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Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders

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Current versions of the DSM and ICD have facilitated reliable clinical diagnosis and research. However, problems have increasingly been documented over the past several years, both in clinical and research arenas (e.g., 1, 2). Diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics. The boundaries of these categories have not been predictive of treatment response. And, perhaps most important, these categories, based upon presenting signs and symptoms, may not capture fundamental underlying mechanisms of dysfunction. One consequence has been to slow the development of new treatments targeted to underlying pathophysiological mechanisms.

History shows that predictable problems arise with early, descriptive diagnostic systems designed without an accurate understanding of pathophysiology. Throughout medicine, disorders once considered unitary based on clinical presentation have been shown to be heterogeneous by laboratory tests—e.g., destruction of islet cells versus insulin resistance in distinct forms of diabetes mellitus. From infectious diseases to subtypes of cancer, we routinely use biomarkers to direct distinct treatments. Conversely, history also shows that syndromes appearing clinically distinct may result from the same etiology, as in the diverse clinical presentations following syphilis or a range of streptococcus-related disorders.

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While the potential advantages of a neuroscience-based approach to psychiatric classification are widely appreciated (3), no consensus exists about how to achieve this goal. The problem is not new. Four decades ago, Robins and Guze suggested five criteria for validating diagnosis (clinical description, laboratory tests, delimitation, follow-up studies, and family data), where the goal was specifying prognosis (4). Reminiscent of the rationale for developing the Research Diagnostic Criteria in the 1970s that led to the innovative DSM-III for clinical use, the question now becomes one of when and how to build a long-term framework for research that can yield classification based on discoveries in genomics and neuroscience as well as clinical observation, with a goal of improving treatment outcomes. As the major federal research agency funding mental health research in the United States, the National Institute of Mental Health (NIMH) believes the time has arrived to begin moving in such a new direction.

The NIMH is launching the Research Domain Criteria (RDoC) project to create a framework for research on pathophysiology, especially for genomics and neuroscience, which ultimately will inform future classification schemes. The RDoC project is intended to be the next step in a long journey, one that continues the process begun in the 1970s of ensuring diagnosis that has both reliability and validity. While the focus of this journey over the past 30 years has been on refinements in clinically based classification, the time has come to lay the groundwork for the next step in this process: incorporating data on pathophysiology in ways that eventually will help identify new targets for treatment development, detect subgroups for treatment selection, and provide a better match between research findings and clinical decision making.

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RDoC classification rests on three assumptions. First, the RDoC framework conceptualizes mental illnesses as brain disorders. In contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits. Second, RDoC classification assumes that the dysfunction in neural circuits can be identified with the tools of clinical neuroscience, including electrophysiology, functional neuroimaging, and new methods for quantifying connections *in vivo*. Third, the RDoC framework assumes that data from genetics and clinical neuroscience will yield biosignatures that will augment clinical symptoms and signs for clinical management. Examples where clinically relevant models of circuitry-behavior relationships augur future clinical use include fear/extinction, reward, executive function, and impulse control. For example, the practitioner of the future could supplement a clinical evaluation of what we now call an "anxiety disorder" with data from functional or structural imaging, genomic sequencing, and laboratory-based evaluations of fear conditioning and extinction to determine prognosis and appropriate treatment, analogous to what is done routinely today in many other areas of medicine.

Clearly, this is a vision for the future, given the rudimentary nature of data relating measures of brain function to clinically relevant individual differences in genomics, pathophysiology, and behavior. In the near-term, RDoC may be most useful for researchers mapping brain-behavior relationships as well as genomic discoveries in human and non-human animal studies. For example, within the broad domain of developmental neuroscience, the emerging fields of imaging genomics and early life programming have already begun to clarify factors that shape the development of select neural circuits (5, 6). But the findings of developmental neuroscience have not yet proven useful for clinicians, often because the results are relevant to broad domains of function such as temperament rather than specific diagnoses. And the recent discovery of structural changes in the genome (copy number variations) associated with psychopathology already suggest the power of modern genomics for psychiatry, but the phenotypes associated with genomic variation do not align with current classifications of autism or schizophrenia or bipolar disorder. RDoC are intended to ultimately provide a framework for classification based on empirical data from genetics and neuroscience. Indeed, in 2010, we do not know how many different disorders are embedded in the current diagnosis of schizophrenia or autism or other current categories that share clinical features. Our expectation, based on experience in cancer, heart disease, and infectious diseases, is that identifying syndromes based on pathophysiology will eventually be able to improve outcomes (e.g., 7, 8).

Research approaches for the RDoC project will differ from current practice, which typically constrains study designs not only to a single DSM/ICD patient group but also to particular clinical features. The primary focus for RDoC is on neural circuitry, with levels of analysis progressing in one of two directions: upwards from measures of circuitry function to clinically relevant variation, or downwards to the genetic and molecular/cellular factors that ultimately influence such function. From this perspective, research for RDoC can be conceived as a matrix in which the rows represent various constructs grouped hierarchically into broad domains of function (e.g., negative emotionality, cognition). The columns of the matrix denote different levels of analysis, from genetic, molecular, and cellular levels, proceeding to the circuit-level (which, as suggested above, is the focal element of the RDoC organization), and on to the level of the individual, family environment, and social context. Importantly, all of these levels are seen as affecting both the biology and psychology of mental illness. With the RDoC approach, independent variables for classification might be specified from any of these levels of analysis, with dependent variables chosen from one or more other columns. Notably, samples might include patients spanning multiple DSM diagnoses. For instance, a study of working memory might recruit patients from a psychotic disorders clinic, with the independent variable a genetic polymorphism and dependent variables comprising cognitive performance and neuroimaging of dorsolateral prefrontal cortex activation. A study of

fear circuitry might include all patients presenting at an anxiety clinic, with an independent variable of defense-system reactivity (e.g., fear-potentiated startle) and dependent variables comprising scores on fear, distress, and symptom measures. While maintaining a clear focus on overt psychopathology, investigators will be encouraged to explicate the full range of a given dimension to develop thresholds for different types of interventions and identify early opportunities for preventive interventions.

How will RDoC alter clinical practice? The answer depends on how well RDoC perform for research. Following Robins and Guze's postulates for the Research Diagnostic Criteria, the critical test is how well the new molecular and neurobiological parameters predict prognosis or treatment response. If a BDNF polymorphism identifies people with anxiety syndromes who do not respond to behavior therapy, if a copy number variant defines a form of psychosis with high remission rates, if neuroimaging yields a subtype of mood disorder that consistently responds to lithium, RDoC could provide a classification scheme that will improve outcomes. But we recognize that there are many "ifs" at this stage. We are still a long way from knowing if this approach will succeed.

NIMH plans to maintain liaison with the American Psychiatric Association and the World Health Organization regarding mutual interests in psychiatric classification. As an initial step, representatives of the APA, WHO, and NIMH met in July 2009 to map out common ground. These organizations have also articulated the importance of adding molecular and neurobiological parameters to future diagnostic systems, but at our current state of knowledge this step seems more appropriate for research than for immediate clinical use. NIMH views RDoC as the beginning of a transformative effort that needs to succeed over the next decade and beyond to implement neuroscience-based psychiatric classification. We recognize that the creation of such a new approach is a daunting task, which will likely require several mid-course corrections and may ultimately fail to deliver the transformation we seek in clinical care. However, NIMH hopes that the scientific and clinical communities will recognize the importance of joining in constructive dialogue on efforts aiming to accelerate the pace of new clinical discoveries and improve clinical outcomes.

References

1. Regier DA, Narrow WE, Kuhl EA, Kupfer DJ: The conceptual development of DSM-V. Am J Psychiatry 2009; 166:1–7
2. Hyman S: Can neuroscience be integrated into the DSM-V? Nat Rev Neurosci 2008; 8:725–732
3. Charney D, Barlow D, Botteron K: Neuroscience research agenda to guide development of a pathophysiologically based classification system, in A Research Agenda for DSM-V. Edited by Kupfer D, First M, Regier D. Arlington, Va, American Psychiatric Association, 2002, pp 31–84
4. Robins E, Guze SB: Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126:983–987
5. Meyer-Lindenberg A: Neural connectivity as an intermediate phenotype: brain networks under genetic control. Human Brain Mapping; 30:1938–1946
6. Barker D, Osmond C, Forsèn T, Kajantie E, Eriksson J: Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005; 353:1802–1809
7. Stefansson H, Ophoff R, Steinberg S Andreassen OA, Cichon S, Rujescu D, Werge T, Pietiläinen OP, Mors O, Mortensen PB, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Børglum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Böttcher Y, Olesen J, Breuer R, Möller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Réthelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeney LA; Genetic Risk and Outcome in Psychosis (GROUP), Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, Ge D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jönsson EG, Terenius L, Agartz I, Petursson H, Nöthen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA: Common variants conferring risk of schizophrenia. Nature 2009; 460:744–747
8. Losh M, Sullivan P, Trembath D, Piven J: Current developments in the genetics of autism: from phenome to genome. J Neuropathol Exp Neurol 2008; 67:829–837

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