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Boundaries of schizophrenia

Caleb M. Adler, MD*, Stephen M. Strakowski, MD

Department of Psychiatry, Bipolar and Psychotic Disorders Research Program, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0559, USA

Psychiatric nosology has been a subject of debate since the earliest classifications of mental illness. Descriptions of affective illnesses were recorded by classical Greek sources, and by the first century AD clear descriptions of psychotic illness appeared in literature [1]. For much of the following 2 millennia, diagnostic debates centered on the cause and nature of mental illness itself, until by the early nineteenth century, the medicalization of psychiatric illness had become well established. The provenance of the specific syndrome now termed *schizophrenia* largely dates back to this period, when Morel first coined the term *dementia precoce*, to describe a syndrome that included a progressive, heritable decline in function [2]. The term was later translated as *dementia praecox* by Kraepelin and broadened to include catatonic, hebephrenic, and paranoid forms of the illness [1–3]. Debate over the boundaries of schizophrenia, similar to the debate over the internal integrity of schizophrenia as an illness, has been present from the first tentative descriptions of the phenomenon as a medical condition. In his description of *dementia praecox*, Kraepelin differentiated this syndrome from the affective disorders that he grouped together as manic-depressive psychosis [1,4,5]. Kraepelin's conceptualization of schizophrenia as a unitary and distinct condition, which is grounded in an internal consistency of symptoms coupled with observed commonality of course and outcome variables, continues to be the prevailing nosologic paradigm today and is reflected in the definitions of schizophrenia and other psychotic and affective illnesses that appear in DSM IV [6,7]. DSM IV also includes "intermediate" syndromes (ie, schizoaffective disorder) that incorporate aspects of schizophrenia and affective disorders. Debate over the separation of schizophrenia from affective disorders, particularly bipolar disorder, has never been resolved. Investigators from the nineteenth century until the present have suggested that

* Corresponding author.
E-mail address: cal.adler@psychiatry.uc.edu (C.M. Adler).

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current classification systems may be flawed, and despite the acceptance of the current diagnostic paradigm in DSM IV, significant objections to the differentiation of schizophrenia from affective disorders, particularly bipolar disorder, continue to be raised.

Other psychotic disorders defined as separate clinical entities in DSM IV have been suggested to be part of a "schizophrenia spectrum." Evidence is particularly strong for the schizotypal personality (SPD) and schizophreniform disorders. To varying degrees, individuals with these disorders manifest aspects of schizophrenia-like symptoms but do not meet full criteria for the illness. Although not classically included in the schizophrenia spectrum disorders, obsessive-compulsive disorder (OCD) also has been suggested to be related to schizophrenia, with obsessive thoughts forming one end of a continuum of symptoms that includes frank psychosis at the other extreme [8,9].

The ultimate answer to where the boundaries of schizophrenia lie with regard to related illness must await better understanding of the cause of schizophrenia and other psychiatric disorders. One approach to addressing this debate, however, is to compare the demographics, evidence for cause, phenomenology, and pathophysiology associated with schizophrenia and other illnesses in an effort to clarify similarities and important distinctions between the disorders.

Bipolar disorder

Schizophrenia is characterized by a combination of psychotic and affective symptoms, including delusions, hallucinations, and negative symptoms, and functional decline over the course of the illness. As described in DSM-IV, bipolar disorder is characterized by a pattern of recurrent affective episodes including depressed and manic phases with intervening periods of euthymia. Although not explicitly included in the illness criteria, there has long been an assumption, now widely questioned, that these euthymic periods are associated with a return to baseline function. During psychotic exacerbations, schizophrenia and bipolar disorder may present similarly and can be difficult to differentiate. Kraepelin, although maintaining the diagnostic distinction between dementia praecox and manic-depressive psychosis, noted the potential impossibility of differentiating acute episodes of each.

In addition to psychotic symptoms, schizophrenia classically is marked by a decline in cognitive function that includes decrements in IQ and a pattern of deficits marked by decreased performance on attention and working memory tasks [10,11]. These deficits have been observed consistently across a wide range of studies and may play a significant role in the functional decline associated with the illness [12,13]. Although relatively few studies have examined schizoaffective disorder alone, patients with schizoaffective disorder also have been observed to experience deficits in attention and memory performance compared with healthy controls [11,14] and to show decrements in performance similar to those seen in patients with schizophrenia [15]. These deficits may persist despite improvement in affective symptoms [14].

Findings in patients with bipolar disorder are more controversial. Although many studies of patients with bipolar disorder have observed subjects to show a normal IQ [10,16], a few studies using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and other neurocognitive batteries noted decreased cognitive performance compared with healthy controls [16–18]. Patients with bipolar disorder show deficits in many of the same cognitive domains as patients with schizophrenia. Although patients with bipolar disorder generally perform well on tests of simple attention, even euthymic bipolar patients perform more poorly than healthy controls on tests of attention that incorporate a measure of executive function [16,19–23]. Similarly, several studies observed decreased working memory performance in euthymic patients with bipolar disorder compared with healthy controls [16,19,23–26]. Cognitive performance is degraded further during affective episodes [22,27–30]. Although most direct comparisons have found patients with schizophrenia to perform more poorly than bipolar patients on cognitive measures, differences seem to be more of degree than of nature [10,13,31]. The gradual decline in function that has characterized schizophrenia since Morel's initial characterization of the illness does not differentiate schizophrenia from bipolar disorder. Several lines of evidence suggest that despite classic conceptualizations to the contrary, many patients with bipolar disorder do not return to baseline between affective episodes. Some studies suggest that bipolar disorder may be marked by a gradual deterioration in function that is accompanied by an increased likelihood to experience further symptoms and decrements in performance on memory tasks [26,32–34].

Cognitive changes in patients with schizophrenia may be related to developmental abnormalities, including behavioral abnormalities, which have been observed quite early [35]. Torrey and associates [36] reported on monozygotic twins discordant for schizophrenia who showed developmental differences by age 5. Patients with schizophrenia also frequently show early evidence of minor physical abnormalities, including dermatoglyphic asymmetries and atypical handedness [37–39]. Other minor physical abnormalities may occur with greater frequency in patients with schizophrenia compared with healthy subjects, versus siblings and healthy controls [40,41]. Alexander and coworkers [42] similarly noted a statistical trend toward a greater number of minor physical abnormalities in schizophrenic patients. Studies of patients with bipolar disorder suggest that the disorder may be associated with fewer developmental abnormalities than schizophrenia. Several studies failed to identify increases in minor physical abnormalities in populations of bipolar patients or of mixed groups including bipolar patients compared with healthy subjects or controls and healthy siblings [40–42]. Jelovac and colleagues [38] on direct comparison reported only minimal differences, however, in dermatoglyphic findings between schizophrenic and bipolar patients. Other investigators reported finding dermatoglyphic asymmetries in patients with bipolar disorder suggestive of congenital abnormalities [43].

Schizophrenia and bipolar disorder are characterized by marked demographic similarities. Schizophrenia occurs with a prevalence of approximately 1% that varies relatively little across demographic groups, although there are regional areas and family groupings in which schizophrenia seems to be more common [37,44–46]. Bipolar disorder shows a lifetime prevalence of approximately 0.8% and shows more variability by region [37,47,48]. Other affective illnesses are more variable; major depression ranges in prevalence by region from approximately 1.5% to 19% [37,48]. Prevalence rates may be highly dependent on diagnostic criteria, however. Kraepelin found manic-depressive psychosis to be significantly more common than dementia praecox in his original treatment studies [7,49]. Schizophrenia and bipolar disorder are approximately equally distributed between genders, with some intra-disorder variation, in contrast to major depression, which occurs significantly more frequently in women than men [37,44,47]. Schizophrenia usually appears in late adolescence or early adulthood, although it may appear in childhood, and there is a secondary peak in early middle age [44]. Bipolar disorder appears at approximately the same age, although it too may appear in childhood; patients documented in the Epidemiologic Catchment Area Study had a mean age of onset of 18 years [47]. In contrast, major depression most commonly appears at approximately 25 to 35 years old. Schizophrenia shares with bipolar disorder a preponderance of winter and spring births. Schizoaffective disorder shares a similar winter/spring skew in births, with births more common from December to March; depression shows a predominance of births from March to May [50–52]. The increase in urban births observed in patients with schizophrenia also may be associated with psychotic affective disorders [53,54]. Nonetheless, despite other demographic similarities, there is a socioeconomic split between schizophrenia and bipolar disorder. Bipolar disorder has a higher prevalence in upper income brackets, whereas schizophrenia is more common in lower socioeconomic groups [37]. This disparity may be related to the "downward drift" theorized to drive the relatively lower socioeconomic status of patients with schizophrenia [55]. It is possible, however, that this split is related more to disparities in diagnosis rather than intrinsic differences in these illnesses and does not negate the clear similarity in the demographics of schizophrenia and bipolar disorder, a similarity that does not extend to other affective illnesses.

There are similarities in the epidemiology of schizophrenia and bipolar disorder. Schizophrenia has long been conceptualized as being at least partially an inheritable disease. As early as Morel's first description of dementia precoce, schizophrenia was regarded as an intergenerational illness [2]. Inheritance patterns support suggestions that development of schizophrenia involves a combination of genetic susceptibility with environmental factors of some kind. The incidence of schizophrenia is approximately 10 times higher in first-degree relatives of patients with schizophrenia than in the general population, and studies of monozygotic twins suggest an approximately 60% concordance [56]. Affective disorders similarly show evidence of requiring a combination of genetic vulnerability with environmental insult. Bipolar disorder occurs with a concordance rate among monozygotic twins of approximately 65% to 80% [57,58], although a high monozygotic concordance rate extends to other affective illness: Major depressive disorder has shown a monozygotic concordance rate of approximately 46% [59]. Although schizophrenia shows a relative stability across populations, schizophrenia and affective disorders have been observed to occur at a higher than expected incidence in several distinct family and geographic groups. Other, less direct evidence of possible genetic links include an association between obstetric complications and familial risk of both disorders. Perinatal complications are more common in individuals with familial risk of schizophrenia and bipolar disorder [60,61].

Studies of familial transmission of these disorders suggest distinct genetic causes. In one study examining the offspring of schizophrenic and affectively disordered patients in New York, children at high risk for schizophrenia were more likely to develop not only schizophrenia, but also schizoaffective disorder. Children of patients with affective disorders were equally as likely as children of schizophrenic patients to develop schizoaffective disorder but did not show an increased incidence of schizophrenia [62]. Maier and colleagues [63] and Gershon and colleagues [64] found no increase in the incidence of bipolar disorder in relatives of patients with schizophrenia, although Meier and colleagues noted an increased incidence of unipolar depression. Kendler and associates [65] found no shared family relationship between schizophrenia and nonpsychotic affective disorders but did find an increased incidence of psychotic affective illness and schizoaffective disorder. Other studies examining first-degree relatives of patients with bipolar disorder observed no increase in the incidence of schizophrenia but observed an increase in the incidence of schizoaffective disorder [57]. Relatives of patients with schizoaffective disorder have an increased risk of schizophrenia and bipolar disorder and other affective illness, although family members diagnosed with affective illnesses were more likely to show psychotic symptoms [57,64–67]. Linkage studies are ambiguous. Although there is some overlap in suspected susceptibility loci between bipolar disorder and schizophrenia, the data are incomplete. Berrettini [57,68] suggested overlap at the 18p11.2, 13q32, 22q11, and 10p14 sites. Other investigators suggested overlaps in loci on chromosomes 10, 13, 18, and 22 [69,70].

The causes of schizophrenia and bipolar disorder have been theorized to involve a combination of genetic susceptibility with environmental insults. Development of schizophrenia has been associated with an increased rate of perinatal complications, including obstetric complications [71–74]. Patients who later develop bipolar disorder also show increased perinatal complications compared with siblings and unrelated, nonaffected control subjects and an increased rate of obstetric complications [75–77]. Gunduz and colleagues [78] found that obstetric complications did not differ among schizophrenic, schizoaffective, and major affective patients but also failed to identify a difference in complication rate between schizophrenic patients and healthy controls. Although the incidence of perinatal complications seems to be similar between schizophrenic and affective patients, pregnancy and birth complications may be more severe in schizophrenic patients than in bipolar patients [60]. Perinatal insults seem to be nonspecific in both populations.

Clearer distinctions arise in comparing evidence of neuropathology. Schizophrenic patients show a pattern of diffuse neurostructural changes suggestive of cortical atrophy compared with healthy subjects, including reduced brain weight and volume and increased ventricular cerebrospinal fluid [79,80]. Studies show enlarged third and lateral ventricles in first-episode and chronic patients, and in a study of monozygotic twins discordant for schizophrenia, larger ventricle-to-brain ratios were found in the affected twins [81–85]. Increased ventricle size correlates with measures of psychopathology in patients with schizophrenia and may be associated with poor outcome [81,83]. In contrast, few studies have observed changes in whole brain volume or cortical atrophy in patients with bipolar disorder. Although ventricular enlargement has been noted consistently, the significance of these findings in the absence of evidence of cortical atrophy is not clear [86]. On direct comparison, postmortem and imaging-based studies showed decreased brain weight and volume in schizophrenic patients compared with patients with mixed affective and bipolar disorders [124,125]. Schizoaffective patients do not differ significantly from either bipolar or schizophrenic patients on ventricular size or evidence of cerebral atrophy [126,127].

In addition to evidence of generalized atrophy, several studies have identified evidence of regional pathology in patients with schizophrenia. Studies suggest that frontal and prefrontal pathology play an important role in the pathophysiology of schizophrenia. Specific functional regions of the frontal cortex, including portions of the prefrontal and orbitofrontal cortex, are decreased in volume, versus healthy controls [87–90]. Prefrontal volume inversely correlates with severity of illness on some measures of psychopathology [90]. Functional imaging studies also support suggestions that prefrontal cortical dysfunction is involved in schizophrenia. Studies using single-photon emission tomography, positron emission tomography, and magnetic resonance imaging found relative hypofrontality in patients with schizophrenia at rest and during performance of specific cognitive tasks requiring prefrontal activation, such as verbal fluency and working memory [91–97]. Magnetic resonance spectroscopy (MRS) studies showing reduced levels of n-acetyl aspartate (NAA) suggest prefrontal pathology as well [98,99]. Significantly fewer studies of prefrontal and frontal cortex structure or function have been performed in patients with bipolar disorder, and these studies produced mixed findings. Some studies noted decreased frontal cortical volume, and there is some evidence for deficits in prefrontal cortical function [86]. Sax and coworkers [100] observed that impaired performance on a continuous performance task in euthymic bipolar patients correlated with decreased prefrontal volume. Using functional magnetic resonance imaging, the authors observed increased dorsolateral prefrontal cortex (DLPFC) activation in euthymic bipolar patients compared with healthy controls during performance of a working memory task [101]. These findings are consistent with observations by Manoach and colleagues [102] of increased DLPFC activation in patients with schizophrenia with a similar working memory task. MRS studies of the frontal cortex in patients with bipolar disorder also consistently noted evidence of altered neuronal membrane qualities, and several positron emission tomography studies noted altered frontal cortical metabolism in patients with bipolar disorder during manic and dysthymic states [86].

Overall, temporal lobe volume and medial temporal structures have been reported widely to be reduced in patients with schizophrenia [87,103]. In postmortem studies, schizophrenia patients showed decreased hippocampal, parahippocampal, and amygdaloid volume compared with controls, and studies of monozygotic twins discordant for schizophrenia showed decreased hippocampi in the affected twin [84]. Decreased hippocampal volumes are associated with decreased cognitive performance in first-episode schizophrenic patients [104]. Other evidence suggests the involvement of amygdala and perihippocampal gyrus in at least some aspects of schizophrenic psychopathology. Other regions, including the superior temporal gyrus of the temporal cortex, also may play an important role in the pathophysiology of schizophrenia and are altered in volume compared with healthy controls [82,87]. In contrast to studies in patients with schizophrenia, studies of the temporal cortex in bipolar disorder typically have not observed changes in overall volume or function [86]. Anterior and medial temporal structures have been noted to be decreased in volume, however [105–108]. Pearlson and coworkers [108] noted enlargement of the anterior superior temporal gyrus, and two other studies observed increased volume of medial temporal structures in patients with bipolar disorder compared with healthy volunteers [86]. Studies of monozygotic twins discordant for bipolar disorder showed similar medial temporal differences [109]. Baseline cerebral metabolism and blood flow also differed in patients with bipolar disorder, in the temporal cortex as a whole and in specific regions, including the superior temporal gyrus and medial temporal structures [110–114]. Other functional studies are limited but also suggest changes in activity in medial temporal structures, including the amygdala and hippocampus [86]. MRS findings are equivocal; temporal NAA-to-creatine ratios did not differ in patients with bipolar disorder, but phosphomonoesters (PME) was found to be elevated [86,115,116]. Investigators directly comparing patients with schizophrenia and bipolar disorder noted alteration in the superior temporal gyrus of patients with schizophrenia but not in a directly compared population of bipolar patients. Similarly, Rossi and colleagues [128] noted decreased temporal cortex and hippocampal volumes in schizophrenic patients but not in a cohort of patients with bipolar disorder.

Some similarities in neurophysiologic findings between patients with schizophrenia and bipolar disorder have been observed elsewhere in the brain. Posterior cortical regions, including areas thought to be involved in the posterior attentional pathways, such as the inferior parietal lobule, seem to be involved in schizophrenia and may be involved in bipolar disorder. Subcortical and midline regions, including the basal ganglia, thalamus, and cerebellum, seem to be structurally and functionally abnormal in patients with schizophrenia [82,87]. Several authors suggested that functional deficits in these regions help account for the wide range of symptoms observed and aspects of the cognitive deficits observed in schizophrenia. Findings in midline structures, such as the basal ganglia, thalamus, and cerebellum, have been more mixed in patients with bipolar disorder. Investigators identified structural and functional changes compared with healthy controls and between monozygotic twins discordant for bipolar disorder [86]. Findings include enlargement of the basal ganglia or portions of the basal ganglia [117,118]. Thalamic findings have been more mixed; although some studies found the thalamus to be enlarged compared with healthy controls, other studies failed to replicate these results [100,118–120]. Similarly, several MRS studies noted evidence of metabolic and structural changes in the basal ganglia and thalamus of patients with bipolar disorder, including elevated NAA-to-creatine/phosphocreatine, choline-to-creatine/phosphocreatine and inositol-to-creatine/phosphocreatine ratios [121–123]. During affective episodes, bipolar patients experienced changes in caudate and thalamic metabolism and changes in cerebral blood flow [106,111].

Although differences in treatment response in schizophrenia and affective disorders, particularly bipolar disorder, previously seemed stark, differences in pharmacologic efficacy have never been as clear-cut as prescribing patterns might suggest. From the 1950s until the relatively recent advent of atypical antipsychotic medications, the mainstay in the treatment of schizophrenia remained neuroleptic medications. These medications also have been used widely in the treatment of acute mania, generally in an adjunctive setting [129,130]. Several studies showed efficacy of neuroleptic medications in the treatment of mania, although some data suggested that these medications are less effective than lithium and may precipitate depressive symptoms in vulnerable individuals [129,131–133]. Similarly, lithium, arguably the most widely used treatment for bipolar disorder, has been reported to include some antipsychotic efficacy in patients with schizophrenia but without demonstrated efficacy in long-term control of symptoms [134,135]. The utility of other antiseizure medications widely used in the treatment of affective symptoms and mood stabilization in bipolar patients has not been shown for the treatment of schizophrenia. Some data suggest, however, that the use of valproic acid combined with antipsychotic medications increases response rates in schizophrenia, and response rates in bipolar disorder increase with the use of a combination of antipsychotic and mood-stabilizing medications.

The advent of the atypical antipsychotics has led to a new convergence in treatment for schizophrenia and bipolar disorder. Clozapine and olanzapine have shown convincing efficacy in the treatment of schizophrenia and bipolar disorder, and other atypical antipsychotic medications widely used with schizophrenia seem promising for the treatment of bipolar disorder [131]. In view of the heterogeneous nature of the symptoms associated with schizoaffective disorder, a wide range of mood stabilizers and antipsychotic medications have been reported to be effective.

Several lines of evidence support suggestions that schizophrenia and bipolar disorder represent aspects of a single, larger illness or group of overlapping disorders. Schizophrenia and bipolar disorder may be indistinguishable in presentation, may include a spectrum of cognitive deficits that seem to increase with severity over time, and may be treated with similar pharmacologic interventions. The demographic overlap is impressive, and there are pronounced similarities in the proposed causes. Both disorders involve suggestions of environmental insults, although the evidence for related developmental abnormalities is greater in schizophrenia. Both disorders are postulated in involve genetic susceptibility, and there are overlaps in proposed susceptibility loci. Schizophrenia and bipolar disorder may be associated with abnormalities of diffuse, largely overlapping brain regions.

Closer review of the data call into question, however, the nature of the observed similarities between schizophrenia and bipolar disorder. The common causative framework, a combination of genetic susceptibility with environmental insult, is unique to neither schizophrenia nor bipolar disorder, and despite some hypothesized overlap between susceptibility loci, the genetic data are unclear for either disorder. Epidemiologic data do not support suggestions that schizophrenia and bipolar disorder represent a single disorder or group of interrelated disorders. There is little convergence of the two disorders within single-family lineages, and in instances in which there is familial concurrence, schizophrenic patients with first-degree relatives diagnosed with bipolar disorder seemed to be qualitatively different from patients with schizophrenia who did not have such a relative [207].

In addition to the epidemiologic data, there are provocative differences in apparent pathophysiology. Evidence of developmental abnormalities is much clearer in patients with schizophrenia, and there seems to be some potentially significant variation in affected brain regions. Cognitive deficits, which presumably reflect the nature of the underlying neuropathology, also vary a great deal in degree. Deficits in performance of attention and memory tests in patients with bipolar disorder frequently are confined to more cognitively complex versions of the task. Although some similarities between schizophrenia and bipolar disorder in treatment are clear, the lack of complete cross-efficacy suggests some fundamental distinctions in psychopathology. Although studies using discriminant analysis of symptom clusters may be limited in their utility, Brockington and colleagues [208] observed a separation of schizophrenia and bipolar disorder consistent with the current nosology.

Although data are limited, there is little convincing evidence that other "intermediate" syndromes, such as schizoaffective disorder, similarly represent distinct clinical entities. The nature of schizoaffective disorder historically has been amorphous; few other psychiatric disorders have undergone as many significant changes in diagnostic criteria since conceptualization. Although studies directly comparing schizophrenic and bipolar patients with patients with schizoaffective disorder have been limited, few clear patterns differentiate schizoaffective disorder from either syndrome. Where schizophrenia and bipolar disorder are most similar, in areas such as demographic distribution and neuroanatomy, there is little to distinguish schizoaffective disorder [127]. Epidemiologically, schizoaffective disorder appears within separate family lineages containing schizophrenic and bipolar family members. Several investigators suggested that rather than representing a distinct disorder, as the current nosologic orthodoxy dictates, or representing the intermediate phenotype in a continuum of illness, as proponents of the unitary nature of schizophrenia and bipolar disorder would suggest, schizoaffective disorder represents an area of overlapping symptoms between schizophrenia and bipolar disorder. Gershon and colleagues [64] noted that with discrimination analysis patients with schizoaffective bipolar type assorted with bipolar disorder, whereas schizoaffective disorder, non–bipolar type patients seemed to assort with schizophrenia.

Obsessive-compulsive disorder

In addition to the long-standing debate as to divisions between schizophrenia and bipolar disorder, observations of phenomenologic overlap between OCD and schizophrenia have led to suggestions that OCD might represent part of a continuum of symptoms or represent a *forme fruste* of schizophrenia, existing on the same psychotic continuum [8,9]. Several lines of evidence lend credence to these suggestions. Prevalence of obsessive-compulsive symptoms in patients with schizophrenia is much higher than is observed in the general population, ranging from 8% to greater than 50%, depending on the methodologies employed [136,137]. OCD symptoms may occur years before psychotic decompensation, but patients initially diagnosed with OCD are significantly more likely to be diagnosed later with schizophrenia [138,139]. Investigators suggested that patients with schizophrenia may have specific obsessive-compulsive subtype of schizophrenia that may be associated with greater functional impairment [140–143]. Nonetheless, OCD symptoms seem to be distinct from psychotic manifestations of schizophrenia. The number of patients with obsessive-compulsive symptoms and the extent of those symptoms did not change with resolution of psychotic symptoms [136].

Structural, neuropsychologic, and functional studies of patients with OCD suggest some overlap with the pathophysiology of schizophrenia, including evidence of structural and functional changes in orbitofrontal cortex; DLPFC; superior frontal cortex; anterior cingulum; structures in the temporal cortex, particularly the anterior temporal cortex and superior regions of the temporal cortex; and midline structures, including basal ganglia and thalamus [101,144–156]. Consistent with the last, Poyurovsky and colleagues [137] and others [157,158] found schizophrenic patients with concomitant symptoms of OCD showed a trend toward increased parkinsonism and increased tardive dyskinesia.

Some neurocognitive studies also reported a degree of commonality between patients with OCD and schizophrenia. Patients with OCD are impaired on the Trail Making Test and other tests of executive function [159]. In contrast, although some studies noted deficits in patients with OCD in performance on the Wisconsin Card Sorting Test (WCST), others did not, and in a direct comparison between patients with OCD and patients with schizophrenia, the former performed better on the WCST [148,159–162].

In treatment, similarities between patients with OCD and patients with schizophrenia are limited. Although some studies have reported efficacy, neuroleptic medications have never been used widely for treatment of OCD [163,164]. Medications efficacious for OCD, such as clomipramine and selective serotoninergic reuptake inhibitors, have not been found to be effective as monotherapy in the treatment of schizophrenia. Newer antipsychotic medications present a more complicated picture. Several case reports, open and single-blind studies, and at least one double-blind study reported positive responses in treatment-resistant patients with OCD to the use of atypical antipsychotics [165–169]. In contrast, several reports noted increases in OCD symptoms in schizophrenic patients receiving these medications [158].

Although the similarities in the phenomenology and some aspects of schizophrenia and OCD are provocative, there is insufficient evidence to conclude that the two disorders represent aspects of a unitary illness. Nonetheless, although speculative, functional evidence of prefrontal and striatal involvement in OCD indicate that obsessive-compulsive symptoms in OCD and schizophrenia arise from involvement in some of the same neuronal pathways. Schizophrenic patients with obsessive-compulsive symptoms may be manifesting the consequences of greater involvement of these regions in their illness.

Schizophrenia Spectrum Disorders

Several nonschizophrenic diagnoses, including SPD and schizophreniform disorder, have been suggested to be part of a schizophrenia spectrum [170], SPD, an Axis II disorder in DSM IV, is characterized by evidence of odd behavior, magical thinking, and problems with social interaction [6]. SPD was identified as part of a schizophrenia spectrum in 1962 and shows some profound similarities with schizophrenia [171]. The incidence of SPD ranges widely from 5.1% to 0.6%, in a large Norwegian study with a greater incidence of SPD in cities similar to that reported with schizophrenia [172,173].

Anatomic imaging studies of patients with SPD suggest several morphometric similarities with schizophrenia, including increased cerebrospinal fluid, decreased temporal cortical volume and gray matter, and decreased caudate volumes that correlate with some working memory deficits [170, 174–176]. Other similarities include a loss of interhemispheric connections and some thalamic changes [170,177]. Important differences between SPD and schizophrenia include normal ventricular size in patients with SPD; smaller putamen; and, significantly, no change in medial temporal structures or prefrontal cortex [170,174,175,178]. Functional imaging studies also show a pattern similar in some respects but not identical to patients with schizophrenia. Patients with SPD show temporal metabolic activity intermediate between healthy controls and patients with schizophrenia but have a relative decrease in putamen metabolism and little prefrontal deficit [179,180]. Functional changes during performance of the WCST also differ from those seen in patients with schizophrenia [170]. Although homovanillic acid levels have been observed to be elevated in patients with SPD, striatal dopamine release in response to d-amphetamine and 2-deoxyglucose provocation studies did not differ from that of healthy controls [170]. Although patients with SPD do not show prefrontal cortical changes, similar cognitive deficits have been identified, including working memory, verbal learning, and sustained attention. Patients with SPD also show slowed visual processing similar to that of schizophrenics [181]. Other findings also mirror those seen in schizophrenia. Patients with SPD show evidence of aberrant eye tracking and reduced prepulse inhibition [170,174].

Epidemiologic studies suggest a link between SPD and schizophrenia [182–184]. Significantly higher rates of SPD occur in families of patients with schizophrenia. Similarly, there is an increased risk of schizophrenia in families with SPD [170,184–188]. Nonetheless, rates of SPD are higher in first-degree relatives of patients with SPD than in first-degree relatives of patients with schizophrenia. In addition to cosegregating with schizophrenia, SPD has been found to be linked with affective disorders [189].

SPD frequently does not require pharmacologic intervention, but antipsychotics may be used to treat symptoms and may improve cognitive performance [170,190,191]. The use of antipsychotics in Axis II disorders is fairly nonspecific, however, and other medications have been reported to be helpful in the treatment of SPD [190].

Several lines of evidence suggest that SPD is related to schizophrenia. In addition to phenomenologic similarities, the genetic links, partial overlap in structural and functional imaging findings, and cognitive similarities support these suggestions. Siever and colleagues [170] and Shihabuddin and coworkers

[179] plausibly suggested that differences observed between the syndromes result from functional sparing, particularly in the prefrontal cortex with resultant lack of general cognitive decline observed with schizophrenia and a less hyperdopaminergic state. Nonetheless, several elements of the disorder suggest that SPD may be a more heterogeneous disorder, elements of which are not related to schizophrenia [192]. The increased rate of SPD versus schizophrenia in first-degree relatives of patients with SPD suggests that the disorder only partially overlaps with schizophrenia, although this equally could be interpreted as arising from a heritability of severity. More telling is familial data suggesting genetic concordance between SPD and affective disorders and schizophrenia. The possibility that SPD includes but is not limited to patients with a mild form of schizophrenia is supported by studies noting distinct heritability patterns for syndrome subsets [189,192–194].

Schizophreniform disorder is another syndrome that has been hypothesized to be part of the schizophrenia spectrum disorders. Schizophreniform disorder first was proposed by Langfeldt [195] as a form of mild schizophrenia and first appeared in DSM III to represent a disorder resembling schizophrenia with a limited duration. Schizophreniform disorder has a prevalence of approximately 3% to 4% and approximately equal gender distribution [66,196,197]. Zarate and associates [196] found no difference between schizophreniform disorder and schizophrenia in demographic characteristics. As defined by the illness, patients with schizophreniform disorder show a schizophrenia-like presentation but with a greater propensity toward positive symptoms and fewer negative symptoms [197]. Although some investigators have observed it to have a more benign course and better outcome than schizophrenia, others note no significant difference between the outcome of the two syndromes [196–198].

Familial studies also support a relationship between schizophreniform disorder and schizophrenia. Kendler and associates [66] found that first-degree relatives of patients with schizophreniform disorder had increased risk for schizophrenia, and Iacono and coworkers [199] found no difference in the prevalence of schizophrenia between relatives of patients with schizophrenia and schizophreniform disorder. Coryell and Tsuang [200] had similar findings, as did Pulver and colleagues [201].

Several investigators previously concluded that schizophreniform disorder is not a meaningful diagnosis and should be classified as schizophrenia [196,202,203]. Although some studies found a few patients with schizophreniform disorder to be experiencing affective, rather than schizophrenia-like, symptoms, which may account for Kendler and Walsh's finding that the increased rate of schizophrenia spectrum disorders in first-degree relatives of patients with schizophreniform disorder is still less than that observed with schizophrenia [197,202,204,206], most studies found that most schizophreniform disorder patients go on to develop schizophrenia, with only a few achieving complete recovery [204,205] and with a long-term outcome similar to that seen in patients with schizophrenia [170].

Summary

The frontiers of schizophrenia are being increasingly challenged from several directions. In addition to ongoing debate as to divisions between schizophrenia and disorders of the schizophrenic spectrum, including schizotypal personality disorder and schizophreniform disorder, it has been suggested that obsessive-compulsive disorder might overlap phenomenologically with schizophrenia. There has been a long debate around the relationship of schizophrenia to affective disorders, particularly bipolar and schizoaffective disorder. The evidence suggests that although schizotypal personality and schizophreniform disorders are not homogeneous syndromes, they are related to or represent milder forms of schizophrenia. Obsessive-compulsive disorder seems to involve pathology in many of the same regions as observed in some patients with schizophrenia, which may account for the significant incidence of obsessive-compulsive symptoms in a subset of patients with schizophrenia. Despite similarities between schizophrenia and bipolar disorder, significant differences extend across suggested causes, phenomenology, and pathophysiology. These findings support the current conceptualization that the two disorders represent distinct disorders, probably with heterogeneous causes, rather than the ends of a spectrum of symptoms comprising a single syndrome. Schizoaffective disorder likely is made up of patients from the schizophrenic and bipolar cluster of illnesses. The long-standing debate as to the boundaries of schizophrenia is ultimately must await the eventual further elaboration of the underlying causes of schizophrenia and other psychotic disorders.

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