Brief report

The role of RDoC in future classification of mental disorders

Bruce N. Cuthbert, PhD

The Research Domain Criteria (RDoC) project constitutes a translational framework for psychopathology research, initiated by the National Institute of Mental Health in an attempt to provide new avenues for research to circumvent problems emerging from the use of symptom-based diagnostic categories in diagnosing disorders. The RDoC alternative is a focus on psychopathology based on dimensions simultaneously defined by observable behavior (including quantitative measures of cognitive or affective behavior) and neurobiological measures. Key features of the RDoC framework include an emphasis on functional dimensions that range from normal to abnormal, integration of multiple measures in study designs (which can foster computational approaches), and high priority on studies of neurodevelopment and environmental influences (and their interaction) that can contribute to advances in understanding the etiology of disorders throughout the lifespan. The paper highlights key implications for ways in which RDoC can contribute to future ideas about classification, as well as some of the considerations involved in translating basic behavioral and neuroscience data to psychopathology.

Introduction

The role of this essay is to provide a brief speculation regarding the role of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project in future psychiatric classification systems. Initiated by NIMH in 2009, RDoC constitutes a framework for translational research that shifts the focus away from traditional *DSM/ICD* disorder categories and toward research on functional dimensions of behavior or cognitive/affective processes (eg, reward learning or working memory) as studied across the entire range of functioning from normal to abnormal.[1-3] The paradigm emphasizes the inclusion in study designs of multiple measures (eg, behavioral/cognitive, phenomenological, physiological) for examining such psychological constructs, thus promoting an integrative rather than reductionistic approach.[4] High priority is placed upon the examination of neurodevelopmental processes and environmental influences (and their interaction) in research designs.[5] *Figure 1* depicts the way in which the various components of the RDoC framework are organized to stimulate transdiagnostic research that can examine the joint influences of biological and external risk factors. Neurodevelopment and environmental effects represent important considerations in research designs, and various domains of function (Negative Valence, etc) are studied across multiple Units of Analysis from Genes to Self-Reports. (Both the Domains and Units of Analysis are considered as heuristic exemplars rather than fixed components.)

A discussion of RDoC's future role in classification necessarily depends upon one's long-term vision of what future nosologies might comprise and what assessment problems they try to address. It is important to emphasize the phrase "long-term vision" since the aim of current diagnostic manuals centers explicitly upon clinical utility[6]; this

Author affiliations: National Institute of Mental Health, Bethesda, Maryland, US. **Address for correspondence:** Bruce N. Cuthbert, PhD, National Institute of Mental Health6001 Executive Blvd, Room 8151, MSC 9632, Bethesda, MD 20892-9632, US (email: bcuthber@mail.nih.gov)
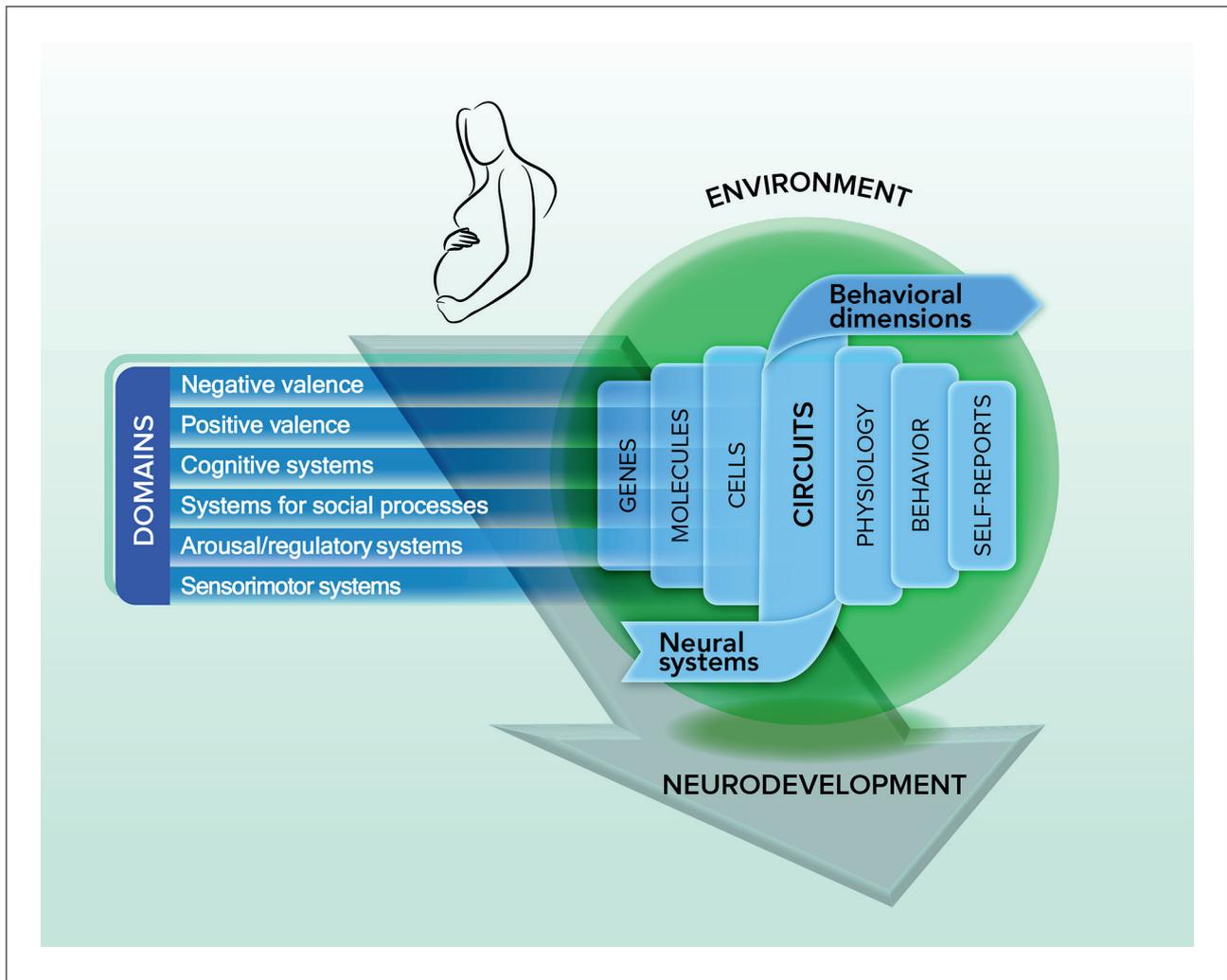
Figure 1. Diagram of the RDoC Framework, illustrating the four major factors of Neurodevelopment, Environment, Domains, and Units of Analysis (ranging from Genes to Self-Reports).

seems to reflect a tacit assumption that current diagnoses and treatments will change only modestly and incrementally over time, and that the symptom-based architecture of disorder categories will remain static. In contrast, a major role of funding agencies is to generate new concepts and research, pursuing breakthroughs that could lead eventually to substantive reductions in the burden of mental illness through enhanced treatment and prevention. As RDoC is a research framework intended to inform future diagnostic systems, the long-term goal envisions a precision-medicine concept that fosters empirically based approaches

to assessment, treatment, and prevention which can be updated rapidly on the basis of ongoing data—much like current practices in other areas of medicine such as cancer.[7]

How can the RDoC framework contribute to this future vision? It is useful to note that NIMH did not initiate the RDoC project as the pilot test for a new classification system as such (much as the Research Diagnostic Criteria of the 1970s represented a stalking horse for the *DSM-III*). Rather, the initiative was a nascent idea that resulted from the increasing realization that traditional disorders were

broad and heterogeneous syndromes that did not correspond to specific biological or behavioral systems and thus were hampering efforts to develop new clinical tests or treatments[8]; the problem was compounded by a de facto practice in grant review committees stipulating that clinical research should only be conducted in terms of *DSM/ICD* disorder categories. The RDoC alternative was to adopt a translational approach: The framework consists of a set of flexible guidelines for approaching psychopathology in terms of departures from normal-range functions rather than starting with a priori disease definitions based upon sets of presenting symptoms.

Key RDoC features

This shift directly connects the accelerating body of basic research on behavioral and neural functioning with psychopathology, enabling several novel approaches. First, functional dimensions are explicitly conceived as psychophysiological constructs that are jointly defined by data for a particular functional aspect of behavior or cognition and data for an implementing neural circuit or system–thus addressing head-on the mind-body challenges that have long stymied attempts to understand biological aspects of mental disorders (and the attendant eliminative reductionism that has proved controversial in so many quarters). Second, such a perspective encourages the study of dysregulated functioning (eg, cognitive problems, disrupted motivational processes), in addition to symptom reports, as significant problems in and of themselves rather than as one of several indices of an "underlying" syndrome.

Relatedly, enhanced assessment of behavioral/cognitive functions enables the use of quantitative measurements that bring to bear modern psychometric and computational techniques as opposed to qualitative symptom reports.[9] The functional domain approach also fosters the exploration of similar mechanisms that are disrupted in multiple disorders (as implied by the extensive comorbidity of current diagnostic classes), and the last decade has seen a notable increase in various types of transdiagnostic studies that can help untangle questions about whether or not similar kinds of impairment or symptoms across disorders can be more efficiently regarded (and treated) as involving similar (or identical) mechanisms.[10,11]

An apt example is provided by a large program of anxiety disorders research in which patients' imagery of fearful and control situations were assessed with psychophysiological measures. Five quintiles of patients were defined transdiagnostically on the basis of highest-to-lowest psychophysiological reactivity during aversive (as compared with neutral) images. Independent of primary diagnosis, greater functional impairment and self-reported symptomatology were associated with blunted physiological reactivity rather than the higher reactivity that might have been expected.[12] These data demonstrate the utility of examining relationships among multiple measures, and suggest the potential of physiological reactivity as a prognostic biomarker for differential treatment (eg, exposure therapy versus medications or cognitive therapy).

Finally, RDoC's role as a flexible research framework serves as a model for further major revisions to conceptions of mental illness–in the near term, in such growing research areas as connectomics[13] and the genomics of functional systems[14]; and in the longer term, potentially radical change stemming from computational modeling and machine learning.[15,16]

Early detection and prevention

A more extended, but critically important, aspect of classification systems in upcoming decades regards the capability for very early detection of future risk for psychopathology. Such a consideration may not seem tethered to a classification system at all with respect to current nosologies; however, a significant weakness of symptom-based diagnostic systems is that, by definition, some pathological process is already established by the time that a diagnosis can be made. The full-range dimensional approach that RDoC embodies is well-positioned in order to reach toward future prevention and pre-emption of disorders, in that growth patterns–whether assessed in behavioral/cognitive, brain-based measures, or both–could be monitored across neurodevelopment in order to detect early aberrations before any overt symptoms are present. For instance, data from the Pennsylvania Neurodevelopmental Cohort have shown that the onset of psychotic symptoms in adolescence is associated with relatively lower cognitive test scores across development (compared with typically developing participants) in an unselected sample of children.[17] These results imply that norms for cognitive and emotional growth across childhood, similar to familiar height and weight charts for children, could be useful tools in standard practice for

early detection. At least one such effort is already under way: A developmental battery that assesses six cognitive domains–employing "gamified" tasks on a mobile e-platform to engage participants' interest–has been piloted for 3-year old children in rural India, with the goal of developing normative curves across development as the project grows.[18] These projects demonstrate that quantitatively based efforts at prevention, assessed relative to continuous population (or large-sample) distributions, are not simply a promissory note but are already being implemented.

Computational approaches

Finally, the newly emerging field of computational psychiatry and the RDoC framework have mutually influenced each other.[19] Given the indeterminate nature of traditional disorder categories, RDoC has provided a more tractable basis for efforts to apply computational procedures to psychopathology. Computational methods have been applied to two broad aspects of research. The first aspect comprises computational modeling to validate model-based predictions about relationships between brain activity and various aspects of behavior in parametrically designed experiments, which typically involve functional operations similar (often identical) to RDoC constructs.[20] The second aspect encompasses the use of computational techniques to identify data-driven phenotypes not dependent upon traditional diagnoses, inspired in no small part by the RDoC framework.[21,22] This has proven to be a promising area for study: Although the subgenre is only a few years old, several results suggesting actionable outcomes for treatment or assessment have already appeared in the literature.[23-24] For instance, a recent study employed a wide variety of measures to analyze the heterogeneity in a large sample of patients diagnosed with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder; a multistep analysis revealed three transdiagnostic clusters ("biotypes") of patients defined primarily by cognitive test scores and electrophysiological responses to various stimuli. Other measures indicated that the biotypes comprised more biologically valid groupings than the diagnostic categories, and the data suggested significant implications for more precise clinical treatment.[25] Machine learning and artificial intelligence (AI) appear poised to produce yet more generative findings, given the power of these techniques to find relationships in high-dimensional data sets that integrate behavioral, symptomatic, and biological measures. While such developments may seem far off, regulatory agencies are already actively considering the process for approving use of AI and machine learning as medical devices.[26]

Conclusion

In conclusion, the RDoC framework has catalyzed activities in multiple areas of mental disorders research that can contribute to future classification systems aligned with precision medicine avenues to diagnosis, treatment, and prevention. A number of caveats are in order. First, a common criticism of RDoC from clinical researchers and service providers holds that RDoC diverges too much from current practice to be used by clinicians–a not unreasonable concern. However, there will inevitably be a transition period as precision medicine procedures are introduced, and the majority of current RDoC-themed research projects involve subgroups of one (or two) current disorder categories. So, it is likely that service settings will experience gradual shifts in assessment and treatment as new "biotypes" are validated and enter the clinic. Second, some observers seem to infer that the introduction of biological and quantified behavioral measures are threats to the use of traditional assessments and individualized treatment plans.[27] However, individual assessments will remain essential for the vast majority of patients, as life histories and symptom reports will be even more important to precision medicine than current syndromal approaches. Finally, some researchers regard the current RDoC framework as a finite set of components and constructs that are insufficient to address the totality of mental illness. However, RDOC is better understood as a set of dynamic principles with which the field can build a cumulating knowledge base about psychopathology and how it emerges from perturbations in normal functioning. Rapidly emerging data, technologies, and concepts consistent with the RDoC approach demonstrate its capability to inform future versions of psychiatric nosologies. ∎

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