

## Toward New Approaches to Psychotic Disorders: The NIMH Research Domain Criteria Project

Bruce N. Cuthbert\* and Thomas R. Insel

National Institute of Mental Health, 6001 Executive Boulevard, MSC 9625, Bethesda, MD 20892

\*To whom correspondence should be addressed; tel: 301-443-4863, fax: 301-443-1425, e-mail: bcuthber@mail.nih.gov

These are interesting times for schizophrenia research. Among the many exciting signs of progress, recent genome-wide association study (GWAS) reports have attracted considerable attention for their unexpected findings. While many genetic factors have been identified to date by GWAS and other case-control studies, in aggregate, these factors have accounted for only a small percentage of the reported heritability of the disorder. Perhaps the most unexpected finding has been the growing recognition that nearly all genetic factors identified thus far, whether common allelic variants or rare structural variants, seem to confer somewhat comparable risk for schizophrenia and bipolar disorder and, perhaps, for other disorders such as unipolar depression, substance abuse, and even epilepsy.<sup>1–3</sup> These are only examples of numerous recent studies suggesting that the biology of psychotic illnesses may fail to align neatly with the classic Kraepelinian distinction between schizophrenia and manic-depressive illness that has served clinical practice and research for well over a century. However, they do resonate with clinical observations that many patients present with a mix of bipolar and schizophrenia symptoms, both at a single admission and also across time. These clinical observations support the accelerating body of literature over the last decade arguing that Kraepelin's classic dichotomy for psychotic disorders may need to be superseded by a new system based on biology as well as observed clinical phenomenology.<sup>4–6</sup>

The problem, of course, is what a new etiological framework would look like.<sup>7</sup> Solidly argued calls for change in clinical and research approaches to psychotic disorders go back decades (eg, Kendell<sup>8</sup>), but relatively minor updates to diagnostic manuals have not altered the fundamental system. Part of the problem is that the Kraepelinian assumptions have become embedded in the machinery of regulatory agencies, granting agencies and their review committees, and journal reviewers. It is accordingly difficult to conduct studies that diverge from current, conventional thinking. The vast majority of published studies includes only one diagnostic category (though articles about schizophrenia often include schizoaffective disorder)

and seldom examine heterogeneity within disorder categories. Thus, the inertia of diagnostic orthodoxy exerts a powerful hegemony over any alternative approaches, leaving us with much debate but little data with which to construct a new nosology.

How can we move beyond these impediments to support revolutionary findings for a new, biologically validated approach to diagnosis? Over the past 2 decades, National Institute of Mental Health (NIMH) and other funding agencies have supported research to understand mental disorders as brain disorders. We are now at a point where we can begin to (1) create neurobiological circuit maps of behavioral and cognitive functioning and (2) explicate the ways in which activity in these circuits becomes dysregulated in mental disorders. These endeavors will likely be guided by 3 defining insights emerging from research on psychotic disorders. First, serious mental illness increasingly appears neurodevelopmental, with onset of prepsychotic symptoms in adolescence, at a time when the cortex is still developing. Second, for most disorders of cortical function, behavior and cognitive changes are late events, suggesting that biological manifestations should be apparent long before manifest psychosis. And finally, as with many complex disorders (eg, hypertension, epilepsy, and diabetes), there appear to be many etiological pathways leading to the final mixed bag of behavioral signs and symptoms we label “schizophrenia.”

The call for a new approach to diagnosis is included as goal 1.4 of the NIMH Strategic Plan,<sup>9</sup> and its implementation has been dubbed the Research Domain Criteria (RDoC) project. A detailed description of this project is available on the NIMH Web site (<http://www.nimh.nih.gov/research-funding/rdoc.shtml>). In brief, the approach is to develop a matrix for translational research, using a consensus conference process similar to the CNTRICS project for cognition in schizophrenia.<sup>10</sup> The matrix's rows represent the functional constructs of interest, grouped into superordinate domains. The initial draft RDoC specification includes 5 domains of Negative Affect, Positive Affect, Cognition, Social Processes, and Arousal/

Regulatory systems. Constructs represent particular circuit-based functions within these domains; eg, the Negative Affect domain includes 3 constructs of Fear, Distress, and Aggression. The columns of the matrix denote particular units of analysis and include genes, molecules, cells, circuits, behavior, and self-reports. The conference process will convene experts in each area to refine the list of constructs/domains; provide working definitions of the constructs; and compile, for each unit of analysis, a listing of the measures and components that contemporary research has identified as pertaining to a particular construct. Conference proceedings will be posted on the NIMH Web site to permit a period of continuing commentary before the specifications are finalized and posted (free for downloading).

Importantly, the purpose of this matrix is to guide novel, dimensionally based classifications of patients in research projects. Investigators are encouraged to study particular constructs in the matrix (or compare 2 or more constructs). Rather than presenting symptoms (ie, diagnosis), the researcher might select the independent variable from any column of the matrix as appropriate to the study's aims. Thus, a study of cognitive dysfunction might include all patients presenting at a clinic for serious mental illness, irrespective of primary diagnosis; scores on a test of cognition (eg, working memory) might comprise the independent variable, and the dependent variable could be both functional outcome measures and symptom measures in various domains. Another study might employ a genomic structural variant (eg, the 22q microdeletion) as an independent variable and cognitive performance or neural circuit function as the dependent variable. For some studies, it may be useful to stratify patients according to their primary diagnosis; however, 2 important goals of this approach are to include (1) individuals who fall just short of a formal diagnosis, in order to obtain information about the dimensional aspects of the construct and (2) patients with NOS diagnoses, typically excluded from most studies in spite of marked impairment. Related to this plan, the DSM-V Psychoses Work Group is proposing clinical pathology domains as dimensions for each psychotic disorder diagnostic class; these clinical domains may have a more meaningful relationship with neural circuit pathology than found at the heterogeneous syndrome level.

What are the implications of the RDoC process for schizophrenia research? As the project develops, NIMH will place increasing priority for funding research grants on applications directed toward RDoC constructs that cut across traditional disorder boundaries, in order to focus attention on mechanisms that can illuminate the marked heterogeneity between and within disorders as well as early stages of serious mental illness. Implementation of the resultant marked shift in sample ascertainment and data analysis will no doubt require collaborative effort from the research community and NIMH. The overriding consideration, however, is that only by combining traditionally

defined schizophrenia- and bipolar-spectrum patients in the same samples can we finally understand the relationships among genetics, neurobiology, symptoms, and functional capacity in these serious illnesses. Whether the result is a refinement of the Kraepelinian duality, or the emergence of multiple new disorder entities as defined by genetics and neurobiology, is an open question for the future.

Such considerations emphasize the point that RDoC is conceived as a research framework that will inform future versions of nosologies and is not intended for clinical use in the near future. The rationale for the RDoC approach is to facilitate translation of modern molecular biology, neuroscience, and behavioral approaches toward explicating the pathophysiology of disorders. By targeting circuit functioning and relevant behaviors, one particular goal is that this process will direct the search for treatment targets in various domains—including new molecular entities, neuroplasticity paradigms, psychosocial treatments, and other potential interventions.

### Acknowledgments

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

### References

1. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–752.
2. Cook EH, Jr, Scherer SW. Copy-number variations associated with neuropsychiatric conditions. *Nature*. 2008;455:919–923.
3. Brandon NJ, Millar JK, Korth C, Sive H, Singh KK, Sawa A. Understanding the role of DISC1 in psychiatric disease and development. *J Neurosci*. 2009;29:12768–12775.
4. Craddock N, Owen MJ. The Kraepelinian dichotomy—going, going ... but still not gone. *Br J Psychiatry*. 2010;196:92–95.
5. Fischer BA, Carpenter WT, Jr. Will the Kraepelinian dichotomy survive DSM-V? *Neuropsychopharmacology*. 2009;34:2081–2087.
6. Ovsiew F. An end to Kraepelinian nosology? *J Neuropsychiatry Clin Neurosci*. 2000;12:297–299.
7. Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or “schizoaffective”) psychoses. *Schizophr Bull*. 2009;35:482–490.
8. Kendell RE. The major functional psychoses: are they independent entities or part of a continuum? Philosophical and conceptual issues underlying the debate. In: Kerr A, McClelland H, eds. *Concepts of Mental Disorder: A Continuing Debate*. London, UK: Gaskell; 1991:1–16.
9. National Institute of Mental Health. *The National Institute of Mental Health Strategic Plan*. Bethesda, MD: National Institute of Mental Health (NIH Publication 08-6368). 2008. <http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml>.
10. Carter CS, Barch DM. Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophr Bull*. 2007;33:1131–1137.