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The National Institute of Mental Health Research Domain Criteria and Clinical Research in Child and Adolescent Psychiatry

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Abstract

Objective—This review discusses the relevance of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) to clinical research in child and adolescent psychiatry.

Method—We summarize the characteristics of the NIMH RDoC project and then provide examples of RDoC designs that are of relevance to clinical investigators in child and adolescent psychiatry. The final section addresses questions regarding the impact of RDoC on clinical care.

Results—RDoC encourages investigators to investigate psychopathology dimensionally: greater or lesser degrees of healthy/adapted functioning of neurobiological, cognitive, and behavioral processes (constructs) that cut across current diagnostic categories. Elucidation of the developmental components of RDoC constructs is needed to ensure they are fully validated. Integrating RDoC approaches into clinical research of child and adolescent psychopathology is contributing to our understanding of development as an aspect of the heterogeneity within *DSM* disorders and commonalities across seemingly disparate disorders. Continued efforts promise to also explain the processes that lead to mental illness in at-risk populations.

Conclusion—Incorporating an RDoC approach in clinical research in child and adolescent psychiatry promises to be a fruitful avenue of research into the root causes and manifestations of mental illness, which will eventually lead to more precise treatments. Although the long-term aspiration of RDoC is to help reduce the burden of suffering for those with mental illnesses, it is not intended to be used for practical clinical purposes at this early stage.

Keywords

Research Domain Criteria; RDoC; clinical research; child and adolescent psychiatry; National Institute of Mental Health

Rethinking Mental Illness at National Institute of Mental Health

In November 2011, the US National Academy of Sciences published a major report on a new “precision medicine” approach, which encourages investigators to “modernize the ways

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in which biomedical research is conducted" (p. 2) using new information and concepts from recent advances in order to more precisely inform healthcare decisions and improve patient care.[1] The National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) project to address the need for a new approach to understanding mental illness and, although its launch predates the Institute of Medicine (IOM) report, it is an effort to develop a precision medicine approach for research on mental disorders[2-5]. The intent of RDoC is not to become a new diagnostic classification system, different from those already in place, but to build a broadly useful and accessible research literature ("information commons"[1]) that investigators will find useful in their search for more precise treatments for mental illnesses. This research literature will be useful for refining diagnostic classifications and potentially inform future revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and other diagnostic classification systems.[6]

The RDoC project – and the IOM report – were prompted by the fact that, frequently, clinical diagnoses and molecular mechanisms do not map directly onto each other. At first sight, it may be difficult to understand how information about genetic, molecular, cellular, and neural networks is relevant to clinical care of patients with mental illnesses. All would agree, however, that there is an urgent need for novel, more effective and specific therapeutics for those who suffer with these illnesses. Nevertheless, in the last 40 years, very few therapeutics with novel mechanisms have progressed to phase-III clinical trials, and even fewer have gained regulatory approval. While careful clinical insights will always be important in the quest for therapeutic innovations, approaches to drug development based on a clear understanding of the biological basis of a disorder are needed to increase the pace at which new compounds reach the clinic. Such approaches have proven beneficial in other areas of medicine, including, for example, the hypothesis-driven development of cholinesterase inhibitors, which improve attention and concentration in patients with mild to moderate Alzheimer's disease and are now standard of care for affected individuals.[7-9]

NIMH RDoC Project

RDoC encourages the integration of many levels of information (from genomics to self-report) to better understand the full range of human behavior, from normal to abnormal. The project encourages investigators to both inventory the fundamental, primary behavioral functions that the brain carries out—specifying the neural systems that are primarily responsible for implementing these functions—and to consider psychopathology in terms of various kinds and degrees of dysfunction in these particular neural systems, studied through an integrative, multi-systems approach.

The RDoC matrix[10] is a visual tool that was developed to help convey some key concepts about the project. The fundamental, primary behavioral functions ("constructs") that are currently included in the rows of the matrix provide examples for researchers interested in carrying out RDoC-informed clinical research. The matrix is not intended to either delimit the number of constructs that are relevant to mental illnesses or to set the parameters of research questions that can be asked by investigators.[6]

The columns of the matrix represent levels of analysis from the molecular to the behavioral levels. RDoC projects are expected to interrogate a construct using multiple levels of analysis, and, eventually, to build conceptual models capable of representing knowledge within and across these levels in order to understand the complexity of mental illness. In this way, results at one level can be interpretable in the context of another level, and studies focusing on one component of a complex theory can contribute to the overall credibility of the theory.

Although not currently represented in the matrix, the NIMH recognizes the critical roles that development, environmental exposures, and the evolution of psychopathology over time will play in the RDoC project if it is to be successful in achieving its goal.

The ultimate goal of the RDoC project is to create an ever-growing body of literature that drives, and is driven by, the dynamic information transfer between research at the basic and translational levels and the clinic. As the project moves forward, current constructs will be validated (or removed from the matrix) and others will be added as we more clearly understand the neural substrates of mental functions and their problems.

RDoC Dimensions

RDoC promotes two distinct dimensional approaches. The first approach assesses the range of functioning of neurobiological, cognitive, and behavioral capacities, representing them along continua of greater or lesser degrees of health or adaptation. This assumes the existence of such a continuum between mental health and illness—an assumption that may or may not hold, or may hold only for some types of psychopathology—and also allows an investigator to test the assumption in an empirical way. Little systematic research has tested this hypothesis for mental illness, yet the following example from internal medicine illustrates how this type of research could help clinical treatment decision making. Four decades of bench-to-bedside translational research has shown continuities between healthy and high blood pressure and has identified precise indicators of risk for developing severe hypertension in specific individuals (eg., individuals with blood pressure in the 130/80 to 139/89 range [“pre-hypertension”] are twice as likely to go on to develop severe hypertension compared with those with lower blood pressure). Discontinuities also exist, especially in children and adolescents, who are more likely to have an identifiable cause for their hypertension (eg., kidney disease, coarctation of the aorta).[11-13] The goal of the RDoC project is to help investigators delineate similar guidelines for clinicians so they can identify particular risk or resilience factors that influence a given individual’s likelihood to transition to psychopathology.[14] The second type of dimensional approach investigates mental illness through the lens of fundamental components of behavior (individual symptoms or symptom clusters) that cut across diagnoses. This approach provides an investigator the freedom to study symptoms that are of particular salience. For example, anhedonia is associated with more severe clinical outcomes for adolescents with major depressive disorder and schizophrenia.[15,16] Determining the cross-diagnostic neural mechanisms responsible for the harmful effect of anhedonia could lead to the development of an adjunctive intervention that, when combined with specific pharmacotherapies for these disorders, can significantly improve functional outcomes.

Focusing on fundamental components of behavior rather than *DSM* diagnoses will also allow for the detection and longitudinal monitoring of emerging symptoms that do not meet criteria for a disorder. Current diagnostic guidelines for autism spectrum disorders (ASD) are difficult to apply to children under 2 years of age, although the development and refinement of diagnostic instruments such as the Autism Diagnostic Observation Schedule–Toddler module have helped.[17] Even so, detecting emerging signs of autism prior to the child meeting full diagnostic criteria could lead to improved outcomes or even preemption. Results from a set of recent longitudinal studies in younger siblings of children with ASD charted the very early development of fundamental components of behavior (motor, language development, and social responsiveness) and found a decline in preferential attention to the eyes of others (an indicator of social attention) between 2 – 6 months of age in those children who were later diagnosed with ASD.[18-21] By understanding the natural progression of eye gaze and its relationship to social attention, investigators found a possible construct associated with ASD that may point to early detection and intervention.

Research Design in the Era of RDoC

RDoC encourages investigators to be agnostic to *DSM* categories when they design research studies if appropriate to the research question. Some research questions may require participant selection based on *DSM* diagnoses for the purpose of exploring heterogeneity within one disorder or the shared mechanisms that underlie seemingly unrelated disorders.

Findings from the studies of three investigators can help demonstrate these RDoC approaches. Nigg et al.[22] used an RDoC approach to understand the heterogeneity within a single *DSM* disorder, attention-deficit/hyperactivity disorder (ADHD), based on biological measures rather than on behavioral criteria defining the different subtypes codified within the *DSM*. They recruited 437 clinically well-characterized, community-recruited children with and without ADHD. Baseline data were entered into a novel community detection algorithm to classify children into subgroups based on temperament dimensions and external validators, including physiological and magnetic resonance imaging measures. The algorithm suggested three novel types of ADHD, labeled as “mild” (normative emotion regulation), “surgent” (extreme levels of positive approach motivation), and “irritable” (extreme levels of negative emotionality, anger, and poor soothability). These novel ADHD types were independent of existing clinical demarcations including *DSM-5* presentations or symptom severity, and each had unique patterns of cardiac physiological response, resting-state functional brain connectivity, and clinical outcomes that were stable at the one-year longitudinal follow up.

Phillips et al.[23] used an RDoC-informed approach to ask whether patterns of altered brain connectivity between two key neural regions that instantiate emotion processing/regulation were similar across multiple *DSM* diagnoses. They recruited a group of children from the Longitudinal Assessment of Manic Symptoms (LAMS) study, classifying the children by diagnosis (bipolar spectrum disorders, ADHD, anxiety disorders, and disruptive behavior disorders), as well as by symptom dimensions (ie., behavioral and emotional dysregulation measured with the Parent General Behavior Inventory – 10 Item Mania Scale [PGBI-10]). Abnormal resting state connectivity between amygdala and posterior insula was unrelated to

diagnosis but, across all diagnoses, was negatively correlated to increasing severity of behavioral and emotional dysregulation (as measured with the PGBI-10) and depression.

Finally, a series of studies by McTeague et al. investigated physiological processes present across multiple *DSM* diagnoses, and this led the way to the detection of previously unrecognized heterogeneity within one of the disorders. They assessed fear-potentiated startle in adults with one of eight different *DSM* anxiety disorders.[24-28] Commonalities were present within groups of disorders characterized by focal fear (e.g., robust responses), commonalities that were different from those within groups of disorders characterized by generalized fear and anxious misery (e.g., blunted responses). The group of participants with posttraumatic stress disorder (PTSD) had exaggerated responses when averaged but showed marked differences when the group was stratified by whether the participant had had exposure to a single, discrete event (exaggerated) or to multiple traumas over an extended period of time (blunted). Interestingly, all participants with PTSD reported equivalently intense aversive arousal during imagery of their trauma narratives. Heterogeneities within all disorders were also found between adult versus childhood onset. In this RDoC-informed study, *DSM* diagnoses were established for each participant at baseline, but differences in responses to fear-potentiated startle did not map on to the diagnoses so much as to the type of anxiety and its duration (focal versus generalized fear; child vs. adult onset). Heterogeneity of responses within a single diagnosis was most clearly seen in PTSD.

These studies demonstrate that, using an RDoC approach, if a *DSM* diagnostic category or subcategory is included in the analyses, it is more likely to be the dependent variable, as this allows the investigator to test the assumptions that support its validity. As in the examples provided above, Nigg et al. chose temperament dimensions, physiological, and magnetic resonance imaging measures to explore heterogeneity within a sample of children with ADHD, while Phillips et al. used measures of behavioral and emotional dysregulation as independent variables in the main analysis and diagnostic categories for a secondary analysis.

RDoC also encourages investigation of the full range of variation of function of the construct under study. This may mean recruiting participants with anomalous functioning at both extremes of the dimension. For example, both extremes of the fear construct may be of interest, since a complete lack of fear may be associated with aggressive or psychopathic behavior. For any given research study, however, it may not be possible or advisable to examine the full functional range. Selection of a constricted range of functioning may be appropriate, depending on the particular hypotheses being tested and the psychopathological dysfunction under study.

Depending on the design of the study, investigators need to determine how they will recruit a population that represents the appropriate dimension under study. For example, recruiting children between six and eight years of age from the community or from local schools could be expected to yield a dimension ranging from no anxiety to clinically significant symptoms, although the majority of participants would have milder symptoms. To adequately cover the full dimension, recruitment could also include treatment-seeking children attending an anxiety disorders clinic, whether or not they met criteria for an anxiety disorder. On the

other hand, in a longitudinal study looking at the relationship between cognitive deficits in youth at ultra-high risk for psychosis and later onset of psychosis, it may be more appropriate to only recruit treatment-seeking individuals from either a general psychiatry clinic or specialty clinic (e.g. for psychotic disorders). Including participants from both outpatient and inpatient services could be a useful strategy to examine whether individuals soon after their first suicide attempt show changes in neurochemical imaging markers of impulsivity and responsivity to reward that differ from those seen in non-attempters with suicidal ideation.[29] Sampling strategies could also include recruitment of a subsample from a larger group of participants. For instance, in a study examining the neural bases for poor functional outcomes in adolescents with ADHD, an investigator could recruit individuals with ADHD who score poorly (e.g. more than one standard deviation below the mean) on a working memory task.

Whatever sampling strategy is used, exclusions for comorbid conditions would be expected to be less stringent, given the goal of examining cross-diagnostic constructs and mechanisms and the dimensional nature of the analysis. Exclusions should be carefully considered and chosen based on their potential to compromise or confound study results.

Development and RDoC

The constructs currently in the RDoC matrix represent complex, differentiated, and integrated behavior and mentation that, when disordered, underlie mental illness. Investigators will need to embrace the complexities of development in order to fully validate current and future constructs in the RDoC matrix. Robust developmental designs are needed to capture changes in the underlying neural circuitry and other biological components of these functions, relating them to changes in their corresponding cognitive and affective capacities as they emerge over time and alter behavior under the influencing role of environment. Studies that seek to elucidate risk for psychopathology will also need to take into consideration factors such as multifinality[30] (i.e., that a single risk factor may constitute risk for multiple disorders later in life) and the mediating role of maladaptive maturation of the nervous system between an individual's interaction with a wide variety of environmental factors and diverse symptoms of psychopathology.[30-33]

Understanding the interaction between constructs as they mature and differentiate is also important, as some capacities do not develop in a linear fashion (e.g. cognitive constructs change linearly, but social and emotional do not). Investigators may decide to stratify participants by chronological age, developmental stage, or developmental processes (e.g., puberty) in order to determine which of these are associated with maturational changes in the construct under study.

Furthermore, it will be important to explore the continuities (greater or lesser degrees of health or adaptation) and discontinuities (qualitative dividing lines between health and disease) that exist across development itself, where behaviors may or may not be expressed differently at different ages and stages (e.g. separation anxiety is normal at certain developmental stages, but a sign of mental illness at others). Recruitment strategies for these types of studies will require careful thought as to the particular age ranges chosen. In

addition, recruiting sufficient numbers of both sexes will allow investigators to examine the effect of sexual dimorphism on typical and atypical development of cognitive and emotional capacities.

Measurement Considerations Specific to RDoC Studies

An important consideration in any RDoC study is the need for adequate tools to collect quantitative, age-appropriate, scaled, and normed behavioral measures that tap behavior consistently across age and developmental stages and can differentiate between competence and performance. Tools to integrate multiple sources of information about a child (child self-report, parent report, teacher ratings) are also important. There are few validated measures for many of the constructs in the matrix, and fewer that are validated to assess the construct across development. It will be important to establish construct validity for any assessment tool to be sure that it measures what it is intended to measure and, as understanding of the construct evolves, to update or replace it when more precise measures become available. An important goal of tool development is to provide a core of common data elements that can be used in studies in such a way that comparison between, and replication of, studies is made possible.

The National Institutes of Health Toolbox[34] is a multidimensional battery of brief cognitive, emotional, motor, and sensory assessments normed for use in individuals from 3 to 85 years of age. Since it is designed to only screen for the presence of problems, most investigators will likely also include tools that provide more in-depth evaluation, such as the Penn Computerized Neurocognitive Battery developed by Gur et al.[35-37] This battery takes one hour to administer and includes 14 tests assessing 5 neurobehavioral domains: executive function, episodic memory, complex cognition, social cognition, and sensorimotor speed. The goal of the developers is to provide clinicians a tool that can assess and plot cognitive functions on growth charts, similar to those used for weight and height, in order to detect emerging cognitive delays, such as those seen in children at risk for psychotic symptoms.[38]

Finally, statistical analyses will need to incorporate methods that allow for investigation of person-centered or dimensional variables in order to understand individual variation within a construct across development. This will require measurement of the effects of the complex longitudinal interactions between individuals and their environments during development. This cannot be achieved using cross-sectional group comparisons of behavior or neurobiological functioning in different categorical diagnoses but by examining individual vulnerabilities and their interactions with environmental risk across levels of analysis and time.[39]

RDoC and the Clinician

RDoC aims to bring new approaches to research on mental illness that will speed the development of more effective drug and behavioral interventions based on the biological basis of a disorder. This is likely to help researchers identify precision interventions that can prevent, preempt, or treat mental illnesses. Since clinicians treating mental illness are most concerned about the welfare of their patients, an important question is whether RDoC will provide them with what they need to adequately care for those who seek their help.

From the foregoing discussion, it is clear that the impact of RDoC on clinical care—in terms of new and more effective interventions—will take effect in terms of years, perhaps decades. It is reasonable to expect that most clinicians will continue to count on the insights they have gained over the years about diagnosis and management of mental illnesses in the *DSM* system.

In the meantime, some academic clinicians have begun to incorporate RDoC into neuroscience courses within their residency training program. In a report on one such course, the authors suggest that the similarity between the RDoC framework and problem-based approaches common in routine clinical care (where treatments are geared towards the alleviation of specific symptoms that patients endorse rather than their *DSM* diagnoses) may explain why residents found the course to be more practical and useful than a course organized around *DSM* diagnoses.[40] Thus, the dimensional nature of RDoC may be a bridge between the rapid advances in psychiatric neuroscience and the clinical education for trainees, who will need to translate the scientific advances to the clinic.

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Clinical Guidance

- The RDoC project aims to develop precision medicine for clinical research in psychiatry. Its focus on integrating many levels of information on behavioral functions that cross current diagnostic categories is likely to help in the search for more effective and precise interventions as has happened in other areas of medicine. It will also aid in the detection of early emergence of psychopathology, which may lead to interventions that preempt or prevent mental illness.
- An essential step in the validation of RDoC constructs is the effort to elucidate the maturational changes associated with the emergence of cognitive and affective capacities across time and under the influencing role of environment. In order to do this, it will be necessary to have adequate measures that are valid across age and developmental stages. The RDoC framework is agnostic to *DSM* categories; however, at this stage, some investigators have found it useful to recruit participants based on their *DSM* diagnoses to examine heterogeneities within single disorders or commonalities that exist across multiple disorders.
- RDoC is not intended for use in the clinic, as its impact on clinical care will be through research findings that can inform revisions of current diagnostic nosologies and fuel development of effective interventions. However, the dimensional nature of RDoC may help future clinicians translate the advances in psychiatric neuroscience into the clinic.