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Psychopathology research in the RDoC era: Unanswered questions and the importance of the psychophysiological unit of analysis

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Abstract

The NIMH Research Domain Criteria initiative (RDoC) seeks to re-conceptualize psychopathology by identifying transdiagnostic constructs that reflect core mechanisms of psychopathology. Although the RDoC framework has been discussed in a many prior papers, there are several methodological and conceptual points that have yet to be fully specified. For example, little discussion exists on the importance of distinguishing each construct's nomological network and linking it to risk for psychopathology. It has also been unclear the extent to which RDoC constructs (within and across systems) should relate to one another and how these associations may differ as a function of developmental period. These are important questions as we enter the RDoC era and psychophysiological measures represent an exciting tool to address these issues. In this paper, we discuss the currently un- (or under-)specified aspects of the RDoC initiative and highlight the advantages of the psychophysiological 'unit of analysis.' We also briefly review existing psychophysiological studies, within the positive and negative valence systems, that exemplify the RDoC approach and make recommendations for how future studies can help the field progress in this mission.

Keywords

Research Domain Criteria; psychophysiology; positive valence system; negative valence system

In response to the well-documented concerns with the current psychiatric diagnostic system and available treatment interventions (Chien and Yip, 2013; Helzer et al., 2006; Kendell and Jablensky, 2003; Krueger and Markon, 2006), the National Institute of Mental Health (NIMH) recently proposed the Research Domain Criteria (RDoC) project. RDoC seeks to re-conceptualize psychopathology by creating a research framework that aims to identify *transdiagnostic* constructs that reflect core mechanisms of psychopathology (Sanislow et al., 2010; Insel et al., 2010; Cuthbert and Kozak, 2013).

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NIMH's ultimate goal for how RDoC should be used can be summarized from a recent quote from a paper by Bruce Cuthbert and Michael Kozak (two prominent NIMH administrators who have been involved in the RDoC initiative from its inception):

> From the perspective of a funding institute whose mission is to reduce the burden of suffering from mental disorders through research, the problem may be stated as follows: It is clear that a diagnostic system based upon empirical data from genetics, neurobiology, and behavioral science is desirable to move toward an era of precision medicine where patients are diagnosed and treated according to accurate and appropriately fine-tuned assessments. However, such a database cannot be created as long as research grants are funded almost exclusively in terms of the current categories
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> (Cuthbert and Kozak, 2013, p. 929).

Thus, it is clear that the hope of the RDoC initiative will be that the science will eventually replace (or perhaps complement) the categorical diagnostic nomenclature espoused in DSM/ICD (Berenbaum, 2013). This will ultimately help researchers develop new and more targeted treatments and help clinicians classify and treat their patients. RDoC therefore represents an exciting new direction for mental health research and offers hope for those dissatisfied with the DSM/ICD.

In the 'RDoC era,' psychophysiological research has the potential to play a prominent role in the reconceptualization of psychopathology. This article therefore has several purposes. First, the article will provide a brief overview of the initial RDoC domains and constructs proposed in NIMH sponsored workshops. Second, we will discuss several points that have yet to be fully articulated in prior RDoC papers and note how psychophysiological methods could make (and have made) significant contributions to this framework. Third, we will highlight a few potential issues with the currently proposed RDoC research matrix and make recommendations to researchers on ways to advance the field during the RDoC era. Given the focus of this special issue of *International Journal of Psychophysiology*, this paper will focus on constructs within the Negative Valence System and Positive Valence System. However, many of the issues and ambiguities of the RDoC system apply to all domains.

RDoC Overview

There have been several detailed overviews of both the rationale and proposed domains of RDoC (Insel et al., 2010; Morris et al., 2014; Sanislow et al., 2010). The reader is also referred to other articles in this special issue. Briefly, a small committee at NIMH proposed an initial research framework with five broad domains - Negative Valence System, Positive Valence System, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems. Within these domains are constructs (e.g., perception within cognitive systems) and sometimes subconstructs (e.g., visual perception and auditory perception within the broader construct of perception). Each of these exemplar constructs and subconstructs is conceptualized as a dimension and "represent the fundamental unit of analysis in this system" (http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml, accessed December 29, 2014).

Constructs and subconstructs make up the 'rows' in a two-dimensional matrix often called 'the RDoC matrix'. The columns of the matrix represent the units (or levels) of analysis. Seven units have been initially proposed - genes, molecules, cells, neural circuits, physiology, behaviors, and self-reports. Of most relevance for this essay, psychophysiological measures can encompass both 'neural circuits' and 'physiology.' The distinction (or lack thereof) between physiology and neural circuits is discussed below.

It is important to highlight that the columns of the matrix are listed with genes on one side of the matrix and self-report on the other. This provides a structure for the identification of causal (or at least associative) chains, as it is assumed that variables in closer nodes in the columns (e.g., physiology to self-report) should be more robustly related than nodes that are more distal (molecules to self-reports). This has important ramifications for studies associating genes with psychopathology, which have yielded mixed findings in both genome wide association studies (GWAS; Cohen-Woods et al., 2013) and linkage studies (Cuthbert and Kozak, 2013; Insel et al., 2010; Roffman et al., 2006). It appears that RDoC hopes to remedy this problem. That is, studies examining genes related to "reward processing' should yield more robust results than studies examining genes related to diagnostic categories such as 'major depressive disorder.'

Points of Emphasis within the RDoC Framework

The Importance of Risk

Implicit in the RDoC initiative is the assumption that the core RDoC constructs should be related to the pathogenesis of relevant psychopathologies, and thus be associated with increased risk for psychopathology. Writings about RDoC do emphasize that the domains are 'mechanisms' of psychopathology. However, in order to elucidate etiology, it is important that these mechanisms not just describe the features of psychopathology, but describe how diseases develop and consequently, who is at risk. Stated another way, if RDoC constructs do *not* connote risk and are just scars or state markers, the explanatory power of the RDoc matrix (which purportedly outline a pathway from genetic abnormality to outwardly expressed phenotype) would be weaker. The existing published papers on RDoC have not directly discussed the importance of risk to the initiative (although see Lilienfeld, 2014). However, this point warrants emphasis as the identification of biosignatures that predict future disease states is key in developing effective prevention and early intervention efforts (Zubin and Spring, 1977).

There are several ways to determine whether an RDoC construct is associated with risk for psychopathology. One way is to examine whether individual differences longitudinally predict future psychopathology (Raulin and Lilienfeld, 2009). These studies are only informative about risk if they exclude (or at least adjust for) baseline psychopathology, as not doing so leaves the possibility that the RDoC domain is just a correlate of the psychopathology. In other words, it is important to examine whether the RDoC construct predicts *change* in symptoms over time.

It is important to add that "exclusion of baseline psychopathology" would usually require the determination of a cutoff (e.g., not full threshold psychopathology). If the

psychopathology (and not just the RDoC domain) is conceptualized as a continuous dimension, then determining a meaningful cutoff may be difficult. Thus, in many cases, a more appropriate analysis within an RDoC framework would be to statistically adjust for levels of baseline psychopathology. This would essentially examine whether the RDoC construct predicts *change* in symptoms over time, rather than predicting *onset* (a 'categorical' term).

To date, many longitudinal studies have examined the predictive power of psychophysiological indicators of various RDoC constructs and subconstructs. Bress et al. (2013a) found that blunted feedback negativity (i.e., FN; an event-related potential associated with reward processing) at an initial evaluation prospectively predicted depressive symptoms and onset of MDD during a 2-year follow-up period, even when controlling for neuroticism. Using fMRI, Morgan et al. (2013) found that less activity in the striatum during reward anticipation predicted increased depressive symptoms two years later. O'Donnell et al. (2007) found that heart rate reactivity one-week post-traumatic event predicted the onset of post-traumatic stress disorder (PTSD) 12-months later. These are just three examples of the many studies that have reported similar findings (e.g., Craske et al., 2012; Nusslock et al., 2012; Sijbrandij et al., 2013; Yaroslavsky et al., 2014). The fact that these studies have utilized a wide array of psychophysiological methods (e.g., EMG startle, spectral EEG, fMRI, ANS indicators, ERP) highlights the important role that psychophysiology has played in these initial studies of whether RDoC domains connote risk for psychopathology.

Another way to determine whether a construct is associated with risk is through the classic family study method (i.e., studying multiple individuals within a family; Robins and Guze, 1970; Raulin and Lilienfeld, 2009). Family study designs can be helpful in this context in several ways. First, given that one of the most robust risk factors for nearly all forms of psychopathology is a family history of psychopathology (Kendell and Jablensky, 2003; Klein and Riso, 1993), one can examine whether individual differences on an RDoC domain in probands is associated with the presence (or levels) of psychopathology in families. That is, if 'abnormal' levels of RDoC domain X are associated with a family history of Y, then RDoC domain X can be construed as a risk factor for Y. Numerous psychophysiological studies have employed this design and demonstrated, for example, that abnormal EEG asymmetry (a putative marker of low approach motivation), startle during a threatening context, and blunted ERPs to reward are all associated with a family history of depression (Dawson et al., 1999; Grillon et al., 2005; Kujawa et al., 2012; Nelson et al., 2013). fMRI studies of reward processing (particularly reward anticipation) have found similar results (Olino et al., 2014) and analogous approaches have been taken examining psychophysiological risk factors of other psychopathologies such as anxiety and psychosis (Nelson et al., 2013; Iacono et al., 1992).

Twin designs, which can tease apart environmental risk from genetic risk, have also been conducted with psychophysiological indicators of RDoC constructs (Ettinger et al., 2006). For example, in a sample of monozygotic and dizygotic female twins, Anokhin and colleagues (2007) found that startle response was highly heritable, but the degree to which startle was modulated by emotional context was not associated with any genetic variance.

Concordance amongst family members may therefore be better explained by shared environmental factors than genetic factors. Interestingly, moderators of environmental and genetic factors have also been identified. In a sample of 19-month-old twins, genetic and environmental contributions to cortisol reactivity to stress (i.e., unfamiliar situations) differed as a function of familial adversity (e.g., single parenthood, low birth weight) (Ouellet-Morin et al., 2008). Among families with low adversity, genetic and unique environmental factors, but not shared environmental factors, were associated with variance in cortisol reactivity. In contrast, among families with high adversity, shared and unique environmental factors, but not genetic factors, were associated with variance in cortisol reactivity. This study highlights how environmental factors can influence how RDoC domains can manifest (see below for further elaboration on this point).

A second way that family studies can be used to examine whether RDoC constructs are vulnerability markers is to test whether the RDoC construct is abnormal in healthy (or low symptom) relatives of symptomatic probands. That is, if the RDoC construct is abnormal in 'unaffected' relatives of symptomatic individuals, then that would be evidence that the RDoC construct is a vulnerability factor (Raulin and Lilienfeld, 2009). One caveat for this design, however, is whether the unaffected relative is still in the 'risk period' for the illness as it would be difficult to argue that a biomarker reflects "risk" for a person who is out of the age window during which the incidence of illness typically occurs. For example, if the unaffected sibling of someone with schizophrenia is in his or her 50's and has yet to develop schizophrenia, it may be difficult to argue that the biomarker represents a risk factor for that sibling, as the first onset of schizophrenia is almost always prior to age 40 (Sham et al., 1994). On the other hand, that sibling could still carry the vulnerability marker, but perhaps have other characteristics that led them to be resilient to this vulnerability.

Many studies in the psychosis literature have utilized this design to identify vulnerability markers and showed that healthy siblings of probands with schizophrenia exhibit abnormal eye-tracking dysfunction (Takahashi et al., 2008; Ettinger et al., 2006). Fewer studies have examined this approach with respect to positive and negative valence domains and internalizing psychopathology. However, it has been demonstrated that healthy siblings of individuals with obsessive-compulsive disorder (OCD) exhibit large error-related brain activity (i.e., the ERN) compared to controls without a family history of psychopathology (Carrasco et al., 2013; Riesel et al., 2011). In addition, healthy adolescent girls with a maternal history of MDD have been shown to display less putamen and left insula, and greater right insula, neural activation during anticipation of monetary rewards relative to healthy adolescent girls without a maternal history of MDD (Gotlib et al., 2010, see also Macoveanu et al., 2014). This design represents an important approach for future work.

Risk for other RDoC units of analysis

Studies conducted in the RDoC framework can also use psychophysiological methods to examine risk in other ways. For example, in addition to examining whether psychophysiological markers connote risk for psychopathology, one can examine whether psychophysiological markers connote risk for *other* units of analysis (e.g., brain circuits, behavior) or whether other units of analysis connote risk for them. These types of studies

could do more than just examine whether units of analysis converge (e.g., examining whether startle response to acute threat correlates with amygdala response to acute threat; Klumpers et al. 2010). Rather, one could examine whether one unit of analysis (e.g., startle) longitudinally predicts changes in another unit of analysis (e.g., amygdala activity).

This line of research is critical for several reasons. Typically, studies examine risk for psychopathologies that are assessed via self or interview report. Since RDoC conceptualizes psychopathology *in terms* of the purported units of analysis (Patrick et al., 2013), and not just what individuals experience on a conscious or phenomenological level, self- (or interview) reported psychopathology should perhaps not be considered the gold standard 'unit of analysis.' For decades, researchers and clinicians have raised concerns regarding the validity and reliance of self-report as the definitive assessment of psychopathology. If psychophysiological variables are indeed indicators of distress, impairment, or other aspects of 'disease states,' (Robins and Guze, 1972; Smith, 2002) then it stands to reason that they should be used as outcome variables in their own right. As an analogy, numerous studies have examined predictors and risk factors for hypertension (Dyer et al., 1999) or lack of condom use (McFarland et al., 2012). Hypertension and lack of condom use are only public health outcome variables because of their association with other indicators of disease states (i.e., the impairment, distress, and mortality associated with heart disease and AIDS, respectively; Strik et al., 1993). A similar argument could be made for psychophysiological variables. That is, assuming that psychophysiological variables are indicators of impairment, distress, and other aspects of disease states, it would be just as valid to examine whether neural circuits connote risk for psychophysiology as it would be to examine whether circuits connote risk for self-reported symptoms. In order for the field to progress, this will be an important area of research for psychophysiological investigators to undertake.

Discriminant Validity of RDoC Domains

Studies that examine whether RDoC domains connote risk can aid in another important goal of RDoC – examining the discriminant validity of the domains. In their classic paper, Campbell and Fiske (1959) outlined that the two components of construct validity are convergent and discriminant validity. Based on the early papers published on RDoC, there appeared to be more discussion on the convergent validity of RDoC domains (e.g., that the multiple units of analysis of a domain would converge) and less on the discriminant validity (e.g., that indicators of putatively separate constructs should not be related). This difference in emphasis may be because a lot of the excitement surrounding RDoC is the idea that the domains represent transdiagnostic constructs. This excitement is not unfounded, as there is a lot of evidence that the RDoC domains do represent transdiagnostic constructs (e.g., the startle indicator of the RDoC construct 'reactivity to potential threat' is associated with multiple disorders including panic disorder and post-traumatic stress disorder [PTSD; Grillon et al., 2008; Grillon et al., 2009]).

However, it is necessary to highlight that transdiagnostic does not mean pandiagnostic. RDoC constructs should not relate equally to all forms of psychopathology and should thus exhibit discriminant validity *in addition to* convergent validity. In other words, each RDoC construct should have a nomological network that reflects the natural clustering of

psychopathology that they *are* related to and those that they *are not*. Until these networks are identified, a new nosology cannot be derived.

Several psychophysiological studies have already attempted to examine the discriminant validity of RDoC constructs. As an example, Nelson et al. (2013) examined whether reactivity to threat and reward anticipation were associated with similar or different familial psychopathology liabilities. The results indicated that reactivity to threat (indexed via startle potentiation) was associated with family history of panic disorder but not MDD and that reactivity to reward anticipation (indexed via EEG asymmetry) was associated with family history of MDD but not panic disorder. Longitudinally, it has been demonstrated that startle potentiation to safety signals predicts onset of anxiety disorders but not depressive disorders (Craske et al., 2012), and reward related neural activation predicts onset of substance use disorders but not unhealthy weight gain (Stice et al., 2013). These findings underscore the point that RDoC constructs can index risk for separate psychopathologies; however, it will be important to assess whether RDoC constructs connote risk for additional disorders than those specifically mentioned above. Perhaps reward related neural activation predicts onset of substance use disorders and mood disorders (for instance), but not eating disorders, or anxiety disorders. A more constructive approach may even be to move away from current DSM diagnoses and examining the discriminant validity between RDoC constructs and specific clusters of symptoms. Researchers, however, should be careful to not allow this design to become circular as the RDoC domain *may be* the symptom of psychopathology. For example, it would be somewhat circular to examine whether the above mentioned ERP, FN is associated with risk for anhedonia (as the FN is an ERP indicator of anhedonia).

Lastly, it is important to note that risk is just one *validator* in which to test discriminant (and convergent) validity (Robins and Guze, 1970; Kendell and Jablensky, 2003). Researchers should therefore examine other reliable validators such as pharmacological and psychological treatment outcomes, changes in other neurobiological systems, and different forms of impairment (e.g., work functioning, social functioning, etc.).

The Importance of Development

Another fundamental area of research within the RDoC framework should be the role of human development. Developmental milestones, as well as their timing and surrounding social context, have long been known to have a profound impact on mental health. Additionally, it has become increasingly accepted that there are multiple etiological pathways to disorder onset that unfold throughout the lifespan (Kaufman et al., 2001; Zucker, 2008). Each pathway is considered the product of variable interactions across multiple levels (i.e., from genetics to environmental context) that can be traced from prenatal exposure to geriatrics.

Consistent with this perspective, studies indicate that risk processes can differ as a function of age and environment (Dick et al., 2006; Kendler et al., 2008). For instance, family relations, family management, peer relations, religious affiliation, and romantic relationship status have all been shown to be risk factors for substance use disorders; although, the extent to which they connote risk depends on age and social context (Stone et al., 2012). Similarly, anxiety disorders have been shown to prospectively predict onset of alcohol use disorders

(AUDs), but at low maternal support, anxiety can function as a risk factor for AUDs and a high maternal support, it can function as a protective factor against AUDs (Gorka et al., 2014). Of course, the importance of development is not specific to substance use disorders, as juvenile-onset and adult-onset MDD have been shown to have different origins and thus, different risk profiles despite being classified as the same disorder (Jaffee et al., 2002).

RDoC domains may also manifest differently as a function of developmental period (Casey et al., 2014). For example, existing literature indicates that adolescence is marked by dramatic neurodevelopmental changes in dopaminergic reward systems and top-down inhibitory control regions (Paus, 2005). These changes are directly linked to age-related increases in reward-seeking and impulsive behavior (Steinberg, 2008), underscoring the fact that reward processing in children is biologically different than reward processing in older adolescents. Unlike reward processing, however, fear conditioning has been shown to be relatively stable – especially across adulthood and late-life (LaBar et al., 2004). Although these studies reflect divergent findings, both of these lines of research provide valuable information, as they shed light on the fact that RDoC domains, and their interactions with one another, will have both static and phasic associations over the course of the lifespan. These associations are what will ultimately give rise to some of the most impactful research from the RDoC initiative.

In this next section, we turn to broader issues and general ambiguities regarding the existing RDoC matrix. We discuss several of these as well as suggestions for how psychophysiology could play a role in elucidating these issues.

Ambiguities Regarding the RDoC Matrix

As stated above, through a series of workshops with experts in the field, the NIMH proposed and disseminated a matrix listing constructs within five broad systems as well as broad units of analysis that the constructs could be studied. It is clear that this matrix is intended to be an initial framework that gets modified regularly as the field develops. However, even though NIMH and the framers of RDoC proposed the matrix to be an extensible system, it is possible that fellow researchers may inadvertently feel constrained by the existing matrix. This concern is fueled by the fact that recent NIMH requests for grant applications (RFAs) under the RDoC initiative include phrases such as “applications must focus on at least one of the constructs that have been defined in these RDoC workshops” (NIMH RFA-MH-14-050). This type of explicit wording may prevent researchers from proposing new constructs or units of analysis due to worries about competitiveness for federal funding. As a result, the existing RDoC matrix may remain unchanged, which is problematic.

In addition to this broad concern with the current RDoC matrix, there are several issues/ambiguities with the current RDoC matrix that researchers need to consider when designing future studies.

The current five systems

As stated above, the initial rows of the RDoC matrix propose five broad domains – Negative Valence System, Positive Valence System, Cognitive Systems, Systems for Social

Processes, and Arousal/Regulatory Systems. According to the RDoC website, these rows represent constructs "grouped into major domains of functioning, reflecting contemporary thinking about major aspects of motivation, cognition, and social behavior." These five domains were created by a panel of experts and not derived empirically as the fundamental building blocks of "motivation, cognition, and social behavior."

One of the criticisms of the *DSM*'s nomenclature for psychopathology (an approach that the RDoC initiative is supposed to ultimately transcend; Insel al., 2010) is that the DSM categories were initially created by a small committee and were not empirically derived (Krueger et al., 2006; Markon, 2013). To be fair, unlike the DSM (which has only been revised every 7–10 years), the RDoC matrix is designed to be a dynamic nomenclature, ever evolving due to new findings.

There are several other concerns with this initial RDoC matrix. For example, the first two systems (positive and negative valence) are "affective" and the third system is "cognitive." The question of whether affective processes are unequivocally distinct from cognitive processes has been hotly contested for decades, with psychological and biological evidence on both sides (Zajonc, 1980; Lazarus, 1982; Eder et al., 2007). One well-studied psychophysiological marker (i.e., ERN) actually appears in both the negative valence matrix (under sustained threat) and cognitive (cognitive control). While it may be possible to separate cognitive from affective processes, the fact that the current RDoC matrix separates them establishes a particular framework that may be pragmatically difficult to venture away from.

As a second example, one could argue that social processes is not a separate "domain of functioning" from the others, but is rather a 'higher order' system that involves both affective (positive and negative) and cognitive systems. Indeed, it is difficult to envision a social process that does not, at least partially, involve cognitive and/or affective processes.

Lastly, the arousal/regulatory system appears to be the least developed of the five domains - consisting of three constructs (Arousal, Biological Rhythms, and Default Readiness) only loosely related to each other. Additionally, similar to the social system, several of the constructs within this system appear to be modulators of processes in other domains (e.g., arousal for both cognitive and affective constructs).

Taken together, it is strongly suggested that psychophysiological researchers respect the existing RDoC matrix, as it was indeed developed by many leading scientists in the field, but also approach it with a critical mindset. Researchers should also remember that the matrix was intended to be a modifiable framework and should therefore not feel constrained by the existing constructs when they propose their studies.

Correlations among Rows

Along these lines, it is critical that researchers consider how RDoC domains relate to one another. Almost all of our current psychopathologies are characterized by deficits in multiple domains (e.g., positive valence system, negative valence system, cognitive systems) and are highly comorbid with one another (Kessler et al., 2005). For example, depression,

anxiety, and substance use disorders are all associated with deficits in both positive and negative affect, and commonly co-occur. This begs the question as to whether there is one 'general factor' that all forms of psychopathology share, a hypothesis supported by both phenotypic (Lahey et al., 2012) and genotypic studies (Hariri et al., 2009; Lahey et al., 2011).

Of course, correlated RDoC domains do not mean that the domains are tapping the same construct. It is possible that two systems are correlated because one *causes* the other. That is, one deficit may be a core dysfunction whereas the other deficit is merely a byproduct of the first. The primary versus secondary deficit could (and likely does) differ by individuals, with it being causal for some people (e.g., a person's stress responsivity leads to reduced reward responding; Dillon et al., 2014) while in others it may reflect a shared etiological process (Klein and Riso, 1993; Neale and Kendler, 1995). This question could be addressed by longitudinal studies that examine not only homotypic associations over time (e.g., psychophysiological indicators of reward predicting changes in neural circuits for reward) but also heterotypic associations (e.g., psychophysiological indicators of threat responding predicting changes in reward responding).

It is important to note that the debate as to whether affective/motivational systems are correlated is not new. However, the empirical literature on this topic is still unclear. Continuing with the example of the positive and negative valence systems, some studies have shown that there is a small, but significant, negative correlation between appetitive and defensive motivation (Elliot and Thrash, 2002; DeYoung, 2006), whereas others have shown them to be orthogonal (Carver and White, 1994; Torrubia et al., 2001). These mixed findings are likely due, in part, to the fact that most of this literature has relied on self-report measures, which have numerous inherent limitations (Lang, 1968). Psychophysiological research, and other studies that rely on more objective indices (e.g., behavioral observation), represent an extremely useful tool in clarifying these mixed findings and elucidating associations between RDoC domains.

As a preliminary examination of this, our group recently examined the relation between two psychophysiological indices of appetitive and defensive motivation - frontal EEG asymmetry during reward anticipation and startle responses during anticipation of predictable and unpredictable threat, respectively (Sarapas et al., 2013). In a sample of psychopathology-free community members and an unselected undergraduate sample, results indicated that individual differences in responding to the two tasks were not significantly correlated. In a separate study, Bress et al. (2013b) also tested whether psychophysiological indices within the positive and negative valence systems were correlated and whether they relate uniquely to anxiety and depression. Specifically, they examined measures of ERN (i.e., an event-related potential [ERP] associated with error monitoring) and FN in a sample of adolescents. The results from this study were consistent with Sarapas et al. (2013), as there was no significant correlation between the two ERP measures. Interestingly, findings from this study also indicated that larger ERN was uniquely associated with greater anxiety symptoms and smaller FN was uniquely associated with greater depressive symptoms. As such, these two RDoC domains (at least as measured by these two physiological indicators), may be biomarkers for unique forms of psychopathology.

Interactions among Rows

Besides assessing whether domains are correlated, it is necessary to explore whether RDoC domains *interact* to predict meaningful outcomes. As was previously mentioned, psychopathology is characterized by deficits in multiple domains and it is reasonable to suspect that these processes do not simply function in parallel. For example, deficits in the positive and negative valence system likely interact, whereby deficits in one system, coupled with deficits in another, reliably lead to a set of symptoms or behaviors. Indeed one recent study found that two domains with the positive valence system (effort for reward and reward valuation) interact at predicting ERP responses during a gambling task (Ma et al., 2014).

Interactions among constructs across the five RDoC systems are also likely. Within the past decade, there has been growing interest in the interplay of positive and negative valence systems. Studies have indicated that threat-related amygdala activation and reward-related ventral striatum activation interact to predict stress-induced problem alcohol use (Nikolova and Hariri, 2012), and that reward-related behaviors are used to regulate negative affect (Garland et al., 2010; Nelson et al., 2009). Unfortunately, however, studies exploring these questions using psychophysiological methods are severely lacking. Given the wealth of research supporting measures of startle potentiation and the ERN during threat, and EEG asymmetry and the FN during reward, it is essential that studies examine the interactive effects of these psychophysiological indices in psychopathology. Only then will the field start to fully appreciate the inter- and intra-relationships amongst psychopathology. More generally, given that one of the major aims of the RDoC initiative is to identify biosignatures of empirically-based disorder constructs, complex interactions across constructs and domains may account for the most variance in clinical outcomes.

Ambiguities/issues with the units of analysis

As discussed in the beginning of this article, the preliminary RDoC matrix lists “physiology” and “neural circuits” as separate units of analysis and yet is unclear how these are separable. NIMH’s RDoC website defines ‘physiology’ as biological variables that “do not necessarily tap [neural] circuits directly (e.g., heart rate, cortisol).” Circuits are defined as “measurements of particular circuits as studied by neuroimaging techniques, and/or other measures validated by animal models or functional neuroimaging (e.g., emotion-modulated startle, event-related potentials with established source localization).” With few exceptions, this distinction between physiology and neural circuits is unfounded as most measures of neural circuits (e.g., fMRI, PET) *are* ‘physiological’ measures (Miller, 2000). Indeed, the researchers and leaders in the field who proposed the initial units of analysis for particular RDoC constructs during the workshops appeared to share this confusion at times. For example, EMG startle, ERPs, and spectral EEG are sometimes listed as ‘physiological’ units of analysis and sometimes as ‘neural circuits.’ Moreover, almost all classic physiology measures are under neural control (e.g., heart rate is mediated by the medulla oblongata; cortisol is mediated by HPA Axis functioning). Of course some measures such as dynamic causal modeling (DCM; Friston et al., 2003) measure the inter-connections of neural regions more directly than measures such as cortisol, and the findings from the human connectome project will only further our understanding of how neural regions are connected (van Essen

et al., 2012). However, listing neural circuits separately from (rather than as part of) physiology could lead to confusion, particularly as researchers are encouraged to include multiple units of analysis.

One of the frequent critiques of RDoC is that it takes a "biological reductionist" stance, placing the biological units of analysis as more prominent over the psychological ones. In a recent paper that critiques RDoC, Berenbaum (2013) argues that brain and neural circuits are essential for complex behaviors, but this does not mean that the best way to understand complex behaviors is to reduce them to a series of biological events and variables (see also Lilienfeld, 2014; Turkheimer, 1998). A broader critique was raised by Eisenberg (2014) in her recent column as president of the Association for Psychological Science (APS) in which she argues that "there seems to be an increasing tendency to assume that studying genetic/neural/physiological processes is more important than research on behavior and psychological processes" (p5).

The concern that RDoC is too reductionistic in its approach towards psychopathology has some validity. In one of the first descriptions of RDoC, NIMH director Thomas Insel and colleagues at NIMH stated that "the RDoC framework conceptualizes mental illnesses as brain disorders" (p749). However, it is important to note that this strong verbiage has been counteracted by other papers from members of the NIMH RDoC workgroup (Cuthbert et al., 2010) in which a more integrated and balanced view of psychology and biology is espoused. For example, Cuthbert and Kozak (2013) state that the "the columns of the matrix were termed 'units of analysis' rather than 'levels of analysis' to avoid an implication of scientific hegemony as one goes from self-reports and behavior to molecules and genes" (p. 929). Thus, the reductionist debate appears to have stemmed from inconsistent views amongst senior NIMH staff, but RDoC, at its core, does not necessarily assume reductionist relationships amongst the units of analysis. Nevertheless, using terminology that moves away from biological reductionism is critical (hence the use of the phrase 'units of analysis' throughout this paper). One of the ways RDoC studies could advance the field would be if they take an *epistemological pluralistic* view of psychopathology in which the units of analysis represent multiple ways of knowing a phenomena (Markon, 2013; Miller, 2010). For example, studies could examine whether the units of analysis in aggregate predict a clinically meaningful outcome (Patrick et al., 2013).

Rather than taking a pluralistic view, some RDoC studies may attempt to separate the units of analysis into separate nodes in a chain rather than use them to 'converge' on some 'truth.' In a sense, these studies would argue that the different units of analysis between genes and self-report would represent endophenotypes (Gottesman and Gould, 2003; Walters and Owen, 2007). It is important, however, that these studies are clear as to what *type* of endophenotype they are testing. The term 'endophenotype' has been used to describe several different types of variables (Kendler and Neale, 2010). Therefore, it would be important that these studies are clear as to whether they view endophenotypes simply as *risk indicators* of pathology (i.e., the genes increase risk for the endophenotypes which increases risk for pathology), or whether the endophenotypes are *mediational* (Walters and Owen, 2007), with the latter definition making a stronger assumption as to how genetic variation passes through the endophenotypes in becoming pathology (Kendler and Neale, 2010). In other words,

these RDoC studies could view the units of analysis in the RDoC matrix either as a causal pathway to illness or simply as risk factors for psychopathology (and/or perhaps other units of analysis).

If RDoC studies do take the more *mediational* approach in which genes lead to neural circuits or physiology, which lead to behavior and self-report, it would be important that studies investigate how this causal chain happens. That is, how do genes (or other biological variables) become 'penetrant' on physiology and then behavior (Miller and Rockstroh, 2013)? For example, one might examine whether the psychophysiological indicator 'startle to unpredictable threat' (Grillon et al., 2004) mediates the effects of genes on abnormal behavior/phenomenology (e.g., self-reported anxiety). If this is indeed a 'causal chain,' *how* does startle to unpredictable threat lead *to* self-reported anxiety? It is these causal mechanisms that would likely be the most fruitful intervention targets (Miller, 2010).

As a final suggestion regarding the columns of the RDoC matrix, all of the units of analysis appear to be largely 'within' an individual. It would be beneficial to also examine more macro-level units beyond the individual as people are 'nested' within families, communities, etc. (Berenbaum, 2013; Lilienfeld, 2014). These units could take several forms. One possibility would be to examine the variance that is common to individuals within a nest. For example, it would be interesting to examine an fMRI indicator of a domain in multiple members of a family and whether (and how) the proband's indicators of that domain relate to the common variance in his/her family. As another example, one could measure RDoC domains in schools in which students are nested within cohorts and classrooms. These nested designs would require large N's. Many psychophysiological measures are well-suited for this type of design, as they can be cost-effective and relatively easy to administer.

Environment: Another unit of analysis

Lastly, it is important that researchers examine the interaction of RDoC domains with environmental events. While some critics of RDoC have suggested that the initiative 'ignores the environment,' this is baseless. For example, the RDoC website states that "environmental influences [are] another critical dimension of the RDoC matrix" and highlights the point that the "social and physical environment comprise sources of both risk and protection for many different disorders." These studies could take several forms. One could be to examine the influence (or at least association) of environmental variables on the expression of the RDoC construct. For example, numerous studies have shown that cortisol functioning is abnormal in those who have experienced a trauma (Yehuda, 2006, although whether this reflects pre-existing neuroendocrine functioning or the effect of the trauma remains an open question).

Another approach to examining the role of environmental events is whether an environmental event or context interacts with an RDoC construct to predict some other variable. For example, Oldehinkel et al. (2008) found that baseline heartrate interacted with subsequent environmental stressors to predict a broad range of mental health problems at follow-up. Specifically, individuals with larger baseline heartrates who experienced subsequent stressors reported both externalizing and internalizing symptoms several years later but individuals with low baseline heartrates did not. If the RDoC construct represents a

pre-existing vulnerability factor, this type of design could be construed as a test of a 'vulnerability-stress' model.

Importantly, these studies could also test the discriminant validity of particular RDoC domains by examining qualitatively different types of environmental events. For example, there is some evidence that stressful life events related to humiliation prospectively predict the onset of depression, but not anxiety, while stressful life events related danger predict the onset of anxiety, but not depression (Kendler et al., 2003, although other studies failed to show this dissociation; Newman and Bland, 1994). While complicated, it would be interesting to examine whether different types of environmental events interact with different RDoC constructs to predict different forms of psychopathology. These models would of course require very large N's but would significantly aid in the identification of specific etiological pathways for different forms of psychopathology.

Clinical application

At this point, RDoc is entirely a research enterprise and how (or if) RDoC will ultimately affect clinical practice remains to be seen. We remain optimistic, though, that RDoC will ultimately impact clinical practice, particularly given the growing frustration with how the DSM defines and conceptualizes psychopathology. For example, suppose RDoC reveals that internalizing psychopathology is best encapsulated by a certain number of constructs that can be measured with reliable psychophysiological indicators (e.g., ERP, startle, etc) for which normative data has been established. Clinicians could then administer this battery of psychophysiological indicators to a patient and examine the pattern of responding in order to make treatment recommendations. This process would be similar to when a patient is administered the Minnesota Multiphasic Personality Inventory (MMPI) and the clinician interprets the pattern of t-scores on the various domains (e.g., which domains are abnormal and which are normal) to make treatment recommendations. Rather than yielding scores on self-reported scales like 'Hypochondriasis' and 'hypomania,' such an approach would yield scores for "reward learning" or "response to sustained threat." This battery could also be used to track treatment progress. It is important to highlight that this approach is already done in other areas of medicine when a clinician conducts a "complete blood count" to examine white blood cell count, glucose, etc. to examine overall health functioning.

Concluding Thoughts

The "age of RDoC" is in its infancy. What will increase the likelihood that RDoC will have lasting impact will be how the RDoC matrix evolves. This is largely dependent on the type of research designs that are used - points that we attempted to emphasize in this article. We also attempted to highlight the role that psychophysiology could play in this new approach to psychopathology research, as not only one of the 'units of analysis' in the RDoC matrix, but potentially, leading the field with integrative designs and questions.

RDoC represents a potential *paradigm shift* in psychopathology research away from DSM. This shift has the ultimate goal of changing how we conceptualize mental disturbance, but also how we ultimately treat suffering. Paradigm shifts, however, are not without their pitfalls. Kuhn (1962), quite controversially, argued that paradigm shifts are a mix of

sociology, hope, and not necessarily objective breakthroughs in scientific discovery. We would also add that in psychopathology research, a paradigm shift away from DSM would require a great deal of investment in time and money from influential institutions. Indeed, the last paradigm shift in psychopathology was the development and publication of the DSM-III in 1980, an event that could not have occurred without 'institutional buy-in' from the American Psychiatric Association (APA; Mayes and Horwitz, 2005; Wilson, 1993). It is therefore interesting that with the RDoC initiative, the NIMH may be breaking the hegemony held by the DSM (and by association the American Psychiatric Association [APA]). As with all scientific paradigm shifts (Kuhn, 1962), the challenge of RDoC to the status quo has not been without conflict. For example, in a now infamous blog post, NIMH Director Thomas Insel stated that "NIMH will be re-orienting its research away from DSM categories" and that "patients with mental disorders deserve better" (Insel, 2013). This was retorted by a press release from the DSM-5 task force (David Kupfer, M.D., May 3, 2013). It remains to be seen how NIMH and the APA will work together given that the 'age of RDoC' began around the same time as the release of the latest version of the DSM (and the first revision in 19 years).

In sum, there is a great deal of hope that the field will eventually benefit from this new approach towards doing psychopathology research. Allowing studies to conceptualize domains of psychopathology in a dimensional (rather than categorical) way and taking multiple units of analysis into account will ultimately uncover more valid etiological and mechanistic processes than requiring studies to only use DSM defined disorders. Most importantly, it is our strong belief that RDoC-ian psychopathology studies will ultimately aid individuals and families who suffer from psychopathology.

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Highlights

- RDoC seeks to identify constructs that reflect core mechanisms of psychopathology.
- Several methodological and conceptual features of RDoC are not fully specified.
- Psychophysiology is well situated to play a key role in the RDoC era.