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COMMENTARY

Connecting Psychopathology Meta-Structure and Mechanisms

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A persistent challenge for the field of psychopathology has been how to best explain mental disorders and organize clinical symptoms into diagnoses. Meta-structural approaches have clarified fundamental problems and made substantial gains by using covariance structures to organize the nature of clinical symptom patterns. A remaining task is how to specify the connections between these patterns across behavioral, cognitive, and neural mechanisms. Together, meta-structural approaches and the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) offer a means to parse out these connections. I comment on the included articles in this special section on psychopathology meta-structure and argue that core dimensions of psychopathology identified with meta-structural approaches can advance the RDoC initiative and that the RDoC framework, in turn, can strengthen structural approaches by providing an organizational scaffold to elucidate the relations of behavioral, cognitive, and neural mechanisms and to relate them to dimensions of human suffering and dysfunction.

General Scientific Summary
The Research Domain Criteria (RDoC) project was initiated by the National Institute of Mental Health to facilitate research on mental disorders by providing a new ways to understand connections of problems in the brain and body with clinical symptoms and distress. The aim is to improve the diagnosis of mental disorders, and facilitate the development of better treatments. In this commentary, ways that RDoC and statistical approaches to complement each other to better understand mental disorders complement are described.

Keywords: RDoC, diagnosis, mechanisms, meta-structure, NIMH

It is a pleasure to have the opportunity to comment on the articles included in this special section in *Abnormal Psychology* on the meta-structure of psychopathology. This is an important and timely topic. Structural approaches to psychopathology have been pivotal for moving clinical research forward, for helping to address the pervasive problem of comorbidity, and for moving the field toward dimensional conceptualizations of psychopathology. RDoC is of particular significance to this special section because findings from meta-structure studies of psychopathology were a cornerstone rationale for its development. In what follows, the theoretical perspective of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) is offered in the context of commentary on the special section articles.

Both RDoC and structural approaches are motivated by problems with descriptively derived diagnoses (e.g., diagnostic overlap, comorbidity, narrow constraints, arbitrary cut points, heterogeneity), but RDoC expressly grapples with the problem that mechanisms from integrative neuroscience (e.g., cognitive control, emotion regulation, reward processing) did not map neatly onto clinical syndromes. Meta-structural research has clarified broad (e.g., internalizing) and specific (e.g., fear) dimensions of psychological and behavioral problems useful to advance RDoC-framed research. If specific dimensions were

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The development and framework of RDoC has been described in other articles and in presentations at professional conferences, workshops, and various meetings; however, this article is an original piece of work that uniquely examines the relation of RDoC and meta-structure and has not been presented elsewhere.

Current members of the NIMH RDoC Internal Working Group are Bruce Cuthbert (Chair), Sarah Morris (acting Chair), William Carpenter, Mindy Chai, Rebecca Garcia, Marjorie Garvey, Dede Greenstein, Arina Kadam, Kristina McLinden, Jennifer Pacheco, Daniel Pine, Syed Rizvi, Matthew Rudorfer, Charles Sanislow, Gretchen Navidi, Janine Simmons, Uma Vaidyanathan, and Carlos Zarate. Deanna Barch and Michael First serve as external consultants to the working group.

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located in the RDoC matrix, connections to internal mechanisms could be clarified and used for convergent validation (e.g., mapping fear onto circuits for acute threat). Broader structural dimensions also provide a means to frame a sample of research participants who are likely to share some degree of a dysfunctional mechanism to be studied in RDoC based research.

To my knowledge, none of the contributors to this special section were aware in advance that there would be an RDoC-themed commentary, yet four of the nine articles in this special section on the meta-structure of psychopathology considered RDoC in relation to their work. Castellanos-Ryan et al. (2016) note that treatment targets that lead to effective change overlap with RDoC constructs. Conway, Starr, Espejo, Brennan, and Hammen (2016) point out that structural dimensions are useful for the sampling frame in RDoC based research. Kotov et al. (2016) note the potential fruitfulness of using a hierarchical dimensional taxonomy to identify phenotypes for RDoC research. Roche, Jacoboson, and Pincus (2016) note the relation of RDoC constructs with internalizing and externalizing dimensions. These authors demonstrate the impact of the RDoC framework on the field and illustrate the natural ways that structural approaches to psychopathology can leverage progress with RDoC.

In this commentary, first a brief description of RDoC is provided, including the background and rationale, structure, and principles. (For more detailed descriptions of the NIMH RDoC, see Cuthbert & Insel, 2013; Insel et al., 2010; Kozak & Cuthbert, 2016; Sanislow et al., 2010.) Then, practical matters for implementation, including how RDoC facilitates translational research, are addressed. Next, the articles in this special section are examined, and strengths and limits of the meta-structure of psychopathology approach are considered. It is argued that core dimensions of psychopathology identified with structural approaches can play a dynamic role in advancing RDoC based research and that RDoC, in turn, can strengthen structural approaches by providing a framework to connect latent dimensions to behavioral, physiological, cognitive, and neural mechanisms.

RDoC Primer

Background and Rationale

The NIMH included in the 2008 Strategic Plan the basis for RDoC. Strategic Objective 1.4 stated the following: "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (National Institute of Mental Health (NIMH) Strategic Plan, 2008). Incorporated in this objective was the need to ". . . to define, measure, and link basic biological and behavioral components of normal and abnormal functioning." Many factors motivated these goals.

One motivation was to fill the gap in research connecting biological mechanisms to clinical disorders (Insel et al., 2010). Advances in integrative neuroscience were not being translated to clinical care. Psychotropic drug development had slowed, with diminished interest in developing new therapeutic agents (Pankevich, Altevogt, Dunlop, Gage, & Hyman, 2014). An often cited problem was that phenotypes based on the *Diagnostic and Statistical Manual of Mental Disorders* (i.e., *DSM*; American Psychiatric Association [APA], 1980, 1987, 1994, 2000) did not map well on to the target mechanisms for drug development. There was a growing recognition that the distance from phenotypes based on clinical syndromes to neural circuits was too great to make one-to-one connections between disorders and mechanisms, and it was argued that a focus on intermediate phenotypes would be more productive (e.g., Meyer-Lindenberg & Weinberger, 2006; see also LaPorte, Ren-Patterson, Murphy, & Kalueff, 2008).

Another problem with using the *DSM* to define study groups was comorbidity, a complication noted in eight of the nine articles in the special section (e.g., Conway et al., 2016; Kotov et al., 2016; Roche et al., 2016; Sellbom, 2016; Slobodskaya, 2016; Waldman, Poore, van Julle, Rathouz, & Lahey, 2016; Wright, Hopwood, Skodol, & Morey, 2016). From a practical standpoint, there was a lack of consensus in peer review for scientific merit for federal funding for how to control for comorbid conditions that were a consequence of research based on *DSM* clinical syndromes. When NIMH encouraged alternative research strategies (e.g., intermediate phenotypes) with "requests for applications" or "program announcements," the response of submitted applications was less than anticipated. Investigators expressed that one reason they were reluctant to develop such proposals was concern that applications for funding not based on *DSM* disorders would not pass muster in peer review.

A second motivation came directly from studies that modeled the structure of psychopathology symptoms and disorders. Before RDoC, this line of work detailed problems with clinical syndrome diagnoses and suggested alternate approaches. Following Achenbach's (1966) seminal work in child psychology, Krueger (1999) broke the mold of *DSM* categories by identifying the latent dimensions of externalizing and internalizing (with fear and anxious misery within the internalizing dimension) in adult mental disorders. Subsequent research has provided a wealth of empirical evidence supporting this approach for parsing adult psychopathology (e.g., Carragher, Krueger, Eaton, & Slade, 2015; Caspi et al., 2014; Krueger & Eaton, 2015; Krueger & Markon, 2006; Watson, 2005; see also Stony Brook School of Medicine, 2016).

Meta-structural research has also shed light on specific *DSM*-based disorders. For posttraumatic stress disorder (PTSD), some posited that it was a disorder of fear circuitry (e.g., Friedman & Karam, 2009), whereas others held that it was more "complex" (e.g., Roth, Newman, Pelcovitz, van der Kolk, & Mandel, 1997). Several studies examined the structural relations of PTSD, fear, and distress disorders and found that although PTSD loaded with anxiety (fear) disorders, it also (in a modest but often replicated finding) loaded with depressive (distress) disorders (e.g., Simms, Watson, & Doebbeling, 2002; see Watson, 2005). Among articles in this special section, results from Conway and colleagues (2016) show PTSD loading more strongly with distress (major depressive disorder) than fear (generalized anxiety disorder or panic) disorders, demonstrating the *DSM*-PTSD phenotype cannot be reduced to a fear disorder.

Other problems with *DSM* syndromes had become well recognized. Core features that varied within disorders also cut across diagnostic boundaries (see Nolen-Hoeksema & Watkins, 2011). Heterogeneity within clinical *DSM* syndromes was also problematic. For borderline personality disorder, there were 256 different combinations of criteria to qualify for the diagnosis, and factor studies pointed to the utility of intermediate components (Sanislow, Grilo, & McGlashan, 2000; Sanislow et al., 2002). For *DSM–5* major depressive disorder (if weight-loss and weight gain were considered separate symptoms), two people could meet criteria and not share a single symptom in common. To account for the relation of depressive and anxiety disorders, Clark and Watson

(1991) proposed the tripartite model to dimensionally parse features disorder features (see also Watson, 2005). These and other studies that empirically tested the organization and structure of mental disorder symptoms raised questions about where the categorical joints of disorders had been carved. In sum, it was in this context that RDoC was developed. RDoC was envisaged as a framework to organize findings and to guide translational research.

Structure of RDoC

RDoC is organized in the form of a matrix, with domains and constructs in the rows, and units of analysis in the columns.[1] Presently, there are five domains: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Social Processes, Arousal and Regulatory Systems.[2] Across the units of analysis, there are Genes, Molecules, Cells, Circuits, Physiology, Behavior, and Self-Reports. A separate column, labeled *Paradigms* is distinct from the other units of analyses. Paradigms may more aptly be considered "tasks" in that the elements in this column are comprised of behaviorally based assessments that are designed to provide a valid link to a specific system/mechanism (or circuit) and reliably assess, on the basis of task performance, how well each respective mechanism is functioning in an individual (or group of individuals). In the cells of the matrix are the elements that correspond to the respective construct (or subconstruct) and unit of analysis.

The RDoC matrix was constructed by the NIMH RDoC Internal Working Group in consultation with the field. The working group drafted a beta version of the matrix with consultation from external consultants and then with input from the scientific community more broadly.[3,4] Surveys were e-mailed to NIMH applicants and investigators, and the NIMH posted online requests for information. Workshops were convened for each domain, where experts in basic, translational, and clinical research were brought together to review evidence and define each construct. Detailed proceedings for each of the workshops are available online.[5] A conservative approach was adopted to include a construct, where each had to fulfill three requirements: (a) evidence for the validity of the construct as a functional unit of behavior, (b) a connection to clinical symptoms, and (c) evidence for a neural circuit or system associated with the construct. The rationale for the focus on neural circuits in RDoC was driven by the gap between neuroscience and clinical diagnosis and not meant as imposing a reductionist philosophy (see Cuthbert & Kozak, 2013; Kozak & Cuthbert, 2016; Sanislow et al., 2010).

The process of determining the threshold to include a construct illustrates the problem of targeting the ideal "grain size," an issue that may also be framed in terms of parsimony. Given that an explicit goal driving the development of RDoC was to connect biological mechanisms and behavior, the connection of a construct to a neural circuit was fundamental to the initial development of RDoC (see Cuthbert & Insel, 2013). Higher order constructs not included in the matrix might be operationalized within a nomological net built from those that are included. There are numerous examples. Emotion dysregulation would involve constructs of negative (or positive) valence, operating in concert with constructs from cognitive control. Emotion dysregulation might be disrupted by any number of the processes involved in the generation of emotional states (negative or positive) and the cognitive processes that interact with those states (reactivation, shifts in attention, response selection, interference). Determining among which of these component processes a disruption occurred would provide finer grained specificity to understanding the manifest symptom expression and thus point to a marker for diagnosis and a potential treatment target.

Psychopathology Meta-Structure and RDoC

So where do the latent variables derived from the meta-structure of psychopathology fit with RDoC? When derived from *DSM*-based symptom or diagnostic data, higher order meta-symptom dimensions are similarly likely to be distal from internal mechanisms. Unlike *DSM* diagnoses, however, meta-symptom dimensions constructs are optimized by their covariance structure and are thus not beholden to the conceptual structure for the clinical syndromes on which *DSM* diagnoses were originally based. Thus, they offer an empirical advantage over categories originally derived from consensus based on clinical description. One focal point in the RDoC matrix for connecting elements of psychopathology meta-structure based on clinical symptoms is the Self-Report column in the units of analysis. As described on the NIMH RDoC website, the Self-Report unit of analysis refers to "interview-based scales, self-report questionnaires, or other instruments that may encompass normal-range and/or abnormal aspects of the dimension of interest". Just as the gap between clinical symptoms and neural circuits is wide, attempts to unite meta-structures (dimensions or component constructs) in a one-to-one fashion to RDoC constructs may be problematic because such an approach skips across intermediary processes that need to be explicated for a full understanding of how a mechanism manifests as a clinical symptom dimension.

Thus, psychopathology meta-structures derived from diagnostic, symptom, or self-report data may be usefully conceptualized in the RDoC Self-Report unit of analysis. Conceptually, they align with other measures designed to assess traits or disorders because they have been derived from self-report measures, or from clinical observations of symptomatic behavior. Here again, an issue to contend with is how best to determine optimal grain size. For this, the concepts *hypothetical construct* and *intervening variable* are useful. Simply put, a hypothetical construct can be distinguished from an intervening variable in that the former may be viewed as being tied to an "entity, process, or event," which herein I argue correspond to an internal mechanism (MacCorquodale & Meehl, 1948, p. 96). In this view, RDoC constructs are hypothetical constructs by definition, as are certain lower order facets with empirical evidence connecting them to an internal mechanism. In contrast, an intervening variable can be viewed as a link between

[1] See http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml for the complete matrix.

[2] Illustrating that RDoC is continually evolving, a sixth domain, Motor Systems, is presently under consideration.

[3] The initial RDoC internal working group members were Bruce Cuthbert (Chair), Marlene Guzman, Robert Heinssen, Michael Kozak, Daniel Pine, Kevin Quinn, Charles Sanislow, Jane Steinberg, and Philip Wang.

[4] External consultants for the RDoC internal working group were Deanna Barch, William Carpenter, and Michael First.

[5] http://www.nimh.nih.gov/research-priorities/rdoc/development-of-the-rdoc-framework.shtml

other variables. Higher order latent variables of psychopathology meta-structure do just that, by providing a link between broad clinical symptom dimensions and lower order constructs.

Several studies in the special section captured a higher-order dimension or "general" factor of psychopathology (e.g., Waldman et al., 2016; Wright et al., 2016). The idea of a general factor, labeled *p* (for psychopathology), has been identified by a number of investigators. Caspi and colleagues (2014) found that a single, general dimension better explained psychopathology variance in the Dunedin sample than did the separate hypothesized dimensions of internalizing, externalizing, and thought disorder. Wright and colleagues (2016) studied personality disorder structure and parsed both general and specific factors. Their findings show that both general and specific factors have predictive validity, and they conclude that there is value in capturing features that overlap so that they can be further studied. Their work suggests that comorbidity may reflect phenomenology and that factors where there is overlap offer possibilities for defining study groups for research using the RDoC framework to disentangle overlapping mechanisms.

As a tool, a meta-approach can simplify a complex reality by distilling a vast array of symptoms to a hierarchical structure with research and clinical utility. Different levels of model hierarchy may serve different purposes, from providing a broad sampling frame for a higher order structure to a very narrow and specific lower order structure that might directly link to a neural circuit. A fertile connection of meta-structures of psychopathology with RDoC is that higher order dimensions can be used to select research participants or define what has been termed the *sampling frame* (see Sanislow et al., 2010). Conway et al. (2016) argued that sampling based on transdiagnostic phenotypes ". . . paralleling RDoC-informed recruitment strategies" could be more effective than making comparisons across syndrome-based disorder categories (Conway et al., 2016, p. 30). At the same time, lower order latent dimensions may be more proximal to an RDoC construct and possibly link to a specific internal mechanism. Such a latent variable would need to meet the three basic requirements for an RDoC construct to be defined as such.

One premise shared among much of the work in this special section is that the structure of psychopathology or personality is optimally determined by using latent variable modeling. Roche et al. (2016) and Grazioplene, Chavez, Rustichini, and DeYoung (2016) went farther by integrating mechanistic features to clarify psychopathology. The study by Grazioplene and colleagues illustrates the challenge of connecting higher order latent variables to neural mechanisms presumed to be associated with the structures that they identified with neuroimaging. Noting that the Big Five trait of Openness/Intellect (O/I) consists of two distinct facets, Openness to Experience (O) and Intellect (I), which relate differentially to positive schizotypy, they reported that previous studies have yielded mixed findings with fractional anisotropy (FA) measures of white matter and its relation to O/I. By parsing out the variance uniquely associated with Openness and positive schizotypy versus Intellect, they demonstrated an inverse relationship between FA in frontal lobe white matter and Openness and the opposite for IQ and FA. Their findings provided evidence that a different methodology, diffusion tensor imaging (DTI), combined with self-report, helps to delineate the constructs of Openness, Intellect, and positive schizotypy better than relying on the structure of self-report data alone.

In future work, the RDoC matrix could be used to extend the Grazioplene et al. (2016) line of research. Aberrations in anatomical brain structures have implications for brain function, but there are presumably intermediary influences between gross structural abnormalities and psychopathology facets. The RDoC matrix could be used as a framework to organize under what conditions circuits, physiology, or behavior relate to each other in order to elaborate connections among them. This could help clarify under what conditions certain disruptions might relate to clinical problems, how disruptions might vary, or uncover compensatory mechanisms that would explain individual differences for those sharing similar structural deficits. To clarify the intermediary processes between psychopathology symptoms and psychopathology mechanisms, RDoC based research aims to delineate connections across two or more RDoC units of analysis.

Kotov and colleagues (2016) worked to connect mechanism to meta-structure by using two well-characterized event-related potential waveforms, error-related negativity (ERN) and error positivity, to parse meta-structure dimensions. Because the reliable elicitation of variations in these waveforms systematically relates to behavioral performance, there is the potential for a strong connection between these well-studied proximal events, rather than by reaching across a wider gap of RDoC units of analysis. In their approach, they wrestled with the problem of choosing the proper "grain size," noting that "[t]here is not necessarily a single 'right' level in this structure, rather the choice may depend on the question" (Kotov and colleagues 2016, p. 7). For example, their two-factor model may be particularly informative for identifying abnormal neurophysiology more broadly, whereas treatment decisions may require the specificity of a lower order five-factor characterization. Their reasoning might be extended to argue further that variation in psychopathology meta-structure could reflect the present state of the symptom data from which the structures were derived, and thus various covariance structures may reflect different changes in development, changes in longitudinal course, or response to treatment.

Castellanos-Ryan and colleagues (2016) report an example that is consistent with the RDoC approach of drawing connections between units of analysis. In a sample of adolescents, they studied intermediary processes provided by differential correlations between internalizing, externalizing, and a general factor of psychopathology, with behavioral performance on a variety of cognitive tasks (e.g., working memory, delay discounting, decision making). Their findings yield useful information for building models because as the hierarchical components can be parsed on behavioral performance. When there are problems in performance that are related to symptom dimensions, performance abnormalities could then be studied using an RDoC approach where, for instance, the performance deficits might be used as independent variables to identify disruptions in neural circuits. In this way, the RDoC framework can serve as a scaffold to build a nomological net (e.g., Cronbach & Meehl, 1955) whereby intermediary connections between basic mechanisms and palpable psychopathology can be

systematically spelled out across the units of analysis in the matrix.

The attention paid to development in the articles in this special issue is important (e.g., Waldman et al., 2016; Slobodskaya et al., 2016, Castellanos-Ryan et al., 2016). Because psychopathology unfolds developmentally, attention to disruptions developmental processes and stressful life events is essential. Likewise, Sellbom and colleagues (2016) attempted to examine the structure of externalizing not just in community participants, but also in samples such as inmates and forensic defendants, with participants of both genders. Environmental and developmental factors are also important considerations in RDoC, and efforts are underway to incorporate these factors into the framework (Garvey, Avenevoli, & Anderson, 2016). Other researchers have put forth cogent proposals for how to proceed on this front (see Franklin, Jamieson, Glenn, & Nock, 2015).

The Problem of Reification

Like any approach, including RDoC, dimensions or constructs derived from the meta-structure approach are not immune to the temptation of reification. Hyman (2010) has cautioned against this human proclivity, as he noted, articulated long ago by John Stuart Mill, and argued that this has been a fundamental problem with the way that *DSM* diagnoses have been used in practice. Because latent variables such as internalizing and externalizing or a general factor of psychopathology derived from statistical models are indeed very compelling from an empirical standpoint (e.g., Castellanos-Ryan et al., 2016; Kotov et al., 2016), it is important to be prudent. Although it may be tempting to infer that meta-constructs are natural kinds, this nonetheless raises the question of what a factor derived from a series of variables beyond that which the variables themselves provide can demonstrate about the realness of mental structures (Meehl, 1993; for detailed consideration of reification, see Kozak & Cuthbert, 2016).

Although a common structure of mental disorders has been replicated many times (see Krueger & Markon, 2006), there is some divergence among the results reported in these special section articles concerning which model best fits the authors' respective data. Some of the differences might reflect variations in approaches to modeling (Edwards, 2010) or variation in statistical procedures (see Barrett, 2007; Vaidyanathan, Vrieze, & Iacono, 2015). But such discrepancies may have theoretical implications or be informative in other ways. Differences in meta-structure may reflect clinically meaningful differences, such as those specific to a sample or type of observation. This is yet another reminder of the importance to view the structures conservatively, to be mindful of reification, and to seek convergence from other kinds of data.

Castellanos-Ryan et al. (2016) found evidence for a general factor in their study. Conway et al. (2016) found that the bifactor model did not quite fit their data, whereas Slobodskaya (2016) and Waldman et al. (2016) found support for the bifactor model. However, for the Slobodskaya findings, the general factor of psychopathology appeared to capture more positive emotionality than hypothesized, whereas with the Waldman et al. findings, the general factor appeared to be weighted more by negative mood (i.e., depression and generalized anxiety disorder). If one views the latent constructs as "truths," then important information may be lost. Variations in the resulting meta-structures can reflect important differences in the state or nature of the sample that could be informative. Moreover, seeing the resulting models as "truths" can stymy the field with endless debates about the "proper" number of factors, and so forth The lack of consensus that obviated the adoption of a dimensional model for the *DSM–5* personality disorders is case in point (Skodol, 2012). This illustrates the value of relating model findings to external validators (e.g., behavioral, cognitive, neural mechanisms) to refine latent constructs.

Connecting Mechanisms to Palpable Psychopathology

Although it may indeed be case that one may better approximate the structure of mental disorders by using latent variable models, another caution rests on other suppositions that such entities are most often modeled using variables limited to one type of observation (e.g., in the case of meta-structural analysis, self-report, and/or symptom/diagnostic data). Four articles in this special section provide exemplars of multiple methods (e.g., Conway et al., 2016 [stress responsivity]; Grazioplene et al., 2016 [DTI]; Kotov et al., 2016 [ERP]; and Roche et al., 2016 [experience sampling]). With models derived from diagnostic, symptom, or self-report data, core elements of an array of symptoms can be extracted on the basis of covariance structures. Although these patterns can be compelling with the parsimony of reducing error variance, using other types of data can provide convergent evidence. Regardless of whether constructs are framed with *DSM*, RDoC, or the hierarchical taxonomy of psychopathology (HiTOP), readers are reminded that such constructs are best considered a work in progress, as the field haltingly bootstraps toward refined targets with better validity and clinical utility. This type of progress is evident in the description by Castellanos-Ryan and colleagues (2016) of the progress made by developing interventions that target transdiagnostic constructs, as first envisaged by Barlow (2014).

As have several authors in this special section, others have worked to connect RDoC-like constructs with the structural dimensions by studying mechanisms. Vaidyanathan, Patrick, and Cuthbert (2009) examined the relationship of constructs that are currently in the RDoC matrix—fear (acute threat) and anxiety (sustained threat)—in relation to various internalizing disorders including phobias, depression, PTSD, generalized anxiety disorder and panic disorder, and personality traits, using the startle blink response paradigm, which has well-delineated neural circuitry. Using the parallels in results among these three realms, the results were linked to the lower order fear and distress facets of internalizing disorders (Krueger, 1999), specifying mechanisms that presumably go awry in these forms of psychopathology. Whereas the results linking startle and internalizing subfactors for disorders such as phobias were more easily interpretable, the pattern was less clear for disorders such as panic disorder, PTSD, and obsessive–compulsive disorder. Neurobiological dimensions were used to further clarify the relation of the three disorders in structural models. Though this is prior to the formal introduction of RDoC, Vaidyanathan et al. (2009) noted that heterogeneity in these disorders (captured by comorbidity) might have led to difficulty placing these disorders in structural models and with inconsistent results in neurobiological studies. Thus, it was concluded that focusing on purer phenotypes might better clarify structure and mechanism.

In a follow up study, Vaidyanathan, Nelson, and Patrick (2012) applied the same strategy to another index of neurophysiology, the ERN (an event-related potential waveform sensitive to error commis-

sion) with the internalizing dimension of psychopathology. Results suggested parallels between startle, ERN, and structural models of psychopathology, but the neurobiological indicators also hinted that various lower order factors of psychopathology were more distinct than indicated by the structural models.

In the above studies, an approach was used where findings from structural models provided a broad frame to organize neurobiological findings (especially for indicators or biomarkers where much is known about neural circuitry) in an initial step. Next, findings from the laboratory studies were incorporated into structural models to refine and clarify the model components. More recently, the strategy to develop a "psychoneurometric" approach has been more fully developed (see Yancey, Venables, & Patrick, 2016). Others have undertaken similar efforts as well (Davis, Walker, Miles, & Grillon, 2010; Lang, McTeague, & Bradley, 2016). In an earlier issue of *Abnormal Psychology*, Bilder, Howe, and Sabb (2013) explicated the challenges of building models that explicate the intermediary processes that connect neural mechanisms to psychopathology-relevant behavior.

RDoC and Meta-Structure: Mission in Common

The commonalities driving research on the meta-structure of psychopathology and RDoC are clear. Both efforts aim to clarify clinical symptoms and improve diagnosis. Both efforts are agnostic to diagnostic categories derived from clinical description. Both efforts embrace dimensions over categories. The two approaches are very complementary in nature. There are also differences. For instance, the HiTOP Consortium aims to "advance the classification of psychopathology to maximize its usefulness for research and clinical practice," to make progress refining the structure and organization of contemporary diagnostic symptom sets. In contrast, the RDoC framework is intended to drive research and provide a means to integrate internal mechanisms to clinical symptoms in order to improve future nosologies. Here it has been argued that clarifying connections with internal mechanisms will make the strides that Wakefield (1992) might have envisioned when he introduced the term *internal mechanism* to the definition of mental disorder. In the near term, structural models provide an improved organization of mental disorder symptoms.

This difference in motivations by the two approaches is reflected in their respective approach to psychopathology. The meta-structure approach begins with the *DSM* symptom sets and seeks to optimize the organization of the symptom sets for a new structure and classification of psychopathology. RDoC, in contrast, explicitly aims to provide a framework to elaborate when mechanisms for normal function go awry and how such aberrations connect to clinical symptoms. The NIMH mission to transform the understanding and treatment of mental illnesses through basic and clinical research requires a major shift from current approaches and will take some time (NIMH Strategic Plan, 2015). Meta-structure approaches, exemplified by the articles in this special section are an important element of progress. Higher order constructs are useful for providing a sampling frame for RDoC research. Lower order constructs are potentially more proximal to internal mechanisms, and researching these connections can provide another form of evidence to inform the organization of clinical symptoms. RDoC offers a framework to organize these efforts.

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