activation in the *right* (*upper row*) and *left* (*lower row*) superior temporal gyrus and the number of correct answers during a prosody recognition task with a significant correlation for healthy control subjects (HC, on the *right*) but no accordant correlations for persons with schizotypal personality disorder (SPD, on the *left*; Dickey et al. [58])

Interaction of Emotion and Cognition

Emotional and cognitive dysfunctions (see also Chapter 38) do not just co-exist without influencing each other mutually. A strict separation of the two domains is artificial – although often necessary in the context of neuroimaging experiments, where valid interpretations are only possible if processes are sub-divided in preferably distinct functions. Nevertheless, cognition can modulate affective states. Emotions, on the other hand, exert an influence on diverse higher cognitive functions. A negative affective state can impair the performance in several cognitive tasks while positive emotion can partly increase some cognitive functions [60, 61]. Dissociations were also found, however, in which negative emotion impaired the performance in one task but improved it in another [62].

It was assumed that the interaction of emotion and cognition relies on the interaction of two networks, the prefrontal and cingulate cognitive control system and the cortico-subcortical emotion-related network including amongst others the orbitofrontal cortex and the amygdala [63–65].

The valence of the stimuli can influence the underlying brain activation during the interaction of emotion and cognition. During working memory, activation in the dorsolateral prefrontal cortex (DLPFC) decreased for unpleasant but increased in reaction to positive stimuli (in comparison to neutral stimuli). The inverse pattern was found for the orbitofrontal cortex [61]. This dissociation between OFC and

DLPFC is in good accordance with the fact that the OFC, which is closely linked to other emotion-related areas, such as the amygdala, is rather attributed to emotional and motivational processes while the DLPFC is a key region of higher order cognitive functions.

Activation changes in the superior frontal gyrus and amygdala were found in subjects performing a working memory task with happy or fearful faces as compared to neutral ones. However, negative stimuli (as compared to neutral or positive faces) yielded activation in the hippocampus and the DLPFC only in patients. Social anhedonia correlated with decreased amygdala but increased DLPFC activation [66]. The authors concluded that the emotional material challenged the dorsolateral control system as compensation for dysfunctions in the limbic system.

As mentioned above, olfactory mood induction is rather automatic with no need for cognitive effort. The possibility of simultaneously challenging two sensory systems (e.g. by olfactory emotion induction during a visual task) also eliminates resource competition in the visual system. It is therefore very suitable for the investigation of the interaction of emotional and cognitive (dys-)functions in healthy subjects and patients with schizophrenia spectrum disorders. During a verbal working memory task patients with schizophrenia revealed a decreased activation in the dorsal ACC (Fig. 18.7) and the medial superior prefrontal cortex when negative emotion was induced via olfactory stimulation while orbitofrontal activation was increased [67]. The anterior cingulate gyrus plays a key role in the interaction of emotion and cognition with the dorsal anterior cingulate gyrus revealing an increase in activation during higher cognitive functions but a decrease during emotional processing [68, 69]. The opposite pattern was found for the ventral ACC, i.e. decreased activation during cognitive tasks but increased activation during emotional conditions [68] (Fig. 18.7). This underlines the notion of deficits in cognitive control processes during emotion regulation in schizophrenia resulting in a dysfunctional modulation of emotion-related brain areas.

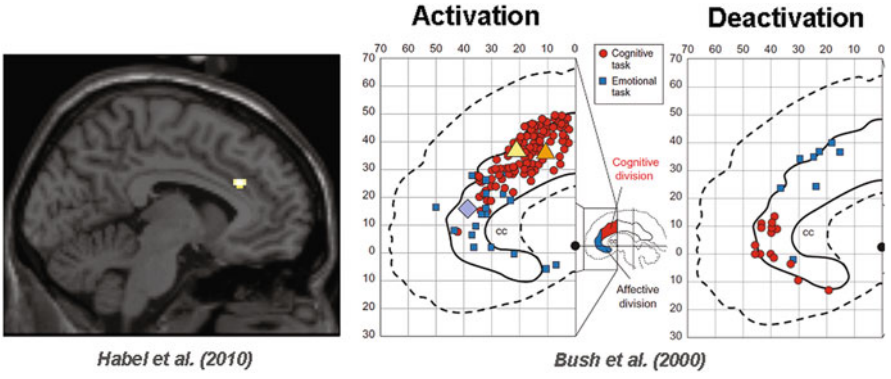

Fig. 18.7 *Left*: Decreased activation in the dorsal anterior cingulate in patients with schizophrenia during the interaction of verbal working memory and olfactory induced negative emotion (data from Habel et al. [67]). *Right*: activation and deactivation of the dorsal and ventral ACC depending on the (cognitive or emotional) task (Bush et al. [68])

During the interaction of negative emotion and working memory patients with early-onset schizophrenia revealed dysfunctions in a thalamo-cortical network particularly involved in the integration of converging information from different systems – either on a subcortical (thalamus) or on a higher-order cortical level including the angular gyrus [20]. This might implicate deficits at an earlier stage of information processing in this sample of patients suffering from an especially dramatic disruption of the adolescent neurodevelopment.

Since patients with schizophrenia show several impairments in emotional as well as cognitive functions the interaction of both dimensions might constitute an especially sensitive measure for early brain dysfunctions. Indeed, despite a lack of behavioral differences brain activation differences were already found in a sample of persons with ultra-high risk for psychosis during the interaction of executive functions and induced negative emotions. Putatively prodromal patients revealed decreased activations in the superior temporal gyrus and the rolandic operculum and an increase of activation in several cerebellar regions, the inferior temporal lobe and the thalamus [17]. The superior temporal gyrus has been related to the processing of affect-laden stimuli [70] and the integration of cross-modal information [71]. Furthermore, the robust findings of increased cerebellar activation in subjects with CHR during the interaction of working memory and emotion could be interpreted as a compensatory mechanism since activation in the cerebellum has been associated with verbal working memory [72–74] and other higher cognitive functions [75] as well as odor discrimination [76, 77]. However, such dysfunctions in individuals with CHR are clearly less specific than those revealed by patients with manifest schizophrenia. One reason may be that not all subjects at high risk really develop schizophrenia subsequently. Furthermore, especially increased activations may be related to successful compensatory strategies, which might only be effective in advance to illness onset.

The complexity of emotion-cognition interactions may result in a high sensitivity of the cerebral dysfunctions found while the specificity seemingly is rather low and strictly depending on the sample characteristics.

In this context, Modinos et al. [63] investigated a non-clinical sample comparing healthy subjects with high and low psychosis proneness during a task of reappraising negative pictures as an emotion control process. During the accordant decrease of negative emotion the higher psychosis-prone subjects revealed increased activation in prefrontal areas including the dorsolateral and ventrolateral prefrontal cortex and the ACC. However, amygdala activation in response to the negative pictures only decreased in the low psychosis proneness group. A decreased functional connectivity between the prefrontal cortex and the amygdala, which was found in the group with higher risk for psychosis, could not only explain the inefficiency of the increased prefrontal activation in reducing the activation in the emotion-related amygdala, but also underlines that changes in the cognitive control system might increase the vulnerability to psychosis.

Another interesting aspect is the interaction of cognition and musically evoked emotion. Results on an attention task revealed that music which could improve mood also enhanced the performance of patients with schizophrenia by reducing

response latencies and errors. The authors explained this with a decrease of the general hyperarousal in patients with schizophrenia [78]. A more complex cognitive task in which psychotic patients often reveal difficulties is decision making under uncertainty. Here, patients with schizophrenia tend to jump into conclusions, i.e. they make faster decisions based on insufficient information. When anxiety-evoking music was presented as a distracting cue deluded patients even made more hasty decisions of liberal acceptance. However, the same was not true for cheerful music [79]. So far, brain imaging data are missing in this context but will be an interesting complement to the data found for the interaction of cognition and induced emotions.

In summary, studies on the interaction of emotional and cognitive functions in schizophrenia spectrum disorders affirm the notion of a dysfunctional cognitive control or emotion regulation system probably located in mainly dorsolateral prefrontal areas and the dorsal ACC interacting with activation changes in a ventral system including amongst others the orbitofronal cortex, the amygdala, and thalamic areas. These brain network dysfunctions might be especially sensitive in the context of early changes in the prodromal phase. On the other hand, there is a strong influence of sample characteristics, which points to state markers of the illness.

Emotional Self-Concept

The self-concept encompasses the cognitive representation of feelings and thoughts about oneself including ideas about personality traits a person attributes to him- or herself. From a neuroscientific perspective these feelings or models of oneself are the result of their neural representations. In schizophrenia, dysfunctions can affect different levels of the self-concept [80]. Patients who tend to attribute their own actions or thoughts to another person or are not able to recognize them as being aspects of themselves experience passivity symptoms. In addition to this rather implicit and automatic idea of the self there are more conscious features, such as the self-attribution of positive, neutral, or negative characteristics. Phenomena in patients with psychosis such as a hypothesized increased *self-serving bias* [81, 82] describing the tendency of patients with positive symptomatology to ascribe negative situations more often to others and positive situations more often to themselves, may also have an influence on self-evaluation. However, literature is inconsistent – especially in the context of self-attribution of positive results, with some studies also reporting an accordant negative bias in patients with schizophrenia spectrum disorders [83, 84]. And indeed, when asked to evaluate themselves according to positive and negative personality traits, in the direct comparison patients ascribed less positive, but more negative personality traits to themselves as compared to healthy subjects [85]. Similar results were found in an interview-based measure of self-evaluation and self-esteem where a more negative self-evaluation was related to an increase in positive symptomatology [86]. Negative cognitive schemes of patients with psychosis [87] may interact with a lower self-esteem and both may contribute to an increase in depressive symptoms [88]. Auditory hallucinations are mostly malevolent and negative self-appraisals are a common

tenor. Corresponding negative affective reactions come along with a negative self-concept [89] and both may reinforce each other mutually.

In healthy subjects, the neural substrates of self-reference were related to the ventro- and dorsolateral prefrontal cortex, the lateral parietal cortex, the insula and both temporal poles. However, a review of Northoff and colleagues [90] on 27 fMRI and PET studies made clear that the most important or most reliable activation pattern for the comparison of self-related vs. not self-related material is located in midline cortical areas, mainly in the medial prefrontal cortex and the posteror cingulate. This is particularly true in the context of (emotional) self-evaluative processes [91–93]. The anterior medial prefrontal cortex is a key region of meta-cognitive processes. Of course, also self-reflection and self-knowledge are meta-cognitive functions [94]. The posterior cingulate cortex, on the other hand, plays an essential role in the episodic autobiographical memory functions but also in processing of emotional material [92] (Fig. 18.8). It may therefore act as a key area of self-related emotional memory. Moreover, the posterior cingulate gyrus has been related to the first-person perspective [95].

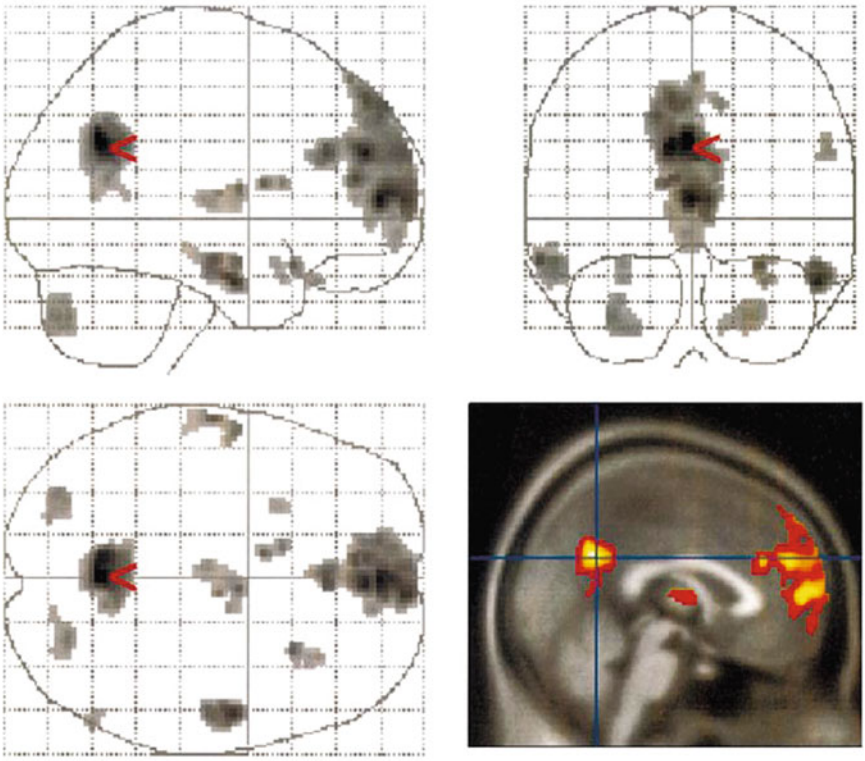

Fig. 18.8 Typical activation in the anterior medial prefrontal cortex and posterior cingulate gyrus during self-reflection concerning mood and own social, cognitive, and physical abilities (vs. general knowledge; Johnson et al. [92])

Although related cerebral dysfunctions are not reported consistently in schizophrenia [96] it seems that dysfunctional self-referential activity in cortical midline structures already becomes apparent in a prodromal phase [97]. This is in good accordance with the fact that patients often report changes in self-experience already at early stages of the illness.

Since negative changes of the emotional self-concept are surely amongst the symptoms least tolerable by patients and closely interact with self-esteem and depressive symptomatology, an increased effort has to be undertaken to enhance our knowledge about the underlying mechanisms. This includes the investigation of cerebral dysfunctions in a midline structure network involving the anterior MPFC and the posterior cingulate gyrus that partly may be the reason for negative meta-cognitive schemes about the self but also about the surrounding world in schizophrenia spectrum disorders.

Conclusions and Future Directions

Imaging techniques such as fMRI allow new insights into the neurobiological correlates of psychopathological phenomena underlying schizophrenia spectrum disorders. We discussed dysfunctions of emotional experiencing, emotion recognition, and the interaction with cognitive functions as well as an altered emotional self-concept as core symptoms of schizophrenia spectrum disorders. The underlying dysfunctions of cerebral networks may act as endophenotypes of schizophrenia.

In the beginning of our chapter we introduced a model by Phillips and colleagues [1, 2] describing theoretical sub-processes of emotion processing and their potential neural networks. Applying this model to a great amount of actual studies on emotion-related functions we saw that – in spite of the high complexity of the topic – this model is still capable of explaining a great amount of the results found in very different experimental designs. Decreased activations but also compensatory activation increases in dorsolateral, dorsomedial, or dorsal ACC mostly come along with activation changes in ventral regions, such as the amygdala, the OFC, or the insula, which can be closely linked to emotional processes. Of course, a model applied in neuroscience has to be simplified. However, extensions of the model might encompass the inclusion of neural changes in schizophrenia spectrum disorders obviously specific to the modality in which the emotional input is processed. Dysfunctions in the fusiform gyrus were found robustly in schizophrenia but only during visual processing of emotional faces. Dysfunctions in the STG, on the other hand, were most prominent during the processing of prosody or emotional music. Furthermore, while some findings, such as activation changes in the fusiform gyrus and the amygdala during the recognition of emotional facial expressions, may represent trait markers of the disorder, other dysfunctions might rather be sensitive state markers.

The reported neuroimaging studies have also immediate *clinical implications*. The combination of the results from different imaging techniques, electrophysiological measures, neuropsychological, genetic, pharmacological, and

psychotherapeutic studies will increase our understanding of schizophrenia spectrum disorders. For affected patient this may imply improvements of a multimodal treatment approach. Neurofeedback may be a promising tool for the self-modulation of emotion-related ventral networks in patients with schizophrenia. During such a training, healthy participants were asked to upregulate individual emotion-related brain regions in response to an accordant visual feedback signal. The successful result was an individual upregulatation of the VLPFC, amygdala, or insula, which was further associated with increased activation in the medial prefrontal cortex, dorsal striatum, anterior and posterior cingulate cortex [98] – with all areas being crucially involved in emotional dysfunctions in schizophrenia.

Furthermore, also psychological interventions which improve affective self-regulation are accompanied by modulations of brain activation in relevant areas, such as the DLPFC, MPFC, VLPFC, anterior and posterior cingulate cortex [99]. Especially an altered emotional self-concept and negative biases in the interpretation of emotional or neutral material may be a starting point for cognitive behavioral therapy in schizophrenia, which could help to change dysfunctional appraisals and cognitive schemes. Indeed, within the last years cognitive behavioral therapy has proven to be considerably more effective in the treatment of psychosis [100] than had been assumed in previous decades.

Finally, neuroimaging could be of help in quality management of various therapeutic methods. This includes pharmacological interventions but also brain activation changes due to psychotherapy. Besides the monitoring of changes in the functional cerebral correlates of cognitive tasks typically impaired in schizophrenia (such as executive functions, for example), also the monitoring of emotional processes and their neural substrates should be taken into account. Functional brain imaging studies may help to differentiate between good and bad responders to certain interventions. Different treatment options could therefore be fitted to patients more individually on the way to a more personalized medicine.

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Chapter 19
Brain Morphological Abnormalities at the Onset of Schizophrenia and Other Psychotic Disorders: A Review of the Evidence

Antonio Vita, Luca De Peri, Cesare Turrina, and Emilio Sacchetti

Abstract A number of structural brain imaging studies and meta-analytic reviews have shown that multiple subtle brain abnormalities are consistently found in schizophrenia. However, quantitative reviews published to date suggest that structural brain changes found at the onset of the disease may be at least partially different from those found in patients with chronic schizophrenia. Some abnormalities seem to characterize schizophrenia at all stages; others seem more specific to the initial phases of the disease. These findings support the hypothesis of different patterns of involvement of various cerebral areas over the time course of schizophrenia. This suggests a complex scenario in which late cerebral changes, possibly related to the disease course and treatment, may complicate other early abnormalities, probably predating the disease onset. The specificity of such brain abnormalities to schizophrenia or the possibility that they may also be relevant to other psychotic disorders is a matter of debate. In particular, there is evidence for the presence of brain abnormalities in bipolar disorder, partially overlapping those found in schizophrenia. In this case, however, different findings have been reported in first-episode and chronic cases, raising the issue of converging trajectories of brain pathomorphology in these disorders, from a more specific pattern of abnormalities at onset, to a higher degree of overlap in chronic cases. In this chapter, the nature and meaning of these components of brain abnormalities, and how they affect the neurodevelopmental versus neurodegenerative hypotheses of psychoses are discussed.

Keywords Schizophrenia · Bipolar disorder · Psychosis · Brain morphology · Magnetic resonance imaging · First-episode · Meta-analysis

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Abbreviations

BD	Bipolar disorder
CT	Computed tomography
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
MRI	Magnetic resonance imaging
ROI	A region of interest
STG	Superior temporal gyrus
VBM	Voxel-based morphometry

Introduction

The occurrence of multiple brain abnormalities in schizophrenia and other psychotic disorders has been shown by many CT and MRI studies performed in the last 40 years, and confirmed by a series of meta-analytic reviews [1–4], demonstrating that psychotic disorders are characterized by several cortical and subcortical brain abnormalities. The investigation of cerebral morphology at different stages of the illness and, in particular, in patients with a first-episode psychotic disorder, is a matter of particular interest for several reasons: (i) patients with chronic psychoses have been exposed for long periods to various potential confounders that can affect brain structures, such as illness duration and cumulative intake of antipsychotic medications; (ii) the possible detection of brain morphologic abnormalities in the first phases of the illness, compared with those found in chronic cases, may provide useful information about the potential progression of changes in the brain after the onset of the disease; (iii) brain abnormalities at illness onset may represent the core and primary pathologic changes in the disorder, and (iv) the identification of specific patterns of morphologic alterations in the brain in the first stages of the disease may provide a useful tool for earlier recognition or diagnosis. Thus, investigation of brain anatomy in patients at the onset of the disease represents a means to get more insight on the nature of brain abnormalities detected in functional psychoses and their role in the pathophysiology of these diseases.

Schizophrenia

Several MRI studies have examined different cortical and subcortical regions of the brain in patients with first-episode schizophrenia using either ROI method or VBM approach. Some ROI studies have demonstrated a similar pattern of brain abnormalities as that reported in samples of patients with chronic schizophrenia, with a reduction in total grey matter volume [5–11], lateral and third ventricular enlargement [10–17], reduction in frontal lobe volume [18–23] and temporo-limbic abnormalities [20, 24–26, 22, 27–30]. The results of these studies, however, have

been put somewhat into question by others that have reported non-significant changes in brain structures such as cerebral ventricles [31–36], temporal lobe [18, 19, 33–35, 37] and temporo-limbic structures [7, 38–40] in similar samples of patients with first-episode schizophrenia.

A lower number of VBM MRI studies, with a more extensive survey of grey matter abnormalities than the manually drawn ROI analyses, has been conducted to compare brain morphology in patients and healthy controls. Investigations of grey matter volume in patients with first-episode schizophrenia using VBM have shown decreased volume of the mediodorsal thalamus and ventral and medial prefrontal cortices [41], prefrontal cortex [42], right medial frontal lobe, left middle temporal gyrus, left postcentral gyrus and the left limbic lobe [43], anterior cingulate cortex [43, 44], left STG, and bilateral anterior cingulate gyri and insula [45]. Three studies that recruited never-medicated subjects [46–48] reported reduction in grey matter volume in fronto-striato-thalamic and parahippocampal regions as well as smaller volume of the caudate [46, 47] and middle STG [48].

The presence of specific brain abnormalities in patients with first-episode schizophrenia has also been confirmed by a number of meta-analyses, which have shown the occurrence of multiple subtle brain abnormalities at the onset of schizophrenia. In particular, two studies have been performed on ROI MRI. The analysis by Vita et al. [49] included 21 cross-sectional studies and indicated that patients with schizophrenia, compared with healthy controls, showed significant overall effect sizes for increase of lateral and third ventricular volume (left ventricle $P \leq 0.001$, right ventricle $P \leq 0.001$, lateral ventricles $P = 0.02$, third ventricle $P \leq 0.001$, respectively), and for reduction of whole brain ($P = 0.002$) and hippocampal volume in both cerebral hemispheres (left hippocampus $P \leq 0.001$, right hippocampus $P \leq 0.001$), but not for temporal lobe, amygdala and total intracranial volume. In line with Vita et al. [49] results, the quantitative review conducted by Steen et al. [50], which considered 52 studies in a cross-sectional analysis of first-episode schizophrenia, demonstrated a reduction of whole brain and hippocampal volume (both $P \leq 0.0001$) and an increase of ventricular volume ($P \leq 0.0001$) relative to healthy controls. Moreover, the more recent meta-analysis of VBM imaging studies conducted in patients with first-episode schizophrenia by Ellison-Wright et al. [51] reported decreases in grey matter volume in the thalamus, the left uncus/amygdala region, the insula and the anterior cingulate bilaterally.

DTI makes it possible to assess microstructural abnormalities of brain white matter. In addition, the probable trajectories of fiber tracts can be calculated and visualized, allowing tract-specific measurements. As reported in the review by Peters et al. [52], DTI studies have produced some evidence of widespread white matter abnormalities in patients with first-episode schizophrenia [53–62], but the findings are not unequivocal. Some studies have shown no differences between patients and healthy controls [63–68], whereas others found no FA abnormalities but did identify abnormalities with other diffusion indices [64, 69, 70]. Overall, the most positive findings come from VBM studies, whereas 6 out of 15 fiber tracking or ROI analyses showed no abnormalities [60, 63, 65–68].

Bipolar Disorder

A large number of studies have been performed to date on brain morphology in patients with BD. These are reviewed by Kempton et al. [2] in a recent meta-analysis, which included up to 98 studies. The most significant anatomical abnormalities in BD were enlargement of the third and lateral ventricles, reduction of the cross-sectional area of the corpus callosum and an increased rate of deep white matter hyperintensities. A relatively small number of studies have considered brain morphology in patients with BD at the illness onset.

ROI MRI studies on first-episode BD have demonstrated a pattern of brain abnormalities similar to those detected in samples of patients with chronic BD, that is, enlargement of the ventricular system [71], smaller area of the corpus callosum [72], and the presence of brain white matter hyperintensities [73]. On the other hand, other MRI studies have reported various cortical and subcortical brain abnormalities at illness onset not detected consistently in patients with chronic BD, such as a reduction of neocortical grey matter [74], smaller amygdala volume [75] and larger than normal striatum [76].

VBM MRI studies conducted on first-episode BD showed decreased volumes of frontal lobe and temporal gyrus grey matter [77], and of cingulate gyrus grey matter [77, 78].

DTI studies of brain white matter abnormalities in the early course of BD showed lower FA in the left anterior frontal white matter, left posterior thalamic radiation, left cingulum and bilateral sagittal striatum [79] and superior frontal white matter [80].

The presence of specific brain abnormalities in patients with first-episode BD has also been confirmed by a recent meta-analysis of ROI MRI studies [81], where a significant reduction in total intracranial ($P = 0.022$) and white matter volume ($P = 0.029$), but not in grey matter and whole brain volume, was demonstrated in patients with first-episode BD compared with healthy controls.

Schizophrenia Compared with Affective Psychoses

The evidence so far indicates a consistent association between brain structural abnormalities and schizophrenia and BD in the early phases of these illnesses. Given the evidence of a significant anatomic overlap between the findings of brain morphologic changes across different diagnostic groups of functional psychoses, the specificity of brain structural abnormalities in schizophrenia and affective psychoses at illness onset could be better addressed by means of studies that directly compare patients with a diagnosis of schizophrenia, patients with a diagnosis of affective psychosis, and healthy comparison groups.

A few cross-sectional MRI studies on this topic have been performed but have led to heterogeneous results. Takahashi et al. [82] investigated the STG subregions in patients with schizophrenia and schizoaffective disorders and subjects with a diagnosis of affective psychosis compared with healthy subjects. They reported that

patients with first-episode schizophrenia had significantly less grey matter in the Heschl gyrus, planum temporale, and caudal STG bilaterally compared with all other groups, but that there were no differences between controls and the affective psychosis, schizophreniform disorder, for any STG subregions. The STG white matter volume did not differ between groups. This finding seems to indicate that morphologic abnormalities of the STG grey matter are specific to schizophrenia among psychotic disorders. The cross-sectional investigation conducted in patients with schizophrenia and affective psychosis at their first hospitalization by Kasai et al. [83] found that a bilateral volume reduction in insular cortex grey matter was specific to patients with first-episode schizophrenia. In contrast, both first-episode psychosis groups showed a volume reduction in left temporal pole grey matter and an absence of normal left-greater-than-right asymmetry. The evaluation of the presence of white matter hyperintensities in a large sample of people with first-episode psychosis conducted by Zanetti et al. [73] reported no difference between the whole group with psychosis and controls for the prevalence or severity of these lesions, independent from their brain localization. Similarly, no statistically significant differences in the frequency and severity scores were identified when comparing patients with affective psychosis (psychotic BD or unipolar depression), non-affective psychosis (schizophrenia or schizophreniform disorder) and control subgroups. Nonetheless, as pointed out by the authors, it is possible that white matter hyperintensities could be a feature related to illness chronicity and this might explain why no group differences emerged in the early course of the illness.

In some studies, including both chronic and first-episode cases, schizophrenia and BD have been studied together as a generic psychosis category, with diagnostic categories analyzed post hoc. For example, Janssen et al. [84] found left medial frontal grey matter deficits in both disorders, and left middle frontal deficits only in schizophrenia. Others have compared schizophrenia and bipolar groups separately with normal controls and reported extensive grey matter deficits in the fronto-temporal-thalamic and cerebellar regions in schizophrenia, and no significant grey matter abnormalities in the bipolar group [85]. Most recently, Ellison-Wright and Bullmore [51] performed a meta-analysis with the newly developed anatomic likelihood estimation to compare the grey matter differences in each condition relative to controls. They found that in BD, reductions in grey matter were present in the anterior cingulate and bilateral insula and that these substantially overlapped with areas of reduction in grey matter in schizophrenia, except for a region of the anterior cingulate where the reduction in grey matter was specific to bipolar disorder.

Schizophrenia Compared with Schizophrenia Spectrum Disorders

A limited number of studies have directly compared brain morphology between patients with schizophrenia and a schizophrenic spectrum disorder. In the ROI MRI study performed by Takahashi et al. [82], patients with first-episode schizophrenia revealed significantly less amount of grey matter in the Heschl gyrus, planum

temporale, and caudal STG bilaterally compared with patients with schizophreniform disorder and healthy controls. On the other hand, no differences between controls and patients with schizophreniform disorder were demonstrated for any STG subregion. White matter volume of the STG did not differ between patients with first-episode psychosis and healthy subjects. Another MRI study by Crespo-Facorro et al. [86] investigating patients with schizophrenia and schizophreniform disorder showed an increase in cortical cerebrospinal fluid volume and a decrease in total brain tissue in psychotic patients at illness onset compared with healthy controls. However, the finding of larger lateral ventricular volume and a reduction in thalamic volume was limited to patients with schizophrenia. The VBM study of Pagsberg et al. [87] reported a reduction in white matter volume in the frontal lobe and an enlargement of lateral ventricular volume in patients with both first-episode schizophrenia and schizophrenia spectrum disorder compared with healthy controls, but the two clinical groups did not differ from controls for grey matter volume.

Trajectories of Brain Abnormalities and Specificity of Brain Morphologic Changes in Schizophrenia and BD

Looking at the literature on this issue, it appears that some of the regions of reduced grey matter in BD overlap with those in schizophrenia. This is consistent with the finding that the genetic risk for schizophrenia may be associated with grey matter deficits in the bilateral fronto-striato-thalamic and left temporal regions, whereas the genetic risk for BD may be associated with grey matter deficits in more limited regions of the right anterior cingulate gyrus and ventral striatum [88].

In agreement with these findings, there is increasing convergence toward dimensional constructs, as opposed to purely categorical ones, in the interpretation of the biologic substrate of schizophrenia and BD. Diagnostic classifications, making a priori assumptions about the illnesses as discrete entities, may be obstacles to our understanding of the aetiology and biology of psychosis. Typically, groups of patients with BD or schizophrenia are compared with healthy controls using classification systems such as the DSM IV. However, both conditions are intimately related, with shared genetic determinants [89].

Meta-analytic estimations of the extent to which BD, schizophrenia or both conditions contribute to brain grey matter differences compared with controls, statistically addressed with the so-called anatomic likelihood estimation [51], indicate substantial overlap in the regions affected in schizophrenia and BD including grey matter deficits in frontal, temporal, cingulate and insular cortex and thalamus. BD and schizophrenia contributed together to clusters of grey matter deficits, but schizophrenia was associated with additional grey matter deficits, especially in the left hemisphere, involving limbic and neocortical structures that go beyond the regions affected in BD [51]. On the other hand, a region of the anterior cingulate where the reduction in grey matter was specific to BD was reported [51]. Common

biologic mechanisms may therefore explain the neuroanatomic overlap between the two disorders, but an explanation of why brain differences are more extensive in schizohphrenia remains challenging.

Therefore, current pattern of results indicates that schizophrenia and BD appear not to be completely distinct entities at the level of the neuroanatomic phenotype. This observation is necessarily simplistic, but has lent support to the argument that they share biologic dimensions. The challenge for the future will be to identify whether the reductions in grey matter in BD and schizophrenia may be related to specific genetic factors [90] and whether common susceptibility genes contribute to the overlap in regional brain changes. The shared prefrontal cortical grey matter deficits observed may well contribute to core common cognitive dysfunctions related to negative functional outcomes in both disorders [91, 92].

Some more specificity of neuroimaging findings emerges, however, when only first-episode patients are considered.

The results of the main meta-analyses conducted on schizophrenia [49, 50, 93] confirm the presence at the onset of the illness of some of the brain abnormalities observed in chronic patients, i.e. enlargement of the ventricular system, and reduction in the volume of whole brain and the hippocampus. On the other hand, changes in the volume of the temporal lobe or amygdala do not appear in patients with first-episode schizophrenia compared with healthy controls, at variance with what was found in chronic patients. This pattern of results would support the hypothesis of an earlier involvement of the hippocampus in the cerebral pathomorphologic trajectory of schizophrenia, followed by a later involvement of the amygdala and other grey matter regions of the temporal or frontal lobe.

On the other hand, the main finding of a recent meta-analysis of patients with first-episode BD [94] was the presence, at the onset of the disease, of a significant reduction in intracranial volume and total white matter volume, at variance with the findings of meta-analyses of brain morphology conducted mainly on chronic patients [2]. Even if it is not possible to exclude the possibility that diagnostic shifts could arise over time for some patients enrolled in the original studies of first-episode BD (i.e. some of the patients classified as BD at disease onset could be re-diagnosed later as suffering from other types of psychoses and so are less represented in samples of chronic patients), some morphologic abnormalities appear early in the course of BD and other (especially lateral ventricular enlargement, grey matter changes and white matter hyperintensities) occur later and possibly increase with age.

The presence of definite brain abnormalities early in the course of schizophrenia and BD supports the hypothesis of a neurodevelopmental nature, even though their aetiology remains unclear. Even more important to the present discussion, it indicates that, at onset, a higher degree of specificity of brain morphologic changes in each of these two disorders is detectable. At a later stage, when the diseases progress, adjunctive, possibly progressive abnormalities appear, reducing the differences in the patterns of abnormalities between the two disorders, as is typically seen in more chronic cases.

Among the many possible explanations for the differences between data found at the onset and those reported in chronic patients, the most convincing are those related to the effects of medications and duration of illness. For example, chronic consumption of antipsychotics has been associated with changes in grey matter volume over time in a number of studies reviewed in [93, 95, 96], with substantial differences between the effects of typical and atypical antipsychotics, pointing towards the possibility of morphologic changes in the brain during the course of the disease, solely as a result of the amount and type of drug treatment received. There is also evidence that antidepressants, lithium or mood stabilizers may affect cerebral structure, as well as function [97], and this may occur in opposite directions for different classes of drugs. On the other hand, some authors have reported significant correlations between length of illness and grey matter volume in schizophrenia [36, 98] and in BD [99, 100]. Changes in grey matter volume over time have been reported in a few longitudinal MRI studies on patients with first-episode schizophrenia and chronic schizophrenia [101, 102] and BD [75, 103]. It would be very informative to perform new analyses on patients with schizophrenia and affective disorder using computational methods to take into account the known or hypothetical effect of drugs and chronicity in order to better understand whether a component of later structural changes in the brain is still demonstrable, and whether a higher specificity of brain pathomorphology could also be demonstrated in chronic cases after separating out the effects of treatment and chronicity.

Conclusions and Future Directions

In conclusion, the finding of different brain abnormalities in chronic versus first-episode schizophrenia and BD supports the notion of different pathophysiologic trajectories of specific brain morphologic characteristics over the course of these diseases. Some of the abnormalities occur early, probably predating the clinical onset, and show some specificity for schizophrenia and BD. Other changes occur later, in the course of the disease and after pharmacological treatment, and may be more similar for psychotic disorders, leading to an increasing overlap of findings in chronic cases, at least for grey matter changes. Whether this later and possibly progressive component of brain abnormalities is just an epiphenomenon of the disease course, treatment or other environmental events, or may be already embedded in the pathophysiologic trajectory of these diseases, possibly under some degree of genetic control, is still a matter for research and discussion. To shed more light on these crucial issues, there is still a need for longitudinal studies conducted on first-episode cases, aimed at specifically addressing the issues of the time of appearance and course of individual brain abnormalities in psychotic disorders, taking into account the effects of several confounders. Such studies may lead to a better understanding of the biologic meaning of brain abnormalities in both schizophrenia and BD and, through this, of the pathogenesis of these diseases.

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Chapter 20
Mapping Prodromal Psychosis

Paolo Fusar-Poli, Stefan Borgwardt, and Philip McGuire

Abstract The onset of schizophrenia is usually preceded by a prodromal phase characterized by functional decline and subtle prodromal symptoms, which include attenuated psychotic phenomena, cognitive deterioration and a decline in socio-occupational function. Preventive interventions during this phase are of great interest because of the potential impressive clinical benefits. However, available psychopathological criteria employed to define an high risk state for psychosis have a low validity and specificity. Consequently there is an urgent need of reliable neurocognitive markers linked to the pathophysiological mechanisms that underlie schizophrenia. Neuroimaging techniques have rapidly developed into a powerful tool in psychiatry as they provide an unprecedented opportunity for the investigation of brain structure and function. We will review in this chapter the potentials of structural, functional, neurochemical and multimodal imaging methods to address the core patophysiological processes underlying psychosis onset.

Keywords Prodromal psychoses · Neuroimaging · High risk subjects · Schizophrenia

Abbreviations

ARMS	At risk mental state
COPS	Criteria for prodromal syndromes
FMRI	Functional magnetic resonance imaging
HR	High risk
HR-NT	High risk subjects without a subsequent transition to psychosis
HR-T	High risk subjects with a subsequent transition to psychosis
MRS	Magnetic resonance spectroscopy
NMDAR	N-methyl-D-aspartate receptor

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PET	Positron emission tomography
SMRI	Structural magnetic resonance imaging
VBM	Voxel-based morphometry

Introduction

The onset of schizophrenia is usually preceded by a prodromal phase characterized by functional decline and subtle prodromal symptoms [1], which include attenuated psychotic phenomena, cognitive deterioration [2, 3] and a decline in socio-occupational function [4]. Research into the early phases of psychosis promises to provide important clues to the mechanisms underlying schizophrenia and other psychotic disorders. Investigation of subjects at the beginning of illness allows researchers to minimize confounders such as neurodegenerative progress of disease, institutionalization and long-term treatment, particularly with antipsychotics. To explore vulnerability to psychosis current literature employs two research paradigms. The genetic high-risk approach usually involves studying monozygotic or dyzigotic twins or the non-psychotic first degree relatives of patients. The clinical high-risk strategy focuses on individuals who are considered to be at an increased risk for psychotic disorders based primarily on the presence of clinical features such as attenuated psychotic symptoms or schizotypal traits, brief limited intermittent psychotic symptoms or a recent decline in functioning, characteristics that significantly increase the risk for imminent onset of psychosis. Although these strategies allow researchers to identify individuals at enhanced risk for psychosis [5], these symptoms overlap with psychotic experiences in healthy individuals who are not at risk and do not seek clinical help. It follows that identification of neurocognitive markers linked to the pathophysiological mechanisms that underlie schizophrenia, may significantly augment the validity and specificity of clinical features preceding illness onset. This is of great interest in the light of the impressive clinical benefits of preventive interventions in psychosis [6–8]. There are, at least, three possible mechanisms for improving the course of the disease by intervention before onset of psychosis. First, it might be possible to prevent psychosis by intervening in a crucial phase of beginning symptoms. Second, it might be possible to improve the course of the disease by improving the mental state in the prodromal phase or by postponing the first psychotic episode. Finally, the first psychotic episode might have a more favorable course after intervention in the prodromal phase, because the patient is already enrolled in a mental health treatment program: a psychosis will be discovered soon after onset, and the patient might be more willing to accept treatment, thus shortening the duration of untreated psychosis.

Brain imaging is a potentially powerful tool to improve the specificity and validity of an early diagnosis and to sustain preventive intervention prior the onset of illness. In this chapter, we will consider the role of neuroimaging techniques in the prodromal phases of psychosis. Neuroimaging methods have rapidly developed

into a powerful tool in psychiatry as they provide an unprecedented opportunity for the investigation of brain structure and function. We will first outline the applications of structural magnetic resonance imaging (sMRI) for the investigation of brain abnormalities underlying the pre-psychotic phases and psychosis onset. Then we will discuss the specific potentials of functional magnetic resonance techniques (fMRI) to address the neurofunctional correlates of an enhanced risk to psychosis, identify neurobiological markers of psychosis transition and evaluate the effects of antipsychotic on brain function during prodromal psychosis. In a third section we will further discuss the role of neurochemical imaging (PET and MRS) to study the role played by central neurotransmitters such as dopamine and glutamate in prodromal psychosis. Finally we will illustrate recent developments of neuroimaging methods which allow the integration of data across different modalities.

Definition of the High Risk for Psychosis

Neuroimaging studies published in current literature included different high-risk samples: (a) genetic high-risk subjects ((a1) monozygotic and dizygotic twins discordant for schizophrenia (non-psychotic twin) (a2) subjects with at least two first- or second-degree relatives of patients affected with psychosis [9, 10]), (b) clinical high-risk subjects ((b1) subjects at ultra high-risk (UHR) and (b2) with an at-risk mental state (ARMS) [11, 12] (b3) subjects with "basic symptoms" (e.g. thought and perception disturbances) [13]). According to recent data, although the risks for psychosis and associated abnormalities are higher in high-risk samples than in the general population, they are not the same across these different groups: monozygotic twins have a 40–50% concordance rate for the illness over lifetime [14], first-degree relatives of schizophrenia patients have approximately a tenfold increased risk for later illness compared to non-relatives over lifetime [15], while in clinical high-risk subjects the probability to develop psychosis ranges from 16% within 2 years [8] and 41% (ARMS) [7, 16] up to 54% (Criteria for Prodromal Syndromes – COPS) [17] within 1 year (for review see [18]), or 49% within 9.6 years [Basic symptoms – Cologne Early Recognition (CER) Project] [13]. Finally, it is worth mentioning schizotypal personality disorder, which is characterized, like schizophrenia, by positive or psychotic-like symptoms and negative or deficit-like symptoms [19]. Although the transition rate to psychosis in such groups is still under discussion [20], schizotypy symptoms in subjects with a genetic risk for schizophrenia or in those with a functional decline (ARMS) are clearly associated with an increased risk for developing a psychotic episode [21].

Two well established centers from the English-speaking area – *Personal Assessment and Crisis Evaluation clinic* (PACE) in Melbourne and *Outreach And Support In South London* clinic (OASIS) in London – have used the instrument called *Comprehensive Assessment of Symptoms and History* (CAARMS) [22] to assess the Attenuated psychotic symptoms (APS), brief limited psychotic symptoms (BLIPS) and trait + state risk factor [23] in the high-risk population. The same criteria with the newly developed shorter *Basel Screening Instrument for*

Psychosis (BSIP) [12, 24] were assessed in Basel in the Early Detection of Psychosis Clinic (FEPSY). The German research network on schizophrenia (GRNS) in Bonn, Düsseldorf, Cologne and Munich working with the ERIRAOS [25] – *Early Recognition Inventory* based on *Interview for the Retrospective Assessment of the Onset of Schizophrenia* (IRAOS) [26] and *Bonn Scale for Assessment of Basic Symptoms* (BSABS) [13] used the same criteria of *Brief Psychiatric Rating Scale* (BPRS) and *Comprehensive Assessment of Symptoms and History* (CASH).

In the light of the heterogeneity of the high risk state for psychosis [27] there is an urgent need of reliable neurofunctional markers linked to the pathophysiological mechanisms underlying the pre-psychotic phases to improve the validity and specificity of an early diagnosis.

Structural Neuroimaging

Structural MRI in Established Psychosis

Neuroimaging studies clearly indicate that schizophrenia is associated with neuroanatomical abnormalities, with the most replicated findings being ventricular enlargement and reductions in frontal and medial temporal lobe grey matter volume [28, 29]. However the extent to which these are related to a vulnerability to schizophrenia, as opposed to the disorder per se, is less certain.

Grey Matter Volume Abnormalities in Prodromal Psychosis: Cross Sectional Studies

Abnormalities qualitatively similar to those observed during a first episode of psychosis are also evident in the first-degree relatives and co-twins of patients with schizophrenia [30–36]. Twin studies suggest that these structural abnormalities [32, 37], as well as others in dorsolateral prefrontal, and superior temporal cortex [38], the hippocampus, and white matter are at least partially genetically determined.

It is not clear as yet at what stage of the disorder these brain abnormalities occur. Neurodevelopmental models of schizophrenia propose that brain abnormalities are present before the onset of psychosis, but there is also evidence that at least some of MRI abnormalities progress over the course of the disorder [39]. MRI studies of non-psychotic subjects who are at high risk of psychosis indicate that regional volumetric abnormalities comparable to those seen in schizophrenia are evident in those who are vulnerable to psychosis.

Using a prospective design, the Edinburgh High Risk study identified reductions in the grey matter volume bilaterally in the anterior cingulate and in the left parahippocampal gyrus in the relatives of patients with schizophrenia [40]. From

the same group, Lawrie et al. found that the relatives of patients with schizophrenia had reduced left medial temporal volume, decreased global white and grey matter volumes were found in the non-psychotic co-twins of patients with schizophrenia [33]. In the same group of subjects with a high genetic risk of developing schizophrenia, Job et al. reported no significant differences between high-risk subjects with or without later transition [41].

Relatively little is known about the nature of the abnormalities in the 'at-risk mental state'. Using a region of interest approach [42], reported that hippocampal volume in clinical high risk (At Risk Mental State, ARMS) individuals was smaller than that in controls but not than in patients with first episode psychosis. However, the prodromal group, those who later developed psychosis (HR-T) had a larger left hippocampal volume than those who did not (HR-NT). More recently, using a voxel-based approach in subjects from the same centre in Melbourne [43], found that subjects with "prodromal" symptoms who later became psychotic had smaller inferior frontal and cingulate gyrus volumes than those who did not. In another longitudinal study, using a region of interest approach [44], reported that patients at high risk of psychosis had normal baseline hippocampal and amygdala grey matter volumes whether or not they subsequently developed psychosis.

In a cross-sectional study from Basel, MRI data from an high risk (ARMS) sample ($n = 35$) (independent of subsequent clinical outcome) were compared with healthy controls and first-episode patients. Compared with healthy controls, both first-episode patients and high-risk subjects showed significantly less gray matter volume in the posterior part of the left superior temporal gyrus and the adjacent part of the left insula, and in a second region involving the posterior cingulate gyrus and precuneus [45, 46] (Fig. 20.1). However, the high risk group was heterogenous including both patients who later developed psychosis and those who did not. Within the high risk group, subjects who developed psychosis (HR-T; $n = 12$) had less grey matter than subjects who did not (HR-NT; $n = 23$) in the right insula, inferior frontal and superior frontal gyrus [45]. These volumetric differences were associated with the subsequent development of psychosis and could be related to a process which underlies a progression from a high risk state towards a suprathreshold psychotic illness.

The subgroup of the HR-T were found to have regional gray matter reductions relative to healthy controls in the posterior cingulate gyrus, precuneus, and paracentral lobule bilaterally which extended into the left superior parietal lobule [47], but more gray matter volume in some areas of the left parietal/posterior temporal region. This was consistent with previous reports of relatively increased hippocampal volume [42] in subjects with an high risk who later develop psychosis. Such differences might be related to an active pathological process that underlies the transition to psychosis. These results suggested that the at-risk mental state is associated with reductions in grey matter volume in areas that are also reduced in schizophrenia, suggesting that these abnormalities do not only occur with transition to psychosis, but are a correlate of an increased vulnerability to psychosis.

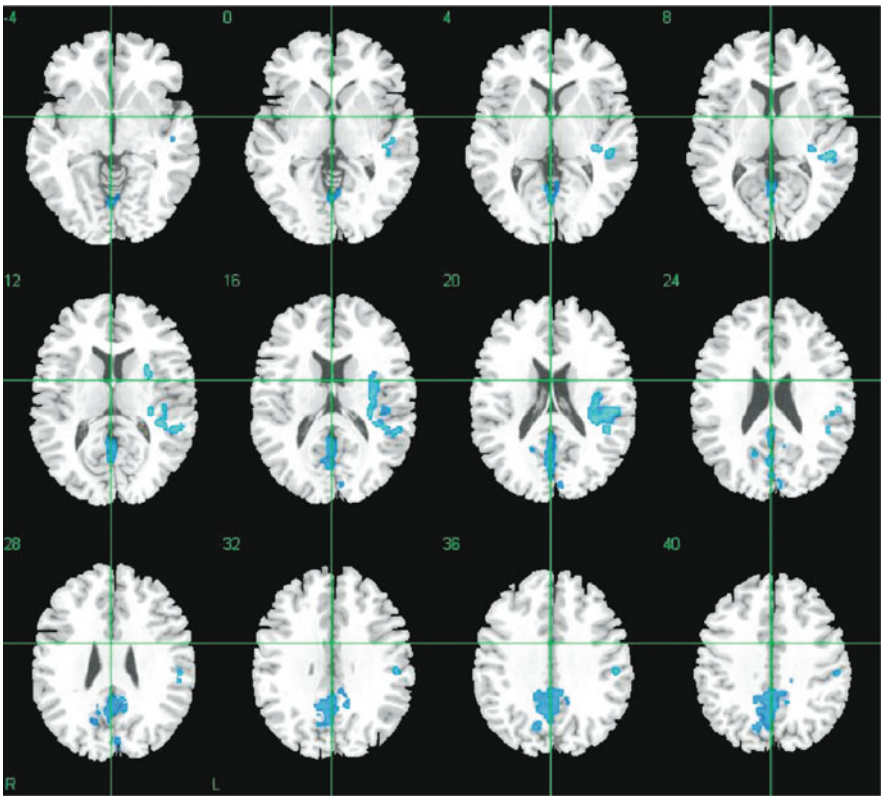

Fig. 20.1 *Structural neuroimaging in prodromal psychosis, neuroanatomical correlates of vulnerability to psychosis.* Gray matter probability maps for comparison of subjects with an At-Risk Mental State (ARMS), first-episode patients and healthy controls [45]

Grey Matter Changes During the Transition to Psychosis: Longitudinal Studies

Relatively little is known about the nature of the brain abnormalities in this high-risk group close to the actual process of transition to psychosis [48]. The transition from prodromal phase into frank psychosis [43, 49] and the first 2 years of the first-episode [50] has been associated with frontal and temporal decreases in gray matter. Using a similar voxel-based approach in subjects with an high risk, [43] HR-T (subjects with "prodromal" symptoms who developed psychosis) showed a longitudinal reduction in gray matter volume in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri. In this first longitudinal MRI study in the ARMS, the HR-T showed a progressive reduction in gray matter volume in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri. In another longitudinal study with largely the same subjects [51], greater brain contraction was found in the right prefrontal region in HR-T compared with

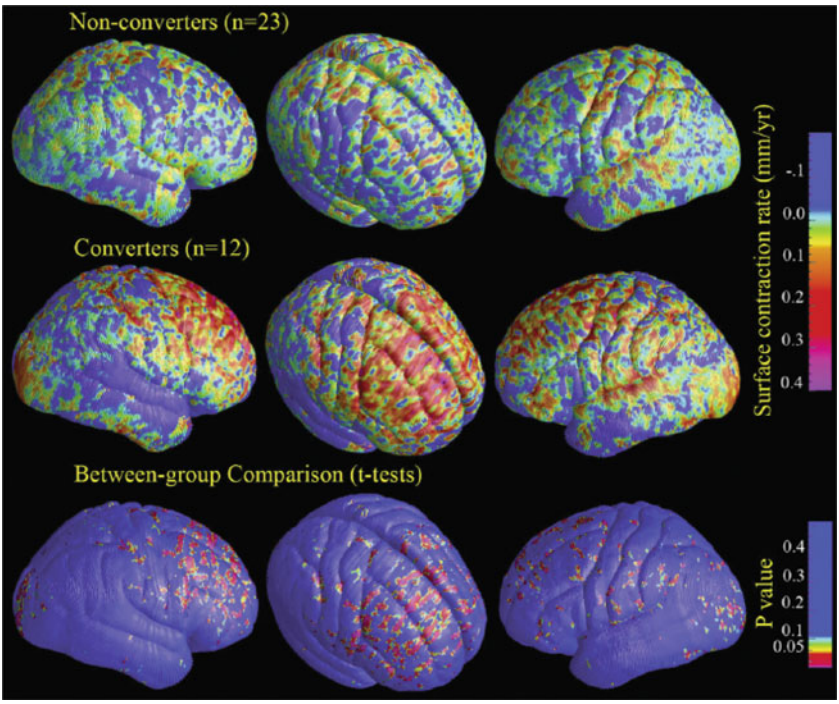

Fig. 20.2 *Structural neuroimaging in prodromal psychosis, surface contraction underlying transition to psychosis*. Average brain surface contraction rate (mm/year) both for high risk individuals who converted to psychosis and individuals who did not convert and the maps of statistical significance (*p* values, uncorrected for multiplevoxel comparisons) in between-group comparison. In contrast to the average rate of surface contraction in nonconverters, the magnitude of which was less than 0.2 mm/year (*upper row*), the converters showed greater brain surface contraction in bilateral dorsolateral prefrontal regions, with a maximum magnitude of 0.4 mm/year (*middle row*). In the between-group comparison, prefrontal regions showed the most prominent difference [51]

HR-NT (Fig. 20.2). Another voxel-based morphometry study in patients at genetic risk of psychosis reported that the onset of psychosis in these individuals was associated with reduced gray matter in the temporal lobes, the right frontal lobe and right parietal lobe [49]. These findings are consistent with prospective studies in patients with established schizophrenia, which indicate that longitudinal reductions in regional gray matter volume also occur in chronic patients [52–57].

In another longitudinal MRI study [58], high risk subjects were scanned when they first presented with "prodromal" symptoms and were then followed clinically the authors tested the hypothesis that transition to psychosis would be associated with longitudinal reductions in gray matter volume in the frontal, cingulate and temporal cortex. In this longitudinal voxel-based morphometry study regional gray matter volumes were analysed in 10 subjects with an ARMS before and after transition to psychosis (HR-T) and in 10 comparable ARMS subjects without transition to psychosis (HR-NT). The main findings of this study were a decrease of cortical

volumes in HR-T in the orbitofrontal cortex that included the right orbital and left rectal gyrus as well as in the right inferior temporal, superior frontal, and superior parietal lobule, the left precuneus, and the right hemisphere of the cerebellum. These findings suggest that at least some of the cortical gray matter abnormalities known in schizophrenia patients occur during the acute process of transition to psychosis.

To summarize the contrasting MRI findings described above here we have recently conducted a voxel based meta-analysis including nineteen studies of

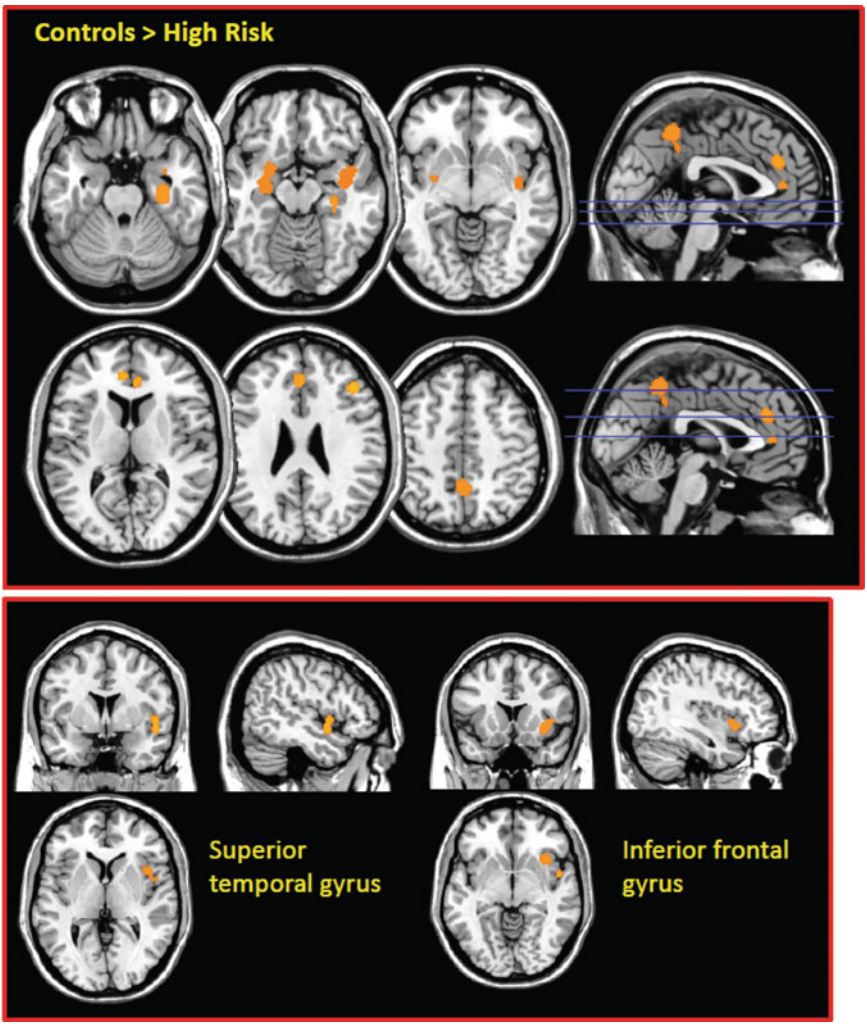

Fig. 20.3 *Structural neuroimaging in prodromal psychosis, voxel-based meta analysis of VBM studies in high risk subjects.* (*Above*): gray matter reductions in subjects at enhanced risk for psychosis as compared to healthy controls. (*Below*) Gray matter abnormalities underlying transition to psychosis (HR-NT > HR-T) [59]

subjects at enhanced risk to psychosis [59]. The overall sample consisted of 746 controls and 920 high risk subjects. We concluded that GM volume reductions in temporo-parietal, bilateral prefrontal and limbic cortex are neuroanatomical correlates of an enhanced vulnerability to psychosis (Fig. 20.3) [59], while transition to psychosis was associated with reductions in superior temporal and inferior frontal areas.

Functional Neuroimaging

fMRI in Established Psychosis

Functional magnetic resonance imaging measuring regional cerebral blood flow has demonstrated that neural activity during a variety of cognitive tasks is abnormal in several brain areas in schizophrenia. These brain areas include the prefrontal, cingulate and temporal cortex, the hippocampus, the striatum, the thalamus and the cerebellum [60]. These abnormalities are small in magnitude and are not evident in all patients within a given sample, making it difficult to use them as diagnostic aid in an individual patient. A further complicating factor is that positive symptoms, disorganized speech and negative symptoms are present to varying degrees in different patients with schizophrenia and are associated with distinct patterns of regional cortical activity [60]. At one stage it was hoped that "hypofrontality", a reduction in task-related activation in the prefrontal cortex, might be pathognomonic for schizophrenia. However, subsequent research revealed that this was an inconsistent finding, varying with the cognitive task being studied, how well patients performed the task and with the symptom profile at the time of scanning.

Neurofunctional Correlates of an Enhanced Risk to Psychosis

A number of fMRI studies of high risk population are available in the current literature. Overall these studies indicate that functional neuroimaging abnormalities in schizophrenia are evident before the onset of the disorder. These alterations are qualitatively similar to the changes seen in established schizophrenia but less marked [61]. For example, our group has recently addressed the neurofunctional correlates of working memory in subjects at enhanced clinical risk for psychosis by employing a traditional n-back task (Fig. 20.4) [62]. Subjects at high risk for psychosis showed reduced prefrontal and parietal activation relative to controls during the menmonic paradigm (Fig. 20.4). The fMRI data revealed a relatively reduced blood oxygen level–dependent response in the dorsolateral and medial prefrontal cortex of subject at high risk for psychosis [62]. Because the differential activation we observed was evident in the context of comparable response accuracy, and the analysis was restricted to images associated with correct responses, it was unlikely to be related to group differences in task performance and may instead reflect a true difference at the neurophysiological level. Abnormalities in

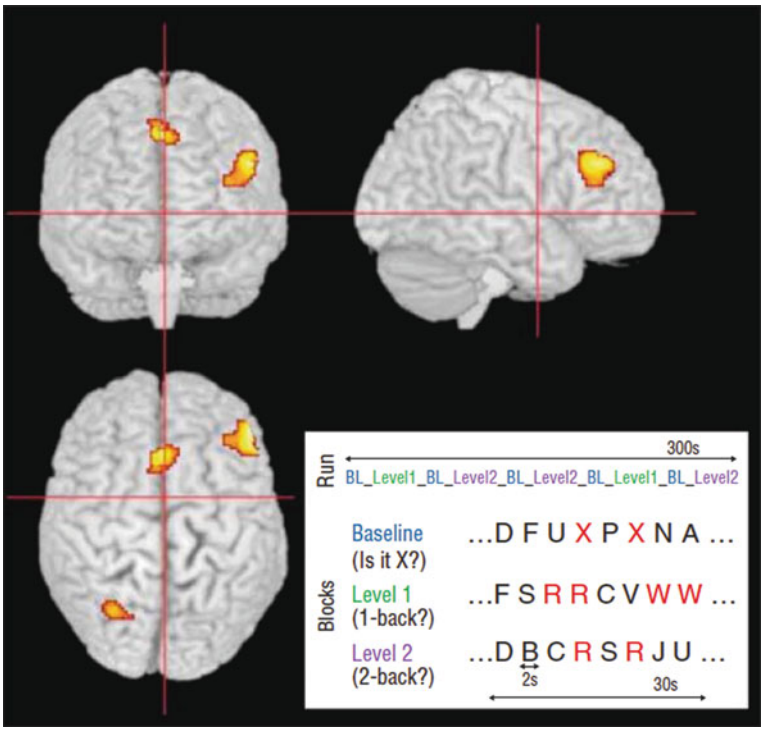

Fig. 20.4 *Functional neuroimaging in prodromal psychosis, neurofunctional correlates of enhanced risk to pychosis.* Reduced prefrontal and parietal activation in subjects with an at-risk mental state relative to controls during the N-back task. The left side of the brain is shown on the *left side* of the Figure [62]

prefrontal activation during cognitive tasks have previously been described in the prodromal phases of psychosis (for a meta-analysis see [63]) and have consistently been reported in the early phases of schizophrenia. Furthermore, alterations in prefrontal regions appear to be more marked in the subgroup of subjects who later develop psychosis, suggesting that prefrontal abnormalities may be particularly related to the later onset of psychosis (see below). Another study used fMRI to investigate cortical function in subjects at enhanced clinical risk for psychosis and in matched controls while they were performing a false memory task [64]. During an encoding phase, subjects read lists of words aloud. Following a delay, they were presented with target words, semantically related lure words and novel words and required to indicate if each had been presented before. Behaviorally, the subjects at clinical risk for psychosis made more false alarm responses for novel words than controls and had a lower discrimination accuracy for target words. During encoding, high risk subjects showed less activation than healthy controls in the left middle frontal gyrus, the bilateral medial frontal gyri, and the left parahippocampal gyrus (Fig. 20.5) [64]. As indicated by the plot in Fig. 20.5, these neurofunctional

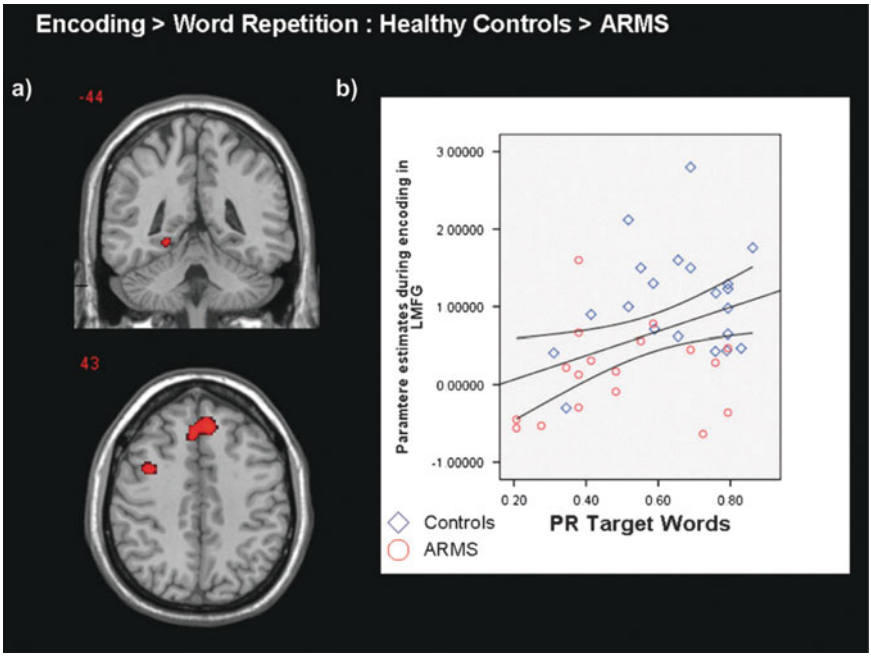

Fig. 20.5 *Functional neuroimging in prodromal psychosis, neurofunctional correlates of enhanced risk to psychosis*. SPM maps displaying coronal and axial sections of regions activated in healthy controls greater than those in the ARMS group during word encoding and (**b**) Scatter plots showing association between LMFG activation during encoding and recognition accuracy (Pr) for target words in controls subjects (*blue*) and ARMS subjects (*red*). The left side of the brain is shown on the *left* of the image. ARMS, at-risk mental state; LMFG, left middle frontal gyrus [64]

differences were associated with diminished recognition performance reflecting the greatly increased risk of psychosis associated with the prodromal phases of psychosis.

Overall, the fMRI studies addressing the neurofuncitonal correlates of vulnerability to psychosis raise the possibility that neuroimaging could be used to detect pathophysiological changes associated with the disorder before the onset of frank illness. This is of particular clinical interest because only a proportion of people with prodromal symptoms go on to develop schizophrenia (see below here), and neuroimaging might facilitate the targeting of novel preventive treatments to this subgroup.

Neurofunctional Mapping of Psychosis Transition

Overall functional imaging studies indicate that the neurofunctional abnormalities during cognitive tasks are qualitatively similar but less severe in high risk subjects compared to first-episode patients [63]. However, the onset and the time

course such alterations are mostly unknown. Indeed, it is critical to the understanding of the pathogenesis of these brain changes to clarify their onset and the dynamic neurobiological processes underlying the transition from a high-risk state to full-blown psychosis. To address this point some fMRI studies have compared high-risk subjects with (HR-T) and without (HR-NT) later transition to psychosis. We have summarized fMRI longitudinal studies addressing psychosis transition in a recent meta-analysis which confirmed abnormalities in the prefrontal cortex [65]. Specifically, decreased activation in anterior cingulate cortex and increased activation in left parietal lobe were described in genetic HR-T relative to controls in a prospective fMRI cross-sectional study [66]. Compared to HR-NT, HR-T subjects showed smaller increases in activation with increasing task difficulty in the right lingual gyrus [66]. Another fMRI "Theory of Mind" imaging study, which requires the ability to understand a joke, investigated prefrontal cortex activation associated with memory and executive functioning tasks. Compared to HR-NT, HR-T showed less neural activation in the middle frontal gyrus [67]. The localization of fMRI abnormalities between HR-T and HR-NT corresponds to the region-specific neuroanatomical abnormalities revealed by structural neuroimaging studies. These neurofunctional abnormalities could delineate a pathological process in the affected brain regions as well as a compensatory process to volumetric region-specific reductions in gray or white matter.

Neurophysiological Correlates of Antipsychotic Treatments in Early Psychosis

fMRI can be used to examine the influence of antipsychotics treatment on regional brain activity and on activation during cognitive tasks and thus indicate their neurocognitive effects in the early phases of psychosis. Subjects at risk for psychosis are antipsychotic-naïve or are administered short term treatments with low-dosage antipsychotics. Although it is widely held that acute treatment does not affect brain function, fMRI studies have documented modulation of the neural substrates of cognitive deficits by short-term atypical antipsychotic treatment [68]. In fact, we observed in a fMRI study that a low-dosage antipsychotic treatment can modulate brain activity during different neurocognitive tasks [69]. These findings are consistent with evidence that substantial blockade of the dopamine system by antipsychotic medications happens within the first hours of treatment [70]. For example, the effects of risperidone on cerebral metabolism were detectable within 2 h of administration of a single dose, both in healthy subjects [71] and in patients with first episode psychosis [72]. Structural MRI studies have confirmed the fMRI findings indicating that short-term treatment with atypical antipsychotics may affect regional grey matter volume [73]. At a behavioural level, recent research has shown that antipsychotic action can be discerned shortly after the first dose. A meta-analysis which included data from 7450 patients in 42 double-blind active/drug

or placebo/controlled trials, showed a significant change in psychotic symptoms within the first week of treatment. They also showed that the greatest improvement in psychotic symptoms was observed in the first week than in any week thereafter [74].

Brain Connectivity in the Pre-psychotic Phases

An alternative approach to identifying functional abnormalities in particular brain regions has been to look for abnormalities in the integration of function between brain regions, such as the prefrontal and temporal cortex. In a recent study we have investigated frontotemporal connectivity in subjects at enhanced clinical risk for psychosis. Superior temporal lobe (STG) dysfunction is a robust finding in functional neuroimaging studies of schizophrenia and is thought to be related to a disruption of fronto-temporal functional connectivity but the stage of the disorder at which these functional alterations occur is unclear. We addressed this issue by using Dynamic Causal Modelling and fMRI to study subjects in the prodromal and first episode phases of schizophrenia during a working memory task (n-back) [75]. We found that the STG was differentially engaged across the three groups. There was deactivation of this region during the task in controls, whereas subjects with a first episode of psychosis showed activation and the response in subjects at high risk was intermediately relative to the two other groups [75] (Fig. 20.6). There were corresponding differences in the effective connectivity between the STG and the middle frontal gyrus across the three groups, with a negative coupling between these areas in controls, a positive coupling in the first episode group, and an intermediate value in the high risk group (Fig. 20.6). We concluded that a failure to deactivate the superior temporal lobe during tasks that engage prefrontal cortex is evident at the onset of schizophrenia and may reflect a disruption of fronto-temporal connectivity [75]. Qualitatively similar alterations are evident in people with prodromal symptoms of the disorder. However, although there appear to be abnormalities in functional connectivity in schizophrenia, a single pattern of disconnectivity that characterises its pathophysiology has yet to be identified.

fMRI and Longitudinal Outcomes in Subjects at High Risk for Psychosis

Although people with prodromal signs of psychosis show neurofunctional alterations underlying executive processes when they first present to clinical services, the longitudinal course of these abnormalities, and how they relate to subsequent clinical and functional outcome is relatively unclear. To address this point we employed fMRI during verbal fluency in a cohort of subjects at clinical risk for psychosis and

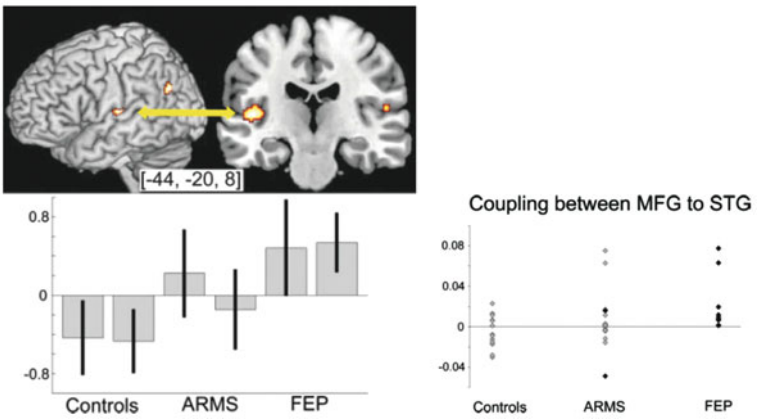

Fig. 20.6 *Functional neuroimaging in prodromal psychosis, brain connectivity in the pre-psychotic phases*. *On the right*: Comparison of first episode psychosis (FEP) and controls when performing a working memory (n-back) task. The *lower graph* depicts bold signal from the highlighted area in the superior temporal gyrus (STG). The two columns in each group represent the 1- and 2-back conditions. Notice that in both conditions the FEP group showed activation of the STG, in contrast to the deactivation evident in controls. The high risk group (ARMS) showed an intermediate pattern of activation in this region. Scatter plot of coupling parameters (rate of change in activation per unit of time) for each subject in the three groups. Functional coupling between prefrontal and superior temporal cortex was positive in the FEP group, negative in controls, and around neutral in the high risk (ARMS) group [75]

in healthy controls. Images were acquired at clinical presentation and again after 1 year. Levels of psychopathology and global functioning were assessed at the same time points using a number of psychometric instruments. At baseline subjects at risk for psychosis showed greater activation in the left inferior frontal gyrus than controls [76]. After 1 year the neural response in the left inferior frontal gyrus normalized and was similar to that in controls. Between presentation and follow up, the severity of perceptual disorder and thought disorder, and of general psychopathology decreased, and the level of global functioning improved. However, the most striking results was that the psychopathological and neurofunctional changes were related [76]. In fact, the normalization of the abnormal prefrontal response during executive functioning was positively correlated with the improvement in severity of hallucination-like experiences.

These studies provide evidence that in prodromal psychosis brain changes concur with symptomatic improvement. In addition they emphasize the importance of early interventions in the treatment of schizophrenia, suggesting that the observed neurophysiological abnormalities are something that could perhaps be modulated by active interventions before the psychosis onset. Although longitudinal randomized controlled fMRI trials in the prodromal population are extremely complex, they will clarify the respective contribution of disease progression and clinical interventions in the phases preceding the illness onset.

Neurochemical Imaging

Dopamine

Dopamine and Psychosis

The most enduring neurochemical theory of schizophrenia centres upon dysregulation of dopaminergic neurotransmission. All currently licensed antipsychotic drugs block dopamine receptors, indicating that manipulation of dopaminergic function is fundamental to therapeutic response in psychosis. Striatal hyperdopaminergia has been postulated to be fundamental to the generation of the psychotic symptoms that characterize schizophrenia. In recent years, neurochemical imaging techniques such as positron emission tomography (PET) have enabled the striatal dopaminergic system to be characterized in vivo in patients with schizophrenia. Studies conducted with radiotracers for which binding is sensitive to endogenous dopamine levels have found that the baseline levels of synaptic dopamine and the dopamine release in response to amphetamine sulfate are increased in patients with schizophrenia [1]. Moreover, the magnitude is directly related to the severity of amphetamine-induced psychotic symptoms and the response to subsequent antipsychotic treatment. Further studies have investigated presynaptic striatal dopaminergic function using the PET radiotracers carbon 11–L-dopa and 6-[18F]-dopa. The accumulation of these radiotracers in the striatum reflects the functional integrity of the presynaptic dopamine system. To date, there have been nine PET studies of dopaminergic availability in patients with schizophrenia; seven have found elevated levels of dopamine synthesis capacity in the striatum of schizophrenic patients compared to control subjects (for a review see [77]). In all studies where patients were acutely psychotic at the time of investigation elevated presynaptic striatal dopamine availability was detected. At present, increased striatal presynaptic dopamine availability is the most widely replicated brain dopaminergic abnormality in schizophrenia, and the effect size is moderate to large (0.63–1.25) [77].

Dopamine Dysregulation Prior to the Onset of Psychosis

Whilst the data reviewed in the section above suggests a link between dopamine dysregulation and psychosis, all the studies were conducted in people who had already developed psychosis. It is therefore possible that rather than causing psychosis, the dopamine dysregulation is secondary- occurring as a consequence of some other factor. To determine whether this is the case or not it is necessary to study people in the phase just preceding the development of psychosis.

Dopamine function has recently studied in subjects with prodromal signs of schizophrenia, all of whom had attenuated psychotic symptoms. Presynaptic striatal dopamine synthesis capacity (Konstant inibhition, Ki see Fig. 20.7) was elevated in people who were at high risk of schizophrenia but did not have the disorder, to a degree approaching that in patients with established schizophrenia (Fig. 20.7). Furthermore, striatal dopamine levels were directly correlated with the

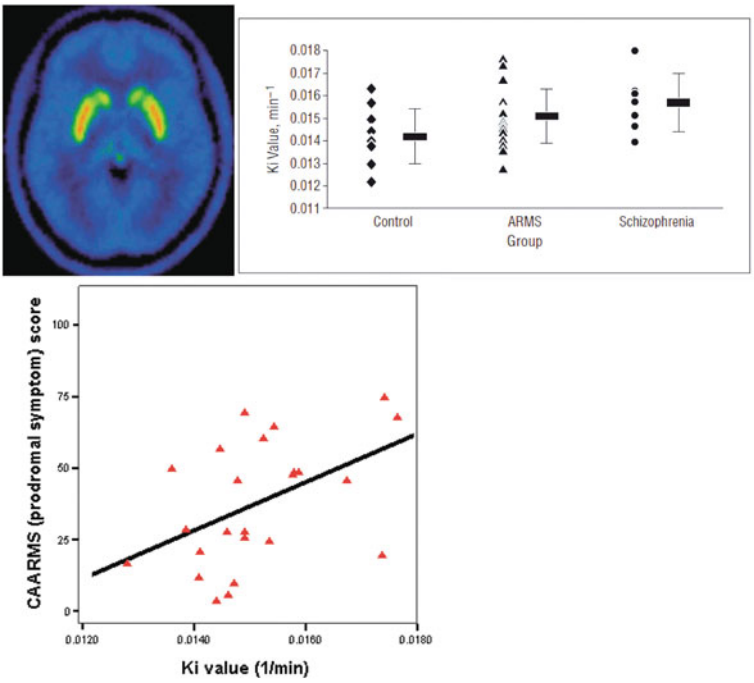

Fig. 20.7 *Neurochemical imaging in prodromal psychosis, dopamine*. *Left of the figure*: striatal 6-fluoro–L-dopa F 18-dopa summation image showing highest signal intensity (*yellow* and *red* areas) in the striatum (indicating the synthesis and accumulation of dopamine in the striatum during positron emission tomography). *Right of the figure*: individual Ki values (influx rate constants), with the mean (SD) by group for the whole striatum. There is a significant difference in presynaptic dopamine synthesis capacity (Ki) values at the group level for the whole striatum and for the associative striatum (data not shown) between controls, high risk subjects (ARMS) and established schizophrenia [1]. *Below*: Plot showing the relationship between striatal dopaminergic function and prodromal symptoms in subjects at high risk of psychosis

severity of prodromal symptoms in high risk subjects (Fig. 20.7). The findings remained robust after adjustment for putative factors that might influence the PET measurements.

These data suggest that increased subcortical dopamine activity is already present before the full expression of schizophrenia, consistent with the putative role of dopamine in the pathophysiology of psychosis. However, as not all high risk subjects go on to develop psychosis, and dopamine dysfunction may also occur in the relatives of patients with schizophrenia, elevated dopamine activity may also be a correlate of an increased vulnerability to psychosis. Follow-up of high risk subjects is therefore needed to determine whether elevated striatal dopamine activity leads to psychosis or is a correlate of vulnerability.

The Revised Dopamine Hypothesis of Schizophrenia

The above findings support a revised version of the original dopamine hypothesis of psychosis (illustrated in Fig. 20.8). The new version proposes that dopamine dysregulation is the final common pathway to psychosis in schizophrenia. The first component of this hypothesis is that multiple, interacting "hits" interact, and lead to dopamine dysregulation. This is analogous to diabetes mellitus, for example, where hyperglycaemia is the final pathophysiology that results in the clinical symptoms, but different paths lead to hyperglycaemia (insulin insensitivity in the case of type II diabetes, or insulin insufficiency in the case of type I diabetes) with an array of risk factors underlie this. The second component of the revised hypothesis is a shift in the localisation of dopaminergic dysregulation from the post-synaptic receptor level to presynaptic dopaminergic regulation. A third component is making a link between dopamine dysregulation and psychosis/ "psychosis proneness" rather than schizophrenia per se, with the exact diagnosis reflecting the nature and interacting effects of the upstream hits, as is the case with diabetes mellitus.

The final component is to propose a mechanism linking the dopaminergic dysfunction and symptoms through altered appraisal of stimuli. What was not apparent from the neurochemical imaging data was how the dopaminergic abnormality led to the psychotic symptoms- this was a major shortcoming of the first versions of the dopamine hypothesis. The new hypothesis proposes that the abnormal firing of dopamine neurons leads to an aberrant assignment of salience to innocuous stimuli. It is argued that psychotic symptoms, especially delusions and hallucinations, emerge over time as the individual's own explanation of the experience of aberrant salience. Psychosis is, therefore, aberrant salience driven by dopamine and filtered through the individual's existing cognitive and socio-cultural schemas – thus allowing the same chemical (dopamine) to have different clinical manifestations in different cultures and individuals.

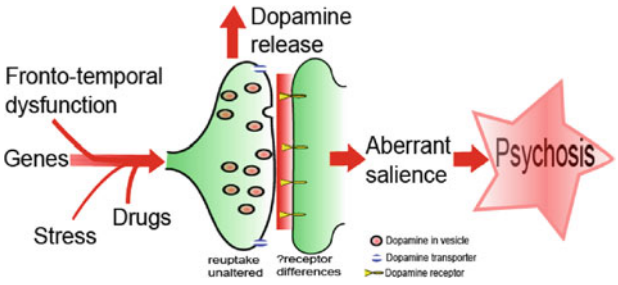

Fig. 20.8 *Neurochemical imaging in prodromal psychosis, the new version of the dopamine hypothesis.* Figure *belows* illustrates the new dopamine hypothesis: version III- the final common pathway, based on the recent findings on dopamine dysregulation in prodromal psychosis [93]

Glutamate

Glutamate in Established Psychosis

Recent years have seen a resurgence of interest of the role of abnormal glutamatergic transmission in schizophrenia – as a factor in the pathoaetiology of the condition, and as a potential target for novel treatments. The glutamate hypothesis of schizophrenia arose in the 1980s from converging findings – firstly, that patients with schizophrenia had reduced CSF glutamate [78], and secondly that drugs such as phencyclidine (PCP) and ketamine, which induce effects markedly similar to both positive and negative symptoms of schizophrenia, act as high affinity antagonists for the N-methyl-D-aspartate receptor (NMDAR) [79, 80]. Although several groups failed to replicate the original finding of reduced CSF glutamate, the unique quality of NMDAR antagonists to induce a much closer approximation to the full picture of psychosis in schizophrenia than drugs affecting the dopamine or serotonin systems [81], led to great interest in the possible role that abnormalities of glutamatergic transmission, particularly NMDAR-mediated dysfunction, might play in the idiopathic condition. This evidence has been further supported by the recent finding that most of the candidate genes for schizophrenia are associated with glutamatergic neurotransmission at the NMDAR containing synapse [82]. In addition to the growing genetic support for a primary glutamatergic basis for the illness [82], two groups have reported reduced NMDAR mRNA in left hippocampus in post-mortem brain [83, 84], while an in vivo single photon emission tomography (SPET) study by Pilowsky and colleagues showed a relative reduction in left hippocampal NMDAR binding in patients with schizophrenia who were not taking any antipsychotic medication [85]. This finding was partially normalised in patients on typical antipsychotics and clozapine [85].

Other groups have examined brain glutamate levels using 1H-MRS. Theberge and colleagues reported elevated glutamine levels in anterior cingulate and thalamus in patients with first episode schizophrenia [86], but in patients with chronic schizophrenia, they reported reduced glutamine levels in anterior cingulate [87]. From these data, it suggests that glutamatergic change and, by extension, excitotoxicity, appears to be a feature of the early phase of psychosis. If glutamatergic changes do drive transition to psychosis, it might be expected that these changes may also be present in individuals prodromal for the illness.

Glutamate Dysfunction in Prodromal Psychosis

Several groups have investigated brain glutamate abnormalities in individuals at high risk of psychosis. Adolescents at high genetic risk of schizophrenia (having relatives with schizophrenia) were reported to have increased glutamine/glutamate in medial frontal cortex by Tibbo and colleagues [88], and work in our laboratory has found increased glutamine in anterior cingulate, but reduced glutamate in left thalamus in subjects at risk of psychosis [89]. Two groups (including our own) have

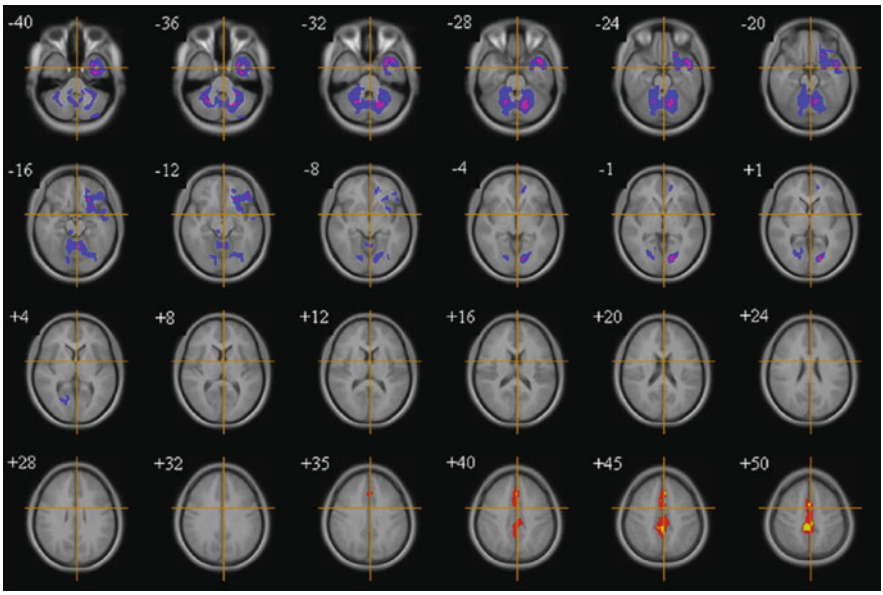

Fig. 20.9 *Neurochemical imaging, glutamate.* Significant correlations between thalamic glutamate and gray matter volume in subjects at high clinical risk for psychosis. Thalamic glutamate levels correlated directly with lower gray matter volume in left prefrontal cortex, insula, cingulate, superior temporal gyrus, and temporal pole, as well as bilaterally in the cerebellum and lingual gyrus (*blue clusters*). They showed an inverse correlation with gray matter volume in dorsal anterior cingulate extending to the posterior cingulate gyrus (*red clusters*) [89]

investigated the relationship between brain glutamate levels and gray matter volume. We found that in ARMS subjects, lower thalamic glutamate levels were associated with reduced gray matter volume in medial temporal cortex and insula [89] (Fig. 20.9), and in a longitudinal study of patients with first episode schizophrenia, Theberge found that reductions in thalamic glutamine levels correlated with reductions in parietal and temporal grey matter [90]. Reductions in thalamic glutamate could lead to reduced thalamic GABAergic interneuron activity and, by extension, disinhibition of thalamocortical glutamate projection neurons. Thus, the reductions in temporal cortex grey matter volume could arise secondary to excess glutamate release. Alternatively, reductions in temporal cortex volume could be primary and lead to secondary reductions in thalamic glutamate levels through reductions in glutamatergic efferents from temporal cortex. Future studies examining the longitudinal change in grey matter and glutamate levels in individuals with prodromal psychosis are required to clarify these points.

Integration of Neuroimaging Findings Across Modalities

Recent advancements in imaging techniques allow researchers to combine different imaging modalities. Multimodal neuroimaging during the prodromal phases of

psychosis is nowadays possible and has the potential to delineate the causal relationship between key pathophysiological processes in the evolution of psychosis. We have described above here a MRS-VBM study addressing the relationship between gray matter and thalamic glutamate in prodromal psychosis. Other examples are given by fMRI-PET [62, 91] and fMRI-MRS [92] and fMRI-VBM [93] studies of subjects at enhanced risk for psychosis. The former studies aimed at investigating the relationship between dopamine function and cortical activation in people experiencing prodromal symptoms of psychosis. Abnormal cortical function during cognitive tasks and elevated striatal dopaminergic transmission [77] are two of the most robust pathophysiological features of schizophrenia. Both alterations in prefrontal activation [63] during working memory/executive processes and elevated subcortical dopamine [1] are also evident in individuals with an enhanced risk for psychosis. However, the exact relationship between them in the development of the disorder remains to be established. To address this issue we studied medication-naive subjects with prodromal signs for psychosis, measuring

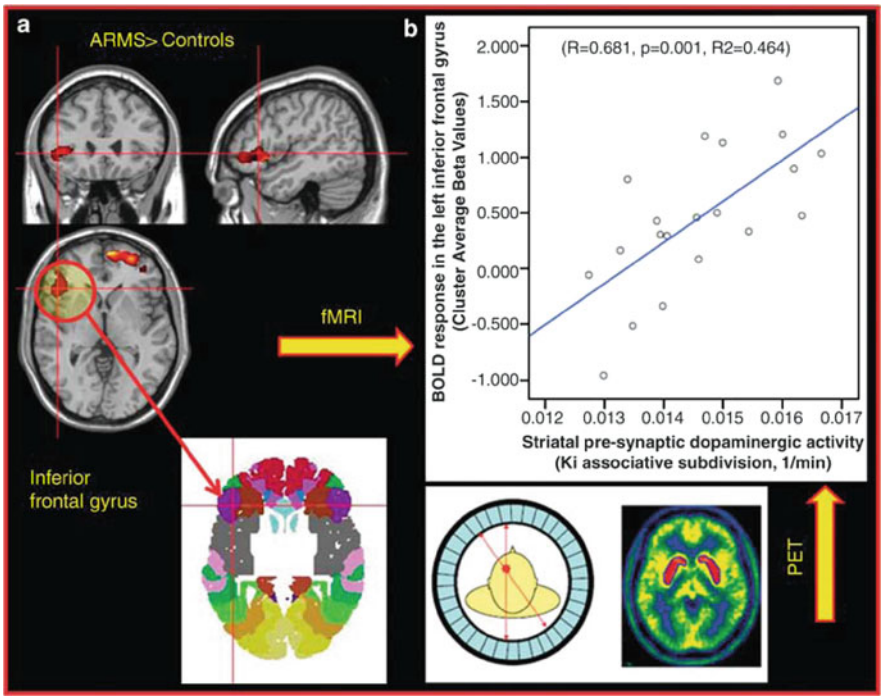

Fig. 20.10 *Integration of neuroimaging across modalities, PET-fMRI*. **a** fMRI results: greater activation in the left inferior frontal gyrus (cross hairs) and right middle frontal gyrus in the high risk (ARMS) group than controls during the verbal fluency task. **b** PET-fMRI results: correlation between left inferior frontal activation during verbal fluency and dopamine function in the associative subdivision of the striatum within the high risk (ARMS) group [91]

prefrontal activation during a verbal fluency task with functional magnetic resonance imaging (fMRI) and measuring dopamine synthesis capacity in the striatum with fluorine18–labeled dopa PET [91]. In line with the fMRI findings described in this chapter, subjects at enhanced risk for psychosis showed increased neural activation in the prefrontal cortex as compared to healthy controls. Similarly, striatal dopamine function was greater in the high risk group than in controls. We then found that altered prefrontal activation in subjects at enhanced risk for psychosis was related to elevated striatal dopamine function (Fig. 20.10) [91]. In a following PET-fMRI study during working memory we uncovered a positive correlation between frontal activation and fluorodopa uptake in the associative striatum in controls but a negative correlation in the high risk group (Fig. 20.11) [62]. These studies taken altogether show that in individuals at very high risk of psychosis, altered prefrontal activation during executive/working memory function is directly related to striatal hyperdopaminergia. This provided in vivo evidence of a link between dopamine dysfunction and the perturbed prefrontal function, which may underlie the deficits in cognitive processing evident in people with prodromal symptoms of psychosis and predate the first episode of frank psychosis.

In another multimodal study using a combination of functional MRI and proton magnetic resonance spectroscopy, we showed that in people with prodromal signs of psychosis, medial temporal activation during a memory task is decoupled from local glutamate levels [92] (Fig. 20.12). Prior to this study, both medial temporal cortical dysfunction and perturbed glutamatergic neurotransmission were regarded as fundamental pathophysiological features of psychosis but their relationship in

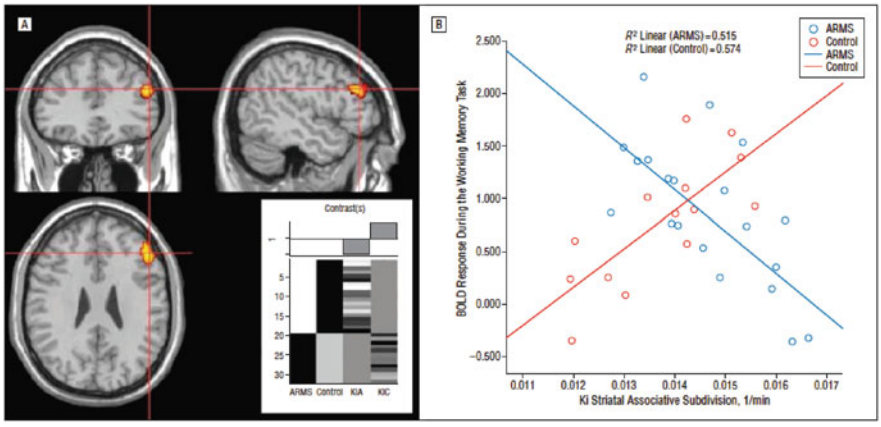

Fig. 20.11 *Integration of neuroimaging across modalities, PET-fMRI*. Group differences in the relationship between prefrontal activation during the N-back task (**a**) and striatal dopamine function. There was a positive correlation between right middle frontal activation and fluorine 18-labeled fluorodopa uptake in the associative striatum in controls (*red*) but a negative correlationin the high risk group (ARMS) (*blue*) (**b**). The left side of the brain is shown on the *left side* of the Figure. BOLD indicates blood oxygen level dependent; and KiA, Ki value for ARMS group; and KiC, Ki value for controls [62]

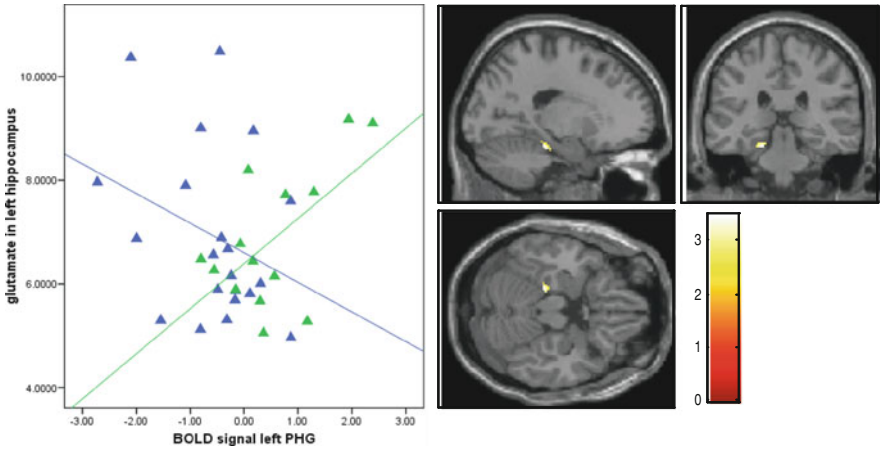

Fig. 20.12 *Integration of neuroimaging across modalities, MRS-fMRI.* Left parahippocampal (PHG) region where high risk (ARMS) subjects showed less activation than controls during encoding. In this region, activation in controls (*green*) was positively correlated with left medial temporal glutamate levels, but there was no correlation in the high risk (ARMS) group (*blue*) [92]

humans was not clear. Such finding suggests that treatment of people with prodromal signs using glutamatergic drugs may have the potential to impact on the subsequent development of psychosis.

Conclusions

Neuroimaging studies of the prodromal phases of psychosis have the potentials to identify core structural and functional markers of an impending risk to psychosis, to clarify the dynamic changes underlying transition from an high risk state to full psychotic episodes and to address significant correlations between brain structure or function and prodromal psychopathology. On the other hand, neurochemical investigations of the pre-psychotic phases can address the key role played by neurotransmitters such as dopamine and glutamate during the psychosis onset. The combination of neuroimaging across modalities may ultimately clarify the neurobiology of the prodromal phases by the integration of functional, structural and neurochemical findings.

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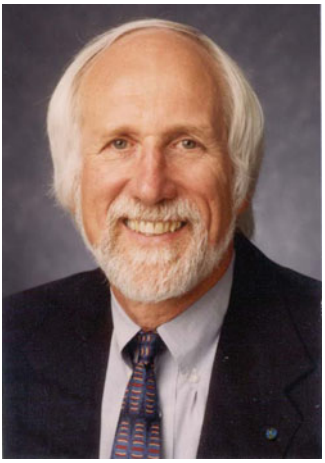
Afterword

William T. Carpenter



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, and etiological and therapeutic discovery. In this Afterword I will briefly comment

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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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