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NIMH Research Domain Criteria (RDoC)

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In the spring of 2009, the National Institute of Mental Health (NIMH) formed a working group to implement Strategy 1.4 of its Strategic Plan that called for the "development, for research purposes, of new ways of classifying psychopathology based on dimensions of observable behaviors and neurobiological measures." This project became known as the Research Domain Criteria (RDoC; Insel et al., 2010). RDoC marks a shift in psychiatric research. For the past 30-plus years, most research on mental disorders has been based on clinical syndromes as defined in the *DSM*. The structure of RDoC departs from clinically described syndromes and attempts to "carve nature at its joints" by studying psychopathology based on objective behavioral, neurobiological, and genetic measures while remaining agnostic concerning traditional diagnoses based on clinical description (Sanislow et al., 2010).

History and Rationale

Efforts to codify psychiatric diagnosis for research purposes began in the 1970s with the advent of the Feighner criteria, later the Research Diagnostic Criteria, which served as the foundation for the 1980 *DSM-III* (Feighner et al., 1972). These developments marked a change from the psychoanalytic Zeitgeist to the goal of validating clinically observed syndromes derived by expert consensus. This shift was influenced by the five criteria for validity set forth by Robins and Guze (1970): clinical description or symptom clusters, laboratory studies, delineation of disorders from one another, follow-up studies, and family studies. More than 40 years later, no single categorical diagnosis has fulfilled all five criteria, and links to laboratory studies are especially weak.

Reliability, not validity, was the sturdiest element of the *DSM*s from 1980 onward. These editions served clinical utility, allowing service providers to communicate clearly and standardize treatments. The improved reliability also helped researchers, increasing confidence that the same problems were being studied, and leading to advances in assessment and treatment. Research on the diagnoses prospered, and empirical findings improved subsequent *DSM*s.

Despite progress, problems persisted. Original diagnoses were based on expert consensus, and subsequent empirical research built on this base suffered from basic questions about the validity of the diagnoses even with empirical fine-tuning. Diagnostic constructs were reified, implying a natural kind without sufficient empirical evidence (Hyman, 2010). Researchers forged ahead, struggling to link diagnoses to discrete psychological or neural mechanisms with limited success. Patients frequently met criteria for several diagnoses, and this "comorbidity" suggested that psychological and biological mechanisms are shared across diagnoses, raising the question of whether or not certain disorders are really separate. Comorbidity may also reflect the progression of illness (e.g., anxiety progressing to depression).

Researchers seeking to reduce heterogeneity in their study groups typically recruited

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patients with a "pure" *DSM* diagnosis, excluding patients with comorbid, possibly related diagnoses. This had the untoward effect of eliminating research participants who might provide important variation in a relevant psychological or biological dimension. For instance, a focus on major depressive disorder that excluded participants with dysthymic disorder and depressive disorder not otherwise specified would potentially lose relevant information about depression mechanisms.

In contrast to overspecificity, heterogeneity within *DSM* diagnoses is amplified by the polythetic approach. With proportional diagnostic cut points, two individuals who share few—and, in some cases, no—clinical symptoms can receive the same diagnosis. For example, two people can meet criteria for major depression without sharing a single symptom (assuming lack of appetite and overeating as separate symptoms). Those diagnosed with borderline personality disorder may share only a single criterion, and there are 256 possible combinations of criteria to qualify for that diagnosis.

The variation of pathology within clinical problems has made it challenging to demonstrate direct links between neurobiological mechanisms and clinical diagnoses. Neural systems cut across a range of *DSM* disorders that involve negative emotional states. Some of the same genes are risk factors for both schizophrenia and bipolar disorder, calling into question the original Kraepelinian split (Kraepelin, 1921). Stronger links between neurobiological mechanisms and specific clinical problems could clarify diagnoses and thereby improve psychopharmacological and psychological treatments.

RDoC addresses these challenges but does not compete with the *DSM*. *DSM* is a diagnostic nosology that informs clinical care and has provided definitions for clinical research. In contrast, RDoC is a framework to guide clinical research and does not begin with a clinically described diagnosis. Rather, it assumes that the neural and psychological mechanisms involved in normal functioning, when disrupted, have relevance for psychopathology.

Development of RDoC: Identifying Domains and Constructs

The RDoC is organized in a matrix where rows represent specific dimensions of function (constructs) and columns represent areas for study (units of analysis). A construct (e.g., "working memory") represents a particular functional aspect of behavior, and it is tied to knowledge about underlying neurobiological and genetic mechanisms. Constructs are grouped together to form "domains." There are five domains in the RDoC matrix: Negative Valence Systems (i.e., systems for aversive motivation), Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems. In the columns, there are eight units of analysis: Genes, Molecules, Cells, Neural Circuits, Physiology, Behavior, Self-Reports, and Paradigms. Self-Reports include clinical reports via interview. Paradigms stand apart from other columns, and they include tasks and methods to measure or reliably interrogate units of analysis.

A multistep, open process was used to identify the current RDoC domains and constructs. The NIMH working group made suggestions for domains and constructs based upon the scientific literature about basic cognitive, behavioral, and neural mechanisms important for functioning that, when disrupted, may be associated with "palpable" psychopathology. Constructs with strong support from basic behavioral and neuroscience research were included. Input was sought from the field using multiple venues. Experts in basic and clinical research were consulted, and their feedback was incorporated. NIMH published a "Request for Information" (NOT-MH-11-007). Inquiries were sent via email to NIMH grantees soliciting additional feedback. Surveys for the respective domains were sent to leading scientists. NIMH also organized a series of workshops

for each domain area where those with expertise in each domain were invited. In those meetings, proposed constructs and domains were critically evaluated based on current research, as were additional constructs proposed by the participants. Some constructs were dropped because there was not enough empirical clarity to justify inclusion at this point in time. Others were refined and some new ones added, depending on empirical support. The RDoC matrix, the "Request for Information," other NIMH RDoC-related announcements, and proceedings from RDoC workshops are all available on the NIMH RDoC website (National Institute of Mental Health, 2013). RDoC depends on the continuation of this scientific interaction and input from the field. As studies provide new evidence—or suggest new ways of thinking about old hypotheses—the structure and content of RDoC will continue to evolve. Constructs lacking empirical support to characterize psychopathology will be dropped; others may be added and tested for utility. Empirical support, not expert consensus, is the mainstay of RDoC.

Fundamental Premises of RDoC

This approach to classification rests on three principal assumptions: (a) that mental illnesses can be conceptualized as dysfunctions in neural circuits, (b) that current neuroscience techniques (e.g., structural and functional imaging, and electrophysiology) can identify disruptions in these circuits, and (c) that findings stemming from genetics and clinical neuroscience research will yield biomarkers for psychopathology that will eventually guide clinical management and improve care (Insel et al., 2010). RDoC emphasizes neural circuit function based on the premise that brain circuitry is pivotal to mental illness.

The Structure of RDoC

As mentioned in this entry, RDoC is structured in a matrix with the rows divided into constructs that are grouped together into five broad domains. Most research projects following the RDoC structure would focus exclusively on one or two constructs within the domains, and integrate two more units of analysis. The current version reflects the existing knowledge in psychopathology and will evolve.

The RDoC Domains and Constructs

Negative valence systems. This domain includes the constructs of acute threat ("fear"), potential threat ("anxiety"), sustained threat, loss, and frustrative nonreward. The constructs of fear and anxiety have been studied in a large number of contexts, and knowledge of their biological and behavioral systems is well developed. They have also been implicated across a variety of *DSM* diagnoses, including major depressive disorder, posttraumatic stress disorder, bipolar disorder, and schizophrenia.

Positive valence systems. This domain includes the construct of approach motivation and, within that, the subconstructs of reward valuation, effort valuation/willingness to work, expectancy/reward prediction error, and action selection/preference-based decision making. Other constructs in this domain include initial responsiveness to reward, sustained responsiveness to reward, reward learning, and habit.

Cognitive systems. This domain includes the construct's attention, perception, declarative memory, language and behavior, cognitive (effortful) control, and working memory. Within perception are two subconstructs, auditory perception and olfactory–somatosensory–multimodal perception. Within cognitive (effortful) control are the following subconstructs: goal selection, updating, representation, and maintenance; response selection, inhibition, or suppression; and performance monitoring. Component processes of working memory include active maintenance, flexible updating, limited capacity, and interference control. Disruptions in declarative

memory, language behavior, and cognitive control have been well studied in schizophrenia spectrum disorders.

Systems for social processes. These constructs are relevant to interpersonal processes that comprise familiar clinical observations. The constructs in this domain include affiliation and attachment and its subconstruct, attachment formation and maintenance. Social communication includes the subconstructs of reception and production of facial communication, and reception and production of nonfacial communication. The construct of perception and understanding of self includes two subconstructs, agency and self-knowledge. Last, the construct of perception and understanding of others includes three subconstructs (animacy perception, action perception, and understanding mental states). Social neuroscience is beginning to provide clues to the neural systems associated with these processes.

Arousal and regulatory systems. Constructs in this domain subserve many of the aforementioned constructs but were grouped into a separate domain because of the common homeostatic systems and functions that they implement. The three constructs in this domain are arousal, circadian rhythms, and sleep and wakefulness. The constructs in this domain are ubiquitous in that they interact with many brain–behavior systems.

Units of Analysis

Accompanying these constructs are units of analysis that can serve as either independent or dependent variables in RDoC-guided studies. As noted, neural circuits are a central focus to integrate biology and behavior. The units Genes, Molecules, and Cells may elucidate variations in these circuits, and the units Physiology, Behavior, and Self-Reports might connect neural circuit dysfunction to familiar manifestations of psychopathology. RDoC is by definition dimensional, and the measurement of all units of analysis can be expected to fall within a certain range of values (from normal to abnormal) capturing the level of that unit in a particular individual (Morris & Cuthbert, 2012).

The RDoC matrix also contains a separate column dedicated to paradigms. In the context of this framework, *paradigms* refer to experimental conditions used to measure units of analysis across the various domain constructs. An example of a commonly used paradigm is the sequential or *affective* priming task, which can be used to measure implicit affective associations mapped onto a set of stimuli. Paradigms such as this and others (e.g., the Flanker task) can be used in conjunction with neuroimaging techniques in order to map behavior to dysfunction in specific areas to abnormalities in specific neural circuits. RDoC Paradigms not only capture valid group differences but also reliably measure individual differences.

Developmental Processes and Environmental Influences

Although developmental processes and environmental influences are not explicitly codified in RDoC, these processes are critically important for understanding psychopathology. One of the difficulties in explicitly coding developmental elements in the RDoC matrix is their ubiquitous importance for any psychopathology: Mental illness is best viewed as it unfolds over the life span. Throughout the course of illness, manifest symptoms may be markedly different yet connected to neural mechanisms that change during development. For example, neural changes from pediatric stress can create vulnerability for adult fear disorders. Mental "disease" may involve progressive neural and psychological change over the life course, not captured by a cross-sectional snapshot of clinical symptoms. When viewing schizophrenia as a neurodevelopmental disorder, the clinical syndrome schizophrenia may actually be the end stage of a long, developmental disease process. A more useful diagnosis might not resemble schizophrenia as we know it but, rather, reveal a mechanism well before the first episode of frank psychosis.

Environmental influences, too, are universal, and they are particularly complex, as epigenetic processes are better understood.

Ideally, all psychopathology research—within the RDoC framework or not—takes into account developmental and environmental factors. Presently, these can be incorporated in the elements of the matrix and by specifying theoretical relations across units of analyses, constructs, or domains. In this way, environmental influences and developmental processes are key to integrating the elements of RDoC. The RDoC approach thus provides a coherent way to focus integrative studies of developmental trajectories that relate to risk for psychopathology, and initial studies in this area may well suggest ways in which such factors may be more formally integrated into the RDoC matrix.

RDoC Research Design

How does one design a nosology for research without using the existing diagnoses based on clinical description? The RDoC approach requires "bootstrapping." Critical to achieving the RDoC objective of integrating neurobiology into our understanding of psychopathology is designing research that involves the appropriate sample with a range of behaviors and neural mechanisms to characterize psychopathology in ways unbiased by current nosologies. Simply put, RDoC study samples are not defined by *DSM* categories.

The Sampling Frame

Instead of seeking participants restricted to discrete *DSM* diagnoses for experimental or psychiatric control groups, RDoC-based studies select participants on a putative dimension of interest. This might be a particular psychiatric symptom (e.g., anhedonia), a relevant risk factor (e.g., impaired cognitive control), or a developmental experience (e.g., childhood abuse). Although such studies do not select participants on the basis of a *DSM* diagnosis, many of the individuals included in these experimental groups would likely satisfy or approach criteria for at least one, but, more typically, several *DSM* diagnoses. The key is to avoid limiting recruitment based on strict *DSM* criteria or cut points.

Dimensions

To characterize constructs dimensionally requires participant recruitment that spans patient and nonclinical populations (allowing measurement across a full neurobehavioral dimension from normal function to dysfunction). Choosing subjects with *DSM*-defined schizophrenia would be too narrow because it could limit variance in mechanisms that cut across other psychotic disorders or related subclinical manifestations, and limit understanding of the range from function to dysfunction. An RDoC perk is that recruiting for a full range of a dimension may ease recruitment demands that often burden patient recruitment for studies based on narrowly defined diagnoses. For experimental clinical trials, targets relevant to a specific clinical problem irrespective of *DSM*-defined disorders can be studied. RDoC studies can zero in on a single clinical problem such as suicidal behavior or hallucinations to clarify various associated mechanisms. With RDoC, a treatment target may be relevant for only a subset of patients within a single *DSM* disorder or may be relevant to patients from seemingly disparate *DSM* disorders.

Independent and Dependent Variables

Another unique feature of RDoC is that elements of the matrix may serve as either dependent or independent variables. For instance, the independent variable used to classify experimental groups may be based on a unit of analysis such as gene variants, a neural circuit response to a salient stimulus, or performance on a behavioral assessment task. Depending on the study design, each of these could alternatively be a dependent variable. Diagnoses or disorders based on current clinical nosologies such as the *DSM* are not appropriate independent variables.

Diagnosis, Treatment, and the Future

RDoC offers a new framework to guide psychopathology research to better connect

knowledge from integrative neuroscience and mental disorder symptoms than is presently possible. Ultimately, the RDoC project aims to improve patient care by informing the development of future nosologies for mental illness that will allow better targeted treatments to be developed, leading to more improved effectiveness than current diagnostic approaches permit. By clarifying connections among brain–behavior systems, RDoC will provide a means to alleviate the human suffering that happens when things are not working properly. In this manner, RDoC will lay the groundwork for personalized psychiatric treatment through identifying specific neurobiological and behavioral dysfunctions to match treatments to specific mechanisms.

RDoC places a premium on transparency. Its development relies on interaction with the scientific community. Peer-reviewed research is critical to empirically guide the development of RDoC. The peer review process for research funding will also play an important role. At this stage, it is too early to tell how long this undertaking will take, or to portend the future structure of RDoC as the project advances. Regardless of the eventual form it takes, RDoC lays out a road map to guide research whose results could ultimately improve our ability to effectively treat those suffering the devastating consequences of mental illness.

SEE ALSO: Clinical Utility; *DSM-III* and *DSM-III-R*; Kraepelin, Emil (1856–1926); Robins, Eli (1921–94)

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