chapter three

New Directions in Diagnosis Research Domain Criteria and Global Mental Health

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CHAPTER OUTLINE

INTRODUCTION

"One of the chief causes of poverty in science is imaginary wealth. The purpose of science is not to open the door to an infinitude of wisdom but to set some limit to the infinitude of error."[1]

Research on the brain and behavior has entered an era of substantial enhancements in visibility with respect to both normal functioning and various types of brain disorders. Recent years have witnessed the Decade of the Brain (1990–2000) and the Decade of Behavior (2000–2010). For mental disorders, the period from approximately 2005 to 2015 might be called the "Decade of Diagnosis." The American Psychiatric Association has been working on

revisions for the fifth edition of its *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), slated for release in 2013. In parallel, the World Health Organization has been preparing for the release of the ICD-11 in 2015, which includes revisions to the sections on mental and behavioral disorders. Finally, in the spring of 2009, the National Institute of Mental Health (NIMH) announced a new initiative, the Research Domain Criteria project (RDoC), intended to provide a research classification system organized around key dimensions of functionality as informed by emerging data from genomics, clinical neuroscience, and behavioral science.

With the intense effort involving revisions to the two major classification systems for psychiatry, it might seem an unusual time for the NIMH to start yet another effort in the diagnostic realm. However, the RDoC project differs from the DSM and ICD revisions in significant ways. First, RDoC is an experimental system, not designed for immediate clinical application. Second, RDoC is meant to be a long-term effort, laying a foundation for future approaches to diagnostic nosology that are based on a systematic neuroscience literature. Finally, RDoC is intended not to be a competing diagnostic scheme but rather to inform future versions of the DSM and ICD. Thus, RDoC is a unique effort, one that signals a shift in direction for how we think about mental disorders and how they are diagnosed. The purposes of this chapter are to describe the rationale for the RDoC project, outline its methods and goals, and finally conclude by sketching ways in which RDoC may be relevant for global mental health.

THE NEED FOR RESEARCH DOMAIN CRITERIA

The framework currently used to classify mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[2] and the mental disorders section of the International Classification of Diseases (ICD-10)[3] is now nearly 40 years old, dating back to the landmark Robins and Guze paper,[4] outlining methods for establishing disease entities and the subsequent "Feighner criteria."[5] These papers established the still-current set of five phases for establishing a disorder: clinical description, laboratory studies, delimitation from other disorders, studies of course and outcome, and family history. It is difficult to imagine modern approaches to the classification of mental disorders without this seminal organizational scheme that builds on clinical consensus regarding phenomenology for creating theory-neutral criteria to increase diagnostic reliability.

At that time, of course, knowledge about the brain and its role in mental disorders remained relatively crude. This limitation necessitated the definition

of disorders almost entirely by presenting symptoms and signs, relying heavily on descriptions of phenomenological states. As is well known, Robins and Guze assumed that success in defining distinct combinations would eventuate in their validation through discovery of specific laboratory findings, course, and genetic factors. Given the lack of knowledge about brain circuits at that time, it was a reasonable assumption that apparently different clinical states would represent distinct diseases as in many other areas of medicine. However, in the event, this assumption has proven to be false. The result has been oft-noted difficulties of extensive comorbidity, an increasing number of overspecified categories to fit variants of presentation, and an excessive prevalence of "Not Otherwise Specified" (NOS) diagnoses, which fail to fit any of the categories. Many commentators have noted these difficulties.[6,7] Further, in one recent survey, 60 ICD-10 diagnoses were not used at all, and another 181 had rates of less than 0.1%, representing nearly 58% of all possible categories.[8] Current diagnostic frameworks also fall short with respect to their utility in dictating proper treatment. Diagnosis provides only limited prediction of who will benefit from any given treatment. Effective treatments for most disorders are available, but the proportion of individuals who benefit from any given treatment—whether pharmacological or behavioral—is far from optimal. This suggests that yet-to-be identified subtypes of disorders may be targets for more tailored or novel interventions.

Perhaps the most troubling aspect of the current system is that a preoccupation with reliability, appropriate at one point in history, has come at a cost of neglecting the need to advance a research agenda on validity. (Somewhat ironically, in retrospect, the classic 1970 Robins and Guze paper was titled "Establishment of Diagnostic Validity in Psychiatric Illness.")[4] The need for a new DSM was mandated by findings in previous decades that diagnosis was highly unreliable and depended heavily on the training and predilection of the assessor. To accomplish any shared understanding about clinical communication, health system records, and research, a more objective set of criteria had to be devised. However, as brain research has advanced, it has become increasingly clear that reliably identified clinical phenotypes do not relate strongly to biological entities. Modern brain research has revealed that, in contrast to the assumptions of the original framers of the DSM-III, psychiatric disorders represent complex and heterogeneous entities that comprise complex genetic risk architectures and multiple pathophysiological components in neurocircuitry and neurotransmitters.[9] Further, a particular brain component may be implicated in multiple disorders as currently defined. The current approach of studying one disorder at a time results in confusion because studies of various diagnoses implicate the same brain systems, so it is

difficult to know exactly how the systems are alike, or different, in different disorders. This is likely also the reason for the excessive comorbidity.

Another unfortunate ramification of the current system has been the reification of DSM/ICD categories into fixed entities, which impedes progress by preempting important questions.[10] (While it is recognized that the DSM and ICD differ in descriptions and specific algorithms for diagnosis, the term "DSM/ICD" is used in this chapter to refer to the fact that the actual diagnostic categories are virtually identical.) Rather than a set of constructs whose definitions might change over time with continued research, diagnostic categories have become fixed entities whose essential validity and existence are unquestioned. A consequence of this situation is that most studies about etiology or pathophysiology are conducted on a single disorder (typically compared to a nonclinical control group), reflecting the implicit assumption that the disorder under study is a unique entity. However, research on genetics or brain mechanisms will be stymied if the disorder is highly heterogeneous or if the boundaries of the disorder are too narrow, excluding groups that may differ clinically but that share the same etiology or pathophysiology. Further, attempts to study comorbidity are complicated not simply by the difficulty in devising a systematic approach to the large number of potentially comorbid disorders but even more by the fact that including comorbid conditions muddies the waters in trying to distill the essence of the putatively "pure" disorder at hand. The resultant exclusion of comorbidity, however, leads to atypical samples that fail to represent the complex comorbidities and functional impairment observed in typical clinical practice.

The problem of diagnostic categories that are too narrow, too broad, or not aligned with pathophysiology is certainly not unique to psychopathology. Throughout medicine, disorders once thought to be unitary based on clinical presentation have been shown to be heterogeneous by laboratory tests. From infectious diseases to subtypes of cancer, we routinely use biomarkers to identify syndromes that require distinct treatments. Conversely, syndromes that may not appear clinically related may result from the same etiology, as we learned decades ago in studies of syphilis and strep-related disorders. In other areas of medicine, diagnostic validity has followed paradigm shifts in understanding pathophysiology, from the ability to identify pathogens for infectious disease to the precision of molecular diagnosis for different forms of cancer. In this vein, the time has come to move in similar directions for mental disorders.

Two important reminders need to be emphasized in any accounting of the problems with current diagnostic schemes. First, these systems in large part reflect long-standing views of mental disorders that antedate the documents themselves. The concept of melancholia is over two millennia old; the classic

Kraepelinian distinction between schizophrenia and manic-depressive disorder is over a century old. Thus, problems are not so much about ICD and DSM per se as about our general understanding of mental disorders. In a related vein, it must be noted at this juncture that the DSM/ICD nosology remains the consensus for diagnosing and treating mental disorders in applied clinical settings. Information about symptom patterns, differential diagnosis, and course in both the DSM and ICD is the result of decades of clinical research and practice. These categories are entirely integrated not only in clinical work but in many other settings as well (e.g., the legal system, eligibility for disabilities, and special programs in educational settings). Therefore, a comprehensive literature will be needed to develop the foundation for a new diagnostic approach that can supersede current systems. However, such a new literature cannot be developed if the research enterprise is organized around the extant categories. This is the essential rationale for the RDoC project.

These diagnostic issues and the problems that they increasingly pose for research comprised some of the most prevalent comments heard by staff at the National Institute of Mental Health (NIMH) as the Institute formulated its strategic plan in 2007 and 2008. This input prompted the Institute to take steps to shift the research enterprise in a new direction that builds an experimental classification of mental disorders based on discoveries in genomics and neuroscience, as well as on clinical observation. The idea is that an approach that starts with the burgeoning fundamental knowledge base about genes, the brain, and behavior and works out toward disorders—as opposed to the current disease-focused mode—may be the most viable way to surmount the current impasse in diagnosis and relate recent gains in neuroscience and behavioral research to psychopathology. The specific statement of this intent was included as Goal 1.4 of the Institute's Strategic Plan: "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures."[11] RDoC represents the implementation of this goal. Consistent with the above statement, RDoC addresses mental disorders as brain disorders related to identifiable brain circuits—as shaped by genetic variation and experience and related to individual patterns of cognition and behavior. Examples where well-developed models of circuitry-behavior relationships now exist include the domains of fear/extinction, reward, executive function, and impulse control. Although there is still only a rudimentary database on how genetic variation or experience shapes the development of these circuits, the emerging fields of imaging genomics and early life programming have already provided heuristic models.[12] For some current diagnostic categories, such as autism and schizophrenia, the recent discovery of structural

changes in the genome (copy number variations), as well as rare mutations that appear to be highly penetrant, already demonstrates the need to identify subsyndromes for research and potentially for treatment.[13,14] These examples illustrate the kind of findings that need to be integrated into a research classification system to advance neuroscience-based diagnosis.

DEFINING THE RESEARCH DOMAIN CRITERIA

The specification of Strategy 1.4 of the Strategic Plan includes four main subpoints that enumerate the tasks to be accomplished in reaching its stated goal,[11] and these have been followed carefully as the project has developed. In brief, these four bullets are to (1) initiate a process for defining the dimensionally oriented domains, (2) integrate multiple units of analysis, (3) determine the full range of variation along dimensions, and (4) develop reliable and valid measures of the dimensions. These subpoints also provide a convenient organizational framework for discussing the process and approach of the RDoC project. Accordingly, these four aspects are discussed in turn.

1. Initiate a process for bringing together experts in clinical and basic sciences to jointly identify the fundamental behavioral components that may span multiple disorders and that are more amenable to neuroscience approaches

The NIMH established an internal working group in early 2009 to develop and coordinate the RDoC process. Members were drawn from all components of the Institute, including the intramural program, and represented a wide variety of basic, translational, and clinical expertise.* Initial progress was slow as the work group members collaborated to find common ground on fundamental substantive and organizational issues. However, an initial framework was established by the summer of 2009. The overarching RDoC organization specifies five broad domains of functioning (the eponymous "Research Domains"): Negative Valence Systems (i.e., aversively motivated behaviors), Positive Valence Systems (appetitively motivated behaviors), Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems. Nested within each of these domains are multiple constructs that represent the fundamental dimensions of interest. For example, the constructs within the Negative Valence Systems domain include Acute Threat (fear), Potential Threat (anxiety), Sustained Threat, Loss, and Frustrative Nonreward. This hierarchical organization was deliberately chosen to

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reflect the complexity of the nervous system and the clear overlaps in functionality among constructs within a given domain. The overlaps acknowledge basic science findings and also current studies regarding the organization of psychopathology; an example is represented by the comorbidity among fear disorders and distress disorders within the overall internalizing factor in structural modeling studies of disorders.[15]

One of the challenges in working with a new dimensional approach is to determine the right "grain size" for the constructs: constructs that are overly broad (as would be the case if only the main domain titles had been included, for example) cannot represent functional dimensions with sufficient specificity. On the other hand, it is relatively easy to add constructs on the basis of common-language words, whether in English or in other languages (e.g., Should the German *schadenfreude* [also adopted as a loanword in English and generally translated as "pleasure derived from the misfortune of others"] be included given that there is a word for it?). More serious, a thesaurus lists many synonyms for words that serve as brief "tags" for constructs. Thus, *fear* has the following synonyms: *terror*, *dread*, *horror*, *fright*, *panic*, *alarm*, *trepidation*, *scare*, and *apprehension*. Some seem roughly identical to the English notion of fear, while others have rather different connotations as felt states; clearly, however, including all of these terms would complicate the list for one component by an order of magnitude.

What should be the criteria for making decisions regarding such potential candidates? The work group established two twin criteria for inclusion of constructs. The first was that the construct needed to represent a functional dimension of behavior that has been well validated by recent research, such as fear, working memory, or positively motivated approach behavior. The second criterion was that it must be possible to specify a reasonably well-identified brain circuit or other neurobiological pathway (e.g., the hypothalamic-pituitary-adrenal, or HPA, axis) that plays a major role in implementing the behavior associated with the candidate construct. This is an intentionally high bar, so devised to ensure (especially at the outset) that the constructs that were identified would have a firm empirical basis. It must also be borne in mind that the constructs reflect a practical goal (i.e., to represent target systems for studying psychopathology in groups of patients classified by new and experimental criteria). Thus, it was considered critical to start with a few strongly validated constructs that have clear import for mental disorders. Had the goal been to compile an exhaustive compendium of possible constructs, the list could easily have been several times longer.

Given this conceptual structure, the work group arrived at the decision to hold one scientific workshop for each of the five domains, inviting 30 to 40 scientists chosen on the basis of relevant basic and clinical expertise and

also representing a broad gamut of scientific areas (ranging from molecular/cellular processes to clinical assessment and psychometrics). Thus, the process specifies five workshops, beginning in March 2011 and finishing in June 2012. Each workshop comprises a series of plenary sessions and breakout groups, with a list of candidate constructs provided by the NIMH work group as the starting point for discussions. The participants are then able to modify or delete the candidate constructs and add new ones, based on current literature and in accord with the two criteria provided for including constructs. For example, the list of preworkshop candidate constructs for the Negative Valence Systems domain included Fear, Distress, and Aggression; the final list compiled by the participants at the workshop comprised Acute Threat, Anxiety, Sustained Threat, Loss, and Frustrative Nonreward. The proceedings of each work group are written up by NIMH staff, circulated to the work group participants for comments, and then posted on the RDoC website.

The RDoC process is intended to be fully transparent to the scientific community and the public. Opportunities for communication were initiated with a Request for Information (RFI), issued in the spring of 2011, and continued via presentations at numerous academic conferences and NIMH meetings with various stakeholders and through journal commentaries.[16,17] Proceedings are open for commentary for several months after each workshop, and suggested modifications are considered carefully by the RDoC work group. Finally, the domains and constructs will be designated as the formal specifications and will be available at no cost on the NIMH website as a series of easily downloadable files. However, as an experimental classification system, it is necessary to incorporate some method to reflect ongoing research advances regarding such aspects as new or modified constructs and new units of analysis; otherwise, the system could quickly impede, rather than facilitate, progress toward neuroscience-based nosology. Accordingly, an integral component of the new system will be decision criteria for the addition and modification of domains or new assessment approaches based on empirical results resulting from periodic formal reviews.

This section has described the RDoC process and the organization of the domains and constructs. The following section is intended to address the other major components of the overall RDoC organization.

2. Integrate the fundamental genetic, neurobiological, behavioral, environmental, and experiential components that compose these mental disorders

The domains and constructs previously discussed may be considered to form the rows of a matrix, with constructs nested under domains. The columns of the matrix represent the various classes of measurement, as called for in Strategy 1.4, that can be used to index constructs. The current RDoC

columns include Genes, Molecules, Cells, Circuits, Physiology, Behavior, and Self-Reports.(Seehttp://www.nimh.nih.gov/research-funding/rdoc/nimh-research-domain-criteria-rdoc.shtml.) Circuits represent the center of this set of columns, in keeping with the role of circuits in defining the constructs. To the left of this column, genes, molecules, and cells are the constituent elements of circuits; to the right are the classes of outputs putatively organized by circuit activity. Circuits may generally be measured by such methods as functional neuroimaging and, in some cases, by source localization techniques employing high-density electrode arrays to record the encephalogram or event-related potentials; circuit activity may also be inferred with measures well validated in animal models, such as the use of the eyeblink startle reflex to measure fear-potentiated startle.[18] A Physiology column was added to accommodate measures that are well-established indices of various constructs, such as skin conductance or heart rate variability, but which are neither direct circuit measures nor behavior in a strict sense. The Behavior column may refer to either observational measures of behavior (e.g., a toddler laboratory temperament test) or to task performance (e.g., a working memory task). Finally, Self-Reports is a shorthand term for both questionnaire measures and for various types of structured interviews.

As the heading of this section implies, a key aspect of the RDoC project is that it is intended to be integrative with respect to the various measurement columns. That is, the constructs are construed in the classic sense outlined by MacCorquodale and Meehl,[19] just as hypothetical concepts regarding aspects of functioning that cannot be directly observed (in most cases) are inferred from multiple indices and are not typically defined by formal mathematical relationships. Thus, the point of the matrix is not to direct research toward a reductionistic goal where higher-level measures are explained in terms of lower-level variables. Rather, the point is to sharpen our understanding of how human functioning can be understood by integrating measurements across many different classes of variables. It is for this reason that the columns are termed "units of analysis" rather than "levels of analysis."

3. Determine the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological

Dimensional aspects to psychopathology have gained an increasing amount of attention in recent years.[20] In fact, an entire volume of the DSM-V conference series was devoted entirely to the topic of dimensional approaches to classification.[21] While personality disorders have historically received particular emphasis in this regard,[22] dimensional or spectrum approaches are also accelerating in prominence in such areas as internalizing disorders [23]

and psychotic spectrum disorders.[24] In spite of such extensive treatment, it has proved difficult in practice to move toward dimensional approaches in actual clinical use. Most often, dimensions are treated as a degree of overall symptom severity given that a diagnosis has been conferred.

The RDoC scheme, as stated in the heading of this section, adopts a rather different, translational approach to dimensionality. Dimensions are construed in terms of adaptive behavior, which exists along some broad range of what is typically considered to be within the normal span of functioning. Like high blood pressure or low IQ, normal-range functioning can shade gradually into a range of mild impairment and then to increasingly severe disruption. Dysregulation that occurs for various reasons may perturb normal functioning, but the individual may still operate at a level that is not considered clinically significant. However, epidemiological research has shown that mild levels of dysfunction are a significant risk factor for more severe disorders a decade hence.[25]

A significant barrier to developing dimensional diagnoses is simply the long history of binary approaches to conceptualizing mental illness—one either has a disorder or not. Once a diagnosis is conferred, of course, scales have been developed to measure disorder severity, primarily for use as continuous measures in clinical trials; such instruments as the Beck Depression Inventory and the PANSS are familiar tools. However, designation of full remission often depends on using the formal diagnostic criteria rather than the scale scores (although cutoff scores, such as Hamilton-17 scores of 7 or less for depression, are sometimes used[26]). In either case, the fundamental distinction is between presence and absence of a putative illness state. In contrast, there is a dearth of scales that attempt to tap functioning on a continuous basis across some normal range and seamlessly out through various levels of pathology. Scales are typically devised either to measure normal personality or similar traits or else to tap various aspects of clinical symptoms, but not both. A notable example of such a translational instrument is a new scale for measuring externalizing behavior developed by Krueger, Markon, Patrick, Benning, and Kramer.[27] This scale was devised expressly to assess self-reported externalizing behavior across a dimension that ranges from normal college students to incarcerated, violent psychopaths. The development of such tools for dimensional assessment will be an important goal for RDoC over the next several years.

4. Develop reliable and valid measures of these fundamental components of mental disorders for use in basic studies and in more clinical settings

For a dimensional system to have practical utility—whether for actual clinical use or for use as end points in clinical trials—valid and reliable

measures of each dimension are obviously obligatory. As yet, the application of such measures to psychopathology is still in its nascent stages. This is not surprising, given that disorder categories were necessarily defined (as discussed previously) with respect to presenting signs and symptoms rather than neurobiological aspects. The first generation of attempts to relate disorder symptoms to the brain largely rested on neurotransmitter hypotheses and empirically derived endophenotypes that might index particular disorder categories. It is only within the past two to three decades that genetics and behavioral neuroscience have begun to relate reasonably specific aspects of behavior to relevant brain circuitry (e.g., for fear behavior,[18] working memory,[28] or reward-related behavior[29]). Thus, the basic research needed for translation is only now coming into focus. Accordingly, it is largely within the past decade that the field has moved beyond such disorder-specific efforts toward intermediate phenotypes that are closer to brain activity [9,30] and toward dimensions of genetic risk and psychopathology.[31]

An apt illustration of the steps that may be needed for measurement development is provided by recent efforts to promote clinical trials for remediation of cognition in schizophrenia. Several years ago, representatives from NIMH, academia, the pharmaceutical industry, and the Food and Drug Administration (FDA) convened to discuss the various steps that would be needed for the FDA to accept cognitive functioning in schizophrenia as a specific indication for drug development. The outcome was an initiative termed MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia).[32] The participants in this initiative conducted an extensive evaluation of many possible measures of neurocognition that would be appropriate for use in schizophrenia and that had well-established psychometric characteristics (reliability, lack of practice effects, etc.). This effort resulted in a test battery, also termed MATRICS, which has quickly become a standard in clinical trials for evaluating new interventions to improve cognition in schizophrenia[33]—not only for new compounds but also for other interventions such as cognitive remediation.

While MATRICS succeeded in its aims, the only tests available with adequate psychometrics were relatively older instruments that were known to involve multiple brain circuits for successful performance, constituting a clear disadvantage for research devoted to evaluating specific circuit-based functions. Accordingly, the NIMH soon initiated a second-generation effort named CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia). This initiative provided funding for a series of consensus conferences intended to identify cognitive systems and their component brain circuitry (as indicated by animal model studies and/or functional neuroimaging), particularly relevant for cognition in schizophrenia, and to delineate

particular tasks that could be useful for measuring these components.[34] A number of such tasks are already in development and nearing the point of release.

This does not, however, necessarily mean that the MATRICS battery will soon be supplanted by tests developed under CNTRICS. Rather, the latter are now at the point where their practical utility can be examined in a series of studies. Precisely because the CNTRICS tasks are more specific and oriented toward one particular circuit (e.g., visual perception, working memory), their relationship to overall cognitive performance is not clear. A finding that a drug compound or behavioral remediation protocol specifically improves, for example, visual perception, invites a number of questions: Does this specific finding ameliorate overall cognitive impairment and, if so, how much? If the treatment is a drug, is some period of cognitive remediation required to detect an improvement in functioning? Can remediation of a number of specific disabilities concatenate to improve overall performance? Are there some specific cognitive impairments that seem to be key elements in overall levels of functioning? Critically, how can the scientific community work with regulatory agencies such as the FDA to provide reasonable policies and guidance for such a complex set of measurements and potential indications?

These considerations are exactly the issues that must be confronted as tasks that measure RDoC constructs are developed over the coming years. The good news in this situation is that the MATRICS/CNTRICS process required only about a decade for development—a relatively rapid time frame considering the three decades in which research on the current DSM/ICD structure has been ongoing. However, it is clear that the shift in clinical targets from phenomenologically based categories to circuit-based dimensions will require some years of evolution in conceptual approaches and practice. Such considerations are a major reason that RDoC has focused in these early stages on circuits with clear referents—such as fear, reward circuits, and working memory—in which new treatments can have reasonably specific clinical targets and intervention effects can be assessed with reasonably specific outcome measures. The hope is that the rapid advances in brain science will hasten this entire process, leading to more effective and personalized therapies with a time frame measured in years rather than decades.

CONCLUSION: DIMENSIONS OF PSYCHOPATHOLOGY IN GLOBAL MENTAL HEALTH

Each culture has its own way of framing problems in living and in the prescribed ways of expressing various kinds of distress to others (e.g., see the classic paper by Kleinman, 1977[35]). It follows that a psychiatric classification system based on phenomenology and symptom reports must inevitably

encounter problems in establishing a uniform worldwide nosological scheme. Such indeed has proved the case, as attested to by the rich literature on cultural differences in mental disorders and the necessity for the World Health Organization to issue a lexicon of cross-cultural terms in mental disorders.[36] Although it is well beyond the scope of this chapter to explore all the ramifications of Research Domain Criteria, a few salient points will be mentioned here.

DSM-IV provides an appendix for *culture-bound syndromes*, a term developed in an attempt to supersede some of the more pejorative descriptions of disorders from other cultures. However, as Guarnaccia and Pincay have noted, "Recent critiques have pointed out that the culture-bound syndrome label, which practically always refers to forms of distress among persons in societies other than the United States or Europe, is not devoid of troublesome assumptions (p. 33)."[37] RDoC is formally agnostic to the current categories as listed in the DSM/ICD system; its emphasis rather is on functioning in particular dimensions of behavior. From this perspective, any one DSM/ICD disorder is likely composed of multiple mechanisms, while any one mechanism (e.g., disrupted reward circuit activity) is involved in multiple disorders. Further, the dimensional constructs are presumed to represent components that are universal across cultures, because they are defined by fundamental behavioral programs and specific brain circuits. Thus, the domains and constructs incorporated in RDoC would appear to possess the potential to sidestep some of the problems encountered with current nosologies that were developed largely within a US and European worldview. In particular, RDoC's theoretical stance, viewing the dimensions as constructs that are to be studied in an integrative manner across the various units of analysis, offers a potential heuristic in circumventing the mind–body problems that are often noted in both US and European research and cross-cultural studies.[38]

In spite of this promise, the way forward with extensions of RDoC measures and other cultures will not be trivial. Another example from the MATRICS project suffices to illustrate this point. The FDA moved to accept the use of the MATRICS test battery as an end point for trials of interventions to improve cognition in schizophrenia but also ruled that investigators must present some evidence of improved performance on an additional measure with real-world functional relevance—the so-called coprimary measure. The MATRICS investigative team tested several potential such measures in a US sample and reported that a number of coprimary indices exhibited acceptable psychometric performance and were suitable for additional evaluation.[39] However, given the number of clinical trials now conducted globally, it was necessary to adapt these coprimary measures to other countries. In a recent study, Velligan, Rubin, Fredrick, et al.[40] asked English-speaking research staff members at 31 sites in eight different countries to rate the extent to which

the various coprimary measures would be appropriate to their countries. The results showed that none of the coprimary measures were entirely suitable. Problems on particular subscales were reported across all of the countries, with India, China, and Mexico posing the greatest challenges. This is hardly surprising, considering that many of the coprimary tasks consisted of items largely confined to Western culture, such as calling one's physician about an appointment. While this particular issue can likely be solved with additional research and scale development, the larger point is that the development and adaption of tasks to measure various dimensional concepts across cultures may be a time-consuming process.

In spite of these initial barriers to dissemination of the RDoC approach on a global basis, the long-term prospects for integration of mental disorders concepts seem more auspicious. At the current time, culture-bound syndromes tend to remain outside the mainstream of psychiatry because of the difficulty of integrating local concepts into the DSM/ICD framework—a problem not only for Western scholars but for those in other cultures as well (e.g., a Latino researcher attempting to deconstruct the Japanese concept of hikikomori, a type of unusual social withdrawal[41]). Widespread acceptance of a common lingua franca for functional dimensions could offer researchers a common basis for studying and communicating about psychopathology.

In summary, the Research Domain Criteria project is a long-term effort to develop an empirical foundation for nosologies based on genetics and neuroscience. Many hurdles need to be overcome and conceptual and technical problems need to be addressed. As Owen and Craddock note in a recent commentary about the disjunction between recent data regarding the genetics of psychosis spectrum disorders vis-à-vis the DSM, "With what should it be replaced? Although it is fairly easy to identify problems with current diagnostic approaches and to describe the desirable properties of a 21st-century classification on the basis of an understanding of pathogenesis, such classification lies some years in the future (p. 191)."[42] However, the move to replace traditional disorder diagnoses with more individuated assessments based on pathophysiology and genetics is forging ahead in all areas of medicine,[43] and nosology in mental disorders is already lagging behind this trend. In this regard, the RDoC project is consistent with the call that many researchers have sounded for dimensions and intermediate phenotypes, which may provide the link between functionality and neuroscience. As Owen and Craddock also state, "In our view the new diagnostic criteria must encourage the careful measurement and reappraisal of psychopathology, including use of dimensional measures of key domains of psychopathology, which can sit alongside the use of categories (p. 191)."[42] While this process will clearly be a long-term effort, it is appropriate

to close with the traditional Chinese saying attributed to Lao Tzu: A journey of a thousand miles begins with a single step.

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