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“The Research Domain Criteria (RDoC): An analysis of methodological and conceptual challenges”

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Abstract

The article by Lillienfeld in this issue comprises a thoughtful critique of the Research Domain Criteria (RDoC) project initiated by the National Institute of Mental Health, and includes four specific theoretical and methodological challenges along with recommendations to address each one. In this commentary, I briefly consider each of the four challenges in turn, noting points of agreement and also clarifying selected points from the NIMH RDoC perspective. Overall, Lillienfeld’s paper represents a valuable contribution to the RDoC literature as research conducted with the new framework continues to accelerate.

Keywords

Research Domain Criteria; RDoC; intermediate phenotypes; endophenotypes; psychopathology

I would like to express appreciation to Professor Lillienfeld for an incisive and thoughtful review of the NIMH Research Domain Criteria (RDoC) project, and also add thanks for the opportunity to write a brief commentary from the NIMH perspective. His critique is particularly valuable because he has provided recommendations for addressing each of the four challenges that he discusses, making for a very constructive piece.

Lillienfeld begins his review with an outline of the problems with the DSM system that prompted the development of RDoC, followed by a brief summary of its framework. He has done an excellent job of capturing the dialectic in RDoC between the need to provide flexibility as a research framework that can accommodate new data (thereby modifying its list of dimensional constructs), while at the same time providing clear standards to applicants and reviewers with respect to research grant applications. The primary means by which this is achieved is the requirement that new constructs to be explored must meet the same evidentiary standards required of constructs defined in the foundational RDoC workshops – data supporting the functional nature of the construct, and data indicating a particular neural circuit or system that plays a predominant role in implementing the

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Competing interests

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proposed function. Further, priority is placed upon studying constructs across multiple Units of Analysis ranging from genetics to self-reports. (It might be noted that although Lillienfeld describes these units as “roughly more to less ‘basic,’” all the units of analysis are viewed similarly as part of the set of measurements that could characterize either normal-range functioning or dysregulated operation.)

Following the concise introduction, Lillienfeld delineates in turn four challenges for the RDoC framework, and this commentary follows that outline. In multiple instances, it appears that he is addressing his challenges equally to the research community and to the framers of RDoC, and so I try to respond from each perspective to the extent that they differ.

Challenge #1: Overemphasis on biological units and measures

This section begins with the quotation from an early RDoC paper that mental disorders are seen as “disorders of brain circuits,” with a subsequent caution about confusing biological mediation with biological etiology (Lillienfeld, 2014). As we have discussed previously (Cuthbert & Kozak, 2013), statements such as these are best interpreted in context as showing the need to emphasize the importance of neuroscience in a clinical environment still fraught with diagnosis by symptoms, trial-and-error treatment selection with modest response rates, and persisting misimpressions among the public regarding the nature of mental disorders. In fact, RDoC is intended as an integrative effort in which the goal is to relate measurements taken across multiple units of analysis rather than trying to work toward an eliminative reductionism.

Thus, we can heartily agree with Lillienfeld in cautioning investigators to be clear that the inclusion of biological measures in an experimental classification system does not mean an exclusion of etiologies derived from social, cultural, or other environmental sources. Unfortunately, RDoC’s two-dimensional matrix has proved to be a compelling figure suggesting that it represents the entire RDoC concept; in fact, the actual framework has always been considered as a four-dimensional matrix that includes environmental effects and neurodevelopmental aspects (in addition to the domains/constructs and units of analysis). In future expositions of RDoC, we hope to make these important dimensions more salient. One point to make in this regard is that the units of analysis encompass data recorded from human subjects, whereas environmental variables can characterize persons but are not measurements taken *from* persons; this is why this class of variables is accorded a separate dimension in the overall scheme.

Later in this section, Lillienfeld notes as a “logical error” that measures drawn from one unit of analysis are assumed to be the best measures of “abnormalities at that level,” with a particular point that self-reports can be equally or more “construct-valid measures of biological systems compared with biological markers of these systems.” (Lillienfeld, 2014, p. xxx). This statement seems to imply that an RDoC construct is construed as a “biological system.” In fact, each RDoC construct is conceived in the classic psychological sense of that term, not as a specific biological system. It is important to bear in mind that the units of analysis are all intended to form a convergent set of measures for the functional construct of interest; in other words, constructs are measured in part by biologically-based

measurements, but are not seen as biological systems themselves since behavioral data are equally important to defining the overall construct. As the authors of the recent NIMH BRAIN report stated, "... new innovation is needed in the analysis of behavior. Dobzhansky once said that 'Nothing in biology makes sense except in the light of evolution,' and it is no exaggeration to say that nothing in neuroscience makes sense except in the light of behavior." (BRAIN Working Group, 2014).

In the next part of this same section, Lillienfeld notes the statement by Cuthbert & Kozak (2013) that research relying only on self-reports would fall outside the RDoC matrix, adding that "such decisions should be adjudicated by data, not by fiat" (Lillienfeld, 2014, p. xxx). This apparent slight to self-report data is not the intention in the original, and can be clarified. RDoC is built upon constructs that are, as noted above, defined by evidence for both behavioral/psychological functioning and an implementing neural system; thus, data stemming only from self-reports simply falls outside the RDoC definitional framework. While this might seem an arbitrary exclusion, RDoC is a focused exercise in experimental classification, with its charter in the 2008 NIMH Strategic Plan to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (NIMH, 2008). We have tried to be clear from the outset that the framework was not intended to address (particularly at its outset) all possible aspects of psychopathology. NIMH continues to accept research grant applications that fall outside the RDoC framework, including those that rely on concepts measured solely by self-report.

Challenge # 2: Neglect of measurement error

This section discusses in some detail the problems of reliability in measurement, which are often moderate to low in laboratory tasks and neuroimaging, and concludes with recommendations that researchers must use care in employing such measures in their assessments. We agree fully with the well-documented points in this section. Formal psychometrics have received relatively little attention in RDoC discussions to date due to the priorities for explaining the major features of the new system, but will be crucial to the success of practical implementation in clinical research (and have been frequently discussed in internal workgroup meetings). The need for such demanding criteria is clear, as exemplified by the standards set in the FDA Biomarker Qualification Program for new drug development (FDA, 2014). Strict attention to such standards will be included in development of new measures that might be used in RDoC studies. A good example, antedating the RDoC project per se, comes from the CNTRACS (Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia) consortium that has adapted several cognitive neuroscience tasks with particular attention to measurement reliability (Gold, Barch, Carter, Dakin, Luck, et al., 2012).

Challenge # 3: Biological and psychometric limitations of endophenotypes

In this section, Professor Lillienfeld provides a generally positive discussion about the use of endophenotypes in the RDoC scheme, while cautioning that endophenotypes may not necessarily be more strongly related to genetics than complex DSM syndromes and that the

assumption that endophenotypes will serve as statistical mediators of genetic effects is not necessarily true. Broadly speaking, I agree with both of these points. Overall, RDoC has a somewhat less prescriptive and more empirical stance about the relationships of various classes of measurement, e.g., whether particular relationships among constructs are better considered in terms of mediators or as parts of a nomological net for construct validation. The GWAS results of recent years have further demonstrated the highly polygenic nature of mental disorders, which are likely to be shared by such complex functions as RDoC constructs. For these reasons, NIMH has somewhat de-emphasized candidate gene research in recent years, awaiting more definitive results from larger GWAS samples and from improved gene ontologies that can better relate genetic architectures to various types of clinical phenotypes (and endophenotypes). As we wrote at the outset of the RDoC project, "... the [constructs] might be considered to represent functional intermediate phenotypes characterized by a set of endophenotypes at different levels of analysis that, in the aggregate, define the [construct]; one advance that we hope to achieve with this approach is to forge more explicit links among these endophenotypes and their functional relevance in the [construct] of interest." (Insel & Cuthbert, 2009, p. 989).

Challenge # 4: Distinguishing biological predispositions from their behavioral manifestations

In this section, Lillienfeld raises the distinction between biological predispositions to psychopathology and the actual manifestations in behavior, outlining the familiar situation of multifinality. This issue also engages the important question of state versus trait distinctions across the full spectrum of mental disorders. The "Recommendations" section includes the statement that RDoC "may need to include indicators of both (a) biological predispositions and (b) the signs and symptoms of mental disorders, which can reveal whether these predispositions have been realized in maladaptive behavior." (Lillienfeld, 2014, p. xxx). Actually, the RDoC framework has included the latter measures from its inception; such instruments reside in the "Self-Reports" unit of analysis (which are defined to include structured clinical interviews, questionnaires, etc.), and also measures from the "Behavior" column in some cases. As with other research issues, relating clinical measures to other units of analysis is a key goal of RDoC-related research. One difference, obviously, is that "psychopathology" in RDoC is defined as dysfunction with respect to the functioning of particular constructs (or interactions of constructs, such as the effects of threat upon various cognitive processes). Overall, RDoC seeks to enhance the study of brain-behavior relationships by focusing on more cohesive behavioral constructs and their related neural systems, and by encouraging measurement across multiple units of analysis (including symptoms as quantitatively assessed). To be sure, issues such as multifinality and state-trait distinctions remain important problems for clinical research; however, by specifying more focused targets for study, including a more specific window through which to view the effects of neurodevelopment and the environment, the hope is that progress can be expedited in unraveling these persistent research challenges.

Professor Lillienfeld concludes the essay with a somewhat cautionary tone, reminding us that past hopes for new technological and methodological advances in assessing and treating

mental disorders have largely disappointed, and that we must avoid over-reaching our data. Such concerns are well-founded. We have often noted that RDoC was founded not out of hubris, but rather from a sense of humility that we know so little about our disorders as currently conceived that it is necessary to start over again with a new approach that can better integrate the data rapidly accumulating from genetics, neuroscience, and behavioral science. As the RDoC program moves forward, the kinds of concerns that Lillienfeld raises will prove valuable in keeping the science well-grounded in both theory and method.

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