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Taking an RDoC lens to the study of panic disorder: A commentary on Hamm et al. and other thoughts on RDoC

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Abstract

The Research Domain Criteria (RDoC) initiative put forth by the National Institute of Mental health represents an exciting new framework in which to study psychopathology. The article by Hamm et al. is an interesting application of an RDoC “lens” towards a program of research on panic disorder. This commentary highlights the many strengths of the Hamm et al. (2015) study – most notably the article’s application of a well-studied animal model of anxiety (Fanselow’s [1994] threat imminence model) to humans, utilization of an interesting behavioral paradigm (as an analog for avoidance behaviors in panic disorder), and using RDoC to examine predictors of treatment response. This commentary also discusses several questions about RDoC that arise out of Hamm et al. For example, (a) how should participants be selected for RDoC studies? (b) Are RDoC constructs risk factors (and risk factors for what)? (c) Besides Hamm et al., approach, how else can RDoC be used in treatment studies? In sum, Hamm et al. is a very good example of an RDoC study and in this early phase of the initiative, more examples for how the approach plays out are needed.

Keywords

panic disorder; agoraphobia; Research Domain Criteria; negative valence system

As discussed in this issue’s target article by Bruce Cuthbert and Michael Kozak, the Research Domain Criteria (RDoC) initiative put forth by the National Institute of Mental Health (NIMH) seeks to change the framework of the study of mental disorders. Instead of the traditional approach of examining differences between and within categorical diagnoses, RDoC seeks to investigate dimensional constructs that cut across diagnoses (Insel et al., 2010; Cuthbert & Kozak, 2013). The goal of the RDoC program is to supplement current symptom data used to classify disorders with “clinically relevant individual differences in genomics, pathophysiology, and behavior” (Insel et al., 2010). RDoC is outlined as a matrix of constructs, which are set within broader domains, and units of analysis to measure those constructs, which range from genes to circuits to behavior and self-report. In this vein, the article by Hamm and colleagues (2015) provides an interesting and integrated examination of panic disorder with agoraphobia (PDwA) through an “RDoC lens”, specifically focusing

on the constructs of acute threat and potential threat within the *negative valence systems* domain.

Hamm et al. contained several strengths. First, the primary theoretical model that guides this study is Fanselow's (1994) threat imminence model, a well-studied and highly influential animal model of anxiety. The article applies the three stages of the model (Pre-Encounter defense, Post-Encounter Defense, Circa-Strike Defense) to the symptom clusters of PDwA. Relying on data from animal and human neuroscience and psychophysiology, the authors establish links between pre-encounter defense and hypervigilance, post-encounter defense and anxious apprehension, and circa-strike defense and acute panic.

A second strength of the paper is that Hamm et al. examined passive and active avoidance during a behavioral paradigm (the behavioral avoidance task, or BAT). Behavior that involves actual movement (in this case, escaping a locked chamber) is an important, yet often overlooked, unit of analysis in RDoC. Often, behavioral intentions (e.g., what people would like to do – sometimes in a hypothetical situation) are considered “behaviors” - the current study's use of the BAT went beyond these variables and examined a laboratory behavior that is a clear analog of a clinically significant behavior. In addition to demonstrating a relationship between escape behaviors during the BAT and escape behaviors during treatment (i.e., avoidance during the BAT was related to study attrition and treatment drop-out), the researchers also related avoidance during the BAT to self appraisal (suffocation subscale of the Claustrophobia Questionnaire) and to symptoms at the end of treatment. Specific links to therapist behaviors were also investigated, lending additional specificity to this unit of analysis.

This attention to behavior highlights a third strength of this investigation - the negative valence constructs were examined at several units of analysis across the RDoC matrix. In addition to examining genetic markers, the researchers also examined anxiety sensitivity (i.e., self-report), the startle eyeblink response (i.e., psychophysiology), and escape during the BAT (i.e., behavior).

One major critique of the RDoC initiative is that, although it is framed as a research rather than clinical endeavor at this point, the clinical applications of taking an “RDoC lens” to one's research is often unclear (Berenbaum, 2013). Hamm et al's (2015) greatest strength is that it uses RDoC in a treatment design (and found that individual differences in aspects of defensive reactivity predicted treatment response).

Thoughts about RDoC Initiative inspired by Hamm et al.

Definitions of RDoC constructs

One of the main RDoC constructs investigated by Hamm et al is ‘potential threat.’ During the NIMH sponsored workshops that outlined possible RDoC constructs of interest, potential threat was defined as a threat that “may potentially occur, but is distant, ambiguous, or low/uncertain in probability...thus requiring vigilance” (NIMH Negative valence workshop, 2011). Hamm et al.'s conceptualization of potential threat (and that of Fanselow, 1994) emphasize the *distant* component of that definition, arguing for the

importance of the “perceived proximity or imminence of the threat” (p. xx). It is important to highlight, however, that other researchers have operationalized potential threat in other ways. For example, several animal and human researchers have shown that the uncertainty or unpredictability of the threat is of particular importance in anxiety disorders (Davis, Walker, Miles & Grillon, 2010; Grillon, 2008; Shankman et al., 2013) as well as substance use disorders (Moberg & Curtin, 2009). A review of the evidence supporting whether threat imminence or threat unpredictability is more central to anxiety (and whether the two are separable given that the exact occurrence of a distal threat is often unpredictable) is beyond the scope of this brief commentary. However, it does raise the possibility that two labs could define and study the same RDoC construct in multiple ways. Defining variables in different ways (in other words, variance in criteria) was of course, one of the main critiques during the 1970s of psychiatric disorders (Kendler, Munoz, & Murphy, 2010) – a critique which led to the creation of standardized criteria for disorders in the third version of the DSM (DSM-III; American Psychiatric Association, 1980). This highlights the importance of identifying specific sub-constructs within RDoC domains that can be compared and contrasted with various units of analysis.

Selection of Participants

One of the appeals of RDoC is that it seeks to examine mechanisms that cut across diagnostic syndromes (Sanselow et al., 2010). Indeed, in outlining the rationale for RDoC in this issue of *Psychophysiology*, Cuthbert and Kozak (2015) state that “the RDoC initiative is intended to uncouple research questions from traditional diagnostic categories that are of limited validity and/or that are too heterogeneously large for productive validation against biological phenomena of smaller granularity (p. XX).”

Although they examined *potentially* transdiagnostic constructs, Hamm et al. only examined these constructs within a sample that met DSM-IV criteria for panic disorder or compared levels of these constructs to those of controls. While more analysis could have been done combining the controls and PDwA groups, this is not meant to be a criticism of Hamm et al. – it seems that their study was not designed to use an RDoC lens (as it began prior to RDoC). Rather, it suggests that their study may have yielded different findings had they included individuals with subthreshold panic symptoms or other anxiety disorders, creating a sample that would have a fuller (or at least different) range on the constructs examined. For example, epidemiological studies have shown that the 12-month prevalence of panic attack is 11.2%, but only 2.8% meet criteria for panic disorder (Kessler et al., 2006). This suggests that several of the processes or mechanisms examined in Hamm et al. may be relevant (although perhaps to lesser degrees) to individuals below diagnostic threshold. One effect of analyzing a sample of only individuals with panic disorder is Hamm et al.’s findings for anxiety sensitivity (AS). As reported on p. XX, Hamm et al. found that AS was not related to active or passive avoidance during the BAT. Although the sample had some variability in AS, this null finding may have in part been due to a restriction of range of AS given that a large percentage of individuals with panic disorder report high levels of anxiety sensitivity (McNally, 2002).

The issue of participant selection (and source of recruitment) is critical to the RDoC initiative overall. In non-RDoC psychopathology studies, participant selection is often fairly straightforward – the inclusion criteria specify the DSM defined diagnostic category of interest (e.g., all participants must meet DSM criteria for Major Depressive Disorder), and the exclusion criteria include potential confounds or rule-outs (e.g., exclude all participants who have ever experienced psychosis). Participant selection with an “RDoC lens” is much more complicated. Indeed, as discussed by Cuthbert & Kozak (2013), in RDoC studies, it may not be “sufficient to gather the usual clinical sample, but rather, the researcher must consider how to recruit so as to ascertain a sample that has appropriate variation to evaluate the dimension(s) of interest” (p. 930). Thus, in an RDoC study, what become the inclusion criteria? If the inclusion criteria are too broad, the mean of the sample on the dimension of interest (e.g., potential threat) might be the mean of the general population. This may limit the clinical relevance of the study, as it is typically assumed that those with clinically significant conditions are at least somewhat rare (i.e., low frequency). If the inclusion criteria are too narrow, then there could be a restriction of range on the dimension of interest. “In sum, while examining dimensions has some of the well-documented advantages over categories, such as better psychometric properties and higher likelihood of reflecting the ‘true’ nature of many psychopathologies (Krueger & Bezdjian, 2009; Krueger, & Piasecki, 2002), it does complicate establishing inclusion and exclusion criteria which are inherently ‘categorical’ decisions (i.e., the subject is either in or out).

RDoC constructs as Risk Factors

One of the interesting findings in Hamm et al. was that fear of suffocation was related to avoidance during the BAT as well as anxiety and panic symptoms during exposure. The authors use these findings and other data to argue that fear of suffocation may be a risk factor for developing panic disorder (Klein, 1993). Of course, without other designs (e.g., longitudinal, etc.) these results could simply reflect that fear of suffocation is a concomitant or characteristic of panic symptomatology and not necessarily a risk factor. This relates to another point about RDoC. Although Hamm et al. do not directly state this, there is a tendency in our field to believe that if a psychological and biological variable correlate that the biological variable *predicts* (or in this case, connotes risk for) the psychological construct. This bias is especially true if the biological variable exhibits trait-like tendencies (i.e., stability). The direction of the association – even if the biological variable is stable – may, of course, go the other way (i.e., having symptoms of panic disorder may predict fear of suffocation). Alternatively, the psychological and biological variable may simply reflect different measures or aspects of the same construct (Miller, 2010). To us, this is one of the most exciting aspects of the RDoC initiative – it allows researchers to combine biological and psychological measures of the same construct and explicitly does not require that the researcher views the biological units of analysis as more fundamental than the psychological ones (see Berenbaum, 2013; Lilienfeld, 2014 for review).

Examining RDoC constructs as risk factors raises another question – if RDoC constructs are risk factors, what are they supposed to predict? The kneejerk answer to this question may be ‘psychopathology.’ However, this logic can become circular. Let us suppose that a researcher is examining whether the RDoC construct of “initial responsiveness to reward” is a risk

factor for major depression. As rewards are often pleasurable and a fundamental feature of major depression is “a loss of enjoyment in activities that were previously considered pleasurable” (p163, APA, 2013), it can be circular to examine whether reward responsiveness predicts depression (see Roth, Wilhelm, & Pettit, 2005 for a similar argument with panic disorder). This becomes even more circular if the researcher examines risk for the symptom of anhedonia more specifically. In other words, examining whether RDoC constructs predict psychopathology can turn into an examination of whether symptoms of psychopathology predict symptoms of psychopathology. Extending the constructs beyond symptoms and self-report into other signs and behaviors is critical. These signs and behaviors should be or at least link to outcomes of impairment that are conceptually separated (as much as possible) from the RDoC construct – such as work and social functioning, criminality, and hospitalization (see Shankman & Gorka, 2015).

Disorder/Construct complexity

Hamm et al. found that particular comorbid diagnoses (e.g., specific phobia) related to more active and passive avoidance behavior on the BAT. These results are similar to the work of Lang and McTeague (Lang & McTeague, 2009; McTeague & Lang, 2012) who have shown that disorder complexity (often defined as the presence of additional comorbid disorders) related to more abnormal defensive reactivity. But how should ‘complexity’ of clinical presentation be taken into account in RDoC studies? Let us suppose that a researcher is examining whether individual differences in potential threat predict some outcome. These individual differences, however, do not occur in a vacuum, and individual differences in other RDoC domains (e.g., acute threat, cognitive control, etc) might correlate and/or moderate the effect of potential threat.’ The bolded and underlined “or” in the previous sentence is critical. If the researcher wants to isolate the effects of potential threat, he/she might regress out the effects of the RDoC constructs that are correlated with potential threat (although see Miller & Chapman’s [2001] caution regarding the mistreatment of covariates). If the researcher is interested in the moderating effects of other RDoC constructs, then he/she would explicitly test whether multiple RDoC constructs interact in predicting particular outcomes (although the researcher would need larger sample sizes to detect interactions, and ideally a sampling/recruitment strategy in which there is enough variation in the two constructs, Aguinias, Beaty, Boik, & Pierce, 2005). Taken together, how the researcher approaches the complexity of the RDoC domains theoretically and analytically will be of critical importance. For instance, Kraemer and colleagues have published a more detailed and thoughtful discussion of how to analyze independent, overlapping, and other types of risk factors (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001).

Suggestions of Future Directions

As stated above, one of the strengths of Hamm et al. is that it examined whether RDoC constructs were predictors or moderators of an efficacious treatment for panic disorder with agoraphobia (exposure therapy). We see two other ways that RDoC could be incorporated into treatment studies. First, indicators of RDoC constructs could be used as outcome variables to track the efficacy of treatment. For example, rather than only examining the course of self-reported symptoms over time (e.g., depressive symptoms on the Hamilton [1960] Depression Scale), indicators of reward responsiveness (e.g., the event-related

potential, feedback negativity [FN; Foti, & Hajcak, 2009]) could be given over the course of treatment and the slope of this indicator could be used as evidence for treatment effectiveness. This, of course, would require that the markers have good reliability and validity and that they are not *too* static. This last point is important. If a marker is too stable over time and not susceptible to state effects, then it may not sufficiently move as a function of treatment.

Second, rather than use RDoC to examine existing treatments (e.g., CBT, SSRIs), RDoC constructs can help with the development of new interventions. This is perhaps best reflected in the origin of cognitive bias modification (CBM) interventions. For decades, researchers have shown that individuals with anxiety disorders exhibit cognitive biases to particular emotional stimuli (Mathews & Macleod, 2005). CBMs were designed to specifically and directly change these cognitive biases by, for example, training the attention of individuals with anxiety using computer administered tasks (Amir et al., 2009; Hakamata et al., 2010). The point here is that this approach could be used to develop other interventions that specifically target other RDoC constructs (see Rose et al., 2015 for another example).

In conclusion, RDoC represents an exciting new approach towards conducting psychopathology research. Hamm et al. represents an excellent example for how researchers can take an RDoC lens to elucidate important mechanisms and treatment predictors for panic and we hope that this brief commentary provides researchers with some guidance in how to conduct other RDoC-consistent treatment studies.

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