The Research Domain Criteria (RDoC) Project and Studies of Risk and Resilience in Maltreated Children

Joan Kaufman, PhD, Joel Gelernter, MD, James J. Hudziak, MD, Audrey R. Tyrka, MD, PhD, Jeremy D. Coplan, MD

Objective: The Research Domain Criteria (RDoC) project was initiated to develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures. This article reviews the rationale behind the RDoC program, its goals, and central tenets; discusses application of an RDoC framework to research with maltreated children; and highlights some clinical implications of this work.

Method: Published RDoC papers were reviewed, together with relevant preclinical and clinical studies that guide our work on risk and resilience in maltreated children.

Results: The ultimate long-term goal of the RDoC initiative is precision medicine in psychiatry. In the interim, the RDoC initiative provides a framework to organize research to help develop the database required to derive a new psychiatric nomenclature that can appropriately match treatments to patients. The primary focus of RDoC is on neural circuitry, with levels of analyses that span from molecules to behavior. There has been some concern that the RDoC framework is reductionist, with an overemphasis on neural circuits and genetics; however, the briefly reviewed, burgeoning literature on neuroplasticity and epigenetics highlights that this concern is unwarranted, as one cannot study neural circuits and genetics without considering experience.

Conclusion: The study of maltreated children has a number of advantages for the RDoC project, including the following: study of a subset of patients who are often not responsive to standard interventions; examination of a relatively homogenous sample with onset of psychopathology proposed to be associated with stress-related mechanisms; and well-established, relevant animal models to facilitate translational research.

Key Words: RDoC, risk and resilience, maltreated children

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The brain is not organized, according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). Although the *DSM* has been an invaluable tool in establishing reliability of psychiatric diagnoses and creating a common language to facilitate communication about mental illnesses,[1,2] the validity of the *DSM* psychiatric nomenclature has come under considerable scrutiny[3,4] and has spurred the initiation of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project.[5,6] This article reviews the rationale for the NIMH RDoC program, its goals, and its central tenets (http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). It also discusses the application of an RDoC perspective in research with maltreated children.

RATIONALE FOR THE NIMH RDoC INITIATIVE

Although rates of infant mortality have dropped 50% since 1980,[7] mortality has not decreased for any psychiatric disorder, and prevalence rates are similarly unchanged.[5] Psychiatry has lagged behind multiple areas of medicine in gaining insights into the pathophysiology of disease.[8] Heterogeneity within diagnostic categories[4,9] and comorbidity among disorders[10,11] are the rule, compromising treatment efficacy and research on pathophysiology of mental illnesses. Related to this, *DSM* diagnostic classifications do not delineate distinct paths of treatment; instead, single classes of drugs, such as selective serotonin reuptake inhibitors (SSRI), are indicated for a wide range of anxiety, mood, and eating disorders.[3] Yet, although SSRIs are approved for these different conditions, treatment response is varied, and on average across diagnoses, a marketed psychiatric drug is efficacious in only half of the patients who take it.[5] The effect size for the drugs used in psychiatry range from small to large, with the efficacy of psychotropic drugs on average in the medium range, which is actually approximately comparable to the efficacy of many drugs used across multiple fields in medicine.[12] Psychiatry, like many areas of medicine, is in need of reliable diagnostic tests to better match treatments to patients. There are currently few data to guide our efforts to determine which patients will have a favorable response to any given treatment, to reliably assess risk of disorder, or to prevent or alter the course of illness onset.

CG Clinical guidance is available at the end of this article.

GOALS AND GUIDING PRINCIPLES OF THE NIMH RDoC INITIATIVE

The ultimate long-term goal of the NIMH RDoC initiative is precision medicine in psychiatry so that clinicians can tailor treatments to optimize outcomes for individual patients.[5,8]

The near-term goal is to devise a framework to organize research to help develop the database required to derive a new psychiatric nomenclature that can use the research findings to appropriately match treatments to patients.[5] It is believed that this new psychiatric nomenclature will facilitate precision medicine in psychiatry. The NIMH is agnostic about what this new nosology will look like but has delineated a set of guiding principles to move toward the goals of the RDoC initiative.

Central tenets of the NIMH RDoC initiative include the following: Mental illnesses are brain circuit disorders[6]; Psychopathology is conceptualized in terms of component abnormalities in discrete, but frequently highly interconnected, brain circuits[13]; Brain circuit abnormalities cut across traditional diagnostic boundaries[13]; Behaviors linked to different brain circuits vary dimensionally from impairment to healthy functioning[13]; and Brain circuit function varies across development and is significantly influenced by experience.[14] The RDoC further assumes that diagnoses based solely on observable signs and symptoms are nonspecific and inevitably reflect heterogeneity in terms of pathophysiology,[8] and that, in time, data from the fields of genetics and clinical neuroscience will yield meaningful biomarkers to augment clinical symptoms in guiding treatment.[6]

Table 1 delineates key features that distinguish RDoC from the *DSM*. First, RDoC is a research framework; it is an evolving structure designed to guide research, not replace the *DSM* as a tool for clinicians at the present time.[15] RDoC also conceptualizes mental illnesses as comprising component parts that can be represented on dimensional scales, not as categorically discrete entities. In addition, the RDoC framework takes a bottom–up approach by starting with neural circuits to understand behaviors, rather than a top–down approach of starting with symptoms to understand the pathophysiology of mental illnesses. It also aims to reflect understanding of the biology of discrete circuits and behaviors, not multifaceted clinical syndromes.

RDoC MATRIX

As depicted in Table 2, the RDoC Matrix currently consists of 5 domains and a series of interrelated constructs. The domains and constructs were selected during a series of thoughtful workshops facilitated by NIMH over the past several years.[16] For constructs to be included in the RDoC Matrix, evidence demonstrating that they are reliable and valid behavioral functions and are subserved by an identified neural circuit was required.[14] The 5 initial domains identified by the RDoC workshops include negative valence (e.g., anxiety, loss), positive valence (e.g., reward), cognitive systems (e.g., attention, working memory), social processes (e.g., affiliation), and arousal/modulatory systems (e.g., sleep–wake). Over time, it is likely that additional domains and constructs will be added to the matrix. Although the table may appear to suggest sharp boundaries between the separate domains and constructs, research has demonstrated that the domains and constructs function interactively via highly integrated brain circuits.[17]

TABLE 1 Primary Distinctions Between the *DSM* and the National Institute of Mental Health's Research Domain Criteria (RDoC)

DSM	RDoC
Clinical nosology	Research framework
Categorical approach	Dimensional approach
Symptom-based definitions of disorders	Neural circuit-based delineation of behaviors

The primary focus of RDoC is on neural circuitry, with levels of analysis progressing in 1 of 2 directions: upward from measures of circuitry to clinical symptomatology, and downward to the genetic and molecular factors that ultimately influence function.[6] The RDoC initiative promotes the examination of each construct across 7 units of analyses: genes, molecules, cells, circuits, physiology, behavior, and self-reports. It also identifies paradigms that can be used to assess each construct. Table 3 delineates a nonexhaustive set of data for each of these units of analyses for the construct "acute threat" (or "fear") to illustrate the clinical utility of the RDoC perspective that calls for incorporating units of analyses from molecules to behavior, with this construct chosen, given its relevance to our work with maltreated children.

Starting with circuits, preclinical and clinical research suggest the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus are key structures within the fear circuit.[18] Moving to symptoms, deficits in fear learning and fear extinction are hypothesized to be related to the onset of posttraumatic stress disorder (PTSD) and other anxiety disorders,[19] with knowledge about fear extinction behavioral paradigms instrumental for the development of exposure therapies.[20] Moving downward, variation in polymorphisms in the serotonin transporter gene (a particular variant, *5-HTTLPR*),[21] γ-aminobutyric acid (GABA) A receptor gene α 2 (*GABRA2),*[22] and *oFK506*-binding protein 5 (*FKBP5*) gene (the protein product that interacts with the glucocorticoid receptor[23,24]) have been found to alter risk for the development of PTSD after child abuse. These gene-by-environment studies have helped to elucidate why some individuals develop psychopathology after abuse and others do not. On the molecular level, glutamate transmission, and particularly its actions at *N*-methyl-D-aspartate (NMDA) receptors, underlies extinction learning.[25] This finding has been translated into clinical practice, with administration of the NMDA receptor partial agonist D-cycloserine (DCS) found to augment the efficacy of exposure therapy for PTSD and other anxiety disorders,[25] providing a powerful illustration of the clinical utility of the RDoC perspective, and incorporating units of analyses from molecules to behavior.

There has been some concern expressed that the RDoC framework is reductionist, with an overemphasis on neural circuits and genetics, and minimal attention to contextual factors.[26,27] The incorporation of preclinical translational studies of fear extinction at both the behavioral and molecular level into treatments (e.g., exposure therapy and DCS) demonstrates the potential value of the integrated approach proposed by RDoC, and the burgeoning literature on neuroplasticity and epigenetics further highlights that this concern is unwarranted, as one cannot study neural circuits