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The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics

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Abstract

This article describes the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative. The description includes background, rationale, goals, and the way the initiative has been developed and organized. The central RDoC concepts are summarized and the current matrix of constructs that have been vetted by workshops of extramural scientists is depicted. A number of theoretical and methodological issues that can arise in connection with the nature of RDoC constructs are highlighted: subjectivism and heterophenomenology, desynchrony and theoretical neutrality among units of analysis, theoretical reductionism, endophenotypes, biomarkers, neural circuits, construct "grain size," and analytic challenges. The importance of linking RDoC constructs to psychiatric clinical problems is discussed. Some pragmatics of incorporating RDoC concepts into applications for NIMH research funding are considered, including sampling design.

Descriptors: Research Domain Criteria, Psychopathology, Psychometrics, Biometrics, Hypothetical constructs, Diagnostic and Statistical Manual, National Institute of Mental Health

Background

Biological Promise Unfulfilled

Despite major advances in the methods and findings of central nervous system (CNS) research in recent years, neuroscience has done little to advance the prevention and cure of mental illness. This is not for lack of trying. Research since the "decade of the brain" has overflowed with attempts to develop a biological understanding of psychopathology and its remediation. However, this has not yielded enough knowledge about mechanisms for the emergence or maintenance of psychopathology to support prevention or cure. Furthermore, genetics and neuroscience research findings have not mapped well onto mental illness diagnoses, such that no satisfactory theory of the pathophysiology of mental disorder has emerged. The National Institute of Mental Health (NIMH) Research Domain Criteria initiative reflects one perspective on what accounts for this failure and constitutes a radical attempt to improve the situation.

One view of why biologically oriented research has failed to yield satisfying results on mental illness is that its powerful investigative techniques are being aimed at mental illnesses that are inadequately conceptualized, such that even the most sophisticated methods have little chance of success. An extreme form of this view is that the putative disorders to be understood are actually "fictive" in that the psychiatric diagnoses do not refer to actual illnesses. An alleged culprit takes the form of the diagnoses in the American Psychiatric Association's *Diagnostic and Statistical Manual* (APA, DSM) and its European counterpart, the *International Classification of Diseases* (American Psychiatric Association 2000; World Health Organization, 2007). These nosologies evolved from a tradition of diagnosis by clinical consensus about observations of patient-reported and clinician-observed behavioral clusters, symptom course, and associated features. By this method, diagnoses were constructed and refined over intermittent iterations of the manuals to constitute the formulations of mental illnesses that are now targets of investigation by contemporary biology. These diagnoses can be seen as hypothetical psychological constructs, that is, theoretical concepts, linked to stipulated observations about behavior. Presumably, if a diagnostic construct refers to some real illness, it is the reality of that illness which accounts for why the observations fit together according to the concept. If a hypothesis is false, the stipulated observations will not obtain as predicted because the supposed illness is not operating as hypothesized. That is to say, the construct is spurious, and its disease referent does not exist as theorized. According to this perspective, many attempts to understand the biology of mental illness have been misdirected at spurious diagnostic entities, such that opportunities for success have been inherently limited.

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Difficulties of Diagnostic Validity

Contemporary papers on nosology sometimes observe that the five phases outlined by Robins and Guze (1970) for establishing diagnostic validity in psychiatry (clinical description, laboratory studies, delimitation from other disorders, follow-up studies, family studies) have failed to stand the test of time, given the increasingly noted difficulties. However, Robins and Guze explicitly stated that disorders failing validation by their steps need to be reconceptualized, as shown by their conclusion that it was possible to separate poor prognosis from good prognosis cases of schizophrenia (with the latter seen as a different illness—a formal distinction that has been lost in the DSM-IV system). The problem, rather, is that the DSM-III categories prematurely became reified and seen as real disease entities (Hyman, 2010). There is thus an a priori assumption that the diagnoses refer to real disorders, with ensuing assumptions that they involve a unitary pathophysiology and psychopathology and that the task of a science of disorders is to find the underlying biology of the specific disease entities. Because the three interrelated assumptions now appear to be false, it is not surprising that these approaches have failed to produce significant advances in understanding or treating mental disorders.

Limitations to the validity of conventional diagnoses have been widely recognized (e.g., Regier, Narrow, Kuhl, & Kupfer, 2009; Sanislow et al., 2010). At least some of the problem rests on the very structure of the classification rules. A fundamental aspect of the DSM rubric is that most of the diagnoses derive from sets of symptoms that are individually neither necessary nor sufficient to indicate the disorder. Accordingly, although each individual with a given diagnosis must possess a minimal number of indicative symptoms, no particular subset of these must be found in everyone with that diagnosis. The upshot of this polythetic method of definition is that individuals with widely different characteristics can fall within a single diagnostic class. A reciprocal issue is that the defining symptom lists for different disorders overlap substantially, so that individuals with different diagnoses can share many symptoms.

The two above-mentioned structural aspects pose serious difficulties for attempts to validate diagnostic constructs of this kind. Demonstrating construct validity requires evidence for both convergent and discriminant validity, but the polythetic and overlapping criteria of the diagnostic rubric militate against such demonstrations. For convergent validity, diagnostic indicators hypothesized to be associated must in fact be found to be correlated. In a polythetic system, it is not necessarily hypothesized that all the indicators in the criterion set will co-occur, so substantial symptom heterogeneity is inherent to the construct. Because of this, correlative relationships among symptom indicators that are required for convergent validity will necessarily be limited. For divergent validity, indicators of diagnostic constructs hypothesized to be distinct should in fact be unrelated. However, the use of overlapping sets of criterion symptoms for different diagnoses will yield positive relationships among measures of what are supposed to be distinct diagnoses.

The framers of the third edition of the DSM, which served as the template for subsequent editions, were well aware of this situation. As they noted, a "misconception is that all individuals described as having the same mental disorder are alike in all important ways. Although all the individuals described as having the same mental disorder show at least the defining features of the disorder, they may well differ in other important ways that may affect clinical management and outcome" (APA, 1980, p. 6). While one might reasonably expect that considerable research into diagnostic heterogeneity would have ensued from this statement, the field's perception of disorders rapidly evolved into one of reified categories; as a result, subsequent studies were largely oriented around the implicit assumption of homogeneity and specific biological etiologies (e.g., Hyman, 2010).

Complexity, Granularity, and Dimensionality

Inherent weaknesses in the prevailing diagnostic rubric seem not to be the only obstacles to advancing the contributions of biology to psychopathology and treatment of mental illness. Even if one were to grant the validity of the available diagnostic categories, it is unwarranted to assume that complex higher-order psychological constructs will map simply onto narrower biological mechanisms of psychopathology. Such mismatch in "granularity" can be expected to impede efforts to relate disparate biological and psychological phenomena. Accordingly, simpler, or "lower order," phenomena that mediate clinical problems but are not themselves end-state clinical symptoms, would seem more likely candidates for biological elaboration. Somewhat narrower psychological constructs such as cognition, emotion, learning, memory, motivation, and perception might be more susceptible to biological analysis than depression, mania, and schizophrenia. But perhaps such narrower constructs are still too broad for practical purposes, and *explananda* of even smaller grain size might be required for informative cross-level analyses of biological and psychological phenomena.

The categorical nature of traditional psychiatric diagnosis affords some simplicity that is desirable for communication and decision making, but "cuts both ways." It is not obvious that psychopathology is all-or-none or even discontinuous in severity, or that the stipulated cut points of traditional diagnostic schemes delineate natural kinds. In fact, an increasing number of commentators hold that dimensionality is integral to common mental disorders, and to an underappreciated degree in serious mental illness (e.g., Johns & van Os, 2001; Krueger & Markon, 2011). Issues regarding the categorical nature of diagnoses and overlap among them were acknowledged by the authors of DSM-III (as was the issue of disorder heterogeneity noted above): "In DSM-III there is no assumption that each mental disorder is a discrete entity with sharp boundaries (discontinuity) between it and other mental disorders, as well as between it and No Mental Disorder" (APA, 1980, p. 6). Unfortunately, the research prompted by DSM-III attended almost exclusively to the categorical nature of the system, rather than explicating the quantitative versus qualitative aspects of psychopathology.

The categorical approach does not code severity conveniently: Problems of mild severity tend to be disregarded or conceptualized as risk factors. Alternatively, the severity dimension has been accommodated via subcategories without associated quantitative criteria, such as the "with poor insight" subcategory in the DSM-IV criteria for obsessive-compulsive disorder. Categorical diagnoses can drive categorical methods of data analysis that unnecessarily ignore variability at the expense of statistical power and experimental sensitivity. This would constitute an extreme case of unwarranted assumptions constraining or distorting results. In general, if linearity is assumed of nonlinear data and inadequate analytic methods are applied, nonlinear relationships are likely to go undetected. Analogously, if unwarranted categorical assumptions determine categorical analyses of dimensional data, fundamental misunderstanding of the phenomenon is likely to result.

An attractive feature of a dimensional approach to psychopathology is that cut points can be stipulated precisely along the

dimension of interest to define mild, moderate, and severe dysfunction. This capability could mitigate unwarranted all-or-none presumption and accurately reflect dimensional phenomena that have been increasingly related to psychopathology, for example, with respect to anxiety and elevated and depressed mood (Clark & Watson, 1991; Helzer et al., 2008). Another advantage is that mild symptoms can be clearly represented as such, perhaps supporting greater attention to subsyndromal problems in and of themselves in addition to their status as risk factors. This could obviate odd categorical disjunctions that obscure the continuity of distress and the predictive value of mild severity for subsequent severe pathology (Kessler et al., 2003). In addition, cut points on accurately measurable dimensions might be more readily amenable to adjustment from new data than qualitative categories based on counts of polythetic symptom markers.

The predominant current approach to studying psychopathology proceeds from a diagnostic system based on relatively informal clinical intuition about the clustering of presenting symptoms—as opposed to dimensional structures built from empirically demonstrated correlations and factor analyses (e.g., Clark, 2005; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Watson, Gamez, & Simms, 2005). This system has provided diagnostic reliability and descriptive utility, but has not led to satisfactory biological elaboration of the diagnostic constructs. Certainly, simple relationships between biological events and hypothesized diagnostic categories have not emerged. Also, more complex and subtle relationships between genetic and neural phenomena and mental illness have been elusive. In response to this situation, the NIMH seeks to promote an approach to research on psychopathology that will circumvent some of the problems that proceed from reliance on the mainstream diagnostic systems. The Research Domain Criteria (RDoC) initiative is intended to advance this goal.

RDoC Goals

In essence, the RDoC initiative is an NIMH effort to promote the development of an interdisciplinary science of psychopathology that consists of dimensional constructs integrating elements of psychology and biology, especially genetics and neuroscience. The RDoC initiative is not a classification system in the traditional sense. Rather, it is a template for psychopathology research. RDoC is a framework intended to reflect the NIMH Strategic Plan articulated in 2008. Objective 1.4 of this plan is to "implement, for research purposes, a classification system based upon dimensions of observable behavior and neurobiological measures" (http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml). The sense in which RDoC approaches this goal is not in the guise of a fully formed classification system with a priori categories (or dimensions) whose clinical utility is then evaluated, as in the classic manner of DSM and ICD field trials. RDoC offers no a priori rules for classifying disorders and does not purport to address all presenting clinical problems. Rather, the equally (or perhaps more) ambitious aim is to elaborate a set of psychological constructs linked to behavioral dimensions for which strong evidence exists for circuits that implement these functions, and relate the extremes of functioning along these dimensions to specified symptoms (i.e., impairment). Thus, the hope is that these constructs can contribute to explaining practical clinical problems. If the RDoC initiative is successful, its theoretical and empirical issue would inform extant classification systems, or perhaps, its products would themselves evolve into such a scheme. That is, in future, mental illness might be considered largely as problems in psychological and related neurobiological systems, rather than as consensually organized clinical phenomena.

The RDoC initiative advocates (a) the development and validation of dimensional constructs that (b) integrate elements of psychology and biology that (c) are theoretically linked to narrowly defined impairments of psychiatric clinical importance. The RDoC initiative is intended to uncouple research questions from traditional diagnostic categories that are of limited validity and/or that are too heterogeneously large for productive validation against biological phenomena of smaller granularity.

Several principles differentiate the RDoC approach from conventional psychiatric nosologies. RDoC takes a translational, dimensional approach to defining psychopathology. Rather than seeking to validate a putative diagnostic category, the RDoC approach seeks biological elaboration of intermediate psychological constructs, to yield biopsychological explanations of clinical problems. These hypotheses take the form of "process" constructs that incorporate biological and psychological elements. Accordingly, psychological processes, such as reward seeking, fear, or memory, would be elaborated biologically and linked theoretically to one or more clinical dimensions. The clinical phenomena to be explained must be narrower than most traditional diagnostic entities or concepts but are not detailed or stipulated in the RDoC template. The intent is to free investigators from heterogeneous nosological categories so that individual symptoms or very homogeneous symptom sets can be objects of explanation. It is not a goal of the RDoC initiative to provide a non-DSM list of "interesting" or "acceptable" symptoms or symptom clusters to be studied, but rather to describe an approach to formulating and evaluating explanatory hypotheses for clinical phenomena that psychopathologists estimate are ripe for biopsychological explanation.

From the RDoC perspective, psychopathology, or "biopsychopathology," eventually might be conceptualized as extremes on psychobiological dimensions that are linked to narrowly determined (in the sense of homogeneity of mechanism) clinical problems. In principle, such deviations could occur at either end of the distribution of a phenomenon of interest. For example, abnormal responses to threat might involve either excessive fear or pathological fearlessness, contributing to phobic or psychopathic clinical phenotypes (Patrick & Bernat, 2010). Alternatively, reward motivation may be excessive, contributing to substance abuse or gambling (O'Brien, 2009), or deficient, contributing to anhedonia (Treadway & Zald, 2011) or anorexia.

Whereas some of the frustrating progress of biological psychiatry may be attributed to the weakness in the DSM categories, other options are available. The methods of classical psychometrics and of item response theory were specifically designed to develop and evaluate theoretical constructs for the purpose of explaining behavior. These constitute sophisticated techniques for construct development and validation, abetted by standards of quality for measurement. Established integrative disciplines such as behavioral neuroscience, psychophysiology, and psychophysics have long utilized psychometric techniques in conjunction with physical and biological measurement to develop and evaluate constructs that are not exclusively psychological or biological. It stands to reason that the same methods could support the integration of psychopathology, neuroscience, and genetics.

Organization

An internal workgroup was created to pursue the NIMH goal of formulating a better framework for psychopathology research. This

workgroup spent considerable time discussing how to organize a provisional scheme and agreed on the desirability of a dimensional multidisciplinary approach, consistent with the statement of Objective 1.4 and its subgoals. The dimensions and measurement classes of interest were less obvious. Eventually, the group decided to try to identify a small set of hypothesized mechanisms, for example, fear, working memory, for behavioral problems that seemed especially promising for biological elaboration and that could illustrate a practical approach to integrative psychopathology.

The workgroup adopted two explicit requirements for a construct to pass muster as especially promising for RDoC purposes. First, there had to be persuasive evidence, on the basis of prior studies from multiple laboratories, for the validity of the construct; and second, there had to be evidence for a neural circuit or system that implements the psychological function described by the construct. In addition to these two explicit criteria, there was also an informal implicit requirement: An RDoC construct had to be linkable to some psychiatric clinical phenomenon. The intent was that most RDoC studies (as with DSM-oriented projects) would focus on areas of mental illness that represent the Institute's core priorities, including (but not limited to) psychotic disorders, autism, or mood/anxiety disorders. RDoC should be viewed as an attempt to accelerate progress in these areas by a shift in experimental approach, rather than a distraction that diverts resources to irrelevant or arcane topics.

Initially, the number of constructs to be enumerated and the relationships among them were unknown. After some deliberation, the workgroup decided to organize constructs that had been proposed into five domains within which individual constructs could be grouped. These domains were Arousal/Modulation, Cognition, Negative Valence, Positive Valence, and Social Processes. A variety of literatures suggested this scheme. This domain framework was intended to be an organizational heuristic that reflected current thinking (in broad strokes) regarding the organization of the nervous system.

Arousal and regulatory processes (the latter referring to systems that serve modulatory or restorative purposes) are central to all aspects of adaptive behavior, and effective orchestration of multiple systems is required for optimal functioning (e.g., Jones, 2005). Cognition is an obvious area, given the disabling impairments seen in many disorders and the traction provided by recent decades of cognitive neuroscience. Not coincidentally, the RDoC effort was modeled after the NIMH-sponsored project on Cognitive Neuroscience for Translational Research in Cognition in Schizophrenia (CNTRICS; Barch, Carter, Arnsten, Buchanan, & Cohen, 2009). CNTRICS involved a series of conferences to identify translational, circuit-based measures of various cognitive dimensions that could serve as targets for new treatments of schizophrenia, and the organization of this effort informed the RDoC initiative.

Multiple strands of research on childhood temperament, adult personality, and structural models of common disorders (e.g., Clark, 2005), point to Negative and Positive Valence as domains of interest. The term *valence* was adopted to code the gist of the threat and reward concepts without usurping related concepts of positive and negative motivation, and without connoting subjectivism. Social processes are self-evidently important for almost all mental disorders, and increasing traction in studying neural circuits for social behavior has occurred over the last several years. The constructs defined within each of these domains are addressed below.

In addition to identifying especially promising constructs for biological elaboration, the internal NIMH workgroup sought to identify classes of measurement that could constitute the multiple levels of analysis that would enrich the constructs. "Talk of analytical or explanatory levels is rampant throughout the literature of the cognitive and neural sciences, but systematic characterizations, let along precise ones, are rare" (Hardcastle, 1996, cited in McCauley, 2007, p. 125). It fell to the internal NIMH workgroup to provide some kind of systematic practical guidance about analytic units of interest. Toward this end, the group considered units of measurement often employed in psychopathology research in various disciplines and compiled a list of levels that could contribute to elaboration of the constructs. The suggested units were gene, molecule, cell, circuit, physiology (added for measures such as heart rate or cortisol that are not direct measures of circuits per se), behavior, and self-report. The hope was and is that data from multiple units of analysis can lead to richer explanations of clinical psychiatric problems. Such mechanistic explanation would involve determination of the components of an operative system, how the components interact, and how the system interacts with other systems and the clinical phenomena to be explained. The desired elaboration of RDoC constructs would involve the development of hypotheses about relationships among phenomena at various levels of analysis that converge upon the constructs.

To depict the proposed conceptual organization of constructs and levels of analysis, the internal workgroup mapped them onto a two-dimensional grid, with domains and their constructs marking rows in the leftmost column, and the levels of analysis heading the columns. The cells at the intersection of the rows and columns were to be populated by actual findings from each level that converged upon each construct.

Once the internal workgroup had provisionally identified a list of constructs and levels of analysis and depicted them in the form of a two-dimensional matrix with empty cells at the intersections of the rows and columns, it convened meetings of extramural scientists selected for their expertise in each domain area and representing scientific subdisciplines for the various levels of analysis. In each workshop, the participants were charged with evaluating the domain organization proposed by the NIMH internal committee and identifying published findings that converge upon the constructs that appear in the matrix. In other words, the workshop participants were charged to evaluate the skeletal matrix proposed by the NIMH internal workgroup, and to populate the cells of the matrix with findings at each level of analysis for which findings were available.

Importantly, the constructs within any given domain show a variety of overlaps in the functions and circuits involved; thus, the domains themselves can be viewed as overarching constructs. Given these considerations, the RDoC workshops were organized around each domain so that overlaps and distinctions among constructs would be considered. Each workshop involved approximately 40 participants, chosen to encompass a variety of disciplines; basic, translational, and clinical areas; developmental expertise; and different scientific areas of focus within the domain. A starting point for discussion was the provisional list of constructs that the RDoC internal workgroup had previously identified, and conferees were charged to recommend additions, deletions, or modifications of constructs as they saw fit. However, the conferees were asked to adopt the same two criteria for adding a construct that had been used by the NIMH internal workgroup: first, strong evidence for the validity of the psychological construct and second, evidence for a neural circuit or system that implements the psychological function.

Five separate domain-specific RDoC workshops were conducted between February 2011 and June 2012. Proceedings of each

v. 5.1, 07/15/2012	RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social Communication								
Perception/Understanding of Self								
Perception/Understanding of Others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

Figure 1. Leftmost column indicates provisional list of promising explanatory constructs, grouped by domain. Remaining column headings indicate suggested measurement units, except that rightmost heading indicates measurement procedure ("paradigms"). Suggested elements at the intersection of constructs and measurement elements can be found at http://www.nimh.gov/research-funding/rdoc/research-domain-criteria-matrix.shtml

workshop were drafted by the RDoC internal workgroup members on the basis of notes and transcripts from the workshops, and posted on the NIMH website (http://www.nimh.nih.gov/research-funding/rdoc/index.shtml).

Constructs

Figure 1 shows a two-dimensional grid depicting the research domains, constructs, and levels of analysis that were identified by the NIMH internal workgroup and the conferees in the RDoC workshops. The participants at each workshop also identified research findings to populate many cells of this matrix. Such populated matrices can be found at the NIMH RDoC site listed above. As can be seen in the figure, and as noted above, five organizing research domains were identified: negative valence, positive valence, cognitive systems, social processes, and arousal/regulatory systems, each of which subsumes several constructs. Discussions of each of the constructs and relevant evidence are available in the proceedings of the workshops via the NIMH RDoC website listed above, and the concepts will be outlined only briefly here.

Negative Valence

Initially, the RDoC internal workgroup identified three provisional constructs in the negative valence domain, but the workshop conferees suggested five constructs that were adopted for the RDoC matrix. These constructs involve responses to acute threat, potential harm, sustained threat, frustrative nonreward, and loss. Response to acute threat involves a defensive motivation system that drives behavior to protect against imminent harm, either exteroceptive or interoceptive. Potential harm is more ambiguous, distant, or uncertain than acute threat. Responses to it involve increased vigilance pursuant to enhanced risk assessment and are qualitatively distinct from those to acute threat. Sustained threat may be actual or anticipated. Responses to sustained threat tend to persist absent the threat and can be distinguished from responses to acute threat. Frustration occurs in response to prevention or withdrawal of a reward, especially after repeated or sustained effort. Loss is deprivation of a desired object or situation, social or nonsocial, episodic or sustained.

Positive Valence

The NIMH internal workgroup suggested three constructs to the conferees, who recommended five constructs: approach motivation, initial responsiveness to reward, sustained responsiveness to reward, reward learning, and habit. Approach motivation is a multicomponent construct including subprocesses of reward motivation, effort valuation, expectancy, and action selection: (a) Reward motivation is the computation of probability and benefit of a potential outcome, involving external information, biases, and deprivation states; (b) Effort valuation is the computation of the cost of obtaining a

potential outcome; (c) Expectancy is a state of reward-probability prediction; and (d) Action selection is the evaluation of costs and benefits in the context of multiple potential choices. Initial responsiveness to reward attainment is the initial activation of hedonic responses to a positive reinforcer, whereas sustained responsiveness to reward attainment is the activation of consummatory responses at the termination of reward seeking. Reward learning is the acquisition of information about stimuli and actions that predict rewards, and the modification of this stored information when expectations are violated. Habit is a pattern of repetitive cognition or motor behavior that, once initiated, can proceed to completion without constant attention.

Cognition

Research that has analyzed cognition into component parts suggests potential building blocks for theories of disrupted cognition in psychopathology. The components provisionally identified by the NIMH internal workgroup for the cognitive systems domain were attention, perception, working memory, declarative memory, language, effortful cognitive control, and working memory. The workshop participants found these defensible and agreed on the following formal definitions. Attention refers to processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes, and motor action. Perception refers to computations that construct and transform sensory data representing the external environment. Working memory is the active maintenance and updating of goal-relevant information in limited capacity and with resistance to interference. Declarative memory is the encoding, consolidation, storage, and retrieval of information about events, and provides an essential foundation for representations of relations among events (episodic memory) and the organization of knowledge (semantic memory). Language is a system of shared symbolic representations and abstract concepts that supports thought and communication. Effortful cognitive control is the modulation of other cognitive and emotion systems in the service of goal-directed behavior absent adequate preexisting modes of responding, and in novel contexts that require selection among competing response alternatives. Overall, cognition is a domain that intersects with other constructs in the RDoC scheme, and the foundational cognitive components identified will bear elaboration in relationship to those of other research domains in the RDoC matrix.

Social Processes

The social processes domain workshop yielded four constructs, with several subconstructs: affiliation and attachment, social communication, self-perception and understanding, and other-perception and understanding. Affiliation is engagement in positive social interaction, whereas attachment is affiliation consequent to social bonding. Both require social motivation, attention to social cues, and attendant social learning. Social communication is a dynamic process that includes receptive and productive exchange of socially relevant information. It is distinguishable from other cognitive functions such as attention, control, memory, and perception in that it necessarily entails social interaction. Four subconstructs of social communication are proposed, involving reception and production of facial and nonfacial expression. Receptive aspects may be implicit or explicit, including affect recognition, facial recognition, and characterization. Productive aspects include eye contact, expressive reciprocation, and gaze following. Self-perception and understanding are cognitive or emotional states or traits such as self-awareness, monitoring, or knowledge. Subconstructs are (a) agency — recognition of self-origin of thoughts and actions and self-body recognition; and (b) self-knowledge — judgment about current cognitive emotional states or traits. Other-perception and understanding involves representations of other animate entities, including their cognitive or emotional states or traits. Subconstructs are (a) animacy perception—detection of another's face, agency, and biological motion; (b) action perception—detection of purposeful action of another animate entity; and (c) understanding mental states—inferences of beliefs, intentions, emotions, or desires of another that supports prediction of behavior.

Arousal

The arousal domain was subdivided into three constructs: arousal, circadian rhythms, and sleep/wakefulness. Arousal is a dimension of sensitivity to external and internal stimuli and facilitates interaction with the environment according to context. It can be evoked by external or internal stimuli and modulated by their physical and symbolic characteristics and regulated by homeostatic factors. Circadian rhythms are endogenous self-sustaining oscillations that organize the timing of biological systems. They are synchronized by recurring environmental cues and modulate homeostasis in the brain and other tissues and organs. Sleep and wakefulness are endogenous behavioral states that reflect coordinated changes in the dynamic functional organization of the brain. Homeostatic and circadian processes regulate the propensity for wakefulness and sleep. Sleep is reversible and typically characterized by postural recumbence, behavioral quiescence, and reduced reactivity. It has a complex architecture with predictable cycling of nonrapid eye movement (NREM)/rapid eye movement (REM) states or their developmental equivalents, which have distinct neural substrates and EEG oscillatory properties. Its intensity and duration are affected by homeostatic regulation and are affected by events during wakefulness. It has restorative and transformative effects that affect neurobehavioral functions during wakefulness. During the arousal/regulation workshop, a default mode network construct was also considered. This was conceptualized as an organized, intrinsic network of neural activity that is modulated during attention-demanding cognition. However, this was not as well developed as the other arousal domain constructs and is not currently included in the RDoC matrix.

Theoretical and Methodological Issues

The RDoC project departs markedly from prior nosologies in many respects. It is thus not surprising that there are many topics that must be considered in order to proceed down this newly platted road. In this section, we consider several of the major issues that ensue from the novel pathways. The first and most salient issue involves a set of theoretical topics that arise in considering the nature of the constructs in RDoC—the dimensions that comprise the heart of the "classification" effort.

Subjectivism and Heterophenomenology

One issue is how the various units of measurement bear upon any particular construct. Integrative constructs that engage multiple levels of analysis involving biological and psychological subdisciplines are not novel with the RDoC initiative. The field of psychophysiology, for example, has grappled with some theoretical and methodological challenges in this regard that seem likely to resurface in attempts to develop a multidisciplinary

psychopathology. An example from the psychophysiological study of fear might inform efforts to develop and elaborate RDoC constructs.

As the RDoC initiative seeks to elevate the contributions of biological subdisciplines, such as genetics and neuroscience, to psychopathology, a multisystems approach to assessing fear elevates biological measures to the importance of overt behavioral and self-report variables in measuring emotion. This view contrasts starkly with a subjectivist tradition that regards phenomenal experience as the primary *explanandum*. According to this tradition, subjective experience is the quintessential feature of an emotion, such as fear, and indicators such as behavior and physiology are taken to indicate this phenomenal state. This Cartesian dualism entails a logical conundrum: An oft-assumed inherent privacy of subjective experience renders it necessarily insusceptible to scientific measurement. Conceptualizing fear (and other emotions) as hypothetical constructs that are subject to convergent validation has been a useful way of circumventing the assumption that emotional experience simply cannot be studied empirically.

An alternative to subjectivism is the view that self-reported experiences have the logical status of fallible hypotheses about the functioning of the reporter (Kozak & Miller, 1982; Miller & Kozak, 1993). Accordingly, experiential claims represent a kind of "folk" psychology of the self that should be neither assumed veridical nor simply discounted. (Dennett termed his somewhat similar but more developed 1991 formulation "heterophenomenology.") Consistent with this view, the RDoC approach accords self-report data no special precedence among different measurement classes, any of which might contribute to a nomological net.

An early methodological exemplar of this heterophenomenological approach is the classic "three systems" view (Lang, 1968) that conceptualizes fear as a hypothetical entity that is measurable by three converging measurement classes: self-report, behavior, and physiology. A critical observation that emerged from three systems assessments is that measures in the different systems can be demonstrated to co-vary, but only modestly (Lang, 1968; Lang, Bradley, & Cuthbert, 1997; Rachman & Hodgson, 1974). In other words, a strong correlation among putative measures of a construct forms a nomological net that evidences construct validity, but measurements in various response systems related to fear evince weaker relationships than one would hope, even for such an apparently fundamental motive state as fear.

Desynchrony Among Units of Analysis

Observed modest covariation among measures of fear across multiple units of analysis presents theoretical and practical *conundra* (Kozak & Miller, 1982; Miller & Kozak, 1993). If fear is not a unitary phenomenon that is indicated by a single defining feature like self-reported subjective states of fear, or even by a collection of multilevel measures that co-vary strongly, how is fear to be inferred? One can envision a similar problem arising with various multidimensional constructs developed in pursuit of RDoC for psychopathology.

How can one develop rules of inference for the presence of fear, or for that matter, any dimensional construct of psychopathology in the face of modest covariation in the very measures that must converge to validate a hypothesized construct? This is not an idle philosophical question, but a crucial problem of inference that seems almost certain to arise in research pursuant to the RDoC aims. Refining RDoC constructs in a way that advances the ultimate goal of classification will likely require continual reevaluation of data and theory, in a kind of "bootstrapping" (Cronbach & Meehl, 1955). In other words, the goal is not simply to identify indicators from various measurement classes, but to elaborate the RDoC construct itself (Patrick et al., 2013). In some cases, relationships will be weaker at moderate levels of a dimension, only becoming stronger as level (e.g., fear intensity) increases. In other cases, different factors might come to bear, such as environmental context, fatigue or temperature, and elusive variations in assessment parameters. In the case of fear, the relative degree of activation of various physiological measures depends on the *perceived* proximity of threat, which is imperfectly correlated with actual physical proximity; some measures increase linearly as threat increases, while others may show a nonlinear response (Lang, Davis, & Öhman, 2000). One might ask how a researcher could know if a given measure is related to a construct of interest. This could be approached in the same way that one evaluates any theoretical proposal, that is, empirically. In other words, the answer would depend on whether the available data comport with the theoretical concept and whether that fit survives various means of convergent validation.

Theoretical Neutrality of Units of Analysis

A topic related to the problem of imperfect covariation of measurement classes is the theoretical relationship of various measurement classes to any particular construct. RDoC dimensional constructs are intended to be integrative, rather than reductionistic. In no small part, this reflects an explicit emphasis on psychological hypothetical constructs (MacCorquodale & Meehl, 1948). In the DSM, the polythetic criteria suggest that symptoms are largely construed as indicators of an underlying disorder; in RDoC, the different units of analysis that are theoretically linked to each construct are seen as important in their own right, in that these units reflect dimensions whose dysregulation constitute impairments that mediate clinical problems. This approach to formulating constructs means that measurements on any particular dimension—whether physiological, behavioral, or verbal—take no a priori theoretical precedence over the other dimensions for defining or measuring the construct. The goal is to develop and evaluate and refine a nomological net that converges on the construct (Cronbach & Meehl, 1955). All measurement classes are potentially relevant in examining the role and functioning of the constructs. (The RDoC internal workgroup's aphorism for this idea was, "Behavioral science studies what the brain does, and neuroscience studies how the brain does it"; both are essential to an understanding of adaptive functioning.) This consideration constitutes a major postulate of the overall RDoC framework, consistent with the goal of promoting an integrative, rather than a reductionist, approach (Bechtel, 2007; Wright & Bechtel, 2007).

Although, as mentioned above, the RDoC guidelines accord no a priori theoretical precedence to any particular unit of analysis, they do advocate multiple measures that include biological variables. From the RDoC perspective, one would not seek to explain self-reported thoughts or feelings on the assumption that they are veridical. Rather, one might make use of the self-reports to inform hypotheses about psychobiological mechanisms (hypothetical constructs) that could be subjected to convergent validation. A challenge arises if self-report is the only available indicator of a clinical problem, such as a delusion, hallucination, or other perception. This issue for the RDoC approach has already been highlighted by Berenbaum (2013) and reiterated by Lilienfield (2014), and addressed directly by Cuthbert and Kozak (2013) and Cuthbert (2014). That RDoC constructs must necessarily involve biological processes reflects the RDoC goal of elevating the contributions of biology to an integrative science of psychopathology, and does not imply that self-report measures alone

have no validity or utility. In fact, they have often been found to be better predictors of clinical problems than any available alternative (Chapman, Chapman, & Raulin, 1976: Heaffel et al., 2008; Kwapil, 1998). Idiosyncratic interpretations can contribute to behavioral problems, and self-report is sometimes the most efficient, or the only way, to assess them. Furthermore, subjective perception of a situation can sometimes be a better predictor of behavior than the objective details of that situation (Cotton, 1980). The RDoC template offers no elegant solution to these methodological problems, leaving investigators to adopt expedient working assumptions about the referents of self-reports.

Reductionism and Emergent Phenomena

The penchant of many contemporary neuroscientists for eliminative reductionism at the expense of psychological constructs is controversial (Miller, 2010). Conceptualizing the RDoC effort as integrated construct development, refinement, and validation does not comport with this kind of "greedy" reductionist position. Thus, it is not clear that ostensible identity claims (e.g., "fear is entirely equivalent to the activity of the amygdala fear-generating circuit") can be reconciled with the conceptual foundations of the RDoC enterprise, except perhaps by construing such claims more as rhetorical stances than as philosophical architecture. The recruitment of multiple units of analysis to elaborate complex constructs is antithetical to "greedy reductionism" (Dennett, 1995), in which concepts encompassing emergent properties of complex systems are to be rendered superfluous by simpler knowledge of the system's component parts. (Neuroscience is not the only offender: Dennett also directed his epithet at the ideas of B. F. Skinner.)

An alternative view that appears compatible with the RDoC framework has been offered by Bechtel and colleagues (Bechtel, 2007; Wright & Bechtel, 2007). It posits a series of hierarchically layered mechanisms. Accordingly, "psychology and other special sciences study phenomena that are outside the scope of more basic sciences but which determine the conditions under which lower-level components interact. In contrast, the lower-level inquiries focus on how the components of mechanisms operate when in those conditions" (Wright & Bechtel, 2007, p. 174). Following this formulation, higher-level sciences such as psychology would be considered autonomous and essential components of the RDoC matrix.

An additional important role for higher-level explanations in an evolving scientific enterprise such as RDoC concerns its ability (and indeed, its responsibility) to contribute substantially to increases in the understanding of complex behavioral systems. For instance, the classic Olds and Milner (1954) depiction of a brain "pleasure center" on the basis of early studies in rodents has, as a result of subsequent decades of both behavioral and brain research, been supplanted by the considerably more differentiated constructs included in the RDoC matrix under the Positive Valence domain. The importance of the prior two points as a perspective on the RDoC framework is shown by its deliberate adoption of the terms *units of analysis*, rather than *levels of analysis*, to depict the columns of the matrix. This terminological convention militates against an unintended suggestion that one measurement class is to be ignored in favor of any other measurement class.

Endophenotypes and biomarkers

An additional question arises regarding the way in which RDoC constructs, and the elements in the matrix, are viewed with respect to other terms currently used to reference features of mental disorders (and other medical illness), such as endophenotype and biomarker.

Endophenotypes were originally conceptualized as biological elements in a causal chain between genes and diseases, in hopes that the causal relationships could be ascertained because the endophenotypes are more proximal to, and more simply determined by, genetic mechanisms than are disease end points (Gottesman & Gould, 2003; Gottesman & Shields, 1972). However, the endophenotype concept has expanded to include nonbiological phenomena, such as cognition (Gould & Gottesman, 2006). Thus, RDoC constructs, which are intended to be of a manageable grain size, bridge multiple units of analysis, and constitute causal elements, share at least some characteristics of endophenotypes.

The formal National Institutes of Health (NIH) definition of a biomarker reads: "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001). Although this somewhat anodyne definition might appear at first to be compatible with RDoC constructs, there is a complication. The NIH definition stipulates that the "processes" of interest are biological, whereas RDoC constructs are not strictly biological, but rather, explicitly interdisciplinary. Of course, one might expand the definition of a biomarker to target psychobiological processes, such that it could encompass RDoC constructs. In either case, however, a biomarker search might be stymied by a false assumption of a "gold standard" biological event that is isometric with the process of interest, when in fact the process can take various forms. Although the hypothetical constructs of the RDoC matrix might seem less vulnerable to mistaken reification, a search for biomarkers of RDoC constructs could also be subject to a misplaced desire for a "gold standard."

Granularity and neural circuits

Another challenge for RDoC projects will be matching the granularity, or "grain size," of the constructs that are subject to multilevel interrogations. Overly broad constructs might invite the same sort of heterogeneity that has been described as problematic in the DSM, whereas overly narrow constructs might lack extension to clinical problems and so necessitate an excessive number of constructs to encompass the phenomena of interest. Subconstructs will probably be useful in some cases. Perception serves as an illustrative example: Within the perception construct, audition and vision are subconstructs with clear relevance to psychiatric problems. Investigations can focus on particular aspects of visual or auditory perception that are of theoretical interest for psychopathology, such as auditory language perception, auditory or visual acuity, relationships of stimulus intensity to neural response, and so forth. The RDoC matrix, however, follows a minimalist course in specifying only one "perception" construct, with the understanding that investigators will target the particular subsystem and aspects of interest.

As the example above illustrates, one important aspect of the grain-size issue involves the definition of a particular neural circuit. The visual perception system, for example, is bifurcated into the familiar dorsal versus ventral streams (broadly, for spatial orientation vs. object identification, respectively) that have differential significance for psychopathology (e.g., facial expression identification in the fusiform gyrus). Even the canonical "fear circuit" from the central nucleus of the amygdala to the pons actually comprises three distinct pathways with slightly different roles (Davis, 2006).

The definition of a particular circuit must be feasible for translational studies in clinical samples.

Beyond these grain-size questions is a more general issue of how to conceptualize a "neural circuit." Note that measures of a circuit (as a column in the matrix) must be distinguished from the particular "circuit" itself for any given construct. Because of differences across constructs in the state of the relevant science, the concepts of circuit are not entirely consistent. For example, the hypothalamic-pituitary-adrenal (HPA) axis of the sustained threat construct is not a neurally "wired" circuit, but rather a hormonal system. Also, it is not clear whether a network that is largely defined by statistical coherence in magnetic resonance imaging signals constitutes a "circuit" in the traditional neuroanatomical sense. The RDoC workgroup accommodated these divergent concepts of "circuit" on practical grounds in order not to exclude potentially important explanatory dimensions. However, as the project progresses, a more satisfactory concept of "circuit" will be desirable, perhaps as itself a hypothesized unit of functional organization, formulated to account for various observations, and subject to refinement in light of experimental findings.

Analytic innovation

In the methodological realm, challenges can be anticipated for attempts to develop analytic methods to support desired rules of inference. One problem is how to choose analytic methods for relating data from multiple levels of analysis and how to test whether the strength of the complex obtained relationships justifies inference to the hypothesized construct. Multilevel data can have distinctive features, such as frequency characteristics, sampling frameworks, time-series of disparate length, distributional properties, and reliabilities of measurement. For example, conceptualizing and estimating the reliability of experimental laboratory procedures, which are fundamental to the RDoC approach, could prove extremely challenging, and such estimates will be essential for evaluating the utility of newly elaborated RDoC constructs. It has been argued that laboratory measures can have "unappreciated psychometric weakness" and "often display low levels of temporal and cross-sectional consistency" (Lilienfield, 2014, p. 133).

Methods will be needed to aggregate, scale, or otherwise transform multilevel data to conform them to the statistical assumptions required for particular analytic procedures. Clustering methods that identify complex relationships among multilevel data by segregating them into coherent groupings will be required. Until such powerful analytic techniques are developed, attempts to relate multilevel data will be hampered by their absence, and data filtering and clustering algorithms, as well as inferential statistical procedures, may have to be developed de novo to accommodate each class of data to be related in RDoC projects.

Symptoms

It should be noted that a column for "symptoms" was not explicitly included in the RDoC matrix due to the emphasis upon assessing the full range of dimensionality for each construct (i.e., including the normal-range span of functioning). However, the "Self-reports" column was intended to serve this purpose where self-reports and related measures reach the point of being denoted as "symptoms." Additionally, the "Self-reports" column includes clinician ratings of patient behavior as well, for example, the assessor's ratings of patient demeanor in the Hamilton Rating Scale for Depression. In some cases, the "Behavior" column may also pertain to clinical assessment, for example, in parental reports of child behavior that are used for diagnostic purposes in such areas as attention-deficit hyperactivity disorder (ADHD).

As noted above, the NIMH RDoC workgroup employed a clinical relevance criterion for RDoC constructs, that is, that they should be relatable to particular symptoms of mental disorders. However, this link was not well explicated in descriptions of the RDoC matrix, not least because of the complex relationships between constructs and traditional psychiatric symptoms. This has resulted in some confusion. It has not been obvious where clinical problems fit into the whole enterprise, and how particular RDoC constructs relate to particular kinds of clinical phenomena. In part, this situation has resulted from the focus of a preponderance of clinical research to date upon characterizing heterogeneous DSM categories rather than explicating particular symptoms or symptom clusters (that might occur in common across categories). Thus, a major task of the RDoC enterprise is to study the dimensionality of measures in various units of analysis for a particular construct, and to determine how these measures relate to homogeneous clinical phenomena.

Some aspects of conventionally defined DSM disorders appear to map rather directly onto defined RDoC constructs and circuits, for example, excessive fear, working memory deficits, and anhedonia. However, even in these instances, any given circuit may account for substantial variance in the behavior under study, but far from 100%. In addition, not all patients will show the extent of response expected by conventional wisdom regarding a given DSM disorder. For instance, many patients with anxiety disorders and posttraumatic stress disorder (PTSD) show a blunted physiological response rather than the hyperreactivity posited by usual canonical models (D'Andrea, Pole, DePierro, Freed, & Wallace, 2013; Hopper, Frewen, van der Kolk, & Lanius, 2007; McTeague & Lang, 2012).

For other clinical phenomena, the mapping is not always obvious. Examples from schizophrenia are the symptoms of hallucinations, delusions, and cognitive slippage. The study of hallucinations (itself a complex and heterogeneous phenomenon) may begin with perceptual systems, but is likely to include acute threat, language, declarative memory, cognitive control, and social processes (Ford et al., 2014). Ways to map RDoC constructs onto delusions and cognitive slippage might be even less straightforward. However, one of RDoC's operating conventions is to focus on dysfunction in one or more behavioral and brain systems and to relate this to clinical phenomena. To explain the clinically observed phenomenon of cognitive slippage, for example, one might try to relate an RDoC cognitive domain, such as language processing, to a dimension of measured language anomalies that are customarily identified clinically with cognitive slippage. The experimental task would then be to ascertain the extent to which the hypothesized RDoC explanatory construct accounts for variance in the overt clinical phenomenon that is measured dimensionally.

There are two other aspects of the mapping between RDoC constructs and symptoms that need to be taken into account, both theoretically and empirically. First, the various symptoms for at least some DSM disorders seem to occur in coherent patterns—for instance, the familiar empirically derived grouping of positive symptoms, negative symptoms, and cognitive disorganization in schizophrenia. These symptom clusters may well represent reasonable groupings for some types of studies—for example, Genome-Wide Association Studies (GWAS) to examine whether there are distinct genetic risk architectures for each cluster—and may in some cases be usefully studied from the RDoC perspective. On

the other hand, these clusters could still represent a "grain size" issue with respect to RDoC studies, in that they are likely to be overly heterogeneous phenomena from the point of view of RDoC constructs (as was noted above for the positive symptom of hallucinations).

The second aspect concerns major dimensions of psychopathology that seem to provide an organizing rubric for broad sets of DSM disorders. A prime example concerns the often-cited analyses that organize common mental disorders into two broad factors of externalizing and internalizing, with the latter further split into "fear" and "distress" disorders (Krueger, 1999). These factors have been developed extensively with respect to the relationships between temperament/personality constructs and psychopathology (e.g., Clark, 2005; Krueger et al, 2007). Such viewpoints influenced the overall structure of the RDoC matrix, for example, the positing of a broad Negative Valence domain and the adoption of a dimensional approach to the entire framework. In both cases, however, the actual mapping of RDoC constructs to such broad concepts as positive symptoms or externalizing represents an empirical issue. Current literature indicates that psychopathology must be viewed in a hierarchical manner, with broad genetic risk factors (e.g., Cross-Disorder Group of the Psychiatric Genetics Consortium, 2013), overarching symptom clusters, and more specific impairments. It is likely that future research will profitably employ all of these perspectives, depending on the goals of the study. While some RDoC studies may focus on domain-level issues, the framework is conceived to facilitate study of circumscribed clinical problems rather than to cluster them into syndromes with larger groups of heterogeneous clinical symptoms (as with most DSM diagnoses). Thus, it invites concentration on narrowly defined complaints or impairments that might be more tractable than heterogeneous symptom clusters. For instance, Maher (2002), in an incisive review of translational issues of cognition in schizophrenia, pointed out that within the overall symptom complex of thought disorder, repetitiousness is associated with poor motor control while neologisms are not. While the empirical task of sorting out these issues is daunting, it should be noted that the research questions being posed are of a very different sort than those that have dominated the discourse over the past several decades, and are better framed to accommodate the different types and scales that are emerging from current research.

In sum, explicating the relationship of symptoms to RDoC constructs will profit both from improved communication about the research issues and from more consideration of the different scales at which clinical problems are conceived. In future iterations of the RDoC matrix, it will prove helpful to stipulate that the constructs are intended to have measurable relationships with clinical problems, as well as to map onto normal-range functioning that graduates into symptoms. One important take-home message is that considerable research is needed to create behavioral and self-report scales that reflect the constructs that they purport to measure, and that exhibit the kind of continuity across the full range that is needed for such a translational approach.

Pragmatics

The RDoC approach differs from traditional nosologies in yet another way. As mentioned above, RDoC necessarily requires empirical approaches to validating constructs and their clinical utility rather than a priori categories (or, for that matter, dimensions). For this reason, a vital aspect of the entire enterprise concerns the very different approach to grant applications that ensues from the RDoC principles. Accordingly, some of these desiderata are considered in this section.

It may be helpful to indicate first what an RDoC application would *not* involve. An application that proposes exclusively psychological or biological hypotheses and does not include measurement across multiple units of analysis would not contain all the RDoC essentials. An application that proposes only categorical analyses, even across multiple levels of analysis, would not contain all the RDoC essentials. An application that proposes to explain or validate a broad diagnostic entity (e.g., a DSM diagnostic category) would not contain all the RDoC essentials, even if it proposed dimensional assessments of psychobiological constructs across multiple levels of analysis.

The clinical phenomena to be explained in an RDoC application must be narrower than traditional diagnostic entities. The DSM enumerates many presenting problems, or "symptoms," that it organizes into putative diagnostic categories via various decision rules. An RDoC-oriented application should specify which homogeneous presenting problem or problems that it seeks to explain via a psychobiological construct, along with a theoretical account of the relationship of the explanatory construct to the *explanandum*. The presenting problem or symptom cluster to be explained might be found among those enumerated in the DSM, but this is not necessary. Attempts to explain or validate heterogeneous DSM entities would violate the RDoC principles, as would attempts to validate heterogeneous non-DSM entities. Substituting a novel heterogeneous diagnostic entity for a heterogeneous traditional DSM diagnostic entity would not conform to the RDoC approach. Aligning the granularity of the measures and phenomena to be related via multilevel analyses is an important goal of the RDoC initiative.

Although the RDoC endeavor is a high priority for the NIMH, not every submission need adopt this approach. If an application poses a research question and approach that are well justified, it could compete successfully for NIMH support even if it does not adopt RDoC concepts. However, when evaluating such applications, the NIMH will consider whether an RDoC approach would be preferable.

Only applications submitted in response to specified funding set-asides ("Requests for Application" [RFAs]) have been required to focus exclusively on one or more constructs identified in RDoC workshop proceedings. The constructs identified in RDoC workshops were deemed especially promising and exemplary for illustrating and promoting the RDoC approach. However, the vetted constructs that appear in the NIMH RDoC matrix are not intended to be exhaustive. Investigator-initiated applications submitted independently of an RDoC RFA may argue for the study of constructs that do not appear in the RDoC matrix; given RDoC's status as a research template, such applications are in fact critical to generate research that will refine the current constructs and add new ones. Applications that propose to study nonvetted constructs should describe theoretical support for the proposed construct, especially in relation to the narrow clinical phenomenon to be explained.

Although constituting study samples according to inclusion criteria that cut across DSM diagnostic categories is consistent with the RDoC approach, simply sampling across multiple disorders does not itself suffice to capture the RDoC concept. Sampling should be appropriate to the construct being interrogated and the question being asked. Because one goal of the RDoC initiative is to uncouple research questions from DSM-IV diagnostic categories, applying DSM diagnostic criteria to assemble experimental groups with DSM-defined disorders is often likely to be unsatisfactory. Instead, sampling should be designed to ensure a broad range of

scores on each dimension of theoretical and experimental interest. For example, if working memory is to be investigated, a sampling strategy that yields a broad rectangular distribution of working memory might be ideal. If the relationship between working memory and cognitive slippage is to be studied, then sampling for a range on both of these dimensions would be advantageous. If prefrontal cortical thickness is to be related to working memory and cognitive slippage, then selecting subjects to achieve a broad distribution on all three variables would be ideal.

The specific subject recruitment tactics used to achieve desired distributions along the dimensional variables to be related would depend upon the sampling goal and the available resources. One might screen many patients at psychiatric clinic to identify patients with cognitive slippage or loose associations. Alternatively, to identify individuals with anhedonia or with low-fear reactivity, newspaper advertisements might be practical. To orchestrate a broad range on a particular dimension of interest, multiple recruitment tactics might sometimes be necessary. In principle, specialty clinics (e.g., anxiety clinic, memory clinic, PTSD clinic, psychosis clinic, sleep clinic) could provide convenient concentrations of individuals with high scores on variables to be studied, but ideal dimensional analyses would require not only high scores but also low and middle scores. So, unless the variable to be studied is distributed broadly among individuals recruited from the specialty clinic, additional sources of enrollees would be needed. An obvious implication of this goal is that the selection of control subjects will in many cases shift markedly: Rather than "supernormal" subjects with no psychiatric history designed to provide maximal discrimination from a putative disease group, controls will need to represent a broad range of functioning that shades into psychopathology, so as to facilitate optimal characterization of the dimension of interest. Pragmatic limitations will routinely prevent accrual of samples with ideal distributions of characteristics along all the dimensions of interest in an RDoC project. A persuasive RDoC application will provide arguments to justify any sampling compromises that must be made.

Conclusions

We have attempted to provide a concise overview of the background and rationale for the RDoC initiative, its organization, some conceptual ambiguities, and pragmatics of implementing this new NIMH template for research on psychopathology. We have highlighted for this readership potential contributions of psychophysiology to the RDoC concepts. Accordingly, we have described the RDoC initiative as an *integrative* psychobiological approach to construct elaboration. It is readily apparent that several aspects of the RDoC framework are consistent with long-term efforts in the fields of psychophysiology and cognitive/affective science, such as dimensional assessment, multivariate and dynamical analytical approaches to multisystem data sets, and modern psychometric methods.

The RDoC project has progressed beyond a mere drawing board exercise at NIMH: As of this writing, 27 research grants have been funded under four RFAs. A set of applications submitted in response to a fifth RFA is pending review. The number of RDoC-oriented investigator-initiated applications is also rising. We expect that the dimensional, integrative approach advocated by the RDoC guidelines will continue to be a priority for NIMH research on psychopathology in the foreseeable future, and if the initiative is successful, that its products will reshape research on treatment development.

We have indicated that RDoC is intended, in its first phases, to promote the elaboration and validation of integrated psychophysiological constructs of clinical relevance, and concomitant efforts toward ancillary measurement approaches. How long could it be until the RDoC initiative fulfills its goal of informing innovative classification schemes? Perhaps such advances will be achieved stepwise, as work on newly elaborated constructs bears sufficient fruit to guide clinical trials and clinical practice. For instance, to compensate for problems with heterogeneous DSM/ICD syndromes that are too broad for the relatively specific actions of most new drugs, some RDoC concepts have been incorporated into NIMH contract solicitations for new treatment development (e.g., https://www.fbo.gov/index?s=opportunity&mode=form&id=01bd3a635f06482ea47a21736b857132&tab=core&_cview=1). Fortunately, measurements in some areas are relatively advanced, such as techniques for assessing various aspects of cognition, perception, and reward-related activity that are informed by contemporary understanding of the related neural systems. Ultimately, the yield from the results of RDoC-themed research will depend on whether those results lead to ways of classifying problems and treating patients that are demonstrably superior to current conventions.

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