

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

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**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.

**Key words:** Research Domain Criteria, RDoC, clinical research, child and adolescent psychiatry, National Institute of Mental Health

*J Am Acad Child Adolesc Psychiatry* 2016;55(2):93–98.

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 in which biomedical research is conducted” (p. 2) using new information and concepts from recent advances to more precisely inform health care decisions and improve patient care.<sup>1</sup> 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; 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.<sup>2–5</sup> 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”<sup>1</sup>) 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 may potentially inform future revisions of the DSM and other diagnostic classification systems.<sup>6</sup>

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 the clinical care of patients with mental illnesses. All would agree, however, that there is an urgent need for novel, more effective, 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. Although 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 proved 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 the standard of care for affected individuals.<sup>7–9</sup>



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## NIMH RDoC PROJECT OVERVIEW

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<sup>10</sup> 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.<sup>6</sup>

The columns of the matrix represent levels of analysis from the molecular to the behavioral. 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 to provide an understanding of the complexity of mental illness. In this way, results at 1 level can be interpretable in the context of another level, and studies focusing on 1 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 2 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 (e.g., 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 (e.g., kidney disease, coarctation of the aorta).<sup>11-13</sup> 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.<sup>14</sup>

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.<sup>15,16</sup> 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, could significantly improve functional outcomes.

Focusing on fundamental components of behavior rather than *DSM* diagnoses will also allow 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 less than 2 years of age, although the development and refinement of diagnostic instruments such as the Autism Diagnostic Observation Schedule–Toddler module have helped.<sup>17</sup> Even so, detecting emerging signs of autism before the child meets 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 and 6 months of age in those children who were later diagnosed with ASD.<sup>18-21</sup> 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 designing 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 a given disorder or the shared mechanisms that underlie seemingly unrelated disorders.

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