Schizophrenia Research 110 (2009) 1–23

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Schizophrenia, "just the facts" 4. Clinical features and conceptualization

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ARTICLE INFO

Article history:
Received 25 January 2009
Received in revised form 28 February 2009
Accepted 3 March 2009
Available online 27 March 2009

Keywords:
Schizophrenia
Clinical features
Diagnosis
Concept
Review
Staging
Dimensions
Boundaries
Evolution
Course
Symptoms
DSM
ICD

ABSTRACT

Although dementia praecox or schizophrenia has been considered a unique disease entity for the past century, its definitions and boundaries have continued to vary over this period. At any given time, the changing concept of schizophrenia has been influenced by available diagnostic tools and treatments, related conditions from which it most needs to be distinguished, extant knowledge and scientific paradigms. There is significant heterogeneity in the etiopathology, symptomatology, and course of schizophrenia. It is characterized by an admixture of positive, negative, cognitive, mood, and motor symptoms whose severity varies across patients and through the course of the illness. Positive symptoms usually first begin in adolescence or early adulthood, but are often preceded by varying degrees of negative and cognitive symptomatology. Schizophrenia tends to be a chronic and relapsing disorder with generally incomplete remissions, variable degrees of functional impairment and social disability, frequent comorbid substance abuse, and decreased longevity. Although schizophrenia may not represent a single disease with a unitary etiology or pathogenetic process, alternative approaches have thus far been unsuccessful in better defining this syndrome or its component entities. The symptomatologic, course, and etio-pathological heterogeneity can usefully be addressed by a dimensional approach to psychopathology, a clinical staging approach to illness course, and by elucidating endophenotypes and markers of illness progression, respectively. This will allow an approach to the deconstruction of schizophrenia into its multiple component parts and strategies to reconfigure these components in a more meaningful manner. Possible implications for DSM-V and ICD-11 definitions of schizophrenia are discussed.

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1. Introduction

Although schizophrenia has been extensively studied and described as a disease entity for the past century, its precise clinical nature remains undefined. Since its demarcation and labeling as dementia praecox by Kraepelin (1919) and schizophrenia by Eugen Bleuler (1911), both its definitions and scope have varied (Nasrallah and Smelzer, 2003). It has been suggested that changing definitions of schizophrenia impede research into its nature as investigators keep chasing a moving target. Conversely, it has been argued that only a better understanding of schizophrenia can lead to its more precise definition. We have previously summarized a series of replicable and durable "facts" in schizophrenia (Tandon et al., 2008a). In this article, we elaborate the core clinical features of schizophrenia (Table 1) and discuss its diagnostic criteria. Since definition of a disorder and description of its nature are two aspects of an iterative process, we begin with a discussion of its evolving definitions leading up to current diagnostic criteria.

2. Evolution of the concept of schizophrenia from Kraepelin to DSM-IV-TR (Fig. 1)

Our present conceptualization of dementia praecox and schizophrenia derives principally from the work of Kraepelin

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doi:10.1016/j.schres.2009.03.005

(1919), Bleuler (1911) and Schneider (1959); differences in their ideas about the basic nature of this illness have caused discrepancies in its definition over the past century (Hoenig, 1983). Although case descriptions resembling schizophrenia go back a few millennia, its consideration as a disease entity dates back to the mid-19th century. Griesinger (1861) described what would now be considered states of chronic schizophrenia as a secondary development in a primary mood disorder and postulated a unitary psychosis disease entity (*enheitpsychose*). Hecker (1871) and Kahlbaum (1874) described *hebephrenia* and *catatonia* respectively as distinctive states of mental deterioration (*dementia*). Falret (1854) had previously described *folie circulaire* (now bipolar disorder). Kraepelin (1899, 1919) noted the similarities between patients with catatonia, hebephrenia, and *paranoid dementia* based on adolescent or early adult onset, tendency towards deterioration, and an outcome of mental dullness or dementia. He distinguished this group (which he called dementia praecox) from folie circulaire (which he termed manic-depressive insanity) which was characterized by episodicity, absence of deterioration, and a more favorable outcome. Kraepelin believed that schizophrenia constituted a unique disease entity with a single etiology and a defined pathology. Since available methods then were insufficient to delineate etiology or pathology, he emphasized the "overall clinical picture" as defining this entity. Influenced by the experience of general paresis of insanity (neurosyphilis or tertiary syphilis) whose distinctive course and outcome were associated with the identification of the causative spirochete and the Wasserman test, Kraepelin felt that course and outcome best distinguished psychiatric disease entities; therefore, he identified schizophrenia on the basis of its onset (in adolescence or early adulthood), course (chronic and deteriorating), and outcome (permanent and pervasive impairment in mental functions). Although Kraepelin (1920) subsequently did acknowledge that dementia praecox and manic-depressive insanity might co-exist and that recovery could occur in schizophrenia, his initial views have been dominant (Berrios and Hauser, 1988) (Fig. 1).

Eugen Bleuler (1911) defined a set of basic or fundamental symptoms which he considered unique to schizophrenia and always present in those with this *group* of diseases. He considered the course and outcome to be variable. He believed that the essence of schizophrenia was not delusions and hallucinations (which he regarded as accessory symptoms) but the disintegration of different psychic functions, leading to its fundamental symptoms of loosening of association, blunt or incongruous affect, ambivalence, and autism (Bleuler's 4 As, now considered negative symptoms) which were present in all cases. He further believed that many mild cases existed and considerably broadened the scope of the disease entity of schizophrenia, adding a substantial subgroup of simple schizophrenia.

Jaspers (1946) believed that impairment of empathic communication was the fundamental defect in schizophrenia and considered "un-understandability" of the individual experience as its distinguishing feature. Operationalizing this concept, Kurt Schneider (1959) defined 11 first-rank symptoms which he considered pathognomonic (Mellor, 1970)—these symptoms would now be considered positive symptoms. Over time, however, the elements of un-understandability and Schneider's emphasis on form rather than content as defining psychosis have faded and these symptoms have not been found to be specific to schizophrenia.

There are clear differences in these three perspectives of the definition of schizophrenia. Kraepelin did not provide specific criteria for its diagnosis ("overall clinical picture") but emphasized longitudinal course and outcome. In contrast, both Bleuler and Schneider provided specific cross-sectional criteria, although their criteria were very different and focused on different aspects of the illness. Current definitions of schizophrenia (including ICD-10 [World Health Organization, 1992] and DSM-IV-TR [American Psychiatric Association, 2000]) incorporate Kraepelinian chronicity, Bleulerian negative symptoms, and Schneiderian positive symptoms, albeit using different combinations and variable interpretations of these elements with limited psychopathological rigor (Andreasen, 2007).

Table 1
Clinical 'facts' of schizophrenia [Disease expression and identification] (Adapted from Tandon et al., 2008a).

Schizophrenia is generally diagnosed on the basis of the presence of positive symptoms in conjunction with impaired social function in the absence of significant mood symptoms, other recognizable neurological illness, or substance use that can account for the psychotic symptoms.
The nosological boundaries between schizophrenia and other psychiatric disorders are indistinct.
There is significant heterogeneity in neurobiology, clinical manifestations, course, and treatment response across patients.
Schizophrenia is characterized by an admixture of positive, negative, disorganization, cognitive, psychomotor, and mood symptoms.
The severity of different symptom clusters varies across patients and through the course of the illness.
There is a generalized but highly variable cognitive impairment.
There may be additional specific impairment in a range of cognitive functions (such as executive functions, memory, psychomotor speed, attention, and social cognition).
Cognitive impairments are present prior to onset of psychosis and persist during the course of the illness.
There is a higher occurrence of obesity and cardiovascular disease.
There is increased prevalence of cigarette smoking and other substance use disorders.
There is increased suicidality.
There is some phase-specific increase in violent behavior.
There are significant premorbid impairments in a substantial proportion of patients.
Onset of psychotic symptoms is usually during adolescence or early adulthood.
The age of onset is earlier in males.
There is an approximate doubling of age-standardized mortality.
Schizophrenia is frequently a chronic and relapsing disorder with generally incomplete remissions.
Social outcomes include reduced rates of employment and financial independence, and increased likelihood of homelessness and incarceration.
Poor outcome is predicted by male gender, early age of onset, prolonged period of untreated illness, and severity of cognitive and negative symptoms.

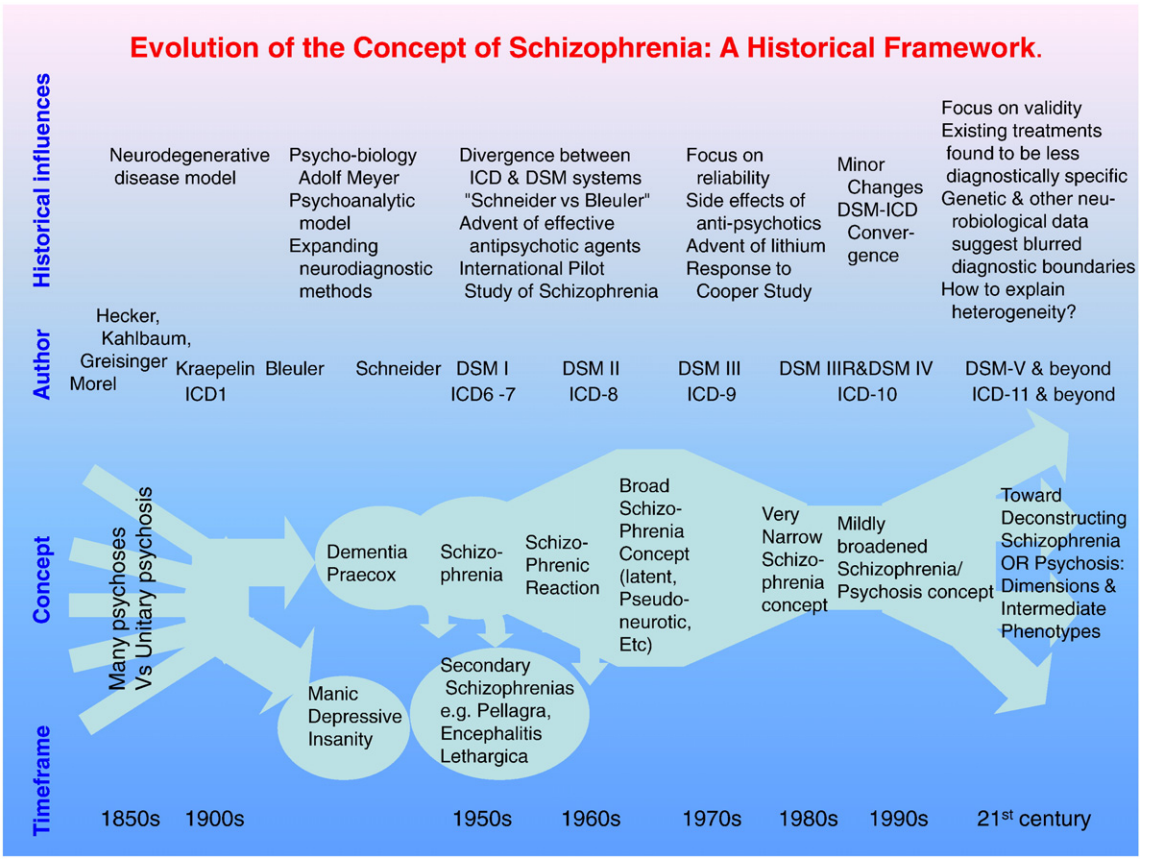


Fig. 1. Time line showing the historical evolution of the concept of schizophrenia since the mid-nineteenth century. Prior descriptions of mental illnesses resembling what we now term schizophrenia, which may date back millennia, are not reflected in this scheme. Kraepelin integrated several entities under the umbrella of Dementia Praecox, later termed schizophrenia by Bleuler; the concept of schizophrenia subsequently was revised several times, expanding, narrowing and re-expanding over the past century as a result of prevailing disease models as well as developments in diagnostic and therapeutic approaches. Currently, the concept of schizophrenia as a disease entity is in flux; there is an emerging consensus of a need to deconstruct schizophrenia as we now know it into etiopathologically meaningful dimensions identifiable clinically, with a view to reconstruct a more valid and useful entity, or more likely, set of entities.

Tracking the evolution of the conceptualization of schizophrenia since the 1920s, in the first 40 years several psychiatrists such as Langfeldt (1960), Leonhardt (1957), and Kleist (1960) attempted to further refine the Kraepelinian definition of schizophrenia by limiting its diagnosis to those with permanent impairments and developing distinctive detailed classification systems of different forms of psychosis. These efforts in Europe to demarcate "true" schizophrenia from pseudo-schizophrenia or schizophreniform psychoses were mirrored in the U.S.A. by attempts to distinguish process from reactive schizophrenia and good prognosis from bad prognosis schizophrenia (Vaillant, 1964; Robins and Guze, 1970). The only perspective to garner much influence, however, was that of Schneider (1959), developing the ideas of Jaspers (1946) who defined psychosis on the basis of irreducible experiences not comprehensible in terms of mood, circumstance, or prior experience. Despite data indicating their nonspecificity (Carpenter et al., 1973), Schneiderian "first-rank" symptoms became the basis of the definition of "nuclear" schizophrenia (Wing and Nixon, 1975). By the 1960s, the Bleulerian viewpoint had become dominant in the USA while the Kraepelinian and Schneiderian concepts broadly prevailed in the rest of the world. Whereas the eighth and ninth revisions of the International Classification of Diseases (ICD-8 and ICD-9, World Health Organization, 1967, 1978) emphasized positive symptoms, chronicity, and poor outcome as defining features of schizophrenia, the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II, American Psychiatric Association, 1968) defined it on the basis of "loss of ego boundaries". These differences led to wide discrepancies in rates of diagnosing schizophrenia between the USA and the rest of the world, a fact that was dramatically illustrated by the US–UK study (Cooper et al., 1972) which found that although patients admitted to public mental hospitals in New York and London had similar symptoms, those in New York had twice the likelihood of receiving a diagnosis of schizophrenia as those in London where the diagnosis of manic-depressive illness dominated. This among other factors led to a marked contraction of the boundaries of schizophrenia in DSM-III (American Psychiatric Association, 1980). Additionally, the perceived urgent need for reliability led to the introduction of operationalized criteria. Whereas DSM-II provided the broadest definition of schizophrenia thusfar, DSM-III provided its

narrowest. From DSM-III to DSM-III-R to DSM-IV to the current DSM-IV-TR, there has been a modest expansion of the boundaries of schizophrenia primarily as a reaction to the overly narrow DSM-III definition. ICD criteria have evolved in a similar manner and the criteria for schizophrenia in ICD-10 and DSM-IV-TR are broadly similar. These criteria require the presence of psychotic symptoms for a minimum period of one month and the exclusion of mood disorder, substance use or other recognizable "organic" etiological explanation for psychotic symptomatology. Additionally, DSM-IV-TR requires social dysfunction and decline for a period of more than six months and the exclusion of pervasive developmental disorder as an explanation for the condition.

Many factors have influenced changes in the conceptualization of schizophrenia over the past century (Tandon and Maj, 2008). These include generation of new research data, availability of specific treatments or lack thereof, what conditions schizophrenia most needs to be distinguished from at that time, and over-riding clinical concerns of the time. Considering our current state of knowledge about schizophrenia and these other factors, how should we now conceptualize and define schizophrenia? It is likely that schizophrenia is not a singular disease entity (Kendell, 1987; Tandon and Maj, 2008), with several etiological factors and pathophysiological processes appearing relevant to its development (Tandon et al., 2008b; Keshavan et al., 2008). Whereas it is almost certain that our construct of schizophrenia encompasses not one but several diseases, precise delineation of this constellation of distinct "individual diseases" that are part of this entity is not possible at present. Can the current construct of schizophrenia serve any useful purpose? What modifications are needed to make it more relevant and useful? How do we best define and characterize it? We first consider the clinical features of schizophrenia before addressing these questions.

3. Clinical features of schizophrenia

Although there is no consensus about the essential criteria that must be met to make a definite diagnosis of schizophrenia, there is broad agreement about the general clinical features of the schizophrenic syndrome. Table 1 summarizes what we currently believe about the clinical expression of schizophrenia with varying degrees of confidence. We briefly discuss each of these clinical features [psychopathology, outcome, and course] and then explore its varied expression (*heterogeneity*).

3.1. Dimensions or domains of schizophrenic psychopathology

Schizophrenic disorders are characterized by a diverse set of signs and symptoms, which include characteristic distortions of thinking and perception, cognitive impairments, motor abnormalities, avolition and apathy, difficulties in communication, and restricted affective expression. These abnormalities are generally classified into positive, negative, cognitive, disorganization, mood, and motor symptom dimensions, with psychopathology differentially expressed across patients and through the course of the illness. With some differences across studies, these symptom clusters have been broadly replicated across a large number of patient cohorts at various stages of schizophrenic illness using a wide range of assessment tools (van der Does, 1993; Kitamura et al., 1995; Lenzenweger and Dworkin, 1996; Bell et al., 1998; Grube et al., 1998; Ratakonda et al., 1998; van Os et al., 1999; Nakaya et al., 1999; Lykouras et al., 2000; Peralta and Cuesta, 2001; Serretti et al., 2001; Scully et al., 2002; Drake et al., 2003; Loza et al., 2003; Alves et al., 2005; Murray et al., 2005; Klingberg et al., 2006; Tirupati et al., 2006; Villalta-Gil et al., 2006; Boks et al., 2007; Levine and Rabinowitz, 2007). Utilizing traditional diagnostic validators (Robins and Guze, 1970), these dimensions show significant familiality (Rietkirk et al., 2008; Vassos et al., 2008) and discriminate with regard to course and treatment response (Davidson and McGlashan, 1997; Salokangas et al., 2002; Dikeos et al., 2006; Harvey et al., 2006).

3.2. Positive symptoms

Positive symptoms involve impaired reality testing and include delusions, hallucinations, and other reality distortions. Several kinds of delusions can occur and they can have varying degrees of persistence and systematization, and influence the individual's functioning to different extents. Although delusions of control, thought insertion, withdrawal and broadcasting (all Schneiderian first-rank symptoms [Mellor, 1970]) are traditionally linked to schizophrenia, persecutory delusions and delusions of reference are most frequent. A variety of other delusions can also occur and the specific delusional content is influenced by the person's life and socio-cultural setting. Hallucinations can occur in any of the five sensory modalities, although auditory hallucinations are the most common. Voices conversing among themselves or commenting on the patient are considered characteristic (Schneiderian first-rank symptoms), but threatening or accusatory voices speaking to the person are more common. Although no single symptom is pathognomonic, bizarre content and mood-incongruence of psychotic symptoms are two elements that suggest a diagnosis of schizophrenia. Reality distortion marks the formal onset of schizophrenic illness (although the pathophysiological process may have been ongoing long before), with the onset of positive symptoms generally in adolescence or early adulthood. Dopaminergic mesolimbic hyperactivity appears to underlie positive symptoms, which are most responsive to antipsychotic medications (Keshavan et al., 2008).

3.3. Negative symptoms

Negative symptoms involve a blunting or loss of a range of affective and conative functions. These include impairments in affective experience and expression, abulia (loss of motivation), alogia (poverty of speech), anhedonia (inability to experience pleasure), avolition (lack of initiative), apathy (lack of interest), and reduced social drive (Crow, 1980; Andreasen, 1982; Carpenter et al., 1988). Since a range of etiological factors can contribute to the expression of negative symptoms in the context of schizophrenic illness, it is important to distinguish between primary and secondary negative symptoms (Carpenter et al., 1988; Kirkpatrick et al., 2006) with primary negative symptoms being fundamental or intrinsic to schizophrenic illness. Secondary negative symptoms are caused by 'extrinsic' factors linked to schizophrenia such as environmental deprivation, neuroleptic

treatment, and depression. It has been suggested that only a subgroup of schizophrenia patients manifest enduring primary negative or deficit symptoms and that their presence distinguishes deficit schizophrenia from nondeficit schizophrenia (Carpenter, 2004). Although this hypothesis has been of great heuristic value, it appears that deficit may be better conceived of as a dimension ("amount of deficit") rather than a dichotomous basis for categorization of two subgroups of schizophrenia. It has also been suggested that negative symptoms intrinsic to schizophrenia may develop at one of three phases of the illness (premorbid, psychotic-phase, and deteriorative) and that unique pathogenetic mechanisms might underlie their development (Tandon et al., 2000). The pathophysiology of negative symptoms is poorly understood (Keshavan et al., 2008) and they remain a relatively treatment-refractory and debilitating component of schizophrenic pathology (Erhart et al., 2006; Stahl and Buckley, 2007).

3.4. Disorganization of thinking and behavior

'Formal thought disorder' refers to fragmentation of the logical, progressive, and goal-directed nature of normal thought process and can range in severity from the relatively mild circumstantiality and tangentiality to the more severe incoherence and word salad (Andreasen, 1979). It includes both derailment and neologisms ("positive formal thought disorder") and poverty of thought content ("negative formal thought disorder"). Hecker (1871) provided the first clear description "a peculiar departure from normal logical sentence structure with frequent changes in direction that may or may not lose the train of thought". Bleuler (1911) considered formal thought disorder as the direct expression of loosening of association, which he considered the fundamental deficit in schizophrenia. This led to long-held beliefs that formal thought disorder is specific for schizophrenia and present in all persons with the disorder. Neither of these claims has held up as loosening of association is observed in a minority of persons with schizophrenia and is not uncommon in mania (Solovay et al., 1987). Disorganization of behavior (e.g., incongruous affect or markedly inappropriate attire) frequently co-occurs with formal thought disorder. Disorganized thinking and behavior are heritable (Shenton et al., 1989; Romney, 1990), more prominent during acute exacerbations, relatively persistent, and associated with poor outcomes. Although a range of cognitive impairments have been linked to formal thought disorder (Kerns and Berenbaum, 2002), precise mechanisms underlying disorganization in schizophrenia are undefined.

3.5. Mood symptoms

Impairments in affective experience and expression have long been considered to be cardinal features of schizophrenia and often precede the onset of psychosis by several years (Yung and McGorry, 1996; Hafner and an der Heiden, 1999). In contrast to these affective impairments (negative symptoms), schizophrenia patients frequently manifest mood symptoms and exhibit increased emotional arousal and reactivity in conjunction with positive symptoms, a phenomenon termed 'the emotional paradox' of schizophrenia (Aleman and Kahn, 2005). Depression is common in schizophrenia, and may be part of the prodrome, the florid phase, follow an acute episode (postpsychotic depression), or occur between psychotic exacerbations (Planansky and Johnston, 1978). Significant depressive symptoms are present in a majority of schizophrenia patients at some point during the illness, are more severe in those with comorbid substance use disorders, can occur in every phase of the illness, increase during acute psychotic exacerbations and partly remit in parallel with psychotic symptoms, and contribute substantially to the disease burden of schizophrenia (Bartels and Drake, 1988; Sands and Harrow, 1999; Siris and Bench, 2003; Conley et al., 2007; Potvin et al., 2007). Several mechanisms may contribute to depression in the context of schizophrenic illness-it is an integral part of the illness, its appearance may correspond to the development of insight, it can be due to another disorder such as major depression co-occurring with schizophrenia, or it might reflect an adverse effect of antipsychotic medications (*neuroleptic dysphoria*).

3.6. Motor symptoms and catatonia

Schizophrenic patients frequently manifest abnormalities in both the extent and nature of psychomotor activity (Marsden, 1982). Slowing of psychomotor activity is common in schizophrenia (Morrens et al., 2007), is variably associated with negative and depressive symptom clusters, and portends a poor outcome (Lehoux et al., 2003). Excessive motor activity, often apparently purposeless, is more often associated with exacerbations of positive symptoms. Disorders of psychomotor activity can range from simple isolated movements of posturing, mannerisms, and stereotypies (Morrens et al., 2006) to more complex patterns of motion as observed in various catatonic states (Ungvari et al., 2007). These abnormalities were described in schizophrenia long before the introduction of antipsychotic agents in the 1950s and spontaneous movement disorders have since been observed in upto a quarter of antipsychotic–naïve patients (Cortese et al., 2005; Honer et al., 2005; McCreadie et al., 2005). The full-blown catatonic syndrome can occur in the context of stupor or excitement, and is characterized by echolalia, echopraxia, automatic obedience, waxy flexibility, and extreme negativism (Weder et al., 2008). In the context of chronic schizophrenia, the presence of catatonic symptoms is associated with greater illness severity and more impairment (Ungvari et al., 2005; Bonnot et al., 2008). Associations with antipsychotic-induced movement disorders have also been noted (McKenna et al., 1991). Of note, catatonic symptoms have become infrequent as presentations of schizophrenia in recent decades (Stompe et al., 2002) and are more often seen in mood disorders (Taylor and Fink, 2003), suggesting that catatonia may not be part of the core psychopathology of schizophrenia (Taylor and Fink, 2003; Tandon and Maj, 2008). Although dopaminergic abnormalities have been implicated, the precise neurobiological basis of motor abnormalities in schizophrenia remains to be clarified.

3.7. Cognition

The past decade has witnessed an explosion of information elucidating the importance and nature of cognitive

abnormalities in schizophrenia. Even though Kraepelin (1919) utilized the term "dementia praecox," which literally means "cognitive decline with onset in youth", to describe the disorder, Bleuler (1911) maintained that cognitive function was essentially unimpaired in schizophrenia. Although intellectual deficits have consistently been reported in schizophrenia over the past century (Johnstone et al., 1978), there was limited research on the topic until the past three decades. Interest in this topic has been fueled by findings of ventricular enlargement (Johnstone et al., 1976), advances in methods of neuropsychological testing and neuro-imaging (Keshavan et al., 2008), the pervasive nature of cognitive deficits in schizophrenia (Heinrichs, 2005), and their profound impact on functional outcome (Green, 1996; van Winkel et al., 2007; Bowie et al., 2008). The following observations about the nature of cognitive abnormalities in schizophrenia can be made with a fair degree of confidence: (i) cognitive impairment is *highly prevalent* (if not universal) in patients with schizophrenia, albeit to varying degrees (Saykin et al., 1991; Keefe et al., 2005); (ii) cognitive impairment distinguishes patients with schizophrenia from healthy comparison subjects to a *robust* degree (i.e., an effect size of approximately 1) and average effect sizes for cognitive impairments are about twice as large as those obtained for structural brain abnormalities in magnetic resonance imaging studies (Heinrichs and Zakzanis, 1998; Dickinson et al., 2007; Reichenberg and Harvey, 2007; Keshavan et al., 2008); (iii) the cognitive deficit in schizophrenia is substantially of a *generalized* nature (Lencz et al., 2006; Dickinson et al., 2008) with additional impairments in specific domains of episodic memory (Aleman et al., 1999; Achim and LePage, 2005; Ranganath et al., 2008), processing speed (Dickinson et al., 2007), verbal fluency (Henry and Crawford, 2005), attention (Orzack and Kornetsky, 1966; Fioravanti et al., 2005), and executive functions and working memory (Laws, 1999; Lee and Park, 2005; Reichenberg and Harvey, 2007; Barch and Smith, 2008); (iv) cognitive deficits are present in the *premorbid phase* of schizophrenic illness with an average effect size of approximately 0.5 (Aylward et al., 1984; Heinrichs and Zakzanis, 1998; Henry and Crawford, 2005; Woodberry et al., 2008); (v) cognitive deficits *persist* through the long-term course of schizophrenia (Rund, 1998; Hoff et al., 2005b); (vi) *modest improvements* (average effect size of 0.5, Klingberg et al., 2008; Szoke et al., 2008) in cognitive function are observed in the course of antipsychotic treatment, although some of this is attributable to practice effects, with no substantial differences noted between first- and second-generation antipsychotic agents (Keefe et al., 2007) controlling for differences in extrapyramidal side-effects (Tandon et al., 2008c); (vii) the *course* of cognitive function through schizophrenic illness has not been definitively outlined: it begins with definite premorbid impairment, a probable deterioration prior to or around the onset of psychotic symptoms, a modest partial improvement with treatment, and relative stability thereafter with heterogeneity across patients (Bilder et al., 2006; Kremen et al., 2008) (viii) a similar pattern of cognitive impairment of lesser severity is present in *non-psychotic relatives* (Sitskoorn et al., 2004; Hoff et al., 2005a; Hughes et al., 2005; Szoke et al., 2005; Whyte et al., 2005; Trandafir et al., 2006; Whalley et al., 2007) and is likely related to a patient's *genetic susceptibility* to schizophrenia (Snitz et al., 2006; Fusar-Poli et al., 2007; Touloupolou et al., 2007); (ix) cognitive impairment is a strong *predictor of poor social and vocational outcome* (van Winkel et al., 2007; Bowie et al., 2008), with *impairments in social cognition* such as theory of mind deficits being particularly potent predictors (Vauth et al., 2004; Sprong et al., 2007; Penn et al., 2008; van Hooren et al., 2008); and (x) although cognitive deficits in patients with schizophrenia tend to be more severe and persistent compared to patients with psychotic and non-psychotic affective disorders, they are *not qualitatively different* (Barch et al., 2003; Daban et al., 2006; Kitamura et al., 2007; Heinrichs et al., 2008). The high prevalence and pervasive nature of cognitive deficits in schizophrenia has led to their being proposed for consideration as diagnostic criteria for this illness, but issues of diagnostic nonspecificity limit the utility of doing so (Tandon and Maj, 2008).

3.8. Anxiety

Symptoms of anxiety have been described as a central feature of schizophrenia since its characterization as a unique disease entity (Kraepelin, 1919; Bleuler, 1911). Although anxiety in the context of schizophrenia today is principally considered from the perspective of comorbidity (Craig et al., 2002; Goodwin et al., 2003), it should be noted that anxiety is a prominent symptom early in the course of the illness (Chapman, 1966) and that this view of anxiety disorders as a "comorbidity" with rather than a clinical expression of schizophrenia may, in part, be an artifact of our current nosological system (Maj, 2005). Anxiety disorders (in particular, comorbid social phobia, obsessive–compulsive disorder, and panic disorder) are common in schizophrenia and adversely impact outcome (Craig et al., 2002; Braga et al., 2004; Muller et al., 2004; Ciapparelli et al., 2007). Consistent with current practice, however, we summarize information on anxiety disorders in schizophrenia in a later section on comorbidity.

3.9. Impaired insight

Lack of insight is a cardinal feature of schizophrenia (Carroll et al., 1999) and a significant majority of patients with schizophrenia either believe that they do not have any disorder, acknowledge symptoms but misattribute them to other causes, or deny any need for treatment (World Health Organization, 1973; Amador and David, 1998; American Psychiatric Association, 2000). Insight is found to be weakly correlated with severity of other psychopathological domains (Mintz et al., 2003; Aleman et al., 2006) in contrast to its strong association with measures of functional outcome (Schwartz et al., 1997; Amador and David, 1998). Analogous to anosognosia in other neurological disorders (Pia and Tamietto, 2006), there have been recent efforts to elucidate the neurobiological basis of poor insight in schizophrenia (Shad et al., 2006). Currently, studies to better define the phenomenology of insight impairments in schizophrenia are ongoing (Dam, 2006) as are investigations to integrate neurobiological and psychological findings (Osatuke et al., 2008). Insight is centrally related to the patient's experience of their disorder and an improved understanding of its

impairment in schizophrenia will significantly enable delineation of the nature of the disorder and improving outcomes for those affected.

3.10. "Minor physical anomalies"

"Minor physical anomalies" refer to subtle morphological abnormalities of little functional or cosmetic significance in the head, face, hands, or feet. Such deviations occur at a much higher frequency in persons with schizophrenia in comparison to the general population (Waddington et al., 1999; Weinberg et al., 2007) and mark developmental aberrations that are assumed to reflect prenatal insults at the time of in-utero brain development. Minor physical anomalies in schizophrenia are observed across ethnic groups (Dean et al., 2007), lack regional specificity (Weinberg et al., 2007), show no association with overall illness severity or any symptom domain (McGrath et al., 1995; Compton et al., 2007), and exhibit some degree of familiality (Compton et al., 2007). Additionally, dermatoglyphic abnormalities are consistently described in schizophrenia (Bramon et al., 2005). Despite the robustness of these findings which reflect gestational ectodermal maldevelopment, their precise relevance to schizophrenia is unclear.

3.11. Neurological signs: "hard" and "soft"

A range of neurological deficits are observed in a majority of patients with schizophrenia (Heinrichs and Buchanan, 1988): these include both "hard" signs that reflect impairments in motor, sensory, or reflex functions which are localizable to a particular brain area/circuit as also "soft" nonlocalizing deficits that do not implicate a specific brain region or demarcate a specific neurological syndrome. In addition to the previously discussed motor abnormalities that reflect pyramidal or extrapyramidal dysfunction, hard neurological signs include hypoalgesia, impaired olfactory function, and oculomotor abnormalities. Kraepelin (1919) and Bleuler (1911) both documented reduced sensitivity to pain in patients with schizophrenia and this has been confirmed in several subsequent studies (Dworkin, 1994; Potvin and Marchand, 2008). The precise pathophysiologic relevance of hypoalgesia to schizophrenia is, however, poorly understood. There is a high prevalence of olfactory dysfunction in patients with schizophrenia, with impairments in odor identification, recognition, and discrimination (Atanasova et al., 2008). Impairment of olfactory function has been found to predict likelihood of developing schizophrenia among individuals at high-risk (Brewer et al., 2003), similar olfactory deficits are observed in first-degree relatives (Turetsky et al., 2008), there is evidence of dysregulation of olfactory receptor lineage in patients with schizophrenia (Arnold et al., 2001), and the severity of olfactory deficits has been found to be associated with the severity of negative symptoms (Malaspina and Coleman, 2003).

Soft neurological signs include impairments in motor dexterity (Ho et al., 2004), presence of primitive reflexes or cortical release signs (Tweedy et al., 1982; Walterfang and Velakoulis, 2005), difficulties in proper sequencing of complex motor tasks (Walker and Green, 1982), and deficits in sensory integration (Tucker et al., 1975); although these signs are not specifically localizable to a particular brain region, they putatively implicate the cerebellum, frontal lobe, prefrontal cortex, and the parietal lobe respectively. Soft neurological signs are observed much more frequently in patients with schizophrenia and found to be associated with the severity of cognitive deficits and negative and disorganization symptoms (King et al., 1991; Bombin et al., 2005; Tosato and Dazzan, 2005). Additionally, they are found to be stable over the course of the illness and independent of antipsychotic treatment (Keshavan et al., 2003; Emsley et al., 2005; Chan and Gottesman, 2008;), and occur more frequently among children (Rieder and Nichols, 1979) and other first-degree relatives (Compton et al., 2007; Gabalda et al., 2008) of persons with schizophrenia than in the general population.

Although not an abnormality, schizophrenia is also characterized by a leftward shift in handedness, with a greater prevalence of left-handedness and mixed-handedness than in the general population (Somner et al., 2001; Dragovic et al., 2005); as discussed in the previous paper in this series (Keshavan et al., 2008), this observation is often invoked in support of the hypothesized role of anomalous cerebral dominance in the etiopathogenesis of schizophrenia.

3.12. Onset and course

Schizophrenia is characterized by a sequential trajectory (Fig. 2) that involves a *premorbid phase* with subtle and nonspecific cognitive, motor and/or social dysfunction (Schenkel and Silverstein, 2004), a *prodromal phase* characterized by attenuated positive symptoms or basic symptoms and declining function (Rossler and Rossler, 1998; Schultze-Lutter, 2009), the *first psychotic episode* heralding formal *onset* of schizophrenia, the initial decade of illness generally marked by *repeated episodes of psychosis* with partial and variable degrees and duration of *inter-episode remission* with accrual of disability with each episode of illness, (decline in function is most pronounced in the first five years after a first episode of psychosis, at which time patients may "bottom out" in terms of deterioration [Bleuler, 1972; Ciompi, 1980; McGlashan and Fenton, 1993]), and finally, a *stable phase* or *plateau,* when psychotic symptoms are less prominent and negative symptoms and the stable cognitive deficits increasingly predominant. *Recovery* of varying degrees can occur at any stage of the illness (Harding et al., 1987) and in contrast to the original Kraepelinian perspective of unalterably progressive deterioration, a significant proportion of individuals with schizophrenia exhibit substantial improvement (Bleuler, 1972; Ciompi, 1980).

Although we describe the course of the illness with reference to these phases in this section, it should be noted that the demarcation between various phases of schizophrenia is imprecise: (i) the distinction between premorbid dysfunction and prodromal symptoms is based on the unproven assumption that premorbid impairments reflect precursors or risk factors for developing schizophrenia in contrast to prodromal symptoms which are considered to be an early manifestation of the actual disorder itself; (ii) over half of the individuals with attenuated psychotic symptoms suggestive of the schizophrenia prodrome do not go on to develop schizophrenia; (iii) the onset of the "initial

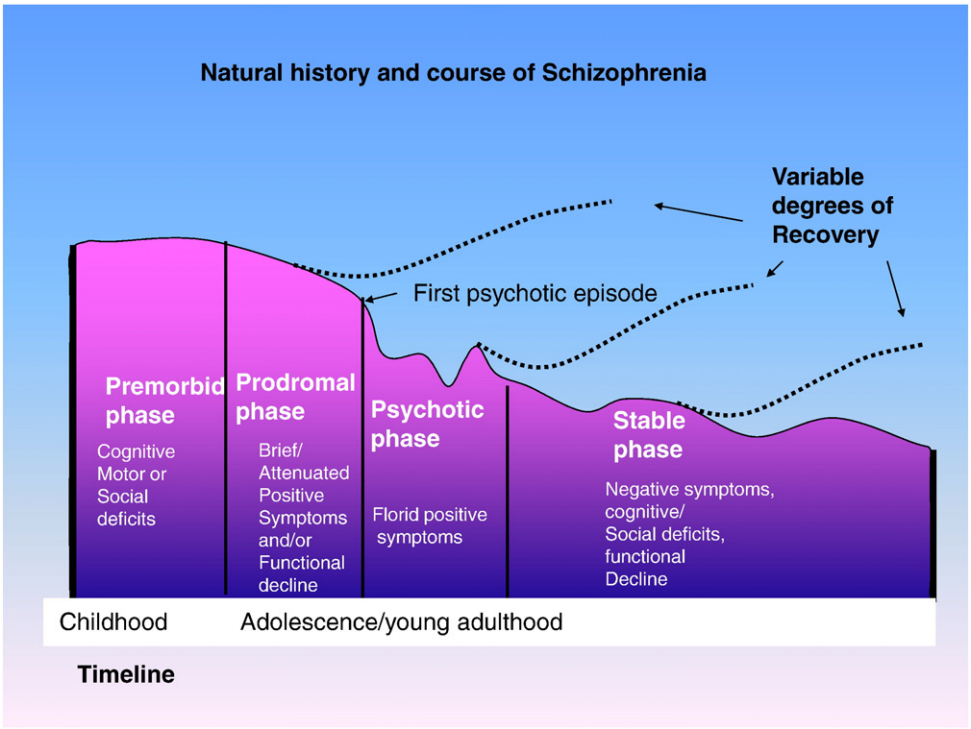


Fig. 2. Evolution of schizophrenia with phases of illness.

psychotic episode" may be insidious or ill-defined; (iv) psychotic manifestations are often not clearly episodic; and (v) there is enormous variation in the progression of the illness across patients. We address the arbitrary nature of the distinction between different stages of the illness and the significant heterogeneity of course across patients in the discussion. For the purpose of this section, we define illness onset on the basis of onset of reality distortion or positive symptoms.

3.13. Premorbid phase

Individuals who go on to develop schizophrenia exhibit a range of developmental behavioral, emotional and cognitive problems, accompanied by *premorbid* impairments in academic and social function. Abnormalities include delays in motor development, attentional dysfunction, deficits in receptive language, poor academic achievement, social isolation, and emotional detachment (Schenkel and Silverstein, 2004). This has been demonstrated in retrospective case-control follow-back studies (Walker et al. 1994; Schmael et al., 2007), population cohort studies (Done et al. 1994; Jones et al. 1994; Cannon et al., 2002), and prospective studies of persons at high risk (Fish et al., 1992; Cornblatt et al., 1999; Keshavan et al., 2005). Among individuals who develop schizophrenia, poor premorbid function is associated with an early age of onset of psychosis and greater severity of negative and cognitive symptoms during the illness (Schmael et al., 2007; Jeppesen et al., 2008; Macbeth and Gumley, 2008). Although characteristics of this premorbid period may shed light on the pathophysiology of the early latent vulnerability to schizophrenia, they are neither universally present in nor specific to those who subsequently develop schizophrenia.

3.14. Prodromal phase

The period of time preceding the first onset of psychosis has been described as the "prodrome" and is characterized by subthreshold psychotic symptoms, as well as a constellation of other clinical signs including cognitive deficits, negative symptoms, mood symptoms, and decline in function (Cornblatt et al., 1999). The prodromal period was initially characterized through retrospective studies of first-episode patients (Chapman, 1966; Varsamis and Adamson, 1971). More recently, information about this phase has been obtained prospectively through the longitudinal study of individuals at high risk for developing schizophrenia either because of a positive family history of schizophrenia or because they are manifesting attenuated signs of the disorder (Olsen and Rosenbaum, 2006; Thomas and Woods, 2006; Addington et al., 2007; Gaebel and Riesbeck, 2007; Wood et al., 2008). The prodrome may last from months to years, with a mean of ~5 years (Hafner and an der Heiden, 1999; Klosterkotter et al., 2008). Cognitive, negative, and depressive symptoms appear an average of about five years prior to the first clinical contact and social disability emerges approximately 1–3 years later. Positive symptoms accumulate for about one year prior to initial clinical contact. Among treatment-seeking individuals who meet criteria for ultra-high risk of developing schizophrenia (with attenuated psychotic symptoms suggestive of schizophrenia prodrome), about one-

sixth to one-half go on to develop schizophrenia depending on the population studied and criteria utilized (Yung et al., 2003; Cannon et al., 2008; Yung et al., 2008). The neurobiological mechanisms which underlie this progression are poorly understood. More severe positive symptoms and greater degree of social impairment predict a higher risk of "converting" to schizophrenia.

Over the past decade, there has been significant interest in trying to prevent the evolution of prodromal subpsychotic symptoms into the florid psychosis of schizophrenia utilizing a range of psychopharmacological and psychological approaches among those meeting criteria for ultra-high risk of developing schizophrenia. Results have been mixed thus far (Lee et al., 2005; Hafner and Maurer, 2006; Phillips et al., 2007).

3.15. Onset of illness and the initial psychotic episode

Defining the onset of schizophrenic illness can be difficult because of variations in definition of onset (first sign of mental disturbance, first positive symptom, first evidence of social dysfunction, first clinical contact, or first hospitalization) and the usually continuous process of illness evolution from prodrome to overt psychosis (Beiser et al., 1993; Hafner et al., 1998). For practical purposes, the development of frank psychotic symptoms marks the formal onset of the first-episode of schizophrenia, consistent with Criterion A in the DSM-IV-TR, (American Psychiatric Association, 2000) which itemizes hallucinations, delusions, disorganized speech or behavior, and negative symptoms. To meet this criterion, individuals must experience two of these five symptoms for one month (or less if appropriately treated), unless they have certain Schneiderian first-rank symptoms, in which case a single symptom is deemed sufficient to fulfill Criterion A. ICD-10 (World Health Organization, 1992) utilizes a similar definition of schizophrenia.

Thus defined, the onset of schizophrenia typically occurs between the ages of 15 to 45 years although rarely it can begin before puberty or after the age of 50 years (Gross, 1997; Hafner et al., 1998; American Psychiatric Association, 2000). In comparison to those with a later age of onset of schizophrenia, individuals with an early age of onset (<20 years) and a very early-onset (<13 years) manifest worse premorbid function, more severe negative and disorganization symptoms, greater cognitive deficits, and inferior overall prognosis (DeLisi, 1992; Hafner and an der Heiden, 1999; Masi et al., 2006; Luoma et al., 2008); using age of onset as a continuous variable without arbitrary cut-off points produces more explicable results (Luoma et al., 2008).

Attenuated psychotic symptoms, the hallmark of most defined putative prodromal syndromes, are the *forme fruste* of full-blown psychotic symptoms; in fact, there appears to be continuity in the clinical psychopathology of the prodrome into the first florid psychotic episode across other symptom domains as well (Iyer et al., 2008). Substance use and life stressors can precipitate the episode (Norman and Malla, 1993; Corcoran et al., 2003 Phillips et al., 2006), although no specific trigger can be identified in the majority of cases. Like subsequent episodes of psychosis, the first episode generally begins with an increase in mood and negative symptoms (prepsychotic phase) accompanying escalating positive symptoms, a florid peak expression of positive symptoms (psychotic phase), followed by resolution of positive symptoms with slower resolution of depressive and negative symptoms (post-psychotic depression), and finally a transitional or resolution phase during which period, psychotic symptoms are in abeyance but can easily re-emerge (Cameron, 1938; Chapman, 1966; Roth, 1970; Donlon and Blackmer, 1973; Docherty et al., 1978; Tandon and Greden, 1989; Drake et al., 2003; Owens et al., 2005).

Although the lifelong risk of schizophrenia is similar in men and women, the onset of the illness on average occurs about 5–7 years later in females (Kraepelin, 1919; Angermeyer and Kuhn, 1988; Hafner et al., 1998). Studies from developing countries are, however, less likely to document gender differences in age of onset (Venkatesh et al., 2008); the basis of this discrepancy is unclear. The age-at-onset distribution is unimodal for men but bimodal for women (American Psychiatric Association, 2000), with a peak of 18–30 years for both genders but an additional second peak later in life among females. Additionally, in comparison to men with the disorder, women with schizophrenia have better premorbid functioning, express more severe affective symptoms and less severe negative symptoms, manifest less severe cognitive impairment, have lower rates of completed suicide, respond better to treatment, and have a better overall prognosis (Seeman, 1982; Goldstein, 1988; Hoff et al., 1998; Salem and Kring, 1998; Lester, 2006; Grossman et al., 2008; Koster et al., 2008). Gender differences are less pronounced in non-Western countries (Jablensky et al., 1992; Thara, 2004).

3.16. Chronicity and recovery: plateau following initial deterioration

Following the first psychotic break, the course of schizophrenia varies substantially across patients (Bleuler, 1972; Ciompi, 1980; Huber et al., 1980; Modestin et al., 2003; Thara, 2004). Classically, the course is characterized by exacerbations and remissions, with psychotic symptoms resolving to varying extents between these episodes across patients and through the course of the illness (Andreasen et al., 2005; Haro et al., 2008). Psychotic exacerbations can be triggered by stress (e.g., exposure to high expressed emotion [Brown et al., 1972; Butzlaff and Hooley, 1998]), nonadherence to treatment, or substance abuse. Positive symptoms tend to become less severe and negative symptoms more prominent over the long-term course of the illness. Cognitive symptoms are generally stable over the course of the illness while mood symptoms vary in severity in partial association with psychotic symptoms. In contrast to the original Kraepelinian perspective of inevitable progressive deterioration, approximately a quarter of patients exhibit full psychopathological remission and about half show social remission (Huber et al., 1980; Watt et al., 1983; Harding et al., 1987; Mason et al., 1996; Rossler and Rossler, 1998; Harrison et al., 2001).

A substantial degree of functional decline is evident at the time of onset. There appears to be some additional deterioration in many patients during the early stages of the illness, with much of this clinical progression occurring within 3–5 years after symptom onset (Bleuler, 1972; Ciompi, 1980; Hafner and an der Heiden, 1999; Harrison et al., 2001). The extent of deterioration appears to be related, in part, to the duration of untreated psychosis (Loebel et al., 1992;

Perkins et al., 2005; Clarke et al., 2006; Malla et al., 2006; Farooq et al., in press) suggesting that untreated psychosis may be biologically noxious (Wyatt and Hunter, 2001). This hypothesis remains unproven (McGlashan, 2006; Morgan et al., 2006), however, even though there is a suggestion of early progressive brain loss (Keshavan et al., 2008; Lawrie et al., 2008; van Haren et al., 2008; Wang et al., 2008). Following the initial years of vulnerability to further deterioration, a plateau is frequently reached, characterized by either remission or chronicity (Thara, 2004). Following this, the illness stabilizes and, although there may be subsequent exacerbations, there is generally no further consistent illness-driven decline in functioning and increase in residual symptoms. Only in a small subgroup of patients is further decline observed during senescence (Mittelman and Buchsbaum, 2007). Several course profiles with varying combinations of psychotic episodes (*single or recurrent; based on the number, frequency, and duration of episodes*) and inter-episode or residual impairment (*varying degrees ranging from none to very severe, progressively increasing or stable, across different domains of psychopathology and function*) have been described (Bleuler, 1972; Huber et al., 1980; Watt et al., 1983; American Psychiatric Association, 2000; Modestin et al., 2003). The extent to which these profiles reflect the intrinsic nature of the illness is unclear because of a range of external modifying factors and methodological constraints (Strauss and Carpenter, 1974; Wing, 1978; Gaebel and Frommann, 2000). Whereas antipsychotic treatment improves functional outcome by reducing the severity of psychotic symptoms and preventing relapses, the extent to which such treatment modifies the long-term course of the illness remains unclear.

3.17. Outcome and comorbidities

Kraepelin (1899) originally defined schizophrenia on the basis of outcome, asserting "under the term dementia praecox, we can subsume a number of disease conditions whose common characteristic is outcome in peculiar states of weakness". As Kraepelin (1920) himself acknowledged later in his career, the outcome of schizophrenia is highly variable and less malignant than he first believed. The distinction between long-term course and outcome in schizophrenia is essentially semantic (Burns, 2007), and as noted above, schizophrenic illness can resolve completely, terminate in a severe defect state, or end in varying degrees of partial or full recovery (Hegarty et al., 1994; Hafner and an der Heiden, 1999; Harrison et al., 2001; Jobe and Harrow, 2005). Individuals with schizophrenia exhibit increased mortality (Brown, 1997; Harris and Barraclough, 1998; Osby et al., 2000; Saha et al., 2007; Seeman, 2007), high risk of suicide (Fenton, 2000; Hawton et al., 2005; Palmer et al., 2005), increased rates of a range of comorbid medical and psychiatric illnesses (Bermanzohn et al., 2000; Carney et al., 2006; Leucht et al., 2007; Newcomer and Hennekens, 2007), reduced likelihood of employment, and impairments in quality of life (Folsom et al., 2005; Eack and Newhill, 2007). These outcomes along with the individual and social consequences of schizophrenic illness are summarized below.

Outcome in the context of schizophrenic illness is a multidimensional construct comprised of distinct domains of psychopathology, different elements of social functioning, life-span and various aspects of quality of life, and societal impact. The outcome of schizophrenia is influenced by several factors including the circumstances under which the illness develops, characteristics of the illness, premorbid personality and abilities of the affected individual at the time of illness onset, available treatments, the social setting, and environmental factors. The course of schizophrenia has become less malignant over the past century, with a greater proportion of patients exhibiting more benign outcome (Hegarty et al., 1994; Rossler and Rossler, 1998). Optimal antipsychotic treatment and psychosocial therapy contribute to better outcome (Menezes et al., 2006)—this will be reviewed in the next planned paper in this series. The outcome of schizophrenia is better in non-Western countries (Sartorius et al., 1986; Jablensky et al., 1992; Harrison et al., 2001; Isaac et al., 2007), although the veracity of this differential outcome has recently been questioned (Patel et al., 2006). Across different settings, predictors of better outcome include acute onset of illness, better premorbid function, superior cognitive function, absence of substance abuse, female gender, and a later age of onset (Shepherd et al., 1989; Breier et al., 1991; Rossler and Rossler, 1998; Flyckt et al., 2006).

3.18. Mortality

Individuals with schizophrenia exhibit increased mortality (Harris and Barraclough, 1998; Brown, 1997; Saha et al., 2007; Seeman, 2007; Meyer and Nasrallah, 2009). Age-standardized mortality rates among persons with schizophrenia are approximately double that of the general population and their lifespan is abbreviated by approximately 15–20 years (Parks et al., 2006; Auquier et al., 2007). Approximately a quarter of the excess mortality in schizophrenia is attributable to higher rates of suicide and about 10% to greater risk of accidents (Brown et al., 2000; Saha et al., 2007); the remainder of the excess mortality is on account of a broad range of "natural medical conditions". Cardiovascular disease contributes to the greatest number of excess deaths. Suicide is the specific cause contributing to the largest number of excess deaths among males whereas cardiovascular disease is the single largest contributor to excess mortality among females with schizophrenia (Osby et al., 2000; Goff et al., 2005). The mortality gap between those with schizophrenia and the general population has progressively increased over the past three decades (Saha et al., 2007; Capasso et al., 2008). A greater prevalence of comorbid medical disorders and a lower quality of overall health care appear to be the principal factors that contribute to the higher mortality associated with schizophrenic illness (Lawrence et al., 2003; Daumit et al., 2006; Nasrallah et al., 2006; Leucht et al., 2007).

3.19. Suicide

Schizophrenia is associated with a substantially increased risk of attempting suicide and a significantly greater likelihood of dying from suicide than the general population (Hawton et al., 2005; Palmer et al., 2005; Pompili et al., 2008). Approximately one-third of individuals with schizophrenia attempt suicide one or more times and 5% of individuals with schizophrenia die of suicide. The risk of this outcome is

highest early in the course of the illness, particularly in association with better premorbid function and good insight (Melle et al., 2006). Factors that increase the risk of suicide among those with schizophrenia include coexisting depressive disorder, history of previous suicide attempts, substance abuse, male gender, poor treatment adherence and response, higher medical comorbidity, akathisia, and impulsivity. In contrast to the association of greater suicide risk with mood and motor symptoms, there is no consistent relationship with positive, negative, cognitive, or disorganization domains of pathology. Protective factors against suicide include family support and social connectedness. Treatment with clozapine in comparison to other antipsychotic agents may reduce the risk of suicide (Meltzer et al., 2003; Hennen and Baldessarini, 2005).

3.20. Violent behavior

Although often feared by others, the vast majority of individuals with schizophrenia are not violent. In fact, they are disproportionately more likely to be victims of violence (Walsh et al., 2003; Teplin et al., 2005). There is, however, a small but statistically significant relationship between schizophrenia and the risk of violent behavior (Swanson et al., 1990; Shaw et al., 2006). A significant part of that relationship is driven by the severity of positive symptoms (Fresan et al., 2005; Volavka and Citrome, 2008), while comorbid substance use and impulsivity explain part of the remainder. In a very small minority of patients, comorbid psychopathy or other personality disorders in conjunction with a history of childhood physical and sexual abuse are associated with violent behavior (Taylor, 2008). Amidst this etiological heterogeneity, the pathophysiological basis of violent behavior is poorly defined.

3.21. Comorbid psychiatric disorders

As discussed in an earlier section, anxiety and depressive syndromes are often evident in the context of schizophrenia. Whereas they were previously considered to be part of the evolution and expression of schizophrenic illness (Griesinger, 1861; Bleuler, 1911; Kraepelin, 1919; Chapman, 1966), these symptoms are now increasingly considered to reflect a distinct condition *comorbid* with schizophrenia. The encouragement in DSM-IV-TR (American Psychiatric Association, 2000) to make multiple diagnoses on Axis 1 as appropriate has substantially accounted for the recent increase in psychiatric comorbidity reported in schizophrenia (Bermanzohn et al., 2000; Maj, 2005). Depressive syndromes in the context of schizophrenia were discussed in an earlier section. Various anxiety disorders are frequently observed in the context of schizophrenic illness with lifetime prevalence rates of about 20% for social phobia, 15% for obsessive–compulsive disorder, 10% for generalized anxiety disorder, and about 5% each for panic disorder, specific phobic disorder, and post-traumatic stress disorder (Craig et al., 2002; Goodwin et al., 2003; Braga et al., 2004; Muller et al., 2004; Ciapparelli et al., 2007). In contrast to a fully developed anxiety syndrome, anxiety *symptoms* are noted in a higher proportion of cases. Since there is significant uncertainty about the attribution of such symptoms to schizophrenic illness or to a separate psychiatric disorder across studies, these estimates must be considered very crude. Anxiety symptoms often precede frank psychotic symptoms in the early stages of schizophrenic illness (Chapman, 1966; Devulapalli et al., 2008). The nature of the relationship between schizophrenic illness and such comorbid anxiety syndromes is poorly understood: does one occur as part of the other, are they unique syndromes with common risk factors or shared pathophysiology, is one a complication of the other, is the appearance of comorbidity artifactual, etc. (First, 2005)? Regardless, the presence of such anxiety disorders causes additional distress and dysfunction and likely warrants separate therapeutic attention.

3.22. Comorbid intellectual disability

Several cognitive impairments as a core clinical component of schizophrenia were discussed in a previous section. Approximately 3–5% of individuals with intellectual disability have co-occurring schizophrenia (Bhaumik et al., 2008; Morgan et al., 2008) and they exhibit higher mortality rates and greater disability than persons with schizophrenia alone. Schizophrenia, but not bipolar disorder or unipolar depression, is over-represented among individuals with intellectual disability and co-occurring psychiatric disorder (MacCabe, 2008; Morgan et al., 2008). Prevalence rates of various personality disorders in the context of schizophrenia have been reported to be both higher and lower than in the general population (Newton-Howes et al., 2008), and no precise statement about their nature or relationship can be made with any degree of confidence.

3.23. Comorbid substance abuse

There is a strong association between schizophrenia and substance abuse and there is both a high prevalence of substance abuse in schizophrenia and increased occurrence of psychotic symptoms in the context of substance abuse (Regier et al., 1990; Westermeyer, 2006; Green et al., 2007). Substance abuse can precede, accompany, or follow the first psychotic episode in schizophrenia. Distinguishing substance-induced psychosis from schizophrenia can pose a difficult diagnostic dilemma, particularly during the first episode of psychosis in the context of substance use (Mathias et al., 2008). Alcohol, nicotine, and cannabis abuse are very common, and lead to considerable additional impairment, worsening of psychosis, and limit the effectiveness of antipsychotic drug treatment (Linszen et al., 1994; Green et al., 2004). As discussed in the second paper in this series (Tandon et al., 2008b), cannabis use is a risk factor for the development of schizophrenia and earlier onset of the disorder (Ongur et al., 2009). Nicotine dependence or smoking is highly prevalent among schizophrenic patients, who are five times more likely to smoke than the general population (de Leon and Diaz, 2005); this is one factor that contributes to the increased mortality observed in persons with schizophrenia (Ziedonis et al., 2008).

3.24. Medical co-morbidity

As noted in a previous section, schizophrenia is associated with a doubling of age-standardized mortality. Comorbid

medical conditions contribute to about 60% of this excess mortality because of (i) an increased prevalence of several comorbid medical conditions on account of a range of factors (Goff et al., 2005; Carney et al., 2006; Iacovides and Siamouli, 2008; Meyer and Nasrallah, 2009) (ii) under-recognition and inadequate treatment of comorbid medical conditions (Dworkin, 1994; Lawrence et al., 2003; Marder et al., 2004; Nasrallah et al., 2006; Fleischhacker et al., 2008; Szpakowicz and Herd, 2008), and (iii) an increased likelihood of adverse outcomes of some treatments for comorbid medical conditions (Daumit et al., 2006). For example, the increased cardiovascular mortality observed in schizophrenia (Osby et al., 2000) occurs on account of an increased risk of cardiovascular disease (because of obesity, hyperlipidemia, diabetes, smoking, sedentary life style, adverse effects of some antipsychotic medications, and other factors) (Dixon et al., 1999; Newcomer and Hennekens, 2007), under-recognition or late recognition of the cardiovascular problem (because of inadequate reporting of symptoms, poor access to medical care, reduced quality of actual medical care, and other factors) (Druss et al., 2001; Leucht et al., 2007), and an increased likelihood of complications of treatment (because of increased vulnerability, poor quality of treatment, treatment interactions, and other factors) (Druss et al., 2000; Daumit et al., 2006). Medical comorbidity substantially adds to the disease burden of schizophrenia (Chwastiak et al., 2008).

3.25. Lower risk of some medical illnesses in schizophrenia

The occurrence of specific physical diseases in schizophrenia has been of interest for the past century, with reports of a higher prevalence of several conditions and a reduced prevalence of others (Leucht et al., 2007). As summarized above, a number of factors contribute to the higher comorbidity of several medical conditions in schizophrenia. From an etio-pathophysiological perspective, reports of a negative association of a few physical illnesses with schizophrenia have received special attention because of the implication that one might be protective against the other. For example, findings of a reduced occurrence of cancer in individuals with schizophrenia and their first-degree relatives (Barak et al., 2005; Hippisley-Cox et al., 2007; Catts et al., 2008) have led to suggestions that some common etiological (Foster and Hoffer, 2004; Levav et al., 2007) or pathophysiological (Androutsellis-Theotakis et al., 2006) factor simultaneously increases the risk of schizophrenia while decreasing the likelihood of cancer. It should be noted, however, that the very finding of a reduced occurrence of cancer in schizophrenia has been questioned (Dalton et al., 2004; Goldacre et al., 2005) and several confounding factors impede a valid assessment of the association. There have been similar reports of a reduced occurrence of rheumatoid arthritis (Oken and Schulzer, 1999) and type 1 diabetes mellitus (Hannu et al., 2007) and conversely there have been reports of an increased occurrence of celiac disease (Kalaydjian et al., 2006) and a range of autoimmune diseases (Eaton et al., 2006) in conjunction with schizophrenia. While caution is necessary in their evaluation in view of ascertainment and selection biases in many of the studies, these findings may generate testable new hypotheses about the etio-pathophysiology of schizophrenia.

3.26. Impact of schizophrenia on individual quality of life and society at large

Schizophrenia is one of the most disabling psychiatric disorders with profound effects on affected individuals and their families. Its impact on society is disproportionately large in comparison to its prevalence of less than 1% because of the many associated functional impairments and the variable and partial efficacy of the range of currently-available treatments for the illness. There is significant diversity in individual outcomes, however, and as discussed in a previous section, varying degrees of recovery are observed in a large number of affected patients. Schizophrenia is associated with significantly increased likelihood of unemployment and homelessness (Thornicraft et al., 2004; Folsom et al., 2005; Rosenheck et al., 2006); although rates are context-dependent, less than one-fifth of affected individuals are fully employed. About two-thirds of affected persons have never been married and reduced contact with families and having few friends characterizes most of their lives. Increased severity of various symptom dimensions reduces both objective and subjective measures of individual quality of life (Eack and Newhill, 2007), with depressive and negative symptoms most strongly linked to reduced subjective sense of well-being and severity of cognitive and negative symptoms most robustly linked to impairments in function (Green, 1996; Narvaez et al., 2008). In comparison to families of patients with other chronic diseases, families of patients with schizophrenia report higher subjective and objective burden in conjunction with lower support from the social network and professionals (Magliano et al., 2005). Both subjective and objective aspects of individual quality of life and perceived family burden are substantially affected by access to evidence-based treatments, quality of available social supports, financial circumstances, and close relationships.

From a societal perspective, schizophrenia is an extremely costly illness principally because of the substantially reduced productivity of affected individuals along with the associated homelessness and unemployment, and high medical comorbidity and substance abuse (Murray and Lopez, 1996; Carr et al., 2004; Wu et al., 2005; Hu, 2006; Kooyman et al., 2007). The continuing stigmatization and increasing incarceration of individuals with schizophrenia (Corrigan et al., 2004; Read et al., 2006) substantially adds to the individual and societal costs of schizophrenic illness.

4. Reconceptualizing schizophrenia

The authors propose that while it is premature to dump the very concept of schizophrenia, it is necessary to discard the current construct, disassemble its components, and reconstruct a more valid and meaningful entity.

Given the extreme heterogeneity across its clinical expression, as also its etiology and pathophysiology as discussed in previously published articles in this series (Keshavan et al., 2008; Tandon et al., 2008b), some have suggested that it is time to completely abandon the construct of schizophrenia (Bentall et al., 1988; Craddock and Owen, 2005; Greene, 2007)? In support of this approach, it should be noted that despite vigorous study over the past century, the etiology and pathophysiology of the disease entity “schizophrenia” remain

relatively obscure and available treatments are only modestly effective. Perhaps, the very notion of schizophrenia is now impeding meaningful scientific inquiry and development of specific treatments, and it is time for us as a field to jettison the concept altogether. Before that is done, however, it would be necessary to examine what we might be giving up and compare the strengths and weaknesses of alternative paradigms.

Does the construct of schizophrenia tell us anything useful? At a minimum, a diagnosis of schizophrenia does distinguish a clinical profile (Table 1) of a chronic illness with psychotic symptoms and cognitive deficits that is generally responsive to antipsychotic treatment but with incomplete remissions, is manifested by an admixture of cognitive, positive, negative, motor and mood symptoms, and is characterized by a range of neurobiological abnormalities which have been linked to putative etiological factors (Keshavan et al., 2008; Tandon et al., 2008b). Second, schizophrenia satisfies criteria for a valid diagnostic entity (Robins and Guze, 1970) better than almost any other psychiatric diagnosis: for example, the diagnosis is one of the most stable in individuals across time irrespective of study population, study setting, or diagnostic criteria utilized (Kendell, 1974; Maziade et al., 1996; Peralta and Cuesta, 2003; Veen et al., 2004; Baca-Garcia et al., 2007; Subramaniam et al., 2007; Fraguas et al., 2008; Haahr et al., 2008; Pihlajamaa et al., 2008). Third, schizophrenia is conceptualized similarly across the world and now consistently demonstrates one of the highest inter-rater diagnostic reliability among all psychiatric diagnoses (Regier et al., 1994; Jakobsen et al., 2006).

A variant of the proposal to abandon the construct of schizophrenia is to retain the concept but call it something else (Levin, 2006; Sato, 2006; Chopra and Doody, 2007; Kingdon et al., 2008). The purported benefits of changing labels in this context may be questionable (Penn and Nowlin-Drummond, 2001) and better elucidating the nature of schizophrenia and developing more effective treatments is more important than semantics (Lieberman and First; 2007). Furthermore, a change in name might suggest that we have newly learned some fundamental truth about schizophrenia; although there is much that we know about schizophrenia, no single fact can be assigned primacy over all others which would warrant such a change in name.

Thus the construct of schizophrenia does convey useful information to patients, clinicians, researchers, and society at large and appears to be a parsimonious concept that currently best provides this volume of information (Wing, 1988; Tandon and Maj, 2008). But it has very serious shortcomings. First, its clinical manifestations are so diverse that its extreme variability has been considered by some to be a core feature (van der Velde, 1976; Wyatt et al., 1988); this *significant heterogeneity must be explained*. Second, schizophrenia is most likely *not a single disease entity*—as discussed in previous papers in this series (Keshavan et al., 2008; Tandon et al., 2008b), there are several etiological factors and pathophysiological mechanisms. Third, its boundaries are ill-defined and it needs to be *better described and demarcated*.

We attempt to better characterize the heterogeneity of schizophrenia by first deconstructing the concept and then reconstructing the derived elements. We additionally consider the syndrome status of schizophrenia. We next attempt to better clarify the boundaries of schizophrenia and suggest some changes in its nosological characterization and taxonomy.

4.1. Heterogeneity is the problem to be solved and not the solution

From the inception of the concept, the heterogeneity of schizophrenia has been well-recognized and there have been several efforts to define its essence while explaining its diverse expression. Kraepelin (1919) considered the end-state (mental dullness or dementia) to be its fundamental characteristic and described different paths to this outcome. Bleuler (1911) considered loosening of association between different psychic functions to be its unifying element while considering other symptoms, course, and outcome to be variable. Jaspers (1946), operationalized by Schneider (1959), considered "un-understandability" to be its hallmark while other elements were variable. Current diagnostic criteria (ICD-10, World Health Organization, 1992; DSM-IV-TR, American Psychiatric Association, 2000) describe requisite clinical features while attempting to explain its heterogeneity by subclassifying schizophrenia into the following "traditional" subtypes originally defined by Kraepelin: (i) *Catatonic type* is characterized by marked psychomotor disturbance involving stupor, negativism, rigidity, excitement, and posturing; (ii) *Disorganized type* is associated with marked loosening of associations, incoherence, grossly disorganized behavior, and flat or grossly inappropriate affect; (iii) *Paranoid type* is characterized by preoccupation with one or more systematized delusions or presence of frequent hallucinations related to a single theme; (iv) *Schizoaffective type* is associated with an admixture of prominent mood disturbance in conjunction with psychotic symptomatology; (v) *Undifferentiated type* is considered when a patient presents with psychotic symptoms that meet criteria for schizophrenia but not for any specific subtype; (vi) *Residual type* is diagnosed by the occurrence of at least one prior episode of florid phase of schizophrenia with a current clinical picture free from prominent psychotic symptoms, but with minimal 'residual' symptoms of the illness (principally cognitive and negative symptoms); Additionally, ICD-10 but not DSM-IV-TR include two additional subtypes: (vii) *simple schizophrenia,* diagnosed by gradual onset of amotivation in the absence of prominent delusions and hallucinations; and (viii) *latent schizophrenia,* characterized by marked aloofness and odd behaviors (similar to DSM-IV-TR schizotypal personality disorder).

The clinical and research utility of these traditional subtypes is limited. Clinically, these subtypes of schizophrenia are unstable over the course of the illness (Fenton and McGlashan, 1991; Deister and Marneros, 1992; van der Does et al., 1993; Helmes and Landmark, 2003) and do not discriminate between patients with regard to treatment response or prognosis (Regier, 2007; Suvisaari et al., 2009). Additionally, these traditional subtypes do not serve to usefully explain the etiological or pathophysiological heterogeneity of schizophrenia (Kendler et al., 1988; Tsuang and Faraone, 1995; Jablensky, 2006; Peralta and Cuesta, 2007; Fanous and Kendler, 2008). In view of the fact that these traditional subtypes of schizophrenia have proved to be of little clinical or research utility, we suggest that they should be abandoned.

Alternative dichotomous approaches to subtyping schizophrenia have been proposed: these include process-reactive, good prognosis versus bad prognosis, early- versus late-onset,

positive versus negative, developmental versus degenerative, Kraepelinian versus non-Kraepelinian, deficit versus non-deficit. These too have been found to be inadequate in substantially explaining the heterogeneity of the disorder (Roy et al., 2001). In the past, heterogeneity of the disorder has been frequently invoked as an explanation of failure to replicate one or other neurobiologic finding in schizophrenia. We argue that heterogeneity is to be tackled as the problem to be solved, and not used as a solution to explain away unexpected findings.

How does one unravel the significant heterogeneity "intrinsic" to schizophrenia? We suggest that (a) cross-sectional heterogeneity in clinical expression may be resolved by identification of distinct psychopathological dimensions; (b) etiological and pathophysiological heterogeneity may best be elucidated by delineating clear pathways mapping the phenotypic dimensions thus identified to markers of biological processes (intermediate phenotypes or endophenotypes) and eventually to the causative etiological factors (Allen et al., 2009); and (c) longitudinal heterogeneity in course may be understood by characterizing stages of schizophrenic illness interacting with the pathoplastic effects of development, aging, and neural repair processes (these were discussed in the third paper in this series, Keshavan et al., 2008). Therapeutic interventions (to be discussed in the next planned paper in the series) and social environment (discussed above) can additionally modify the clinical expression of schizophrenia and "extrinsically" compound this heterogeneity. Fig. 3 illustrates the dimensional approach to addressing cross-sectional heterogeneity and the clinical staging approach to resolving heterogeneity in course and outcome.

4.2. Dimensions of schizophrenia and Intermediate phenotypes (Endophenotypes)

The clinical features of schizophrenia can be deconstructed into a range of dimensions (positive, negative, disorganization, cognitive, mood, motor), the severity and relative proportions of which can vary across patients and through the course of the illness (Fig. 3). As discussed in a previous section, these symptom clusters have been broadly replicated across a large number of patient cohorts at various stages of schizophrenic illness using a wide range of assessment tools. Additionally, these dimensions show significant familiality and discriminate with regard to course

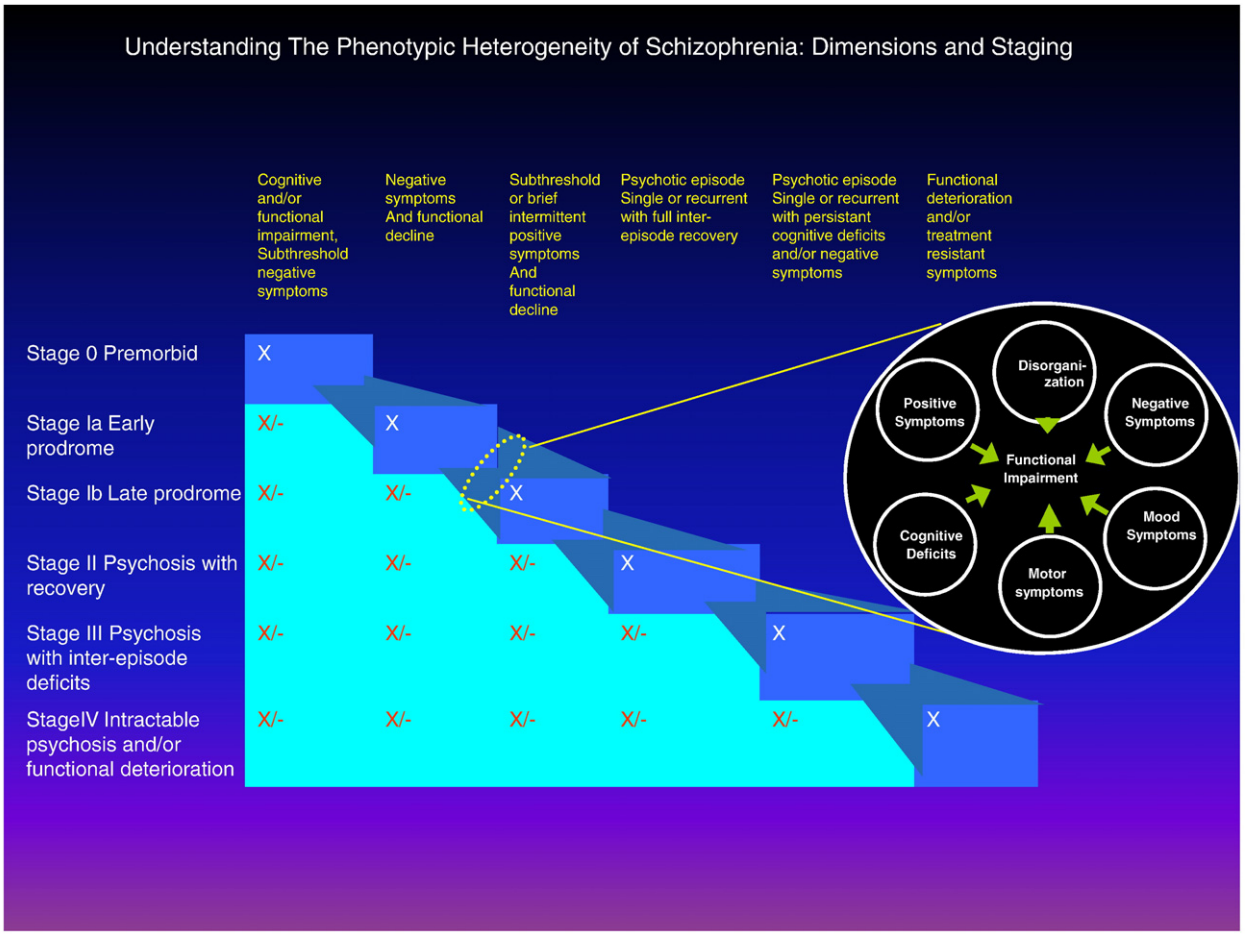


Fig. 3. Phenotypic heterogeneity of cross-sectional presentation and longitudinal course can best be resolved by the Dimensional approach to psychopathology (the six symptom clusters in black circles) and the Staging approach to illness evolution/course respectively.

and treatment response. The dimensions are analogous to the subtypes (positive-paranoid; negative-simple; disorganization-disorganized; mood-schizoaffective; motor-catatonic) with one important difference—instead of persons with schizophrenia expressing just one syndrome (*subtyping*), they express varying proportions of different symptom complexes (*dimensions*).

These symptom dimensions, in turn, may reflect distinct etio-pathogenetic processes associated with distinct risk factors (etiology) (Rietkirk et al., 2008) and marked by measurable components that serve as "footholds" along the pathophysiological pathway from etiology to clinical expression (intermediate phenotypes or endophenotypes) (Gottesman and Gould, 2003; Preston and Weinberger, 2005; Owen et al., 2007; Braff et al., 2008; Keshavan et al., 2008; Allen et al., 2009). Endophenotypes, in turn, may better define more specific treatment targets (Thaker, 2007). As we plan to elaborate in a subsequent paper in this series, risk factors (genetic and environmental) likely modify neuro-biological processes (marked by endophenotypes) that, in turn, lead to the expression of symptom domains. Individual clinical presentation and course are additionally influenced by the phase of brain development, interaction with restitutive processes, stage of illness evolution, in conjunction with the effects of the environment and treatment.

4.3. Is schizophrenia one disease or many?

If the clinical diversity in schizophrenia can thus be successfully mapped to pathophysiological and etiological heterogeneity, questions of the utility of this illness as a unitary disease construct will inevitably arise. As discussed previously, schizophrenia is probably neither a single disease entity and nor is it a circumscribed syndrome—it is likely to be a conglomeration of phenotypically similar disease entities and syndromes. Given current knowledge, however, these entities cannot be distinguished or demarcated. As the psychopathologic dimensions are mapped on to intermediate phenotypes and related etiological factors (i.e., "extended endophenotypes", Prasad and Keshavan, 2008) with distinct course and treatment response profiles, it will enable the reconstruction of schizophrenia as a "group" of biologically valid disease entities (e.g., Bleuler, 1911).

4.4. Longitudinal heterogeneity and staging of illness

The poor validity of our characterization of schizophrenia and explanation of its heterogeneity is, in part, because it is principally based on the cross-sectional presentation of the illness. It is well-known, however, that different psychopathological dimensions of schizophrenia vary in their longitudinal course (discussed in a previous section) and evolve during the natural course of the illness (Fig. 3). A more useful framework, used with success elsewhere in other chronic disease clusters in medicine (such as malignancies, osteomyelitis, and hypertension), is the delineation of discrete stages of an illness and the development of operational criteria to define these stages. Clinical staging attempts to define the degree of disease progression in an individual patient at a given point in time and thereby places the individual at a specific position along the continuum of illness course; different locations are putatively associated with differences in prognosis, optimal treatment, and pathology. As originally proposed for Hodgkin's disease, staging was based completely on clinical criteria. Currently, clinicopathological staging which combines information from clinical examination with that from pathological and radiological test results (e.g., biopsy, imaging, blood tests) is more common. It was first introduced to psychiatric disorders by Fava and Kellner (1993) who proposed the utility of staging for anxiety and mood disorders. McGorry (2007, 2008) has since developed a staging system for psychotic disorders. We suggest the addition of neurobiological changes to clinical criteria as part of such staging (Keshavan et al., 2008; Lawrie et al., 2008) and the articulation of specific prognostic and treatment implications of these distinct stages; these, in turn, should lend themselves to testing and falsification (Popper, 1959; Carpenter, 2004).

Defined stages of schizophrenia should map the known variations in the course of schizophrenic illness, have operationalized criteria, and have clear treatment and prognostic implications. Fig. 3 incorporates criteria adapted from McGorry et al. (2006), which additionally lend themselves to easy clinical and research application. Different pharmacological and psychosocial prevention and treatment approaches might be more useful at different stages of the illness. The premorbid stage (stage 0, Fig. 3) defines the presence of varying degrees of risk for developing schizophrenia (based on genetic features, environmental exposures, behavior, and social function) but without any clinical evidence of schizophrenia itself. The implication is that reducing the "psychosis load" may decrease the risk of developing schizophrenia (Compton, 2004; van Os and Delespaul, 2005). Those with identifiable risk factors for developing schizophrenia may particularly benefit from targeted approaches to reduce other risk factors or enhance protective factors (Lee et al., 2005). Additionally, population-level strategies (Mojtabai et al., 2003; Cannon and Clarke, 2005) would be of particular importance in reducing overall risk.

The prodrome (stages Ia and b, Fig. 3) defines the clinical expression of some of these risk factors and the manifestation of basic or sub-threshold psychotic symptoms (stages Ia and Ib, respectively). Presumably, a specified set of interventions may prevent the progression to psychosis (Lee et al., 2005). The prodrome thus potentially represents a reversible stage in the early evolution of schizophrenia, with stage Ia (early prodrome) being less likely to devolve into schizophrenia than the later stage Ib (late prodrome). Antidepressant medications (Cornblatt et al., 2007), GABA-ergic agents (Geffen et al., 2009), cognitive-behavior therapy (McGorry et al., 2006), and low-dose antipsychotics in the late prodrome (McGorry et al., 2006) may be of particular utility in this stage of the illness.

Stage II (Fig. 3) indicates the prior occurrence of at least one full psychotic episode without any discernible deterioration during remission. The implication is that although the threshold for psychosis has been crossed, the deterioration generally associated with schizophrenia has not occurred. Clinical staging of psychotic disorders has thusfar been principally applied to early detection and treatment of schizophrenic illness (prodrome or initial psychotic episode) (Hafner and Maurer, 2006; Lieberman et al., 2006; Riecher-Rossler et al., 2006; Salokangas and McGlashan, 2008) with a

view to more benignly "reshape the course" of the psychotic disorder (Cannon, 2008).

Stage III (Fig. 3) denotes the appearance of inter-episode deficits in conjunction with psychosis. The implication is that while some irreversible deficits associated with schizophrenia have occurred, additional potentially preventable deterioration can still occur and this warrants effective control of psychosis to limit such deterioration. Stage IV (Fig. 3) implies that substantial deterioration may have occurred and that treatments can at best be symptomatic and rehabilitative.

The proposed clinical staging should be supplemented by imaging and other neurobiological criteria (Wood et al., 2006; Keshavan et al., 2008; Wood et al., 2008) to enhance their utility.

4.5. Diagnostic criteria for schizophrenia and ICD-11/DSM-V nosology

The nosological boundaries between schizophrenia and other psychiatric disorders remain blurred despite several changes in diagnostic criteria over the past century (Adler and Strakowski, 2003). Boundaries remain blurred between schizophrenia on the one hand, and personality disorder, developmental disorders, mood disorders, substance-induced psychotic disorders, and other psychotic disorders. Nowhere are such indistinct boundaries more hotly debated than between schizophrenia and the mood disorders. For example, a "point of rarity" between schizophrenia and affective disorders, needed for clear demarcation between these disorders, is not demonstrable (Kendell and Brockington 1980) and observations from neurobiological and genetic research also belie such blurred boundaries (Owen et al 2007). Schizoaffective disorder, defined as a distinct entity between schizophrenia and major mood disorders, remains a conundrum. Because of its low reliability and longitudinal stability along with its limited clinical utility (Schwartz et al., 2000; Jager et al., 2004; Vollmer-Larsen et al., 2006; Cheniaux et al., 2008), we recommend that this diagnostic category be deleted from DSM-V and ICD-11 (Malhi et al., 2008; Tandon and Maj, 2008). Instead, the many patients who present with an admixture of psychotic and mood symptoms could be better characterized by precisely describing the severity of mood and psychotic dimensions over the course of the illness while receiving a diagnosis of either a psychotic mood disorder or schizophrenia. This would be far more useful and informative from both a clinical and research perspective.

As discussed in a previous section, the current subtypes of schizophrenia in DSM-IV-TR and ICD-10 should be deleted. Instead, the heterogeneity of schizophrenia is better described by clinical dimensions (Regier, 2007; Fiedorowicz et al., 2008) and staging (as discussed above). Both the symptom dimensions and stages of schizophrenia should be clearly operationalized and validated instruments to simply and reliably assess them formalized.

Schizotypal personality disorder represents another important boundary problem. Even as a genetic relationship to schizophrenia is suggested (Siever and Davis, 2004; Seeber and Cadenhead, 2005), its relationship to the schizophrenia prodrome needs to be better clarified. The boundaries with developmental disorders and substance-induced psychotic disorders were discussed in previous sections.

5. In conclusion

The clinical characterization of schizophrenia is marked by several paradoxes. It is very unlikely to be a unitary disease entity and yet it appears to be one of the best validated psychiatric diagnoses. Despite the absence of pathognomonic clinical features or specific laboratory tests, it has high inter-rater diagnostic reliability and universally accepted broad prognostic and treatment implications. We know enough about the present construct of schizophrenia to recognize that it may be a conglomeration of disparate entities but our current knowledge is insufficient to delineate them. Only a better dissection of the elements of schizophrenia and a testable hypothesis-driven reformulation will elucidate its basic nature and enable its more precise definition. As reviewed in this article, we have accumulated a substantial amount of information about the clinical expression of schizophrenia. Yet, many important questions remain. We propose a rigorous dimensional/endophenotype approach in conjunction with clinical staging to explain the significant heterogeneity of schizophrenic illness. As with any other hypothesis, it needs to be meticulously evaluated to assess its broad utility and applicability.

As we digest the known clinical facts of schizophrenia, it is useful to recall the following admonition from Lichtenberg 200 years ago "Nothing is more inimical to the progression of science than the belief that we know what we do not yet know" (Lichtenberg, 2000).

Role of funding source

Independently prepared by authors. No external funding.

Contributors

Contributors to research and writing of manuscript. Rajiv Tandon, Henry Nasrallah, and Matcheri Keshavan.

Conflict of interest

This statement was independently developed by Rajiv Tandon, Matcheri S. Keshavan, and Henry A. Nasrallah.

Acknowledgements

We acknowledge the tens of thousands of patients who have taught us what really matters in schizophrenia and our clinical and research colleagues who continually help us sharpen our thinking about its essential nature.

References

Achim, A.M., LePage, M., 2005. Episodic memory-related activation in schizophrenia: meta-analysis. Br. J. Psychiatry 187, 500–509.

Addington, J., Cadenhead, K.S., Cannon, T.D., et al., 2007. North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. Schizophr. Bull. 33, 665–672.

Adler, C.M., Strakowski, S.M., 2003. Boundaries of schizophrenia. Psychiatr. Clin. N. Am. 26, 1–23.

Aleman, A., Agrawal, N., Morgan, K.D., David, A.S., 2006. Insight in psychosis and neuropsychological function: meta-analysis. Br. J. Psychiatry 189, 204–212.

Aleman, A., Hijman, R., de Haan, E.H., et al., 1999. Memory impairment in schizophrenia: a meta-analysis. Am. J. Psychiatry 156, 1358–1366.

Aleman, A., Kahn, R.S., 2005. Strange feelings: do amygdale abnormalities dysregulate the emotional brain in schizophrenia? Progr. Neurobiol. 77, 283–298.

Allen, A.J., Griss, M.E., Folley, B.S., et al., Endophenotypes in schizophrenia: a selective review. Schizophr. Res.,2009; in press.

Alves, T.M., Pereira, J.C.R., Elkis, H., 2005. The psychopathological factors of refractory schizophrenia. Rev. Bras. Psiquiatr. 27, 108–112.

Amador, X.F., David, A.S. (Eds.), 1998. Insight and Psychosis. Oxford University Press, New York.

American Psychiatric Association, 1968. Diagnostic and Statistical Manual of Mental Disorders, 2nd edition. American Psychiatric Association, Washington D.C. (DSM-II).

American Psychiatric Association, 1980. Diagnostic and Statistical Manual of Mental Disorders, 3rd edition. American Psychiatric Association, Washington D.C. (DSM-III).
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. American Psychiatric Association, Washington D.C. Text Revision (DSM-IV-TR).
Andreasen, N.C., 1979. Thought, language, and communication disorders: I. Clinical assessment, definition of terms, and evaluation of their reliability. Arch. Gen. Psychiatry 36, 1315–1321.
Andreasen, N.C., 1982. Negative symptoms in schizophrenia. Definition and reliability. Arch. Gen. Psychiatry 39, 784–788.
Andreasen, N.C., 2007. DSM and the death of phenomenology in America: an example of unintended consequences. Schizophr. Bull. 33, 108–112.
Andreasen, N.C., Carpenter, W.T., Kane, J.M., et al., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatry 162, 441–449.
Androutsellis-Theotokis, A., Leker, R.R., Soldner, F., et al., 2006. Notch signaling regulates stem cell numbers in vitro and in vivo. Nature 442, 823–826.
Angermeyer, M.C., Kuhn, L., 1988. Gender differences in age at onset of schizophrenia. An overview. Eur. Arch. Psychiatry Neurol. Sci. 237, 351–364.
Arnold, S.E., Han, L.Y., Moberg, P.J., et al., 2001. Dysregulation of olfactory receptor neuron lineage in schizophrenia. Arch. Gen. Psychiatry 58, 829–835.
Atanasova, B., Graux, J., El Hage, W., et al., 2008. Olfaction: a potential cognitive marker of psychiatric disorders. Neurosci. Biobehav. Rev. 32, 1315–1325.
Auquier, P., Lancon, C., Rouillon, F., Lader, M., 2007. Mortality in schizophrenia. Pharmacoepidemiol. Drug Saf. 16, 1308–1312.
Aylward, E., Walker, E., Bettes, B., 1984. Intelligence in schizophrenia: meta-analysis of the research. Schizophr. Bull. 10, 430–459.
Baca-Garcia, E., Perez-Rodriguez, M.M., Basurte-Villamor, I., et al., 2007. Diagnostic stability of psychiatric disorders in clinical practice. Br. J. Psychiatry 190, 210–216.
Barak, Y., Achiron, A., Mandel, M., et al., 2005. Reduced cancer incidence among patients with schizophrenia. Cancer 104, 2817–2821.
Barch, D.M., Braver, T.S., Carter, C.S., et al., 2003. Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. J. Abnorm. Psychology 112, 132–143.
Barch, D.M., Smith, E., 2008. The cognitive neuroscience of working memory: relevance to CNTRICS and schizophrenia. Biol. Psychiatry 64, 11–17.
Bartels, S.J., Drake, R.E., 1988. Depressive symptoms in schizophrenia: comprehensive differential diagnosis. Compr. Psychiatry 29, 467–483.
Beiser, M., Erickson, D., Fleming, J.A.E., Iacono, W.G., 1993. Establishing the onset of psychotic illness. Am. J. Psychiatry 150, 1349–1354.
Bell, R.C., Dudgeon, P., McGorry, P.D., Jackson, H.J., 1998. The dimensionality of schizophrenia concepts in first-episode psychosis. Acta Psychiatr. Scand. 97, 334–342.
Bentall, R.P., Jackson, H.F., Pilgrim, D., 1988. Abandoning the concept of 'schizophrenia'. Br. J. Clin. Psychol. 27, 303–324.
Bermanzohn, P.C., Porto, L., Arlow, P.B., et al., 2000. Hierarchical diagnosis in chronic schizophrenia: a clinical study of co-occurring syndromes. Schizophr. Bull. 26, 517–525.
Berrios, G.E., Hauser, R., 1988. The early development of Kraepelin's ideas on classification: a conceptual history. Psychol. Med. 18, 813–821.
Bhaumik, S., Tyrer, F.C., McGrother, C., Ganghadaran, S.K., 2008. Psychiatric service use and psychiatric disorders in adults with intellectual disability. J. Intell. Disability Res. 52, 986–995.
Bilder, R.M., Reiter, G., Bates, J., et al., 2006. Cognitive development in schizophrenia: follow-back from the first episode. J. Clin. Experiment Neuropsychol. 28, 270–282.
Bleuler, E., Dementia Praecox, or the group of Schizophrenias, 1911. Translated by J Zinkin, International University Press, New York, 1950.
Bleuler, M., 1972. The Schizophrenic Disorders. Yale University Press, New Haven.
Boks, M.P.M., Leask, S., Vermunt, J.K., Kahn, R.S., 2007. The structure of psychosis revisited: the role of mood symptoms. Schizophr. Res. 93, 178–185.
Bombin, I., Arango, C., Buchanan, R.W., 2005. Significance and meaning of neurological signs in schizophrenia: two decades later. Schizophr. Bull. 31, 962–977.
Bonnot, O., Tanguy, M.L., Consoli, A., et al., 2008. Does catatonia influence the phenomenology of childhood onset schizophrenia beyond motor symptoms? Psychiatry Res. 158, 356–362.
Bowie, C.R., Leung, W.W., Reichenberg, A., et al., 2008. Predicting schizophrenia patients' real world behavior with specific neuropsychological and functional capacity measures. Biol. Psychiatry 63, 505–511.
Braff, D.L., Greenwood, T.A., Swerdlow, N.R., et al., 2008. Advances in endophenotyping schizophrenia. World Psychiatry 7, 11–18.
Braga, R.J., Petrides, G., Fifueira, I., 2004. Anxiety disorders in schizophrenia. Compr. Psychiatry 45, 460–468.
Bramon, E., Walshe, M., McDonald, C., et al., 2005. Dermatoglyphics and schizophrenia: a meta-analysis and investigation of the impact of obstetric complications upon a–b ridge count. Schizophr. Res. 75, 399–404.
Breier, A., Schreiber, J.L., Dyer, J., Pickar, D., 1991. National Institute of Mental Health Longitudinal Study of Chronic Schizophrenia. Prognosis and predictors of outcome. Arch. Gen. Psychiatry 48, 239–246.
Brewer, W.J., Wood, S.J., McGorry, P.D., et al., 2003. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am. J. Psychiatry 160, 1790–1794.
Brown, G.W., Birley, J.L.T., Wing, J.K., 1972. Influence of family life on the course of schizophrenic disorders: a replication. Br. J. Psychiatry 121, 241–258.
Brown, S., 1997. Excess mortality in schizophrenia. A meta-analysis. Br. J. Psychiatry 171, 502–508.
Brown, S., Inskip, H., Barraclough, B., 2000. Causes of the excess mortality of schizophrenia. Br. J. Psychiatry 177, 212–217.
Burns, T., 2007. Evolution of outcome measures in schizophrenia. Br. J. Psychiatry 191 (Suppl.50), S1–S6.
Butzlaff, R.L., Hooley, J.M., 1998. Expressed emotion and psychiatric relapse: a meta-analysis. Arch. Gen. Psychiatry 55, 547–552.
Cameron, D.E., 1938. Early schizophrenia. Am. J. Psychiatry 95, 567–578.
Cannon, M., Caspi, A., Moffitt, T.E., et al., 2002. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder. Results from a longitudinal birth cohort. Arch. Gen. Psychiatry 59, 449–456.
Cannon, M., Clarke, M.C., 2005. Risk for schizophrenia-broadening the concepts, pushing back the boundaries. Schizophr. Res. 79, 5–13.
Cannon, T.D., 2008. Neurodevelopment and the transition from schizophrenia prodrome to schizophrenia: research imperatives. Biol. Psychiatry 64, 737–738.
Cannon, T.D., Cadenhead, K., Cornblatt, B., et al., 2008. Prediction of psychosis in youth at high clinical risk. Arch. Gen. Psychiatry 65, 28–37.
Capasso, R.M., Lineberry, T.W., Bostwick, J.M., et al., 2008. Mortality in schizophrenia and schizoaffective disorder: an Olmstead County, Minnesota cohort: 1950–2005. Schizophr. Res. 98, 287–294.
Carney, C.P., Jones, L., Woolson, R.F., 2006. Medical comorbidity in women and men with schizophrenia: a population-based study. J. Gen. Intern. Med. 21, 1133–1137.
Carpenter, W.T., 2004. Clinical constructs and therapeutic discovery. Schizophr. Res. 72, 69–73.
Carpenter, W.T., Heinrichs, D.W., Wagman, A.M.I., 1988. Deficit and nondeficit forms of schizophrenia: the concept. Am. J. Psychiatry 145, 578–583.
Carpenter, W.T., Strauss, J.S., Muleh, S., 1973. Are there pathognomonic symptoms in schizophrenia? An empiric investigation of Schneider's first-rank symptoms. Arch. Gen. Psychiatry 28, 847–852.
Carr, V.J., Lewin, T.J., Neil, A.L., et al., 2004. Premorbid, psychosocial and clinical predictors of the costs of schizophrenia and other psychoses. Br. J. Psychiatry 184, 517–524.
Carroll, A., Fattah, S., Clyde, Z., et al., 1999. Correlates of insight and insight change in schizophrenia. Schizophr. Res. 35, 247–253.
Catts, V.S., Catts, S.V., O'Toole, B.I., Frost, A.D., 2008. Cancer incidence in patients with schizophrenia and their first-degree relatives: a meta-analysis. Acta Psychiatr. Scand. 117, 323–336.
Chan, R.C., Gottesman, 2008. Neurological soft signs as candidate endophenotypes for schizophrenia: a shooting star or a Northern star? Neurosci. Biobehav. Rev. 32, 957–971.
Chapman, J., 1966. The early symptoms of schizophrenia. Br. J. Psychiatry 112, 225–251.
Cheniaux, E., Landeira-Fernandez, J., Lessa Telles, L., et al., 2008. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. J. Affect. Disord. 106, 209–217.
Chopra, A.K., Doody, G.A., 2007. Schizophrenia, an illness and a metaphor: analysis of the use of the term 'schizophrenia' in the UK national newspapers. J. R. Soc. Med. 100, 423–426.
Chwastiak, L.A., Rosenheck, R.A., McEvoy, J.P., et al., 2008. Inter-relationship of psychiatric symptom severity, medical comorbidity, and functioning in schizophrenia. Psychiatr. Serv. 57, 1102–1109.
Ciapparelli, A., Paggini, R., Marazziti, D., et al., 2007. Comorbidity with axis 1 anxiety disorders in remitted psychotic patients 1 year after hospitalization. C.N.S. Spectr. 12, 913–919.
Ciompi, L., 1980. The natural history of schizophrenia in the long term. Br. J. Psychiatry 136, 413–420.
Clarke, M., Whitty, P., Browne, S., et al., 2006. Untreated illness and outcome of psychosis. Br. J. Psychiatry 189, 235–240.
Compton, M.T., 2004. Considering schizophrenia from a prevention perspective. Am. J. Prev. Med. 26, 178–185.
Compton, M.T., Bollini, A.M., Mack, L.M., et al., 2007. Neurological soft signs and minor physical anomalies in patients with schizophrenia and related disorders, their first-degree biological relatives, and non-psychiatric controls. Schizophr. Res. 94, 64–73.
Conley, R.R., Ascher-Svanum, H., Zhu, B., et al., 2007. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. Schizophr. Res. 90, 186–197.

Cooper, J.E., Kendell, R.E., Gurland, B.J., et al., 1972. Psychiatric Diagnosis in New York and London. Oxford University Press, Oxford.
Corcoran, C., Walker, E., Huot, R., et al., 2003. The stress cascade in schizophrenia: etiology and onset. Schizophr. Bull. 29, 671–692.
Cornblatt, B., Obuchowski, M., Roberts, S., et al., 1999. Cognitive and behavioral precursors of schizophrenia. Dev. Psychopathol. 11, 487–508.
Cornblatt, B., Lencz, T., Smith, C.W., et al., 2007. Can antidepressants be used to treat the schizophrenia prodrome? J. Clin. Psychiatry 68, 546–557.
Corrigan, P.W., Markowitz, F.E., Watson, A.C., 2004. Structural levels of mental illness stigma and discrimination. Schizophr. Bull. 30, 481–491.
Cortese, L., Caliguri, M.P., Malla, A.K., et al., 2005. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naïve schizophrenia patients. Schizophr. Res. 75, 65—75.
Craddock, N., Owen, M.J., 2005. The beginning of the end for the Kraepelinian dichotomy. Br. J. Psychiatry 186, 364—366.
Craig, T., Hwang, M.Y., Bromet, E.J., 2002. Obsessive–compulsive and panic symptoms in patients with first-episode psychosis. Am. J. Psychiatry 159, 592–598.
Crow, T.J., 1980. Molecular pathology of schizophrenia: more than one disease process? Br. Med. J. 280, 66–68.
Daban, C., Martinez-Aran, A., Torrent, C., et al., 2006. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. Psychother. Psychosom. 75, 72–84.
Dalton, S.O., Laursen, T.M., Mellemkjaer, L., et al., 2004. Risk for cancer in parents of patients with schizophrenia. Am. J. Psychiatry 161, 903–908.
Dam, J., 2006. Insight in schizophrenia: a review. Nord. J Psychiatry 60, 114–120.
Daumit, G.L., Pronovost, P.J., Anthony, C.B., et al., 2006. Adverse events during medical and surgical hospitalizations for persons with schizophrenia. Arch. Gen. Psychiatry 63, 267–272.
Davidson, L., McGlashan, T.H., 1997. The varied outcomes of schizophrenia. Can. J. Psychiatry 42, 34–43.
Dean, K., Dazzan, P., Lloyd, T., et al., 2007. Minor physical anomalies across ethnic groups in a first-episode psychosis sample. Schizophr. Res. 89, 86–90.
Deister, A., Marneros, A., 1992. Long-term stability of subtypes in schizophrenia disorders: a comparison of four diagnostic systems. Eur. Arch. Psychiatry Clin. Neurosci. 242, 184–190.
de Leon, J., Diaz, F.J., 2005. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr. Res. 76, 135–157.
DeLisi, L.E., 1992. The significance of age of onset for schizophrenia. Schizophr. Bull. 18, 209–215.
Devulapalli, K.K., Welge, J.A., Nasrallah, H.A., 2008. Temporal sequence of clinical manifestation in schizophrenia with co-morbid OCD: review and meta-analysis. Psychiatr. Res. 161, 105–108.
Dickinson, D., Ragland, J.D., Gold, J.M., Gur, R.C., 2008. General and specific cognitive deficits in schizophrenia: Goliath defeats David. Biol. Psychiatry. 64, 823–827.
Dickinson, D., Ramsey, M.E., Gold, J.M., 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch. Gen. Psychiatry 64, 532–542.
Dikeos, D.G., Wickham, H., McDonald, C., et al., 2006. Distribution of symptom dimensions across Kraepelinian divisions. Br. J. Psychiatry 189, 346–353.
Dixon, L., Postrado, L., Delahanty, J., et al., 1999. The association of medical comorbidity in schizophrenia with poor physical and mental health. J. Nerv. Ment. Dis. 187, 496–502.
Docherty, J.P., Van Kammen, D.P., Siris, S.G., Marder, S.R., 1978. Stages of onset of schizophrenic psychosis. Am. J. Psychiatry 135, 420–426.
Done, D.J., Crow, T.J., Johnstone, E.C., Sacker, A., 1994. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. BMJ 309, 699–703.
Donlon, P., Blackmer, K., 1973. Stages of schizophrenic decompensation and reintegration. J. Nerv. Ment. Dis. 157, 200–208.
Dragovic, M., Hammond, G., 2005. Handedness in schizophrenia: a quantitative review of evidence. Acta Psychiatr. Scand. 111, 410–419.
Drake, R.J., Dunn, G., Tarrier, N., et al., 2003. The evolution of symptoms in the early course of nonaffective psychosis. Schizophr. Res. 63, 171–179.
Druss, B.G., Bradford, D.W., Rosenheck, R.A., et al., 2000. Mental disorders and use of cardiovascular procedures after myocardial infarction. J.A.M.A. 283, 506–511.
Druss, B.G., Bradford, D.W., Rosenheck, R.A., et al., 2001. Quality of medical care and excess mortality in older patients with mental disorders. Arch. Gen. Psychiatry 58, 565–572.
Dworkin, R.H., 1994. Pain insensitivity in schizophrenia: a neglected phenomenon and some implications. Schizophr. Bull. 20, 235–248.
Eack, S.M., Newhill, C.E., 2007. Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. Schizophr. Bull. 33, 1225–1237.
Eaton, W.W., Byrne, M., Ewald, H., 2006. Association of schizophrenia and auto-immune diseases: linkage of Danish national registers. Am. J. Psychiatry 163, 521–528.
Emsley, R., Turner, H.J., Oosthuizen, P.P., Carr, J., 2005. Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical and outcome correlates. Schizophr. Res. 75, 35–44.
Erhart, S.M., Marder, S.R., Carpenter, W.T., 2006. Treatment of schizophrenia negative symptoms: future prospects. Schizophr. Bull. 32, 234–237.
Falret, J., 1854. Lecons Cliniques de Medicine Mentale. Bailliere, Paris.
Fanous, A.H., Kendler, K.S., 2008. Genetics of clinical features and subtypes of schizophrenia: a review of the recent literature. Current Psychiatry Reports 10, 164–170.
Farooq, S., Large, M., Nielssen, O., Waheed, W., The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta-analysis. Schizophr. Res., in press.
Fava, G.A., Kellner, R., 1993. Staging: a neglected dimension in psychiatric classification. Acta Psychiatr. Scand. 87, 225–230.
Fenton, W.S., 2000. Depression, suicide, and suicide prevention in schizophrenia. Suicide Life-Threat. Behav. 30, 34–49.
Fenton, W.S., McGlashan, T.H., 1991. Natural history of schizophrenia subtypes. 1. Longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. Arch. Gen. Psychiatry 48, 969–977.
Fiedorowicz, J.G., Epping, E.A., Flaum, M., 2008. Toward defining schizophrenia as a more useful clinical construct. Curr. Psychiatry Rep. 10, 344–351.
Fioravanti, M., Carlone, O., Vitale, B., et al., 2005. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. Neuropsychol. Rev. 15, 73–95.
First, M.B., 2005. Mutually exclusive versus co-occurring diagnostic categories: the challenge of diagnostic comorbidity. Psychopathology 38, 206–210.
Fish, B., Marcus, J., Hans, S.L., et al., 1992. Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. Arch. Gen. Psychiatry 49, 221–235.
Fleischhacker, W.W., Cetkovich-Bakmas, M., De Hert, M., et al., 2008. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. J. Clin. Psychiatry 69, 514–519.
Flyckt, L., Mattsson, M., Edman, G., et al., 2006. Predicting 5-year outcome in first-episode psychosis: construction of a prognostic rating scale. J. Clin. Psychiatry 67, 916–924.
Folsom, D.P., Hawthorne, W., Lindamer, L., et al., 2005. Prevalence and risk factors for homelessness and utilization of mental health services among 10,340 patients with serious mental illness in a large public mental health system. Am. J. Psychiatry 162, 370–376.
Foster, H.D., Hoffer, A., 2004. Schizophrenia and cancer: the adrenochrome balanced morphism. Med. Hypotheses 62, 415–419.
Fraguas, D., de Castro, M.J., Medina, O., et al., 2008. Does diagnostic classification of early-onset psicosis change over follow-up? Child Psychiatry Hum. Dev. 39, 137–145.
Fresan, A., Apiquian, R., de la Fuente-Sandoval, C., et al., 2005. Violent behavior in schizophrenic patients: relationship with clinical symptoms. Agg. Behav. 31, 511–520.
Fusar-Poli, P., Perez, J., Broome, M., et al., 2007. Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 31, 465–484.
Gabalda, M.K., Weiss, P.S., Compton, M.T., 2008. Frontal release signs among patients with schizophrenia, their first-degree biological relatives, and non-psychiatric controls. Schizophr. Res. 106, 275–280.
Gaebel, W., Frommann, N., 2000. Long-term course in schizophrenia: concepts, methods, and research strategies. Acta Psychiatr. Scand. 102 (Suppl.407), 49–53.
Gaebel, W., Riesbeck, M., 2007. Revisiting the relapse predictive validity of prodromal symptoms in schizophrenia. Schizophr. Res. 95, 19–29.
Geffen, Y., Nudelman, A., Gil-Ad, I., et al., 2009. BL-1020: a novel antipsychotic drug with GABAergic activity and low catalepsy, is efficacious in a rat model of schizophrenia. Eur. Neuropsychopharmacol. 19, 1–13.
Goff, D.C., Cather, C., Evins, A.E., et al., 2005. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. J. Clin. Psychiatry 66, 183–194.
Goldacre, M.J., Kurina, L.M., Wotton, C.J., et al., 2005. Schizophrenia and cancer: an epidemiological study. Br. J. Psychiatry 187, 334–338.
Goldstein, J.M., 1988. Gender differences in the course of schizophrenia. Am. J. Psychiatry 145, 684–689.
Goodwin, R.D., Amador, X.F., Malaspina, D., et al., 2003. Anxiety and substance abuse comorbidity among inpatients with schizophrenia. Schizophr. Res. 61, 89–95.
Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 636–645.
Green, A.I., Drake, R.E., Brunette, M.F., Noordsy, D.L., 2007. Schizophrenia and co-occurring substance use disorder. Am. J. Psychiatry 164, 402–408.
Green, A.I., Tohen, M., Hamer, R.M., et al., 2004. First-episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr. Res. 66, 125–135.
Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.

Greene, T., 2007. The Kraepelinian dichotomy: the twin pillars crumbling? Hist. Psych. 18, 361–379.
Griesinger, W., 1861. Die Pathologie und therapie der Psychischen Krankheiten. Krabbe, Stuttgart.
Gross, G., 1997. The onset of schizophrenia. Schizophr. Res. 28, 187–198.
Grossman, L.S., Harrow, M., Rosen, C., et al., 2008. Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. Compr. Psychiatry 49, 523–529.
Grube, B.S., Bilder, R.M., Goldman, R.S., 1998. Meta-analysis of symptom factors in schizophrenia. Schizophr. Res. 31, 113–120.
Haahr, U., Larsen, T.K., Melle, I., et al., 2008. First-episode psychosis: diagnostic stability over one and two years. Psychopathology 41, 322–329.
Hafner, H., an der Heiden, W., 1999. The course of schizophrenia in the light of modern follow-up studies: the ABC and WHO studies. Eur. Arch. Psychiatry Clin. Neurosci. 249 (Suppl 4), 14–26.
Hafner, H., an der Heiden, W., Behrens, S., et al., 1998. Causes and consequences of the gender differences in age of onset of schizophrenia. Schizophr. Bull. 24, 99–113.
Hafner, H., Maurer, K., 2006. Early detection of schizophrenia: current evidence and future perspectives. World Psychiatry 5, 130–138.
Hannu, J., Reunanen, A., Haukka, J., et al., 2007. Incidence of schizophrenia in a nationwide cohort of patients with Type 1 diabetes mellitus. Arch. Gen. Psychiatry 64, 894–899.
Harding, C.M., Brooks, G.W., Ashikaga, T., et al., 1987. The Vermont longitudinal study of persons with severe mental illness, II: Long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. Am. J. Psychiatry 144, 727–735.
Haro, J.M., Novick, D., Suarez, D., et al., 2008. Predictors of the course of illness in outpatients with schizophrenia: a prospective three year study. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1287–1292.
Harris, E.C., Barraclough, B., 1998. Excess mortality of mental disorder. Br J Psychiatry 173, 11–53.
Harrison, G., Hopper, K., Craig, T., et al., 2001. Recovery from psychotic illness: a 15- and 25-year international follow-up study. Br J Psychiatry 178, 506–517.
Harvey, P.D., Green, M.F., Bowie, C., Loebel, A., 2006. The dimensions of clinical and cognitive change in schizophrenia. Psychopharmacology 187, 356–363.
Hawton, K., Sutton, L., Haw, C., et al., 2005. Schizophrenia and suicide: systematic review of risk factors. Br. J. Psychiatry 187, 9–20.
Hecker, E., 1871. Die Hebephrenie. Ein Beitrag zur klinischen Psychiatrie. Archiv fur pathologische Anatomie und Physiologie und fur klinische Medicin 25, 394–429.
Hegarty, J.D., Baldessarini, R.J., Tohen, M., et al., 1994. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 151, 1409–1416.
Heinrichs, D.W., Buchanan, R.W., 1988. Significance and meaning of neurological signs in schizophrenia. Am. J. Psychiatry 145, 11–18.
Heinrichs, R.W., 2005. The primacy of cognition in schizophrenia. Am Psychol 60, 229–242.
Heinrichs, R.W., Ammari, N., Vaz, S.M., Miles, A.A., 2008. Are schizophrenia and schizoaffective disorder neuropsychologically distinguishable? Schizophr Res 99, 149–154.
Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12, 426–445.
Helmes, E., Landmark, J., 2003. Subtypes of schizophrenia: a cluster analytic approach. Can J Psychiatry 48, 702–708.
Hennen, J., Baldessarini, R.J., 2005. Suicidal risk during treatment with clozapine: a meta-analysis. Schizophr. Res. 73, 139–145.
Henry, J.D., Crawford, J.R., 2005. A meta-analytic review of verbal fluency deficits in schizophrenia relative to other neurocognitive deficits. Cognit Neuropsychiatry 10, 1–33.
Hippisley-Cox, J., Vinogradova, Y., Coupland, C., Parker, C., 2007. Risk of malignancy in patients with schizophrenia or bipolar disorder. Arch Gen Psychiatry 64, 1368–1376.
Ho, B.C., Mola, C., Andreasen, N.C., 2004. Cerebellar dysfunction in neuroleptic-naïve schizophrenia patients. Biol. Psychiatry 55, 1146–1153.
Hoenig, J., 1983. The concept of schizophrenia. Kraepelin–Bleuler–Schneider. Br J Psychiatry 142, 547–556.
Hoff, A.L., Wieneke, M., Faustman, W.O., et al., 1998. Sex differences in neuropsychological functioning of first-episode and chronically ill schizophrenic patients. Am. J. Psychiatry 155, 1437–1439.
Hoff, A., Svetina, C., Maurizio, A., et al., 2005a. Familial cognitive deficits in schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet. 133, 43–49.
Hoff, A., Svetina, C., Shields, G., et al., 2005b. Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. Schizophr. Res. 78, 27–34.
Honer, W.G., Kopala, L.C., Rabinowitz, J., 2005. Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. J. Psychopharmacol. 19, 277–285.
Hu, T.W., 2006. An international review of the national cost estimates of mental illness, 1990–2003. J. Ment. Health Policy 9, 3–13.
Huber, G., Gross, G., Schuttler, J.E., 1980. A long-term follow-up study of schizophrenia: psychiatric course of illness and follow-up. Acta Psychiatr. Scand. 52, 49–57.
Hughes, C., Kumari, V., Das, M., et al., 2005. Cognitive functioning in siblings discordant for schizophrenia. Acta Psychiatr Scand 111, 185–192.
Iacovides, A., Siamouli, M., 2008. Comorbid mental and somatic disorders: an epidemiological perspective. Curr. Opin. Psychiatry 21, 417–421.
Isaac, M., Chand, P., Murthy, P., 2007. Schizophrenia outcome measures in the wider international community. Br. J. Psychiatry 191 (Suppl.50), s71–s77.
Iyer, S.N., Boekestyn, L., Cassidy, C.M., et al., 2008. Signs and symptoms in the pre-psychotic phase: descriptions and implications for diagnostic trajectories. Psychol. Med. 38, 1147–1156.
Jablensky, A., 2006. Subtyping schizophrenia: implications for genetic research. Mol Psychiatry 11, 815–836.
Jablensky, A., Sartorius, N., Ernberg, G., et al., 1992. Schizophrenia: manifestations, incidence, and course in different cultures. Psychol. Med. 22 (Suppl 20), 1–97.
Jager, M., Bottlender, R., Strauss, A., Moller, H.J., 2004. Fifteen-year follow-up of ICD-10 schizoaffective disorders compared with schizophrenia and affective disorders. Acta Psychiatr. Scand 109, 30–37.
Jakobsen, K.D., Frederiksen, J.N., Parnas, J., Werge, T., 2006. Diagnostic agreement of schizophrenia spectrum disorders among chronic patients with functional psychoses. Psychopathology 39, 269–276.
Jaspers, K., 1946. Allgemeine Psychopathologie. Springer Verlag, Heidelberg.
Jeppesen, P., Petersen, L., Thorup, A., et al., 2008. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. Psychol. Med. 38, 1157–1166.
Jobe, T.H., Harrow, M., 2005. Long-term outcome of patients with schizophrenia: a review. Can. J. Psychiatry 50, 892–900.
Johnstone, E.C., Crow, T.J., Frith, C.D., et al., 1978. The dementia of dementia praecox. Acta Psychiatr Scand 57, 305–324.
Johnstone, E.C., Crow, T.J., Frith, C.D., et al., 1976. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2 (7992), 924–926.
Jones, P., Rodgers, B., Murray, R., Marmot, M., 1994. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344, 1398–1402.
Kahlbaum, K., 1874/1973. Catatonia. John Hopkins University Press, Baltimore. Translated by Levij Y and Priden T.
Kalaydjian, A.E., Eaton, W., Cascella, N., Fasano, A., 2006. The gluten connection: the association between schizophrenia and celiac disease. Acta Psychiatr. Scand. 113, 82–90.
Keefe, R.S.E., Eesley, C.E., Poe, M.P., 2005. Defining a cognitive function decrement in schizophrenia? Biol Psychiatry 57, 688–691.
Keefe, R.S.E., Bilder, R.M., Davis, S.M., et al., 2007. Neurocognitive effects of antipsychotic medications in patients with schizophrenia in the CATIE Trial. Arch. Gen. Psychiatry 64, 633–647.
Kendell, R.E., 1974. The stability of psychiatric diagnoses. Br. J. Psychiatry 124, 352–356.
Kendell, R.E., 1987. Diagnosis and classification of functional psychoses. Br. Med. Bull. 43, 499–513.
Kendell, R.E., Brockington, I.F., 1980. The identification of disease entities and the relationship between schizophrenia and affective psychoses. Br. J. Psychiatry 137, 324–331.
Kendler, K.S., Gruenberg, A.M., Tsuang, M.T., 1988. A family study of the subtypes of schizophrenia. Am. J. Psychiatry 145, 57–62.
Kerns, J.G., Berenbaum, H., 2002. Cognitive impairments associated with formal thought disorder in people with schizophrenia. J. Abnorm. Psychol. 111, 211–224.
Keshavan, M.S., Diwadkar, V.A., Montrose, D.M., et al., 2005. Premorbid indicators and risk for schizophrenia: a selective review and update. Schizophr Res 79, 45–57.
Keshavan, M.S., Sanders, R.D., Sweeney, J.A., et al., 2003. Diagnostic specificity and neuroanatomic validity of neurological abnormalities in first-episode psychoses. Am. J. Psychiatry 160, 1298–1304.
Keshavan, M.S., Tandon, R., Boutros, N., Nasrallah, H.A., 2008. Schizophrenia, "just the facts". What we know in 2008. Part 3: Pathophysiology. Schizophr. Res 106, 89–107.
King, D.J., Wilson, A., Cooper, S.J., Waddington, J.L., 1991. The clinical correlates of neurological soft signs in schizophrenia. Br. J. Psychiatry 158, 770–775.
Kingdon, D., Gibson, A., Kinoshita, Y., et al., 2008. Acceptable terminology and subgroups in schizophrenia: an exploratory study. Soc. Psychiatry Psychiatr. Epidemiol. 43, 239–243.
Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S., 2006. The NIMH-matrics consensus statement on negative symptoms. Schizophr Bull 32, 214–219.
Kitamura, T., Okazaki, Y., Fujinawa, A., et al., 1995. Symptoms of psychoses: a factor-analytic study. Br J Psychiatry 166, 236–240.
Kitamura, H., Shioiri, T., Itoh, M., et al., 2007. Does operational diagnosis of schizophrenia significantly impact intellectual deficits in psychotic disorders? J Intell Disabil Res 51, 812–820.

Kleist, K., 1960. Schizophrenic symptoms and cerebral pathology. J Ment Sci 106, 246–255.
Klingberg, S., Wittorf, A., Sickinger, S., et al., 2008. Course of cognitive functioning during the stabilization phase of schizophrenia. J Psychiatr Res 42, 259–267.
Klingberg, S., Wittorf, A., Wiedemann, G., 2006. Disorganization and cognitive impairment in schizophrenia: independent symptom dimensions. Eur Arch Psychiatry Clin Neurosci 256, 532–540.
Klosterkotter, J., Schultze-Lutter, F., Ruhrmann, S., 2008. Kraepelin and psychotic prodromal conditions. Eur. Arch. Psychiatry Clin. Neurosci. 258 (Suppl.2), 74–84.
Kooyman, I., Dean, K., Harvey, S., Walsh, E., 2007. Outcomes of public concern in schizophrenia. Br. J. Psychiatry 191 (Suppl.50), s29–s36.
Koster, A., Lajer, M., Lindhardt, A., Rosenbaum, B., 2008. Gender differences in first-episode psychosis. Soc. Psychiatry Psychiatr. Epidemiol. 43, 940–946.
Kraepelin, E., 1899. Psychiatrie. Ein Lehrbuch fur Studierende und Arzte, 6. Barth, Leipzig.
Kraepelin, E., Dementia Praecox and Paraphrenia, 1919, edited by Robertson, G., Krieger, New York, 1971.
Kraepelin, E., 1920. Die Erscheinungsformen des Irreseins. Zeitschrift fur Neurologie und Psychiatrie 62, 1–29.
Kremen, W.S., Seidman, L.J., Faraone, S.V., Tsuang, M.T., 2008. IQ decline in cross-sectional studies of schizophrenia: methodology and interpretation. Psychiatry Res 158, 181–194.
Langfeldt, G., 1960. Diagnosis and prognosis of schizophrenia. Proc Royal Soc Med 53, 1047–1052.
Lawrence, D.M., Holman, C.D., Jablensky, A., Hobbs, M.S., 2003. Death rate from ischemic heart disease in Western Australian psychiatric patients 1980–1998. Br J Psychiatry 182, 31–36.
Lawrie, S.M., McIntosh, A.M., Hall, J., 2008. Brain structure and function changes during the development of schizophrenia. Schizophr. Bull. 34, 330–340.
Laws, K.R., 1999. A meta-analytic review of the Wisconsin Card Sort studies in schizophrenia: general intellectual deficit in disguise? Cognit Neuropsychiatry 4, 1–30.
Lee, C., McGlashan, T.M., Woods, S.W., 2005. Prevention of schizophrenia: can it be achieved? CNS Drugs 19, 193–206.
Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. J Abnormal Psychology 114, 599–611.
Lehoux, C., Everett, J., Laplante, L., et al., 2003. Fine motor dexterity is correlated to social functioning in schizophrenia. Schizophr Res 62, 269–273.
Lencz, T., Smith, C.W., McLaughlin, D., et al., 2006. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol. Psychiatry 59, 863–871.
Lenzenweger, M.F., Dworkin, R.H., 1996. The dimensions of schizophrenic phenomenology. Br J Psychiatry 168, 432–440.
Leonhardt, K., 1957. Aufteilung der Endogen Psychosen. Akademie Verlag, Berlin.
Lester, D., 2006. Sex differences in completed suicide by schizophrenic patients: a meta-analysis. Suicide and Life-Threatening Behavior 36, 50–56.
Leucht, S., Burkard, T., Henderson, J., et al., 2007. Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand 116, 317–333.
Levav, I., Lipshitz, I., Novikov, I., et al., 2007. Cancer risk among parents and siblings of patients with schizophrenia. Br. J. Psychiatry 190, 156–161.
Levin, T., 2006. Schizophrenia should be renamed to help educate patients and the public. Int. J. Soc. Psychiatry 52, 324–331.
Levine, S.Z., Rabinowitz, J., 2007. Revisiting the 5 dimensions of the Positive and Negative Syndrome Scale. J Clin Psychopharmacol 27, 431–436.
Lichtenberg, G.C., 2000. The Waste Books. New York Review Books, New York. Translated by R.J. Hollingdale.
Lieberman, J.A., First, M.B., 2007. Renaming schizophrenia. Diagnosis and treatment are more important than semantics. BMJ 334, 108.
Lieberman, J.A., Jarskog, L.F., Malaspina, D., 2006. Preventing clinical deterioration in the course of schizophrenia: the potential for neuroprotection. J. Clin. Psychiatry 67, 983–990.
Linszen, D., Dingemans, P., Lenior, M., 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch. Gen. Psychiatry 51, 273–279.
Loebel, A.D., Lieberman, J.A., Alvir, J.M.J., et al., 1992. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 149, 1183–1188.
Loza, B., Kucharska-Pietura, K., Kopacz, G., Debowska, G., 2003. Factor structure of paranoid schizophrenia: a prospective study. Psychopathology 36, 132–141.
Luoma, S., Hakko, H., Ollinen, T., et al., 2008. Association between age at onset and clinical features of schizophrenia: the Northern Finland 1966 Birth Cohort Study. European Psychiatry 23, 331–335.
Lykouras, L., Oulis, P., Psarros, K., et al., 2000. Five-factor model of schizophrenic psychopathology: how valid is it? Eur Arch Psychiatr Clin Neurosci 250, 93–100.
MacBeth, A., Gumley, A., 2008. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical appraisal. Acta Psychiatr. Scand. 117, 85–99.
MacCabe, J.H., 2008. Population-based cohort studies on premorbid cognitive function in schizophrenia. Epidemiol. Rev. 30, 77–83.
Magliano, L., Fiorillo, A., De Rosa, C., et al., 2005. Family burden in long-term diseases: a comparative study in schizophrenia versus physical disorders. Soc. Sci. Med. 61, 313–322.
Maj, M., 2005. "Psychiatric comorbidity"; an artifact of current diagnostic systems? Br J Psychiatry 186, 182–184.
Malaspina, D., Coleman, E., 2003. Olfaction and social drive in schizophrenia. Arch. Gen. Psychiatry 60, 578–584.
Malhi, G.S., Green, M., Fagiolini, A., et al., 2008. Schizoaffective disorder: diagnostic issues and future recommendations. Bipolar Disorders 10, 215–230.
Malla, A., Norman, R., Schmitz, N., et al., 2006. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol. Med. 36, 649–658.
Marder, S.R., Essock, S.M., Miller, A.M., et al., 2004. Physical health monitoring of patients with schizophrenia. Am J Psychiatry 161, 1334–1349.
Marsden, C.D., 1982. Motor disorders in schizophrenia. Psychol. Med. 12, 13–15.
Masi, G., Mucci, M., Pari, C., 2006. Children with schizophrenia. CNS Drugs 20, 841–866.
Mason, P., Harrison, G., Glazebrook, G., et al., 1996. The course of schizophrenia over 13 years. A report from the International Study on schizophrenia (ISOS) coordinated by the World Health Organization. Br. J. Psychiatry 169, 580–586.
Mathias, S., Lubman, D.I., Hides, L., 2008. Substance-induced psychosis: a diagnostic conundrum. J. Clin. Psychiatry 69, 358–367.
Maziade, M., Gingras, N., Rodrigue, C., et al., 1996. Long-term stability of diagnosis and symptom dimensions in a systemic simple of patients with onset of schizophrenia in childhood and early adolescente. I: Nosology, sex, and age of onset. Br. J. Psychiatry 169, 361–370.
McCreadie, R.G., Srinivasan, T.N., Padmavati, R., Thara, R., 2005. Extrapyramidal symptoms in unmedicated schizophrenia. J. Psychiatr. Res. 39, 261–266.
McGlashan, T.H., 2006. Is active psychosis neurotoxic? Schizohr Bull 32, 609–613.
McGlashan, T.H., Fenton, W.S., 1993. Subtype progression and pathophysiologic deterioration in early schizophrenia. Schizophr. Bull. 19, 71–84.
McGorry, P.D., 2007. Issues for DSM-V: Clinical staging: a heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. Am. J. Psychiatry 164, 859–860.
McGorry, P.D., 2008. Back to the future: predicting and reshaping the course of psychotic disorder. Am. J. Psychiatry 65, 25–27.
McGorry, P.D., Hickie, I.B., Yung, A.R., et al., 2006. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust. N.Z.J. Psychiatry 40, 616–622.
McGrath, J.J., van Os, J., Hoyos, C., et al., 1995. Minor physical anomalies in psychoses: associations with clinical and putative etiological variables. Schizophr. Res. 18, 9–20.
McKenna, P.J., Lund, C.E., Mortimer, A.M., Biggins, C.A., 1991. Motor, volitional and behavioral disorders in schizophrenia. 2: The "conflict of paradigms" hypothesis. Br J Psychiatry 158, 328–336.
Melle, I., Johannson, J.O., Friis, S., et al., 2006. Early detection of the first episode of schizophrenia and suicidal behavior. Am. J. Psychiatry 163, 800–804.
Mellor, C.S., 1970. First rank symptoms of schizophrenia. Br J Psychiatry 117, 15–23.
Meltzer, H.Y., Alphs, L., Green, A.I., et al., 2003. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch. Gen. Psychiatry 60, 82–91.
Menezes, N.M., Arenovich, T., Zipursky, R.B., 2006. A systematic review of longitudinal studies of first-episode psychosis. Psychol. Med. 36, 1349–1362.
Meyer, J.M., Nasrallah, H.A. (Eds.), 2009. Medical Illness and Schizophrenia. American Psychiatric Press, Washington D.C.
Mintz, A.R., Dobson, K.S., Romney, D.M., 2003. Insight in schizophrenia: a meta-analysis. Schizophr Res 61, 75–88.
Mittelman, S.A., Buchsbaum, M.S., 2007. Very poor outcome schizophrenia: clinical and neuroimaging aspects. Int. Rev. Psychiatry 19, 347–359.
Modestin, J., Huber, A., Satirli, E., et al., 2003. Long-term course of schizophrenia reconsidered: Bleuler's study reconsidered. Am. J. Psychiatry 160, 2202–2208.
Mojtabai, R., Malaspina, D., Susser, E., 2003. The concept of population prevention: application to schizophrenia. Schizophr. Bull. 29, 791–801.
Morgan, C., Abdul-Al, R., Lappin, J.M., et al., 2006. Clinical and social determinants of duration of untreated psychosis in the AESOP first-episode psychosis study. Br. J. Psychiatry 189, 446–452.
Morgan, V.A., Leonard, H., Bourke, J., Jablensky, A., 2008. Intellectual disability co-occurring with schizophrenia and other psychiatric illness: population-based study. Br. J. Psychiatry 193, 364–372.
Morrens, M., Hulstijn, W., Lewi, P.J., et al., 2006. Stereotypy in schizophrenia. Schizophr. Res. 84, 397–404.
Morrens, M., Hulstijn, W., Sabbe, B., 2007. Psychomotor slowing in schizophrenia. Schizophr. Bull. 33, 1038–1053.

Muller, J.E., Koen, L., Soraya, S., et al., 2004. Anxiety disorders and schizophrenia. Curr. Psychiatry Rep. 6, 255–261.
Murray, C.J.L., Lopez, A.D. (Eds.), 1996. The Global Burden of Disease: a Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Harvard University Press, Cambridge, Massachussetts.
Murray, V., McKee, I., Miller, P.M., et al., 2005. Dimensions and classes of psychosis in a population cohort. Psychol Med 35, 499–510.
Nakaya, M., Suwa, H., Ohmori, K., 1999. Latent structures underlying schizophrenic symptoms: a five-dimensional model. Schizophr Res 39, 39–50.
Narvaez, J.M., Twamley, E.W., McKibbin, C.L., et al., 2008. Subjective and objective quality of life in schizophrenia. Schizophr. Res. 98, 201–208.
Nasrallah, H.A., Meyer, J.M., Goff, D.C., et al., 2006. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophr. Res. 86, 15–22.
Nasrallah, H.A., Smelzer, D.J., 2003. Contemporary Diagnosis and Management of the Patient with Schizophrenia. Handbooks in Healthcare, Newtown, Pennsylvania.
Newcomer, J.W., Hennekens, C.H., 2007. Severe mental illness and risk of cardiovascular disease. JAMA 298, 1794–1796.
Newton-Howes, G., Tyrer, P., North, B., Yang, M., 2008. The prevalence of personality disorder in schizophrenia and psychotic disorders: systematic review of rates and explanatory modeling. Psychol. Med. 38, 1075–1082.
Norman, R.M.G., Malla, A.K., 1993. Stressful life events and schizophrenia I: A review of the research. Br. J. Psychiatry 162, 161–166.
Oken, R.J., Schulzer, M., 1999. At issue: schizophrenia and rheumatoid arthritis: the negative association revisited. Schizophr. Bull. 25, 625–638.
Olsen, K.A., Rosenbaum, B., 2006. Prospective investigations of the prodromal state of schizophrenia. Acta Psychiatr. Scand. 113, 247–272.
Ongur, D., Lin, L., Cohen, B.M., 2009. Clinical characteristics influencing age at onset in psychotic disorders. Compr. Psychiatry 50, 13–19.
Orzack, M.H., Kornetsky, C., 1966. Attention dysfunction in schizophrenia. Arch Gen Psychiatry 14, 323–326.
Osatuke, K., Ciesla, J., Kasckow, J.W., et al., 2008. Insight in schizophrenia: a review of etiological models and supporting research. Compr. Psychiatry 49, 70–77.
Osby, U., Correia, N., Brandt, L., et al., 2000. Mortality and causes of death in Stockholm county, Sweden. Schizophr. Res. 45, 21–28.
Owen, M.J., Craddock, N., Jablensky, A., 2007. The genetic deconstruction of schizophrenia. Schizophr. Bull. 33, 905–911.
Owens, D.G.C., Miller, P., Lawrie, S.M., Johnstone, E.C., 2005. Pathogenesis of schizophrenia: a psychopathological perspective. Br. J. Psychiatry 186, 386–393.
Palmer, B.A., Pankratz, V.S., Bostwick, J.M., 2005. The lifetime risk of suicide in schizophrenia: a re-examination. Arch. Gen. Psychiatry 62, 247–253.
Parks, J., Svendsen, D., Singer, P., Foti, M., 2006. Morbidity and mortality in people with serious mental illness. National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council. Alexandria, Virginia. Available at www.nasmhpd.org/publications/technical reports.
Patel, V., Cohen, A., Tharyan, P., Gureje, O., 2006. Is the outcome really better in developing countries. Rev Bras Psiquiatr 28, 149–152.
Penn, D.L., Nowlin-Drummond, A., 2001. Politically correct labels and schizophrenia: a rose by any other name? Schizophr. Bull. 27, 197–203.
Penn, D.L., Sanna, L.J., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schizophr. Bull. 34, 408–411.
Peralta, V., Cuesta, M.J., 2001. How many and which are the psychopathological dimensions of schizophrenia? Issues influencing their ascertainment. Schizophr Res 49, 269–285.
Peralta, V., Cuesta, M.J., 2003. The nosology of psychotic disorders: a comparison among competing classification systems. Schizophr. Bull. 29, 413–425.
Peralta, V., Cuesta, M.J., 2007. Familial liability and schizophrenia phenotypes: a polydiagnostic approach. Schizophr Res 96, 125–134.
Perkins, D.O., Gu, H., Boteva, K., et al., 2005. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 162, 1785–1804.
Phillips, L.J., McGorry, H.P., Garner, B., et al., 2006. Stress, the hippocampus and the hypothalamo-pituitary-adrenal axis: implications for the development of psychotic disorders. Aust NZ J Psychiatry 40, 725–741.
Phillips, L.J., McGorry, H.P., Yuen, J., et al., 2007. Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk for schizophrenia. Schizophr Res 96, 25–33.
Pia, L., Tamietto, M., 2006. Unawareness in schizophrenia: neuropsychological and neuroanatomical findings. Psychiatry Clin. Neurosci. 60, 531–537.
Pihlajamaa, J., Suvisaari, J., Henriksson, M., et al., 2008. The validity of schizophrenia diagnosis in the Finnish Hospital Discharge Register: findings from a 10-year birth cohort sample. Nord. J. Psychiatry 62, 198–203.
Planansky, K., Johnston, R., 1978. Depressive syndrome in schizophrenia. Acta Psychiatr Scand 57, 207–218.
Pompili, M., Lester, D., Innamorati, M., et al., 2008. Assessment and treatment of suicide risk in schizophrenia. Expert Rev. Neurotherapeutics 8, 51–74.
Popper, K., 1959. The Logic of Scientific Discovery. Basic Books Inc. Publishers, New York, NY.
Potvin, S., Ali, A., Stip, E., 2007. Meta-analysis of depressive symptoms in dual-diagnosis schizophrenia. Austral NZ J Psychiatry 41, 792–799.
Potvin, S., Marchand, S., 2008. Hypoalgesia in schizophrenia is independent of antipsychotic drugs: a systematic quantitative review of experimental studies. Pain 138, 70–78.
Prasad, K.M., Keshavan, M.S., 2008. Structural cerebral variations as useful endophenotypes in schizophrenia: do they help construct "extended endophenotypes"? Schizophr. Bull. 34, 774–790.
Preston, G.A., Weinberger, D.R., 2005. Intermediate phenotypes in schizophrenia: a selective review. Dialogues in Clinical Neuroscience 7, 165–179.
Ranganath, C., Minzenberg, M.J., Ragland, D.J., 2008. The cognitive neuroscience of memory function and dysfunction in schizophrenia. Biol. Psychiatry 64, 18–25.
Ratakonda, S., Gorman, J.M., Yale, S.A., et al., 1998. Characterization of psychotic disorders. Arch Gen Psychiatry 55, 75–81.
Read, J., Haslam, N., Sayce, L., Davies, E., 2006. Prejudice and schizophrenia: a review of the "mental illness is an illness like any other" approach. Acta Psychiatr. Scand. 114, 303–318.
Regier, D.A., Farmer, M.E., Rae, D.S., et al., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. JAMA 264, 2511–2518.
Regier, D.A., Kaelber, C.T., Roper, M.T., et al., 1994. The ICD-10 clinical field trial for mental and behavioral disorders: results in Canada and the United States. Am. J. Psychiatry 151, 1340–1350.
Regier, D.A., 2007. Time for a fresh start? Rethinking psychosis in DSM-V. Schizophr Bull 33, 843–845.
Reichenberg, A., Harvey, P.D., 2007. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. Psychol Bull 133, 833–858.
Riecher-Rossler, A., Gschwandtner, U., Borgwardt, U., et al., 2006. Early detection and treatment of schizophrenia: how early? Acta Psychiatr. Scand. 113 (Suppl.429), 73–80.
Rieder, R.O., Nichols, P.L., 1979. Offspring of schizophrenia. III. Hyperactivity and neurological soft signs. Arch. Gen. Psychiatry 36, 665–674.
Rietkirk, T., Boks, M.P.M., Sommer, I.E., et al., 2008. The genetics of symptom dimensions of schizophrenia: review and meta-analysis. Schizophr Res 102, 197–205.
Robins, E., Guze, S.B., 1970. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am. J. Psychiatry 126, 983–987.
Romney, D.M., 1990. Thought disorder in the relatives of schizophrenics: a meta-analytic review of selected studies. J. Nerv. Ment. Dis. 178, 481–486.
Rosenheck, R.A., Leslie, D., Keefe, R., et al., 2006. Barriers to employment for people with schizophrenia. Am. J. Psychiatry 163, 411–417.
Rossler, A.R., Rossler, W., 1998. The course of schizophrenic psychoses: what do we really know? A selective review from the epidemiological perspective. Eur. Arch. Psychiatry Clin. Neurosci. 248, 189–202.
Roth, S., 1970. The seemingly ubiquitous depression following acute schizophrenic episodes. Am. J. Psychiatry 127, 91–98.
Roy, M.A., Merette, C., Maziade, M., 2001. Subtyping schizophrenia according to outcome or severity: a search for homogeneous subgroups. Schizophr. Bull. 27, 115–138.
Rund, B.R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia. Schizophr Bull 24, 425–435.
Saha, S., Chant, D., McGrath, J., 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time. Arch Gen Psychiatry 64, 1123–1131.
Salem, J.E., Kring, A.M., 1998. The role of gender differences in the reduction of etiological heterogeneity in schizophrenia. Clin. Psychol. Rev. 18, 795–819.
Salokangas, R.K.R., Honkonen, T., Stengard, E., Koivisto, A.M., 2002. Symptom associations and their association with outcome and treatment setting in long-term schizophrenia. Nord J Psychiatry 56, 319–327.
Salokangas, R.K.R., McGlashan, T.H., 2008. Early detection and intervention of psychosis: a review. Nord J Psychiatry 62, 92–105.
Sands, J.R., Harrow, M., 1999. Depression during the longitudinal course of schizophrenia. Schizophr. Bull. 25, 157–171.
Sartorius, N., Jablensky, A., Korten, A., et al., 1986. Early manifestations and first-contact incidence of schizophrenia in different cultures. Psychol Med 16, 909–926.
Sato, M., 2006. Renaming schizophrenia: a Japanese perspective. World Psychiatry 5, 51–53.
Saykin, A.J., Gur, R.C., Gur, R.E., et al., 1991. Neuropsychological function in schizophrenia: selective impairment in memory and learning. Arch. Gen. Psychiatry 48, 618–624.
Schenkel, L.S., Silverstein, S.M., 2004. Dimensions of premorbid functioning in schizophrenia: a review of neuromotor, cognitive, social, and behavioral domains. Genetic, Social, and General Psychol. Monogr. 130, 241–270.

Schmael, C., Georgi, A., Krumm, B., et al., 2007. Premorbid adjustment in schizophrenia—an important aspect of phenotype definition. Schizophr. Res. 92, 50–62.
Schneider, K., 1959. Clinical Psychopathology. Grune and Stratton, New York. Translated by Hamilton, MW.
Schultze-Lutter, F., 2009. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. Schizophr. Bull. 35, 5–8.
Schwartz, J.E., Fennig, S., Tanenberg-Karant, M., Carlson, G., et al., 2000. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. Arch Gen Psychiatry 57, 593–600.
Schwartz, R.C., Cohen, B.N., Grubaugh, A., 1997. Does insight affect long-term inpatient treatment outcome in chronic schizophrenia? Compr. Psychiatry 38, 283–288.
Scully, P.J., Owens, J.M., Kinsella, A., Waddington, J.L., 2002. Dimensions of psychopathology in bipolar disorder versus other affective and non-affective psychoses among an epidemiologically complete population. Bipolar Disord 4 (Suppl.1), 43–44.
Seeber, K., Cadenhead, K.S., 2005. How does studying schizotypal personality disorder inform us about the prodrome of schizophrenia? Curr. Psychiatry Rep. 7, 41–50.
Seeman, M.V., 1982. Gender differences in schizophrenia. Can J Psychiatry 27, 107–112.
Seeman, M.V., 2007. An outcome measure in schizophrenia: mortality. Can J Psychiatry 52, 55–60.
Serretti, A., Rietschel, M., Lattuada, E., et al., 2001. Major psychosis symptomatology: factor analysis of 2241 subjects. Eur Arch Psychiatr Clin Neurosci 251, 193–198.
Shad, M.U., Tamminga, C.A., Cullum, M., et al., 2006. Insight and frontal cortical function in schizophrenia: a review. Schizophr. Res. 86, 54–70.
Shaw, J., Hunt, I.M., Flynn, S., et al., 2006. Rates of mental disorder in people convicted of homicide. Br. J. Psychiatry 188, 143–147.
Shenton, M.E., Solovay, M.R., Holzman, P.S., et al., 1989. Thought disorder in the relatives of psychotic patients. Arch Gen Psychiatry 46, 897–901.
Shepherd, M., Watt, D., Falloon, I., Smeeton, N., 1989. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychol. Med. Monogr. Suppl. 15, 1–46.
Siever, L.J., Davis, K.L., 2004. The pathophysiology of schizophrenia: perspectives from the spectrum. Am. J. Psychiatry 161, 398–413.
Siris, S.G., Bench, C., 2003. Depression and schizophrenia, In: Hirsch, S.R., Weinberger, D.R. (Eds.), Schizophrenia, 2nd edition. Blackwell Publishing, Malden, MA.
Sitskoorn, M.M., Aleman, A., Ebisch, S.J., et al., 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr. Res. 71, 285–295.
Snitz, B.E., Macdonald III, A.W., Carter, C.S., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative phenotypes. Schizophr Bull 32, 179–194.
Solovay, M.R., Shenton, M.E., Holzman, P.S., 1987. Comparative studies of thought disorder: I Mania and schizophrenia. Arch. Gen. Psychiatry 44, 13–20.
Somner, I., Ramsey, N., Kahn, R., et al., 2001. Handedness, language lateralization and anatomical asymmetry in schizophrenia: a meta-analysis. Br. J. Psychiatry 178, 344–351.
Sprong, M., Schothorst, P., Vos, E., et al., 2007. Theory of mind in schizophrenia: meta-analysis. Br. J. Psychiatry. 191, 5–13.
Stahl, S.M., Buckley, P.F., 2007. Negative symptoms of schizophrenia: a problem that will not go away. Acta Psychiatr. Scand. 115, 4–11.
Stompe, T., Ortwein-Soboda, G., Ritter, K., et al., 2002. Are we witnessing the disappearance of catatonic schizophrenia? Compr. Psychiatry 43, 167–174.
Strauss, J.S., Carpenter, W.T., 1974. Characteristic symptoms and outcome in schizophrenia. Arch. Gen. Psychiatry 30, 429–434.
Subramaniam, M., Pek, E., Verma, S., et al., 2007. Diagnostic stability 2 years after treatment initiation in the Early Psychosis Intervention Program in Singapore. Aust. N.Z. J. Psychiatry 41, 495–500.
Suvisaari, J., Perala, J., Saarni, S.I., et al., 2009. The epidemiology and descriptive and predictive validity of DSM-IV delusional disorder and subtypes of schizophrenia. Clin. Schizophr. Related Psychoses 2, 289–297.
Swanson, J.W., Holzer, C.E., Ganju, V.K., Jono, R.T., 1990. Violence and psychiatric disorder in the community: evidence from the epidemiologic catchment area surveys. Hosp Community Psychiatry 41, 761–770.
Szoke, A., Schurhoff, F., Mathieu, F., et al., 2005. Tests of executive function in first-degree relatives of schizophrenic patients: a meta-analysis. Psychol Med 35, 771–782.
Szoke, A., Trandafir, A., Dupont, M.E., et al., 2008. Longitudinal studies of cognition in schizophrenia: meta-analysis. Br. J. Psychiatry 192, 248–257.
Szpakowicz, M., Herd, A., 2008. "Medically cleared": how well are patients with psychiatric presentations examined by emergency physicians? J. Emer. Med. 35, 369–372.
Tandon, R., Greden, J.F., 1989. Cholinergic hyperactivity and negative schizophrenic symptoms. Arch. Gen. Psychiatry 46, 745–753.
Tandon, R., DeQuardo, J.R., Taylor, S.F., et al., 2000. Phasic and enduring negative symptoms in schizophrenia: biological markers and relationship to outcome. Schizophr. Res. 45, 191–201 erratum 51:185.
Tandon, R., Keshavan, M.S., Nasrallah, H.A., 2008a. Schizophrenia, "just the facts". What we know in 2008. Part 1: Overview. Schizophr. Res. 100, 4–19.
Tandon, R., Keshavan, M.S., Nasrallah, H.A., 2008b. Schizophrenia, "just the facts". What we know in 2008. Part 2: Epidemiology and etiology. Schizophr. Res. 102, 1–18.
Tandon, R., Maj, M., 2008. Nosological status and definition of schizophrenia: some considerations for DSM-V and ICD-11. Asian J. Psychiatry 1, 22–27.
Tandon, R., Moller, H.J., Belmaker, R.H., et al., 2008c. World Psychiatry Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 100, 20–38.
Taylor, M.A., Fink, M., 2003. Catatonia in psychiatric classification: a home of its own. Am J Psychiatry 160, 1233–1241.
Taylor, P.J., 2008. Psychosis and violence: stories, fears, and reality. Can. J. Psychiatry 53, 647–659.
Teplin, L.A., McClelland, G.M., Abram, K.M., et al., 2005. Crime victimization in adults with severe mental illness: comparison with the National Crime Victimization Survey. Arch. Gen. Psychiatry 62, 911–921.
Thaker, G.K., 2007. Schizophrenia endophenotypes as treatment targets. Expert Opin. Ther. Targets 11, 1189–1206.
Thara, R., 2004. Twenty-year course of schophrenia: the Madras Longitudinal Study. Can. J. Psychiatry 49, 564–569.
Thomas, L.E., Woods, S.W., 2006. The schizophrenia prodrome: a developmentally informed review and update for psychopharmacologic treatment. Child Adolesc. Psychiatric Clin. N. Am. 15, 109–133.
Thornicraft, G., Tansella, M., Becker, T., et al., 2004. The personal impact of schizophrenia in Europe. Schizophr. Res. 69, 125–132.
Tirupati, S.N., Padmavati, R., Thara, R., McCreadie, R.G., 2006. Psychopathology in never-treated schizophrenia. Compr Psychiatr 47, 1–6.
Tosato, S., Dazzan, P., 2005. The psychopathology of schizophrenia and the presence of neurological soft signs: a review. Curr. Opinion Psychiatry 18, 285–288.
Toulopoulou, T., Picchioni, M., Rijsdijk, F., et al., 2007. Substantial genetic overlap between neurocognition and schizophrenia. Arch Gen Psychiatry 64, 1348–1355.
Trandafir, A., Meary, A., Schurhoff, F., et al., 2006. Memory tests in first-degree adult relatives of schizophrenic patients: a meta-analysis. Schizophr Res 81, 217–226.
Tsuang, M.T., Faraone, S.V., 1995. The case for heterogeneity in the etiology of schizophrenia. Schizophr. Res. 17, 161–175.
Tucker, G.J., Campion, E.W., Silberfarb, P.M., 1975. Sensorimotor function and cognitive disturbance in schizophrenia. Am. J. Psychiatry 132, 17–21.
Turetsky, B.I., Kohler, C.G., Gur, R.E., Moberg, P.J., 2008. Olfactory physiological impairment in first-degree relatives of schizophrenia patients. Schizophr. Res. 102, 220–229.
Tweedy, J., Reding, M., Garcia, C., et al., 1982. Significance of cortical inhibition signs. Neurology 32, 169–173.
Ungvari, G.S., Goggins, W., Leung, S.K., Gerevich, J., 2007. Schizophrenia with prominent catatonic features ('catatonic schizophrenia') II. Factor analysis of the catatonic syndrome. Prog Neuropsychopharmacol Biol Psychiatry 31, 462–468.
Ungvari, G.S., Leung, S.K., Ng, F.S., et al., 2005. Schizophrenia with prominent catatonic features. Prog Neuropsychopharmacol Biol Psychiatry 29, 27–38.
Vaillant, G., 1964. Prospective prediction of schizophrenic remission. Arch. Gen. Psychiatry 11, 509–518.
van der Does, A.J.W., Linszen, D.H., Dingemans, P.M.A.J., et al., 1993. A dimensional and categorical approach to the symptomatology of recent-onset schizophrenia. J Nerv Ment Dis 181, 744–749.
Van der Velde, C.D., 1976. Variability in schizophrenia: reflection of a regulatory disease. Arch. Gen. Psychiatry 33, 489–496.
Van Haren, N.E.M., Cahn, W., Hulshoff Pol, H.E., Kahn, R.S., 2008. Schizophrenia as a progressive brain disease. European Psychiatry 23, 245–254.
van Hooren, S., Versmissen, D., Janssen, I., et al., 2008. Social cognition and neurocognition as independent domains in psychosis. Schizophr Res 103, 257–265.
Van Os, J., Delespaul, P., 2005. Toward a world consensus on prevention of schizophrenia. Dialogues Clin. Neurosci. 7, 53–67.
van Os, J., Gilvarry, C., Bale, R., et al., 1999. A comparison of the utility of dimensional and categorical representations of psychosis. UK 700 group. Psychol Med 29, 595–606.
van Winkel, R., Myin-Germeys, I., De-Hert, M., et al., 2007. The association between cognition and functional outcome in first-episode patients with schizophrenia: mystery solved. Acta Psychiar Scand 116, 119–124.
Varsamis, J., Adamson, J.D., 1971. Early schizophrenia. Can. Psychiatr. Assoc. J. 16, 487–497.

Vassos, E., Sham, P.C., Cai, G., et al., 2008. Correlation and familial aggregation of dimensions of psychosis in affected sibling pairs from China. Br J Psychiatry 193, 305–310.
Vauth, R., Rusch, N., Wirtz, M., Corrigan, P.W., 2004. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? Psychiatry Res. 128, 155–165.
Veen, N.D., Selten, J.P., Schols, D., et al., 2004. Diagnostic stability in a Dutch psychosis incidence cohort. Br. J. Psychiatry 185, 460–464.
Venkatesh, B.K., Thirthalli, J., Naveen, M.N., et al., 2008. Sex difference in age of onset of schizophrenia: findings from a community-based study in India. World Psychiatry 7, 173–176.
Villalta-Gil, V., Vilaplana, M., Ochoa, S., et al., 2006. Four-symptom dimensions in outpatients with schizophrenia. Comp Psychiatry 47, 384–388.
Volavka, J., Citrome, L., 2008. Heterogeneity of violence in schizophrenia and implications for long-term treatment. Int. J. Clin. Pract. 62, 1237–1245.
Vollmer-Larsen, A., Jacobsen, T.B., Hemmingsen, R., Parnas, J., 2006. Schizoaffective disorder—the reliability of its clinical diagnostic use. Acta Psychiatr Scand 113, 402–407.
Waddington, J.L., Lane, A., Scully, P.J., et al., 1999. Early cerebro-craniofacial dysmorphogenesis in schizophrenia: a lifetime trajectory model from neurodevelopmental basis to "neuroprogressive" process. J. Psychiatr. Res. 33, 477–489.
Walker, E., Green, M., 1982. Soft signs of neurological dysfunction in schizophrenia. Biol. Psychiatry 17, 381–386.
Walker, E., Grimes, K., Davis, D., Smith, A., 1994. Childhood precursors of schizophrenia" facial expressions of emotion. Am. J. Psychiatry 150, 1654–1660.
Walsh, E., Moran, P., Scott, C., et al., 2003. Prevalence of violent victimization in severe mental illness. Br. J. Psychiatry 183, 233–238.
Walterfang, M., Velakoulis, D., 2005. Cortical release signs in psychiatry. Aust. N.Z. Journal Psychiatry 39, 317–327.
Wang, L., Mamah, D., Harms, M.P., et al., 2008. Progressive deformation of deep brain nuclei and hippocampal-amygdala formation in schizophrenia. Biol. Psychiatry 64, 1060–1068.
Watt, D.C., Katz, K., Shepherd, M., 1983. The natural history of schizophrenia: a five-year follow-up of a representative sample of schizophrenics by means of a standardized clinical and social assessment. Psychol. Med. 13, 663–670.
Weder, N., Muralee, S., Penland, H., Tampi, R.R., 2008. Catatonia: a review. Annals Clinical Psychiatry 20, 97–107.
Weinberg, S.M., Jenkins, E.A., Marazita, M.L., Maher, B.S., 2007. Minor physical anomalies in schizophrenia: a meta-analysis. Schizophr. Res. 89, 72–85.
Westermeyer, J., 2006. Comorbid schizophrenia and substance abuse: a review of epidemiology and course. Am. J. Addict. 15, 345–355.
Whalley, H.C., Harris, J.C., Lawrie, S.M., 2007. The neurobiological underpinnings of risk and conversion in relatives of patients with schizophrenia. Int. Rev. Psychiatry 19, 383–397.
Whyte, M.C., McIntosh, A.M., Johnstone, E.C., et al., 2005. Declarative memory in unaffected adult relatives of patients with schizophrenia: a systematic review and meta-analysis. Schizophr. Res. 78, 13–26.
Wing, J.K., 1978. who becomes chronic? Psychiatric Quarterly 50, 178–190.
Wing, J.K., 1988. Abandoning what? Br. J. Clin. Psychol., 7, 325–328.
Wing, J.K., Nixon, J., 1975. Discriminating symptoms in schizophrenia. A report from the international pilot study of schizophrenia. Arch. Gen. Psychiatry 32, 853–859.
Wood, S.J., Berger, G.E., Lambert, M., et al., 2006. Prediction of functional outcome 18 months after a first psychotic episode. Arch. Gen. Psychiatry 63, 969–976.
Wood, S.J., Pantelis, C., Velakoulis, D., et al., 2008. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risks. Schizophr. Bull. 34, 322–329.
Woodberry, K.A., Giuliano, A.J., Seidman, L.J., 2008. Premorbid IQ in schizophrenia: a meta-analytic review. Am. J. Psychiatry 165, 579–587.
World Health Organization, 1967. Manual of the International Statistical Classification of Diseases, injuries, and Causes of Death, Eighth Revision. World Health Organization, Geneva. (ICD-8).
World Health Organization, 1978. Manual of the International Statistical Classification of Diseases, injuries, and Causes of Death, Ninth Revision. World Health Organization, Geneva. (ICD-9).
World Health Organization, 1973. The International Pilot Study of Schizophrenia. World Health Organization, Geneva.
World Health Organization, 1992. The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. (ICD-10)—Section V. Mental and Behavioral Disorders. World Health Organization, Geneva.
Wu, E.Q., Birnbaum, H.G., Shi, L., et al., 2005. The economic burden of schizophrenia in the United States in 2002. J. Clin. Psychiatry 66, 1122–1129.
Wyatt, R.J., Alexander, R.C., Egan, M.F., Kirch, D.G., 1988. Schizophrenia, just the facts. What do we know, how well do we know it? Schizophr. Res. 1, 3–18.
Wyatt, R.J., Hunter, I., 2001. Rationale for the study of early intervention. Schizophr. Res. 51, 69–76.
Yung, A.R., McGorry, P.D., 1996. The prodromal phase of first-episode psychosis. Schizophr. Bull. 22, 353–370.
Yung, A.R., Phillips, L.J., Yuen, H.P., et al., 2003. Psychosis prediction: 12-month follow-up of a high-risk ("prodromal") group. Schizophr. Res. 60, 21–32.
Yung, A.R., Nelson, B., Stanford, C., et al., 2008. Validation of "prodromal" criteria to detect individuals at ultra high risk for psychosis. Schizophr. Res. 105, 10–17.
Ziedonis, D., Hitsman, B., Beckham, J.C., et al., 2008. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine and Tob. Res. 10, 1691–1715.