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Achieving Success with the Research Domain Criteria (RDoC): Going beyond the Matrix

William G. Iacono

University of Minnesota

Abstract

Achieving Research Domain Criteria (RDoC) goals depends in part on how well scientists can grasp its principles and execute studies within its framework. Ford provides an exemplary illustration of a research program that aligns with RDoC guidelines. The future success of RDoC depends not just on research like that of Ford and colleagues. RDoC also must inspire the development of reliable neurobehavioral measures with demonstrable clinical validity that produce replicable findings leading to the establishment of neurocircuit-based behavioral dimensions that inform clinical work. Large samples not typically attainable in a clinical neuroscience laboratory or easily imagined within the confines of the RDoC matrix will be required if RDoC is to develop the insights and tools needed to establish incremental value over the DSM. Innovation that goes beyond reliance on the RDoC matrix and measures of neurocircuitry can help facilitate achievement of RDoC's goal of developing a science of psychopathology based on neurobiological systems.

Keywords

auditory verbal hallucinations; event-related potentials; endophenotypes; molecular genetics

Much has been written by the proponents of the Research Domain Criteria (RDoC) characterizing its goals and clarifying what research approaches are compatible with RDoC (Cuthbert, 2014a, 2014b; Cuthbert & Kozak, 2013; Insel et al., 2010; Sanislow et al., 2010; Simmons & Quinn, 2014). The current contribution by Kozak and Cuthbert (2015) further extends this worthwhile discussion by fleshing out its conceptual underpinnings and providing practical recommendations regarding its implementation. While these RDoC policy papers are helpful and welcomed, it is also of value to have illustrations of the successful application of a psychiatric research program that fits the RDoC agenda, especially using psychophysiological methods. The paper by Ford (2015) provides a brilliant and elegant example of such an application.

Ford's Approach as RDoC Exemplar

Ford (2015) outlines a program of research that, although begun well before its introduction, nevertheless falls within the RDoC framework. Simply put, she and her colleagues want to

Correspondence to: William G. Iacono, Department of Psychology, University of Minnesota, 75 East River Road, Minneapolis, MN 55455 wiacono@umn.edu.

understand the brain mechanisms associated with the auditory verbal hallucinations (AVH) that many people with schizophrenia report, and are using psychophysiological methods to identify a neural signature associated with this symptom. In their model, vocal utterances generated by the motor cortex lead to two commands, one to initiate the motor act of speaking, and the other to send an efferent copy of this command to the auditory cortex. A corollary discharge of the efferent copy is generated at this brain site, representing the expected sensation associated with the utterance, and this discharge is compared to the actual acoustic sensation arising from the utterance. In healthy individuals, the match between the corollary discharge and the sound entering the ear leads to suppression of auditory cortical responsiveness. In those with schizophrenia, this dampening of the auditory cortical response when speaking is less pronounced. Thinking is presumed to involve the same mechanisms, also generating corollary discharges, with this neural system working to distinguish self-generated sensations such as AVH from actual acoustic sensations delivered from external sources. For those with AVH, the system responds the same way to thoughts and vocalizations, making differentiation of the two difficult. Hence, mismatches between the brain's predictions and sensations in this neural pathway can lead to thoughts being perceived as alien to the individual, and their being interpreted by the individual as originating outside the self, thus constituting AVH.

Thinking cannot be measured directly, but overt speech can. Ford and colleagues have cleverly adapted a vocalization paradigm developed on non-human primates that allows for the manipulation of speech in a manner that makes it possible to use the millisecond precision afforded by EEG to distinguish the cortical activity preceding speech sound onset from the activity associated with the processing of the predicted speech sound itself. In a series of programmatic investigations that build on and extend their initial work, Ford and colleagues have made several insightful and notable discoveries. Healthy suppression of auditory cortex processing during vocalization can be seen in reduced N1 event-related potential amplitude to the onset of spoken sound as it is being generated. In addition, pre-speech neural synchrony between Broca's area and the auditory cortex is attenuated in schizophrenia and associated with N1 suppression during talking, indicating that the efferent copy preceding vocalization was affected. Moreover, this effect correlates with the severity of hallucinations, indicating that it indexes the quality of neural processing associated with hallucinatory activity. Ford goes onto to place her work within the RDoC scheme, noting that N1 represents the physiological unit of analysis within the RDoC matrix. In addition, she highlights how her research intersects with the rest of the matrix, and notes the challenges that remain to move her work forward within RDoC.

Ford's work clearly advances the RDoC goal of developing a biologically-based integrative science of psychopathology. Kozak and Cuthbert make the important point that RDoC constructs need to be related to clinically relevant symptoms of mental disorder, but note that guidance regarding how to achieve this objective has been inadequate, leading to confusion regarding where clinical problems fit in the RDoC matrix. Ford has focused on a symptom that while prominent in schizophrenia, is observed in those with other psychoses, and she and her colleagues have shown that the AVH neural signature does not depend on the diagnosis. Also in line with RDoC aims, her work elevates this symptom, which historically has only been identifiable through self-report and is challenging to assess in uncooperative

patients, to one that may potentially be ascertained through a neurobiologically relevant measure. Kozak and Cuthbert lament that DSM/ICD disorders are too broad for the specific actions of most new drugs. As Ford's work continues, we may look forward to a time when a drug trial is launched that targets AVH, the effectiveness of which can be documented by examining convergent effects involving self-report, N1 suppression, and pre-speech EEG synchrony across frontal motor and temporal auditory cortices.

Do We Need the RDoC matrix?

Ford's (2015) article is not unlike others that have been written about the application of RDoC to existing research programs in that it shows how extant literature can be organized and related to the RDoC framework (e.g., Badcock & Hugdahl, 2014; Bauer et al., 2013; Franklin, Jamieson, Glenn, & Nock, 2015; Tanofsky-Kraff, Engel, Yanovski, Pine, & Nelson, 2013). Taking this step is valuable given the relative newness of RDoC coupled with its standing as a radical alternative to the status quo, and given that NIMH research funding is increasingly being tied to the ability of investigators to adapt their work to satisfy RDoC guidelines. In Ford's case, we can see how her research program can be fit into the RDoC matrix. However, it is more difficult to see how our knowledge of matrix constructs is improved or might be modified by her findings, and, importantly, how her work is inspired and enriched by its being linked to RDoC.

Ford posits that her research falls under the Social Processes domain and is related to the RDoC construct of “agency”, given its focus on the ability to recognize one's self as the agent of one's actions and thoughts. Because hallucinations are generally not recognized as originating within the self, agency is obviously relevant. However, Ford's model, which is derived from an experimental paradigm examining speech generation and auditory processing, involves brain mechanisms important to language, perception, and sensory motor integration, in which case it might be placed alternatively in RDoC's Cognitive Systems domain. In an earlier paper, she and her collaborators (Ford et al., 2014) considered how AVH may relate to multiple RDoC constructs, including those involving cognitive systems. The point is not that one domain or construct works best for AVH, or that multiple domains may be relevant, but that ultimately, one would hope that the significance of Ford's work and that of other clinically-oriented psychophysiologists will be enhanced by mapping it to RDoC domains. If RDoC cannot achieve this objective, it would be better to emphasize the sound principles guiding the development of RDoC, many of which Ford coincidentally embraced in her research prior to RDoC's initiation, and drop the matrix.

Is It Advantageous to Put Neurocircuitry First?

RDoC is designed to “promote the development of an interdisciplinary science of psychopathology that consists of dimensional constructs integrating elements of psychology and biology, especially genetics and neuroscience” (Kozak & Cuthbert, 2015, p. 9) leading to validated “fundamental circuit-based behavioral dimensions ... useful for eventual clinical work” (Cuthbert, 2014a, p. 28). Achieving this laudable objective will require developing reliable measures with demonstrated construct validity that generate reproducible findings, a demanding task if the measures are to be anchored in neurobiology. Study samples,

including replication samples, will need to be much larger than is typical in clinical neuroscience. Neurobiological investigations that are designed to detect group effects are typically underpowered, making it difficult to replicate findings and accurately estimate effect sizes (Button et al., 2013). Especially large samples will be needed if the objective is to develop psychometrically sound procedures for assessing individual differences in neural function.

In a groundbreaking report that highlights what we might hope to accomplish through RDoC, the IMAGEN consortium used clinical, behavioral, and neuroimaging measures to successfully identify neurobehavioral configurations that differentiated subdimensions of externalizing psychopathology from each other (Castellanos-Ryan et al., 2014; for additional perspective, see Iacono, 2014). Correlations between variables from differing measurement domains (e.g., brain, clinical) were small (~ .10); without the sample size of almost 1800 individuals, this investigation, which must be replicated before we can have full confidence in the results, would have failed to uncover the reported configural patterns.

However, even with samples this large, it is not likely that neurophysiological measures will help fill the “genes” column in the RDoC matrix. Psychophysiological endophenotypes have been advocated for their potential advantage over the study of DSM constructs to identify psychopathology-relevant genetic variants (Iacono, 1998; see also Gottesman & Gould, 2003). In the most comprehensive undertaking to date of their ability to achieve this goal, Iacono and associates (Iacono, Vaidyanathan, Vrieze, & Malone, 2014) examined 17 psychophysiological measures tapping into multiple RDoC domains (e.g., arousal, negative valence, cognitive systems). Genome wide association analyses, exome rare variant analyses, and whole genome rare variant sequencing failed to uncover any solid leads or to replicate any past findings. This work was based on data from a sample of nearly 5000 individuals using data that took over two decades to collect. The authors concluded that immense samples would be required to detect specific gene effects; e.g., a minimum N of 20,000 would be needed to establish the single strongest effect identified as statistically significant in this work (e.g., for the P300 ERP measure; Malone et al., 2014).

Although few would argue at this point in time that the key to uncovering the pathophysiology of psychopathology is to study DSM categories, it is not the case that neurobiological studies of DSM constructs have met with no success, an assessment RDoC does not dispute. The insights into the neural mechanisms associated with AVH generated by Ford's research program have derived mostly from studies of schizophrenia patients. The one credible report of genetic variants associated with schizophrenia involved pooling GWAS data from over 35,000 schizophrenia patients and 100,000 controls to identify 108 genome-wide significant loci (Schizophrenia Working Group of the Psychiatric Genomics, 2014). It is unlikely that such an encouraging result would derive from the use of an RDoC construct because there is no reason to think it could be accomplished using anything less than a similarly sized but likely unattainable sample.

Evidence from other sources points to the value of using behavioral measures linked to RDoC constructs to enable work with the large samples that will be needed to flesh out the RDoC matrix. Patrick and colleagues (Nelson, Strickland, Krueger, Arbisi, & Patrick, 2015;

Patrick et al., 2013) have used this approach to illustrate how self-report measures with known psychophysiological correlates and in combination with neurophysiological variables can be used to predict externalizing symptoms, and provide insights into the type of RDoC-relevant nomological net that Kozak and Cuthbert hope will emerge through RDoC research. However, it need not be a requirement that a biologically informed phenotype be adopted to find RDoC relevant genetic variants. Because sample size is so important, even crude measures that are commonly assessed in most any health study that collects DNA, like cigarettes smoked per day (a proxy measure of nicotine dependence, a problem confronting most individuals with schizophrenia), can be profitably examined to uncover verifiable genetic results (Saccone et al., 2010).

An example relevant to the RDoC Cognitive Systems domain derives from genetic investigations of how far a person goes in school, a proxy measure for the cognitive skills associated with educational attainment. Rietveld et al. (2013, 2014) identified education-associated genetic variants in a pooled sample of over 100,000, and showed in much smaller samples that the identified variants were associated with cognitive test scores, memory, and cognitive health in older age. The identified variants were linked to a neurotransmitter pathway associated with synaptic plasticity, a sensible association given the importance of learning and memory to cognitive performance. Such work indicates how biologically significant headway can be gained from research that puts behavioral, rather than neural, measures first, making possible large sample studies that would be prohibitive in terms of cost if the required focus had first been on developing and refining neurophysiological assessments.

Conclusion

The work of Ford and colleagues provides a blueprint for how inventive research design consistent with RDoC principles can lead to a successful melding of basic and clinical science with the potential to advance public health. As valuable as they are, small-sample investigations like these with a primary neurophysiological focus will not be enough to enable RDoC to reach its ambitious aims. Large sample studies focused on behavioral dimensions informed by neurobiology will be required and should be supported even if at first glance, they seem to fall outside of the “RDoC box.” Encouraging data sharing and the recent establishment of an RDoC database (http://rdocdb.nimh.nih.gov) constitute important steps toward facilitating the creation of the large samples of harmonized data that will be needed to further RDoC's goals. Success with RDoC will require more than fitting one's program of research into the proper rows and columns of the matrix (cf. Simmons & Quinn, 2014, p. 26). It will also require leveraging all the research tools available to integrate findings across diverse approaches, ideally evaluating competing theoretical accounts of the mechanisms relevant to the development of psychopathology (Vaidyanathan et al., 2015a, 2015b).

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