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Reconciling RDoC and DSM Approaches in Clinical Psychophysiology and Neuroscience

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Abstract

The Research Domain Criteria (RDoC) initiative endeavors to foster a science of psychopathology based around dimensions of brain-behavior relationships as opposed to subjectively based diagnostic categories. A rapidly accumulating array of transdiagnostic commonalities, across multiple objective and subjective measures, underscores the clear potential of this initiative. At the same time, a roadmap for guiding future RDoC research efforts is needed that draws upon the wealth of extant disorder-specific findings. In this issue, Hamm and colleagues provide an example of conceptualizing within-disorder processes in terms of dimensional brain-behavior relationships that advances the understanding of panic disorder with agoraphobia beyond the conventional nosological framework. Their findings and conceptual model are reviewed and discussed in terms of broader transdiagnostic implications.

Keywords

RDoC; anxiety; threat imminence; transdiagnostic; startle; heart rate; psychophysiology; panic; agoraphobia; apprehension; anxiety sensitivity; diagnosis

RDoC, DSM, and Transdiagnostic Patterns

The Research Domain Criteria (RDoC) initiative endeavors to promote “an interdisciplinary science of psychopathology that consists of dimensional constructs integrating elements of psychology and biology, especially genetics and neuroscience” (Kozak & Cuthbert, this issue). While not an alternative diagnostic classification scheme itself, it directly challenges us as biologically oriented clinical scientists to assess our implicit biases about the conceptualization of dysfunction, and accordingly, adjust our investigative lens.

For over three decades, the mental health field has relied upon a psychiatric nosological tradition of primarily subjective symptom clusters to guide diagnostic classification. Without question, the advent of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013), and the corresponding International Classification of Diseases (ICD; World Health Organization, 1992), established essential common standards to facilitate patient care. As Kozak and Cuthbert (this issue) highlight, the authors of the third edition of the DSM (American Psychiatric Association, 1980) explicitly

cautioned that the operationalization of diagnostic criteria should not prompt the assumption of discrete entities with sharp discontinuities between disorders. Nonetheless, over time and over nosological revisions, clinicians and researchers alike have unintentionally reified these consensus-based subjective categories as discrete states of dysfunction (Hyman, 2010). Not surprisingly, the body of work that has emerged from biological psychopathology research, including psychophysiological and neuroscience studies, has by and large utilized a narrow lens reflecting this perspective. For instance, a typical study would compare patients with a target disorder to healthy control participants, the latter often rigorously screened to exclude even normative symptom elevations—based on the idea that purportedly discrete states of dysfunction should have unique neurobiological substrates.

At the same time, symptom-based diagnoses have multiplied across revisions of the DSM. Additionally the polythetic criteria of some diagnoses have also multiplied—in some cases such as PTSD exponentially (Galatzer-Levy & Bryant, 2013)—yielding dramatically increased within-disorder heterogeneity. Arguably, despite theoretical refinement of subjective diagnostic criteria, reliability and validity remain suboptimal, and comorbid cases far exceed ‘pure’ cases (Regier et al., 2013). Most importantly, little corresponding increase has occurred in the specificity and efficacy of treatment for most disorders, whether the intervention be psychosocial, pharmacological, or neuromodulatory.

Instead, transdiagnostic commonalities have become increasingly evident across a striking number of measured phenomena, ranging from symptom severity (Mineka, Watson & Clark, 1998) and comorbidity profiles (Vaidyanathan et al., 2011; Wright et al., 2013) to functional (Hägele et al., 2015; Oathes et al., 2015) and structural (Shang et al., 2014; Goodkind et al., 2015) neuroimaging effects, candidate genes (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), neuroinflammatory markers (Furtado & Katzman, 2015), defensive physiology (Lang, McTeague, & Bradley, this issue; McTeague & Lang, 2012), and pharmacological (Goodwin, 2015) and psychosocial (Farchione et al., 2012) treatment response.

The article by Kozak and Cuthbert in this issue provides a compelling overview of the RDoC initiative and its bold invocation to move beyond discrete diagnostic categories as major targets for physiologically oriented research on mental illness. Their discussion of the limitations of investigative work based on conventional diagnoses also aids in understanding the rapidly accumulating evidence for common or transdiagnostic aberrations in many dependent measures. As noted by Kozak and Cuthbert (p. 3): “These diagnoses can be seen as hypothetical psychological constructs, i.e., theoretical concepts, linked to stipulated observations about behavior. Presumably, if a diagnostic construct refers to some real illness, it is the reality of that illness which accounts for why the observations fit together according to the concept. If a hypothesis is false, the stipulated observations will not obtain as predicted because the supposed illness is not operating as hypothesized. That is to say, the construct is spurious and its disease referent does not exist as theorized.” If reported symptom patterns (i.e., disorder diagnoses) do not correspond to distinct neurobiological processes, then it should not be surprising that many of our “biomarkers” or “endophenotypes” appear to be transdiagnostic rather than disorder-specific.

Moving forward, how do we reconcile the persisting focus of research on specific disorders with the RDoC initiative call for “biological elaboration of intermediate psychological constructs [leading to] biopsychological explanations of clinical problems” (Kozak & Cuthbert, this issue)? In their article for the current issue, Hamm and colleagues illustrate a strategy for broadening our interpretation of extant disorder-specific findings while guiding future research on dimensional constructs and mechanisms that potentially underlie transdiagnostic processes. More specifically, working within the Negative Valence Domain, Hamm and colleagues reconceptualize hallmark symptoms of panic disorder with agoraphobia into narrower clinical phenomena. The authors first translate panic and related anxious apprehension to behavioral stages of the predatory (i.e., threat) imminence continuum, a preclinical model with strong evidence for separable neural circuits that implement these behaviors (Perusini & Fanselow, 2015). The authors then elaborate a systematic series of studies entailing measurement across “multiple units of analysis”, as recommended by RDoC, to converge upon candidate processes contributing to associated clinical impairment in defense-cascade responses.

Panic, Anxious Apprehension, & Threat Imminence: An RDoC Approach to Understanding Anxious Dysfunction

Hamm and colleagues reconceptualize panic attacks and anxious apprehension about future panic attacks as responses to acute threat and potential harm, respectively, two of five constructs from the Negative Valence Systems domain of the RDoC matrix. The authors in turn operationalize panic attacks and associated anxious apprehension in terms of the predatory imminence continuum (Fanselow, 1994; Lang et al., 1997), which organizes defensive behaviors along a dimension of perceived threat proximity. Notably, the perception of threat proximity is a psychological function of spatial, temporal, and probabilistic likelihood of threat contact (Perusini & Fanselow, 2015), rendering it an excellent model for psychophysiological experimentation.

Briefly, the imminence continuum encompasses three successive stages, each associated with prototypical defensive behaviors (Timberlake & Lucas, 1989): pre-encounter (e.g., vigilance for threat), post-encounter (e.g., freezing), and circa-strike (e.g., fight/flight). Due to constraints on overt behavioral responding in the human neuroimaging context, the neural circuits prompting transitions along this continuum are largely predicated on animal models. However, emerging human studies with computer simulations in which predators pursue and endanger the participant in a virtual environment have yielded findings consistent with the animal work. For example, Mobbs and colleagues (2007; 2009) presented evidence that the shift from prominent forebrain to midbrain activation in the transition from post-encounter to circa-strike may apply to humans as well as animals.

Hamm and colleagues (this issue) propose that panic attacks—characteristically marked by surges in autonomic activation and a strong behavioral disposition to escape—are instances of circa-strike (e.g., fight/flight) behavior. Further, anxious apprehension about future panic attacks and even mild somatic symptoms are considered an aberrant activation of post-encounter defense in otherwise innocuous contexts. Along this line, Perusini and Fanselow

(2015) have postulated that distortion of predatory or threat imminence can, in fact, more broadly explain anxiety spectrum disorders in that unwarranted post-encounter or circa-strike behaviors intrude into everyday life.

In support of their proposition that panic and affiliated anxious apprehension reflect aberrations in the threat imminence stages, Hamm and colleagues present analyses of multimodal data from more than 450 treatment-seeking patients with principal diagnoses of panic disorder with agoraphobia collected during a standardized behavioral avoidance task—anticipation of, and subsequent enclosure in, a dark, locked chamber. To assess evoked defensive responding, and consistent with the import placed by the RDoC initiative on multiple units of analysis, the investigators measured self-reported anxiety, observable behavior, startle reflex modulation, and autonomic reactivity—focusing not simply on absolute levels, but on the high-resolution temporal dynamics of the defense cascade.

Consistent with evidence for meaningful variability within unitary diagnostic categories (McTeague & Lang, 2012), dramatic heterogeneity emerged in behavioral and physiological responding to the chamber challenge amidst this sample. That is, despite the prominence of fears of enclosure in tight spaces among panic disorder patients with agoraphobia, approximately one-third of the sample completed the entire chamber challenge without any appreciable distress or physiological arousal during entrapment (non-anxious completers). Another third of the sample (anxious completers) endured the entire exposure despite intense defensive mobilization. The remaining third refused to enter the chamber (passive avoiders) or experienced physiological arousal and distress that prompted premature termination of exposure (active escapers). Even in light of the well-known heterogeneity in polythetic diagnostic categories, it is striking that a third of these principal panic disorder patients exhibited no avoidance and no signs of defensive arousal during in vivo exposure to a context representing one of the disorder's central concerns. These findings highlight the frequently stark discordance between behavior and nosologically based predictions of that behavior.

A psychophysiological investigation of the predator/threat imminence model in this population is especially instructive as very little is known about panic attacks beyond retrospective self-report. During entrapment separate from panicking or escape, Hamm and colleagues observed robustly elevated defensive reactivity (startle, heart rate, skin conductance, subjective anxiety) consistent with a state of post-encounter freezing. For those who progressed to panicking or escape, nearly identical defensive dynamics preceded panic attack onset and the overt decision to exit the chamber. The similarity between the physiological reactivity immediately preceding escape behavior and that during panic attacks provides a potential target for therapeutic intervention for panic—i.e., learning to counter the escalating escape disposition.

In considering how to translate these findings to the clinical context, a natural question is whether physiological and behavioral covariation as a function of threat imminence could be assessed more easily through symptom report. In fact, very few between-group differences emerged among the subgroups distressed by the chamber challenge (i.e., anxious completers, active escapers, and passive avoiders; Richter et al., 2012). Scores that reflected

DSM-based conceptualizations of symptom domains (e.g., agoraphobia, claustrophobia) or that reflected more diffuse higher-order factors (e.g., anxious apprehension, non-specific anxiety or depression) were similarly elevated and correlated across the subgroups showing post-encounter defense. In contrast, a more nuanced symptom dimension less clearly related to panic disorder—fear of suffocation—predicted differences in the propensity for overt avoidance. Essentially, dynamic escape dispositions evoked by the chamber could not be captured by conventionally defined indices of disorder severity.

Incorporating yet another unit of analysis from the RDoC matrix, Hamm and colleagues sought to identify specific genes accounting for variation in defensive reactivity in the chamber challenge among panic disorder with agoraphobia patients. Acute, robust defensive mobilization, panic proneness, and enhanced avoidance/escape likelihood were related to gene alleles associated with reduced serotonergic neurotransmission (Reif et al., 2014; Straube et al., 2014). In contrast, allelic variation in the receptor for corticotropin releasing hormone was associated with reduced acute fear as measured by attenuated heart rate responding, reduced escape likelihood, and higher trait negative affect and anxious apprehension (Weber et al., in press). While reduced fear reactivity and behavior simultaneous with increased negative affectivity may seem paradoxical, other investigators have reported similar blunting of defensive reflexes in chronic, broad distress within panic disorder (McTeague et al., 2011) as well as across the wider anxiety spectrum (McTeague & Lang, 2012). Considering their results as a whole, Hamm and colleagues suggest that reductions of serotonergic functioning contribute to exaggerated circa strike defense to cued threat, while allelic variation in the receptor for corticotropin releasing hormone is more predictive of chronic apprehension and hypervigilance in the absence of tangible threat.

In an often neglected but essential translation of laboratory-based psychophysiological findings to clinical application, Hamm and colleagues also examined the association of chamber-evoked escape dispositions to outcome in a randomized controlled trial of cognitive-behavioral therapy for panic disorder with agoraphobia (Gloster et al., 2011). Those patients who showed either passive avoidance or escape from entrapment relative to those who remained in the chamber were twice as likely to drop out of treatment. Further suggestive that defensive dynamics reflect more than disorder severity, among those predisposed to avoidance behavior, the subset that completed treatment showed larger gains than non-avoiders (even after accounting for baseline symptoms). As an important caveat to moving towards personalized medicine, the more robust treatment gains observed by avoiders were only evident for those who engaged in therapist led (versus self-directed) exposure—possibly an indication of disrupted escape dispositions that facilitated exposure and extinction.

The use of behavioral avoidance tasks has substantially diminished in clinical research. Yet Hamm and colleagues have demonstrated the utility of standardized in vivo exposure in conjunction with psychophysiological assessment to 1) identify meaningful individual differences in escape dispositions, 2) discern the temporal unfolding of robust fear versus chronic apprehension, 3) reliably evoke real-world circa-strike behavior, 4) relate defensive reactivity profiles to allelic variations in candidate genes for affective dysfunction, and 5) inform treatment prognosis and planning. In contrast, many of our most common

experimental tasks have questionable ecological validity for elucidating the real-world experience of debilitating fear and anxiety.

Relatedly, Lissek and colleagues (2006) have proposed that in contrast to unambiguous threats, which prompt robust, adaptive, and often uniform defensive responding across patients and control participants, weakening elicitation parameters (i.e. certainty, proximity, intensity) may actually enhance the power to detect patient-control differences in objective measures of anxious arousal. While reduced levels of salience or imminence may increase variance in reactivity attributable to individual differences, does this variance in turn map onto real-world dysfunction and prognosis? Importantly, as reported in an earlier report of the current work by Hamm and colleagues (Richter et al., 2012), subjective and objective reactivity during anticipation of the enclosed chamber (unlike actual entrapment) was insufficient for distinguishing completers from non-completers—and did not predict the more nuanced but clinically meaningful distinction of avoiders, escapers, and anxious completers. The power of this exposure paradigm to identify meaningful subgroups of responders may lie in its intermediacy between ambiguous and unambiguous threats, and its ability to capture variance in outcomes ranging from covert anxious arousal and/or apprehension to overt escape. If so, this has substantial implications for many widely used assessment procedures that rely (for reasons of practicality) on a restricted repertoire of overt defensive behavior. Furthermore, it underscores the central importance of more readily assessed and flexible psychophysiological measures in furthering the RDoC initiative, despite their inability to directly index circuit function.

While the multimodal findings by Hamm and colleagues are compelling and the approach provides important guidance on how to consider historic diagnosis-specific findings from a more dimensional and mechanistic perspective consistent with the RDoC initiative, the question necessarily remains as to the extent of transdiagnostic relevance of escape disposition aberrations. Speaking to this to some degree, it is well established that self-reported anxiety sensitivity or chronic apprehension of physiological arousal is prominent across anxiety and depressive disorders (Deacon & Abramowitz, 2006; Lang et al., this issue; McTeague & Lang, 2012; Naragon-Gainey, 2010). Taylor et al., 1992), and individuals high in anxiety sensitivity show abnormal defensive reflexes during paradigms hypothesized to invoke post-encounter defense (e.g., McTeague & Lang, 2012).

Though less well-recognized, panic attacks are also prevalent across psychiatric disorders other than panic disorder (e.g., Kessler et al., 2006; Kinley et al., 2011; Reed & Wittchen, 1998). For example, in an epidemiological sample, Kessler et al. (2006) reported that 71.9% of individuals with lifetime panic attacks in the absence of panic/agoraphobia (i.e., isolated panic attacks) met criteria for at least one Axis I disorder. Of this portion, isolated panic attacks signaled increased risk across mood disorders (36%), impulse control disorders (33.7%), and substance use disorders (21.4%) as well as anxiety conditions other than panic with agoraphobia (45%). Other epidemiological studies have highlighted the prominence of panic attacks in somatoform and dissociative disorders (Goodwin et al., 2004; Panè-Farrè et al., 2013) and their clear association with multimorbidity and functional impairment (Klerman et al., 1991). Importantly, from a lifespan-developmental perspective the experience of panic attacks and even limited/subclinical attacks strongly signals the

development of wide ranging future psychopathology and worsening of existing impairments (Goodwin et al., 2004; Panè-Farrè et al., 2013; Reed & Wittchen, 1998). In fact, in a longitudinal developmental sample, Goodwin and colleagues (2004) observed that over one-third of children who endorsed panic attacks at baseline surpassed a threshold of at least three disorders by young adulthood.

Similar to chronic anxious apprehension, rather than signaling a diathesis or dysfunction specific to panic disorder and agoraphobia, panic attacks may be indicative of transdiagnostic liability for broad-spectrum dysregulation of affective chronometry and salience detection. In a panic attack, otherwise adaptive defensive responses are discharged without warrant. Hamm and colleagues have demonstrated that panic attacks are akin to avoidance and escape-related preparation and are aptly considered a manifestation of circa-strike behavior—rather than a pathological phenomenon unique from other defensive responses. As such, characterizing the entire trajectory that gives rise to circa-strike preparation and defenses would likely be informative. Parallel to the insights that Hamm and colleagues have provided for panic disorder, systematic and multimodal assessment of defensive dynamics along the threat imminence continuum may provide valuable insight into transdiagnostic emotion dysregulation as well as reveal promising avenues for tailoring intervention.

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