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## Psychophysiological Science and the Research Domain Criteria: A Commentary

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### Abstract

The current special issue, devoted to the Research Domain Criteria (RDoC) initiative of the US National Institute of Mental Health, showcases a variety of empirical and review articles that address issues related to this dimensional and multi-method approach to research on mental disorders. Here, we provide an integrative perspective on various aspects of these articles, focused around the primary principles of the RDoC approach and the practical and methodological issues related to conducting RDoC-informed research. The chief point we wish to highlight is that these articles demonstrate the ways in which the field of psychophysiology already thinks along the lines of RDoC in terms of using biobehavioral constructs, looking for convergence amongst constructs using various methodologies, and utilizing dimensional measurements in studies. In this sense, RDoC is not novel; however, by specifying a formal research platform it provides explicit encouragement and guidance for using such principles in understanding psychiatric phenomena, rather than continuing to focus research efforts on traditional diagnostic categories alone.

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We appreciate the opportunity to comment on this excellent collection of papers. Psychophysiology, as a field, is especially well positioned to conduct the type of dimensional, integrative, translational research that RDoC is meant to stimulate. The empirical papers in the current special issue provide well-considered examples of the implementation of RDoC principles. The accompanying review papers help to bridge the span between existing research – much of which has been done using categorical diagnostic approaches – and future work informed by RDoC. In this commentary, we provide an update regarding the RDoC initiative and discuss future next steps with the project, highlighting various issues raised by the papers in the current collection.

RDoC is no longer a new initiative and has entered the parlance of the scientific and regulatory communities. As a blunt measure of its penetrance, the number of published scientific papers that include RDoC in the title or abstract now exceeds 200. With regard to research support, NIMH has funded more than two dozen grants via RDoC-specific funding opportunities and over ten times that number to investigators who incorporate RDoC principles into applications submitted under general funding announcements. Researchers are engaged in a challenging and exciting discussion about new approaches to psychiatric

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nosology, focusing on dimensional conceptualizations, integrative methodologies, and alternatives to heterogeneous diagnostic classifications. This conversation was not initiated by RDoC, of course, and several authors in this special issue review the historical origins of these ideas. Beauchaine and Thayer's (2015 - this issue) summary of the contributions of Herman van Praag (2000) is especially illuminating; his perspective on the problems with heterogeneous categories aligns completely with the arguments that have been made in connection with RDoC. Similarly, their presentation of Don Fowles' hypothetical matrix for psychopathology (Fowles, 1988), which preceded RDoC's by twenty years, serves as a reminder that these scientific challenges are not easily overcome. RDoC's contribution to the effort has been to provide the field with a specific framework upon which the discussion can be anchored and new research hypotheses based, backed with NIMH's investment in research based on this framework.

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The papers in this volume touch upon the principles that are central to the RDoC approach as well as the practical aspects of conducting RDoC-informed research. One of the central principles of RDoC is that psychopathology should be classified on the basis of dimensional neurobehavioral constructs rather than putatively discrete but heterogeneous diagnostic categories. Research that is centered on diagnostic classifications that precede modern neuroscience has hindered the field's ability to accurately characterize the nature of psychiatric symptoms and their nosological organization. This disorder-focused approach has yielded a disappointing track record in terms of research breakthroughs. By using disorder categories as the organizing units for psychopathology, and constraining research to focus on complex, heterogeneous, symptom-based diagnoses, the field has run the risk of missing important signals in data and failing to detect new biomarkers or treatments that may be relevant to only a subset of individuals within a diagnostic category, or symptoms/mechanism that cut across disorder categories. The analyses conducted by Nusslock and colleagues (2015 - this issue) provide an exemplar of how a biobehavioral measure, namely left versus right frontal EEG activity, can be used to identify clusters of symptoms that help to differentiate individuals within and between diagnostic categories. Ultimately, the most powerful test of this and similar approaches to dissecting heterogeneity will be to determine whether these subgroups exhibit meaningful differences in etiology and are responsive to differing forms of treatment.

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Another foundational RDoC principle is that psychiatric pathology is best studied along continuous dimensions. The RDoC approach argues that conceptualizations and scientific approaches to mental disorders should be similar to those used for other complex medical disorders in which there are degrees of illness and impairment that are distributed along a dimension. Most psychiatric research instead uses the infectious disease model in which the presence or absence of disease sorts individuals into distinct groups. This between-groups approach ignores the substantial number of individuals whose number or severity of symptoms places them in between diagnostic categories, or in a sub-clinical space that is often ignored by investigators. The dimensional approach aims to capture more fully the variance that lies in between individuals who fall at one extreme – those deemed to meet the criteria for an established diagnosis – and “normal” controls who are atypical by virtue of their lack of even mild symptoms. Even for psychopathological conditions that may not be truly dimensional in nature, a dimensional approach to investigation can provide more

information about where discontinuities occur. The work of Norrholm and colleagues (2015 - this issue) exemplifies this principle by examining a dimension of symptom severity and trauma exposure in a participant sample recruited from a general medical setting. Their analyses may have identified a naturally-occurring discontinuity in fear extinction between those with the highest frequency of intrusive distressing thoughts (13% of their sample) and those who reported less frequency of (or did not report experiencing) that symptom. In addition, developmental processes and environmental influences (such as stress, poverty, and nutrition) are dimensional variables that can be assumed to affect each of the RDoC constructs.

A third RDoC principle is that self-reported symptoms need not be the “gold standard” of psychopathology research. The RDoC initiative encourages use of multiple units of analysis, from genetic and molecular to behavioral and self-report. This integrative approach confers many advantages. It allows psychiatry research to capitalize on the advances made by basic neurobehavioral, molecular, and genetic research to inform our understanding of mental health problems. By attending to signs and signals in other assessment domains instead of relying exclusively on self-reported symptoms, mental disorders may be detected at earlier stages when intervention is likely to be more impactful. Operationalizing constructs using multiple methods yields increased measurement validity and reduces the likelihood of spurious results due to idiosyncratic measurement characteristics of a single test. Finally, novel treatment targets may be revealed by considering diverse units of analysis. The finding of Norrholm and colleagues (2015 - this issue) that intrusive thoughts were not associated with enhanced fear conditioning but rather with reduced early extinction suggests that extinction-related processes might be a more promising treatment target than acquisition-related processes. Likewise, Nees et al (2015 - this issue) also provide a comprehensive review of differing aspects of classical conditioning that are implicated in various mental disorders. As they point out, their mechanistic perspective is very much in line with RDoC and highlights the various learning processes that may be impaired within or across multiple psychological disorders.

In addition to these three core principles, the papers in this issue address some of the practical aspects of conducting RDoC-informed research. One of these is the challenge of selecting tasks and tools that are optimal for use across patient groups and in individuals with varying degrees of impairment. Norrholm et al (2015 - this issue) and Baskin-Sommers and Foti (2015 - this issue) note that differing types of stimuli are likely to be optimal for studying different symptom phenomena. For example, within a fear-eliciting paradigm, stimuli may need to be personalized depending on the type of fear (e.g., air-travel simulation for flight phobia, virtual “tunnel” for claustrophobia). Similarly, drug-related stimuli may be used to elicit reward-related responses in individuals with substance problems whereas monetary rewards might be used with individuals exhibiting anhedonic or hyperthymic mood. However, the use of differing stimuli for participants who vary in symptomatology introduces potential confounds that may make it difficult to compare results across studies. One of RDoC’s goals is to help move the field toward use of common tasks and increased comparability of findings across studies.

At present, there is no standardized battery of measures for RDoC, but the project is progressing in the direction of common data elements in two ways. First, the RDoC Unit at NIMH has established a data repository (RDoCdb) to allow for web-based sharing of data (including neuroimaging and EEG/ ERP measures) from RDoC studies. This web-based resource will allow the scientific community to develop methods for combining and comparing data collected using disparate measures, and encourage the use of consensus measures in order to maximize the availability of overlapping data across studies. Second, the RDoC matrix includes a list of experimental paradigms that were identified by RDoC workgroup participants as especially promising for assessment of each construct. Research is expected to inform future revisions to this list and foster the development of brief batteries similar to the one envisioned by (Baskin-Sommers and Foti, 2015 - this issue) for reward-related processes. Further, the emergence of new technologies such as wearables (as in the study by Gruber et al., 2015 - this issue) provides further opportunities for collecting novel types of data, and fostering real world approaches to understanding RDoC constructs that can serve as a complement to tightly controlled experimental studies.

Another practical consideration related to the RDoC research initiative is the need for innovative approaches to data analysis. RDoC projects generally involve dimensional analyses that integrate multiple units of analysis, each with different measurement characteristics. It should be noted that RDoC-informed research may use between-groups analyses, but the groupings should be based on the presence of naturally-occurring discontinuities or ‘tipping points’ that are discovered by studying the full range of variation in the construct of interest. Gatzke-Kopp and colleagues (2015 - this issue) provide an example of hierarchical analyses examining relationships among differing behavioral and physiological measures, leading to integrative conclusions regarding the autonomic and cognitive responses to frustration associated with conduct problems in children. Shankman and Gorka (2015 - this issue) highlight a distinct analytic and interpretive complication inherent to developmental hypotheses, namely: Are RDoC constructs predictors of change in symptoms over time, or static markers of current pathology? Yancey and colleagues (2015 - this issue) pose a similar question: Are measures of RDoC constructs indicators of processes or dispositions? Longitudinal studies will help to distinguish between individuals who are likely to remain at a steady sub-clinical level of dysfunction and those for whom modest symptoms are predictive of more severe pathology in future. Shankman and Gorka (2015- this issue) helpfully outline various research approaches that can help to address these questions, and Yancey and colleagues (2015- this issue) provide an example of careful analysis of the relationships and interplay between pathology-related constructs, revealing for example a moderating effect of generalized distress on the relationship between threat sensitivity and affective startle potentiation.

Implicit in these examples and others is the importance of examining interactions among explanatory constructs. The RDoC matrix serves as an organizing structure for the constructs and units of analysis, but provides little information regarding the nature of the relationships among the constructs. Just as neural circuits are densely integrated and interactive, RDoC constructs are assumed to operate in close and dynamic relationship with each other. Likewise, any particular unit of analysis need not be uniquely indicative of just a single construct; the experimental paradigm and study sample could influence the

interpretation of that unit of analysis as an indicator of some process or mechanism. The presence of overlapping matrix elements among constructs reflects the integrative nature of neural systems related to them. Several examples of multi-construct interactions are provided in this collection of papers, including the analysis of affective, cognitive, and arousal/regulatory indicators as described above, and a well-developed model of the interactive effects of mesolimbic and septo-hippocampal circuits in which mesolimbic dopamine (DA) dysfunction places individuals at risk of externalizing behavior except when trait anxiety is also present (Gatze—Kopp, et al., 2015 - this issue). Verona and Bresin (2015- this issue) make a compelling case for positioning aggression as a process occurring at the intersection of Negative Valence and Cognitive Systems domains by showing that offenders with increased tendencies towards aggression show reduced P300 responses in a Go No-Go paradigm, for aggression-relevant stimuli specifically. Careful tests of models are necessary to make explicit the nature of the relationships between constructs, which can be, for example, either causative or modulatory (Shankman and Gorka, 2015 - this issue). Likewise, Weinberg and colleagues (2015 - this issue) provide a comprehensive and incisive review of the error-related negativity, the processes it reflects, its reliability, and its links to several RDoC domains. In a similar vein, Siegle and colleagues (2015 - this issue) note that even a construct like loss, which appears in the Negative Valence domain of the RDoC framework, can entail both cognitive and affective aspects; they show using pupillary activity that it is more the latter aspects of loss that are modified after exposure to negative stimuli, suggesting dissociable components even within a single construct. Such work emphasizes how tightly interwoven the RDoC constructs and their indicators are.

Looking toward the future of RDoC-oriented research, several themes were apparent in this collection of papers. One prominent thread involves the need to establish a process for modifying the matrix. The NIMH RDoC group has considered this issue for some time and intends to finalize such a process in coming months; as with the original workgroups, the intent is that modifications will be based on converging results in the literature as reflected in a number of papers by multiple research groups. Several such changes are suggested by the authors of this collection of papers. Nusslock and colleagues (2015 - this issue) suggest that a motivation-based framework, focusing on approach versus withdrawal tendencies rather than the current domains of positive and negative valence, would be more consistent with the literature on anger, aggression, and the phenomenology of mood disturbance. They note that anger arises when approach behavior is thwarted and is associated with aggressive approach behaviors aimed at the object of the anger. Consistent with this, participants in the Positive Valence Systems (PVS) workshop noted that not all forms of approach are positive and discussed specifically the aggression issue, highlighting the dissociations among different types of positive and negative approach behaviors as a possible area for future research. Discussion of this theme continued in the Negative Valence Systems (NVS) workshop in the course of efforts to define the Frustrative Non-Reward construct, which includes physical and relational aggression and proactive and reactive aggression as behavioral elements. Although the data on this issue are mixed, with some studies showing approach and avoidance to be correlated and others finding them to be orthogonal (Shankman and Gorka, 2015 - this issue), the separation of the NVS and PVS domains was thought to be supported by evidence of distinct neural circuits for avoidance and approach,

suggesting that these orientations are not opposite ends of a single dimension. As discussed above, the constructs associated with these domains do not operate in isolation and future research will determine if and how they might be modified.

Other suggested modifications to the matrix include the addition of a trans-domain terminology for constructs such as “anxious apprehension” or “aggression” that span existing RDoC constructs in differing domains, and inclusion of superordinate constructs to capture processes or traits that are intermediate between constructs and domains (Sharp et al., 2015). Another suggestion is to include more “macro” level information in order to incorporate the effects of family and community, for example, on individual variation in RDoC-specified processes (Shankman and Gorka, 2015). Norrholm and colleagues (2015 - this issue) provide a useful table summarizing properties that an element in the matrix should have (Table 5).

Regarding modifications to the RDoC domains and constructs, an important note of clarification concerns the point raised by Shankman and Gorka (2015 - this issue) that NIMH Requests for Applications (RFAs) for R01 grants to date have included a specific requirement that applications focus on one or more specific constructs from the RDoC matrix, which could have the effect of hindering research on alternative constructs. This constraint was included in these announcements because the RDoC workgroup felt that was important to stimulate research focusing on the initial set of matrix-specified constructs as a starting point for evaluating these constructs, and as a point of reference for subsequent work directed at revising the matrix. Notably, there is no such constraint on grant applications submitted under the regular (parent) NIH funding announcements, and we encourage research that will inform future versions of the matrix. As noted above, approximately ten times more investigator-initiated grants have been funded as compared to those awarded under RDoC RFAs.

We are grateful to the authors for their thoughtful consideration of the RDoC framework and for the opportunity to comment on this special issue, which we expect will serve as an important resource to the field. It is very heartening to see the prominent focus on RDoC principles in the empirical and review articles in this issue. Indeed, it serves to reinforce the idea that many scientists in the field already think along the lines of biobehavioral constructs, dimensionality, and convergence among different types of methodologies. The major aim of the RDoC framework is to provide a springboard for this type of conceptual thinking and allow researchers more freedom in their work, rather than tethering it to an artificial framework of disorder-based categories—and the current collection of articles provides a highly effective illustration of differing creative applications of this research framework.

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