Research Domain Criteria: Controversial Paradigm

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Schizophrenia Bulletin is very glad for the initiation of a cascade journal and welcome Schizophrenia Bulletin Open. Silvana Galderisi and Steve Marder represent the best of our field and will assure a critical role for communication. Responding to an invitation from the editors, the following is my first opportunity to contribute to SBOpen.

In the May 2018 issue of Schizophrenia Bulletin I provided a list of things I do not like in a tweet format. Here I comment on an issue representing new opportunities for advancing knowledge and understanding psychopathology. The Research Domain Criteria is an NIMH initiative and extensive information is available (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/index.shtml).

RDoC had a rocky start about 10 years ago. Much misunderstanding and distress in the initial period. What did NIMH want, was it a required framework for funding, and replete with misunderstanding by applicants and reviewers. Much has been resolved over the first several years but the question, “what is RDoC,” still generates a range of answers. My view is as a semi-insider having been the DSM-5 liaison with NIMH at the outset, then external advisor, and presently as a participating member of the RDoC Unit.

RDoC is a research paradigm intended to advance knowledge regarding mechanisms of psychopathology. How does the brain generate illness manifestations. The paradigm requires a behavioral construct presumed associated with aspects of psychopathology (the Domains) and sufficient knowledge of neural circuit involvement in the behavior to provide a starting point for discovery of more fundamental elements of psychopathology (eg, molecules, gene expression, cells, physiology, neural networks). There is now general acceptance that most elements of psychopathology cut across present nosological categories and are dimensional relating to severity and that each dimension may extend from severe symptom to non-pathologic. In this regard, the RDoC initiative encourages a dimensional view and may include several disorders and non-ill participants. The dimensional framework is required and while several disorders are often included in the study design multiple disorders are not required.

There are many paradigms associated with NIMH funding, but the RDoC NIMH initiative is of special interest as an attempt to advance knowledge in areas that have not been well-served with paradigms based on heterogeneous clinical syndromes. Success of the RDoC initiative will eventually depend on how basic brain mechanism discovery related to behavioral constructs translates to clinical psychopathology.

The RDoC initiative has generated controversy but also initiatives. An example is found as regulatory bodies such as the FDA prepare for viewing targets for efficacy, not in diagnosis of clinical syndromes, but rather in specific psychopathology. And the likelihood that specific elements of psychopathology (eg, anhedonia) will have a similar mechanism and efficacy response across diagnoses. Here the first hurdle will be the determination of whether anhedonia is really the same psychopathology across disorders. The RDoC approach will generate relevant data to address such issues. When a drug with efficacy for impaired cognition is discovered it will be urgent to determine to which cognitive disorders efficacy applies. RDoC may provide critical information to determine issues such as whether anhedonia in major depression is the same pathophysiology as anhedonia in schizophrenia. A closing comment on several vexing issues:

1. Does RDoC constrain innovation by limiting domains of interest and assessment methods? The current matric provides exemplars and the paradigm can be applied with a behavioral construct or an assessment methodology not included in the matric. The applicant can defend the selection. The recent addition of the...
motor domain illustrates that RDoC is not set in stone and a motor based RDoC application could have been successful before the domain was added.

2. Is RDoC intended to replace DSM in nosology or as a diagnostic manual? No! The initiation of RDoC reflected the inadequacy of clinical syndromes for advancing scientific knowledge on brain mechanisms. DSM-5 and ICD versions are not the problem; they are just not the solution to the challenge of understanding how the brain creates psychopathology. Nosology and diagnostic manuals are vitally important for many purposes. A reasonable expectation is that paradigms that advance understanding of brain mechanisms in psychopathology will provide critical knowledge for next-generation concepts of mental disorders.

3. Has RDoC neglected neurodevelopment? Yes and no. In concept, the paradigm is applicable to all stages of development. However, much more is known about the assessment of the behavioral constructs in late adolescence and adulthood than in aging or early development. A critical issue for RDoC is access to valid assessment procedures for each domain at all points of development. Much of the pathology associated with the behavioral constructs is observed early in life. An additional problem pointed out at a November 2019 RDoC workshop on development and environment is that manifestation of a behavioral construct may vary within individual in a qualitative as well as quantitative manner across development stages. Addressing these issues is a challenge and should be considered urgent.

4. Has NIMH turned away from environment and prevention with the emphasis on the RDoC program? In principle, no. But whether in fact RDoC funding has curtailed funding in other specific areas is difficult to assess. My view here is focused on what the potential results from application of the RDoC paradigm may mean to environmental and prevention issues.

a. Understanding environmental risk/causation is absolutely critical. The RDoC paradigm may produce mechanism knowledge now missing in the study of environmental impact on psychopathology. If so, the field may move more quickly in treatment and prevention with novel targets more proximal to pathophysiology.

b. Application of environment risk factor knowledge may inform methods within the RDoC framework providing proof of principle testing of a causal hypothesis generating change at some or all levels of the RDoC matrix.

c. The field needs to greatly increase prevention trials for psychopathology. Launching a prevention trial related to known risk factors backed up with evidence of involved brain mechanisms in the context of knowledge of to whom the intervention is relevant will be a giant step forward.

In summary, RDoC is an NIMH initiative intended to address the shortcomings of heterogeneous syndromes as the starting point for discovery. The RDoC paradigm is illustrative, subject to modification, and joins other paradigms in the attempt to advance knowledge. It is designed to enhance knowledge of brain mechanisms in psychopathology. To the extent that it is successful, it will enhance prevention and identify targets for therapeutic discovery.

Acknowledgment

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Reference