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Reshaping clinical science: Introduction to the Special Issue on *Psychophysiology and the NIMH Research Domain Criteria (RDoC) initiative*

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Abstract

The National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) initiative seeks to establish new dimensional conceptions of mental health problems, through the investigation of clinically relevant "process" constructs that have neurobiological as well as psychological referents. This special issue provides a detailed overview of the RDoC framework by NIMH officials Michael Kozak and Bruce Cuthbert, and spotlights RDoC-oriented investigative efforts by leading psychophysiological research groups as examples of how clinical science might be reshaped through application of RDoC principles. Accompanying commentaries highlight key aspects of the work by each group, and discuss reported methods/findings in relation to promises and challenges of the RDoC initiative more broadly.

Descriptors: Research Domain Criteria (RDoC), Psychopathology, Psychotic symptoms, Anxiety pathology, Error-related negativity, Comparative research

"Better to light a candle than to curse the darkness."
– Ancient Asian proverb

Since the earliest days of our discipline, researchers in the field of psychophysiology have had a strong interest in applying brain and bodily measurement to the study of clinical problems and related individual difference characteristics. The founder and third president of the Society for Psychophysiological Research (SPR), and inaugural editor of this journal, Albert Ax, focused throughout his career on quantification of variations in affective response (Ax, 1990; Courter, Wattenmaker, & Ax, 1965) and developed a conditioning-based procedure for indexing emotional deficits in schizophrenia (Ax, 1970). The Society's first and second presidents, Chester Darrow and John Lacey, likewise devoted substantial effort to the study of individual differences in relation to psychopathology assessment (e.g., Darrow, 1943; Darrow & Solomon, 1934; Lacey, 1950, 1955, 1959; Lacey & Lacey, 1958). The published address papers of many subsequent SPR presidents have included a prominent emphasis on clinical assessment. Some of these papers focus on the investigation of specific clinical conditions (e.g., Ford, 1999; Iacono, 1998; Lang, 1979; Öhman, 1986; Simons, 2007), some on psychopathology more generally (e.g., Dawson, 1990; Fowles, 1988; Miller, 1996), and others on conceptual and methodological issues in physiological quantification of clinically relevant dispositions (e.g., Davidson, 2003; Katkin, 1985; Venables, 1978).

During the 1990s, biological research on psychopathology took a dramatic turn from the measurement-oriented approach of psychophysiologists, with the ascendance of criterion-based definitions for mental disorders (American Psychiatric Association, 1980, 1994) and increasing emphasis on brain and genetic studies fueled by developments in human neuroimaging and the mapping of the human genome. The dominant investigative approach became one of comparing patient groups with one another and with healthy controls on measures of brain structure and task-related neural activation, and in presence versus absence of specific gene alleles. Studies of these types were prioritized for publication in older and newer fast-break, high-impact outlets. The term *imaging genomics* (*genetics*) was coined to reflect the combined use of these two measurement methods in the study of mental disorders (Hariri & Weinberger, 2005). Momentum grew around the idea of identifying distinct biological markers of underlying genetic risk

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(endophenotypes; Gottesman & Gould, 2003) for specific forms of psychopathology.

However, enthusiasm for this general research approach has been tempered in recent years by mounting concerns with the categorical system for diagnosing mental disorders (e.g., Markon & Krueger, 2005; Widiger & Samuel, 2005), meta-analyses challenging the findings of high-profile published works (e.g., Murphy et al., 2013; Risch et al., 2009), methodological critiques of small-*N* neuroimaging research (e.g., Ioannidis, 2011; Vul, Harris, Winkielman, & Pashler, 2009; see also Iacono, 2014), genome-wide association studies (GWAS) demonstrating either null or minute effect sizes for allelic variants identified as risk factors for psychopathology by candidate gene studies (Psychiatric GWAS Consortium Coordinating Committee, 2009), and recent GWAS work reporting null findings for candidate genes believed to be associated with neurophysiological endophenotypes (Iacono, Malone, Vaidyanathan, & Vrieze, 2014). The Research Domain Criteria (RDoC) initiative, spotlighted in this special issue of *Psychophysiology*, was advanced by the National Institute of Mental Health (NIMH) as a step toward changing the way biological research on psychopathology is conducted to improve prospects for success.

The major focus of the RDoC initiative is on conventional psychodiagnosis as an impediment to progress. As described in the lead article by **Kozak and Cuthbert (2016)**, the initiative seeks to establish new dimensional conceptions of mental health problems—through the investigation of clinically relevant "process" constructs that have neurobiological as well as psychological referents—to replace traditional categorical diagnoses as targets for research and clinical intervention. To serve as a guide for investigative efforts, RDoC provides a provisional matrix that includes, as rows, multiple specific constructs (e.g., acute threat, reward valuation, response inhibition) organized within broad systems domains, and as columns, differing complementary approaches to measuring and studying these constructs (i.e., "units of analysis," including genetic, molecular, cellular, neural-circuit, physiological, etc.). A dimensional approach is encouraged both in the operationalization of explanatory (i.e., process) constructs and in the formulation and quantification of clinical targets for study. As noted by Kozak and Cuthbert, quantitative approaches developed for use in continuous-score assessment work are advocated: "The methods of classical psychometrics and of item response theory … constitute sophisticated techniques for construct development and validation … Established integrative disciplines … have long utilized psychometric techniques in conjunction with physical and biological measurement to develop and evaluate constructs that are not exclusively psychological or biological. It stands to reason that the same methods could support the integration of psychopathology, neuroscience, and genetics" (p. 288).

However, RDoC is less explicit about the nature of clinical problems to be investigated: "[T]he framework is conceived to facilitate study of circumscribed clinical problems rather than to cluster them into syndromes … Thus, it invites concentration on narrowly defined complaints or impairments that might be more tractable than heterogeneous symptom clusters" (**Kozak & Cuthbert, 2016**, p. 295). General guidelines are presented (e.g., clinical targets should be narrow vs. broad, potentially transdiagnostic rather than disorder specific, assessed dimensionally as opposed to categorically, etc.), and some illustrative examples are provided (e.g., excessive fear, anhedonia, hallucinations). However, new ways of conceptualizing clinical problems themselves, and alternative methods for operationalizing them, are expected to evolve out of creative applications of RDoC principles to the investigation of more circumscribed ailments or impairments.

In this sense, RDoC is intended as a largely blank canvas on which researchers are encouraged to render their own investigative visions, within the lines of a core set of "aesthetic" principles. Through ongoing research efforts, the matrix framework itself is expected to evolve in ways that best facilitate the formulation of new, biologically oriented conceptions of mental health problems. The six empirical-conceptual articles that follow **Kozak and Cuthbert's (2016)** overview of the RDoC framework reflect differing creative visions of established research groups as to how clinical science might be reshaped through application of RDoC principles. Of note, five of these six articles focus on constructs from the RDoC Negative Valence Systems domain, in particular acute threat ("fear") and potential threat ("anxiety")—providing perspective on how particular constructs from the RDoC matrix are being investigated in differing but complementary ways. Accompanying these six target articles are commentaries by distinguished experts from the biological psychopathology area who highlight key points and discuss broader implications of each. In addition to addressing one designated target article, all commentators were asked to also provide input on Kozak and Cuthbert's opening review paper.

Overview of Target Articles and Commentaries in the Special Issue

The first empirical-conceptual article, by **Ford (2016)**, focuses on disturbances in neural processes underlying an individual's sense of agency, entailing the perceived "relation between actions and their consequences … triggered by efferent motor commands," as a mechanism for auditory verbal hallucinations (AVHs). More specifically, Ford presents evidence that brain-based processes that normally operate to identify ("tag") speech as self-generated are reduced in schizophrenia patients with AVH symptomatology, and that AVHs arise from impairment in this internal tagging mechanism. The research is RDoC oriented in that it focuses on a specific construct from the matrix framework (i.e., agency, within the Social Systems domain), studied using differing units of analysis (including brain circuitry, neurophysiology, self-report), in relation to a circumscribed symptom feature (AVHs) evident in differing diagnostic conditions (e.g., schizophrenia, bipolar disorder, schizoaffective disorder). Accompanying commentaries discuss (a) merits and limitations of Ford's hypothesis-driven approach to studying AVHs relative to an alternative "symptom-capture" strategy (**Heckers, 2016**); and (b) Ford's work as both emblematic of how to conduct RDoC research, and illustrative of weaknesses of RDoC including problems in mapping processes of interest to constructs in the matrix, overemphasis on neural circuitry in accounting for clinical problems, and issues of statistical power and replicability in smaller-*N* experimental studies (**Iacono, 2016**).

The second target article, by **Hamm and colleagues (2016)**, conceives of two constructs from the RDoC Negative Valence Systems domain, acute threat and potential threat, as reflecting differing points along a defensive reactivity continuum inferred from research on threat imminence and behavioral responding in animals (e.g., Fanselow, 1994). Hamm et al. report on work examining these constructs in patients suffering from panic disorder with agoraphobia, presenting evidence for differential physiological, self-report, and genomic correlates of (a) acute defensive reactivity associated with panic episodes, and (b) potential threat as reflected by attentive freezing behavior and reported awareness of bodily

symptoms. RDoC-related aspects of this research include its focus on specific constructs from the matrix, use of measures reflecting multiple units of analysis (genes, physiology, overt behavior, self-report), and investigation of symptom expressions corresponding to panic and anxious apprehension. Commentaries for this article consider (a) the novel in vivo exposure methodology used in this work, and its transdiagnostic relevance and implications for treatment (**McTeague, 2016**); (b) RDoC-related issues highlighted by this work including definitional and epistemological status of RDoC matrix constructs and appropriate procedures for subject selection (**Shankman, Katz, & Langenecker, 2016**); and (c) ways in which Hamm et al.'s work departs from the RDoC framework (e.g., by focusing on a specific diagnostic condition), and concerns regarding the RDoC initiative raised by this work (e.g., neglect of complex higher-order psychological constructs, devaluation of self-report assessment, neglect of environmental influences; **Zoellner & Foa, 2016**).

The next article, by **Lang, McTeague, and Bradley (2016)**, reports evidence from analyses of a large ($N = 425$) patient-imagery dataset for a continuum of anxiety-related pathology, ranging from focal phobias entailing exaggerated reactivity of the brain's core defensive system to pervasive distress conditions marked by salient reductions in defensive-system reactivity. Findings from this work point to distinct pathophysiologies for anxiety conditions involving generalized distress and dysphoria versus those involving focal fear. RDoC-compatible elements of this work include its transdiagnostic (psychopathology spectrum) focus, its emphasis on acute threat as an explanatory construct, and its use of differing units of analysis consisting of physiology, behavior, and self-report. Accompanying commentaries (a) discuss Lang et al.'s findings in relation to behavior genetic data suggesting differing etiologies for fear versus distress conditions, in the process highlighting the value of retaining traditional DSM assessment in RDoC studies (**Hettema, 2016**); and (b) relate Lang et al.'s physiologically informed concept of an anxiety-disorders continuum to recent movements in the field toward an integrative dimensional model encompassing mental disorders as a whole, highlighting ways in which RDoC research can benefit from linkages to this model (**Krueger & DeYoung, 2016**).

The fourth target article, by **Latzman, Young, and Hopkins (2016)**, documents a novel program of research directed at clarifying the biological basis of individual differences in potential harm (anxiety) reactivity using primates (chimpanzees) as subjects. Their approach is unique relative to other work in the current series in that their clinical-symptom variable, anxious responding, was (by necessity, given the nature of the sample) defined behaviorally rather than through report—in terms of self-scratching activity. The authors report evidence for gender-specific associations of anxiousness with allelic variation in a distinct gene implicated in social behavior, and with volumes of brain regions found to be related to variation in this gene. This work aligns with RDoC in terms of its use of multiple units of analysis (genes, circuits, overt behavior) to clarify the biological basis of variations in responsiveness to potential threat, with the aim of elucidating mechanisms of clinical anxiety. Commentaries for this article key in on (a) conceptual and methodological issues regarding the use of scratching behavior to index anxiety or negative affect, and positive features of the RDoC research approach highlighted by the work of these authors (**Krystal, 2016**); and (b) Latzman et al.'s research as an illustration of the value of animal models for investigating processes relevant to psychopathology, and questions regarding the RDoC research approach raised by this work—including the potential incremental value of nonreport-based measures for indexing psychopathology-relevant processes, and drawbacks associated with RDoC's emphasis on "narrow" clinical-symptom variables as opposed to conventional diagnoses (**Maestripieri & Lilienfeld, 2016**).

The fifth empirical-conceptual article, by **Weinberg and collaborators (2016)**, focuses on the symptom correlates and psychological meaning of a specific brain potential measure, the error-related negativity (ERN). The authors posit that variability across individuals in the magnitude of the ERN reflects the degree to which errors in responding are evaluated as threatening. Using data from a large female adolescent sample ($N = 515$), they report evidence for opposing relations of ERN magnitude with self-reported checking behavior versus depressive symptomatology—linking their results to the above-noted work by **Lang et al. (2016)** on physiological reactivity in fear versus distress pathology. The work is RDoC oriented in that it focuses on clarifying relations of two distinct symptom variables (anxious checking, depressivity) with the construct of sustained threat from the Negative Valence Systems domain using a physiological response measure shown in previous work to index an endogenous "early-warning" process. Commentaries focus on (a) methodological issues in quantifying and analyzing ERN response data, and the need for follow-up work to replicate and clarify the reported findings (**Hanna & Gehring, 2016**); and (b) questions regarding the authors' interpretation of ERN as an index of sustained threat reactivity that should be addressed through further research, and the need to consider motivational context and developmental factors in testing for ERN/psychopathology associations (**Ladouceur, 2016**).

The final target article, by **Yancey, Venables, and Patrick (2016)**, reports on efforts to quantify an individual difference variable corresponding to the RDoC construct of acute threat using indicators from the domains of both self-report and affective-task physiology. The authors suggest that this approach to quantifying threat sensitivity, as a composite psychometric-neurophysiological (psychoneurometric) dimension, can serve as a vehicle for connecting clinical problems to neural systems, and a mechanism for reshaping conceptions of problem-related trait dispositions. RDoC-related aspects of this research include its focus on a dispositional counterpart to the construct of acute threat, its use of measures from domains of self-report and physiology to quantify variations in threat sensitivity, and its focus on a transdiagnostic, dimensional clinical criterion (i.e., fear psychopathology symptoms). Accompanying commentaries discuss (a) methodological issues raised by this measurement-oriented work—including how best to select and refine candidate items, what validity criteria to use in work of this type, and the critical need to establish reliability in physiologically oriented assessments (**MacNamara & Phan, 2016**); and (b) limitations of the work including its lack of focus on mechanisms for observed relations among indicator variables, and related conceptual issues including how best to characterize associations between psychological and biological variables, and potential weaknesses in the row/column organization of the RDoC matrix (**Miller, Rockstroh, Hamilton, & Yee, 2016**).

Concluding Comment

The NIMH RDoC initiative represents a major development in the field of psychopathology that has gained considerable momentum since its inception in 2009. The initiative presents major opportunities for psychophysiological researchers to contribute to reshaping how mental disorders are conceptualized and studied, along lines presaged by the work of early eminent investigators in our discipline. Although as noted by some of the commentators in this

special issue and as discussed in our closing article for the issue (**Patrick & Hajcak, 2016**), the RDoC matrix framework as it currently stands is limited in important respects, the framework is clearly intended as an "open system" to be improved upon as research efforts proceed. The empirical-conceptual articles featured in this special issue provide valuable examples of avenues along which research can proceed according to this initiative, and these articles and the commentaries that accompany them serve to highlight potential benefits of the RDoC framework and ways in which the framework can be profitably refined.

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