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Psychophysiology of threat response, paradigm shifts in psychiatry, and RDoC: Implications for genetic investigation of psychopathology

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I am pleased to have the opportunity to comment on two articles in this special issue that I expect will be widely read and highly influential. The first, by Lang, McTeague, and Bradley, describes an elegant series of experiments that methodically constructs a physiological index of fear response and analyzes its relationship to the anxiety disorders. The second, by Kozak and Cuthbert, provides further elaboration on the conceptualization, rationale for, and unfolding of the Research Domain Criteria (RDoC) initiative.

Both articles represent important refinements of prior work by two strong forces that are operating to shape the landscape of psychopathology research in the United States and abroad. Together, these articles illustrate the complementary and nuanced ways in which the RDoC framework, as intended, is both influencing research efforts by investigators in the field (in this case Lang and colleagues) and being informed in turn by the empirical findings of investigative groups. This process can be understood in figurative terms as an interactive, likely nonlinear feedback circuit akin to the circuits in the brain that RDoC is encouraging researchers to study as a basis for understanding human psychopathology. This intentional bidirectional influence between the RDoC conceptual framework and front-line investigative work can be seen in the statement from Insel et al.'s 2010 seminal article in the *American Journal of Psychiatry* describing a hypothetical study implementing a prototypical "RDoC-ian"¹ approach: "A study of fear circuitry might include all patients presenting to an anxiety clinic, with an independent variable of defense system reactivity (e.g., fear-potentiated startle) and dependent variables comprising scores of fear, distress, and symptom measures" (Insel et al., 2010, p. •).

It is clear from the content of the two target articles in question that some of the seeds for the RDoC initiative were sown in the lab of Peter Lang—including scholarly influences on, and seminal empirical work by Dr. Cuthbert himself. In what follows, I consider key features of these articles and share personal reflections called to mind by each. My foci and viewpoints are naturally shaped by own my intellectual trajectories as a former physicist and current anxiety disorders clinician and genetics researcher. In full disclosure, my current

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¹Indicative of the RDoC initiative's influence, this neologism is seeing increasingly broad use.

developmental twin study (R01 MH098055) is funded under the same National Institute of Mental Health (NIMH) program mechanism (RFA MH-12-100) as Dr. Lang's RDoC grant project.

The article by Lang et al. summarizes, integrates, and updates their lab's long-standing program of research into the psychophysiological manifestations of fear reactivity and its expression across differing forms of internalizing psychopathology. Lang et al. describe the largest and most comprehensive study to date of defensive reactivity to threat. They collected extensive data on a diverse sample of 425 treatment-seeking patients in a multidomain protocol including clinical-diagnostic, self-report, and laboratory-based measures. A key feature of their work is the inclusion of sufficiently large groups of each *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) anxiety-related disorder to permit analyses across disorders as well as within each, with the opportunity to examine more diagnostically homogeneous subgroups such as panic with versus without agoraphobia, and posttraumatic stress disorder (PTSD) resulting from single versus cumulative traumas.

In the work reported by Lang et al., "defensive reactivity" was assessed in relation to multiple conditions in the anxiety disorder spectrum through use of concurrent measures of electrodermal response, heart rate reactivity, and startle-blink potentiation. The latter two indices were combined into a composite measure that reflects a correlated physiological phenotype. A key finding of their work is evidence for an inverse relationship between this composite physiological index of defensive reactivity and severity of anxiety pathology, across a continuum ranging from simple "fear" conditions like specific phobias and single-trauma PTSD to more complex "distress" disorders such as panic, Generalized Anxiety Disorder (GAD), and cumulative-trauma PTSD. The authors then utilized latent-variable modeling to parse multiple self-report symptom, stress, and impairment scales into a three-factor structure of negative affectivity, anxious arousal, and life stress. Notably, it is the first dimensional factor, negative affectivity, that appeared to drive the inverse relationship with defensive physiology at more severe levels of pathology—owing in particular to the salient dysphoria component of the more complex distress-related disorders (cf. Yancey et al., in press). This finding can be related to evidence for differential patterns of common and specific genetic factor loadings across the anxiety disorders (Hettema, Prescott, Myers, Neale, & Kendler, 2005) and for broader internalizing phenotypes including neuroticism and major depression (Hettema, Neale, Myers, Prescott, & Kendler, 2006), as documented in multivariate twin studies by our research group. I look forward to the incorporation of functional neuroimaging assessment into Dr. Lang's research program as a means for clarifying the underlying circuit-level processes associated with this pattern of findings.

The other target article, by Kozak and Cuthbert, further explicates the background and rationale for the NIMH RDoC initiative. Prior articles introduced and attempted to "sell" the approach to a generation of researchers who were indoctrinated into a schema that relied on clinical nosology to largely define (and restrict) investigation of psychopathology. As emphasized in their current paper, RDoC itself does not propose an alternative nosology, but rather seeks to unfetter research from clinical definitions and provide an initial framework and set of constructs for reconceptualizing psychiatric research directions in line with basic

neuroscience concepts. Basic neuroscience research has, of course, progressed along its own path just fine. However, a persisting problem has been in its general independence from conceptions of psychopathology as defined in DSM (American Psychiatric Association, 2013). The RDoC framework seeks to reorient conceptions of psychopathology by encouraging infusion of neuroscientific thinking and data into such conceptions.

As one who has formulated research directions through collaborations with a diverse investigative team including psychiatrists, psychologists, and geneticists, I view myself as having been a proponent of an RDoC-like approach even before its inception. In my capacity as a clinician-scientist (and former physicist), I see no inherent contradiction between the DSM diagnostic system and RDoC-inspired mental-health research. Our descriptions of purely physical phenomena, like electromagnetic radiation, continue to benefit from explanations involving the dual conceptualization of particles and waves. Similarly, we may continue to utilize DSM conceptions to identify and treat psychiatric patients as practitioners, while striving as scientists to devise alternative “research nosologies” to better understand their biological mechanisms.

At the same time, while the DSM’s long-standing, evolved, and clinically valid descriptive approach has a firm hold on how we conceptualize psychopathology clinically (i.e., in terms of observable symptomatology), it does nothing to explain why or how psychological dysfunction arises (i.e., its mechanisms). Newtonian, relativistic, and quantum mechanical theories each have their realms of validity and applicability. The principles and equations of Newtonian theory elegantly and precisely describe physical phenomena at the levels perceivable by human senses, but they break down at minute distances, super-high speeds, or in strong gravitational fields, all of which are outside of the observation-based understanding we develop through our five senses. In a similar manner, most areas of medicine have been faced with apparent contradictions during their early development. For example, the most historically, systematically described, and clinically obvious symptoms of heart failure are manifestations of fluid excess accumulated in the lungs and extremities; clinical manifestations of diabetes were first observed in the kidneys, eyes, and other end organs that foretold nothing of mechanisms. In these fields of medicine, objectively measured biomarkers such as baseline measures of ejection fraction or glycosylated hemoglobin, or response to perturbations of the systems such as glucose tolerance tests or stress echocardiograms, have replaced age-old clinical procedures like heart sound auscultation and urine tasting.

The message of these historic examples is that if we direct our research toward the etiology of psychopathology with exclusive focus on its clinical manifestations (symptoms), or on drugs that alter symptomatology as the primary outcome measure, we can easily be “led down the garden path.” As a recent example of this, the scientific community has wasted substantial time and effort investigating genes presumed to shape the “end organ” systems on which our drugs act. However, this approach is inherently flawed: There is no reason to expect, for example, that we can discover the etiology of heart failure by investigating the organ on which the drug Lasix acts—that is, the kidneys. Similarly, a decade of candidate gene studies of the serotonin neurotransmitter system, the target of most antidepressants, has failed to identify clear genetic loci for depression or anxiety pathology.

While useful for clinical purposes, observable symptoms are not effective targets for research seeking to elucidate disease mechanisms. Other fields of health research have only begun to clearly understand the etiology and mechanisms of specific diseases; the discovery and utilization of biomarkers in these fields has only occurred in recent decades, following centuries of more primitive, clinically driven practices. Practically, it is unrealistic to expect that psychiatry will transition into a neuroscience-driven specialty in the next few decades. Most fields of medicine value and retain their age-old tradition of detecting clinical signs and symptoms while gradually incorporating the findings of basic science as they unfold. The brain is the most complex organ of the body (and perhaps the most complicated system in the known universe). It controls all other systems in the body and directs behaviors that shape the environment surrounding it. In analogy with the history of diabetes, psychopathological understanding is likely still in the era of “tasting the urine to see if it is sweet.”

To identify a biological marker like physiological defensive reactivity that relates to a previously reported, higher-level phenotypic (and genetic) cross-disorder factor structure as Lang et al. have done is heartening for researchers like me who focus on the use of psychometric methodologies to better understand the genetic basis of psychopathology. However, our celebration of this incremental step of discovery from a categorical symptom-based nosology toward a dimensional physiologically oriented approach should be tempered by the enormous distance yet to be traveled to achieve NIMH’s goal of identifying *mechanisms* of psychopathology. As a point of reference for this, one can consider the path of future genetic discovery. To identify molecular genetic mechanisms for a clinical condition, one first needs to identify a heritable phenotype via genetic epidemiological designs such as twin studies. Thus far, identifying a heritable component of emotion-modulated startle as an indicator of psychopathology has proven elusive.

Two twin studies to date have reported relevant findings. The first, conducted in 123 twin pairs examining startle response to emotional faces, estimated the heritability of overall startle magnitude at 59%–61%, but found no evidence for a significant genetic contribution to emotion-modulated startle (Anokhin, Golosheykin, & Heath, 2007). A more recent and much larger ($N = 3,323$) twin-molecular genetic study (Vaidyanathan, Malone, Miller, McGue, & Iacono, 2014) estimated heritability of overall startle reactivity across pleasant, neutral, and unpleasant foreground contexts at 37%–52% based on twin-modeling analysis, and at 49% based on genomic analysis, but found no evidence of significant genetic effects on emotional modulation of the startle response. It is not clear whether the null findings for startle modulation in these studies might reflect something intrinsic to its definition or measurement, such as the unreliability of condition-difference scores for this response measure, or other factors. Further systematic research will be needed to resolve this. However, even for a phenotypic indicator that exhibits significant twin-based heritability, no single group can collect data in a sample size of sufficient power to detect a significant association signal, given extant data indicating very small genetic effect sizes for most complex phenotypes.

Along these lines, the RDoC initiative can be valuable not only for promoting investigation of alternative phenotypes that may relate more closely to neuropathological mechanisms

and, possibly, exhibit stronger genetic signals, but also for encouraging (and indeed requiring, in the case of its Requests for Applications (RFA)-funded investigators) sharing of both phenotypic and genetic data via RDoCdb, the initiative's shared online database. This collective approach has been the basis of important advances made by the Psychiatric Genomics Consortium (PGC). By pooling data from multiple research groups to form combined samples of tens of thousands of subjects, the PGC and similar consortia have achieved successes in identifying robust susceptibility variants related to psychopathology using crude DSM-based case-control comparisons. However, as the PGC's founder, Patrick Sullivan, has acknowledged, this is a brute-force approach; its success has been quite variable for psychiatric conditions as it has been with other medical conditions. For schizophrenia—a disorder with high heritability, marked phenotypic differences from “normal controls,” and the largest pooled sample size to date—more than 100 genome-wide significant variants have been identified (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). More common, less heritable, and likely more heterogeneous disorders like depression, on the other hand, have largely resisted such efforts until only recently (CONVERGE Consortium, 2015).

With continuing inspiration (and resources) provided by RDoC, one hopes that sharing of construct-level phenotypic and genotypic data among researchers will lead to more powerful and informative association studies. However, as cautioned by Kozac and Cuthbert, the level and granularity of current RDoC-formulated constructs may still not map more strongly onto molecular genetic signals: “[P]erhaps such narrower constructs (as cognition, emotion, learning, memory, motivation, and perception) are still too broad for practical purposes, and *explananda* of even smaller grain size might be required for informative cross-level analyses of biological and psychological phenomena.” Apropos this point, it is estimated that about half of the estimated 30,000 genes in our genome are expressed in the brain, so the challenges associated with identifying genes for neural-based phenotypes will likely remain as formidable in the RDoC era as they have been under DSM.

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