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Editorial

Situating psychophysiological science within the Research Domain Criteria (RDoC) framework

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ABSTRACT

The Research Domain Criteria (RDoC) reflects a paradigm shift in mental health research aimed at establishing a science of psychopathology that is grounded in neuroscience. In many ways, the RDoC approach to research has been utilized for decades by psychophysiologists who have leveraged a range of biological measures to study variability in psychological processes as a function of individual differences. We highlight the critical role of psychophysiology in the era of RDoC, and briefly review the 13 papers and commentary that form the current special issue.

1. The Research Domain Criteria (RDoC)

Although the field of neuroscience has made tremendous strides in understanding how the brain works, this knowledge has not translated into significant advances in understanding, treating, and preventing mental illness. One potential reason has to do with the questionable validity of the diagnoses we study. A research investigation that compares a group of individuals diagnosed with major depressive disorder (MDD) to a group of healthy controls lumps individuals together based on a collection of polythetic diagnostic criteria — and the resulting group will be characterized by significant heterogeneity. Two individuals with the same diagnosis of MDD can look very different symptomatically. Moreover, MDD is highly comorbid with other psychiatric disorders, further limiting the interpretability and utility of simple between-groups, diagnosis-based designs. If our categorical system for characterizing psychopathology is misguided, then the quest for valid psychophysiological indicators ('biomarkers') is doomed to failure (Beauchaine and Thayer 2015). The National Institute of Mental Health's RDoC initiative calls for a new investigative approach to research that can lead to a neuroscientifically-informed science of psychopathology, and in the process transform our ideas about the nature of mental disorders and how best to prevent and treat them.

Rather than focusing on traditional disorder categories, the RDoC initiative encourages researchers to focus on continuous variability in more specific clinical phenomena. As targets for study, RDoC provides an initial matrix of constructs for which compelling evidence exists regarding relevant neural circuits, and that appear likely to relate to variations in behavioral functioning (e.g., clinical symptoms). The RDoC matrix itself reflects a proposed taxonomy of measures (i.e., units of analyses) for indexing specific processes (i.e., psychobiological constructs/subconstructs organized within broader thematic domains), rooted in our best available knowledge about how the brain works. In this way, it is a perceptual lens through which psychopathology researchers are encouraged to see their world. For conceptual overviews, see: Cuthbert and Insel 2013; Insel et al. 2010; Kozak & Cuthbert, in press; Sanislow et al. 2010; for a critique, see Kirmayer and Crafa 2014.

2. RDoC and psychophysiology

Although RDoC is a matrix of process constructs and methods for indexing them, most measurements of these constructs implicitly need to reflect relatively stable individual differences relevant to mental health.[1] This presents a dilemma. The RDoC framework is based on constructs that have well-defined neural circuits—and this circuitry

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[1] In conceiving psychopathology in individual difference terms, a key point to consider is that manifest symptomatology reflects dysfunction arising from the interplay of basic dispositions with pathogenic experiences (Monroe and Simons 1991; Rosen and Schulkin 1999), making it important to distinguish between liability and expression (Cicchetti and Rogosh 1996). From this perspective, measurement of clinical symptoms and characteristics relevant to symptomatology (i.e., variation across people in processes such as acute threat or reward responsiveness, represented by constructs of the RDoC matrix) can entail a focus on more or less stable tendencies—ranging from dispositions that predate but promote symptom development, to evolved but enduring dysfunction, to transient episodic dysregulation. Although all can be considered person-characteristics, investigation of less versus more stable tendencies may require different research designs, assessment methods, strategies, and criteria for evaluating score reliability, etc. As noted in the current commentary by Morris et al. (2015), the RDoC framework is expected to evolve with advances in ideas and data, and the parameter of liability versus expression in is one the framework would do well to formally accommodate.

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has been validated mostly using *within-subject* experimental designs intended to elaborate neural function. However, RDoC calls for measures of these neural circuits to be leveraged to understand *between-subject* variability linked to mental illness. The move from within- to between-subject comparisons requires that a given unit of analysis is itself trait-like, and this requires that measures have good psychometric properties. This issue is particularly salient because fMRI is the sine qua non method for studying neural circuitry in human studies—and fMRI measures of neural function that have been evaluated to date for psychometric properties have proven unsatisfactory in this respect (Lilienfeld 2014). Although fMRI measures are undeniably useful for elucidating neural function (i.e., through within-subjects comparisons), if fMRI measures of neural activity exhibit poor reliability internally and temporally, they *cannot* explain meaningful variance in stable individual differences. As one example, amygdala reactivity to emotional faces is commonly used as a 'probe' of negative valence system activation—and yet, the test–retest reliability of this measure is moderate to poor (Sauder et al. 2013). This issue is not specific to dependent measures derived from neuroscience: behaviorally-assessed attentional bias toward threat, for example, has been studied extensively in relation to individual differences in fear and anxiety, but this behavioral measure likewise shows poor psychometric properties (Kappenman et al. 2014). The psychometric limitations of physiological and behavioral indicators of person-characteristics are a serious issue that the clinical neuroscience literature has by-and-large not dealt with. Measures in the RDoC matrix need to have reasonable psychometric properties.

Other than using fMRI, how else can we measure individual differences in activity within well-defined neural circuits? Psychophysiologists have been doing so for decades using the electroencephalogram (EEG) and event-related brain potentials (ERPs)—measures that index the coordinated activity of neural circuits in relation to discrete stimuli, or in some cases emitted responses. In fact, EEG/ERPs provide a *direct* measure of neural activity – unlike compensatory measures of blood oxygenation reflected in fMRI. The historic neuroscientific objection to ERP quantification of brain reactivity has been its poor spatial resolution: for many ERPs, it is unclear if there is a single neural generator, and the inability to specify neural generators has been considered a drawback. However, as the fMRI literature moves more toward focusing on circuits, often using the identical experimental paradigms as ERP research, the low spatial resolution of ERPs becomes less of a shortcoming. Indeed, it seems unreasonable to use neural activity recorded using fMRI within well-defined experimental paradigms to *define* neural circuits, and then to question the validity and meaning of neural activity indexed by ERPs in the *same* paradigm. ERPs are direct measures of activity in neural circuits, and belong in the "circuits" units of analysis of the RDoC matrix. We would also note that many ERPs have excellent psychometric properties—making them highly desirable as measures for research on individual differences (Weinberg et al. 2015).

The activation of neural circuits can also be indexed less directly, through changes in other psychophysiological systems that interface with central brain systems. For instance, the startle reflex is a well-validated measure of defensive activation that has been linked to specific neural circuits (Nees et al. 2015; Norrholm et al. 2015; Yancey et al. 2015). At least in some task paradigms, startle reflex magnitude appears to have excellent psychometric properties (Nelson et al. 2015). Heart rate variability has also been linked to neural circuits that regulate emotion, cognition, and behavior (Beauchaine and Thayer 2015; Gruber et al. 2015). As such, so-called "peripheral" psychophysiological measures can be considered proxy indices of neural circuit activation—consistent with the 'physiology' unit of analysis in the RDoC matrix.

Importantly, dimensional trait models of psychopathology have a longstanding place and tradition within psychophysiological research (Beauchaine and Thayer 2015). As evident from the various articles in this special issue, EEG/ERPs, startle, and HRV have all been examined in relation to both diagnostic categories of psychopathology, and personality and other individual difference constructs that cut across specific diagnoses. Thus, our field has been conducting research in line with RDoC aims and principles for decades. Indeed, Kozak and Cuthbert (in press) note that RDoC was formulated to "promote the elaboration and validation of integrated psychophysiological constructs of clinical relevance." Within that context, the current special issue is intended to highlight the crucial role that psychophysiological science stands to play in the future of this pivotal NIMH initiative.

3. Overview of articles in the special issue

Baskin-Sommers and Foti (2015) consider reward-related neural abnormalities across MDD and substance use disorders (SUD) in terms of dissociable aspects of reward processing (i.e., liking, wanting, and learning). The authors articulate an integrative model that ranges from primarily hyperthymic on the one end (e.g., 'pure SUD', characterized by impaired wanting and intact liking) to primarily anhedonic (e.g., 'pure MDD', characterized by impaired liking and intact wanting) on the other, and discuss how hyperthymic and anhedonic profiles could lead to reward-related learning deficits that distinguish SUD from MDD.

Gruber et al. (2015) discuss HF(high frequency)-HRV in the context of positive emotionality and functioning. The authors describe work examining HF-HRV in natural, everyday contexts and report data indicating higher *intra-individual variability* in HRV-HF in individuals with bipolar disorder compared to MDD and healthy control participants; taking a dimensional approach, this index of cardiac function is shown to relate specifically to reported symptoms of mania across groups.

Nusslock et al. (2015) review the large literature on approach motivation and increased relative left frontal activity reflected in alpha power—and do so in the context of both unipolar and bipolar depression. Going beyond diagnoses, the authors consider EEG asymmetry in relation to specific symptoms of depression (i.e., anhedonia and certain symptoms of mania). Nusslock and colleagues raise the possibility that RDoC domains organized by emotional valence (i.e., 'negative' versus 'positive' valence) might be better-conceptualized in terms of motivational direction (i.e., withdrawal-related versus approach-related).

Yancey et al. (2015) conceptualize threat sensitivity as a dispositional counterpart to acute (as opposed to potential or sustained) threat in the RDoC framework, reflecting variation along a trait dimension ranging from extreme fearfulness to fearlessness. The authors report data indicating increased aversive startle potentiation (ASP) among individuals with fear disorders—but not when accompanied by comorbid depression. Further, continuous scores on a scale measure of threat sensitivity correlated with ASP among non-MDD individuals, and mediated the relationship between fear disorders and ASP in this subsample. The implication, from an RDoC perspective, is that heightened reactivity of acute-threat circuitry increases risk for fear disorders, and that it can be indexed via ASP when not accompanied by major depression (or perhaps distress conditions more broadly).

Norrholm et al. (2015) define "fear load" as increased startle potentiation during early phases of fear extinction—a phenomenon that has been linked to post-traumatic stress disorder. The authors examined startle modulation during fear learning and extinction in a diverse sample of 269 traumatized individuals and found that fear load was related to self-reported intrusive thoughts and intense physiological reactions to trauma reminders. In this way, Norrholm and colleagues link fear load to more specific phenotypic variation than PTSD diagnosis.

Weinberg et al. (2015) present a tour-de-force review of the literature on the error-related negativity (ERN) across various forms of psychopathology. The authors consider how the ERN may reflect multiple processes, and in turn, routes to dysfunction. Weinberg and colleagues go further to consider the impact of task-related psychometrics on the ERN—and address issues of convergent validity of measures within the negative valence system domain.

Gatzke-Kopp et al. (2015) focus on frustrative non-reward, defined in terms of blocking or removing a previously available reward—and how heightened arousal can interfere with regulatory processing. The authors present data showing increased heart rate and decreased P3b responding among children with conduct problems, specifically within a frustrative non-reward condition.

Siegle et al. (2015) explore the RDoC construct of loss through measures of rumination (i.e., repetitive thinking), feelings (e.g., sadness and associated crying), and prolonged physiological reactivity—finding that these measures cohere in a factor analysis. However, within this construct, sustained and increased pupillary response to emotional stimuli were associated with depressive symptoms and cognitive symptoms of loss—but not negative thinking and rumination. In supplemental analyses, Siegle and colleagues show that this pattern of physiological activity may generalize to response to positive information.

Verona and Bresin (2015) focus on aggressive behaviors that cut across both externalizing and internalizing forms of psychopathology, highlighting the unique concept of "affective disruption of cognitive control" and the critical interplay between RDoC motivational (i.e., negative valence) and cognitive systems domains. Working from this conceptual framework, the authors present data demonstrating that P300 differentiation between go and no-go trials was reduced among individuals scoring high on a continuous self-report measure of dispositional aggression, specifically on trials involving aggression-related words.

Shankman and Gorka (2015) highlight the need for RDoC measures and constructs to be relevant to mechanisms of risk—reviewing alternative study designs that can be used to validate a measure of risk. The authors discuss key issues pertaining to development and convergent–discriminant validity, and consider how RDoC opens the door to treating psychophysiological measures either as dependent or independent variables—depending upon investigative aims and purposes.

Beauchaine and Thayer (2015) review data indicating that low resting high-frequency heart rate variability (HF-HRV) and excessive HF-HRV reactivity to emotional challenge are abnormal across many forms of psychopathology. The authors argue that HF-HRV serves as a peripheral index of prefrontal cortex function, and reflects a non-specific biomarker of a general liability factor for psychopathology. Their paper highlights the potentially shared neurobiological substrates of internalizing and externalizing disorders, and argues that HF-HRV is a physiological indicator of what these two sets of conditions share.

Nees et al. (2015) present a comprehensive qualitative review of fear conditioning studies across a range of clinical disorders, and highlight several factors that vary across studies (e.g., simple vs. differential conditioning, unconditioned stimuli that are generally aversive vs. aversive in way that is disorder-specific). The authors argue that differential fear acquisition and extinction deficits are important mechanisms for diverse forms of psychopathology, and highlight the need to parse heterogeneity of patient samples in investigating conditioning mechanisms.

Sharp et al. (2015) distinguish between anxious apprehension and anxious arousal—as trait variables—and the states of worry and fear/panic, respectively; they suggest that the interaction of core affect and executive inflexibility may give rise to the emergent phenomenon of anxious apprehension. The authors further discuss how variations in traits such as anxious apprehension could reflect a lower threshold for certain states (i.e., worry)—and highlight habituation to fearful stimuli as an important area for future research.

Finally, Morris et al. (2015) provide a thoughtful integrative commentary on the foregoing papers, focused around major RDoC principles. In this context, they discuss practical issues related to conducting RDoC research (e.g., the need for innovative data analytic approaches to integrate across units of analysis), as well as future directions of RDoC itself (e.g., a potential expansion of the framework to include common data elements; a process for modifying the RDoC matrix).

4. Summary

Papers in the current special issue highlight a range of psychophysiological measures that are relevant to the RDoC framework and its aims. Specific ERPs (e.g., the P300 and ERN), EEG asymmetry, HRV, startle blink, and pupillometry can all be utilized to study processes and constructs relevant to RDoC. Notably, almost all of the current papers consider relations of psychophysiological measures with both diagnostic groupings and variability along more specific symptom dimensions—an approach that is consistent with RDoC.

A number of the papers converge on similar large-scale conceptual issues that are highly relevant for work that cuts across diagnostic boundaries. For instance, several papers find that depression—though overlapping and highly comorbid with anxiety—may have suppressive effects on the relationship between psychophysiological responding and anxiety-related problems (Nusslock et al. 2015; Weinberg et al. 2015; Yancey et al. 2015). Several papers suggest promise for utilizing psychophysiological measures to account for the substantial comorbidity among certain traditional disorders (e.g., substance use disorders and MDD; Baskin-Sommers and Foti 2015). Many papers in the current issue focus on the interplay between measurements across different RDoC domains (e.g., Sharp et al. 2015; Verona and Bresin 2015)—and this is clearly an important approach for future RDoC-inspired studies. Finally, multiple papers focus on issues of convergent validity — i.e., the ways in which differing measures of a given construct hang together (Siegle et al. 2015). Along this line, it will be increasingly important in future RDoC research to systematically examine and characterize relationships across differing units of analyses and domains of functioning. As an example of this, it will be valuable to evaluate whether and how HF-HRV relates to other measures of process constructs within the positive valence system domain (Gruber et al. 2015).

The RDoC matrix encourages the study of clearly-defined processes that have relatively well-delineated neural circuits—in relation to more specific clinical symptom dimensions that transcend traditional diagnostic boundaries. Psychophysiological science is ideally-suited to contribute to RDoC and its mission to advance our understanding of mental illness in biobehavioral process terms. The 13 papers in the current special issue are exemplars of this promise (Morris et al. 2015). At the same time, doing "RDoC" research is not without challenges. Integrating information across measures and specifying the nature of their interrelations across multiple units of analysis is a distinct challenge (Miller et al., in press). As Shankman and Gorka (2015) point out, RDoC should inform our understanding of risk and resilience. Indeed, both startle and ERP measures have been linked to risk for psychopathology (Grillon et al. 1997; Kujawa et al. 2012, 2014; Yancey et al. 2013) and used to prospectively predict new-onset disorders (Bress et al. 2013; Craske et al. 2012; Iacono et al. 2002; Meyer et al. 2015). Future studies will need to go further — to determine whether variations in biobehavioral risk for psychopathology indexed by psychophysiological measures are modifiable, and if they predict illness course or treatment amenability and outcome. Additionally, future work will need to consider the interaction of core biobehavioral measures with environmental influence across differing stages of development (Shankman and Gorka 2015). In sum, there is considerable work to be done, and psychophysiological science is well positioned to make major contributions on many fronts.

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