Whither Research Domain Criteria (RDoC)?
The Good, the Bad, and the Ugly

Do we need to replace categorical with dimensional diagnoses to make progress in psychiatry research? No.

The release of Research Domain Criteria (RDoC), which occurred coincident with publication of the DSM-5, has been touted as offering a superior classification system for psychiatric disorders. Its advantage is supposedly based on mechanisms rather than symptoms. Pushback from clinicians and researchers has led to partial refashioning of RDoC goals, from initial emphasis on improved diagnosis to revised claims of a scientific nosology for clinical research. For any new scheme for patient categorization to be an advance, it has to prove superior on multiple levels to the consensus clinical tactics of DSM-5. We doubt that this will occur with RDoC because it lacks the very scientific foundation that it proclaims. We lay out our “con” argument in homage to Sergio Leone.

What Seems Good About RDoC
That DSM-5 is a less than ideal approach to clinical diagnosis is evident. It is purely phenomenological and largely arbitrary, and not based on valid etiological concepts or mechanisms of illness or genetic predispositions. Improving diagnosis by substantive discriminating criteria based on genetics and neuroscience would be a clear advance. RDoC proposes using concepts from cognitive, affective, and social neuroscience as well as from clinical genetics to introduce more precision into characterization. Its goes so far as to suggest a relabeling of psychiatric disorders as “neural circuit disorders,” a seductive phrase. The appeal of RDoC rests on how good this sounds.

Supporters of RDoC suggest that it will lead to more personalized medicine, which would be an advance, if true. Of course good clinicians already use symptomatic and severity dimensions to individualize treatment independent of diagnosis. Thus, depressed symptoms may be treated with antidepressant drugs across diagnoses, anxiety symptoms are sometimes treated with antianxiety drugs regardless of primary diagnosis, and anticonvulsants are used to treat explosive behavior, per se. Clinicians recognize that current psychiatric medications treat symptoms, not diagnoses, but they also recognize that symptoms in different contexts merit decidedly different treatments, eg, apparent anxiety in one context may reflect agitation or psychosis in another.

Regardless, that RDoC makes researchers and clinicians think about genetic and neurophysiological factors in the context of abnormal behavior is a positive influence. However, beyond the obvious that brain circuits and genetics are relevant to behavior, RDoC ultimately has to tell us something that matters to the lives of our patients, eg, what makes them sick and how to make them better.

What Seems Bad
One of the striking omissions in the RDoC “matrix” is any appreciation of the remarkable difference between well and sick, or the critical importance of time in defining course or prognosis and in clinical decision making. How one determines that somebody is a “case” with disability and distress remains obscure, as there is no tactic, for example, to distinguish unhappiness or demoralization from clinical depression. RDoC also does not recognize the implications for categorization incurred by the unexpected discoveries of psychopharmacologic treatment. Lithium is not antipsychotic, even though patients with bipolar disorder and schizophrenia will share many RDoC domains. Further, that the major psychotropic drugs have no parallel benefits on normal individuals contradicts the rheostat model of too little or too much of a particular biologic dimension reflecting a continuous range from severely ill to varieties of normality. Height is a continuous metric, but do we assume that all short individuals just happen to have gotten a bad spin at normal DNA roulette? This logic rejects the fact of distinct pathophysiologicals, eg, achondroplasias and growth hormone deficiency. It is a fallacious assumption that a continuous measure reflects homogeneity across its range.

The RDoC approach promises that if data from our advanced genetic, neurophysiologic, and perhaps cellular measures are collated in mixed patient and normal samples in a diagnostically agnostic framework, clinical precision will be enhanced. However, patients with depression and patients with schizophrenia may show similar abnormalities on cognitive testing, similar engagement during functional magnetic resonance imaging protocols involving working memory, and even similar erythrocyte sedimentation rate, just as patients with anxiety and psychosis may show similar fear behavior ratings, negative valence ratings, and overactivation of the amygdala using functional magnetic resonance imaging fear paradigms. But the underlying reasons for these superficial similarities in fractionated behaviors and biological measures are different. RDoC would suggest that these underlying differences are not as important as the superficial similarities across diagnostic categories. For clinical treatment, it is critical not to be misguided by superficial similarities in such domains. The assumption that a clinician could successfully treat in a singular fashion all individuals who score high on a negative valence scale or amygdala reactivity or working memory is non-scientific and clinically irresponsible. Indeed, one might
argue that RDoC similarities across diverse samples are particularly ill suited to explain why some individuals are sick and how they get better.

RDoC rationalizes its origins in the notion that DSM-5 diagnoses are invalid. What is meant by validity in this context? To raise questions about diagnostic validity is to question the ability to correctly make statements about some clinical validator, such as making a correct prognosis, performing correct treatment, and making correct predictions of outcome. Each of these medical activities serves as a key validator. Is there any potential finding from RDoC likely to uniquely validate the course and treatment of a given patient? Before making a heavy financial and professional commitment to this initiative, it would have been appropriate first to undertake preliminary work gathering objective data addressing the likelihood that this approach pays off. Instead, we are asked to be content with opinions based on small group meetings comprised largely of nonclinicians that affirm that RDoC is correct and that it will be closely monitored. Yet, the monitoring criteria and procedures are unspecified while study sections obediently impose RDoC as a prerequisite for funding.

What Seems Ugly
The RDoC “matrix” enumerates a series of “domains” and analytic “units” that represent the meat of the proposal. The term matrix here is more a buzzword than a helpful concept, as it actually precludes studying interactions between concepts that lie on the same (domain) axis. How valid are any of the RDoC rows and columns? The spreadsheet lists mostly phenomenological measures based largely on rarefied experimental paradigms that are themselves poorly defined, and often use subjective, highly context- and sample-dependent measures (eg, “understanding of self,” “of others,” and “reward learning”). Most measures are not based on rigorous experimentation, with sample criteria, test-retest and interrater reliability, sensitivity and specificity analyses, and normative definitions. The meaning and utility of the domains in real-world clinical samples are virtually unknown. Much is made, for instance, of the overlap of genes across psychiatric diagnoses, as if diagnosis does not matter in psychiatric genetics. While it is certain that the human genome did not evolve to validate DSM-5 criteria, current evidence actually suggests that genes light up DSM-5 better than RDoC. In a study of a combined sample of 5 psychiatric diagnoses, 5 genes were identified seemingly unrelated to any specific diagnoses. In fact, the genes reported to be positive in the lumped diagnoses group show stronger associations in smaller samples having only one diagnosis. In other words, mixing diagnostic groups actually dilutes the genetic findings. It is also doubtful that the small genetic overlap across diagnostic groups advances clinical diagnosis and practice. The genetics of multiple sclerosis and Crohn disease also show overlap but these are distinct pathological conditions, with divergent mechanisms and presentations requiring different clinical interventions.

We strongly encourage rerouting of resources overinvested in RDoC to a carefully constructed pilot program focused on whether data acquired on the RDoC spreadsheet add anything to the well-being of patients. While it is possible that research about neurocircuits and genes may eventually refine categories and identify subgroups, this seems most plausible when examined in the context of a particular diagnosis, which we envision as a more fruitful endeavor (“RDoC Unchained”). The RDoC initiative claims that it is meant to encourage research to improve our case definition system, but its goal is clearly to revise how we assign case status. In our view, RDoC will not achieve this goal. It is not based on the science it proclaims and it ignores the key clinical reality of sickness vs wellness.

ARTICLE INFORMATION
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REFERENCES