RDoC: Translating promise into progress

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Abstract

As highlighted by articles in the current special issue, the RDoC initiative holds promise for advancing understanding of mental health problems. However, the initiative is at its early stages and it remains unclear what level of progress can be achieved and how quickly. In this closing article, we identify major challenges facing RDoC and propose concrete approaches to addressing these challenges, including (a) clearer specification of clinical problems for study, with use of symptom dimensions from integrative dimensional models of psychopathology as provisional, modifiable referents; (b) encouragement of research on a distinct set of traits corresponding to process constructs from the RDoC matrix—those represented across animal, child temperament, and adult personality literatures—to serve as interfaces between matrix constructs and clinical problems; (c) an emphasis in the near term on use of proximal units of analysis in RDoC studies— in particular, on physiological, behavioral, and self-report measures of matrix constructs (examined as states or traits, or both); (d) inclusion of a clear ontogenetic-developmental component in RDoC research projects; (e) routine analysis of the psychometric properties of nonreport (e.g., physiological, task-behavioral) variables, including systematic evaluation of their reliability and convergent-discriminant validity; (f) modification of existing grant review criteria to prioritize replication and synergy in RDoC investigative work; and (g) creation of a cumulative data network system (RDoC–DataWeb) to encourage and facilitate coordination of research efforts across RDoC research groups.

Descriptors: Research Domain Criteria (RDoC), Psychophysiology, Psychopathology, Clinical science, Neuroscience, Multidomain assessment

"Between the idea and the reality . . . Falls the Shadow"
– T. S. Eliot (1925)

The National Institute of Mental Health's Research Domain Criteria (RDoC) initiative is still in its early stages, with the RDoC matrix having been posted online in the latter part of 2012. The six empirical-conceptual articles in the current special issue illustrate differing approaches to investigating clinical problems in line with RDoC principles (as described by **Kozak and Cuthbert, 2016**), through their focus on specific constructs from the RDoC matrix and use of multiunit assessments, with particular emphasis on measures from the domain of physiology. As such, articles for the current issue highlight the potential the RDoC framework has to advance conceptualization and understanding of mental health problems, and the valuable role that psychophysiological research-

ers can play in this endeavor. At the same time, leading scholars in the psychopathology area have called attention to limitations of the RDoC research framework and raised questions about its ability to alter diagnostic conceptions and advance knowledge in significant ways (Kraemer, 2015; Lilienfeld, 2014; Weinberger, Glick, & Klein, 2015). Concerns along these lines are voiced in some of the commentaries for the current special issue.

Our own view is that the RDoC framework holds considerable promise for improving research practices and understanding in the mental health field, but that strategic steps can and should be taken to address existing challenges and achieve progress in a timely manner. In this closing article for the current issue, we identify major challenges facing the RDoC initiative and propose concrete approaches to addressing these challenges that can enhance its prospects for success. Considering these issues from a psychophysiological perspective, we emphasize the need for a systematic measurement-oriented approach to clarifying relations between psychological phenomena and physiological variables in the service of understanding clinical problems.

Need for Clearer Specification of Clinical Problems as Targets for RDoC Research

The major focus of the RDoC initiative is on the obstacles posed by the existing psychiatric diagnostic system, the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013), to biologically oriented analysis and

understanding of psychopathology. Modern criterion-based conceptions of psychiatric disorders introduced in the third edition of the DSM provided an improvement over earlier prototype-based conceptions, and have served over the years as concrete points of reference for research and practice. At the same time, however, the well-documented problems with DSM categorical diagnoses (**Kozak & Cuthbert, 2016**; Kraemer, 2015; **Krueger & DeYoung, 2016**) are a major reason why the RDoC initiative was advanced. Through the process of reification, DSM disorders have become largely immovable anchors, impermeable to data and resistant to revision.

As described in the lead article by **Kozak and Cuthbert (2016)**, the RDoC initiative seeks to foster new dimensional conceptions of mental health problems based around clinically relevant process constructs that have neurobiological as well as psychological referents. Our view is that, to achieve this aim in an efficient and effective manner, RDoC needs to delineate more specifically the nature of clinical problems to be targeted for study at this formative stage of the initiative, and describe in clearer terms how conceptions of clinical problems can be expected to change as RDoC-oriented research proceeds. Notably, alternative frameworks for clinical assessment/psychodiagnosis have been proposed, in the form of quantitative-empirical models that conceive of clinical problems in terms of continuously varying individual difference factors (i.e., dimensions). The latest of these models are hierarchical-dimensional models that characterize sets of interrelated problems ("psychopathology spectra") in terms of broad dimensions reflecting commonalities among differing problems, and narrower subdimensions reflecting specific, nonshared elements of particular conditions; models of this type exist for internalizing problems (e.g., Watson, 2005; Watson et al., 2007, 2012), externalizing problems (Krueger et al., 2007; Patrick, Kramer, Krueger, & Markon, 2013), and personality pathology (American Psychiatric Association, 2013; Krueger, Derringer, Markon, Watson, & Skodol, 2012). As discussed by **Krueger and DeYoung (2016)**, some recent work has focused on formulating a comprehensive hierarchical-dimensional model for the full range of adult psychopathology, referenced to the well-established five factor model of general personality tendencies. However, from an RDoC perspective, the problem with shifting from the DSM categorical framework to a dimensional-descriptive model is that this simply replaces one phenomenological report-based system for clinical description with another—and will similarly impede progress toward a biologically based science of psychopathology. The widespread emphasis in the psychological literature on dimensions and facets of the language-based five factor model of personality as anchors for research of all types highlights the potential for reification of descriptive units of an alternative personality-based nosological system.

As it stands, RDoC's position on the nature of clinical problems to be studied, per **Kozak and Cuthbert (2016)**, is that they should consist of "narrowly defined impairments of psychiatric clinical importance . . . [that is,] individual symptoms or very homogeneous symptom sets," in order to "free investigators from nosological categories." (p. 288). These impairments should be "measured dimensionally (p. 294)." While some specific examples of such "narrowly defined impairments" are provided in this and other RDoC writings (e.g., anhedonia, rumination, sleep disturbance), RDoC purposefully avoids a more detailed taxonomy so as not to constrain investigators, and (per its principal specified aims) to allow new conceptions of clinical problems to evolve out of RDoC-oriented research efforts directed at examining core processes through multiple units of analysis. As to what the new clinical conceptions emerging from RDoC can be expected to look like,

Kozak and Cuthbert suggest that "psychopathology, or 'biopsychopathology,' eventually might be conceptualized as extremes on psychobiological dimensions that are linked to narrowly determined (in the sense of homogeneity of mechanism) clinical problems" (p. 288)—citing as examples "excessive fear or pathological fearlessness," manifested as "phobic" avoidance or "psychopathic" risk taking, respectively, and excessive or deficient reward motivation, manifested as problematic substance use or gambling on one hand, or as general anhedonia or severely restricted eating (anorexia) on the other.

Our view is that this stance on target clinical problems is underdeveloped, confusing to researchers because the proffered examples are isolated and diffuse (with some characterized in relation to disorders, and others not), and as such likely to hamper rather than facilitate progress. A clearer, more organized approach to clinical-target specification that considers the problem context in which individual psychological symptoms occur (as is routinely done with physical symptoms such as cough, headache, or fever), and patterns of relations among them, is needed to guide RDoC research efforts and foster coordination among differing investigative groups. Existing dimensional systems (e.g., Clark, 2009; Kruger, Derringer et al., 2012; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Livesley & Jackson, 2009; Watson et al., 2007, 2012) and emerging hierarchical-dimensional systems (e.g., Kotov, 2016; Kotov et al., 2015; Wright & Simms, 2015) for characterizing symptoms and their interrelations can and should be used as points of reference for the time being, as research moves forward—but with due consideration for the tenets of RDoC (in particular, operationalization of constructs using variables from multiple domains), so that the clinical-descriptive system remains permeable to new data and can evolve with advances in multiunit, process-based understanding. For example, at this point in time, RDoC-oriented studies could investigate symptom dimensions of depressivity or irritability, or perhaps negative affective tendencies more broadly, quantified continuously using either DSM criterion counts or dimensional-model scores (e.g., Krueger et al., 2012; Watson et al., 2007, 2012),[1] but with collection of other types of data (e.g., informant ratings, observable behavior, circuitry/physiological measures) to be evaluated as complementary symptom indicators. Papers by **Ford (2016)** and **Yancey, Venables, and Patrick (2016)** in the current issue provide concrete examples of how measures from the domain of physiology[2] might be incorporated into assessments of hallucinatory and excess-fear

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1. While the current discussion focuses on investigation of clinical problems in continuous dimensional terms, we also acknowledge the value of examining patterns of problems at the level of individuals—through use of person-centered analytic approaches (e.g., latent class/profile analysis; model-based cluster analysis), as a complement to variable-centered approaches (e.g., factor analysis; item response modeling). The person-centered approach has proven useful, for example, for clarifying sources of systematic covariation among clinical symptom variables, in terms of individuals who contribute most to observed co-occurrence patterns (Vaidyanathan, Patrick, & Iacono, 2011). Along similar lines, person-centered approaches are likely to be helpful for clarifying sources of covariance among differing indicators of a biobehavioral process construct, or between indicators of a biobehavioral process and clinical symptom variables.

2. Throughout the current article, we refer to *measures from the domain of physiology*, or *physiological measures*, rather than *psychophysiological measures*—because the focus of our conceptual points is on physiology as a domain of assessment (or unit of analysis, in RDoC terms). At the same time, we affirm (as does RDoC) the importance of investigating physiological and other biological variables in concert with behavioral and report-based variables, in order to clarify their interface

symptomatology, respectively. Hierarchical-dimensional models of clinical symptomatology that incorporate data from measurement domains (units) other than self-report and clinician- or informant-rating could be established through work of this type.

Large Number of Constructs in the RDoC Matrix and Variable Interpretation of Constructs

The RDoC matrix as currently formulated contains 39 constructs organized within five higher-order domains (five within the Negative Valence Systems domain, eight within the Positive Valence Systems domain, etc.), and RDoC explicitly encourages diversity in approaches to operationalizing and studying these constructs. This pluralism is evident in the differing ways that contributors to the current issue approached the investigation of Negative Valence Systems constructs. For example, acute threat was operationalized in alternative affective-state terms by **Lang, McTeague, & Bradley (2016)** and **Hamm et al. (2016)**, as phasic responding during imagery of feared situations and confinement-induced panic, respectively, whereas **Yancey, Venables, and Patrick (2016)** studied this construct in affective-trait terms, as threat sensitivity quantified using trait-scale and task-physiology indicators. The construct of potential threat was operationalized as self-scratching behavior during stressful video viewing by **Latzman, Young, & Hopkins (2016)** and as attentive freezing behavior and reported awareness of bodily symptoms during physical confinement by Hamm et al. The emphasis in these two studies was on potential threat as an evoked affective state. A different approach to a third construct from the Negative Valence domain, sustained threat, was taken by **Weinberg et al. (2016)**. These authors focused on a specific variable from the domain of physiology, the error-related negativity (ERN), and posited that it indexes a distinct type of threat processing—reactivity to potential adverse consequences associated with the commission of errors. Notably, Weinberg et al. considered the ERN in both affective-state and affective-trait terms (as reactivity to errors in a performance task, and as a measure of variability across individuals in the extent to which errors are evaluated as threatening [endogenous threat sensitivity])—and in turn, related it to two clinical symptom variables (checking behavior, depressivity).

The fact that constructs from the matrix can be conceptualized and measured in a variety of ways is both a strength and a potential weakness of the RDoC framework. The strength lies in the advantages, from a classic psychometric perspective, of treating psychological constructs as "open" and modifiable based on accumulating findings and advances in knowledge (Cronbach & Meehl, 1955; Loevinger, 1957; Meehl, 1977). This openness protects against the reification and stagnation that RDoC seeks to address. At the same time, the large number of constructs included in the RDoC system and the multitude of ways in which they can be interpreted and operationalized (in particular, given the system's explicit emphasis on multiunit assessment) raise questions about the extent to which investigative efforts by differing groups will synergize, and how quickly a new, coherent nosological system for psychopathology is likely to emerge from such efforts. Given the costly toll that problems such as psychotic episodes, debilitating dysphoria or anxiousness, violent victimization, and suicide exact on individuals in society and those connected to them, it may be useful to consider ways in which progress toward a biobehavioral process-oriented understanding of psychological problems can be expedited. In the

with psychological constructs—a perspective that is central to the discipline of psychophysiology.

subsections that follow, we suggest some ways in which research efforts can be effectively coordinated within the context of an open, pluralistic investigative framework.

Trait Counterparts to RDoC Process Constructs

The foregoing description of differing investigative approaches used by contributors to the current special issue makes it clear that certain constructs in the RDoC matrix can be conceptualized and studied both as situation-related psychobiological conditions (states), and as psychobiological dispositions (traits). It is also clear that these alternative ways of framing RDoC constructs are potentially compatible, rather than separate or competing. For example, the physiological variables used as indicators of dispositional threat sensitivity by **Yancey, Venables, and Patrick (2016)** overlap with measures of situational threat reactivity used by **Lang et al. (2016)** and **Hamm et al. (2016)**, although the contexts in which measures were recorded differed. Nonetheless, their focus on a common construct operationalized in related ways gives these studies the potential to complement one another in clarifying the role of acute threat in fear/anxiety pathology: A *state* focus is informative about online, in-the-moment aspects of a hypothesized process; a *trait* focus is informative about general proclivities toward occurrence of, or engagement in, processes of interest. Notably, this complementarity of state and trait conceptions has been highlighted over many years in the literature on emotion and personality (e.g., Larsen & Ketelaar, 1989; Watson, Clark, & Tellegen, 1988; see also: Eysenck, 1947; Spielberger, Gorsuch, & Lushene, 1970).

We believe that it would be strongly advantageous for online descriptions of the RDoC system and RDoC-related publications to explicitly encourage investigation of matrix constructs in these alternative but complementary ways (i.e., as states and as traits). In particular, we suggest that progress toward an effective biobehavioral nosology for mental disorders will be facilitated by focusing in the near term on a distinct set of trait dispositions corresponding to RDoC matrix constructs—those represented clearly in the animal behavior and child temperament literatures, as well as in the adult personality literature. Examples of such dispositional constructs include threat sensitivity, reward sensitivity, inhibitory control, and affiliativeness (attachment capacity). RDoC-oriented research on dispositional constructs in human samples would differ from conventional research on temperament and personality in that (a) studies would be framed in terms of constructs from the RDoC matrix, operationalized both in state terms (e.g., within relevant lab tasks or in vivo contexts) and in trait-dispositional terms, in each case using (b) multiunit assessment methods, with the specific aims of (c) establishing novel cross-domain operationalizations of these dispositional constructs connected empirically to RDoC process constructs, and (d) relating measured variations along these cross-domain trait continua to variations in neural-circuit functioning within health-relevant contexts and to dimensions of clinical impairment. Notably, this approach to investigation of dispositional constructs aligns closely with Allport's (1937) classic conception of traits as "psychophysical systems."

An example of how constructs from the RDoC matrix can be studied as both states and traits is the use of startle reflex potentiation as an index of acute threat (fear). Startle potentiation can be used to index the defensive activation state elicited on average by an acute threat manipulation, such as the presentation of a visual cue signaling delivery of shock. In this case, the increase in startle blink magnitude evident during the threat cue relative to a non-threat (safe) cue is a general within-subject effect that reflects the

impact of threat-cue presentation on defensive reflex priming. Alternatively, variations in startle potentiation within a threat-cuing context can be used as an index of individual differences in threat sensitivity, as was done by **Yancey, Venables, and Patrick (2016)**. In this case, aversive startle potentiation is used as a trait measure—i.e., tapping the extent to which individuals exhibit defensive reflex priming in the face of threat, with stimuli in the startle assessment serving as "samples" of threat encounters. As another example, ERN can also be investigated either as a state or a trait measure. For example, a state-oriented study may reveal that the ERN is larger on average when errors are punished, and a trait-oriented study may show that ERN is larger among high-anxious individuals. These state and trait effects may or may not be interrelated—that is, high-anxious participants may show either large, small, or similar enhancement of ERN for punished errors (vs. non-punished errors) relative to controls.

Proximal Versus Distal Units of Analysis

Although the columns of the RDoC matrix are referred to as units of analysis rather than levels, the sequence of columns nonetheless reflects a hierarchical ordering—particularly the first four, which entail levels of anatomic organization, that is: genes; endogenous chemicals (termed molecules); neurons, glia, and individual brain structures (collectively referred to as cells); and sets of linked brain structures (circuits). Units beyond these are less clearly hierarchical, although physiology can be seen as physically more proximal to circuits than behavior, self-reports, or paradigms, which in turn appear more proximal to physiology than to genes, molecules, or cells. Given this hierarchical aspect of units in the matrix, and RDoC's stated aim of advancing process-based understanding of linkages among biological and psychological variables as relevant to clinical problems, it seems advisable to focus (in the near term, at least) on studies that index constructs through units of analysis that are more proximal to one another, as opposed to more distal. This issue was addressed in a classic article by Cacioppo and Berntson (1992), who noted that "the mapping between elements across levels or organization becomes more complex (e.g., many-to-many) as the number of intervening levels of organization increases ... because an event at one level of organization (e.g., depressive or schizophrenic behavior) can have a multiplicity of determinants at an adjacent level of organization (e.g., cognitive), which in turn may have a multiplicity of implementations at the next level of organization (e.g., neurophysiological), and so forth." (p. 1024).

From this perspective, even the task of delineating relationships among units in close proximity to one another is likely to be challenging and time consuming—and systematic work of this type in the psychopathology area remains limited, even with respect to self-report, behavioral, and physiological measures often included together in clinical research protocols. Most typically, measures from these differing domains are utilized in separate analyses focusing on predictive relations with clinical phenotypes. Associations among measures across domains are typically not reported, or are deemphasized, because they tend to be weak and inconsistent (Lang, 1968)—a point we return to below in the section on measurement issues. Given this state of affairs, it would be worthwhile and productive to focus major effort for the time being on studies utilizing physiological, behavioral, and self-report measures of RDoC constructs (framed as states, traits, or both), and seek to examine their relations with one another as well as with clinical outcomes of interest—ideally assessed using measures of these differing types, also. Notably, the five human studies in the current issue utilized measures from these domains—which facilitated comparisons among them. The sixth study, which investigated primates, sought to relate lower-level units of the matrix—genes and cells (brain anatomy)—to a behavioral index of anxiousness in the form of self-scratching behavior. This approach is consistent with our suggested emphasis on more proximal units of analysis, given the contributory role of genes to brain morphology. Studies examining the interplay of genomic and neurochemical variables in relation to clinical problems, or interplay among cellular, circuit, and physiological units, would also meet with this suggestion.

Approaching RDoC Research from an Ontogenetic Perspective

In research directed at examining clinical symptoms or impairments in terms of process constructs from the RDoC framework, it is important to consider the progression that occurs across time from genotypic propensity to phenotypic expression (e.g., Cicchetti & Rogosh, 1996; Durbin & Hicks, 2014; Lillie, 1927; Senner, Conklin, & Piersma, 2015). For example, it is well known from work with twins that psychotic symptoms reflect the impact of genetic liability factors operating in conjunction with experiential influences, with the estimated heritability for dimensional measures of specific symptoms including hallucinations being modest to moderate (e.g., Hur, Cherny, & Sham, 2012; Zavos et al., 2014). In studying mechanisms for hallucinations, therefore, one could study (a) individuals at elevated genetic risk (i.e., with a family history of hallucinations) who have never experienced symptoms themselves, (b) at-risk (positive family history) individuals who are beginning to exhibit hallucinationlike experiences that later evolve into full symptom episodes, or (c) individuals either with or without a family history who experience prominent and recurrent hallucinatory episodes. Studies of the first type would address elements of latent liability; those of the second type, characteristics present at the time of transition from liability to symptom expression; and those of the third type, dysfunction associated with active symptom expression (pathophysiology). The role of biobehavioral processes corresponding to RDoC constructs (e.g., acute threat responding, working memory function, perceived agency) could well differ across these points in the ontogenetic sequence. Studies of all three types—taking into account normative variations in the functioning of neural systems across development (Casey, Oliveri, & Insel, 2014), and tracking environmental influences and their impact on neural functioning and behavior across time (Durbin & Hicks, 2014)—would be needed to fully elucidate mechanisms contributing to hallucinations.

As another example, **Lang et al. (2016)** present evidence for reduced physiological-defensive activation during imagery of feared situations in patients with pervasive distress pathology versus enhanced activation in patients with focal fear problems. In line with this, **Yancey, Venables, and Patrick (2016)** note that startle potentiation operated less effectively as an indicator of dispositional threat sensitivity among participants in their sample with a history of major depression (or distress pathology more broadly; see Yancey, Vaidyanathan, & Patrick, 2015), and **Weinberg et al. (2016)** report reduced versus enhanced ERN in participants exhibiting depressive symptoms compared to those exhibiting fearful vigilance in the form of pathological checking behavior. **Lang et al. (2016)** theorize that focal fear pathologies involve exaggerated reactivity of a still ostensibly normatively functioning defensive circuitry, whereas pervasive distress conditions entail dysregulation

of this circuitry (cf. Rosen & Schulkin, 1998). However, as acknowledged by these authors, the origins of defensive circuitry dysfunction in distress conditions remain unclear. Prospective-longitudinal studies of individuals at risk for conditions of this type, as described above, will be needed to determine the roles that core dispositional liabilities, adverse experiences, and interplay between the two play in the emergence of circuitry dysfunction as described in the work by Lang et al.

Related to the foregoing, it is important to consider the proximity of processes under study to behavioral outcomes of clinical interest. Two extreme, high-impact examples of this are suicide and mass murder. In cases of these types, a progression typically occurs across time from milder affective-cognitive precursors to more specific contemplation of destructive behavior to strongly motivated intent immediately preceding action. In the case of suicide, feelings of social disconnection and burden are theorized to promote passive ideation, with an active desire for death emerging if these feelings persist and worsen over time to the point of hopelessness; a third process, entailing erosion of the natural fear of dying, is posited to underlie the shift from active desire to suicidal intent and action (Van Orden et al., 2010). Because of their strong ability to predict suicide-related outcomes including documented attempts (Van Orden et al., 2010), these psychological variables are important to consider in RDoC-oriented studies. From an onto-genetic perspective, they can be viewed as proximal pathogenic processes to which variations or alterations in psychobiological-system functioning contribute. RDoC constructs of potential relevance to these suicide-promoting processes include threat reactivity and response inhibition (given well-known associations of negative affect and impulsivity with suicidal behavior; Joiner, Brown, & Wingate, 2005; see also Venables et al., 2015), along with affiliation and reward valuation/responsiveness (because of their ostensible relevance to social connectedness). Research efforts could focus on these basic psychobiological constructs (quantified in both trait and state terms; see above) as more distal contributors to distinct psychological processes that lie closer to suicidal behavior.

With these points in mind, we suggest that the RDoC framework can help to coordinate efforts among differing research groups and expedite progress by encouraging investigators to specify what stage(s) in the ontogenetic progression of a clinical phenomenon of interest (i.e., from latent liability to active expression) their work focuses on, and how the RDoC constructs they are using as explanatory vehicles can be expected to advance understanding of the phenomenon from a developmental perspective. As others have recently argued (Durbin & Hicks, 2014), the issue of ontogenetic progression is also crucial to consider in research focusing on relations between normative trait dimensions and clinical symptomatology. While clinical symptom variables may intersect with normative trait dimensions, and the two may function together as effective indicators in joint structural models (e.g., Krueger et al., 2002), clinical variables are not likely to be interchangeable with or "reducible" to everyday traits—because they will in most cases reflect, at least in part, dysregulation in the functioning of biobehavioral systems (i.e., emergent pathophysi-ologies) resulting from genotype-environment interplay across time. The point is that dimensional models of clinical problems based on normative personality models need to consider the possibility of discontinuities along the ontogenetic road from liability to expression—discontinuities that may not be clearly delineable from report-based data alone (cf. Durbin & Hicks, 2014; Vaidya-nathan, Vrieze, & Iacono, 2015).

Consensus-Based Categorical Diagnosis is Not the Only Problem

While the RDoC initiative focuses especially on limitations of the traditional categorical approach to diagnosis represented in the DSM, and calls for the development of an alternative system for classification involving dimensional conceptions of clinical problems referenced to psychobiological systems constructs, other notable reasons exist for the unsatisfactory progress to date of biologically oriented psychopathology research. We consider two of the most important of these, with an emphasis on how such problems can be addressed.

Attend to Basic Measurement Principles

The RDoC initiative has a strong assessment focus in that it encourages operationalization of matrix constructs and clinical problems using variables from multiple measurement domains (units of analysis). Given this, basic measurement principles from the psychological assessment literature are crucial to consider in RDoC-oriented research. Report-based measures, for example, show highly predictable relations with one another (e.g., scale measures of traits with scale measures of other related traits, scales measures of traits with clinician ratings of clinical problems) because—aside from shared method variance (see below)—substantial efforts are typically devoted to establishing their score stability (reliability) and psychological meaning (validity). By contrast, systematic efforts are less commonly devoted to establishing the reliability and validity of behavioral performance measures in psychopathology research, and are rarely directed at evaluating the psychometric properties of variables from the physiological domain as indicators of clinically relevant characteristics (e.g., **MacNamara & Phan, 2016**; **Yancey, Venables, & Patrick, 2016**).

As a rejoinder to this, it could be argued that behavioral and physiological measures used in studies of psychopathology are in fact routinely validated—through experimental studies that evaluate effects of condition manipulations on scores for such measures. However, studies of this type only consider within-subject manipulations as validation of a between-subjects score. The assumption that between-subjects variance in a dependent measure reflects processes in common with task manipulations that affect the measure is an example of faulty reverse-inference reasoning; as noted earlier, between-subjects variance may reflect processes separate from those associated with task manipulations. Additionally, large-N studies involving domain-representative samples are needed to generate stable estimates of reliability and validity, and collection of measures other than the one under evaluation is necessary in order to examine convergent and discriminant validity.

These points are readily illustrated with reference to dependent measures from the domain of physiology frequently used in psychopathology research. For example, amygdala reactivity to affective face stimuli (fearful faces, in particular) has been extensively examined in studies of clinical conditions including anxiety disorders, major depression and bipolar disorder, and psychopathy. Test-retest reliability for this measure has been evaluated in a handful of small-sample studies to date ($ns = 13$–27), with reported reliability estimates for fear-face reactivity in the range of .3 to .6 (Sauder, Hajcak, Angstadt, & Phan, 2013)—indicating moderate stability, but well below psychometric standards. Another approach to evaluating the reliability of measures from the physiological domain is through internal consistency analysis (e.g., examining

correspondence of scores based on differing half-sets of data across participants); at the least, reliability of this type should be reported routinely for physiological (and also task-performance) measures. If the reliability of individual response measures is found to be sub-optimal, an approach to addressing this (as illustrated by **Yancey, Venables, & Patrick, 2016**) is to aggregate differing individual indicators of a common construct into a composite-score variable.

Beyond this, it remains unclear at this time what the reliable person-variance in amygdala reactivity to fear faces reflects psychologically, because convergent and discriminant relations for this response measure have not been examined in large-*N*, multidomain/multimeasure investigations. However, the same could be said of most if not all variables from the domain of physiology—whether neuroradiological or electrophysiological. For example, as noted above, **Weinberg et al. (2016)** found that ERN response in adolescent girls was associated with both checking behavior (positively) and depressive symptoms (negatively). In a separate participant sample, this research group found that a larger ERN at age 6 prospectively predicted the emergence of anxiety disorder symptoms by age 9 (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015). Within the same sample, Kessel et al. (in press) found that, among children rated as highly irritable by their mothers at age 3, those exhibiting larger ERN at age 6 showed salient internalizing symptoms at age 9, whereas those exhibiting smaller ERN at age 6 showed prominent externalizing symptoms at age 9. Thus, variability in the ERN appears not only to relate to specific symptom types cross-sectionally, but prospectively predicts various psychopathology-related outcomes. As suggested by **Hanna and Gehring (2016)**, it is likely that the ERN is multidetermined (see also Gehring, Liu, Orr, & Carp, 2012; Moser, Moran, Schroder, Donnellan, & Yeung, 2013), and thus conceivable that differing components of variance in the ERN reflect differing psychopathology-related processes. Large-*N*, multimeasure studies examining relations of the ERN not just with differing report-based phenotypes (clinical symptom variables and affiliated traits) but with other physiological variables and task-behavioral measures will be needed to clarify this.

Work of this type is also needed to clarify reliable, clinically relevant sources of interindividual variation in other physiological measures commonly used in psychopathology research, such as startle reflex modulation (as assessed in differing task contexts), P3 brain response, resting frontal-EEG asymmetry, and baseline or stimulus-elicited autonomic activity.[3] As illustrated by long-standing practice in the psychophysiological literature, an integrative systems approach that examines brain responses in relation to activity in sensory input and somatic/visceral output systems will contribute more to understanding of the functional meaning of variables of each type than a focus on one system alone. In addition, systematic evaluation of convergent and discriminant relations among differing physiological measures will be valuable for clarifying overlap versus distinctiveness of measures of subconstructs from a particular RDoC domain, as individual difference variables. For example, measures of acute threat and potential threat reactivity may covary so highly across individuals that they can be viewed as indicators of a common dispositional construct.

In addition to reliability and convergent/discriminant validity, another psychometric concept that needs to be considered in multi-unit RDoC research is that of domain-specific (i.e., method) variance (Campbell & Fiske, 1959; Lang, 1968; Mischel, 1968): Measures of the same construct from differing assessment domains (e.g., self-report, behavior, physiology) can be expected to correlate only moderately, and measures of related constructs from differing domains are likely to correlate only modestly. For this reason, physiological measures of psychological constructs such as threat sensitivity are likely to show only weak (.1–.3) correlations with fear- or anxiety-related symptoms as assessed by clinician ratings or questionnaires. **Yancey, Venables, and Patrick (2016)** suggest an approach to addressing this issue, by aggregating indicators of a common construct from differing domains into a cross-domain composite. Advanced quantitative methods such as structural equation modeling and multidimensional item response modeling could also be used for this purpose.

Prioritize Replicability and Synergy Along with Innovation and Significance

In his commencement address to the student body of Caltech in 1974, Nobel prize-winning physicist Richard Feynman commented on practices he saw as limiting progress in the field of psychological science (Feynman, 1974). Chief among these was a tendency on the part of researchers to address topical questions in an isolated manner without concern for the replicability of reported findings: "It seems to have been the general policy . . . to not try to repeat psychological experiments, but only to change the conditions and see what happens" (p. 13). Major reasons for this according to Feynman included rewards of "temporary fame and excitement" attainable through publication of ostensibly innovative work, and the high priority placed on work of this type by funding agencies. These concerns have been echoed and amplified in recent published writings (Pashler & Wagenmakers, 2012; Simmons, Nelson, & Simonsohn, 2011).

Relevant to Feynman's points, two of the official criteria for evaluating grant applications submitted to the National Institutes of Health are "innovation" and "significance"—referring, respectively, to the application's use of "novel theoretical concepts, approaches or methodologies, instrumentation, or interventions," and the potential of the proposed work to "change the concepts, methods, technologies, treatments, services, or preventative interventions" in an important problem area. Applications perceived as lacking in these overlapping respects are unlikely to receive a priority score (and thus be rendered ineligible for funding) under current evaluation guidelines, which call for elimination of 50% of all applications from further consideration at the point of initial review. This practice of "triaging" work deemed to be lacking in innovation (i.e., novelty) and significance (i.e., topicality) is also standard practice these days at prominent mental health journals in psychology (e.g., *Clinical Psychological Science*) and psychiatry (e.g., *American Journal of Psychiatry*, *Biological Psychiatry*, *JAMA Psychiatry*). Thus, from the standpoint of Feynman's core argument, a substantial portion of the work that is assured the highest impact in terms of scholarly visibility and citations consists of one-shot studies destined to have limited "staying power."

Our view, in line with Feynman's, is that this dominant emphasis on novelty and topicality in the evaluation of grant applications for funding, and submitted manuscripts for publication, has as much to do with the limited progress of biologically oriented research on psychopathology as the field's reliance on the DSM nosological system.

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3. Variables such as startle modulation that are quantified in terms of condition differences are potentially of unique value because variance associated with a distinct process manipulation can, in principle, be isolated through subtraction. However, they pose distinct challenges, because difference scores are known to exhibit lower reliability than scores for individual conditions—particularly when scores are highly correlated across conditions, as is the case with startle.

We are hardly alone in this view. Others have commented on the adverse effects of positive publication bias in contemporary scientific work broadly (Ioannidis, 2005a), and in clinical research more specifically (Ioannidis, 2005b). Influential critiques have appeared regarding practices and findings of neuroimaging work as it is typically conducted by psychopathology researchers (Button et al., 2013; Ioannidis, 2011). Consistent with concerns raised in these critiques, and with points made in the last section above, recent large-*N* neuroimaging studies demonstrate relationships of only modest magnitude for brain activation measures with clinical phenotypes—even when operationalized dimensionally (e.g., Castellanos-Ryan et al., 2014). In parallel with this, large-scale genome-wide association studies have roundly challenged the findings of extensive small-*N* work reporting significant relationships for specific candidate genes with target clinical conditions (Psychiatric GWAS Consortium Coordinating Committee, 2009).

We propose two specific strategies for addressing the progress-limiting problems of positive publication bias and lack of systematic replication within the context of the RDoC initiative:

1. We propose that the National Institute of Mental Health implement an alternative set of review criteria for RDoC research applications,[4] entailing two changes: (1) merging of "innovation" and "significance" into a composite "innovation and significance" criterion, and (2) addition of a separate "replication and synergy" (R & S) criterion. The merging of innovation and significance would reconcile existing overlap in the wording of these criteria and establish a balance with the new R & S criterion. The R & S criterion would entail evaluation of the application's effectiveness in terms of (a) ensuring the replicability of findings from the proposed research (e.g., through use or development of reliable/criterion-validated physiological or behavioral measures; reliance on iterative, overlapping designs; use of large-*N* design with split-half cross-validation), and (b) demonstrating synergy with established (i.e., well-replicated) findings from prior work, through use of common procedures and dependent variables, and explicit description of how the proposed work both complements and extends already-existing work.

2. To encourage and facilitate coordination of research efforts (i.e., synergy) among differing investigative groups, we propose an extension of the RDoC framework, in the form of a cumulative data network system for mental health research. This network system, described in the next section below, can evolve out of, and in turn serve as a concrete point of reference for, RDoC-oriented research efforts that align with the above-mentioned R & S criterion.

RDoC–DataWeb: A Developmentally Oriented, Multidomain, Empirical-Nomological Network for RDoC-Oriented Research

A major benefit of the RDoC matrix framework is that the constructs and units of analysis it specifies provide concrete points of reference for new research, with the initiative's call for researchers to "fill in" the cells of the matrix serving as a direct impetus for

coordination of investigative efforts around these constructs and units. As such, the RDoC framework offers a much-needed organizational scheme for biologically oriented research on psychopathology, and a partial remedy for the fractionation of efforts that the longstanding "independent investigator" model and overemphasis on novelty and topicality have promulgated to date. At the same time, as highlighted in the foregoing sections of this article, there are a number of ways in which the coordinating function of the RDoC framework can be enhanced to improve the prospects for systematic advances in knowledge and progress toward an alternative, biologically informed nosology for mental disorders. Fortunately, the framers of the RDoC initiative in their wisdom have left the door open to such enhancements, by encouraging modifications to the RDoC matrix framework based on advancing knowledge and creative input from investigators in the field.

With points from the preceding sections in mind, we advance one additional proposal—namely, that the coordinating function of the RDoC framework and its prospects for advancing conceptualization and understanding of psychopathology be further enhanced by moving toward a cumulative web-formatted data network system for research focusing on RDoC constructs and multiunit assessment. We refer to this proposed system as the Research Domain Criteria DataWeb (RDoC–DataWeb). We conceive of this system as an empirical, data-based representation of a nomological network (cf. Cronbach & Meehl, 1955; see also Patrick, Venables et al., 2013) encompassing RDoC constructs and clinical outcome variables, with inclusion of a distinct ontogenetic/developmental component. Notably, the RDoC initiative already includes the foundation for a network system of this type, in its Research Domain Criteria Database (RDoCdb; http://rdocdb.nimh.nih.gov/), an online vehicle for archiving and sharing data from RDoC-funded research projects. RDoCdb is cross-referenced to two other major data repositories, the National Database for Autism Research (NDAR; https://ndar.nih.gov/index.html) and the National Database for Clinical Trials related to Mental Illness (NDCT; http://ndct.nimh.nih.gov/). A key feature of these online repositories is their use of data harmonization—a set of standard procedures for formatting data files and designating independent and dependent variables within files that allows datasets from differing studies to be effectively merged with one another. The ability to connect datasets in this manner can enhance power to test hypotheses using large combined samples and, through use of bridging variables and statistical imputation, allow for estimation of relationships between variables unique to one dataset and those unique to another (Friedman, Kern, Hampson, & Duckworth, 2014).

Our concept of an RDoC–DataWeb is compatible with the existing RDoCdb web resource, but would adapt/extend it in the following ways: (a) the RDoC–DataWeb would be organized around the five broad systems domains of the RDoC matrix (and would be extensible, as is the RDoC matrix); (b) datasets included in the RDoC–DataWeb would be harmonized around independent variables (IVs) reflecting clinical problem dimensions, and dependent variables (DVs) reflecting measures of specific RDoC process constructs from differing domains of measurement (i.e., units of analysis);[5] (c) the emerging hierarchical-dimensional model of

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4. Our proposal is for use of an alternative set of review criteria by National Institute of Mental Health for RDoC applications specifically, based on the latitude it has to modify standard agency-wide criteria of the National Institutes of Health (NIH) in evaluating applications submitted for specific funding opportunity announcements (FOAs). However, we would welcome consideration of a revision along this line to the existing NIH-wide criteria.

5. Over time, and with accumulating knowledge of the psychological meaning of nonreport measures, gained through systematic analysis of their interrelations and associations with report-based measures, it is anticipated that this data network system could move toward harmonization around latent-variable approximations to constructs, rather than specific manifest measures.

general psychopathology (Kotov, 2016; Kotov et al., 2015; Wright & Simms, 2015) would serve as a provisional organizing scheme for clinical problem IVs; (d) construct-measure DVs would be classified as either established or provisional, depending upon the state of evidence for their reliability and construct validity; (e) a subset of RDoC process constructs would be represented also as traits in the DataWeb system (e.g., threat sensitivity, reward sensitivity, inhibitory control, affiliativeness), to serve as interfaces between RDoC systems domains and clinical problem dimensions; and (f) archived datasets would be coded not only for chronological age of participants, but for ontogenetic focus (e.g., on liability, incipient symptomatology, or active psychopathology), with a distinct code applied to longitudinal-developmental studies examining the progression from liability to active psychopathology.

These features of the proposed DataWeb system dovetail with suggestions advanced in preceding sections for enhancing progress based on RDoC research efforts. As such, the system provides a concrete platform for implementing these suggestions. Additionally, a DataWeb system with these features can serve as a useful adjunct to the traditional independent-investigator model, and an evolving point of reference for evaluating the potential that new proposed lines of research hold for systematically advancing knowledge about psychopathology.

Concluding Comment

To summarize major points made in this article, our specific proposals for enhancing progress based on RDoC research efforts include (a) a near-term shift in RDoC's definition of clinical problems to be studied, going beyond permitting to actively encouraging use of symptom dimensions specified by newer hierarchical systems for psychopathology, but with reliance on multiunit assessment to fulfill the aim of incorporating biological findings/measures into problem classification; (b) a near-term focus on the study of a distinct set of trait-dispositional counterparts to RDoC matrix constructs (trait constructs represented across the animal behavior, child temperament, and adult personality literatures), which can serve as interfaces between RDoC process constructs and clinical-problem dimensions; (c) an emphasis for the present time on proximal units of analysis in RDoC studies—in particular, combined use of physiological, behavioral, and self-report meas-

ures of matrix constructs (framed as process-related states, process-related traits, or both) directed at clarifying their functional relations with one another and with clinical problems; (d) a clear ontogenetic component in RDoC investigative efforts (e.g., explicit consideration of liability versus expression, and developmental issues more broadly, in research design and interpretation of findings); (e) adherence to core measurement principles in RDoC research, including evaluation/optimization of reliability of nonreport- as well as report-based measures, and delineation of validity through examination of convergent and discriminant relations with other measures in a multivariate assessment context; (f) modification of existing grant review criteria to prioritize replication and synergy alongside innovation and significance; and (g) development of a cumulative web-based system for archiving and interfacing datasets from RDoC-funded projects, to serve as a resource for addressing novel research questions and an evolving point of reference for evaluating the scholarly potential of new proposed work—in terms of replication and synergy as well as innovative and significance.

The RDoC initiative has gained impressive momentum in the short time since its inception, making this an exciting time for biologically oriented researchers with interests in psychopathology. The major aim of the initiative—to reframe conceptions of clinical problems around psychobiological dimensions through investigation of process constructs operationalized across multiple domains—has a strong assessment focus, which creates opportunities for experts in psychological measurement and quantitative analysis to contribute in essential ways. And RDoC's emphasis on the systematic mapping of relations between psychological and physiological aspects of behavior places the initiative squarely in the purview of psychophysiologists (see https://www.sprweb.org/). In the context of its substantive goals, the RDoC matrix framework also has the potential to serve a crucial coordinating function for clinical research efforts—harnessing investigative efforts around a finite set of core constructs, with openness to revision based on accumulating knowledge and developing theory. Our hope is that the proposals we have advanced in this article will prove useful in moving the promising idea of the RDoC initiative more swiftly and effectively toward the reality of progress in understanding and ameliorating pressing mental health problems.

References

Allport, G. (1937). *Personality: A psychological interpretation.* New York, NY: Holt, Rinehart, & Winston.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Button, K. S., Ioannidis, J. P. A, Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14*, 365–376. doi: 10.1038/nrn3475

Cacioppo, J. T., & Berntson, G. G. (1992). Social psychological contributions to decade of the brain: Doctrine of multi-level analysis. *American Psychologist, 47*, 1019–1028. doi: 10.1037/0003-066X.47.8.1019

Campbell, D. T., Fiske D. W. (1959). Convergent and discriminant validation by the multitrait-multimethod matrix. *Psycholological Bulletin, 56*, 81–105. doi: 10.1037/h0046016

Casey, B. J., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the Research Domain Criteria (RDoC) framework. *Biological Psychiatry, 76*, 350–353. doi: 10.1016/j.biopsych.2014.01.006

Castellanos-Ryan, N., Struve, M., Whelan, R., Banaschewski, T., Barker, G.J., Bokde, A. L. W., . . . The IMAGEN Consortium. (2014). Neural and cognitive correlates of the common and specific variance across externalizing problems in young adolescence. *American Journal of Psychiatry, 171*, 1310–1319. doi: 10.1176/appi.ajp.2014.13111499

Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology, 8*, 597–600. doi: 10.1017/S0954579400007318

Clark, L. A. (2009). *Schedule for Nonadaptive and Adaptive Personality–2nd edition (SNAP-2).* Minneapolis, MN: University of Minnesota.

Cronbach, L. J. & Meehl, P. E. (1955). Construct validity in psychological tests. *Psychological Bulletin, 52*, 281–302. doi: 10.1037/h0040957

Durbin, C. E., & Hicks, B. M. (2014). Personality and psychopathology: A stagnant field in need of development. *European Journal of Personality, 28*, 362–386. doi: 10.1002/per.1962

Eliot, T. S. (1925). The hollow men. In *Poems: 1909–1925.* London, England: Faber & Gwyer.

Eysenck, H. J. (1947). *Dimensions of personality.* London, England: Routledge & Kegan-Paul.

Feynman, R. (1974). Cargo cult science. *Engineering and Science, 37*, 10–13.

Ford, J. M. (2016). Studying auditory verbal hallucinations using the RDoC framework. *Psychophysiology, 53*, 298–304.

Friedman, H. S., Kern, M. L., Hampson, S. E., & Duckworth, A. L. (2014). A new life-span approach to conscientiousness and health: Combining the pieces of the causal puzzle. *Developmental Psychology, 50*, 1377–1389. doi: 10.1037/a0030373

Gehring W. J., Liu Y., Orr J. M., & Carp J. (2012). The error-related negativity (ERN/Ne). In S. J. Luck, & E. Kappenman (Eds.), *Oxford handbook of event-related potential components* (pp. 231–291). New York, NY: Oxford University Press.

Hamm, A. O., Richter, J., Pane-Farre, C., Westphal, D., Wittchen, H., Vossbeck-Elsebusch, A. N., . . . Deckert, J. (2016). Panic disorder with agoraphobia from a behavioral neuroscience perspective: Applying the research principles formulated by the Research Domain Criteria (RDoC) initiative. *Psychophysiology*, *53*, 312–322.

Hanna, G. L., & Gehring, W. J. (2016). The NIMH Research Domain Criteria initiative and error-related brain activity. *Psychophysiology*, *53*, 386–388.

Hur, Y-M., Cherny, S. S., & Sham, P. C. (2012). Heritability of hallucinations in adolescent twins. *Psychiatry Research*, *199*, 98–101. doi: 10.1016/j.psychres.2012.04.024

Ioannidis, J. P. A. (2005a). Contradicted and initially stronger effects in highly cited clinical research. *Journal of the American Medical Association*, *294*, 218–228. doi: 10.1001/jama.294.2.218

Ioannidis, J. P. A. (2005b). Why most published research findings are false. *PLoS Medicine 2*, 8, e124. doi: 10.1371/journal.pmed.0020124

Ioannidis, J. P. A. (2011). Excess significance bias in the literature on brain volume abnormalities. *Archives of General Psychiatry*, *68*, 773–780. doi: 10.1001/archgenpsychiatry.2011.28

Joiner, T. E., Brown, J. S., & Wingate, L. R. (2005). The psychology and neurobiology of suicidal behavior. *Annual Review of Psychology*, *56*, 287–314. doi: 10.1146/annurev.psych.56.091103.070320

Kessel, E. M., Meyer, A., Hajcak, G., Dougherty, L. R., Torpey-Newman, D. C., Carlson, G. A., & Klein, D. N. (in press). Transdiagnostic factors and pathways to multifinality: The error-related negativity distinguishes developmental trajectories from preschool irritability to internalizing and externalizing symptoms at age 9. *Development and Psychopathology*.

Kotov, R. (2016). The quantitative classification of mental illness: Emerging solution to boundary problems. In E. Bromet (Ed.), *Long-term outcomes in psychopathology research: Rethinking the scientific agenda* (pp. 140–157). New York, NY: Oxford University Press.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, M., . . . Zimmerman, M. (2015). *The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies*. Manuscript submitted for publication.

Kozak, M. J., & Cuthbert, B. N. (2016). The NIMH Research Domain Criteria Initiative: Background, issues, and pragmatics. *Psychophysiology*, *53*, 286–297.

Kraemer, H. C. (2015). Research Domain Criteria (RDoC) and the DSM—Two methodological approaches to mental health diagnosis. *JAMA Psychiatry*, *72*, 1163–1164. doi: 10.1001/jamapsychiatry.2015.2134

Krueger, R. F., Derringer, J., Markon, K. E., Watson, D., & Skodol, A. E. (2012). Initial construction of a maladptive personality trait model and inventory for DSM-5. *Psychological Medicine*, *42*, 1879–1890. doi: 10.1017/S0033291711002674

Krueger, R. F., & DeYoung, C. G. (2016). The RDoC initiative and the structure of psychopathology. *Psychophysiology*, *53*, 351–354.

Krueger, R. F., Hicks, B., Patrick, C. J., Carlson, S., Iacono, W. G., & McGue, M. (2002). Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology*, *111*, 411–424. doi: 10.1037/0021-843X.111.3.411

Krueger, R. F., Markon, K. E., Patrick, C. J., Benning, S. D., & Kramer, M. D. (2007). Linking antisocial behavior, substance use, and personality: An integrative quantitative model of the adult externalizing spectrum. *Journal of Abnormal Psychology*, *116*, 645–666. doi: 10.1037/0021-843X.116.4.645

Lang, P. J. (1968). Fear reduction and fear behavior: Problems in treating a construct. In J. M. Shlien (Ed.), *Research in psychotherapy* (Vol. *3*, pp. 90–102). Washington, DC: American Psychological Association. doi: 10.1037/10546-004

Lang, P. J., McTeague, L. M., & Bradley, M. M. (2016). RDoC, DSM, and the reflex physiology of fear: A biodimensional analysis of the anxiety disorders spectrum. *Psychophysiology*, *53*, 336–347.

Larsen, R. J., & Ketelaar, T. (1991). Personality and susceptibility to positive and negative emotional states. *Journal of Personality and Social Psychology*, *61*, 132–140. doi: 10.1037/0022-3514.61.1.132

Latzman, R. D., Young, L. J., & Hopkins, W. D. (2016). Displacement behaviors in chimpanzees (*Pan troglodytes*): A neurogenomics investi-gation of the RDoC Negative Valence Systems domain. *Psychophysiology*, *53*, 355–363.

Lilienfeld, S. O. (2014). The Research Domain Criteria (RDoC): An analysis of methodological and conceptual challenges. *Behaviour Research and Therapy*, *62*, 129–139. doi: 10.1016/j.brat.2014.07.019

Lillie, F. R. (1927). The gene and the ontogenetic process. *Science*, *66*, 361–368. doi: 10.1126/science.66.1712.361

Livesley, W. J., & Jackson, D. N. (2009). *Manual for the dimensional assessment of personality pathology*. Port Huron, MI: Sigma Press.

Loevinger, J. (1957). Objective tests as instruments in psychological theory. *Psychological Reports*, *3*, 635–694. doi: 10.2466/pr0.1957.3.3.635

MacNamara, A. M., & Phan, K. L. (2016). Psychobiological operationalization of RDoC constructs: Methodological and conceptual opportunities and challenges. *Psychophysiology*, *53*, 406–409.

Meehl, P. E. (1977). Specific etiology and other forms of strong influence: Some quantitative meanings. *Journal of Medicine and Philosophy*, *2*, 33–53. doi: 10.1093/jmp/2.1.33

Meyer, A., Hajcak, G., Torpey-Newman, D. C., Kujawa, A., & Klein, D. N. (2015). Enhanced error-related brain activity in children predicts the onset of anxiety disorders between the ages of 6 and 9. *Journal of Abnormal Psychology*, *124*, 266–274. doi: 10.1037/abn0000044

Mischel, W. (1968). *Personality and assessment*. New York, NY: Wiley.

Moser, J. S., Moran, T. P., Schroder, H. S., Donnellan, M. B., & Yeung, N. (2013). On the relationship between anxiety and error monitoring: A meta-analysis and conceptual framework. *Frontiers in Human Neuroscience*, *7*, 40–58. doi: 10.3389/fnhum.2013.00466

Pashler, H., & Wagenmakers, E. J. (2012). Editors' introduction to the special section on replicability in psychological science: A crisis of confidence? *Perspectives on Psychological Science*, *7*, 528–530. doi: 10.1177/1745691612465253

Patrick, C. J., Kramer, M. D., Krueger, R. F., & Markon, K. E. (2013). Optimizing efficiency of psychopathology assessment through quantitative modeling: Development of a brief form of the externalizing spectrum inventory. *Psychological Assessment*, *25*, 1332–1348. doi: 10.1037/a0034864

Patrick, C. J., Venables, N. C., Yancey, J. R., Hicks, B. M., Nelson, L. D., & Kramer, M. D. (2013). A construct-network approach to bridging diagnostic and physiological domains: Application to assessment of externalizing psychopathology. *Journal of Abnormal Psychology*, *122*, 902–916. doi: 10.1037/a0032807

Psychiatric GWAS Consortium Coordinating Committee (2009). Genomewide association studies: History, rationale, and prospects for psychiatric disorders. *American Journal of Psychiatry*, *166*, 540–556. doi: 10.1176/appi.ajp.2008.08091354

Rosen, J. B., & Schulkin, J. (1998). From normal fear to pathological anxiety. *Psychological Review*, *105*, 325–350. doi: 10.1037/0033-295X.105.2.325

Sauder, C. L., Hajcak, G., Angstadt, M., & Phan, K. L. (2013). Test-retest reliability of amygdala response to emotional faces. *Psychophysiology*, *50*, 1147–1156. doi: 10.1111/psyp.12129

Senner, N. R., Conklin, J. R., & Piersma, T. (2015). An ontogenetic perspective on individual differences. *Proceedings of the Royal Society B: Biological Sciences*, *282*, 20151050. doi: 10.1098/rspb.2015.1050

Simmons, J. P., Nelson, L. D., & Simonsohn, U. (2011). False-positive psychology: Undisclosed flexibility in data collection and analysis allows presenting anything as significant. *Psychological Science*, *22*, 1359–1366. doi: 10.1177/0956797611417632

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Vaidyanathan, U., Patrick, C. J., & Iacono, W. G. (2011). Patterns of comorbidity among common mental disorders: A person-centered approach. *Comprehensive Psychiatry*, *52*, 527–535.

Vaidyanathan, U., Vrieze, S. I., & Iacono, W. G. (2015). The power of theory, research design, and transdisciplinary integration in moving psychopathology forward. *Psychological Inquiry*, *26*, 209–230. doi: 10.1080/1047840X.2015.1015367

Van Orden, K. A., Witte, T. K., Cukrowicz, K. C., Braithwaite, S., Selby, E. A., & Joiner, T. E. (2010). The interpersonal theory of suicide. *Psychological Review*, *117*, 575–600. doi: 10.1037/a0018697

Venables, N. C., Sellbom, M., Sourander, A., Kendler, K. S., Joiner, T. E., Drislane, L. E., . . . Patrick, C. J. (2015). Separate and interactive contributions of weak inhibitory control and threat sensitivity to prediction of

suicide risk. *Psychiatry Research*, *226*, 461–466. doi: 10.1016/j.psychres.2015.01.018

Watson, D. (2005). Rethinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. *Journal of Abnormal Psychology*, *114*, 522–536. doi: 10.1037/0021-843X.114.4.522

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality & Social Psychology*, *54*, 1063–1070. doi: 10.1037/0022-3514.54.6.1063

Watson, D., O'Hara, M. W., Naragon-Gainey, K., Koffel, E., Chmielewski, M., Kotov, R., . . . Ruggero, C. (2012). Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment*, *19*, 399–420. doi: 10.1177/1073191112449857

Watson, D., O'Hara, M. W., Simms, L. J., Kotov, R., Chmielewski, M., McDade-Montez, E. A., . . . Stuart, S. (2007). Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). *Psychological Assessment*, *19*, 253–268. doi: 10.1037/1040-3590.19.3.253

Weinberg, A., Meyer, A., Hale-Rude, E., Perlman, G., Kotov, R., Klein, D. N., & Hajcak, G. (2016). Error-related negativity (ERN) and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology*, *53*, 372–385.

Weinberger, D. R., Glick, I. D., & Klein, D. F. (2015). Whither RDoC: The good, the bad, and the ugly. *JAMA Psychiatry*, *72*, 1161–1162. doi: 10.1001/jamapsychiatry.2015.1743

Wright, A. G. C., & Simms, L. J. (2015). A metastructural model of mental disorders and pathological personality traits. *Psychological Medicine*, *45*, 2309–2319. doi: 10.1017/S0033291715000252

Yancey, J. R., Vaidyanathan, U., & Patrick, C. J. (2015). Aversive startle potentiation and fear pathology: Mediating role of threat sensitivity and moderating impact of depression. *International Journal of Psychophysiology*, *98*, 262–269. doi: 10.1016/j.ijpsycho.2014.10.014

Yancey, J. R., Venables, N. C., & Patrick, C. (2016). Psychoneurometric operationalization of threat sensitivity: Relations with clinical symptom and physiological response criteria. *Psychophysiology*, *53*, 393–405.

Zavos, H. M. S., Freeman, D., Haworth, C. M. A., McGuire, P., Plomin, R., Cardno, A. G., & Ronald, A. (2014). Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: A twin study of specific psychotic experiences in adolescence. *JAMA Psychiatry*, *71*, 1049–1057. doi: 10.1001/jamapsychiatry.2014.994