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Developing Constructs for Psychopathology Research: Research Domain Criteria

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There exists a divide between findings from integrative neuroscience and clinical research focused on mechanisms of psychopathology. Specifically, a clear correspondence does not emerge between clusters of complex clinical symptoms and dysregulated neurobiological systems, with many apparent redundancies. For instance, many mental disorders involve multiple disruptions in putative mechanistic factors (e.g., excessive fear, deficient impulse control), and different disrupted mechanisms appear to play major roles in many disorders. The Research Domain Criteria (RDoC) framework is a heuristic to facilitate the incorporation of behavioral neuroscience in the study of psychopathology. Such integration might be achieved by shifting the central research focus of the field away from clinical description to more squarely examine aberrant mechanisms. RDoC first aims to identify reliable and valid psychological and biological mechanisms and their disruptions, with an eventual goal of understanding how anomalies in these mechanisms drive psychiatric symptoms. This approach will require new methods to ascertain samples, relying on hypothesized psychopathological mechanisms to define experimental groups instead of traditional diagnostic categories. RDoC, by design, uncouples research efforts from clinically familiar categories to focus directly on fundamental mechanisms of psychopathology. RDoC proposes a matrix of domains and levels of analyses and invites the field to test and refine the framework. If RDoC is successful, the domains will ultimately relate to familiar psychopathologies in ways that promote new knowledge regarding etiology and more efficient development of new preventive and treatment interventions.

Keywords: RDoC, psychopathology research constructs, research diagnoses

Currently, the predominant approaches to the classification of psychopathology include the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM–IV–TR*; American Psychiatric Association, 2000) and the International Classification of Diseases (10th ed.; ICD-10; World Health Organization, 2007). These nosologies are in the process of revision, and the anticipated revision of the *DSM* is of central consideration in this special section of the *Journal of Abnormal Psychology*. Both the *DSM* and the ICD grew out of a tradition that utilized a clinical consensus approach informed largely by clinical observation, clustering of symptoms, the course of the disorder, and other related indices. Successive editions of diagnostic manuals based on these approaches have increasingly considered empirical studies, leading to substantial improvements in the diagnostic constructs in more recent revisions. However, aspects of the original diagnoses limit their utility when trying to integrate clinically oriented findings with research based in behavioral neuroscience. Here, we describe a new effort stemming from the recently published *National Institute of Mental Health Strategic Plan*[1] (National Institute of Mental Health [NIMH], 2008), designed to provide a framework to integrate modern neuroscience and psychopathology research.

Background

Current conceptions of mental disorders have long roots in Western cultural history. The concept of melancholia, for example, goes back thousands of years to a time when the idea of four bodily humors prevailed. Notions about psychosis are more recent but still over a century old, with lineage from the distinction between schizophrenia and manic–depressive illness described by Kraepelin (1896/1987) and Bleuler (1911/1950). These fundamental outlooks on mental disorder are reflected in current psychiatric no-

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Updates on the Research Domain Criteria project can be found at its website: http://www.nimh.nih.gov/research-funding/rdoc.shtml

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[1] For the full text of the plan, see http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml

sologies, the *DSM–IV–TR* (American Psychiatric Association, 2000) and the ICD-10 (World Health Organization, 2007), and capture unique aspects of clinical presentation recognized by practitioners for decades.

As is well known, the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; *DSM–III*; American Psychiatric Association, 1980) was a departure from the loosely described categories of its predecessors, which were heavily influenced by psychoanalytically derived theory. The *DSM–III*, motivated by a strong need to improve reliability in diagnosis, achieved this goal at least partly by loosening the connection with psychoanalytic theory and by emphasizing observables. Accordingly, *DSM–III* (American Psychiatric Association, 1980) categories were defined by specific sets of criteria symptoms that were readily ascertained by outside observers, either through reports from patients or from ancillary information (e.g., direct observation, parallel history).

Although research has increasingly revealed weaknesses in this system, it and its successors have persisted. These weaknesses have been thoroughly discussed elsewhere, including other articles in this special section, and therefore need not be detailed here (see also Regier, Narrow, Kuhl, & Kupfer, 2009). In brief, however, among the thornier problems are high rates of comorbid disorders, raising questions about the core features of a specific diagnosis. How can one judge whether two "co-occurring disorders" are really separate "entities" or are simply alternative clinical manifestations of one core, underlying pathophysiological process? Thus, specifically, to what extent do co-occurring disorders share pathological mechanisms? To what extent do the problems of comorbidity reflect overlapping criteria sets? Another problem is that the categories are highly heterogeneous. Membership in categories is based on symptoms selected from larger lists ("polythetic criteria") that, by definition, will lead patients to be classified similarly even when they exhibit wide differences in the number and nature of symptoms. Unfortunately, diagnostic conventions are vulnerable to reification, in which categories may become viewed as natural kinds instead of conventional names for assemblies of related observations. When diagnostic constructs are weak, this reification can hinder progress to clarify mechanisms of psychopathology.

These problems specifically hamper attempts to integrate clinical and integrative neuroscience research, in turn limiting descriptive nosologies' ability to facilitate scientific gains through neuroscience-informed approaches (Hyman, 2008a). Although some gains have been made, psychiatric research continues to struggle to develop knowledge about the relationship of higher order clinical phenomena to their molecular corollaries. Moreover, results from the initial attempts at such integration suggest that any given disorder can be marked by disruptions among multiple mechanisms, and one particular mechanism may contribute to the psychopathology of a large number of disorders. Thus, the same mechanisms can be implicated in "different" disorders, whereas multiple mechanisms can be implicated in "one" disorder.

Dependence on conventional nosologies leaves the enterprise of understanding mechanisms of psychopathology in the awkward position of assuming the validity of single disorders and organizing research accordingly. This approach implicitly assumes that a given disorder maps onto mechanisms amenable to discovery via suitable investigations. However, it is not clear that conventional diagnoses can fulfill this role, and it may be important for researchers to develop constructs and theories that are not tightly bound to extant diagnostic conventions. Specifically, it may be necessary to deconstruct currently defined higher order clusters of complex behaviors (or subsets of these clusters) into intermediate functions that are not themselves clinical symptoms in order to understand the relationship of higher order "criterion" symptoms to lower order causal networks that include cognition, emotion, hormones, neural circuits, and their molecular pathways and structures.

Put another way, current research approaches begin with classifications based on clinical presentation. This invites researchers to seek more-or-less one-to-one relationships of putative mechanisms with current clinically defined disorder categories. However, it becomes increasingly evident that such one-to-one relationships do not exist. The question then becomes how best to advance psychiatric research that integrates higher and lower order constructs from different scientific disciplines. This problem is especially acute for the biological sciences, where major advances in understanding brain circuitry, and its genetic corollaries, have not contributed commensurately to the understanding of psychopathology, diagnosis, and treatment. Recognizing these challenges, the NIMH included in its current *Strategic Plan* (NIMH, 2008; see Insel, 2009) a goal to develop a new approach to defining constructs for integrative research purposes (see Table 1).

The motivation for Strategy 1.4 is articulated in the *Strategic Plan* as follows:

> Currently, the diagnosis of mental disorders is based on clinical observation—identifying symptoms that tend to cluster together, determining when the symptoms appear, and determining whether the symptoms resolve, recur, or become chronic. However, the way that mental disorders are defined in the present diagnostic system does not incorporate current information from integrative neuroscience research, and thus is not optimal for making scientific gains through neuroscience approaches. It is difficult to deconstruct clusters of

Table 1
NIMH Strategy and Goals Encouraging New Approaches to Diagnosing Mental Disorders to Facilitate Research Is the Foundation for RDoC

Strategy 1.4	Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures.
Specific goals	Initiate a process for bringing together experts in clinical and basic sciences to jointly identify the fundamental behavioral components that may span multiple disorders (e.g., executive functioning, affect regulation, person perception) and that are more amenable to neuroscience approaches. Develop reliable and valid measures of these fundamental components of mental disorders for use in basic studies and in more clinical settings. Determine the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological. Integrate the fundamental genetic, neurobiological, behavioral, environmental, and experiential components that comprise these mental disorders.

Note. NIMH = National Institute of Mental Health; RDoC = Research Domain Criteria.

> complex behaviors and attempt to link these to underlying neurobiological systems. Many mental disorders may be considered falling along dimensions (e.g., cognition, mood, social interactions), with traits that exist on a continuum ranging from normal to extreme. Co-occurrence of multiple mental disorders might reflect different patterns of symptoms that result from shared risk factors and perhaps the same underlying disease process. (NIMH, 2008, pp. 9–10)

At least two salient points emerge. The first is that a satisfactory classification system must integrate research about the fundamental dimensions of behavioral functioning, the brain circuits that implement them, and the genetic and epigenetic factors that shape their development. The second point, implied by the first, is that research on mental disorders depends essentially on construct development and validation. To be clear, although not always recognized as such, enduring concepts of mental disorders typically have been hypothetical constructs, whether they are based on reported experience, physiological measures, overt behaviors, or clinical observation (see Miller & Kozak, 1993). In light of the problems described earlier, we propose to change the usual approach for studying mental disorders. Rather than starting with particular disorder groups or symptom clusters, one can identify research domains that constitute specific psychological processes (e.g., stimulus-reinforcement learning of fear, disruptions in working memory) and relate them to specific biological processes (e.g., disruptions in neural circuits).

The Research Domain Criteria (RDoC) Framework

Recent gains in basic neuroscience and genomics (see Hyman, 2008b) have made clear a need for alternative approaches to classification in psychiatric research, specifically, to link basic biological and behavioral components of normal and pathological functioning in order to create valid and reliable phenotypes for mental disorders. The RDoC project was born out of this recognition by the NIMH (see Insel et al., 2010). The charge was to formulate an innovative approach to classification that might circumvent some of the problems that have hampered integrative work. A long-term goal is to promote a research nosology that will incorporate rigorous behavioral neuroscience evidence to identify aberrant systems that implement psychopathology. With a strong focus on biological processes, and emphasis on neural circuits at the outset, the RDoC effort could be construed as reductionist. However, a focus on "lower" level mechanisms does not necessitate that "higher" level constructs be dismissed (Wright & Bechtel, 2007). Most researchers agree that causal influences are multidirectional across levels (e.g., across genes, molecules, cellular systems, neural circuits, and behavior), leading some (e.g., Kendler, 2005) to consider "explanatory pluralism" (pp. 436–438) or "patchy reductionism" (p. 438) as an alternative to reductionism. Regardless, the immediate goal of RDoC is to devise a system for identifying and integrating constructs for disordered cognitive, neural, genetic, or epigenetic processes that hold particular promise to explain the psychiatric symptoms. An ultimate goal is the translation of this knowledge to inform patient care, but this goal is further in the future and beyond the scope of the present effort.[2]

The RDoC project aims to identify domains that constitute promising avenues of research that can relate and integrate molar components of psychopathology. The effort encourages integration of clinical and experimental findings from multiple approaches, including, for example, behavioral, neurophysiological, and genetic discoveries. RDoC is intended to serve as a framework to stimulate and organize the identification of valid, reliable phenotypes (measurable traits or characteristics) for mental disorders that integrate biological and psychological components, while taking full advantage of the perspective of systems neuroscience. One goal is to advance understanding of the nature and causes of mental disorder and thereby ultimately to better define the boundaries and overlap between mental disorders. Recent efforts in other quarters have conceptualized a similar focus in terms of endophenotypes, which are hypothesized to be at a level intermediate between gene expression/protein production and the higher level phenotypes implied by current psychiatric nosology (see e.g., Meyer-Lindenberg, 2008). The RDoC effort will undoubtedly gain purchase from extant research aimed at intermediate phenotypes (see Insel & Cuthbert, 2009), but RDoC is distinct because the aim is to illustrate an innovative research framework for identifying exemplary intermediate phenotypes that might lead to more powerful theories of psychopathology than those that have emerged to date.

Approach

The RDoC group elected to adapt a method that was successfully deployed for studying cognition in schizophrenia, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project.[3] The CNTRICS project brought together experts in the cognitive aspects of schizophrenia to identify laboratory-based measures with potential immediate use for clinical diagnoses. Through a series of meetings, hypotheses that integrated biological and psychological—cognitive—findings were developed to clarify component processes and their disruptions relevant to cognitive anomalies in schizophrenia. In CNTRICS, putative constructs were proposed and refined, benchmarks were set, and the deliberations were transparent to the research and clinical communities. Criticism from the field was solicited in a series of evaluative meetings and peer review of published progress. In a similar manner, RDoC will move forward in stages addressing various domains and more specific constructs, prioritizing those for which substantial knowledge exists to draw from and for which there is direct import for psychopathology. With RDoC, the research domains are purposefully broad, constrained by the availability of potential for theoretical integration. The initial set of candidate domains and related constructs is described next.

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[2] The goals of RDoC differ from those of the *DSM* and the ICD; and the NIMH convened a meeting (chaired by former NIMH director Steven Hyman) in July 2009 with representatives of the American Psychiatric Association leadership for the *DSM–V* revision and the World Health Organization leadership for the ICD-11 revision to map out common ground and distinct goals. There was agreement that each effort has a separate audience: mental health practitioners for the *DSM–V*, primary care providers for the ICD-11, and researchers for RDoC. If successful, RDoC will eventually inform clinical assessment and treatment, but this is a long way off and well beyond the next revisions of the *DSM* and the ICD.

[3] More detail about CNTRICS can be found at http://cntrics.ucdavis.edu/index.shtml

Units of Analysis

A first step in the development of RDoC was to consider units of analysis that create a framework for efforts toward scientific integration. The RDoC framework can be represented by a matrix in which the rows represent the constructs, grouped into superordinate domains, and the columns represent the units of analysis typically employed in psychopathology research (e.g., genes, molecules, cells, neural circuits, behaviors, self-reports). However, research spanning these units of analyses is important for clarifying the nature of psychopathology. Various factors influence any particular choice of what to study and how to study it. One purpose of RDoC is to promote integration of knowledge across multiple disciplines, especially in certain biological areas in which recent advances in basic science have not been integrated into theoretical psychopathology. Thus, the RDoC framework emphasizes the integration of knowledge about genes, cells, and neural circuits with knowledge about cognition, emotion, and behavior.

Proposed Domains

Candidate research domains were developed from extensive and well-developed bodies of research that have significant potential to link directly to psychopathological mechanisms. As described in the previous section, these constitute multiple units of analyses. The domains are "superordinate" in that they are comprised of multiple, more specific constructs. In a perfect world, one might hope for a well-organized, hierarchical structure with parallel constructs on each level. In reality, there are a number of constructs that capture mechanisms of behavior that overlap both within and across units of analysis. The candidate domains and their accompanying constructs initially identified in the RDoC are intended to be starting points that aptly reflect the current state of knowledge. They will probably undergo revisions in response to continuing scientific work. On the basis of reviews of relevant empirical literature, the RDoC working group identified five initial candidate domains: negative affect, positive affect, cognition, social processes, and arousal/regulatory systems. These candidate domains, to serve as starting points for RDoC, are considered briefly next.

Negative affect. This domain captures constructs that include fear, distress, and aggression. The psychology of fear has been studied in a large number of contexts and across a number of species and is relatively well developed (see e.g., Delgado, Olsson, & Phelps, 2006; LeDoux, 2000; Quinn, Ma, Tinsley, Koch, & Fanselow, 2008). In addition, there is substantial knowledge of the biology of fear, which has been found to involve multiple neural systems, including the various regions of the amygdaloid complex. Neural circuits connecting the basolateral amygdala with ventral medial areas of the prefrontal cortex are particularly important in the extinction of fear (Milad & Quirk, 2002; Pine, 2009). Systems involved in distress and anxiety have also been well studied, including the distinction between the amygdala and bed nucleus of the stria terminalis in fear and anxiety, respectively (see e.g., Davis, 2006). Changes in the hypothalamic–pituitary–adrenal (HPA) axis in response to stress have been well characterized (Charney, Grillon, & Bremner, 1998), and the HPA axis has been linked to a range of psychopathologies, including posttraumatic stress disorder, major depressive disorder, bipolar disorder, and schizophrenia (see e.g., Pariante & Lightman, 2008). Differences in the effects of acute versus chronic stress, or predictable versus unpredictable stress, have documented the role of the medial prefrontal cortex (see Maier et al., 2009). Brain regions involved in aggressive responses have been studied in a variety of species as well, including primates (see e.g., Baumann, Toscano, Mason, Lavenex, & Amaral, 2006), hamsters (e.g., Jasnow & Huhman, 2001), and rats (e.g., Wood, Young, Reagan, & McEwen, 2003). The amygdala, ventral tegmental area, nucleus accumbens, and mesolimbic dopamine pathway all play a role in aggression. Obviously, these areas are involved in other important systems as well (e.g., reward), and the point here is to illustrate starting points for the development of the RDoC framework.

Positive affect. Candidate constructs that aggregate for positive emotionality include reward seeking and learning, and habit formation. The mesolimbic dopamine system is well known for its role in incentive motivation and reward. Activity in this system is relevant at one pole of functioning to substance abuse and other addiction-like behaviors, and at the opposite, hypoactive pole to the anhedonia and lack of energy implicated in clinical depression (Nestler et al., 2002). Sustained activity in this system has also been linked to temperament characteristics of extraversion and surgency (see e.g., Depue & Collins, 1999). Mechanisms involved in reward learning and habit formation make up another important aspect of positive motivational systems. These functions involve interaction between a number of different brain areas, such as the orbital frontal cortex (OFC) and both the ventral and dorsal striatum. Neural circuits connecting these regions offer starting points to gain traction in clarifying mechanisms that are functioning normally versus those that have gone awry. This can include disorders that are not classically characterized in terms of positive emotionality; as one notable example, it is now increasingly clear that obsessive–compulsive disorder involves dysregulated functioning in the connection between the OFC and the dorsal striatum (Graybiel, 2008).

Cognition. Cognition is a broad domain that can be represented in many different ways, and of course it is a domain that cuts across other constructs considered for development in the RDoC scheme. The interrelation of cognition and affect (see Gray, Braver, & Raichle, 2002) is the focus of much research that will likely be fruitful for the goals of the RDoC initiative at different levels of explanation (e.g., fear conditioning can be viewed in the context of cognitive processing models). A component–process approach to cognition, which aims to break down complex cognitive functions into their more simple component processes, has driven basic research in cognitive neuroscience (see e.g., Johnson et al., 2005) and research into cognitive disruptions in attention disorders (Fan, McCandliss, Sommer, Raz, & Posner, 2002), regulatory disorders (Posner et al., 2002), and schizophrenia (Carter et al., 2008). In this area, the RDoC effort will be able to draw upon the products of the CNTRICS project for a list of candidate constructs that include attention, perception, working memory/executive function, long-term memory, and cognitive control. Although these constructs are well studied (see e.g., D'Esposito, Postle, & Rypma, 2000; Hopfinger, Buoncore, & Mangun, 2000; Pochon, Riis, Sanfey, Nystrom, & Cohen, 2008; Squire, 2004), they might be analyzed into finer grained components to isolate abnormalities. A number of brain areas and neural systems have been implicated in cognitive processing and cognitive control:

parietal areas (attention), thalamic and occipital areas (perception), dorsolateral prefrontal cortex (working memory/executive functioning), hippocampus and distributed areas of the prefrontal cortex (long-term memory), and anterior cingulate (cognitive control). There also exists a large literature addressing cognition–emotion interactions (see e.g., Ochsner & Phelps, 2007; Pessoa, 2008), highlighting an area where the overlap in neural systems may be directly addressed in the RDoC framework.

Social processes. Social processes are critical because interpersonal manifestations may be the most familiar observation of psychopathology. Attachment processes have been studied in a number of organisms, and disordered relationships have been implicated in various manifestations of psychopathology in humans (Ahnert, Gunnar, Lamb, & Barthel, 2004; Bales & Carter, 2009; Gonzalez, Atkinson, & Fleming, 2009; Tarullo & Gunnar, 2005). Studies grounded in solid animal model systems have provided important insights into the neural mechanisms underlying pair-bonding and alloparental behaviors, both strong examples of attachment phenomena. Much of this work stems from original observations on the role of oxytocin and vasopressin systems in prairie voles, a species that exhibits both strong pair-bonding and alloparental behavior (see e.g., Pitkow et al., 2001; Williams, Insel, Harbaugh, & Carter, 1994; Winslow, Hastings, Carter, Harbaugh, & Insel, 1993). These studies have been extended to other species (see e.g., Ferguson, Aldag, Insel, & Young, 2001) and have led increasingly to studies looking at the role of vasopressin and oxytocin systems in humans (see e.g., Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Thompson, Gupta, Miller, Mills, & Orr, 2004), including some work pointing to potential therapeutic effects for specific disorders (Hollander et al., 2007; Insel, 1999). Historically, social processes have been more difficult to study, but recent work in the area of social neuroscience is providing some important clues to systems underlying aberrant social processes. More specific constructs—such as separation fear, facial expression recognition, behavioral inhibition, emotion regulation, and others—have shown direct links to specific neural systems (see e.g., Adolphs, Sears, & Piven, 2001; Dalton et al., 2005; Davidson, Irwin, Anderle, & Kalin, 2003).

Regulatory systems. As with cognition, regulatory systems might subserve many of the other domains in certain respects but were included among the candidates because of the importance of homeostatic functions and the systems underlying them. Arousal systems include basic glutamatergic and cholinergic reticular systems involved in sleep and wakefulness. However, a number of midbrain systems that are critical for arousal are also complexly related to many areas of motivational processes, such as the ventral tegmental area, locus coeruleus, and raphé nuclei. Circadian rhythms and sleep are increasingly recognized to be critically involved in the regulation of a variety of cognitive systems, including memory (see e.g., Tononi & Cirelli, 2006), and the role of various arousal systems in the complex regulation of sleep (as, for example, in the recently demonstrated role of orexins in narcolepsy; see Hungs & Mignot, 2001) shows the potential of these systems for contributing to an understanding of psychopathology.

One advance that we hope to achieve with this approach is to forge more explicit links between these constructs in the domain of interest. It bears repeating that the proposed set of candidate domains and constructs is not fixed and is intended as a heuristic for integrative psychopathology research.[4] As noted previously, the RDoC framework will be refined with input from the scientific community via web interaction and planned meetings sponsored by the NIMH. This refinement could take the form of identification of new candidate domains, analysis of the extant domains into components, merging of constructs into broader groupings, or abandonment of candidate domains or their constructs. Candidate domains to be engaged in scientific meetings planned for the RDoC effort will be prioritized on the basis of the extent of knowledge from animal and human studies.

Implementation of RDoC

For the RDoC, there is a shift of emphasis from conventionally defined mental disorders to crosscutting mechanisms such as fear or working memory in classifying groups of participants for research studies. Accordingly, there is corresponding de-emphasis on conventionally defined categories of mental disorder. Of course, candidate research domains identified by this project must derive their clinical relevance from something. Therefore, a priority for RDoC candidate domains is that they can be related to problem behaviors that can be found in the symptom lists that constitute the symptom criteria for conventional mental disorder categories such as those found in the *DSM* and the ICD. However, research using the RDoC approach will be organized on the basis of the putative mechanisms rather than the conventional diagnostic categories.

Ascertaining Clinical Samples for Studies Using the RDoC Framework

Research protocols based on RDoC would presume that samples would include those with recognizable "disorders" as we know them, at least at some level. The domains would of course be expected to account for significant proportions of variance in a number of different *DSM* disorders as well. Therefore, study groups may or may not be classifiable in terms of specific *DSM* diagnoses, though it would be expected that the population be clinical, with participants meeting or approaching criteria for one or more *DSM* disorders. Individuals may be selected for study on the basis of varying criteria. For instance, participants may be included for study because they display certain psychiatric symptoms hypothesized to be relevant to a particular mechanism of interest (e.g., anxiety symptoms), or perhaps because they had associated risk factors falling along a certain risk or severity dimension (e.g., impairment in working memory), or because they had a specific developmental experience (e.g., sexual abuse). As an example, research in the area of addictions defines study groups in a similar matter (e.g., grouping participants on the basis of "abstinence" and "relapse").

As our previous discussion suggests, a primary feature of RDoC is a break from the traditional rationale for selecting study groups. Rather than participant selection being based on *DSM* categories, the between-subject independent variables used to define and select experimental study groups might be based on any of a

[4] The RDoC website established by the NIMH will keep the research and clinical community apprised of the most recent developments, as well as provide a forum for feedback.

number of levels of analysis (e.g., one or more genes, activation of a neural circuit following exposure to a salient stimulus, or response latency during a behavioral assessment task). The procedures for selecting clinical samples to develop RDoC will require figuring how best to determine the appropriate variance to detect pathological differences in relevant mechanisms. For instance, selecting only patients with *DSM*-defined schizophrenia is too narrow to detect relevant variance in other psychotic/bipolar disorders that may share, for instance, relevant genetic or neural mechanisms. On the other hand, combining patients with schizophrenia and attention-deficit hyperactivity disorder in a study of executive functioning could generate meaninglessly large variance. The real key is to select the "patient" group in such a way that it encompasses a full range of participants that exhibit deficits in the construct of interest (e.g., memory or attention). Thus, RDoC aims to clarify what sorts of criteria are useful for a first pass at selecting a group that may be narrowed later. One goal is to enhance the probability of deriving a sample for which the presence of a relevant mechanism will be maximized—hence, the systematic focus on relevant groupings for putative mechanisms of clinical import rather than on groups based on the parsing of signs and symptoms.

The anxiety disorders provide an example of how the RDoC framework might work in actual practice. Although the various anxiety disorders are considered to be distinct entities, articles exploring their psychopathology almost invariably appeal to the same mechanisms in considering etiology and treatment—conditioning (direct or vicarious) for the former and extinction/habituation for the latter; accounts also typically invoke the same brain circuits—the amygdala and hippocampus in fear onset and response, the ventromedial prefrontal cortex in fear-responding control, and the prefrontal cortex in extinction. Recently, however, studies from a variety of sources have suggested that systematic differences may exist both across and within the various categories of anxiety disorders, with data ranging from clinical and behavioral genetics studies (e.g., Hettema, Prescott, Myers, Neale, & Kendler, 2005) to psychophysiology experiments (e.g., Lang, McTeague, & Cuthbert, 2007). These data suggest that more fundamental mechanisms of elevated or inhibited fear responding may cut across the various disorders and be more significant for diagnosis and treatment than is the category per se.

In order to explore these effects, a hypothetical study of fear responding might include as participants all those presenting for treatment at an anxiety disorders clinic, without respect to the particular diagnosis. All participants would receive the usual clinical assessment, including a battery of relevant questionnaire instruments, and would also participate in a functional neuroimaging session in which a variety of fearful stimuli (some tailored to the individual's presenting problems, some given to all participants) are presented. The independent variable in such a study (established post hoc) would be the formation of two groups on the basis of a median split of amygdala responses to fearful stimuli on the neuroimaging assessment (a dimensional approach could also be used and is more powerful, but the median split is used as an easier example); the dependent variables could be overall severity of distress on various measures, plus duration of disorder, to establish whether participants who are hyporeactive on a fear challenge show overall higher levels of severity and longer durations than do those who are hyperreactive. A corollary hypothesis would be that patients who show more robust fear responses would show superior outcomes to a standard cognitive–behavioral therapy, regardless of presenting *DSM* diagnosis (with the hypothesis that a palpable fear response is more amenable to successful extinction). A similar approach could be used in subsequent studies to examine whether, among patients who are hyperreactive to fear challenges, differences in ventromedial PFC activation affect overall severity of disorder and response to treatment. It would be hoped that the long-term outcome of a series of such studies would be to develop accurate predictors of optimal treatment modality and prognosis that could eventually be instantiated with relatively straightforward laboratory procedures (employing, for example, faster and less expensive methods than functional neuroimaging).

Many other iterations of this approach could be envisioned. For instance, measures of overall disorder severity (on standard questionnaire instruments of distress, fear, and anxiety, which tend to covary significantly) might serve as the independent variables, with fear-potentiated startle and other psychophysiological measures as the dependent variables. The point is that by opening up research designs to a variety of methods for classifying and selecting patient groups, a research base that reflects fundamental neurobehavioral mechanisms might develop that in turn will facilitate improved treatments in a variety of modalities.

Guiding Principles

RDoC endorses the study of genetic, molecular/cellular, systems, and behavioral neuroscience approaches spanning affective, social, and cognitive systems. The candidate domains identified in RDoC imply an interest in integrating theories of information processing (e.g., cognitive component processes) and brain-system activity. This in turn could support studies that work up from brain systems and constructs related to learning theory, with the goal of understanding individual differences in behavior. Conversely, the candidate domains identified in RDoC also imply an interest in working down from behavior to integrated theories of brain-system functioning with epigenetic theories to understand how epigenetic factors, viewed from molecular to molar perspectives, lead to dysfunctional or compensatory mechanisms over the course of maturation.

RDoC is largely agnostic with respect to contemporary diagnostic classifications (i.e., the *DSM* and the ICD). One premise of RDoC is that mental disorders are implemented in individual differences in brain function. Understanding how such individual differences are related to perturbed cognitive and behavioral processes, as typically studied in cognitive neuroscience, and the potential to dissociate such dysfunctions and differentially relate them to palpable psychopathology seems to be a promising avenue. Trying to map cognitive functions onto neural systems rather than trying to map conventional diagnostic categories onto neural functions might be more efficient because the relationships that are discovered will not be prejudged by descriptive practices that may not reflect singular pathological systems and may not clearly distinguish underlying pathologies from the "clinical surface."

The distinction between schizophrenia and bipolar disorder is illustrative. It has been supported by a century of research on differential course and response to medications. Nevertheless, a variety of recent studies have noted considerable overlaps in familial and genetic risk (International Schizophrenia Consortium,

2009; Losh, Sullivan, Trembath, & Piven, 2008; Stefansson et al., 2009). Studies that include patients from these two clinical groups (plus related disorders) should produce knowledge that leads to improved treatment and prevention, whatever the eventual implications for classification. Thus, it may be the case that separating these types of psychopathology in our current framework may be premature and limit further understanding of their pathophysiological basis. In contrast, if disturbed neural–cognitive systems are discovered that appear to be shared by each of these diagnostic states, this might not only clarify etiology but also suggest new treatment targets or interventions in the prodromal stage.

Shaking loose from constraints imposed by current conceptions of diagnosis is a formidable task for clinical researchers and perhaps more so for those who are also clinical practitioners. However, from a historical perspective, even key diagnostic conceptions have had changing boundaries. For example, consider the following trends in rates of diagnosis between the United States and the United Kingdom. In the 1930s, about 20% of the patients at the New York State Psychiatric Institute were diagnosed with schizophrenia, but there was a steady increase that peaked at 80% in the 1950s. In contrast, patients admitted to London's Maudsley Hospital were diagnosed at a steady rate of 20% over a 40-year period (Kuriansky, Deming, & Gurland, 1974). More recent studies have suggested a marked reduction in the number of patients who would have received a schizophrenia diagnosis (a correction for overdiagnosis?) according to the *Diagnostic and Statistical Manual of Mental Disorders* (2nd ed.; *DSM–II*; American Psychiatric Association, 1968) compared with the number who would have received a *DSM–III* schizophrenia diagnosis, with 41% (Harrow, Carone, & Westermeyer, 1985) to 51% (Winters, Weintraub, & Neale, 1981) of those making the cut. If the RDoC effort is to succeed, it will require the uncoupling of research efforts from current diagnostic conceptions. Rooted in this effort is a belief that integrating knowledge of neural systems with functional constructs will lead to a different perspective on psychopathology.

Neurodevelopment

To a substantial degree, mental disorders are disorders of development, first appearing prior to full adulthood. Thus, the developmental aspects of mental disorders, and the process of neurodevelopment itself, have implications for the "observables" used in understanding psychopathology. Genes code for proteins that, through developmental processes, lead to neural circuitry with a variable and complex relationship to cognition, affect, and social behavior. These developmental processes are critical parts of gene expression. During neurodevelopment, periods of risk and opportunities for resilience open and close, likely at critical times that have yet to be well characterized. The RDoC project will encourage the use of information from specific periods of development to facilitate a neurodevelopmental understanding of how biology constrains and implements cognition, affect, and social behavior. Disorders as they present in adults reflect the effect of prior psychopathology and possible compensatory mechanisms upon functioning. For instance, how people respond to new stress depends on developmental history, and compensatory mechanisms have been identified in fear processing (see Pine, 2009; Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2008) and depression (see e.g., Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002) that vary as a result of early alteration to these neural systems. In the case of schizophrenia, increasing knowledge suggests that the schizophrenia diagnosis merely captures the end stage of an aberrant developmental process.

Construct Development and Bootstrapping

Clearly, the task of revising concepts of psychopathology by incorporating knowledge from multiple scientific disciplines is daunting. The effort is humbled by the idea that constructs are useful ideas yet imperfect representations, even at the level of neurobiology. Seen in this light, the best possible outcome is a sort of continual improvement in the refinement of the constructs. RDoC is based on the premise that solid anchors to behavioral neuroscience will help in the refinement process. The initial efforts will involve mapping out a set of heuristics to allow, through a bootstrapping approach, the refinement of constructs that will contribute to our understanding of mental disorders.

Transparency and Interaction With the Scientific and Clinical Communities

RDoC will maintain transparency throughout the process of its development. Input from the scientific community will be invited in the form of workgroups, annual meetings, a website (that will provide the latest updates and a means to provide feedback to the process and final product), and peer review of RDoC publications. Success will require the coordinated efforts of basic and clinical researchers with continual, interactive input from the broader scientific community. At this early stage, one can only speculate how long it will take to meet the objective of valid and reliable research diagnostic constructs, let alone those that will translate to inform clinical practice. The development of the RDoC will take an extended period of time that will not coincide with timelines for the revisions for the *DSM–V* and the ICD-11. Nonetheless, because the hope is that this effort will eventually contribute to diagnostic and treatment formulations for clinical practice, it is important for RDoC developers to maintain a liaison with the American Psychiatric Association and the World Health Organization regarding the agencies' respective areas of emphasis in psychiatric classification so that research goals will remain consistent with clinical needs. Translation from the lab to the bedside is an ultimate goal (cf. Wolf, 2008).

Concluding Comments

This project stems from the perspective that in order to develop an integrative approach to classification that incorporates neuroscience and behavior, it is necessary to free research from constraint by current diagnostic entities. Ultimately, the fundamental psychopathology is likely to be disrupted neural circuits—the failure of a system to extinguish an aberrantly conditioned response, or a misstep in a specific neurodevelopmental process. What is now regarded as a diagnosis may turn out simply to be indicative of a range of possible pathologies. In this manner, for example, depression might be viewed akin to the way that a fever is viewed today, suggesting specific tests for a panel of potentially active diagnostic markers that will steer the clinician to the appropriate treatment among any number of possible disordered pro-

cesses that might underlie the depression. Using modern behavioral neuroscience to accelerate progress in understanding mental disorders is motivated by the longer range goal to help address specific needs. The hope is that the RDoC, through its focus on discrete domains of function, will contribute to the identification of improved phenotypes and enhanced understanding of mechanisms at all levels of analysis. These are critical steps in identifying new treatments and, perhaps even more importantly, personalizing treatments to match more specific psychopathology mechanisms than the familiar signs and symptoms that individual patients may present. The process initiated with RDoC is an early step in what is expected to be a long journey toward a new approach to classification.

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