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# Transdiagnostic dimensions of anxiety: Neural mechanisms, executive functions, and new directions

Paul B. Sharp [a,*], Gregory A. Miller [a,b], Wendy Heller [a]

[a] University of Illinois Champaign-Urbana, United States
[b] University of California Los Angeles, United States

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ABSTRACT

Converging neuroscientific and psychological evidence points to several transdiagnostic factors that cut across DSM-defined disorders, which both affect and are affected by executive dysfunction. Two of these factors, anxious apprehension and anxious arousal, have helped bridge the gap between psychological and neurobiological models of anxiety. The present integration of diverse findings advances an understanding of the relationships between these transdiagnostic anxiety dimensions, their interactions with each other and executive function, and their neural mechanisms. Additionally, a discussion is provided concerning how these constructs fit within the Research Domain Criteria (RDoC) matrix developed by the National Institutes of Mental Health and how they relate to other anxiety constructs studied with different methods and at other units of analysis. Suggestions for future research are offered, including how to (1) improve measurement and delineation of these constructs, (2) use new neuroimaging methods and theoretical approaches of how the brain functions to build neural mechanistic models of these constructs, and (3) advance understanding of the relationships of these constructs to diverse emotional phenomena and executive functions.



## 1. Introduction: transdiagnostic constructs in psychopathology

Since Paul Meehl's (1962) discussion of schizotaxia, clinical scientists have been faced with an imperative to uncover a specific, sine qua non etiology for any of the numerous forms of mental illness. For the past six decades, however, little progress has been made, due in part to a stagnant nosology. That nosology, the Diagnostic and Statistical Manual (DSM: now in its 5th edition), defines disorders based on how symptoms covary within a clinical population. One is diagnosed with a disorder only when meeting benchmarks (determined by a board of experts appointed by the American Psychiatric Association) for number and duration of symptoms. Almost 30 years after his seminal paper, Meehl (1989) identified a key problem that undermines this nosology today: the inability to differentiate between identical symptom presentations that are caused by two different etiologies (and likely have different psychobiological mechanisms). Conversely, the DSM may also separate disorders with identical etiologies into different categorical taxa simply because their manifest symptoms differ. In a recent theoretical report, Berenbaum (2013) described how the creation of this nosology was justified by a tacit, weak theory (despite its claim to be atheoretical), which is that latent disorder constructs (the hypothesized, underlying diseases) should be defined solely by patterns of symptom covariation.

In response to these shortcomings, and the widening gap between the DSM and contemporary neuroscientific and psychological research on psychopathology, the National Institute of Mental Health developed the Research Domain Criteria (RDoC) initiative (Cuthbert and Kozak, 2013; Insel and Cuthbert, 2015; Insel et al., 2010). This enterprise promotes research in the biological and psychological sciences that can help reconstruct mental health nosology, with an explicit emphasis on transdiagnostic components of psychopathology. These components are conceptualized as primarily dimensional (although categorical threshold cut-offs may be warranted, for example for bimodal distributions), and are presumed to reflect phenomena that can and should be described and measured from both biological and psychological perspectives. For example, anxious arousal, a type of anxiety that can be present in individuals with various DSM disorders, can be measured dimensionally via self-report and distinguished from other dimensions of anxiety behaviorally and neurobiologically (Engels et al., 2007; Heller and Nitschke, 1998; Nitschke et al., 1999; Silton et al., 2011).

Neurobiological evidence suggests that many types of psychological dysfunction are "continuous with normalcy," a view largely incompatible with categorically-based DSM disorders (Hyman, 2010; Sanislow et al., 2010). Conversely, transdiagnostic factors common to multiple DSM taxa (e.g., anxious apprehension and anxious arousal) have robust, particular relationships with neurobiological activity in morbid and at-risk populations (Buckholtz and Meyer-Lindenberg, 2012; Engels et al., 2007; Herrington et al., 2010; Silton et al., 2011; Yehuda and Ledoux, 2007). Thus, transdiagnostic constructs can measure the full

* Corresponding author.
*E-mail address:* psharp3@illinois.edu (P.B. Sharp).

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spectra of severity within a dimensionally-conceptualized psychological dysfunction and are more highly correlated with measurements of neurobiological dysfunction. Additionally, these constructs may help elucidate biological and psychological antecedents to disease states as younger, pre-morbid groups may present with less severe forms of psychopathology. The identification and explication of such transdiagnostic constructs promises to build an etiologically-based nosology that would foster the clinical use of dimensional measurements, thereby improving prevention, diagnosis, and treatment of psychopathology.

RDoC has organized these transdiagnostic factors in a comprehensive matrix that is intended to guide research and eventually inform a future classification system. The domains are examples of a more extensive map of psychopathology the literature will eventually develop, rather than exhaustive. The rows of the matrix consist of five domains (e.g., negative valence systems) each of which contains several constructs (e.g., sustained threat, potential threat), which themselves may contain subconstructs (e.g., for approach motivation (construct) reward valuation is a subconstruct; see Fig. 2). The columns comprise several *units* (not levels, which may imply naively reductionistic or hierarchical relationships; Miller, 2010) of analysis that include genes, molecules, cells, circuits, physiology, behavior, and self-report (Morris and Cuthbert, 2012).

The present article reviews how transdiagnostic factors that are commonly found in DSM-defined anxiety and mood disorders have helped to integrate psychological and neurobiological models of pathological anxiety. Issues that are addressed include: (1) how best to conceptualize and measure anxious apprehension and anxious arousal, (2) how these constructs may relate to various executive dysfunctions, (3) how an integration of findings on associated neural mechanisms informs an understanding of the neural and psychological mechanisms giving rise to these constructs, (4) where to appropriately place these constructs within the RDoC matrix, and (5) how to empirically test hypotheses offered below in future research.

## 2. RDoC: dimensional and categorical constructs

RDoC remains agnostic in terms of how psychopathology should be conceptualized, remaining open to traditional or new categorical constructs while encouraging research using dimensional constructs. The present review argues that two transdiagnostic types of anxiety are best conceptualized dimensionally, given the empirical coherence across psychological and neurobiological domains for these constructs. This contention does not assume either (1) that RDoC will prioritize psychological or biological constructs or (2) that mechanistic models relating psychological phenomena to neurobiological phenomena should favor dimensionally-conceptualized constructs over categorically-conceptualized constructs.

The main objective of RDoC is to bridge the gap between biological and psychological sciences in order to refine the delineation of psychological constructs relevant to psychopathology and the relationships among them, and to improve the effectiveness and availability of psychological and biological treatments. Even though to date many categorically-defined DSM disorders have not cohered with neurobiological data, it may be because the categories themselves were poorly delineated, not because all psychopathological constructs are best conceptualized dimensionally.

Additionally, it should not be assumed that all neurobiological mechanisms are best represented with dimensional constructs. Although we may measure activity and structure of neural mechanisms dimensionally, the physical activity of the mechanism may behave qualitatively differently at critical points along the continuum of activity or structure or may follow threshold functions that can better be understood categorically. An example of this is Dehaene's work on neural mechanisms implementing consciousness. Within mechanisms that support consciousness, a distinctly different activity pattern distinguishes conscious from unconscious states (Dehaene et al., 2014). Thus, both the neurobiological mechanisms implementing consciousness and the conceptually yoked psychological constructs may be best conceptualized categorically.

Recent work in clinical neuroscience and psychology has also shed light on the possibility of hybrid models of psychopathology that include subordinate categorical and dimensional constructs (Oathes et al., 2015; Pickles and Angold, 2003). For example, Elton et al. (2014) tested competing categorical and dimensional models of ADHD. Dimensionally-conceptualized constructs measured with self-report data correlated with resting-state fMRI activity in certain functional networks a priori defined, and categorical differences between healthy controls and those with ADHD diagnoses explained differences in activity in other functional networks. Thus, the variation in neural activity could not be explained by a single conceptualization of ADHD as either dimensional or categorical.

The process of delineating psychological phenomena and the putative neural mechanisms that instantiate them requires an iterative testing of hypotheses across psychological and biological domains and revising of constructs and theory when the data do not uphold a priori predictions. The goal of such work is to achieve generative coherence across psychological and neurobiological domains. As knowledge accumulates regarding how the brain functions, the standards by which we evaluate how well we have achieved such coherence will undoubtedly be more rigorous.

## 3. Transdiagnostic anxiety constructs: background and current issues

### 3.1. Past and current conceptualizations

To clarify some potential misconceptions in previous literature, we now define anxious apprehension and anxious arousal as traits that describe psychologically and neurally separable dimensions of anxiety. Anxious apprehension is marked by a propensity to engage in negative, repetitive thinking (Burdwood et al., in revision; Ruscio et al., 2001), which can also be thought of as an enduring pattern of state worry. Anxious arousal consists of an enduring pattern of hypervigilance, sympathetic nervous system hyperarousal to mild stressors (Nitschke et al., 1999), and state fear. These are working definitions, as past research has frequently conflated state and trait aspects of anxiety, and more empirical work is needed to verify the stability of these traits over time and their relationship with their state counterparts. Despite many studies tacitly treating anxious apprehension and anxious arousal as trait constructs, they have often defined these constructs as synonymous with state phenomena. This article offers a resolution of this lack of clarity.

Heller et al. (1995, 1997), Heller and Nitschke (1998), and Keller et al. (2000) first distinguished anxious apprehension and anxious arousal from each other and from anhedonic depression to explain mixed findings in neuropsychological, neuroimaging, and other psychophysiological studies. Their distinction between anxiety dimensions borrowed elements from two separate frameworks of anxiety: anxious apprehension from the fundamental process of generalized anxiety disorder (Barlow, 1991) and anxious arousal from the tripartite model of anxiety and depression (Clark and Watson, 1991; Watson et al., 1995). It should be noted that, since both anxious apprehension and anxious arousal fall under the superordinate construct of anxiety, the two constructs share variance. Further work is needed to characterize common functions present in both dimensions of anxiety and their likely (partially) shared neurobiological mechanism(s).

### 3.2. State vs. trait anxiety

Although some studies (e.g., Heller et al., 1997) have used descriptors such as “worry” as synonymous with anxious apprehension and “panic” or “fear” as synonymous with anxious arousal, these terms

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