Updating the Research Domain Criteria

Two and a half years ago, *World Psychiatry* published a Forum about the US National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative¹. In it, there was spirited commentary with divergent views of diagnosis and critical examination of RDoC², but the discussion captured the challenge of shifting the paradigm for psychiatric nosology. Here I provide an update on RDoC, while articulating some fundamental issues.

The RDoC idea was introduced 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”, because advances in integrative neuroscience were not being realized in patient care. Decades since Robins and Guze³ proposed validity criteria that included laboratory tests, and years since Wakefield⁴ articulated the “harmful dysfunction” definition of mental disorder, there was still no valid laboratory test – biological or otherwise – linking any psychiatric diagnosis to an internal mechanism. Syndrome-based diagnoses (DSM/ICD) did not map to disrupted neural mechanisms⁵, and there was a steep decline in the development of new therapeutic agents⁶. It was argued that clinical syndromes were too distal from genetic mechanisms to research connections, and suggested that an intermediate phenotype approach would be more viable⁷. Regardless, funding for psychopathology research in the US remained harnessed to the DSM. RDoC was introduced to allow researchers to pursue funding for translational research without the limitation of DSM independent variables.

RDoC differs from syndrome-based research by incorporating a dimensional approach. Rather than beginning with diagnoses based on clinical description and then trying to connect them to mechanisms, RDoC research begins with dysfunctional mechanisms and works toward clinical symptoms. The process is to identify a mechanism used for functional behavior, and to link its improper function to clinical problems. The aim is to inform nosology, including future DSM and ICD revisions, to ultimately help those suffering clinical problems by clarifying homogeneous treatment targets. RDoC is not a clinical manual or a replacement for the DSM or the ICD. It is an evolving structure, intended to facilitate translational research.

The RDoC matrix is organized with Domains and Constructs in the rows, and Units of Analysis in the columns (see www.nimh.nih.gov/research-priorities/rdoc). It was developed in consultation with the scientific community, including NIMH workshops where experts in each of the respective domains refined construct definitions. Constructs required validity for a functional unit of behavior and a link to clinical problems. Connection to a neural circuit was emphasized to fill the gap between neuroscience and psychopathology research, and does not necessitate a reductionist philosophy;

indeed, observations of different systems provide different forms of important evidence⁸.

There are at present five RDoC Domains: Negative Valence, Positive Valence, Cognitive Systems, Social Processes, Arousal and Regulatory Systems. Within each domain are a number of constructs. Evidence for a new domain, Motor Systems, is under review with an NIMH-sponsored workshop, and there are plans for annual consideration to accommodate new findings indicating revisions. Across the columns of the matrix are Units of Analysis, which include Genes, Molecules, Cells, Circuits, Physiology, Behavior, and Self-Reports (self-reports include patient-reported symptoms). Elements in each cell hold findings that correspond to respective constructs, within a particular unit of analysis.

A unique column, Paradigms, is for behavioral tasks designed for valid and reliable assessment of a specific mechanism or circuit (e.g., an “n-back” task for working memory). Such tasks are routine in experimental research but, for RDoC, these approaches need to be more fully developed to meet acceptable psychometric standards, including sensitivity and specificity. A National Advisory Mental Health Council Workgroup was convened and evaluated the state of the research in this area and formulated recommendations, reported at its September 2016 meeting.

Since the *World Psychiatry* Forum, RDoC impact has accelerated. RDoC Workgroup members now have over 30 papers, published or in press, detailing the rationale, description, and development of RDoC (see www.nimh.nih.gov/research-priorities/rdoc). Many of these are in collaboration with non-NIH affiliated clinical scientists. Seminal papers published by the RDoC Workgroup have collectively been cited over 2,000 times. In addition to *World Psychiatry*, several journals have devoted special sections to RDoC (e.g., *International Journal of Psychophysiology*, *JAMA Psychiatry*, *Journal of Abnormal Psychology*, *Neuropsychiatric Genetics*, and *Psychophysiology*), with others in the offing. Presently, there are 38 active projects funded by NIMH RDoC Requests for Applications (RFAs), three active program announcements. A search with NIH Reporter (<https://projectreporter.nih.gov/reporter.cfm>) reveals the term “RDoC” in 273 currently funded grants. RDoC figures prominently in the recent NIMH Strategic Plan (www.nimh.nih.gov/about/strategic-planning-reports).

Regular RDoC Internal Workgroup meetings continue to solicit and incorporate feedback from the field, while guiding ongoing development. In 2014, the RDoC Unit was created within the Office of the NIMH Director. The Unit has been instrumental for codifying a number of RDoC-related efforts, including improvements to the on-line version of the matrix, which now links constructs to definitions, as well as common elements across Units of Analysis. In this form, the matrix can be used to facilitate research design and identify areas where more knowledge is needed. It can also serve as a teaching tool.

Future possibilities include linking matrix elements to the US National Library of Medicine. The RDoC Database repository (RDoC-db) collates subject-level data, creating a common-use data set for future data mining (<https://data-archive.nimh.nih.gov/rdocdb>). Other web-based tools include a discussion forum, and an ongoing series of webinars, archived on the website. Planning is underway for another major update of the RDoC website.

RDoC does not mandate a unitary approach to translational research. Rather, it provides a scaffold to organize findings, and on which a nomological net may be constructed. Theories of development, environmental influences, and psychopathology are needed to spell out the connections between constructs. A research exemplar is the Bipolar Schizophrenia Network on Intermediate Phenotypes (B-SNIP), which recently reported emergent biotypes that overlapped in different degrees across psychosis spectrum patients, evidencing systematically varying levels of cognitive control as well as differences in grey matter⁹. With RDoC, these biotypes offer new possibilities for independent variables in future studies¹⁰.

As a research tool, RDoC has the luxury to evolve incrementally, with regular updates. Its web-based format facilitates faster-paced change and allows open access. In contrast, any modification to a DSM or ICD diagnosis can have immediate consequences for patients (e.g., treatment decisions,

reimbursement for services, disability accommodations). For meaningful progress, ongoing collaboration with stakeholders is valued (e.g., professional and health organizations, regulatory agencies, and patient advocacy groups). Combined efforts will encourage new ways to think about diagnosis for clinicians and researchers alike.

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DOI:10.1002/wps.20374

Adopting a continuous improvement model for future DSM revisions

The approach used for making changes to both the DSM and ICD has been up to now to revise the manuals in their entirety at fixed (albeit variable) intervals. Typically, these diagnostic revision efforts have been multi-year affairs involving the appointment of committees of experts tasked with making changes with the goal of improving the validity, reliability, and clinical utility of the diagnostic systems^{1,2}.

While this approach has the advantage of facilitating standardized communication among users of the classifications by ensuring the uniformity and stability of the diagnostic definitions in the time interval during which that edition of the manual is in effect, it prevents the incorporation of new scientific knowledge into the manual as it emerges, a limitation that has become especially problematic given the extended intervals between revisions that have characterized the most recent editions of the DSM and ICD (19 years and 23 years, respectively).

Advances in digital publishing that allow instantaneous dissemination of changes at minimal cost have paved the way towards the American Psychiatric Association (APA) adopting a continuous improvement model for the DSM, in which revisions are pegged to specific scientific advances. Thus, rather than waiting until the next wholesale revision to implement a

clinically useful change (such as incorporating a solidly validated biomarker into the definition of a disorder), such a change could be put into effect as soon as it has been determined that it is diagnostically advantageous to do so. Moreover, implementing a continuous data-driven approach has the added advantage of discouraging changes that are not well supported by empirical evidence. As described by Kendler in his accounting of the history of the DSM-5 Scientific Review Committee, there is an inherent trend towards making changes built into the DSM revision process: “for workgroup members, it is a natural source of pride to ‘make a difference’, to ‘put their mark’ on the document” (3).

A new DSM web portal (www.dsm5.org) has been set up by the APA to field proposals for changes on a continuous basis. Submissions will be web-based, with proposers required to provide supportive information in a structured format, including the reasons for the change, the magnitude of change, data documenting improvements in validity across a range of validators, evidence of reliability and clinical utility, and a consideration of current or potential deleterious consequences associated with the proposed change. It is anticipated that most submissions will come from interested persons (e.g., psychiatric researchers, individual clinicians) or organizations