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Research Domain Criteria (RDoC): Progress and Potential

Bruce N. Cuthbert, Ph.D.

National Institute of Mental Health

Abstract

The National Institute of Mental Health (NIMH) addressed in its 2008 Strategic Plan an emerging concern that the current diagnostic system was hampering translational research, as accumulating data suggested that disorder categories constituted heterogeneous syndromes rather than specific diseases. However, established practices in peer review placed high priority on extant disorders in evaluating grant applications for mental illness. To provide guidelines for alternative study designs, NIMH included a goal to develop new ways of studying psychopathology based on dimensions of measurable behavior and related neurobiological measures. The Research Domain Criteria (RDoC) project is the result, intended to build a literature that informs new conceptions of mental illness and future revisions to diagnostic manuals. The framework calls for the study of empirically-derived fundamental dimensions as characterized by related behavioral/psychological and neurobiological data (e.g., reward valuation, working memory). RDoC also emphasizes full-range dimensional approaches (from typical to increasingly abnormal), neurodevelopment and environmental effects, and research designs that integrate data across behavioral, biological, and self-report measures. This commentary provides an overview of the project's first decade and its potential future directions. RDoC remains grounded in experimental psychopathology perspectives, and its progress is strongly linked to psychological measurement and integrative approaches to brain-behavior relationships.

Keywords

Research Domain Criteria; RDoC; psychological constructs; experimental psychopathology; computational psychiatry

INTRODUCTION

The Research Domain Criteria (RDoC) project represents a framework for research on mental disorders that focuses on dimensions of behavioral/psychological functioning and their implementing neural circuits. RDoC originated from one element of the National Institute of Mental Health (NIMH) Strategic Plan for Research released in 2008, a document motivated throughout by the need to accelerate progress in reducing the burden of suffering from mental illness.

Corresponding author: Bruce N. Cuthbert, Ph. D., National Institute of Mental Health, 6001 Executive Blvd, Room 8151, MSC 9632, Bethesda, MD 20892-9632, bcuthber@mail.nih.gov, 301.276.1076, Mailing address: 3054 Bosshard Drive, Fitchburg, WI 53711-5860.

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Unveiled in 2010, RDoC addresses an emergent obstacle to progress regarding the Institute's mission: the use of traditional diagnostic manuals for research on mental disorders. The primary manual in the United States is the Diagnostic and Statistical Manual of Mental Disorders, currently in its fifth edition (DSM; American Psychiatric Association, 2013). Its fundamental architecture remains based upon the DSM-III of 1980, with disorder categories defined primarily by sets of presenting signs and symptoms. This approach was developed to optimize reliability of diagnosis, but the validity of disorder classes has been questioned as a result of indeterminate and inconsistent findings from contemporary research methodologies such as neuroimaging, sophisticated behavioral science, and genetics (Kapur, Phillips, & Insel, 2012). As summarized in the 2008 NIMH strategic plan, "The way that mental disorders are defined in the present diagnostic system does not incorporate current information from integrative neuroscience research, and thus is not optimal for making scientific gains. …. It is difficult to deconstruct clusters of complex behaviors and attempt to link these to underlying biological systems" (NIMH, 2008).

The problem was not so much the diagnostic system per se, but rather that disorder categories became reified soon after the release of DSM-III and became the norm for peer review committees in evaluating grant applications about mental disorders. As a former NIMH Director summarized the issue: "The DSM system was a critical platform for research that made possible shared understandings of disease models or affected populations under study. At the same time, it created an unintended epistemic prison that was palpably impeding scientific progress. Outside of their ongoing research projects, most investigators understood that the DSM-IV was a heuristic, pending the advance of science. In practice, however, [for grant applications] DSM-IV diagnoses controlled the research questions they could ask, and perhaps, even imagine" (Hyman, 2010, p. 157).

Put in another way, scientific review depends upon conceptual paradigms shared among applicants and reviewers, and the DSM's hegemony was mostly due to a lack of alternative approaches. RDoC thus propounds directions that diverge from traditional study designs comparing a single DSM patient group (e.g., bipolar disorder) to healthy controls; instead, in the tradition of experimental psychopathology, RDoC provides a new set of guidelines and criteria for studying the ways that basic functions (e.g., cognitive control, reward processing) become dysregulated to eventuate in symptoms and impairment.

The framework has been extensively described elsewhere (Cuthbert & Kozak, 2013; Kozak & Cuthbert, 2016; National Institute of Mental Health, 2021) and is only summarized briefly here (see Figure 1). Constructs are the main focus of experimental attention, similar to the usual notion of psychological constructs but defined in terms of empirical evidence for both a basic functional dimension of behavior or psychological processes and for a neural circuit or system implementing the function. Constructs are nested in six broad domains (Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Social Processes, Arousal and Regulatory Systems, and Sensorimotor Systems); for instance, the Cognitive Systems domain includes such constructs as Attention, Cognitive Control, and Perception.

Experimental designs typically focus on one or two constructs, resulting in studies that are narrower in scope than typical DSM research but much more tightly connected

to mechanisms across multiple systems. Constructs are regarded from a dimensional perspective that covers the full range from normality to varying degrees of dysfunction so as to explicate transitions from healthy to increasingly abnormal performance. RDoC prioritizes research that includes a substantial proportion of treatment-seeking participants (and controls with a range of sub-syndromal psychopathology); experiments comprised only of normal-range subjects are typically not considered as RDoC projects (although potentially appropriate for basic-science grant applications).

Investigators are encouraged to acquire data from multiple response systems (termed "Units of Analysis," e.g., circuit measures, behavioral performance, self-reports) in order to address the well-known lack of coherence among measurement classes by conducting integrative analyses across systems. High priority is placed upon neurodevelopmental studies and environmental effects. An essential point is that both the domains/constructs and Units of Analysis are considered to be heuristic exemplars rather than fixed sets, as fostering development of new or refined domains/constructs and innovative measurement techniques are salient; it is the principles of the framework that comprise its capstone rather than current specific elements.

PROGRESS

The RDOC project has attracted considerable attention regarding all aspects of mental disorders, including research, clinical issues, and philosophical debates about the nature of mental illness. Given the complex and extensive nature of RDoC activities, this brief review highlights a few selected topics with particular relevance to psychological science.

Dissemination and Discussion

RDoC has generated a sizable body of experimentation and commentary across multiple areas of science (Gordon, 2020a). The NIH RePORTER grants database indicates nearly 500 active grants involving reference to RDoC, funded mostly by NIMH but other institutes as well. A Google search returns over 150,000 hits (as of June 2021), comprising a broad mix of scientific reports, commentaries, clinical considerations, and various blogs that all reflect a full range of positive to negative opinions. Notably, the project has attracted wide attention internationally (e.g., Schumann et al., 2014).

Views of mental disorders have changed considerably over the past decade, and RDoC likely has played a significant role in that shift. (Related initiatives include the move from diseases to syndromes in DSM-5, and other efforts to develop alternative conceptual and research approaches to psychopathology – e.g., Borsboom, 2017; Kotov et al., 2017). As one example, an editorial in a major schizophrenia journal noted that an "…emerging change in research priorities reflects a new emphasis on porous diagnostic boundaries with increased attention to similarities and differences between disorders. Also, a focus on deconstructing heterogeneous clinical syndromes in order to identify specific elements of pathology is advancing science, often in a dimensional framework without diagnostic specificity" (Carpenter, 2016, p. 863). This statement is consistent with a marked increase in occurrences of the term "transdiagnostic" in the literature since RDoC began; a PubMed

search tabulating four successive three-year epochs from 2009 to 2020 returned 92, 308, 953, and 1,745 hits, respectively.

Clinical Applications

These changes have begun to spread from academic research to clinical discussions. For instance, as stated in a recent psychiatric trade publication, “Over the last decade or so, our field has experienced a rapid shift in our understanding of schizophrenia and other serious psychotic disorders …. Accumulating evidence indicates that psychotic disorders constitute syndromes rather than diseases per se. … Patients with different clinical diagnostic phenotypes (such as schizophrenia rather than bipolar disorder with psychosis) can show similar underlying patterns of cognitive dysfunction and neurobiological abnormalities” (Vinogradov, 2019, pp. 4–5). Further, clinical assessments and treatment inspired by RDoC are beginning to appear (e.g., Shinn et al., 2017). While many factors slow progress in clinical innovation (such as insurance reimbursements tied to traditional diagnoses), consideration of more precise assessments and treatments is underway.

RDoC principles have also extended into clinical treatment studies, arriving sooner than expected due to the departure of pharmaceutical companies from drug development for mental disorders due to familiar problems of heterogeneity and co-morbidity. Constructs that attempt to link psychological aspects of disorders (anhedonia, cognitive impairment) with biological systems offer potential new, precision-medicine targets for compounds and medical devices; for example, a recent proof-of-concept trial demonstrated the use of a kappa-opioid blocker as a potential treatment for anhedonia (Krystal et al., 2020). The same treatment principles apply for behavioral treatments as well (Premo et al., 2020). Such developments reinforce the need for new measurement tools, both to provide valid constructs for treatment targets and to supply instruments for initial assessment and clinical outcomes.

Reductionism and Mind-body issues

Early papers that included statements like “mental disorders are brain disorders” understandably prompted the impression that RDoC advocated a purely biological, reductionistic view of mental illness (Insel, 2009). However, such statements were better interpreted as attempts to shift the zeitgeist from phenomenological views of disorder to a more balanced, multi-systems approach. As an early RDoC commentary noted, “… an essential point is that the RDoC initiative does not rely upon assumptions of eliminative reductionism, or even of biological fundamentalism” (Cuthbert & Kozak, 2013, p. 931). Rather, a major goal of RDoC is to address mind-body issues directly by focusing on dimensions that are understood by conjoining psychological and biological aspects (Kozak & Cuthbert, 2016). RDoC builds upon theories that acknowledge the need to address empirically the typically modest covariation observed among various response systems (e.g., the three-systems model of emotion; Lang, 2010), with an emphasis on mechanistic relationships that do not privilege particular measurement classes (Lake, Yee, & Miller, 2017).

Developmental Research

Development studies are a high priority for RDoC. Almost all mental disorders have neurodevelopmental origins, manifesting genetic influences, growth trajectories, and multiple domains of environmental influences that interact with development (Pollak, 2015). RDoC principles comport particularly well with developmental disorders, which are now generally understood to involve multiple dimensions with considerable overlaps among relevant categorical disorders. Their extensive heterogeneity and comorbidity have resulted in increasing calls to move beyond current nosologies to explore dimensional and transdiagnostic mechanisms (e.g., Nigg, 2015), transcending "core-deficit" hypotheses of specific disorders (Astle & Fletcher-Watson, 2020). Communications with the field in this area have focused on ways of depicting RDoC constructs across development, given evolving trajectories of psychological/behavioral functions and brain circuits. In this regard, commentaries have provided thoughtful contributions as to how developmental studies can be considered from the RDoC perspective (e.g., Mittal & Wakschlag, 2017), and how misguided assumptions in the current literature can be addressed in moving toward future research agendas (Beauchaine & Hinshaw, 2020).

One somewhat underdeveloped aspect of developmental work under the RDoC aegis relates to the normal-to-abnormal dimensions of constructs. The study of dimensional functions as they progress across neurodevelopment, and interact with environmental influences, may provide information about changes in risk or resilience that could provide opportunities for prevention that are not feasible in binary (well/sick), symptom-based disorders (e.g., Zalta & Shankman, 2016). For example, a recent project recruited over 9,000 youth (aged 8 to 21 years) hospitalized for diverse medical reasons, obtaining extensive data collection that included a neurocognitive test battery and a structured instrument for psychiatric symptoms; the large sample size enabled the formation of 13 one-year groupings (age 8 to 20) for analysis. Participants with psychotic symptoms showed consistent cognitive delays (compared to the typically-developing group) across the entire age range, with particular deficits in complex cognition and social cognition (Gur et al., 2014). These data suggest that cognitive growth charts, analogous to developmental height-weight graphs, could provide data for etiological and prevention studies both for child-onset neurodevelopmental psychopathology and for later early-adult disorders. In fact, an international group of investigators is beginning the implementation of such a concept in India, assessing six cognitive domains in young children with a developmental battery of "gamified" tasks (Mukherjee et al., 2020).

Measurement and Assessment

The original goals of RDoC to conduct integrative analyses across multiple units of measurement were in some respects aspirational due to the lack of appropriate analytic methodologies. However, computational methods for studying mental disorders (often termed "computational psychiatry") have rapidly emerged as invaluable tools (Ferrante et al., 2018). This area represents a priority for RDoC due to its emphasis on multi-system integration, enhancing the ability to define psychophysiological constructs validated by quantitative analyses of relationships among various measurement systems (Sanislow, Ferrante, Pacheco, Rudorfer, & Morris, 2019). In fact, these features of RDoC played

a palpable role in stimulating the development of computational approaches to mental disorders (Marquand, Rezek, Buitelaar, & Beckmann, 2016).

Broadly speaking, two main types of computational approaches have been deployed (Huys, 2018). The first comprises theory-driven models, in which a paradigmatic model is tested to evaluate how closely its parameters fit observed data. Reinforcement learning paradigms have been a productive exemplar in testing model paradigms to date; while basic experiments have focused on dopamine signaling and reward prediction errors, studies focusing on behavioral measures have been valuable for basic and clinical research (e.g., Barch et al., 2017). Devising valid and reliable computationally-based measures of RDoC dimensions represents a high priority in coming years. Accordingly, NIMH has issued funding announcements both for validating brain-behavior relationships of RDoC tasks (MH-19–242) and for the creation of new behavioral tasks based on computational models (MH-19–240).

The second set of computational tools is generally termed a data-driven approach (Huys, 2018). As applied to RDoC, data-driven analyses are often used to derive potential clinical phenotypes via analyses of multiple response systems. One exemplary study to date has been the B-SNIP (Bipolar-Schizophrenia Network for Intermediate Phenotypes) project. Analyses conducted on a large sample of patients with psychotic disorders (schizophrenia, schizoaffective disorder, and psychotic bipolar disorder) revealed three biotypes (clusters) based on measurements integrating cognitive task measures and event-related potentials. Biotypes showed a stronger relationship to other measures, such as social functioning and gray matter loss, than disorder categories (Clementz et al., 2016). Such analyses are not only useful for new ideas about psychopathology and assessment, but also augur the possibility of new precision-medicine treatments derived from such biotypes (Sanislow et al, 2019).

Digital phenotyping comprises another rapidly emerging measurement class with great promise for RDoC studies. Data are generated from smart phones and similar devices, mostly employing passive methods that do not disrupt ongoing behavior. Smart devices can gather a variety of data that are not available from other sources, such as GPS for assessing behavior, number of social contacts, brief cognitive assessments, and increasing numbers of physiological measures (Torous, Onnela, and Keshavan, 2017). A different type of digital assessment comes from natural language processing (NLP) of various text materials. These can include analyses of texts generated by participants, but other sources are also promising. A recent study demonstrated the feasibility of NLP to extract measures of RDoC domains from narrative inpatient chart notes, which predicted pertinent clinical outcomes such as length of stay and increases in readmission risk (McCoy et al., 2018). These advanced technologies, combined with computational methods for analysis, have the potential to revolutionize the understanding of real-world behavior and its relationship to psychopathology on an individual basis.

Challenges

As would be expected of an experimental framework, RDoC has experienced numerous challenges of various types. Some of these involve misunderstandings about the framework and its process. For instance, some investigators have inferred that only constructs listed on

the RDoC web site can be used in RDoC-themed applications; this is not the case, since (as noted above) the development of new (or revised) constructs is a high priority. Many other misapprehensions are clarified on the FAQ section of the RDoC web page (NIMH, 2021).

Less obvious issues have also arisen for the set of constructs. One example concerns the granularity of constructs, given hierarchies of behavior and of neural systems (Kozak & Cuthbert, 2016). As one example, cognition in many areas (e.g., schizophrenia) is often studied at the cognitive domain level; however, successively finer-grained components also studied by scientists include executive function, working memory, and several sub-components of working memory (as noted in the RDoC matrix). The appropriate level of granularity for understanding real-world dysfunction or treatment interventions is not obvious, and likely varies across different domains/constructs, types of psychopathology, contexts, level of development, and other variables.

Another challenge relates to important issues of measurement and psychometrics. Group effects relating different measurement systems have shown strong relationships in innumerable studies. However, many behavioral tasks and neuroimaging results demonstrate rather modest test-retest reliability (Hedge et al., 2018). This challenge is of course not confined to RDoC, but is shared with the majority of contemporary research for mental disorders. There are no easy solutions for these issues, but research in various areas has progressed. For instance, behavioral tasks are often developed to minimize between-subject variability in order to highlight the nature of the function being studied, which statistically results in low reliability across repeated testings; accordingly, developing and selecting tasks tailored to the study of individual differences may greatly enhance test-retest reliability (Hedge, et al., 2018). Progress has also been made in mitigating similar challenges with neuroimaging (Etkin, 2019). New generations of behavioral tasks are moving toward shorter administrations (five minutes or less) administered on mobile devices at the subject's convenience, but with numerous test sessions across time; in this manner, more stable estimates can be established with potentially less sample attrition.

Summary and Conclusion

As this overview of activities across its first decade illustrates, RDoC is fundamentally an experimental psychopathology initiative whose roots in psychological theory and measurement are clear – as illustrated by its incorporation of long-established research areas such as dimensional analyses, psychological constructs, and developmental trajectories. A key aspect concerns attention to mind-body issues that can begin to reconcile and integrate separate research traditions (e.g., phenomenology, behaviorism, neurobiology, and genetics) into a coherent view of mental disorders supported by empirical research.

The sections above augur the diverse palette of possibilities for RDoC's next decade (Gordon, 2020b). It can be anticipated that research directions will evolve yet more rapidly as students trained in RDoC and related approaches build careers built on these concepts. It is difficult to predict how the field will change, and the rate at which ideas continue disseminating into clinical venues. In the longer term, the crystal ball is yet cloudier in terms of revisions to diagnostic manuals and corresponding alterations in approved indications

for regulatory agencies. Extensive debate will be necessary, but the field now seems much more open to various possibilities. As NIMH Director Joshua Gordon concluded in a recent message, "… the RDoC framework has changed the conversation in mental health" (Gordon, 2020a).

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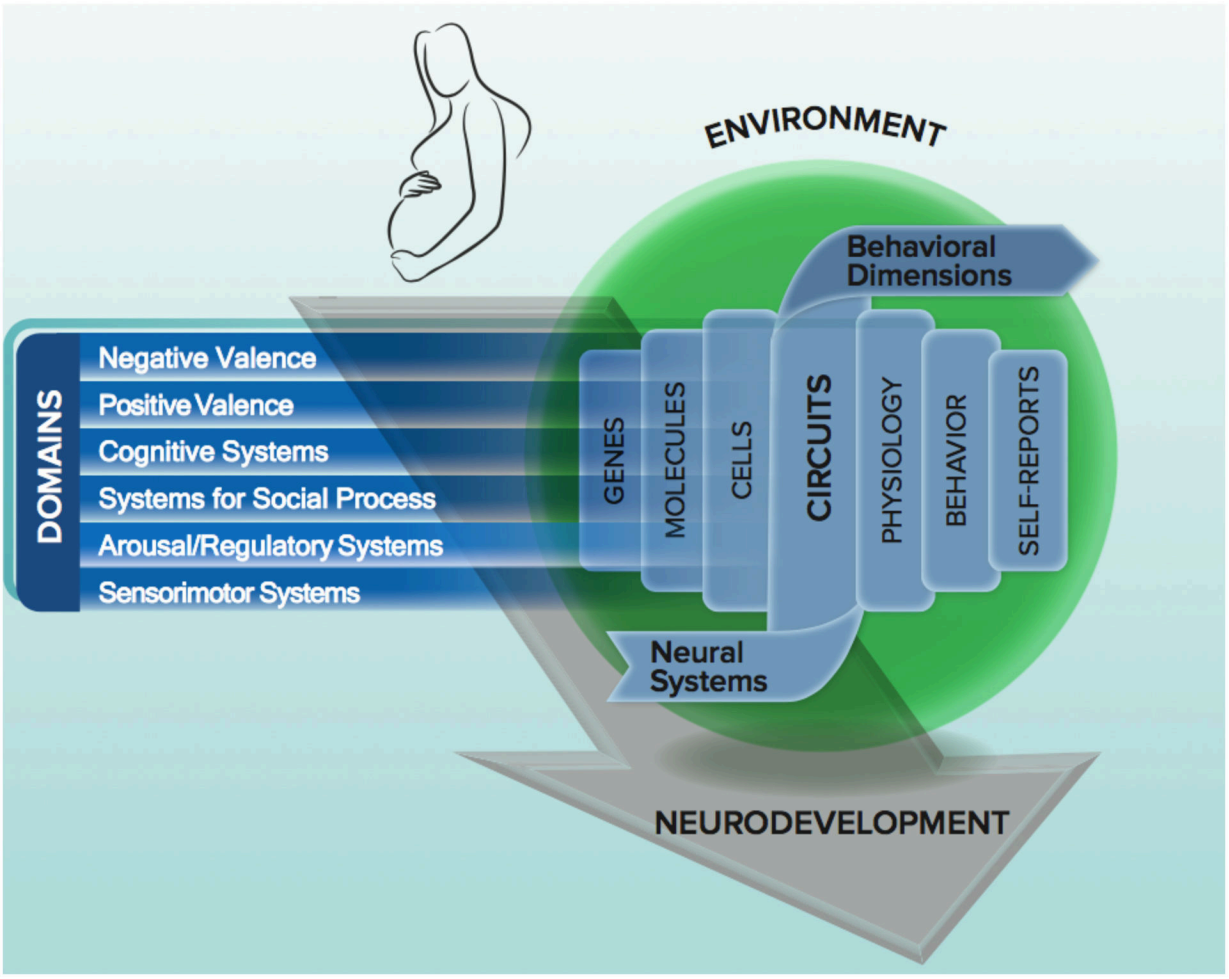

Fig. 1.

Major elements of the RDoC framework. Domains represent the major focus of study, with each domain containing three to six related constructs (and sub-constructs in some instances); the vertical blue bars ranging from Genes to Self-Reports depict examples of various Units of Analysis that might be incorporated in RDoC studies. The Neurodevelopment arrow represents a life span approach, starting with conception and continuing through the stages of adulthood; Environment is used as a catch-all term for all potential aspects that might be included in study designs, such as family, schools, neighborhoods, and culture, but also including individual events such as accidents or assaults. Inclusion of one or both of these latter elements is encouraged in study designs to examine the context in which domains and constructs are studied.