Psychophysiology, 53 (2016), 367–371. Wiley Periodicals, Inc. Printed in the USA.

DOI: 10.1111/psyp.12552

COMMENTARY

Using the NIMH Research Domain Criteria (RDoC) in human and nonhuman primate research

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Abstract

In this article, we provide a commentary on Kozak and Cuthbert (2016)'s theoretical paper discussing the NIMH Research Domain Criteria (RDoC) initiative and on Latzman et al. (2016)'s empirical investigation of the RDoC negative valence systems domain in chimpanzees, conducted with experimental procedures across genetic, neurobiological, and behavioral levels of analysis. We discuss the pros and cons of the RDoC approach to research on mental illness as well as the strengths and weaknesses of the implementation of this approach in the chimpanzee study.

The field of psychophysiology has long been bedeviled by a vexing problem: The correlations between biological dependent variables and measures of psychopathology have typically been at best modest in magnitude (Martin & Paulus, 2015; see also Miller & Rockstroh, 2013, and Shankman & Gorka, 2015, for helpful discussions). For example, even the best established biological markers of major depression and schizophrenia possess inadequate levels of sensitivity and specificity to permit routine clinical use. The recently released fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013) has, for the first time, incorporated lab-physiological indicators into its diagnostic criteria for selected mental disorders. Nevertheless, this change was limited only to a subset of sleep-wake disorders (e.g., hyporcretin deficiency and polysomnography for the diagnosis of narcolepsy; Reynolds & O'Hara, 2014) and has yet to extend to any other disorders in the manual. In large measure, this is because no other psychophysiological indicators have yet to achieve sufficient validity to merit inclusion.

One might be tempted to place the lion's share of the "blame" for the low statistical associations between most psychophysiological variables and measures of mental illness on the psychophysiological variables themselves, many of which probably contain nontrivial amounts of psychometric "noise." For example, many cardiovascular indices are impure indicators of mental states, such as anxiety, owing to the fact that much of their variance is attributable to metabolic demands that are largely irrelevant to psychological processes.

At the same time, another crucial reason for these low associations is probably the questionable construct validity of many DSM categories themselves. If so, it may be unreasonable to expect psychophysiological variables to relate highly to measures of DSM-operationalized mental disorders or perhaps even to symptom dimensions that comprise these disorders. Instead, psychophysiological variables may prove to be better markers of psychobiological systems, such as threat, reward, and working memory systems, that are tied more proximally to neural circuitry. This possibility is consistent with the Research Domain Criteria (RDoC) initiative recently launched by the National Institute of Mental Health (NIMH; Insel et al., 2010).

In their well-articulated and thought-provoking article for this special issue, Kozak and Cuthbert lay out the overarching rationale for RDoC. They correctly point out that the neo-Kraepelinian approach of recent DSMs (Krueger, McGue, & Iacono, 2001), which have focused on the signs (observable indicators) and symptoms (subjective reports) of psychopathology, is marked by numerous limitations. In fairness, the DSM approach has undeniably been useful for certain purposes. For example, it has served as the primary basis for the development of empirically supported therapies for many serious mental disorders, such as major depression, panic disorder, bulimia nervosa, and posttraumatic stress disorder (Chambless & Ollendick, 2001), and has thereby enhanced the quality of mental health care.

Nevertheless, the DSM sign-symptom approach has yet to bear fruit in the form of discernable reductions in the morbidity or mortality of most major mental disorders (Insel, 2009; Pine & Liebenluft, 2015), and it may soon be approaching an asymptote in terms of scientific progress. As Kozak and Cuthbert observe, some of the shortcomings of the DSM approach are structural. The polythetic system of diagnosis that characterizes most DSM categories has generated enormous heterogeneity at the phenotypic level (see also Monroe & Anderson, 2015). As one extreme example, DSM-5 allows posttraumatic stress disorder to be diagnosed using any of

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636,120 different sign-symptom combinations (Galatzer-Levy & Bryant, 2013); the manual also allows two individuals to be diagnosed with obsessive-compulsive personality disorder without sharing even a single sign or symptom (Lilienfeld, Smith, & Watts, 2013). Although phenotypic heterogeneity does not guarantee causal heterogeneity, it almost certainly decreases the likelihood of identifying variables that can constitute "specific" or "strong' forms of etiology (Meehl, 1977). The odds that a single etiological factor can account for tens or hundreds of thousands of symptom-sign combinations, especially when these symptoms and signs are only modestly correlated, seem slim.

Although we concur with Kozak and Cuthbert's analysis of the effects of the DSM polythetic system, we are doubtful that the largely monothetic approach of DSM-III (American Psychiatric Association, 1980), which was probably associated with lower diagnostic reliability than its DSM successors (Widiger, Frances, Spitzer, & Williams, 1988), was any better in yielding etiologically homogeneous categories. Instead, the deeper problem may be that the signs and symptoms emphasized by the DSM may be too distal from the etiological systems predisposing to psychopathology to allow the manual to "carve nature at its joints."

The RDoC initiative, which appears to be a calculated gamble (Lilienfeld, 2014), is a worthwhile effort to generate an alternative to the DSM approach. As Kozak and Cuthbert note, RDoC aims to identify intermediate phenotypes, including psychophysiological variables, that hold promise as markers of psychobiological systems tied to risk for mental disorders. In so doing, RDoC seeks to establish a transdiagnostic conceptual-descriptive framework that dissolves the often arbitrary boundaries separating DSM categories. The RDoC initiative also seeks to align psychiatric diagnosis more closely with etiology.

Kozak and Cuthbert wisely emphasize that RDoC does not endorse an eliminative reductionist position that prioritizes biological variables above variables drawn from other units of analysis, such as self-report or behavioral observations. Instead, RDoC is open to variables that span multiple levels of analysis, provided that they demonstrate construct validity for one or more cells in its provisional matrix. It is perhaps concerning, however, that at least some prominent researchers apparently view RDoC differently. For example, a recent past president of the American Psychiatric Association described RDoC as a blueprint for "the creation of a new diagnostic system based upon genetics, neurobiology, brain circuits, and biomarkers" (Lieberman & Ogas, 2015, p. 284). This erroneous interpretation of RDoC as a strictly biological endeavor is by no means unique among researchers (Lilienfeld, 2014). Moving ahead, it will be crucial for the NIMH to continue to make clear that RDoC, although striving to conceptualize psychopathology in terms of dysfunctions of neural circuitry, values multiple levels of analysis when operationalizing these dysfunctions.

We are left with two main questions in the wake of Kozak and Cuthbert's comprehensive and informative exposition. First, they maintain that studies relying on self-report alone are inconsistent with the RDoC framework. Although methodological pluralism is a worthy goal, decisions regarding whether and how to use multiple measures should be guided by data. In this regard, we are left to wonder how RDoC would handle findings demonstrating that self-reports (a) were the most valid indicators of a psychobiological system in the RDoC matrix, and (b) indicators at other levels of analysis afforded little or no incremental validity above and beyond self-reports. Second, we wonder about Kozak and Cuthbert's stipulation that "the clinical phenomena to be explained in an RDoC application must be narrower than traditional diagnostic entities." Their assumption appears to be that the principal problem afflicting DSM categories is heterogeneity, that is, excessive breadth. Nevertheless, are not some DSM categories excessively narrow? For example, it seems likely that many DSM personality disorders, such as histrionic, borderline, and narcissistic personality disorders, represent only slightly different variations of one or more personality-based predispositions (Lilienfeld, Waldman, & Israel, 1994). If so, might not the most fruitful RDoC approach in certain instances entail focusing on constructs that cut across multiple DSM categories? These questions notwithstanding, we share Kozak and Cuthbert's view that RDoC is a viable and potentially valuable alternative to the DSM that warrants further research.

Animal models have provided one bedrock set of empirical foundations for the RDoC initiative, as these models have allowed researchers to map out much of the neural circuitry relevant to major psychobiological systems, such as positive and negative valence systems. Research using animal models has already operated—albeit implicitly—with principles similar to those of the RDoC framework. Clearly, when studies are conducted with an animal model of depression, schizophrenia, or autism, there is no assumption that research will be undertaken on these mental disorders as they are identified in the DSM-5—that is, because depression, schizophrenia, and autism per se do not naturally occur in animals. Rather, the rationale behind the development and use of an animal model has always been that researchers could isolate a particular component (or analogue) of a mental disorder, which naturally occurs in animals and can be studied in a simplified and highly controlled experimental situation. The elements of mental disorders that can be modeled in animals are similar to the domains and constructs of the RDoC. For example, research with an animal model of autism might focus on the genetic and neurobiological correlates of naturally occurring variation in affiliation/attachment or social communication (two constructs from the RDoC Social Processes domain), whereas research with an animal model of depression might focus on the genetic and neurobiological correlates of naturally occurring variation in the deprivation of desired social or nonsocial stimuli (similar to the construct of loss in the RDoC Negative Valence Systems domain).

Animal models have historically played an important role in research on the genetic, neuroendocrine, and neurobiological correlates of fear and anxiety. Although most of this research has involved laboratory rodents, nonhuman primates—cercopithecine monkeys and great apes in particular—provide excellent animal models for research on fear and anxiety in ecologically valid settings (Maestripieri, 2003). Like humans, cercopithecine monkeys and great apes communicate their fear to others through specific facial expressions and vocalizations (Maestripieri, 1996; Maestripieri & Wallen, 1997), whereas they often express anxiety in the form of self-directed behaviors, primarily scratching.

The study by Latzman, Young, and Hopkins in this issue effectively illustrates the use of a nonhuman primate model to investigate constructs from the RDoC Negative Valence domain across multiple units of analysis (e.g., genes, neural circuits, physiology, and behavior). Latzman and colleagues examined the genetic and neurobiological correlates of interindividual variation in scratching in response to mild stress in chimpanzees. Since it was first suggested that scratching may reflect anxiety in primate subjects (Maestripieri, Schino, Aureli, & Troisi, 1992), increased scratching behavior has been documented in a number of anxiety-eliciting situations in different species of primates. Among the most common

anxiety-eliciting situations in nonhuman primates are those in which risk of aggression from another group member is high. These include the aftermath of aggression (e.g., 1–2 min after being the victim of aggression or being in the vicinity of another individual who has been attacked); being directly approached by a higher-ranking individual; and standing, sitting, feeding, walking, or even sleeping in the vicinity of a higher-ranking group member (Castles, Whiten, & Aureli, 1999; Schino, Maestripieri, Scucchi, & Turillazzi, 1990). Monkeys and apes also scratch themselves at higher rates when they are exposed to visual or auditory stimuli from conspecifics who are highly aroused or in distress (Hopkins et al., 2006). Finally, increased scratching also occurs when primates must solve difficult or stressful cognitive tasks in the laboratory (Leavens, Aureli, Hopkins, & Hyatt, 2001).

The use of scratching as a measure of anxiety has been validated with pharmacological and physiological data: The frequency of scratching is increased by anxiogenic drugs and reduced by anxiolytics, respectively, and scratching rates are positively correlated with heart rate and cortisol levels (Troisi, 2002). Scratching has also been used to assess the well-being of nonhuman primates housed in captivity (e.g., Whitham & Wielebnowski, 2013) and in studies of responses to acute challenges, often in relation to adverse early experiences (Maestripieri, McCormack, Lindell, Higley, & Sanchez, 2006). Finally, scratching has been used to identify stable individual differences in temperament (Maestripieri, 2000). Although studies of these types have often revealed substantial interindividual variation in scratching rates, both under baseline conditions and in response to challenges, the genetic and neurobiological bases of this variation are poorly known.

Latzman and colleagues (2016) recorded scratching behavior under baseline conditions and after viewing video clips showing unfamiliar chimpanzees emitting arousal vocalizations during both affiliative and agonistic encounters as they negotiated possession and sharing of food. They focused on a polymorphism in the gene that codes for a vasopressin receptor as a potential contributor to variations in scratching under stressful conditions. Vasopressin is a neuropeptide similar to oxytocin that has been implicated in the regulation of social behavior and social attachments in mammals. The polymorphism in question involves the promoter region of the vasopressin V1a receptor gene (AVPR1A), in which there is a repeat region known as RS3. In chimpanzees, there are two known alleles of the AVPR1A gene, one that possesses a duplicated region in RS3 known as DupB (DupB+) and one that lacks such a region (Dup B–). **Latzman and colleagues (2016)** focused on this polymorphism because a previous study from the same research group found it to be associated with certain aspects of chimpanzee personality. Specifically, Hopkins, Donaldson, and Young (2012) found that among chimpanzees possessing one copy of the long allele (DupB+/–) of the AVPR1A gene, males scored higher on Dominance and lower on Conscientiousness than females, whereas gender differences in personality were not evident among chimpanzees homozygous for the short allele (DupB–/–). Additionally, in humans, AVPR1A promoter polymorphisms have been found to be associated with variations in Novelty Seeking, Harm Avoidance, and Reward Dependence, which in turn are related to Neuroticism and Extraversion (Latzman, Hopkins, Keebaugh, & Young, 2014).

In the current work, **Latzman and colleagues (2016)** first compared the scratching responses to mild stress of males and females possessing different AVPR1A alleles (DupB–/– and DupB–/+), and investigated brain areas that differed in gray matter (GM) as a function of the AVPR1A genotype. They then evaluated whether these genotype-related differences in GM covaried with individual differences in scratching behavior. They found that chimpanzees scratched themselves significantly more after viewing the stressful/arousing video compared with the baseline condition. They found no main effect of the AVPR1A genotype on scratching behavior, but did find a significant interaction between genotype and sex such that among males, DupB+/– individuals showed significantly higher rates of scratching than DupB–/– individuals. In contrast, for females, DupB+/– individuals scratched significantly less than DupB–/– apes. However, the extent to which this effect was accounted for by differences in baseline scratching rates versus differences in scratching rates in response to stress remained unclear. The interpretation of the results was also complicated by the fact that the DupB–/+ males were high ranking whereas the DupB–/+ females were low ranking. Thus, seeing and hearing unfamiliar chimpanzees squabble and negotiate over food might have evoked different emotional responses in chimpanzees depending on their rank, and rank-related differences in scratching responses may have contributed to the statistical interaction between the AVPR1A genotype and sex. In future research, it will be important to ascertain whether the same pattern of findings observed by Latzman and colleagues holds up even within ranks.

Variation in GM distribution in the brain was assessed using voxel-based morphometry (VBM). The VBM analyses revealed significant differences between DupB–/– and DupB–/+ apes in 12 distinct brain regions, with the largest clusters evident within the frontal lobe. When separate correlations between scratching and GM intensity values for the 12 VBM-identified brain regions were computed for subjects of each sex, significant sex differences in magnitudes of association between scratching rate and mean GM intensity value were found for 6 anatomic clusters, corresponding to the right central sulcus, right superior precentral sulcus/gyrus, left dorsal lateral prefrontal cortex (PFC), left precentral inferior sulcus, left ascending limb of the cingulate sulcus, and the right anterior insula, respectively (some of these regions, such as the PFC and the insula, play a role in the appraisal of negative emotions). Correlations in each of these instances were in opposing directions for males and females: For males, increased scratching rates were associated with lower GM values, whereas for females increased scratching rates were associated with higher GM values. Again, despite problems of interpretation due to the confounding effect of rank, these findings suggest that the observed associations between AVPR1A variation and scratching behavior may be attributable in part to gene expression associated with the presence or absence of the DupB region in the brain.

The contextual occurrence of scratching in chimpanzees and other nonhuman primates makes this variable relevant to at least three of five constructs situated within the RDoC Negative Valence Systems domain: response to acute threat, potential harm, and frustrative nonreward (**Kozak & Cuthbert, 2016**). Studying the occurrence of scratching in these contexts with the approach exemplified by Latzman et al.'s study can therefore shed new light on the genetic and neurobiological correlates of these affect-related constructs in nonhuman primates and humans. In turn, a better understanding of the biological substrates of the response to acute threat and potential harm in nonhuman primates can enhance our knowledge of the etiology of primate personality, both normal and abnormal (Gosling, Lilienfeld, & Marino, 2003), of individual differences in different aspects of social behavior, including their pathological manifestations (e.g., hyperaggressiveness toward

conspecifics, parental abuse or neglect of offspring; Saltzman & Maestripieri, 2011), of the effects of adverse early life experience on subsequent sociobehavioral and neuroendocrine functioning (Parker & Maestripieri, 2011), and of the effects of psychosocial stress on health, reproduction, and aging (Maestripieri & Hoffman, 2011).

One other important direction in this comparative research program will be to expand the nomological network of correlates of manifest indicators of anxiety beyond scratching behavior. Although Latzman et al. make a compelling case that scratching constitutes a promising candidate marker of anxiety in chimpanzees, it is likely to be limited in several respects. Behaviorists routinely distinguish between the function and form (topography) of a behavior, noting that the same psychological function can express itself in diverse behaviors, and that diverse psychological functions can express themselves in similar or identical behaviors (Carr, 1993). Developmental psychologists are well aware of these ambiguities, referring to the former process as multifinality and the latter as equifinality (Cicchetti & Rogosch, 1996). In this regard, it is plausible that scratching may sometimes reflect psychological states other than anxiety, such as boredom. For example, some human stereotypies, such as trichotillomania (compulsive hair pulling), are commonly associated not only with anxiety, but also with boredom, frustration, and perhaps other negative affective states (Diefenbach, Mouton-Odum, & Stanley, 2002). Conversely, it also plausible that nonhuman primates sometimes express their anxiety via displacement behaviors other than scratching, such as yawning and self-grooming (Baker & Aureli, 1997).

Hence, consistent with the RDoC emphasis on methodological pluralism and, more broadly, with the well-established principle that essentially all behaviors are at best fallible indicators of their respective constructs (Epstein & O'Brien, 1985; Lilienfeld, 2014), it will be important for nonhuman primate researchers to combine scratching with other candidate behavioral indicators of anxiety to provide a more comprehensive characterization of the Negative Valence system. If sample sizes are sufficient, such work is especially likely to be useful in latent variable models that combine indicators of anxiety across multiple levels of analysis, including the behavioral and psychophysiological (see Patrick et al., 2013, for an illustration from the human literature).

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