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Distinguishing Between Schizophrenia and Other Psychotic Disorders

Godfrey D. Pearlson*[,1,2] and Judith M. Ford[3,4]

[1]Departments of Psychiatry and Neurobiology, Yale University, New Haven, CT; [2]Olin Neuropsychiatry Research Center, Institute of Living, Hartford, CT; [3]San Francisco VA Medical Center, San Francisco, CA; [4]Department of Psychiatry, University of California, San Francisco (UCSF), San Francisco, CA

*To whom correspondence should be addressed; Whitehall Building 207, ONRC, IOL, 200 Washington Street, Hartford, CT 06106, US; tel: 860-545-7678, fax: 860-545-7797, e-mail: godfrey.pearlson@yale.edu

***The Diagnostic and Statistical Manual of Mental Disorders* (DSM) has provided diagnostic reliability across observers while neglecting biological validity. The current theme issue explores the boundaries between schizophrenia and bipolar disorder, using neuro-cognition, systems neuroscience, and genetics as points of departure to begin consideration of a biologically based reclassification of these illnesses.**

Key words: schizophrenia/bipolar/validity/classification

> "Ce n'est qu'un début, continuons le débat." (*"This is just the beginning, let's continue the debate."*)
>
> French students (May 1968)

In the ongoing debate over where to draw the boundary (if any) between schizophrenia and bipolar disorder, the arguments are familiar, the battle lines clearly drawn, but the scientific observations continue to be updated in important ways that make a reassessment timely. The current issue of the Bulletin features comprehensive overviews from the vantage points of genetics and systems neuroscience that continue to reshape the nature of the debate.

Arguments over the discrete vs continuous nature of schizophrenia and bipolar disorder are important because they promise to translate into improved, more patient-specific prognoses and therapies.

Disease classifications proceed from some logical beginning: In the absence of both informative biological data and clinical physical signs, clinical phenomenology, family history, and disease course constitute the mandatory starting points on the road to meaningful diagnostic categories. Hence, Kraepelin began in 1893 by defining these 2 entities based on longitudinal course and outcome. He had already begun to backtrack from this dichotomy by 1920 in the final edition of his Lehrbuch.[1] Before that, the follow-up studies from his pupil Zendig[2] demonstrated favorable outcome in a third of Kraepelin's own large schizophrenia case series. The boundaries between clinical entities defined by phenomenology appear to be distributed on a continuum and to lack sharp demarcations. Thus, one-third of patients with schizophrenia simultaneously meet criteria for major depression,[3] one-third of patients with bipolar illness manifest psychotic symptoms, which in some cases persist between overt episodes of mood disturbance.[4] Recently, Keshavan[5] showed no point of symptomatic rarity between schizophrenia, psychotic bipolar disorder, and schizoaffective disorder in the large Bipolar Schizophrenia Network on Intermediate Phenotypes sample. Similarly, the Suffolk County mental health project showed a lack of boundary, defined in terms of functioning, between schizoaffective disorder and schizophrenia,[6] although there are occasional reports of biological distinctions between them, for example.[7]

Response to medications has not been especially helpful as a guide. The early Northwick Park studies offered some suggestion that patients with psychosis responded to antipsychotics, patients with mood disorders responded to lithium, and patients with features of both syndromes responded to both medicines.[8] However, antipsychotic medications are now prescribed routinely for schizophrenia, bipolar disorder, and antidepressant treatment–resistant major depression, presumably, in part because they are effective in these conditions. Real-world experience with these patients shows that many are being prescribed polypharmaceutical cocktails of antipsychotic, antidepressant, and mood stabilizer medications. As is frequently pointed out, the one exception to this cross-diagnostic promiscuity seems to be lithium, to which about one-third of nonpsychotic bipolar patients and a much smaller proportion of classic schizophrenia patients respond with symptom remission.[9]

Although both schizophrenia and bipolar disorder are clearly heritable, as Cardno and Owen[10] illustrate in this issue, segregation within families is less clear-cut than believed previously, and these conditions do not decisively "breed true,"[11] although psychotic bipolar illness may aggregate familially.[4] Genome wide–association studies tend to uncover candidate single-nucleotide polymorphisms that confer risk for both disorders, and genes such as *DISC-1* are also associated with increased risk for schizophrenia, bipolar illness, major depression, and other conditions.

As pointed out by Frangou[12] in this issue, emergent properties such as cognition are an excellent starting point for examining differences between syndromes because they are reliably assessed across centers with standardized tests. Because they demonstrate both heritability and frequent abnormality in unaffected first-degree relatives, they constitute phenotypes, conceptually.[11] In this issue, Reilly and Sweeney[13] point out, "Considerable evidence supports the notion that broadly impaired cognitive functioning is central to the pathophysiology of psychosis, and … [its] magnitude, rather than [its] presence differentiates syndromes within the psychosis spectrum." They further suggest, "The detection of specific effects … is challenging yet critical if the field is to further advance development of pharmacological treatments targeting cognitive deficits … ." In our search for specificity, we ask if there is any point in the illness course where differences emerge? Frangou[12] notes that important differences are detectable in that premorbid cognitive and social abnormalities appear to be less marked in bipolar illness, although these differences diminish after illness onset. Similarly, copy number variants occurring in central nervous system–relevant genes are significantly commoner in schizophrenia than bipolar disorder, although, as mentioned earlier, genetic differences are not schizophrenia-specific, being found in association with other serious neurodevelopmental disorders, including epilepsy, learning disabilities, and autism spectrum disorders.

Where do we go from here? This debate will continue until distinct etiopathologies for schizophrenia and bipolar disorder emerge—parallel events that ultimately ended this type of debate in clinical medicine. Ultimately, though, we are likely to define the new "illnesses" based on regularly co-occurring biological (including genetic) characteristics. One possibility in the short term is that we remain diagnostically uncommitted and code psychosis and mood disorder separately, as suggested by Kotov.[14] Some researchers have argued strongly against this stance.[15] Different associations with indices of neurodevelopmental impairment may be one point of departure as suggested in this issue by Cardno and Owen[10] and Frangou.[12] Frangou suggests that "abnormalities in multiple large-scale neural networks and alterations in local micro-scale circuitry within associative and sensory cortices" caused by environmental insults and genetic variation, "disrupt processes responsible for orderly neuronal configuration" (eg, synaptic integrity, neurotransmission). Identifying such abnormalities then proceeds logically toward a redefinition of major mental illnesses based on systems neuroscience and the defining of "more homogeneous groups of patients."[12] This strategy may reveal similarities across all putatively developmentally based psychiatric illnesses, including autism and learning disabilities, extending beyond schizophrenia and bipolar disorder. Cardno and Owen[10] suggest we move away from lifetime diagnostic categories toward a system that relies more on "categorical or dimensional syndromes, networks of correlated symptoms, and/or endophenotypes … according to particular research or clinical requirements."

Regarding the genetic underpinnings of these disorders, we ask, "Precisely what is being inherited?" One possibility is that a small number of genes are being passed on that are responsible for multiple clinical manifestations, from mood instability to psychoticism (ie, an instance of pleiotropy). Another possibility is that risk is being inherited for more than one behavioral trait, which happens to commonly co-occur, for a variety of reasons including assortative mating. For example, "psychoticism," whose pure form is expressed as Kraepelinian schizophrenia, and "mood instability," whose pure form is expressed as nonpsychotic bipolar illness, may both be passed on, with the possibility of them being mixed together in various combinations to produce, eg, schizoaffective or psychotic bipolar disorder.

What might the new disease landscape look like, whether based on neuronal circuit-based endophenotypes or commonalities in risk genes and their associated molecular biological processes? One possibility is that several clinical groupings will emerge that are phenomenologically heterogeneous, containing examples of what we now define clinically as schizophrenia and bipolar disorder, but consistent in their underlying biological markers. This would be analogous to the fate of "dropsy" in medicine. A less satisfactory outcome would be that more knowledge of etiopathology would result in the fissuring of familiar clinical syndromes into unique biological clusters, representing agglomerations defined by differing pathologic processes leading to disruption in final common biological pathways, more along the lines of the manner in which Alzheimer's disease is now considered. The ultimate hope is to aggregate disorders according to biological mechanisms that underlie clinical phenomena and that point us toward evidence-based treatment targets and interventions. This is consistent with the National Institute of Mental Health's Research Domain Criteria[16] and the earlier cognitive neuropsychiatric approach.[17–19] This debate began with Kraepelin, is moving forward, but continues.

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