

UCSF

UC San Francisco Previously Published Works

Title

Distinguishing Between Schizophrenia and Other Psychotic Disorders

Permalink

<https://escholarship.org/uc/item/00j792m7>

Journal

Schizophrenia Bulletin, 40(3)

ISSN

0586-7614

Authors

Pearlson, Godfrey D
Ford, Judith M

Publication Date

2014-05-01

DOI

10.1093/schbul/sbu055

Peer reviewed

Distinguishing Between Schizophrenia and Other Psychotic Disorders

Godfrey D. Pearlson^{*,1,2} and Judith M. Ford^{3,4}

¹Departments of Psychiatry and Neurobiology, Yale University, New Haven, CT; ²Olin Neuropsychiatry Research Center, Institute of Living, Hartford, CT; ³San Francisco VA Medical Center, San Francisco, CA; ⁴Department 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 Zendig² 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, Keshavan⁵ 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 Owen¹⁰ 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 familiarly.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 Frangou¹² 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 Sweeney¹³ 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? Frangou¹² 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 Owen¹⁰ 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 Owen¹⁰ 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 Criteria¹⁶ and the earlier cognitive neuropsychiatric approach.^{17–19} This debate began with Kraepelin, is moving forward, but continues.

Funding

National Institute of Mental Health grants (5 R37 MH43775, MERIT) and (R01 MH077945 to G.D.P.); National Institute of Mental Health (MH058262 and Veterans Administration to J.M.F.).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Kraepelin E. *Psychiatry: A Textbook for Students and Physicians*. Diefendorf AR, 7th ed. London, UK: Macmillan; 1912.
2. Zendig E. Beiträge zur Differentialdiagnose des manisch-depressiven Irreseins und der Dementia praecox. *Allg Z Psychiatr*. 1909;66:932–833.
3. Majadas S, Olivares J, Galan J, Diez T. Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. *Compr Psychiatry*. 2012;53:145–151.
4. Potash JB, Willour VL, Chiu YF, et al. The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. *Am J Psychiatry*. 2001;158:1258–1264.
5. Keshavan MS, Morris DW, Sweeney JA, et al. A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: the Schizo-Bipolar Scale. *Schizophr Res*. 2011;133:250–254.
6. Bromet EJ, Schwartz JE, Fennig S, et al. The epidemiology of psychosis: the Suffolk County Mental Health Project. *Schizophr Bull*. 1992;18:243–255.
7. Mathalon DH, Hoffman RE, Watson TD, Miller RM, Roach BJ, Ford JM. Neurophysiological distinction between schizophrenia and schizoaffective disorder. *Front Hum Neurosci*. 2010;3:70.
8. Johnstone EC, Crow TJ, Frith CD, Owens DG. The Northwick Park “functional” psychosis study: diagnosis and treatment response. *Lancet*. 1988;2:119–125.
9. Potash JB. Carving chaos: genetics and the classification of mood and psychotic syndromes. *Harv Rev Psychiatry*. 2006;14:47–63.
10. Cardno AG, Owen M. Genetic relationships between schizophrenia, bipolar disorder and schizoaffective disorder. *Schizophr Bull*. In press.
11. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160:636–645.
12. Frangou S. A systems neuroscience perspective of schizophrenia and bipolar disorder. *Schizophr Bull*. In press.
13. Reilly JL, Sweeney JA. Generalized and specific neurocognitive deficits in psychotic disorders: utility for evaluating pharmacological treatment effects and as intermediate phenotypes for gene discovery. *Schizophr Bull*. In press.
14. Kotov R, Leong SH, Mojtabai R, et al. Boundaries of schizoaffective disorder: revisiting Kraepelin. *JAMA Psychiatry*. 2013;70:1276–1286.
15. Lawrie SM, Hall J, McIntosh AM, Owens DG, Johnstone EC. The ‘continuum of psychosis’: scientifically unproven and clinically impractical. *Br J Psychiatry*. 2010;197:423–425.
16. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*. 2013;11:126.
17. David AS. Cognitive neuropsychiatry? *Psychol Med*. 1993;23:1–5.
18. David AS, Halligan PW. Cognitive neuropsychiatry: potential for progress. *J Neuropsychiatry Clin Neurosci*. 2000;12:506–510.
19. Frith CD. *The Cognitive Neuropsychology of Schizophrenia*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1992.