4. Clinical features and conceptualization

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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 etiopathological 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 (1899, 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, blunted 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]) but...
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).

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? Is it 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 (Soloyay et al., 1987). Disorganization of behavior (e.g., incongruous affect or markedly inappropriate attitude) 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 (postsy psychotic 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 stereotypes (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 up to 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.

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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 (Lenz 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; Touloupoulo 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; Capparelli 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 (Pa 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

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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 intrauterine 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 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 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 (Andreassen 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., 2000; 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 multi-dimensional 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 I 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., 2005; 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 (Thornicroft 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 (Maglione 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

![Understanding The Phenotypic Heterogeneity of Schizophrenia: Dimensions and Staging](image-url)

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.

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and treatment response. The dimensions are analogous to the subtypes (positive-paranoid; negative-simple; disorganization-disorganized; mood-schizo-affective; 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 etio-pathogenetic processes associated with distinct risk factors (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 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 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, clinico-pathological 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 Delespauil, 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 Ib, 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 thus far been principally applied to early detection and treatment of schizophrenic illness (prodrome or initial psychotic episode) (Hafner and Maurer, 2006; Lieberman et al., 2006; Rieber-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 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.

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).

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Conflict of interest

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