Etiologic, Phenomenologic, and Endophenotypic Overlap of Schizophrenia and Bipolar Disorder

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Abstract

This review examines the history of psychiatric nosology, with particular reference to the nineteenth-century origins of the concepts of manic-depressive illness and schizophrenia as distinct clinical syndromes and their evolution and diagnostic refinement over time. I document how the terminology applied to these entities has generated controversy, and discuss the ways in which the resulting diagnostic entities as defined by pure phenomenological symptom descriptors fail to capture discrete diagnostic distinctions, leading some researchers to posit an illness continuum rather than separate disorders. Furthermore, the two syndromes overlap substantially on multiple biologic measures, and clarity is lacking as to the underlying etiology and pathology necessary to move from descriptions of clinical syndromes to diseases. I next examine how biologically based classifications agnostic to conventional diagnostic schemes may be useful and how these are being implemented in practice, and conclude by summarizing where such approaches are likely to lead.

Contents

INTRODUCTION

> The ultimate aim of clinical medicine is to discover the causes of disease, to classify diseases by their causes and to base prevention and treatment on this etiological knowledge.
>
> Mayer-Gross et al. (1969)

> We have in front of us a fruit called psychosis, and we don't know whether it's a citrus that will divide itself into separable sections or an apple that we must divide along arbitrary lines.
>
> Belmaker & van Praag (1980)

A BRIEF OVERVIEW OF TAXONOMY

In reviewing the evidence for the nature of the overlap (if any) between schizophrenia and bipolar disorder, we first need to take a brief detour through the context in which separate syndromes and disease entities are delineated. Nosology, the discipline of classification in medicine, draws many concepts and procedures from taxonomy, the theory and practice of classifying living organisms (although diseases are not objects in the world), but their classification similarly necessitates processes of careful observation and factual differentiation.

The ultimate goals of classification in psychiatry are similar to those in natural science generally, and to discard classification completely is to discard scientific thinking. There is no universally accepted classification of major psychiatric disorders. Lieber (1975) has argued that the concept of a disease's classification is limited by the extent of our understanding of that disease: Thus, the terms "symptom complex," "syndrome," "illness," and "disease" should be given only practicable definitions because we have limited understanding of pathology, i.e., no natural foundation for classification. As a consequence, our typical "taxa" are inevitably ill defined and grade diffusely into each other (Boteva & Lieberman 2003, Parshall & Priest 1993, Ruscio et al. 2006).

Diseases are generally classified by etiology (cause) or pathogenesis (mechanism of causation). A major problem in nosology is that diseases often cannot be defined and classified where etiology or pathogenesis is unknown, a particular problem for mental disorders, where the brain-mind gap is a large hurdle. Thus, diagnostic terms often only reflect a set of descriptions of a symptom or set of symptoms (syndrome). Problems inevitably arise when attempts are made to impose top-down biologically defined constructs onto traditional clinical syndromes, analogous to eighteenth-century physicians attempting to parse—in the absence of a known etiology—various forms of dropsy (edema or swelling of soft tissues due to accumulation of excess water), then considered a disease. In order to understand why administration of foxglove leaves (*Digitalis*) was efficacious in some cases of dropsy but not in others showing identical symptoms and signs, physicians first had to discover the underlying difference between edema due to heart failure and that due to kidney disease, protein deficiencies, and other underlying causes. Thus, one would not dismiss the use of laboratory tests for protein in the urine because they were negative in many cases of dropsy; in fact, such tests identify a subgroup of individuals with dropsy suffering from a particular disease who respond to a specific treatment. Similarly, premature labor and epilepsy are familiar examples of a single syndrome in which identical clinical manifestations may have many underlying causes (Romero et al. 2014) and in which identification of the correct cause can lead to a specific rational basis for prognosis and treatment. A small number of psychiatric syndromes have yielded to the search for diseases (e.g., neurosyphilis, Alzheimer's disease); however, most have not. Unfortunately, despite the absence of useful knowledge regarding etiology or pathogenesis, most clinicians dealing with psychiatric illnesses have treated syndromes as if they were diseases, presuming biological knowledge that we substantially lack and inviting diagnostic confusion. Psychotic disorders such as schizophrenia are likely heterogeneous syndromes, currently grouped together by surface descriptions in the absence of etiologic and pathologic understanding. In a taxonomic parallel, a group of "flying things" would include bees, most birds, and flying fish (Ruscio et al. 2006).

Delineating diseases follows the rules of taxonomy, the branch of science involved in identifying and classifying organisms using information from a wide range of biological measurements and that has been widely applied in psychiatry to define putative syndromes and diseases. Distinctions between branches of living organisms are conceived as representing differences in quality and kind, not separation in seamless dimensions (degree, quantity, or magnitude)—for example, an animal may be a fish or insect but cannot be both (Ruscio et al. 2006). McHugh & Slavney (1998) clearly described "disease reasoning," a categorical method for disease differentiation and the necessary stages in demarcating the nature of any medical syndrome. Investigators begin with the use of clear, reliable, operational definitions of the stereotypical symptom clusters and clinical course, then the parsing of clusters by their underlying biologic abnormalities, followed by research directed at uncovering etiology, and ending with the demarcation of a disease entity. Ultimately, such categorization is important to psychiatrists and psychologists because it provides specific information for determining prognosis, appropriate treatment, and prevention. Similarly, deconstructing diseases is also important "for differential diagnosis, epidemiology, genetics and an understanding of the biological and psychological evidence" (Goodwin & Jamison 1990, p. 61).

KRAEPELIN'S CONTRIBUTIONS TO PSYCHIATRIC DIAGNOSIS

Prior to Kraepelin, classification of serious mental illnesses/major psychiatric disorders during the nineteenth century was messy and models were divided between "lumpers," e.g., adherents of the *Einheitspsychose* or unitary psychosis of Griesinger (1845) and Neumann, who conceived of all serious psychiatric illness as variants of a single disorder with no clear disease entities, and "splitters," e.g., advocates of the multiple French fine subdivisions among mood disorders.

Kahlbaum (1863, 1874) considered there was a correlation between etiology, brain pathology, symptom patterns, and outcomes that united some seemingly disparate clinical states into diseases. In 1863 he defined two logical groupings of major psychiatric disorders, with one such group having a poor course that progressed to dementia (Kahlbaum 1863). Kahlbaum's mode of thinking was taken up by Kraepelin, who—shocked by wide differences in terminology and conceptions among psychiatrists (Schorer 1982)—divided psychosis into two major discrete functional entities: dementia praecox (now termed schizophrenia) and manic-depressive illness; classifications were based on criteria including symptom patterns (as opposed to individual symptoms), clinical course, and outcome.

Kraepelin (1887, p. 294) stated, "The importance of external clinical science has been subordinated to consideration of the conditions of origin, course and will resulting from individual disorders. Thus all purely symptomatic categories have disappeared from the nosology." Kraepelin (1904) delineated manic-depressive illness as characterized by a repeated episodic course with intermittent recovery and possibly affectively tinged premorbid personality. In contrast, dementia praecox was marked by a steady downhill course into chronic dementia.

Kraepelin's approach was nosological and data oriented, with clinical summaries of individual patients being recorded on individual clinical record cards and typical case descriptions in his articles and books constituting vivid portrayals. He attempted to classify psychiatric syndromes by following up large numbers of patients over many years, endeavoring to (*a*) uncover commonalities, (*b*) define and operationalize disorders to derive a small number of natural disease units and serious mental illnesses, and (*c*) predict prognosis and history. Over time, he revised his classification scheme numerous times. His major classifications were "organic psychoses" of identifiable etiology or pathology (such as neurosyphilis and Alzheimer's disease) and "endogenous psychoses" lacking known structural pathology, such as schizophrenia, manic-depressive psychosis, paranoia, and personality deviations. He felt that schizophrenia and manic-depressive psychosis were expressions of real biological illnesses whose etiopathology he was initially confident would be elucidated quickly (Kraepelin 1909–13). Kraepelin postulated that schizophrenia was caused by "a definite disease process in the brain" with "impairment of function that is permanent and progressive" [Kraepelin 1912 (1907), pp. 221–23]. He posited the existence of a cortical pathology ("a disease process in the brain involving cortical neurons brought about by autointoxication as a result of a disorder of metabolism") [Kraepelin 1912 (1907), pp. 220–21] that he believed would yield to imminent neuropathologic discovery, paralleling the description of the dementing illness that had been recently described by his colleague and collaborator Alois Alzheimer. He also theorized that the associated poor clinical outcome implied ongoing brain degeneration. For manic-depressive illness, he believed that the main etiological factor was "defective heredity," i.e., genetic/familial influences [Kraepelin 1920b (1919), p. 219].

The hope was always that psychiatry would move from "merely classifying and categorizing diseases" to "understanding disease processes and how they interrelate" (Kraepelin 1920a). Thus, Kraepelin posited that "mental illness consisted of a finite number of natural disease units, each with its own distinct pattern of symptoms, etiology and anatomy, and that symptomatology could provide a means for classifying disease" (Greene 2007, p. 362).

It is important to note that Kraepelin's concept of manic-depressive illness differed from current American concepts of bipolar disorder in that it was based on recurrent major mood symptoms with and without mania and "on periods of exacerbation and remission... without significant deterioration" (Goodwin & Jamison 1990, p. 20). Thus, if recurrent, both unipolar mania and unipolar depression constituted particular manifestations of the illness, but mania not as "the distinguishing sign of a separate bipolar disorder as it is in today's American diagnostic

practice" (Goodwin & Jamison 1990, Introduction p. 20). Consistent with his emphasis on the course and outcome, Kraepelin subsumed severe, recurrent mood disorders into manic-depressive illness. Again, contrary to current understanding, Kraepelin viewed dementia praecox as a diverse grouping, subsuming several clinical forms and including what would now be termed schizoaffective disorder (Owen et al. 2007).

Also contrary to common belief, Kraepelin's models were guided by new observations, and he did not hold rigidly to his diagnostic dichotomy. By 1920 he actively debated whether his prior division of the two psychoses was correct: "We must, then, accustom ourselves to the idea that the phenomena of illness which we have hitherto used are not sufficient to enable us to distinguish reliably between manic-depressive illness and schizophrenia in all cases" (note the use of the word "schizophrenia" here) (Kraepelin 1920a, p. 730). In the same year, in his observations on patterns of mental disorder, he stated, "No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis. . . it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect" (Kraepelin 1920a, p. 730).

Manic-Depression Is Revised

In addition to the fact that the "natural course" of these illnesses is now inevitably affected by drug and other treatments not available in the late nineteenth century, it should be noted that many of the terms previously used by clinicians to define psychiatric disorders were imprecise and their meanings have changed over time; thus, the ground has shifted from the original constructs as delineated by Kraepelin and his generation of psychiatrists.

First, manic-depressive illness (originally conceived by Kraepelin as manic-depressive insanity) represented an agglomeration of illnesses described previously by French psychiatrists as many types of periodic disorders characterized by depressive or manic phases with variable lucid intervals. Kraepelin's contribution was to recognize these multiple manifestations as comprising a single nosologic entity in which he included isolated attacks of mania and depression [what would now be termed bipolar disorder and recurrent major depression, which are separated in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)]. The bipolar/unipolar distinction was elaborated by Angst (1966) and was proposed by Karl Leonhard (1979): "By which manic-depressive patients were grouped according to the presence or absence of a prior history of mania"(Goodwin & Jamison 1990, p. 66). The current US definition is much broader, as a single manic episode qualifies for diagnosis. Unipolar diagnosis required no prior course of illness, which also departed from Kraepelin's concept.

Dementia Praecox Becomes Schizophrenia

Kraepelin's work was built on by Eugen Bleuler (1911), who renamed the disorder "schizophrenia" and extended the boundary/inclusion criteria of the syndrome in his book *The Schizophrenias*. For example, Bleuler did not require the presence of clear-cut psychotic symptoms to make a diagnosis of schizophrenia. Like Kraepelin (although emphasizing this aspect much more), Bleuler doubted the existence a single etiology or a single disease entity for schizophrenia, and he tried to establish primary abnormalities common to all cases of the illness that were based on symptoms, albeit not ones that would be recognized currently as important in diagnosis. Thus, certain schizophrenia symptoms became identified as both specific and pathognomonic (i.e., splitting of thought

from feeling and behavior, formal thought disorder, blunted affect, autism, and ambivalence). In contradistinction, symptoms of affective illness were considered to be nonspecific, and manic-depressive illness could be diagnosed only after schizophrenia had first been excluded. Over time, as pointed out by Fischer & Carpenter (2009), the "dementia" of dementia praecox was ignored or explained away (e.g., any cognitive difficulties were attributed to distraction by hallucinations or sedation by antipsychotic medications). Cognitive impairment did not feature in Bleuler's descriptions or even in the fourth edition of the DSM (DSM-IV; Am. Psychiatr. Assoc. 1994), as diagnostic criteria relied on positive symptoms or noncognitive negative symptoms.

The term "psychosis" is also confusing because it has been used to denote conditions characterized by hallucinations, delusions, and formal thought disorder but alternatively to designate a mental illnesses as severe without reference to specific symptomatic content. Although Kraepelin clearly used the latter of these two definitions, in this article we use only the first. Psychotic symptoms can be seen in disorders of multiple etiology, including Alzheimer's and Huntington's diseases, sensory deprivation, cocaine-induced psychosis, and alcoholic delirium tremens. Clarifying which designation of psychosis is being employed has important consequences because the form of manic-depressive/bipolar illness with psychotic symptoms may be etiologically and pathologically distinct from that without; the Kraepelinian system draws no such clear distinction (e.g., Ketter et al. 2004), although Kraepelin clearly described cases of bipolar disorder with psychosis (Jablensky et al. 1993). As discussed below, the psychotic and nonpsychotic forms of bipolar disorder may be biologically distinct (Pearlson & Schaepfer 1999); unfortunately, many published studies do not draw this important distinction, so data are difficult to interpret.

Attempts to Refine Content Validity: Rise of the Neo-Kraepelinians

As outlined above, Kraepelin delineated dementia praecox in 1896 as a disease entity characterized by poor cognitive and social outcomes, and despite his reluctance to rely on particular pathognomonic symptoms (unlike Bleuler), he mentions both disorganization of thought and/or beliefs (positive symptoms) and decreased volition (a negative symptom) (Fischer & Carpenter 2009), plus an onset in youth or early life. Kurt Schneider (see Marneros et al. 1987) attempted to define schizophrenia-specific forms of psychotic symptoms (such as auditory hallucinations in which the patient is discussed in the third person). However, the specificity of such symptoms to schizophrenia was refuted by Carpenter and colleagues (1973), and consequently, current diagnostic systems contain no pathognomonic symptoms of schizophrenia, thus defining it as a diagnosis of exclusion (again, contrary to Bleuler). This issue had been stressed by Kraepelin himself (1920a, p. 518): "We must be very wary of claiming that a particular disorder is characteristic of one and only one particular disease process." Interestingly, Kraepelin [1990 (1899)] did not appear to regard mood as a primary classifier of manic-depressive illness; rather, circularity and good long-term prognosis were the defining features.

Problems with Kraepelin's Division

As recognized by most practicing psychiatrists, although a small number of patients are Kraepelinian prototypes, few patients with schizophrenia or bipolar illness fit the mold. As a consequence of the marked variability in symptoms and outcome, the apparent lack of a point of diagnostic rarity, and the unclear boundaries between the two illnesses, many patients are left in a diagnostic no-man's land and often receive different diagnoses at different times. Furthermore, outcome can be variable, and cross-sectional symptoms overlap considerably. The psychotic syndromes themselves often do not "obey the rules." For example, patients with a chronic persistent course often have marked affective symptoms and family histories of bipolar disorder (Ivleva

et al. 2010). Attempts to clarify diagnosis by carefully examining longitudinal outcome further reveal that some otherwise typical bipolar patients follow a progressive chronic course (Fischer & Carpenter 2008, Fischer & Carpenter 2009, Lee & Murray 1988, Malhi et al. 2001, Post 1992) or show chronically impaired functioning (Judd et al. 2005). Conversely, some otherwise typical schizophrenia patients appear to show good clinical recovery. Kraepelin's pupil's Zendig (1909) demonstrated that up to one-third of Kraepelin's original dementia praecox patients ultimately had good outcomes. Similarly, a more recent reanalysis by Kick (1981), who reassessed Kraepelin's own records of schizophrenia patients, detected many diagnostically intermediate cases. Other recent reanalyses demonstrate similarly significant rediagnosis rates between schizophrenia and bipolar illness in both directions. For example, multiple studies of schizophrenia patients using recent diagnostic criteria report good outcomes in significant subgroups on long-term follow-up (Harding et al. 1987, Mason et al. 1997, Sheldrick et al. 1977). Furthermore, some schizophrenia patients seem to lack cognitive impairment despite abnormal brain structure identified with magnetic resonance imaging (MRI) (Wexler et al. 2009). Kraepelin himself ultimately concluded that "we cannot satisfactorily distinguish between these two diseases. The suspicion remains that we are asking the wrong questions" (Kraepelin 1920c, p. 527; Kraepelin & Lange 1927).

Subsequent Attempts to Clarify and Improve Diagnostic Reliability

Post-Kraepelin, twentieth-century formal diagnostic systems came to reflect primarily either Kraepelinian or Bleulerian concepts of psychosis, and diagnostic criteria tended to become more loose and idiosyncratic. The United Kingdom adopted Schneiderian symptoms to help define schizophrenia in the late 1960s. A series of landmark studies that was initiated to account for large discrepancies in hospital admission rates for schizophrenia and bipolar illness in the United States versus the United Kingdom reported significant overdiagnoses of schizophrenia in the United States, almost double the rate of that in the United Kingdom (Wing 1972; see also Jablensky et al. 1992). This high rate was in part a consequence of the tendency of US psychiatrists to favor psychoanalytic approaches, in which precise clinical diagnosis is preempted by a focus on unearthing early-life influences on psychopathology, and mental illness is viewed as being on a continuum with normal behavior. An additional explanation for the difference in rates is that a diagnosis of schizophrenia in the United States was applied to almost all patients with psychotic symptoms.

An Emerging Focus on External Validation

Following publication of the US/UK study (Wing 1971), a direct consequence in the 1970s was a movement within psychiatry that recommended the use of clear clinical descriptions to tighten construct validity, laboratory studies to detect underlying biological abnormalities, longitudinal follow-ups to assess stability, and investigations of familial aggregation (Robins & Guze 1970). Adherents of this view emphasized the use of standardized diagnostic criteria based on the idea that diagnostic precision would follow more carefully defined, phenomenologically based operational criteria. As a result of this upsurge, the third version of the DSM (DSM-III; Am. Psychiatr. Assoc. 1980) modified American diagnostic practices and clarified diagnostic distinctions between schizophrenia and bipolar disorder.

DSM-III maintained the distinction between schizophrenia and affective psychotic disorders; because it listed absence of affective symptomatology among the criteria for a diagnosis of schizophrenia, any co-occurring manic or depressive symptoms were treated as secondary. Although the intended effect of this rule was diagnostic clarity, it fit rather poorly with clinical reality; for example, a recent study (Majadas et al. 2012) showed that 33% of schizophrenia patients

met criteria for major depressive disorder if the exclusionary rule were ignored. DSM-III introduced criteria that yielded immediate benefits, including high diagnostic/interrater reliability and relative conceptual simplicity that allowed clinicians both to reach clear syndromal diagnoses and to talk to each other and to patients and families using shared terminology. However, DSM-III did not address issues of validity of diagnostic categories. This latter point is extremely important and over the years has garnered much criticism within psychiatry (see, for example, Craddock et al. 2005, Craddock & Owen 2005, van Os et al. 1999). As articulated by Hyman (2010), an unintended consequence of the DSM-III approach was that diagnostic categories became reified and treated as if they represented natural kinds or taxa (i.e., true diseases) despite the absence of the necessary validating biological observations. Despite the pioneering effort of DSM-III, diagnostic boundaries often remained unclear, and many cases remained hard to classify. Ultimately, reliability came at the cost of a polythetic "Chinese menu" approach that allowed choices among combinations of criteria, one effect of which was to create naturally rigid criteria that in some respects interfered with the ability to differentiate syndromes. As reviewed by Potuzak and colleagues (2012), some researchers have attempted to apply modern statistical methods to more effectively parse traditional symptom and course measures (e.g., Jablensky et al. 1993, Jablensky & Woodbury 1995). However, such attempts generally fail to obtain clear-cut separations within or across clinical syndromes.

In the early 1970s, it became increasingly clear from the work of Carpenter, Strauss, and others (e.g., Carpenter & Strauss 1974, Carpenter et al. 1973) that traditional diagnostic subtypes of schizophrenia, such as hebephrenia and paranoid schizophrenia, were not stable entities over time. In a (somewhat late) recognition of this documentation, key changes related to psychotic disorders in DSM-5 (Am. Psychiatr. Assoc. 2013) include eliminating classic schizophrenia subtypes, reducing overreliance on Schneiderian first-rank symptoms, and clearly delineating schizoaffective disorder from both schizophrenia and psychotic mood disorders (Carpenter & Tandon 2013).

CONTINUUM CONCEPTS

Confronted with the type of evidence discussed in the preceding paragraph, some influential clinicians in the 1960s and 1970s began questioning the Kraepelinian dichotomy and posited the existence of a continuum between bipolar disorder and schizophrenia. Much of the intellectual and statistical underpinning for continuum concepts was delineated by psychologist Paul Meehl (1962), who sought biological markers as validation. The phrase "continuum of psychosis" is employed in two distinct senses in modern literature. The first use refers to a lack of boundaries between conventional psychotic illnesses (e.g., between schizophrenia and bipolar illness). The second application refers to a continuum extending beyond those same illnesses, all the way through individuals with minor psychotic features such as schizotypal or paranoid personality disorders, in some definitions even encompassing putatively healthy individuals with dilute psychosis-like symptoms, e.g., "voice hearers." Continuum in the first sense of the concept was favored by Crow (1986) and is commented on by others (Meltzer 1984, Moldin et al. 1987). The model receives some support from the observation that combining schizophrenia, bipolar, and schizoaffective disorders yields a unimodal outcome distribution (Coryell et al. 1984).

Also as a consequence of the lack of clear diagnostic boundaries between schizophrenia and bipolar illness, a hybrid concept, schizoaffective psychosis, was adopted by Jacob Kasanin (1994), although its reliability and temporal stability are questionable (Jager et al. 2011). In part, schizoaffective psychosis was adopted as a diagnostic evasion because many clinical cases are hard to classify and because numerous patients' "characteristics place them somewhere between schizophrenia and manic-depressive illness" (Mayer-Gross et al. 1969, p. 222), although these

investigators believed that the term reflects "incomplete or imperfect diagnosis not a meaningful diagnostic entity" (Goodwin & Jamison 1990, p. 102). Despite its problems, the category offers a conceptual challenge to the distinct dichotomous categories, and its status as a unique category versus one along a continuum continues to be debated. Advantages certainly accrue from adopting dimensional perspectives. If the illnesses reflect a true continuum of psychosis in the community, ranging from self-reported rare psychotic symptoms all the way through to primary psychotic disorder, then study samples to probe underlying causes immediately enlarge manyfold. For example, using the dimensional perspective enables inclusion of many subclinical cases, such as those having cluster A and cluster B personality disorders, which could be considered as attenuated forms of illness. The frequent use of "not-otherwise-specified" and "schizoaffective" diagnoses would disappear, and the extensive comorbidity documented among DSM-IV-TR (Am. Psychiatr. Assoc. 2000) disorders (Krueger 2005) would no longer be problematic. Currently, many individuals meeting criteria for one DSM disorder simultaneously meet criteria for one or more other disorders, necessitating the use of awkward exclusionary rules. Dimensional approaches actually prove better at predicting treatment response and outcome (Peralta et al. 2002; van Os et al. 1996, 1999). In recent years, dimensional approaches have been discussed by multiple authors (Boteva & Lieberman 2003; Hyman 2010; Insel & Cuthbert 2009; Keshavan et al. 2013, 2011).

The question of a continuum versus a dichotomy of bipolar illness and schizophrenia arises in part because we are unclear as to whether these illnesses themselves are unique homogeneous entities (Esterberg & Compton 2009). As discussed above, progress from the description of a syndrome to the definition of a disease requires etiopathologic information. In the absence of such a biological gold standard, data must be interpreted subjectively, so categories become unclear. In the 1980s, a lively scientific debate, excellently summarized by Greene (2007) and Decker (2007), focused on two related questions: (*a*) Can schizophrenia be reliably separated from other psychiatric disorders (i.e., issues of discriminant validity), and (*b*) Is schizophrenia a single heterogeneous disease or is it composed of several homogeneous diseases lumped together (as suggested by Bleuler)? As summarized by Kendell & Brockington (1980), Kraepelin's concepts of dementia praecox and manic-depressive insanity became the "twin pillars on which our classifications have been based" (p. 326). If these diagnostic categories are genuine disease entities, then logically "It should imply a natural boundary or discontinuity" (p. 324) between the disorders, and it should be possible to identify this break or "point of rarity" (p. 324). The absence of persuasive data to identify the latter led them to conclude that such a demarcation point did not exist and that it was impossible in practice to carve nature at its joints. On the basis of similar logic, Crow (1986) also argued for a continuum. Kendell (1991) conceptualized that the origin of the problem was that the etiology of psychotic disorders is not understood. Therefore, clinicians and researchers are obliged to fall back on the use of symptoms to differentiate among psychotic disorders, but the significant degree of overlap between symptoms causes inevitable problems: "Not one of them [psychotic disorders] is yet demarcated by its neighbors by clear boundaries. All are still defined by the clinical syndromes, and these syndromes merge imperceptibly into one another" (Kendell 1987, p. 511).

Striking support for this viewpoint derives from a recent study (Keshavan et al. 2011) of 762 probands classified (using diagnoses based on the Structured Clinical Interview for DSM-IV-TR) as having schizophrenia, bipolar disorder, and schizoaffective disorder. The probands were rated on a newly developed schizo-bipolar scale that used both lifetime and cross-sectional symptom information to assess three key elements of schizophrenia–psychotic bipolar disorder continuum: relative proportion of nonaffective psychosis, extent of the manic syndrome as a proportion of overall illness duration, and predominant polarity (depressive versus manic) of the affective

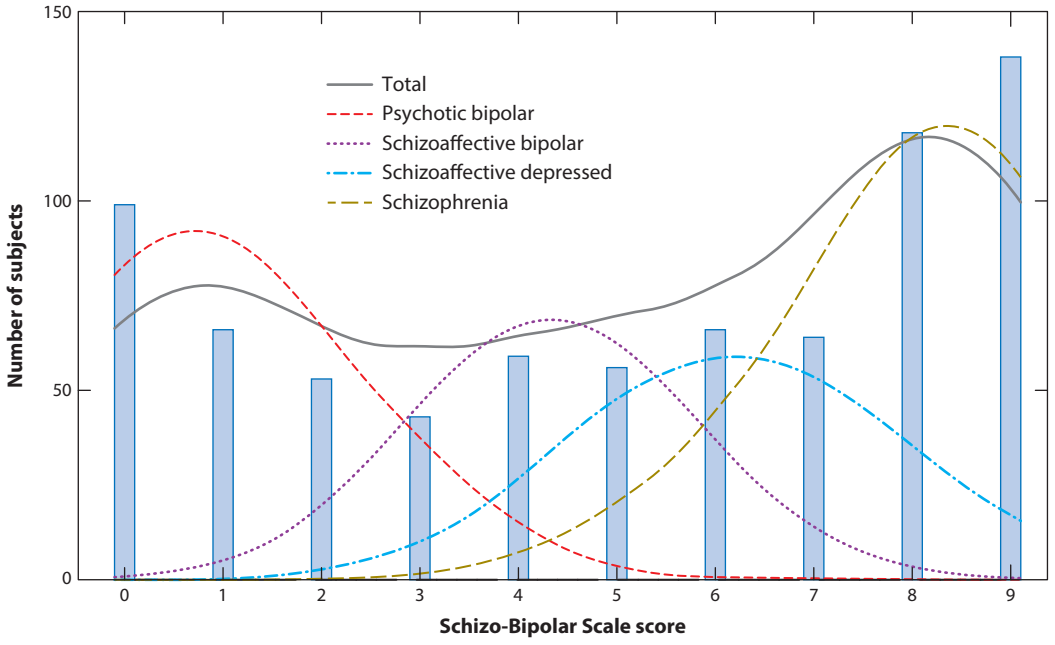

Figure 1

Scale scores across diagnostic groups, with distributions represented by cosine curves. Low scores represent more bipolar-like and high scores more schizophrenia-like symptoms and course. Considerable overlap exists in scores among diagnoses, with no obvious points of rarity. Figure adapted with permission from Keshavan et al. (2011).

syndrome (see **Figure 1**). The summed scores of these three elements could be rated very reliably and yielded totals between 0 (most bipolar-like value) and 9 (most schizophrenia-like value) for each subject. In terms of score distribution, although many cases were distributed at the high and low ends, 45% of the sample lay in the middle range, yielding a multimodal distribution with significant overlap between schizophrenia and bipolar disorder. Contrary to Kraepelinian expectation, there was no point of rarity between the adjacent categories, which supports a continuous rather than categorical distribution of these illnesses and suggests that schizoaffective disorder is indeed an intermediate category.

In the general community, schizotypy, schizotaxia, and schizotypal personality disorder occur with relatively high prevalence compared with rates of schizophrenia or bipolar disorder. There have been discussions on boundaries between schizophrenia and schizotypal personality disorder and whether the latter is a dimension or a category (Raine & Lencz 1995). Implicit in the DSM categorization is the acknowledgment that Axis II cluster A (eccentric behavior) could be considered a continuum of psychotic illnesses, a concept that receives some support from endophenotype measures (discussed below) (Tamminga et al. 2014).

Relevance of Psychotic Bipolar Disorder

As briefly discussed above, psychotic bipolar disorder might constitute a meaningful bipolar subgroup. Lost amid much of the discussion regarding boundaries between schizophrenia and bipolar disorder is the fact that approximately 50% of individuals with bipolar disorder exhibit hallucinations, delusions, and/or disordered form of thought during illness episodes (Coryell et al.

2001, Keck et al. 2003). From the DSM viewpoint, such psychotic symptoms are seen as secondary within mood disorders. Attention has been paid mainly to whether or not the phenomenology of the psychotic symptoms is mood congruent (e.g., grandiose delusions during an episode of mania). However, Carlson & Goodwin (1973) and Abrams & Taylor (1981) demonstrated that mood-incongruent psychotic symptoms, including first-rank Schneiderian phenomena, occur frequently amid otherwise typical manic or depressive illness episodes; this finding was subsequently confirmed by others (e.g., Pacheco et al. 2010). Investigators noted not only the high prevalence of psychotic symptoms in bipolar illness (Abrams & Taylor 1981, Pope & Lipinski 1978) but also that such symptoms can persist between illness episodes in a diagnostically confusing manner. Psychotic bipolar illness may possess a distinct prodrome (Correll et al. 2007). Additionally, the often-used clinical distinction between bipolar I and bipolar II disorders (Dunner et al. 1976) may be capturing differences that result from the frequent association of the first, but not the second, with psychosis.

Evidence for psychotic bipolar disorder as a meaningful subclassifier comes from several sources outside of its phenomenology (Parker et al. 2013, Pearlson & Schaepfer 1999), including its distinct familial aggregation (Potash et al. 2001) and the substantial overlap between psychotic (as opposed to nonpsychotic) bipolar illness and schizophrenia within families (Goes et al. 2008). Similarities between schizophrenia and psychotic bipolar disorder also exist for biological measures, including dopamine D2 receptor numbers measured using positron emission tomography (Pearlson et al. 1995). Structural and functional brain differences distinguish psychotic from nonpsychotic bipolar illness (Ketter et al. 2004, Strasser et al. 2005), as do both genetic risk loci and genetic liability (Lett et al. 2011). Anticevic and colleagues (2014) examined resting-state functional MRI connectivity data based on placement of a ventral anterior cingulate cortex (vACC) seed in 73 remitted bipolar I patients (33 with a history of psychosis) and demographically matched chronic schizophrenia and healthy comparison subjects (see **Figure 2**). The major finding was that both chronic schizophrenia patients and bipolar patients with psychosis showed characteristic connectivity alterations along the dorsal-medial prefrontal cortical surface based on the vACC seed. Specifically, patients with a psychosis history (psychotic bipolar and schizophrenia subjects) showed significantly reduced connectivity and did not differ from each other, whereas bipolar patients without psychosis showed significantly increased vACC coupling.

EMPLOYING BIOLOGICAL AND ALLIED CLASSIFICATIONS

Given some of the evidence reviewed above, it is reasonable to ask why categorical descriptions of schizophrenia and bipolar disorder persist. Addressing this, Craddock & Owen (2005) argue that Kraepelin's dichotomy "forms the basis of the operational diagnostic criteria that brought a degree of rigor and reproducibility to psychiatric research"; these criteria are important in rational clinical decision making, particularly in allocating treatments and conducting clinical trials. The criteria aid clinical research in deciding whether treatments are effective according to well-demarcated syndromic boundaries, and they offer improved diagnostic reliability (consistency, stability, agreement) that enables comparisons across studies and improves communication among clinicians, researchers, and patients/families. The disadvantages of the categorical approach are that Kraepelinian diagnostic distinctions have perpetuated the existence of separate clinical services, drug trials, and scientific research investigations (Craddock & Owen 2007) where combined observations may have proven more fruitful. A reasonable assumption is that the Kraepelinian diagnostic structure remains unchanged not because of any clear-cut demonstration of valid independent diagnostic entities but simply because no better classification has yet been devised. So, what is the way forward?

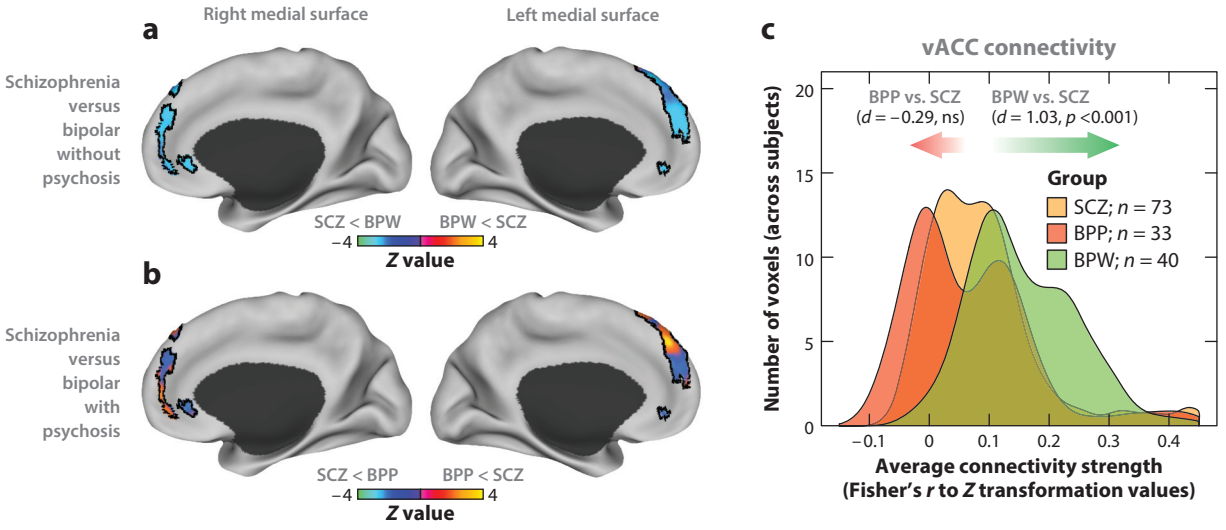

Figure 2

Differences between schizophrenia groups and bipolar illness groups with and without psychosis in medial prefrontal cortical (PFC) connectivity: pairwise group comparison for a ventral anterior cingulate (vACC) seed. Direct threshold-free contrast maps within the medial PFC borders (*left panel*) mark the cluster that survived a one-way ANOVA (analysis of variance) for the bipolar analysis compared with healthy controls (not shown). (*a*) The direct contrast of bipolar subjects without psychosis and schizophrenia subjects shows a pattern of reduced vACC seed coupling for schizophrenia. (*b*) A comparison of bipolar subjects with psychosis to schizophrenia subjects reveals a mixed pattern of increased and reduced connectivity with no specific directional effect. (*c*) Effect size estimates (Cohen's *d*) show robust increases in connectivity for bipolar patients without psychosis relative to schizophrenia patients and a contrasting substantially smaller difference for psychotic bipolar patients relative to schizophrenia patients; the increases are evident in the almost complete overlap for schizophrenia and psychotic bipolar distributions in the panel. Abbreviations: BPP, psychotic bipolar; BPW, nonpsychotic bipolar; ns, not significant; SCZ, schizophrenia. Figure adapted with permission from Anticevic et al. (2014).

If we proceed from an idea shared by both Kraepelin and Bleuler, that both schizophrenia and bipolar disorder are clinical syndromes, with each comprising several specific disease entities (Fischer & Carpenter 2009) (resembling dementia or dropsy in this respect), and that even scrupulously gathered data on cross-sectional symptoms and longitudinal course have failed to yield a clear distinction, then logically one could parse them more effectively using biological, including genetic, observations. If successful, such an effort would proceed to etiopathologic classification, resulting in demarcation of true diseases. Kidd & Mathysse (1978) were among the first to assert that molecular genetic data could help sharpen nosologic categories. Murray & Foerster (1987) similarly proposed that although schizophrenia is a useful provisional category, it may well be abandoned in the future, as mechanisms of psychosis are better understood. This point was echoed by Kendell: "Perhaps in the near future we will be able to take our stance on the subdivision of psychosis according to etiological principles rather than on the quicksands of symptomatology and course" (Kendell 1987, p. 138). In line with these ideas, the past several decades have seen an increasingly strong trend to employ biology to help better classify major mental illnesses, with the aim of improving the understanding of etiology and improving treatment specifications.

Major questions to consider before beginning such an enterprise are (*a*) which types of measures are likely to be most informative, (*b*) what best overall strategy will answer the most important questions, (*c*) what sort of conceptual framework should biological findings be fitted into, and (*d*) what are the conceptual traps to avoid?

These questions are addressed in detail in the following sections, but to address the last issue first, an inherent design problem with such efforts is that biological observations (including the endophenotype studies discussed below) are usually related to gold standard clinical diagnosis. Clearly, circular reasoning is involved in trying to relate biological measurements back to the familiar clinically defined diagnoses; many unclear cases have to be excluded, and this exclusion undermines the strategy of biological classification if the gold standard is clinical phenomenology and biological data are construed merely as secondary evidence validating a static classification based on this (Kapur et al. 2012). As argued below, conceptually we would be better served by turning the tables and reclassifying syndromes agnostically as biologically based entities. From this perspective, biological data are the independent organizing principle of classification (Boteva & Lieberman 2003) rather than secondary evidence for validating clinical diagnoses. Another possibility, of course, is that such an effort will redefine new biologically based categories that to a large extent cut across several clinically defined traditional entities, each comprising a proportion of members from several such traditional categories. Some of the statistical approaches referenced above, including taxometric procedures (Ruscio et al. 2006), can be used to reveal latent categories in this context. The ultimate purpose is to gather data that will themselves serve as a diagnostic gold standard to either cement the validity of current clinically defined diagnostic syndromes or to redefine these phenotypes, with the aim of reducing heterogeneity. Over the past several years, multisite efforts and consortia have formed as an important strategy to assemble large data sets that are sufficiently powered to answer the above questions definitively and to collect multiple measures in a comparable standardized manner both within and across traditional diagnostic boundaries.

For example, one could look across the domains of psychosis, subsuming schizophrenia, schizoaffective-affective, and psychotic bipolar disorder as well as cluster A disorders, to determine whether biological measures share commonalities (even if these represent differences in degree) across the psychosis dimension/spectrum/continuum that distinguishes them from other disorders. Consistent with this notion, such an approach was adopted by multicenter studies such as the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) (Tamminga et al. 2014, Thaker 2008) for the study of various putative psychosis endophenotypes and the Consortium on the Genetics of Schizophrenia (Braff et al. 2007, Calkins et al. 2007), which assessed multiple endophenotype measures in schizophrenia. Both studies collected data in large numbers of individuals, either for schizophrenia probands and relatives in the latter case or for schizophrenia, psychotic bipolar, and schizoaffective disorder probands and relatives in the former. Such studies can address important issues, such as the comparative distinctiveness versus overlap/redundancy among various endophenotype measures. Increasingly, these measures are shared not only among the original investigators but also ultimately with the broader scientific community through secure research data repositories facilitated by the National Institute of Mental Health [e.g., the Psychiatric Genome-Wide Association Study Consortium (Sullivan 2010)], the National Database for Autism Research (Hall et al. 2012), and a forthcoming psychosis database (B.N. Cuthbert, personal communication). We next review why such endophenotype measures have become more widely employed in this context.

Using Endophenotypes

Endophenotypes are defined as quantifiable, heritable, measurable, and reproducible biologic traits that vary continuously in the population at large. Endophenotypes are unobservable by the naked eye, are correlated with an illness in the population in part due to shared underlying genetic influences, are primarily state independent (perhaps revealed only through a provocative test), segregate with illness within families, and are found in nonaffected family members at a

higher rate than in the general population (thus constituting a risk indicator distinct from simple illness-related biomarkers) (Glahn et al. 2014, Gottesman & Gould 2003). Relative rates in affected and nonaffected family members versus healthy controls are often compared using the lambda statistic and heritability by calculating h^2. Because endophenotypes are conceived of as having a simpler genetic structure than conventional illnesses have, being closer than the latter to the effect of underlying genes, with correspondingly greater effect sizes compared to those contributing to conventionally defined disease susceptibility, they should provide added leverage to detect genes influencing particular illness risk. A single disorder may be associated with a range of endophenotypes that in turn may be intercorrelated/redundant or uncorrelated if representing different aspects of risk for the disorder. Traditional endophenotypes for psychotic illnesses have included measures of brain structure and function and related cognitive and physiologic phenomena (for comprehensive reviews, see Allen et al. 2009, Braff et al. 2007, Cannon & Keller 2006, Keshavan et al. 2013, Pearlson & Folley 2008); however, as pointed out by Glahn and colleagues (2015), they can certainly include proteomic or transcriptomic phenotypes. The hope offered by endophenotypes is that they will (more straightforwardly than heterogeneous clinical conditions) point toward specific associated genes that provide insight into the underlying biology, thus aiding in classification. Some of the advantages assumed for endophenotypes (a simpler genetic structure and that all genetic effects impacting endophenotypes also significantly alter risk for associated psychiatric disorders) have been questioned (e.g., see Kendler & Neale 2010). Particular care needs to be taken in documenting that putative endophenotypes are indeed stable over time and are not affected significantly by treatments for the associated illness. As explained in detail by Glahn and colleagues (2014), useful endophenotypes do not have to possess heritabilities superior to the psychiatric diagnostic phenotypes with which they are correlated. For example, the polygenic architecture of an endophenotype may be associated only with a subset of cases of underlying risk for a defined syndrome. Glahn et al. (2014) proposed the use of an endophenotype ranking value (ERV) to categorize endophenotypes empirically, based on genetic similarity to the relevant illness, via estimation of the standardized genetic covariance between each endophenotype and the illness. Because in practice endophenotypes often point to risk for multiple clinical psychiatric disorders, they potentially would be useful in reordering psychiatric nosology based on common genetic pathways as well as in leveraging the National Institute of Mental Health's Research Domain Criteria (RDoC; discussed below in detail) (Insel & Cuthbert 2009) approach by cutting across traditional diagnostic categories while attempting to reduce phenotypic heterogeneity. The study by the Consortium on the Genetics of Schizophrenia (Braff et al. 2007) usefully documented the comparative heritability of multiple schizophrenia-related endophenotypes in a large number of the same individuals. Although relatively few studies have compared individuals with schizophrenia and bipolar disorder directly, and fewer yet additionally have included unaffected first-degree family members, **Table 1** summarizes a number of the more important examples that have accomplished one or more such comparisons for a variety of endophenotypic and related measures in schizophrenia and bipolar disorder.

Table 1 reveals that although some of these various measures differ between schizophrenia and bipolar disorder, many of them are similarly abnormal between the two illnesses and/or exist on a continuum of severity (usually being more markedly abnormal in schizophrenia probands). Some of the studies also document that schizoaffective probands lie intermediately between schizophrenia and psychotic bipolar illnesses.

What are the results of biological classification efforts to date not only in the realm of endophenotypes but also across a variety of allied measures such as genetics and psychopharmacologic response? The overall picture, not unexpectedly, is that biologic data seem to offer only tepid support for the classic diagnostic dichotomy, particularly when psychotic bipolar patients

Table 1 Studies that have directly compared individuals with schizophrenia and bipolar disorder

Candidate endophenotype	Similarities	Differences	Continuum of severity	Effects in relatives
Smooth pursuit oculomotor	Barabasi 2007, Ivleva et al. 2014[a], Kathmann et al. 2003, Lencer et al. 2010, Moates et al. 2012[a]		Tien et al. 1996	Ivleva et al. 2014[a]
Saccadic eye movements	Harris et al. 2009, Reilly et al. 2014, Tien et al. 1996	Harris et al. 2009[a], Martin et al. 2007	McDowell & Clementz 1997, Reilly et al. 2014[a]	McDowell & Clementz 1997, Reilly et al. 2014[a]
Structural magnetic resonance imaging (MRI) gray matter volume (global and regional)	Anderson et al. 2013, Cui et al. 2011b, De Peri et al. 2012, Haukvik et al. 2015, Hulshoff Pol et al. 2012, Ivleva et al. 2013[a], Mathew et al. 2014[a], Molina et al. 2011, Nanda et al. 2014[a], Rimol et al. 2010, Womer et al. 2014[a]	Anderson et al. 2013, Arnold et al. 2015[a], Cui et al. 2011b, Haukvik et al. 2015, Hulshoff Pol et al. 2012, Ivleva et al. 2013[a], Mathew et al. 2014, Molina et al. 2011, Rimol et al. 2012, Schnack et al. 2014, Womer et al. 2014[a]	De Peri et al. 2012, Ivleva et al. 2013[a]	Ivleva et al. 2013[a], Nanda et al. 2014[a]
Diffusion tensor imaging	Cui et al. 2011a[a], Li et al. 2014, Skudlarski et al. 2013[a]	Skudlarski et al. 2013[a]	Skudlarski et al. 2013[a]	Skudlarski et al. 2013[a]
Task-based functional MRI (fMRI)	Costafreda et al. 2011[a], Sepede et al. 2014	Delvecchio et al. 2013, Jamadar et al. 2013, Morris et al. 2012	Costafreda et al. 2011[a]	Brandt et al. 2014
Resting fMRI	Anticevic et al. 2014[a]; Argyelan et al. 2014; Baker et al. 2014[a]; Chai et al. 2011; Lui et al. 2015[a]; Mamah et al. 2013; Meda et al. 2012[a], 2014[a]; Ongur et al. 2010	Argyelan et al. 2014; Chai et al. 2011; Khadka et al. 2013[a]; Liu et al. 2014[a], 2014b; Mamah et al. 2013; Meda et al. 2012[a], 2014[a]; Ongur et al. 2010; Yang et al. 2014	Argyelan et al. 2014	Khadka et al. 2013[a]; Lui et al. 2015[a]; Meda et al. 2012[a], 2014[a]
Prepulse inhibition	Perry et al. 2001[a]			
P300 event-related potential	Baker et al. 2014, Bestelmeyer et al. 2009, Ethridge et al. 2015[a], Hamm et al. 2013[a], Jahshan et al. 2012, Johannesen et al. 2013, O'Donnell et al. 2004, Salisbury et al. 1999[a], Vilela et al. 1999	Chun et al. 2013, Domjan et al. 2012[a], Ethridge et al. 2015[a]	Bestelmeyer 2012	Ethridge et al. 2015[a]
P50/paired stimulus processing	Ethridge et al. 2012[a]; Hamm et al. 2012[a], 2014[a]; Johannesen et al. 2013; Sanchez-Morla et al. 2008[a]	Domjan et al. 2012[a], Hamm et al. 2012[a], Martin et al. 2007		Hamm et al. 2014[a]

(*Continued*)

Table 1 (*Continued*)

Candidate endophenotype	Similarities	Differences	Continuum of severity	Effects in relatives
Resting electroencephalogram	Narayanan et al. 2014[a]	Kam et al. 2013, Narayanan et al. 2014[a]		Clementz et al. 1994[a], Narayanan et al. 2014[a]
Cognition	Ancin et al. 2013[a], Hill et al. 2014[a], Krishnadas et al. 2014, Lewandowski et al. 2014[a], Schretlen et al. 2013, Smith et al. 2009[a], Wang et al. 2013		Hill et al. 2013[a], Krishnadas et al. 2014, Ruocco et al. 2014[a], Schretlen et al. 2007, Vohringer et al. 2013	Chan et al. 2013; Hill et al. 2013[a], 2014[a]; Ruocco et al. 2014[a]

[a]Study included unaffected first-degree family members.

are compared to schizophrenia patients. B-SNIP (Tamminga et al. 2014) is a systematic attempt to instantiate a multisite, multiendophenotype approach to study psychotic disorders using endophenotype assessments conducted in a standardized and reliable manner across all collection sites and including data from electrophysiological, oculomotor, cognitive, and brain structural and functional domains in addition to genotyping. Thus far B-SNIP results reveal that clinical symptoms, psychosocial function, and familial lineage overlap among the three diagnostic groups (Tamminga et al. 2014). Additionally, as summarized in part in **Table 1**, a substantial overlap exists in endophenotype data across the schizophrenia/psychotic bipolar continuum, with generally poor discriminability and no points of rarity among diagnoses of the type required to demonstrate biological differences between categorical diagnoses. Structural brain MRI measures quantified by voxel-based morphometry showed the greatest discrimination, with schizophrenia and schizoaffective disorder most similar to each other in terms of neocortical volume reductions; psychotic bipolars showed the fewest differences from normal, perhaps explained in part by the neurotrophic effects of lithium treatment. Several of the B-SNIP phenotype analyses (e.g., Ivleva et al. 2013, Skudlarski et al. 2013) show effects in cluster A relatives of either schizophrenia or psychotic bipolar probands similar to those demonstrated in the probands themselves, providing support for a continuum concept.

Because by definition B-SNIP did not assess individuals with nonpsychotic bipolar disorder, the Psychosis and Affective Research Domains and Intermediate Phenotypes project is in the process of repeating all B-SNIP endophenotype measures in a comparable group of bipolar I patients who have never manifested psychotic symptoms in any episode of illness, in order to explore the specificity of the psychosis dimension. As discussed above, the work of Anticevic et al. (2014) has shown strong evidence of separation within bipolar illness.

Familial Overlap

According to the Kraepelinian model, if the two cardinal disorders are unrelated disease entities, each with a distinct genetic basis, then one would expect to see an increased propensity for schizophrenia in family members of schizophrenia patients and for bipolar disorder among family members of those patients with bipolar disorder; there would be no increased likelihood of finding the bipolar disorder among family members of schizophrenia patients and vice versa.

Both schizophrenia and bipolar illness are substantially heritable (with h^2 values ~0.8 for both). Gershon and colleagues (1982, 1988) hypothesized shared genetic liability between schizophrenia and bipolar illnesses after observing greater-than-expected prevalence of major depressive and schizoaffective disorder in relatives of both bipolar and schizophrenia probands, with similar observations being reported by Kendler and colleagues (1985) in the Roscommon Family Study. In a very large study of more than 2 million Swedish nuclear families, Lichtenstein et al. (2009) demonstrated substantial overlap in genetic susceptibility to schizophrenia and bipolar illness. Approximately 60% variance in each group was genetic and was equally split between unique and shared liability. The illnesses do not "breed true" in other respects; Potash and coworkers (2001, 2003) reported that hallucinations and delusions show evidence of familial aggregation in bipolar I families; this finding has been replicated by others (O'Mahony et al. 2002, Schurhoff et al. 2003). Twin studies are useful in allowing one to disambiguate shared environmental factors, and several studies that examined identical twin pairs within each illness reported discordance (i.e., overlap) for bipolar illness/schizophrenia (e.g., Farmer et al. 1987).

Risk Genes

Risk genes identified through common DNA single-nucleotide polymorphism (SNP) variants via genome-wide association studies (GWAS) in large-scale analyses such as the International Schizophrenia Consortium show modest effect sizes but explain approximately one-third of the total variation in liability to schizophrenia and also reveal consistent overlap in genetic susceptibility between the two disorders (Cross-Disord. Group Psychiatr. Genomics Consort. 2013). The latter revealed several genes associated with multiple psychiatric disorders including schizophrenia and bipolar illness that included the L-type voltage-gated calcium channel subunits *CACNA1C* and *CACNB2* as well as *ANK3*, *ZNF804A*, and *NCAN*. Biological pathways identified with the risk SNPs in common between schizophrenia and bipolar illness point to processes generally associated with neurodevelopment, learning and memory, and synaptic plasticity as well as *N*-methyl-D-aspartate and activity-regulated cytoskeleton-associated scaffold protein of the postsynaptic density.

Unexpected differences have been found in the relative importance of highly penetrant copy number variants (CNVs) implicated for schizophrenia and bipolar disorder (Sebat et al. 2009), with this mechanism much more closely identified with schizophrenia cases. In contrast, Sebat and colleagues have demonstrated that such genetic disruptions (even identical deletions within the same gene) do not necessarily specify outcome in a particular syndrome, being variably associated with learning disabilities, schizophrenia, autism spectrum disorders, intellectual disability, or seizures. Similarly, the originally described *DISC-1* mutation within different family members is associated with schizophrenia, bipolar disorder, major depression, alcoholism, or no psychiatric diagnosis. Thus, there is no one-to-one correspondence between penetrant mutations and particular psychiatric diagnoses.

Comparative Psychopharmacology

To date, there is little evidence of unique responses to treatment by syndrome, symptom domain, or endophenotype in psychotic disorders. It is worth recalling that the initial, successful clinical trial of chlorpromazine was conducted in patients with mania. Many cases of schizophrenia and bipolar illness respond to second-generation antipsychotic medication (as do some cases of

major depressive disorder), perhaps in line with Kraepelin's initial delineation, which included all cyclical mood disorders. For example, as shown in the pharmacological treatment trial embedded within Northwick Park study (Johnstone et al. 1988), irrespective of the diagnosis within psychotic illnesses, psychotic symptoms responded to treatment with antipsychotic drugs, and mood symptoms responded to treatment with lithium. Conversely, although positive symptoms of schizophrenia such as hallucinations and delusions respond (albeit variably) to treatment with antipsychotic medications whose common mode of action is blockade of dopamine D2 receptors, the cognitive and negative symptoms of the disorder are persistently unresponsive to such treatment approaches, which suggests that these symptoms possess distinct pathophysiologies. It should also be noted, however, that although a subgroup of bipolar patients responds to lithium, only a tiny minority of schizophrenia subjects do so (Post 1999). The B-SNIP study (Tamminga et al. 2014) recorded substantial overlap in polypharmaceutical treatment of large numbers of typical clinic-derived schizophrenia, schizoaffective, and psychotic bipolar patients, reflecting real-world treatment of these patients. For example, schizophrenia patients were frequently prescribed antiepileptic, mood-stabilizing and antidepressant drugs in addition to antipsychotics, whereas psychotic bipolar patients were frequently prescribed second-generation antipsychotic medications (Tamminga et al. 2014). Because the majority of patients in the study were stable and between episodes of illness, one assumption is that clinicians employ such polypharmaceutical approaches because they are effective and that this is the case because symptoms themselves cross traditional boundaries.

Research Domain Criteria

Gathering the above-mentioned types of biological data ultimately allows one to develop an empirical nosology that is based empirically on biological classifiers and not primarily on phenomenological diagnoses, as suggested by Keshavan and colleagues (2013). Several authors have advocated recently for the utility of a systems neuroscience perspective encompassing cognitive and affective domains in the consideration of psychosis (Craddock & Owen 2010, Frangou 2014, Owen et al. 2010).

Similarly, the National Institutes of Health (NIH)-sponsored RDoC initiative (Insel 2010, Insel & Cuthbert 2009) is intended to help researchers transcend the problems associated with clinically defined syndromes by providing a logical framework for relating different biological levels of measurement to specific endophenotypic constructs that have been the focus of clinical neuroscience inquiry over the past decade. RDoC has as its goals (*a*) the construction of a research framework for collecting data needed for a new nosology in straightforward, productive ways for neuroscientific inquiry, based on emerging research data gathered across different levels of analysis (such as genes, brain circuits, and behavioral domains) and across functional dimensions (such as working memory and positive valence) rather than within current diagnostic categories and (*b*) the deconstruction of psychiatric illnesses based on crosscutting reliable biological measurements and endophenotypic strategies. A major objective of the RDoC initiative is to identify dimensions of behavior and map their underlying biobehavioral substrates, including genes, molecular biology, and neural circuits. Although the phenomena of psychosis do not fit obviously into this schema, Ford and colleagues (2014) have sketched out what shape such an enterprise might take for the case of hallucinations.

The purpose of such a framework would be to identify disease markers and endophenotypes and to map them across translational domains from behaviors to molecules, followed by agnostic deconstruction of disease dimensions. A process of reclustering crosscutting biobehavioral data

using modern phenotypic and biometric approaches is therefore used to construct a bottom-up rather than a top-down reclassification of diseases. Such novel rederived entities themselves can then be validated using etiopathology, outcome, familial consistency (i.e., whether these measures "breed true"), and treatment response measures. As reviewed above, because endophenotypes are presumed to be close to the underlying risk genes, such a strategy is theoretically also more likely to lead directly to those genes that in turn provide clues to the molecular biological pathways underpinning etiology. Similar types of approaches have been used with some success elsewhere in medicine, such as the recent subdivision of breast cancers on the basis of genetic criteria that are histologically indistinguishable, which has resulted in a reclassification of breast cancer into newly defined disorders, bringing the hope of more individualized treatments (Curtis et al. 2012). Potential treatment implications for newly defined psychiatric disorders in this context have been discussed in some detail by Keshavan and colleagues (2013). Worthy of brief mention is the fact that as well as larger-scale, rare, penetrant genetic events such as copy number variants that contribute a small amount of risk for schizophrenia cases as a whole, common disease, common variant (CDCV) models of risk for schizophrenia and bipolar illness are presumed to occur through interaction (perhaps multiplicatively) between large numbers of common genetic variants. Such variants (for example as derived from GWAS) themselves carry little individual risk for the disorders. Multivariate approaches such as functional MRI and parallel independent component analysis have been employed recently to derive large clusters of interacting genes and their associated physiologic processes such as activation networks in psychosis (Meda et al. 2014) in order to explore the underlying biological processes that might be associated with large-scale SNP components. The resulting data are consistent with a CDCV model.

Other biological observations across the Kraepelinian divide offer some interesting contrary biological evidence supporting the existence of distinct disorders (Craddock & Owen 2010, Murray et al. 2004). These authors of these observations argue that schizophrenia has a stronger neurodevelopmental component than does bipolar disorder. **Figure 3** illustrates this model.

Evidence supporting this assertion includes observations that schizophrenia is much more likely than bipolar illness to be associated with larger-scale structural genomic variants, such as copy number variants (Grozeva et al. 2010, McCarthy et al. 2009), that also accompany neurodevelopmental disorders, including infantile-onset seizure disorders, mental retardation, and specific learning disabilities. More marked cognitive impairment (although this likely is in degree rather than kind) (Schretlen et al. 2007, 2013; Schulz et al. 2014) is seen in abnormal childhood developmental symptoms for schizophrenia; less impairment is seen in bipolar disorder (Schretlen et al. 2013, Schulz et al. 2014). Similarly, premorbid cognitive impairments are significantly more marked for schizophrenia (van Os et al. 1997) than for bipolar disorder in comparisons of the two disorders, although cognitive abnormalities are certainly seen in bipolar disorder following illness onset (Lewandowski et al. 2011, Trotta et al. 2014). A recent examination of bipolar and schizophrenia probands and their discordant cotwins in the Swedish Twin Registry demonstrated that unaffected bipolar cotwins scored higher on a scale of positive temperament and on tests of verbal fluency and learning in comparison with controls and bipolar probands (Higier et al. 2014). These traits are significantly heritable, and their presence in unaffected bipolar probands may partly explain the persistence of this disorder (as opposed to schizophrenia) in the population. [For a review of related concepts, see Pearlson & Folley (2008).] Together, these studies support the idea that cognitive deficits are more marked and significant in schizophrenia than in bipolar disorder both premorbidly and following illness, although individuals in both conditions display cognitive decline after onset to some degree (see **Table 1** for studies suggesting a continuum of severity).

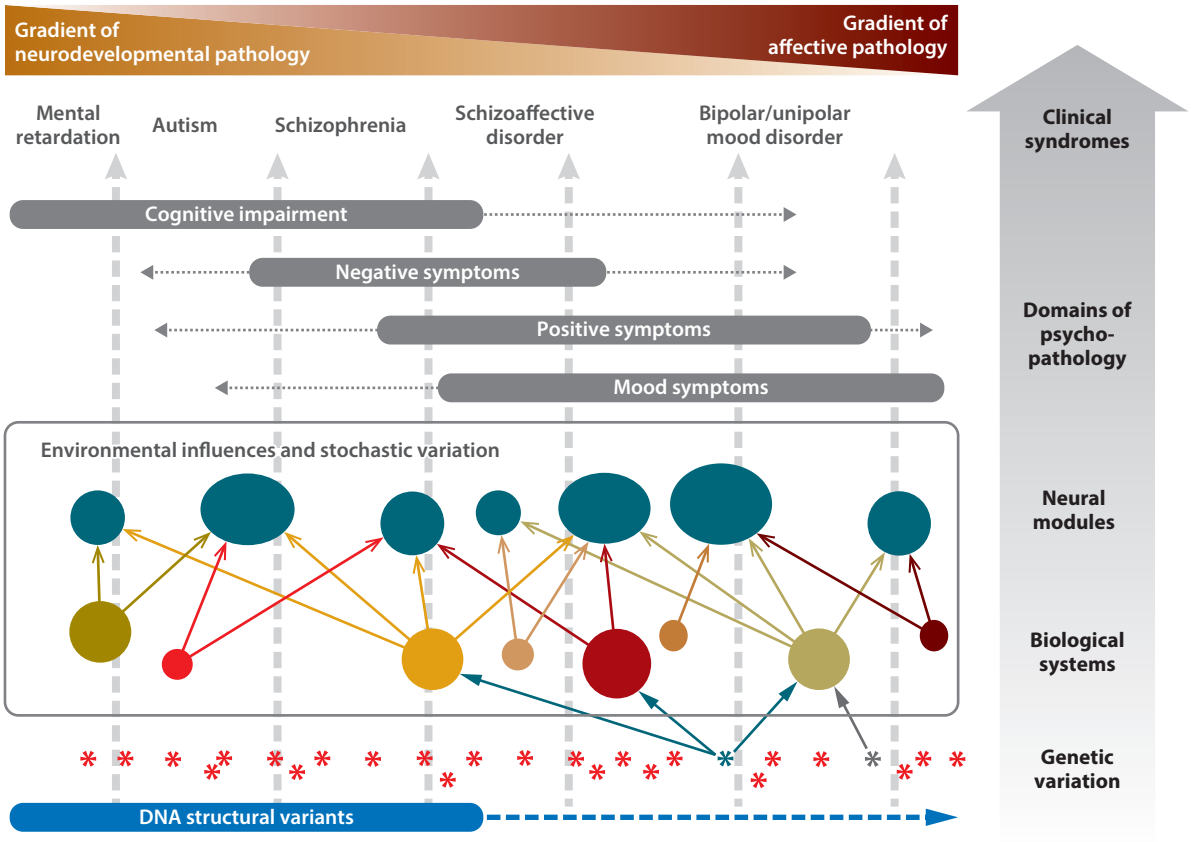

Figure 3

A hypothesized continuum model of the complex relationship between biological variation and some major forms of psychopathology. This conceptual model shows relationships between genotype and clinical phenotype, starting at the level of genetic variation (the bottom tier of the figure). The DNA structural variants in dark blue are shown to be contributing particularly to neurodevelopmental disorders and also are associated with lasting cognitive and functional impairment. Multiple biological systems influence each neural module; the numerous single-nucleotide polymorphism variants are shown as asterisks. Abnormal functioning of the neural modules influences the domains of psychopathology expressed and ultimately the clinical syndromal phenotype. Major clinical syndromes are arrayed along a single major axis with a gradient of decreasing (from left to right) proportion of neurodevelopmental contribution to causation and a gradient of reciprocally increasing proportion of episodic affective disturbance. Among other familiar disorders, schizophrenia, schizoaffective disorder, and bipolar/unipolar mood disorder (with and without psychosis) are arrayed along this continuum. Parallels with the National Institutes of Mental Health (NIMH) Research Domain Criteria initiative are apparent. Adapted with permission from Craddock & Owen (2010).

Finally, a longitudinal follow-up of a first-episode psychosis cohort (McCarley et al. 2008) demonstrates progressive structural brain changes that occur in first-episode schizophrenia but do not occur in psychotic bipolar disorder.

CONCLUSIONS

Psychoses are highly morbid, disabling conditions each with an approximate population prevalence of 1%. Psychoses are stable across countries and cultures (Berrettini 2003) and currently are

diagnosed primarily on the basis of clinical phenomenology. This review examined some historical origins of these diagnostic divisions and emphasized that some of the issues raised by psychiatrists in the nineteenth century are now being reconsidered on the basis of recent biological evidence. For example, recent research offers support for the "dementia" of dementia praecox, for the fact that schizophrenia may be a group of illnesses, and perhaps even for the pre-Kraepelinian unitary psychosis concept. At the time he articulated his diagnostic distinctions, Kraepelin's hope was that these disorders would prove to have demonstrable pathologies and perhaps clear etiologies, as was emerging for other neuropsychiatric disorders such as Alzheimer's disease and neurosyphilis. Unfortunately, these hopes have not come to pass, and over a century later we are still left with putative disease entities defined mainly on the basis of cross-sectional clinical symptoms and course.

Over time, the various terms used to define the constructs of schizophrenia and bipolar illness and critical features such as psychosis have changed in significant ways. However, cases of schizophrenia and bipolar disorder as currently diagnosed correspond broadly (albeit differing in some notable ways) to Kraepelin's constructs of dementia praecox and manic-depressive insanity. Problems in separating the two disorders on the basis of clinical symptoms and course have been obvious since the diagnostic distinction was first drawn. The syndromes are not cleanly separable, lacking zones of rarity, and many intermediate examples are commonly found. Thus, although it is possible to find "typical" examples of manic-depressive illness and schizophrenia, there are impressive numbers of individuals whose phenomenology exhibits overlap. The marked clinical heterogeneity in these phenomenologically defined constructs, which exhibit reliability but uncertain validity, likely mirrors etiological heterogeneity.

Additionally, despite some differences, substantial overlap exists between the two disorders in terms of risk factors, epidemiology, treatment response, and for multiple biological measures, including virtually all major endophenotypes. Although these illnesses may "breed true" to an extent, it is clear that they often do not, as perhaps expected from large numbers of overlapping common risk genes (now clearly demonstrated through large-scale GWAS) that mix together, perhaps to some degree from assortative mating (Parnas 1985). However, evidence favors a stronger association of schizophrenia with neurodevelopmental abnormalities. Although a continuum model across the psychoses seems to remedy some of the problems associated with the current categorical diagnostic system, neither approach seems ideal.

A clear conclusion drawn from the present review of the literature is that there is an obvious failure to carve nature at its joints: Phenomenological diagnoses are failing to capture the biological distinctiveness that is necessary for improved therapeutic and prognostic purposes. The focus on distinct clinical entities within psychosis blocks the development of biologically based targeted treatment interventions. Consideration of the psychosis dimension may be necessary, with a more clear-cut separation between psychotic and nonpsychotic bipolar disorder. Importantly, such a psychosis syndrome could then be meaningfully split into homogeneous groups based on systems neuroscience and genetics. Although this effort could be carried out within existing syndromes—such as the recent attempt to dissect schizophrenia into several genetically determined subgroups, each with its own characteristic symptom patterns (Arnedo et al. 2015)—the focus of many new studies will undoubtedly be to look across different DSM disorders within the scope of a single study and, where relevant, among individuals on a related spectrum.

Ultimately, evidence suggests that approaches based on clinical symptoms and course alone are bound to fail in that they are unable to advance beyond what is already well established. At its root, this is not a philosophical question to be settled on the battleground of clinical phenomenology but rather a debate that can only be resolved on the basis of biological observations.

Several major questions related to a biological examination of schizophrenia and bipolar disorder were posed above. With regard to the types of measures that are likely to be most

informative, the measurement of endophenotypes was identified as particularly important, although the degree to which major endophenotypes of psychosis overlap biologically or genetically remains to be determined. The endophenotype enterprise is still at a relatively early stage, and its promise is not yet realized. The hope is that endophenotypes will yield genes that in turn illuminate the underlying biology of schizophrenia and bipolar disorder, thus acting as an anchor for classification. The best overall strategy to answer the most salient questions clearly necessitates more research across the schizophrenia/bipolar spectrum, including (rather than excluding) cases of schizoaffective disorder and subclinical syndromes. Such enterprises are best carried out through multicenter consortium studies in order to capture sufficient number of cases for statistical leverage to address major questions. Making such data sets publicly available is clearly advantageous to the scientific community as a whole. With regard to the conceptual framework into which biological findings should be fitted, I have advocated that the best way forward is a bottom-up reclustering starting with neuroscience-based measurements, particularly of endophenotypes because they allow easier genotyping (Fernandes et al. 2013, Keshavan et al. 2013) and because such data do not map onto particular conventional diagnostic entities but rather cross such boundaries frequently; reclustering leverages neurobiological heterogeneity. Although this approach could derive more uniform subgroups from within existing diagnostic categories, it is more likely to define completely new biologically coherent entities that cut across conventional diagnoses (B. Clementz, J. Sweeney, J. Hamm, E. Ivleva, L. Ethridge, G.D. Pearlson, M.S. Keshavan & C.A. Tamminga, manuscript under review; Hall et al. 2012). It is likely that schizophrenia and bipolar illness as traditionally defined each contain a mixture of several such entities, some of which are symptomatically identical and that need separation using biologic criteria (and of course replication). The elucidation of genes and molecular biological pathways associated with each biologically defined subgroup will lead logically to novel treatments that are based on etiology and mechanism. Such a process is clearly aligned with the aims of the NIH's RDoC initiative. For example, future studies are likely to elucidate the roles of the ion channels (primarily potassium and calcium) that are repeatedly implicated by risk genes and interactions between glutamate and dopamine systems that are clearly important but not well understood; unraveling which biological mechanisms are applicable to which classes of patients will ultimately lead to individualized treatments. Finally, the importance of psychotic versus nonpsychotic bipolar illness was stressed in the context of increasing evidence for a psychosis dimension. The next few years will prove extremely exciting in deconstructing schizophrenia and bipolar illness in a more definitive way than has proved possible since Kraepelin's initial formulation over 100 years ago.

DISCLOSURE STATEMENT

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LITERATURE CITED

Abrams R, Taylor MA. 1981. Importance of schizophrenic symptoms in the diagnosis of mania. *Am. J. Psychiatry* 138:658–61

Allen AJ, Griss ME, Folley BS, Hawkins KA, Pearlson GD. 2009. Endophenotypes in schizophrenia: a selective review. *Schizophr. Res.* 109:24–37

Am. Psychiatr. Assoc. 1980. *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: Am. Psychiatr. Publ. 3rd ed.

Am. Psychiatr. Assoc. 1994. *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: Am. Psychiatr. Publ. 4th ed.

Am. Psychiatr. Assoc. 2000. *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: Am. Psychiatr. Publ. 4th ed., text rev.

Am. Psychiatr. Assoc. 2013. *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: Am. Psychiatr. Publ. 5th ed.

Ancin I, Cabranes JA, Santos JL, Sanchez-Morla E, Barabash A. 2013. Executive deficits: a continuum schizophrenia-bipolar disorder or specific to schizophrenia? *J. Psychiatr. Res.* 47:1564–71

Anderson D, Ardekani BA, Burdick KE, Robinson DG, John M, et al. 2013. Overlapping and distinct gray and white matter abnormalities in schizophrenia and bipolar I disorder. *Bipolar. Disord.* 15:680–93

Angst J. 1966. *Zur Atiolgie und Nosologie endogener depressiver Psychosen: Eine genetische, soziologische und klinische Studie*. Berlin: Springer

Anticevic A, Yang G, Savic A, Murray JD, Cole MW, et al. 2014. Mediodorsal and visual thalamic connectivity differ in schizophrenia and bipolar disorder with and without psychosis history. *Schizophr. Bull.* 40:1227–43

Argyelan M, Ikuta T, DeRosse P, Braga RJ, Burdick KE, et al. 2014. Resting-state fMRI connectivity impairment in schizophrenia and bipolar disorder. *Schizophr. Bull.* 40:100–10

Arnedo J, Svrakic DM, Del Val C, Romero-Zaliz R, Hernandez-Cuervo H, et al. 2015. Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies. *Am. J. Psychiatry* 172:139–53

Arnold SJ, Ivleva EI, Gopal TA, Reddy AP, Jeon-Slaughter H, et al. 2015. Hippocampal volume is reduced in schizophrenia and schizoaffective disorder but not in psychotic bipolar I disorder demonstrated by both manual tracing and automated parcellation (FreeSurfer). *Schizophr. Bull.* 41:233–49

Baker JT, Holmes AJ, Masters GA, Yeo BT, Krienen F, et al. 2014. Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry* 71:109–18

Barabasi AL. 2007. Network medicine—from obesity to the "diseasome." *N. Engl. J. Med.* 357:404–7

Belmaker RH, van Praag HM. 1980. *Mania, an Evolving Concept*. Jamaica, NY: SP Med. Sci. Books

Berrettini W. 2003. Evidence for shared susceptibility in bipolar disorder and schizophrenia. *Am. J. Med. Genet. C Semin. Med. Genet.* 123C:59–64

Bestelmeyer PE. 2012. The visual P3a in schizophrenia and bipolar disorder: effects of target and distractor stimuli on the P300. *Psychiatry Res.* 197:140–44

Bestelmeyer PE, Phillips LH, Crombie C, Benson P, St Clair D. 2009. The P300 as a possible endophenotype for schizophrenia and bipolar disorder: evidence from twin and patient studies. *Psychiatry Res.* 169:212–19

Bleuler E. 1911. Dementia praecox or the group of schizophrenias. *Vertex* 21:394–400

Boteva K, Lieberman J. 2003. Reconsidering the classification of schizophrenia and manic depressive illness—a critical analysis and new conceptual model. *World J. Biol. Psychiatry* 4:81–92

Braff DL, Freedman R, Schork NJ, Gottesman II. 2007. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr. Bull.* 33:21–32

Brandt CL, Eichele T, Melle I, Sundet K, Server A, et al. 2014. Working memory networks and activation patterns in schizophrenia and bipolar disorder: comparison with healthy controls. *Br. J. Psychiatry* 204:290–98

Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, et al. 2007. The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. *Schizophr. Bull.* 33:33–48

Cannon TD, Keller MC. 2006. Endophenotypes in the genetic analyses of mental disorders. *Annu. Rev. Clin. Psychol.* 2:267–90

Carlson GA, Goodwin FK. 1973. The stages of mania. A longitudinal analysis of the manic episode. *Arch. Gen. Psychiatry* 28:221–28

Carpenter WT, Tandon R. 2013. Psychotic disorders in DSM-5: summary of changes. *Asian J. Psychiatry* 6:266–68

Carpenter WT Jr, Strauss JS. 1974. Cross-cultural evaluation of Schneider's first-rank symptoms of schizophrenia: a report from the International Pilot Study of Schizophrenia. *Am. J. Psychiatry* 131:682–87

Carpenter WT Jr, Strauss JS, Muleh S. 1973. Are there pathognomonic symptoms in schizophrenia? An empiric investigation of Schneider's first-rank symptoms. *Arch. Gen. Psychiatry* 28:847–52

Chai XJ, Whitfield-Gabrieli S, Shinn AK, Gabrieli JD, Nieto Castanon A, et al. 2011. Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. *Neuropsychopharmacology* 36:2009–17

Chan RC, Lui SS, Wang Y, Liu AC, Chui WW, et al. 2013. Patients with bipolar disorders share similar but attenuated prospective memory impairments with patients with schizophrenia. *Psychol. Med.* 43:1639–49

Chun J, Karam ZN, Marzinzik F, Kamali M, O'Donnell L, et al. 2013. Can P300 distinguish among schizophrenia, schizoaffective and bipolar I disorders? An ERP study of response inhibition. *Schizophr. Res.* 151:175–84

Clementz BA, Sponheim SR, Iacono WG, Beiser M. 1994. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients, and their first-degree relatives. *Psychophysiology* 31:486–94

Correll CU, Penzner JB, Frederickson AM, Richter JJ, Auther AM, et al. 2007. Differentiation in the preonset phases of schizophrenia and mood disorders: evidence in support of a bipolar mania prodrome. *Schizophr. Bull.* 33:703–14

Coryell W, Lavori P, Endicott J, Keller M, VanEerdewegh M. 1984. Outcome in schizoaffective, psychotic, and nonpsychotic depression. Course during a six- to 24-month follow-up. *Arch. Gen. Psychiatry* 41:787–91

Coryell W, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J. 2001. The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. *J. Affect. Disord.* 67:79–88

Costafreda SG, Fu CH, Picchioni M, Toulopoulou T, McDonald C, et al. 2011. Pattern of neural responses to verbal fluency shows diagnostic specificity for schizophrenia and bipolar disorder. *BMC Psychiatry* 11:18

Craddock N, O'Donovan MC, Owen MJ. 2005. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J. Med. Genet.* 42:193–204

Craddock N, Owen MJ. 2005. The beginning of the end for the Kraepelinian dichotomy. *Br. J. Psychiatry* 186:364–66

Craddock N, Owen MJ. 2007. Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry* 6:84–91

Craddock N, Owen MJ. 2010. The Kraepelinian dichotomy—going, going. . . but still not gone. *Br. J. Psychiatry* 196:92–95

Cross-Disord. Group Psychiatr. Genomics Consort. 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 381:1371–79

Crow TJ. 1986. The continuum of psychosis and its implication for the structure of the gene. *Br. J. Psychiatry* 149:419–29

Cui L, Chen Z, Deng W, Huang X, Li M, et al. 2011a. Assessment of white matter abnormalities in paranoid schizophrenia and bipolar mania patients. *Psychiatry Res.* 194:347–53

Cui L, Li M, Deng W, Guo W, Ma X, et al. 2011b. Overlapping clusters of gray matter deficits in paranoid schizophrenia and psychotic bipolar mania with family history. *Neurosci. Lett.* 489:94–98

Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, et al. 2012. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 486:346–52

De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A. 2012. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Curr. Pharm. Des.* 18:486–94

Decker HS. 2007. How Kraepelinian are the neo-Kraepelinians?—from Emil Kraepelin to DSM-III. *Hist. Psychiatry* 18(71 Part 3):337–60

Delvecchio G, Sugranyes G, Frangou S. 2013. Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies. *Psychol. Med.* 43:553–69

Domjan N, Csifcsak G, Drotos G, Janka Z, Szendi I. 2012. Different patterns of auditory information processing deficits in chronic schizophrenia and bipolar disorder with psychotic features. *Schizophr. Res.* 139:253–59

Dunner DL, Gershon ES, Goodwin FK. 1976. Heritable factors in the severity of affective illness. *Biol. Psychiatry* 11:31–42

Esterberg ML, Compton MT. 2009. The psychosis continuum and categorical versus dimensional diagnostic approaches. *Curr. Psychiatry Rep.* 11:179–84

Ethridge LE, Hamm JP, Pearlson GD, Tamminga CA, Sweeney JA, et al. 2015. Event-related potential and time-frequency endophenotypes for schizophrenia and psychotic bipolar disorder. *Biol. Psychiatry* 77:127–36

Ethridge LE, Hamm JP, Shapiro JR, Summerfelt AT, Keedy SK, et al. 2012. Neural activations during auditory oddball processing discriminating schizophrenia and psychotic bipolar disorder. *Biol. Psychiatry* 72:766–74

Farmer AE, McGuffin P, Gottesman II. 1987. Twin concordance for DSM-III schizophrenia. Scrutinizing the validity of the definition. *Arch. Gen. Psychiatry* 44:634–41

Fernandes CP, Christoforou A, Giddaluru S, Ersland KM, Djurovic S, et al. 2013. A genetic deconstruction of neurocognitive traits in schizophrenia and bipolar disorder. *PLOS ONE* 8:e81052

Fischer BA, Carpenter WT Jr. 2009. Will the Kraepelinian dichotomy survive DSM-V? *Neuropsychopharmacology* 34:2081–87

Fischer BA, Carpenter WT Jr. 2008. Remission. In *Clinical Handbook of Schizophrenia*, ed. KT Mueser, DV Jeste, pp. 559–65. New York: Guilford

Ford JM, Morris SE, Hoffman RE, Sommer I, Waters F, et al. 2014. Studying hallucinations within the NIMH RDoC framework. *Schizophr. Bull.* 40(Suppl. 4):S295–304

Frangou S. 2014. A systems neuroscience perspective of schizophrenia and bipolar disorder. *Schizophr. Bull.* 40:523–31

Gershon ES, DeLisi LE, Hamovit J, Nurnberger JI Jr, Maxwell ME, et al. 1988. A controlled family study of chronic psychoses. Schizophrenia and schizoaffective disorder. *Arch. Gen. Psychiatry* 45:328–36

Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, et al. 1982. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch. Gen. Psychiatry* 39:1157–67

Glahn DC, Knowles EE, McKay DR, Sprooten E, Raventos H, et al. 2014. Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 165B:122–30

Glahn DC, Williams JT, McKay DR, Knowles EE, Sprooten E, et al. 2015. Discovering schizophrenia endophenotypes in randomly ascertained pedigrees. *Biol. Psychiatry* 77:75–83

Goes FS, Sanders LL, Potash JB. 2008. The genetics of psychotic bipolar disorder. *Curr. Psychiatry Rep.* 10:178–89

Goodwin FK, Jamison KR. 1990. *Manic-Depressive Illness*. New York: Oxford Univ. Press

Gottesman II, Gould TD. 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160:636–45

Greene T. 2007. The Kraepelinian dichotomy: the twin pillars crumbling? *Hist. Psychiatry* 18:361–79

Griesinger W. 1845. *Mental Pathology and Therapeutics*. New York: Hafner Publ.

Grozeva D, Kirov G, Ivanov D, Jones IR, Jones L, et al. 2010. Rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. *Arch. Gen. Psychiatry* 67:318–27

Hall D, Huerta MF, McAuliffe MJ, Farber GK. 2012. Sharing heterogeneous data: the National Database for Autism Research. *Neuroinformatics* 10:331–39

Hamm JP, Ethridge LE, Boutros NN, Keshavan MS, Sweeney JA, et al. 2014. Diagnostic specificity and familiality of early versus late evoked potentials to auditory paired stimuli across the schizophrenia-bipolar psychosis spectrum. *Psychophysiology* 51:348–57

Hamm JP, Ethridge LE, Shapiro JR, Pearlson GD, Tamminga CA, et al. 2013. Family history of psychosis moderates early auditory cortical response abnormalities in non-psychotic bipolar disorder. *Bipolar. Disord.* 15:774–86

Hamm JP, Ethridge LE, Shapiro JR, Stevens MC, Boutros NN, et al. 2012. Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis. *Psychophysiology* 49:522–30

Harding CM, Brooks GW, Ashikaga T, Strauss JS, Breier A. 1987. The Vermont longitudinal study of persons with severe mental illness, II: long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. *Am. J. Psychiatry* 144:727–35

Harris MS, Reilly JL, Thase ME, Keshavan MS, Sweeney JA. 2009. Response suppression deficits in treatment-naive first-episode patients with schizophrenia, psychotic bipolar disorder and psychotic major depression. *Psychiatry Res.* 170:150–56

Haukvik UK, Westlye LT, Morch-Johnsen L, Jorgensen KN, Lange EH, et al. 2015. In vivo hippocampal subfield volumes in schizophrenia and bipolar disorder. *Biol. Psychiatry* 77:581–88

Higier RG, Jimenez AM, Hultman CM, Borg J, Roman C, et al. 2014. Enhanced neurocognitive functioning and positive temperament in twins discordant for bipolar disorder. *Am. J. Psychiatry* 171:1191–98

Hill SK, Reilly JL, Keefe RS, Gold JM, Bishop JR, et al. 2013. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Am. J. Psychiatry* 170:1275–84

Hill SK, Reilly JL, Ragozzino ME, Rubin LH, Bishop JR, et al. 2014. Regressing to prior response preference after set switching implicates striatal dysfunction across psychotic disorders: findings from the B-SNIP study. *Schizophr. Bull.* In press

Hulshoff Pol HE, van Baal GC, Schnack HG, Brans RG, van der Schot AC, et al. 2012. Overlapping and segregating structural brain abnormalities in twins with schizophrenia or bipolar disorder. *Arch. Gen. Psychiatry* 69:349–59

Hyman SE. 2010. The diagnosis of mental disorders: the problem of reification. *Annu. Rev. Clin. Psychol.* 6:155–79

Insel TR. 2010. Rethinking schizophrenia. *Nature* 468:187–93

Insel TR, Cuthbert BN. 2009. Endophenotypes: bridging genomic complexity and disorder heterogeneity. *Biol. Psychiatry* 66:988–89

Ivleva EI, Bidesi AS, Keshavan MS, Pearlson GD, Meda SA, et al. 2013. Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am. J. Psychiatry* 170:1285–96

Ivleva EI, Moates AF, Hamm JP, Bernstein IH, O'Neill HB, et al. 2014. Smooth pursuit eye movement, prepulse inhibition, and auditory paired stimuli processing endophenotypes across the schizophrenia-bipolar disorder psychosis dimension. *Schizophr. Bull.* 40:642–52

Ivleva EI, Morris DW, Moates AF, Suppes T, Thaker GK, Tamminga CA. 2010. Genetics and intermediate phenotypes of the schizophrenia–bipolar disorder boundary. *Neurosci. Biobehav. Rev.* 34:897–921

Jablensky A, Hugler H, Von Cranach M, Kalinov K. 1993. Kraepelin revisited: a reassessment and statistical analysis of dementia praecox and manic-depressive insanity in 1908. *Psychol. Med.* 23:843–58

Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, et al. 1992. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol. Med. Monogr. Suppl.* 20:1–97

Jablensky A, Woodbury MA. 1995. Dementia praecox and manic-depressive insanity in 1908: a Grade of Membership analysis of the Kraepelinian dichotomy. *Eur. Arch. Psychiatry Clin. Neurosci.* 245:202–9

Jager M, Haack S, Becker T, Frasch K. 2011. Schizoaffective disorder—an ongoing challenge for psychiatric nosology. *Eur. Psychiatry* 26:159–65

Jahshan C, Wynn JK, Mathis KI, Altshuler LL, Glahn DC, Green MF. 2012. Cross-diagnostic comparison of duration mismatch negativity and P3a in bipolar disorder and schizophrenia. *Bipolar Disord.* 14:239–48

Jamadar S, O'Neil KM, Pearlson GD, Ansari M, Gill A, et al. 2013. Impairment in semantic retrieval is associated with symptoms in schizophrenia but not bipolar disorder. *Biol. Psychiatry* 73:555–64

Johannesen JK, O'Donnell BF, Shekhar A, McGrew JH, Hetrick WP. 2013. Diagnostic specificity of neurophysiological endophenotypes in schizophrenia and bipolar disorder. *Schizophr. Bull.* 39:1219–29

Johnstone EC, Crow TJ, Frith CD, Owens DG. 1988. The Northwick Park "functional" psychosis study: diagnosis and treatment response. *Lancet* 2:119–25

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, et al. 2005. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch. Gen. Psychiatry* 62:1322–30

Kahlbaum KL. 1863. *Die Gruppierung der psychischen Krankheiten und die Eintheilung der Seelenstörungen*. Danzig: Kafemann

Kahlbaum KL. 1874. *Die Katatonie, oder das Spannungsirresein; eine klinische Form psychischer Krankheit*. Berlin: Hirschwald

Kam JW, Bolbecker AR, O'Donnell BF, Hetrick WP, Brenner CA. 2013. Resting state EEG power and coherence abnormalities in bipolar disorder and schizophrenia. *J. Psychiatr. Res.* 47:1893–901

Kapur S, Phillips AG, Insel TR. 2012. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol. Psychiatry* 17:1174–79

Kasanin J. 1994. The acute schizoaffective psychoses. 1933. *Am. J. Psychiatry* 151:144–54

Kathmann N, Hochrein A, Uwer R, Bondy B. 2003. Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. *Am. J. Psychiatry* 160:696–702

Keck PE Jr, McElroy SL, Havens JR, Altshuler LL, Nolen WA, et al. 2003. Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Compr. Psychiatry* 44:263–69

Kendell RE. 1987. Diagnosis and classification of functional psychoses. *Br. Med. Bull.* 43:499–513

Kendell RE. 1991. The major functional psychoses: Are they independent entities or a part of a continuum? Philosophical and conceptual issues underlying the debate. In *Concepts of Mental Disorder: A Continuing Debate*, ed. A Kerr, H McClelland, pp. 1–16. London: Royal Coll. Psychiatr.

Kendell RE, Brockington IF. 1980. The identification of disease entities and the relationship between schizophrenic and affective psychoses. *Br. J. Psychiatry* 137:324–31

Kendler KS, Gruenberg AM, Tsuang MT. 1985. Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients. A family study using DSM-III criteria. *Arch. Gen. Psychiatry* 42:770–79

Kendler KS, Neale MC. 2010. Endophenotype: a conceptual analysis. *Mol. Psychiatry* 15:789–97

Keshavan MS, Clementz BA, Pearlson GD, Sweeney JA, Tamminga CA. 2013. Reimagining psychoses: an agnostic approach to diagnosis. *Schizophr. Res.* 146:10–16

Keshavan MS, Morris DW, Sweeney JA, Pearlson G, Thaker G, et al. 2011. A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: the Schizo-Bipolar Scale. *Schizophr. Res.* 133:250–54

Ketter TA, Wang PW, Becker OV, Nowakowska C, Yang Y. 2004. Psychotic bipolar disorders: dimensionally similar to or categorically different from schizophrenia? *J. Psychiatr. Res.* 38:47–61

Khadka S, Meda SA, Stevens MC, Glahn DC, Calhoun VD, et al. 2013. Is aberrant functional connectivity a psychosis endophenotype? A resting state functional magnetic resonance imaging study. *Biol. Psychiatry* 74:458–66

Kick H. 1981. Die Dichotomie der idiopathischen Psychosen im Syndromprofilvergleich der Kraepelinschen Krankheitsbeschreibungen. *Nervenarzt* 52:522–24

Kidd KK, Mathysse S. 1978. Research designs for the study of gene-environment interactions in psychiatric disorders. Report of a Foundations Fund for Research in Psychiatry Panel. *Arch. Gen. Psychiatry* 35:925–32

Kraepelin E. 1887. The directions of psychiatric research. Transl. E Engstrom, 2005, in *Hist. Psychiatry* (16):345–64

Kraepelin E. 1904. Vergleichende Psychiatrie. *Zentbl. Nervenheilk. Psychiatr.* 15:433–37

Kraepelin E. 1909–13. *Psychiatrie*. Leipzig: Barth. 8th ed.

Kraepelin E. 1912 (1907). *Psychiatry: A Textbook for Students and Physicians*. Leipzig: Barth. Transl. AR Diefendorf. New York: McMillan. 7th ed.

Kraepelin E. 1920a. Der erschenungsformen der irreseins. *Z. Ges. Neurol. Psychiatr.* 62:1–29 Transl. SR Hirsch, M Shepherd, 1974, in *Themes and Variations in European Psychiatry*, Charlottesville: VA Univ. Press

Kraepelin E. 1920b (1919). *Dementia Praecox and Paraphrenia*. Transl. R Mary Barclay. Edinburgh: E & S Livingstone (reprinted 2002; Bristol: Theommes Press)

Kraepelin E. 1920c. Der erschenungsformen der irreseins. *Z. Ges. Neurol. Psychiatr.* 62:1–29 Transl. D Beer, 1992. The manifestations of insanity. *Hist. Psychiatry* 3:509–29

Kraepelin E, Lange J. 1927. *Psychiatry*, Vol. 1, 2. Liepzig: Barth. 9th ed.
Kraepelin E. 1990 (1899). *Psychiatry: A Textbook for Students and Physicians*, ed. JM Quen, transl. H Metiu, S Ayed. Canton, MA: Sci. History Publ.
Krishnadas R, Ramanathan S, Wong E, Nayak A, Moore B. 2014. Residual negative symptoms differentiate cognitive performance in clinically stable patients with schizophrenia and bipolar disorder. *Schizophr. Res. Treat.* 2014:785310
Krueger RF. 2005. Continuity of Axes I and II: toward a unified model of personality, personality disorders, and clinical disorders. *J. Personal. Disord.* 19:233–61
Lee AS, Murray RM. 1988. The long-term outcome of Maudsley depressives. *Br. J. Psychiatry* 153:741–51
Lencer R, Reilly JL, Harris MS, Sprenger A, Keshavan MS, Sweeney JA. 2010. Sensorimotor transformation deficits for smooth pursuit in first-episode affective psychoses and schizophrenia. *Biol. Psychiatry* 67:217–23
Leonhard K, ed. 1979. *The Classification of Endogenous Psychoses*. New York: Irvington Publ.
Lett TA, Zai CC, Tiwari AK, Shaikh SA, Likhodi O, et al. 2011. ANK3, CACNA1C and ZNF804A gene variants in bipolar disorders and psychosis subphenotype. *World J. Biol. Psychiatry* 12:392–97
Lewandowski KE, Cohen BM, Ongur D. 2011. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychol. Med.* 41:225–41
Lewandowski KE, Sperry SH, Cohen BM, Ongur D. 2014. Cognitive variability in psychotic disorders: a cross-diagnostic cluster analysis. *Psychol. Med.* 44:3239–48
Li J, Kale Edmiston E, Chen K, Tang Y, Ouyang X, et al. 2014. A comparative diffusion tensor imaging study of corpus callosum subregion integrity in bipolar disorder and schizophrenia. *Psychiatry Res.* 221:58–62
Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, et al. 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 373:234–39
Lieber B. 1975. Die Nosologie auf dem Wege zu neuen Ordnungssystemen: Syndrome und Syndromatologie. *Internist* 16:56–60
Liu H, Tang Y, Womer F, Fan G, Lu T, et al. 2014. Differentiating patterns of amygdala-frontal functional connectivity in schizophrenia and bipolar disorder. *Schizophr. Bull.* 40:469–77
Lui S, Yao L, Xiao Y, Keedy SK, Reilly JL, et al. 2015. Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. *Psychol. Med.* In press
Majadas S, Olivares J, Galan J, Diez T. 2012. Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. *Compr. Psychiatry* 53:145–51
Malhi GS, Mitchell PB, Parker GB. 2001. Rediscovering chronic mania. *Acta Psychiatr. Scand.* 104:153–56
Mamah D, Barch DM, Repovs G. 2013. Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. *J. Affect. Disord.* 150:601–9
Marneros A, Rohde A, Deister A, Sakamoto K. 1987. Kurt Schneider's schizophrenia—the picture of schizophrenia in a Schneider-oriented university clinic. *Jpn. J. Psychiatry Neurol.* 41:171–78
Martin LF, Hall MH, Ross RG, Zerbe G, Freedman R, Olincy A. 2007. Physiology of schizophrenia, bipolar disorder, and schizoaffective disorder. *Am. J. Psychiatry* 164:1900–6
Mason P, Harrison G, Croudace T, Glazebrook C, Medley I. 1997. The predictive validity of a diagnosis of schizophrenia. A report from the International Study of Schizophrenia (ISoS) coordinated by the World Health Organization and the Department of Psychiatry, University of Nottingham. *Br. J. Psychiatry* 170:321–27
Mathew I, Gardin TM, Tandon N, Eack S, Francis AN, et al. 2014. Medial temporal lobe structures and hippocampal subfields in psychotic disorders: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *JAMA Psychiatry* 71:769–77
Mayer-Gross W, Slater E, Roth M. 1969. *Clinical Psychiatry*. London: Cassell. 3rd ed.
McCarley RW, Nakamura M, Shenton ME, Salisbury DF. 2008. Combining ERP and structural MRI information in first episode schizophrenia and bipolar disorder. *Clin. EEG Neurosci.* 39:57–60
McCarthy SE, Makarov V, Kirov G, Addington AM, McClellan J, et al. 2009. Microduplications of 16p11.2 are associated with schizophrenia. *Nat. Genet.* 41:1223–27
McDowell JE, Clementz BA. 1997. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. *Exp. Brain Res.* 115:333–44

McHugh P, Slavney PR. 1998. *The Perspectives of Psychiatry*. Baltimore, MD: Johns Hopkins Univ. Press. 2nd ed.
Meda SA, Gill A, Stevens MC, Lorenzoni RP, Glahn DC, et al. 2012. Differences in resting-state functional magnetic resonance imaging functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives. *Biol. Psychiatry* 71:881–89
Meda SA, Ruano G, Windemuth A, O'Neil K, Berwise C, et al. 2014. Multivariate analysis reveals genetic associations of the resting default mode network in psychotic bipolar disorder and schizophrenia. *Proc. Natl. Acad. Sci. USA* 111:E2066–75
Meehl P. 1962. Schizotaxia, schizotypy, schizophrenia. *Am. Psychiatry* 17:827–38
Meltzer HY. 1984. Schizoaffective disorder: Is the news of its nonexistence premature? Editor's introduction. *Schizophr. Bull.* 10:11–13
Moates AF, Ivleva EI, O'Neill HB, Krishna N, Cullum CM, et al. 2012. Predictive pursuit association with deficits in working memory in psychosis. *Biol. Psychiatry* 72:752–57
Moldin SO, Gottesman II, Erlenmeyer-Kimling L. 1987. Psychometric validation of psychiatric diagnoses in the New York High-Risk Study. *Psychiatry Res.* 22:159–77
Molina V, Galindo G, Cortes B, de Herrera AG, Ledo A, et al. 2011. Different gray matter patterns in chronic schizophrenia and chronic bipolar disorder patients identified using voxel-based morphometry. *Eur. Arch. Psychiatry Clin. Neurosci.* 261:313–22
Morris RW, Sparks A, Mitchell PB, Weickert CS, Green MJ. 2012. Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation. *Transl. Psychiatry* 2:e90
Murray RM, Foerster A. 1987. Schizophrenia: Is the concept disintegrating? *J. Psychopharmacol.* 1:133–39
Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. 2004. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr. Res.* 71:405–16
Nanda P, Tandon N, Mathew IT, Giakoumatos CI, Abhishekh HA, et al. 2014. Local gyrification index in probands with psychotic disorders and their first-degree relatives. *Biol. Psychiatry* 76:447–55
Narayanan B, O'Neil K, Berwise C, Stevens MC, Calhoun VD, et al. 2014. Resting state electroencephalogram oscillatory abnormalities in schizophrenia and psychotic bipolar patients and their relatives from the Bipolar and Schizophrenia Network on Intermediate Phenotypes study. *Biol. Psychiatry* 76:456–65
O'Donnell BF, Vohs JL, Hetrick WP, Carroll CA, Shekhar A. 2004. Auditory event-related potential abnormalities in bipolar disorder and schizophrenia. *Int. J. Psychophysiol.* 53:45–55
O'Mahony E, Corvin A, O'Connell R, Comerford C, Larsen B, et al. 2002. Sibling pairs with affective disorders: resemblance of demographic and clinical features. *Psychol. Med.* 32:55–61
Ongur D, Lundy M, Greenhouse I, Shinn AK, Menon V, et al. 2010. Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Res.* 183:59–68
Owen MJ, Craddock N, Jablensky A. 2007. The genetic deconstruction of psychosis. *Schizophr. Bull.* 33:905–11
Owen MJ, Craddock N, O'Donovan MC. 2010. Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia. *Arch. Gen. Psychiatry* 67:667–73
Pacheco A, Barguil M, Contreras J, Montero P, Dassori A, et al. 2010. Social and clinical comparison between schizophrenia and bipolar disorder type I with psychosis in Costa Rica. *Soc. Psychiatry Psychiatr. Epidemiol.* 45:675–80
Parker G, Graham R, Hadzi-Pavlovic D, McCraw S, Hong M, Friend P. 2013. Differentiation of bipolar I and II disorders by examining for differences in severity of manic/hypomanic symptoms and the presence or absence of psychosis during that phase. *J. Affect. Disord.* 150:941–47
Parnas J. 1985. Mates of schizophrenic mothers. A study of assortative mating from the American-Danish high risk project. *Br. J. Psychiatry* 146:490–97
Parshall AM, Priest RG. 1993. Nosology, taxonomy and the classification conundrum of the functional psychoses. *Br. J. Psychiatry* 162:227–36
Pearlson G, Schaepfer T. 1999. Brain imaging in affective disorders. In *Psychopharmacology: The Fourth Generation of Progress*, ed. FE Bloom, DJ Kupfer. New York: Raven
Pearlson GD, Folley BS. 2008. Schizophrenia, psychiatric genetics, and Darwinian psychiatry: an evolutionary framework. *Schizophr. Bull.* 34:722–33
Pearlson GD, Wong DF, Tune LE, Ross CA, Chase GA, et al. 1995. In vivo D2 dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch. Gen. Psychiatry* 52:471–77

Peralta V, Cuesta MJ, Giraldo C, Cardenas A, Gonzalez F. 2002. Classifying psychotic disorders: issues regarding categorical versus dimensional approaches and time frame to assess symptoms. *Eur. Arch. Psychiatry Clin. Neurosci.* 252:12–18

Perry W, Minassian A, Feifel D, Braff DL. 2001. Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. *Biol. Psychiatry* 50:418–24

Pope HG Jr, Lipinski JF Jr. 1978. Diagnosis in schizophrenia and manic-depressive illness: a reassessment of the specificity of "schizophrenic" symptoms in the light of current research. *Arch. Gen. Psychiatry* 35:811–28

Post RM. 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am. J. Psychiatry* 149:999–1010

Post RM. 1999. Comparative pharmacology of bipolar disorder and schizophrenia. *Schizophr. Res.* 39:153–58; discuss. 163

Potash JB, Chiu YF, MacKinnon DF, Miller EB, Simpson SG, et al. 2003. Familial aggregation of psychotic symptoms in a replication set of 69 bipolar disorder pedigrees. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 116B:90–97

Potash JB, Willour VL, Chiu YF, Simpson SG, MacKinnon DF, et al. 2001. The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. *Am. J. Psychiatry* 158:1258–64

Potuzak M, Ravichandran C, Lewandowski KE, Ongur D, Cohen BM. 2012. Categorical versus dimensional classifications of psychotic disorders. *Compr. Psychiatry* 53:1118–29

Raine A, Lencz T. 1995. Conceptual and theoretical issues in schizotypal personality research. In *Schizotypal Personality*, ed. A. Raine, T. Lencz, S.A. Mednick, pp. 3–17. New York: Cambridge Univ. Press

Reilly JL, Frankovich K, Hill S, Gershon ES, Keefe RS, et al. 2014. Elevated antisaccade error rate as an intermediate phenotype for psychosis across diagnostic categories. *Schizophr. Bull.* 40:1011–21

Rimol LM, Hartberg CB, Nesvag R, Fennema-Notestine C, Hagler DJ Jr, et al. 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biol. Psychiatry* 68:41–50

Rimol LM, Nesvag R, Hagler DJ Jr, Bergmann O, Fennema-Notestine C, et al. 2012. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biol. Psychiatry* 71:552–60

Robins E, Guze SB. 1970. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am. J. Psychiatry* 126:983–87

Romero R, Dey SK, Fisher SJ. 2014. Preterm labor: one syndrome, many causes. *Science* 345:760–65

Ruocco AC, Reilly JL, Rubin LH, Daros AR, Gershon ES, et al. 2014. Emotion recognition deficits in schizophrenia-spectrum disorders and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Schizophr. Res.* 158:105–12

Ruscio J, Haslam N, Ruscio AM. 2006. *Introduction to the Taxometric Method: A Practical Guide*. Mahwah, NJ: Erlbaum

Salisbury DF, Shenton ME, McCarley RW. 1999. P300 topography differs in schizophrenia and manic psychosis. *Biol. Psychiatry* 45:98–106

Sanchez-Morla EM, Garcia-Jimenez MA, Barabash A, Martinez-Vizcaino V, Mena J, et al. 2008. P50 sensory gating deficit is a common marker of vulnerability to bipolar disorder and schizophrenia. *Acta Psychiatr. Scand.* 117:313–18

Schnack HG, Nieuwenhuis M, van Haren NE, Abramovic L, Scheewe TW, et al. 2014. Can structural MRI aid in clinical classification? A machine learning study in two independent samples of patients with schizophrenia, bipolar disorder and healthy subjects. *NeuroImage* 84:299–306

Schorer CE. 1982. The rediscovery of Kraepelin. *J. Oper. Psychiatry* 13:73–75

Schretlen DJ, Cascella NG, Meyer SM, Kingery LR, Testa SM, et al. 2007. Neuropsychological functioning in bipolar disorder and schizophrenia. *Biol. Psychiatry* 62:179–86

Schretlen DJ, Pena J, Aretouli E, Orue I, Cascella NG, et al. 2013. Confirmatory factor analysis reveals a latent cognitive structure common to bipolar disorder, schizophrenia, and normal controls. *Bipolar Disord.* 15:422–33

Schulz J, Sundin J, Leask S, Done DJ. 2014. Risk of adult schizophrenia and its relationship to childhood IQ in the 1958 British birth cohort. *Schizophr. Bull.* 40:143–51

Schurhoff F, Szoke A, Meary A, Bellivier F, Rouillon F, et al. 2003. Familial aggregation of delusional proneness in schizophrenia and bipolar pedigrees. *Am. J. Psychiatry* 160:1313–19

Sebat J, Levy DL, McCarthy SE. 2009. Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders. *Trends Genet.* 25:528–35

Sepede G, Spano MC, Lorusso M, De Berardis D, Salerno RM, et al. 2014. Sustained attention in psychosis: neuroimaging findings. *World J. Radiol.* 6:261–73

Sheldrick C, Jablensky A, Sartorius N, Shepherd M. 1977. Schizophrenia succeeded by affective illness: catamnestic study and statistical enquiry. *Psychol. Med.* 7:619–24

Skudlarski P, Schretlen DJ, Thaker GK, Stevens MC, Keshavan MS, et al. 2013. Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. *Am. J. Psychiatry* 170:886–98

Smith MJ, Barch DM, Csernansky JG. 2009. Bridging the gap between schizophrenia and psychotic mood disorders: relating neurocognitive deficits to psychopathology. *Schizophr. Res.* 107:69–75

Strasser HC, Lilyestrom J, Ashby ER, Honeycutt NA, Schretlen DJ, et al. 2005. Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. *Biol. Psychiatry* 57:633–39

Sullivan PF. 2010. The psychiatric GWAS consortium: Big science comes to psychiatry. *Neuron* 68:182–86

Tamminga CA, Pearlson G, Keshavan M, Sweeney J, Clementz B, Thaker G. 2014. Bipolar and Schizophrenia Network for Intermediate Phenotypes: outcomes across the psychosis continuum. *Schizophr. Bull.* 40(Suppl. 2):S131–37

Thaker GK. 2008. Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophr. Bull.* 34:760–73

Tien AY, Ross DE, Pearlson G, Strauss ME. 1996. Eye movements and psychopathology in schizophrenia and bipolar disorder. *J. Nerv. Ment. Dis.* 184:331–38

Trotta A, Murray RM, MacCabe JH. 2014. Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. *Psychol. Med.* In press

van Os J, Fahy TA, Jones P, Harvey I, Sham P, et al. 1996. Psychopathological syndromes in the functional psychoses: associations with course and outcome. *Psychol. Med.* 26:161–76

van Os J, Gilvarry C, Bale R, Van Horn E, Tattan T, et al. 1999. A comparison of the utility of dimensional and categorical representations of psychosis. UK700 Group. *Psychol. Med.* 29:595–606

van Os J, Jones P, Lewis G, Wadsworth M, Murray R. 1997. Developmental precursors of affective illness in a general population birth cohort. *Arch. Gen. Psychiatry* 54:625–31

Vilela C, Vallet M, Salazar J, Tabares R, Selva G, et al. 1999. [P300 and neuropsychological tests in schizophrenia and bipolar patients]. *Rev. Neurol.* 28:608–12

Vohringer PA, Barroilhet SA, Amerio A, Reale ML, Alvear K, et al. 2013. Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. *Front. Psychiatry* 4:87

Wang K, Song LL, Cheung EF, Lui SS, Shum DH, Chan RC. 2013. Bipolar disorder and schizophrenia share a similar deficit in semantic inhibition: a meta-analysis based on Hayling Sentence Completion Test performance. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 46:153–60

Wexler BE, Zhu H, Bell MD, Nicholls SS, Fulbright RK, et al. 2009. Neuropsychological near normality and brain structure abnormality in schizophrenia. *Am. J. Psychiatry* 166:189–95

Wing JK. 1971. International comparisons in the study of the functional psychoses. *Br. Med. Bull.* 27:77–81

Womer FY, Wang L, Alpert KI, Smith MJ, Csernansky JG, et al. 2014. Basal ganglia and thalamic morphology in schizophrenia and bipolar disorder. *Psychiatry Res.* 223:75–83

Yang GJ, Murray JD, Repovs G, Cole MW, Savic A, et al. 2014. Altered global brain signal in schizophrenia. *Proc. Natl. Acad. Sci. USA* 111:7438–43

Zendig E. 1909. Beiträge zur Differentialdiagnose des manisch-depressiven Irreseins und der Dementia praecox. *Allg. Z. Psychiatr.* 66:932–33