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

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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

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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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better represent state anxiety and do not sufficiently characterize the neuropsychological patterns that comprise anxious apprehension and anxious arousal. Thus, we now discriminate trait anxiety dimensions (anxious apprehension and anxious arousal) from state anxiety phenomena (worry or panic/fear). Although many studies have acknowledged distinctions among state and trait anxiety constructs, few have distinguished anxious apprehension from anxious arousal, and when they do, they do not differentiate state and trait constructs. Defining anxious apprehension and anxious arousal specifically as traits is a refinement of our conceptualization of these constructs.

Worry, panic, or fear experienced in an acutely threatening situation is an emotional process that may be adaptive and occurs regardless of an individual's personality. Empirically, state anxiety has been associated with better performance (an adaptive response) on an executive function task, unlike trait anxiety, which correlated with poorer performance (Ursache and Raver, 2014).

Empirical work suggests that anxious apprehension and anxious arousal are better conceptualized as traits in resting-state fMRI and EEG paradigms (Burdwood et al., in revision; Nitschke et al., 1999) as well as in emotional challenge tasks (Engels et al., 2007; Heller et al., 1997). Given that (1) anxious apprehension and anxious arousal were assessed via self-report several weeks before the administration of the aforementioned experimental paradigms and (2) the aforementioned paradigms lacked experimental manipulation of worry and fear, one would not expect a priori hypotheses (which operationalized state worry and fear based on associated neural mechanisms) to hold if self-report measures were strictly measures of state constructs. In other words, it is highly unlikely that individuals experiencing a certain state at time 1 (several weeks before experiment) are in the same state at some later time 2 (time of experiment) in the absence of either (A) experimental induction of such a state or (B) that individual being predisposed to experience such a state at a much greater rate than most individuals (having a trait for the given state). That (A) was not part of any prior experiment, we reason that (B) accounts for the group differences observed in previous experiments; that is, anxious apprehension and anxious arousal questionnaires measure trait constructs.

Anxious apprehension as measured by the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) has been shown to have high test–retest reliability in a university (Meyer et al., 1990) and a community sample (Rodríguez-Biglieri and Vetere, 2011). Similarly, anxious arousal has been shown to be a stable trait in at least one study (Sass et al., 2010). More research is needed to differentiate state fear/panic and trait anxious arousal via enhanced self-report measures and assessment of the test–retest reliability of measures of anxious arousal.

Previous studies have also failed to distinguish fear and anxious arousal (Heller et al., 1997; Dien, 1999), although this is mainly due to a lack of an explicit discussion of anxious arousal as a trait.[1] As mentioned above, past work has treated anxious arousal as a trait implicitly (e.g., Nitschke et al., 1999; Engels et al., 2007, 2010; Spielberg et al., 2013; Silton et al., 2011) or has referred to anxious arousal by a different name (e.g., "trait fearfulness" in Dien, 1999). In essence, it is proposed here that anxious arousal be thought of as a propensity to experience state fear more often and more easily (a lower threshold), with a temporally stable pattern of hypervigilance between acute fear responses. Although the relationship between fear and panic is not well-articulated, high levels of (trait) anxious arousal may be predictive of or accompanied by (state) panic, which can be viewed as involving an intense and prolonged fear state.[2] This definition was formulated inductively from available literature (e.g., Engels et al., 2007) and requires empirical validation.

Other psychological constructs may also characterize anxious arousal. For example, although future-oriented thinking is often conceived of as characteristic of anxious apprehension due to increased worry, heightened attentional anticipation or expectation of threat and readiness to respond to threat could be a type of future orientation that would characterize anxious arousal. Some accounts of anxiety (Bradley, 2009; Lang et al., 1990; Somerville et al., 2013; Watson et al., 1995; Poulos et al., 2009) that have focused on the sympathetic arousal symptoms that characterizes anxious arousal have articulated an accompanying trait of "defensive preparedness", which could be a candidate for such a future-focused construct.

In labeling anxious apprehension and anxious arousal as traits, we use the criteria used in the sociogenomic model of personality to define states and traits (Roberts, 2009). State constructs are defined as thoughts, feelings, and behaviors that are transient and circumscribed by their real-time instantiation in the individual (albeit for an unspecified, temporal range), whereas traits are enduring patterns (occur more than once, although presumably, quite frequently or on a sustained basis) of a specific constellation of states evoked by similar contexts. In other words, "it is the repetitions in states that capture what we mean by a trait" (Roberts, 2009). States are necessary but not sufficient components of traits; in this model, it is the temporal stability (unspecified) of a unique grouping of states that differentiates psychological traits from states.

For example, one instance in which an individual experiences extreme panic (a state) during an earthquake is not sufficient to describe the individual as having high anxious arousal (a trait). Similarly, if an individual is shown to have sympathetic hyperarousal to mildly threatening stimuli (implied greater fear/panic) during one task, this finding is insufficient to establish trait anxiety. To label someone as having high anxious apprehension and/or anxious arousal, it must be demonstrated that the manifest, observable indicators of these traits are stable across time and similar contexts.

Although it is clear that instances of worry and panic (states) are conceptually different from anxious apprehension and anxious arousal (traits), it is unclear what processes lead to these trait patterns of anxiety. Two critical questions are: (1) what are the psychological states to which anxious apprehension and anxious arousal predispose? and (2) what are the mechanisms that give rise to these stable patterns of anxiety?

If only one psychological state comprises a trait, such as worry and anxious apprehension, respectively, it is theoretically challenging to articulate under what circumstances a pattern of occurrence of the state (in frequency or intensity or both) should be defined as a trait. However, if the trait is defined by a pattern of different states, then by definition, the trait categorically differs from any constituent state. Anxious apprehension could be operationalized solely as an extreme and stable pattern of worry (as indicated by self-reported answers on a selection of questionnaires: Ruscio et al., 2001). However, it might be hypothesized that additional constructs, such as executive inflexibility (e.g., impairment in shifting, for review see Snyder et al., 2014), are important components of anxious apprehension. Such a conceptualization might posit that a breakdown in executive flexibility interacting with a rise in negatively-valenced/high-arousal affect sustains a pattern of negative, repetitive thinking (see Crocker et al., 2013; Gotlib and Joormann, 2010) leading to a persistent pattern that constitutes anxious apprehension. This conceptualization borrows from psychological constructionist theory (e.g., Russell, 2003), which posits that basic

[1] Fear has been distinguished from anxiety (Davis et al., 2010; Hofmann, Ellard and Siegle, 2012). Fear is defined as a basic emotion that is an adaptive response to threat marked by quick, automatic onset, brief duration, and sympathetic arousal (Ekman, 1992). Anxiety has been described as a "future-focused cognitive association that connects basic emotions (such as fear) to events, meanings and responses" (Hofmann et al., 2012) which would typically be consistent with anxious apprehension but could also possibly apply to anxious arousal, depending on the way future-focused cognition is defined.

[2] This distinction is supported by the National Institutes of Mental Health's definition of panic disorder, in which they state, "Panic Disorder: When Fear Overwhelms." (http://www.nimh.nih.gov/health/publications/panic-disorder-when-fear-overwhelms/index.shtml).

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psychological processes such as executive function and core affect (defined by Russell, 2003, as a "single integral blend of…valence and arousal") interact in specific ways to give rise to most psychological phenomena (e.g., anxious apprehension). Rather than investigating causal relationships demonstrating how different phenomena may affect each other, constructionist models of psychological and biological phenomena are concerned with explicating mechanisms of emergent phenomena (see Fig. 1).

We use Herschbach and Bechtel's (2015) definition of mechanism: "A mechanism comprises an organized set of parts performing different operations whose orchestrated functioning results in the phenomenon of interest…. A phenomenon [such as anxious apprehension] and its mechanism [interplay of core affect and executive flexibility] are not separate entities, with the mechanism causing the phenomenon. Rather, the activity of the mechanism is said to constitute or realize the phenomenon of interest." Although oversimplified, the constructionist diagram (our Fig. 1) is mechanistic because it describes a higher-level emergent phenomenon (anxious apprehension) and its lower-level component parts (in this case, psychological processes that interact). This mechanistic description leaves the dynamics of the mechanism (activity between core affect and executive inflexibility) unspecified, so this description is intended to be generative rather than explanatory. The traditional causal models depicted in Fig. 1 are not mechanistic because none describes how anxious apprehension comes about. That is, the causal models do not describe the lower order phenomena (objects and/or processes) that constitute anxious apprehension. Rather, they describe two discrete phenomena that are related to each other in a linear, causal way.

Importantly, in Herschbach & Bechtel's definition mechanisms do not cause the resultant phenomenon. While the issue of causality in mechanistic descriptions is debated in philosophy of science literature, we contend that mechanistic descriptions need not imply causality. In mechanistic descriptions in the biological and psychological sciences, interlevel causation is most problematic, and considered by some to be incoherent (for example, neural mechanisms causing anxious apprehension or vice versa; for a more thorough discussion on causation and levels in mechanistic explanation, see Craver and Bechtel, 2007; Miller, 2010). A goal of mechanistic descriptions is to find patterns among the activity of component parts that constitute a phenomenon in order to better understand 'functional' and 'dysfunctional' states of a phenomenon and to better predict how interventions on the mechanism can shift the phenomenon into a functional state. This mechanistic model may inform psychological measures of and clinical neuroscience paradigms examining anxious apprehension that could provide new insights into the relationship between worry and anxious apprehension, and executive function and anxious apprehension.

Future research should examine whether anxious apprehension and/or anxious arousal (1) are more prolonged, extreme, and/or frequent instances of normative worry and fear/panic, (2) are amalgams of multiple states (worry *and* executive inflexibility; fear *and* hypervigilance) comprising unique patterns of states that categorically differ from worry and fear/panic, and (3) are as stable as other well-studied psychological traits. Further explication of the component constructs and their interactions (the psychological mechanisms) that constitute anxious apprehension and anxious arousal will shed light on the relations between anxious apprehension and worry and between anxious arousal and fear/panic.

3.3. Executive function impairments

As evidence from clinical neuroscience and psychology has accumulated regarding the interactions among executive functions and dimensions of anxiety (e.g., Crocker et al., 2013; Levin et al., 2007; Snyder et al., 2014), it has become clear that deficits in executive function capacities can be predisposing risk factors, maintaining components, and/or negative consequences of anxiety disorders. Executive function is a broad term encompassing many cognitive processes, which in general coordinate behavior adaptively toward a goal (Banich, 2009). These processes allow individuals to successfully "break out of habits, make decisions and evaluate risks, plan for the future, prioritize and sequence our actions, and cope with novel situations" (Snyder et al., 2014).

Two models of executive function have been particularly well-studied in relation to both DSM-defined anxiety disorders and transdiagnostic dimensions of anxiety. The first is the *unity/diversity model* (Miyake et al., 2000), which originally parsed executive function into three components: updating working memory, shifting between task demands, and inhibition. Updating is defined as replacing information that is no longer germane to the task with new, relevant information. Flexibility enables shifting, allowing quick transitions between alternative task rules and representations. Inhibition refers to the capacity to override prepotent responses, although recent studies suggest that a common executive function mechanism subsumes this function, as inhibition failed to add unique variance over and above common executive function (Miyake and Friedman, 2012).

The second model of executive function is Banich's cascade-of-control framework (for review, see Banich, 2009; Banich et al., 2009), which describes a temporal sequence of neurobiological mechanisms that may implement components of executive function. Key regions in this sequence include posterior dorsolateral prefrontal cortex (DLPFC), mid-DLPFC, posterior dorsal anterior cingulate cortex (dACC), parietal cortex, and a more rostral region of the dACC, which are involved in psychological processes such as biasing attention to goal-relevant stimuli, selecting appropriate responses, and evaluating those responses. Empirical work testing this model has supported the temporal sequence of activity among these regions in frontal and parietal cortex and also their disruptions in anxiety and depression and relevant constructs

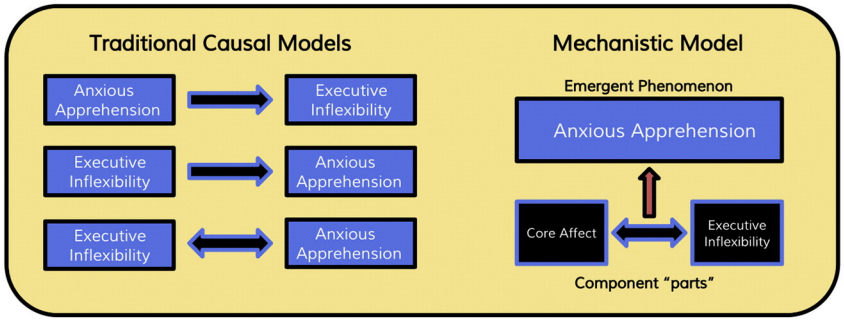

Fig. 1. Comparison of possible relationships between anxious apprehension and executive function. On the left are traditional ways of thinking about how anxious apprehension relates to executive function. Most construe these as separate phenomena, in which either anxious apprehension causes executive inflexibility (top), executive inflexibility causes anxious apprehension (middle), or both constructs influence each other (bottom). On the right, anxious apprehension is conceptualized as an emergent phenomenon that arises from dynamical interactions (oversimplified with a bidirectional arrow) of executive inflexibility and core affect, which are constituent psychological elements that are thought to be implemented by basic functional brain networks such as the frontoparietal network and limbic circuit, respectively (e.g., Barrett and Russell, 2015).

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(Banich et al., 2009; Crocker et al., 2012; Silton et al., 2011: see Section 5.1, Neural correlates of anxious apprehension, for more detailed discussion).

Anxious apprehension and anxious arousal are both associated with self-reported and overt performance deficits in executive function and are predictive of distinct neural profiles that are hypothesized to disrupt executive function in particular ways (Engels et al., 2007; Nitschke et al., 1999). Broadly speaking, anxious apprehension and anxious arousal have been associated with poorer behavioral performance and less efficiency (Eysenck et al., 2007; Silton et al., 2011; Warren et al., 2013) on tasks requiring attentional control. More specifically, anxious apprehension tends to correlate more with shifting impairments (Snyder et al., 2014) and anxious arousal more with dysfunctions in updating and inhibition (Warren, Heller, and Miller in prep). Additionally, these anxiety constructs correlate with distinct neural mechanisms that may disrupt specific executive functions e.g., for anxious apprehension, there is a negative correlation between neural activity in Broca's area, which putatively implements aspects of worry, and activity in DLPFC, which putatively implements top-down control of attention (Banich et al., 2009; Spielberg et al., 2013). However, further inquiry is needed to identify the mechanisms by which these trait anxiety dimensions differentially affect diverse executive functions. In studies reviewed below anxious apprehension is conceptualized as a separate phenomenon from executive flexibility (as depicted on the left side of Fig. 1). As the mechanisms (psychological and biological) giving rise to anxious apprehension and anxious arousal become clearer, such knowledge may help explicate the pathogenesis of various forms of anxiety and inform treatment strategies for individuals with different profiles of these transdiagnostic anxiety dimensions and executive function deficits.

4. Problems when treating anxiety as a unitary construct

Research on the neural correlates of anxiety was stymied entering the so-called "Decade of the Brain" (1990–2000) due to inconsistent and sometimes conflicting findings across studies (for review, see Heller and Nitschke, 1998; Baxter et al., 1988; Reiman et al., 1989). Psychological models of anxiety were not adequately integrated into neuroscience research to reflect the diverse pattern of results, a long-standing problem (Lang, 1968, 1978; Kozak and Miller, 1982) with the consequence that functional relationships between brain activity and symptoms were not well-articulated. Theoretical progress was required to resolve the gap between neurobiological evidence, self-report, and clinical data (for further discussion, see Miller and Kozak, 1993).

To this end, transdiagnostic constructs have been particularly useful for linking psychophysiological data and psychological models of anxiety. Heller and Nitschke (1998) and Nitschke et al. (2000) outlined reasons for parsing the unitary view of anxiety into two constructs and distinguishing them from anhedonic depression in order to resolve apparently contradictory findings in EEG and fMRI studies examining neural correlates of anxiety. Specifically, studies had found both heightened right-lateralized activity and heightened left-lateralized activity across a range of DSM anxiety disorders including generalized anxiety disorder, panic disorder, social anxiety disorder, and obsessive–compulsive disorder. These discrepant results were clarified by distinguishing anxious apprehension and anxious arousal, with anxious apprehension associated with greater left-lateralized activity and anxious arousal with greater right-lateralized activity (Heller et al., 1997; Nitschke et al., 1999). Subsequent work contributed to the development of models that distinguished more specific brain regions and networks as a function of anxiety dimension (e.g., Engels et al., 2007, 2010).

Based on these findings, results of studies that do not account for a distinction between anxious apprehension and anxious arousal when examining anxiety in relation to other constructs (e.g., executive function) may be confounded. For example, a meta-analysis examining the relationship between anxiety defined as a unitary construct and executive function found a small relationship with error-related monitoring (evidenced by greater amplitude of the error-related negativity (ERN), a specific component in event-related brain potential studies: Moser et al., 2013). When using the more specifically-defined and theoretically relevant construct of anxious apprehension in relation to error monitoring, effect size was three times higher.

5. Neural mechanisms associated with transdiagnostic anxiety constructs

Anxious apprehension and anxious arousal are dissociable constructs when measured psychometrically and neurobiologically via multiple methods and task paradigms. In particular, these dimensions have been studied in relation to tasks probing executive function, in which high levels of these anxiety dimensions are differentially associated with executive function impairments observed in both neural dysfunction and concomitant maladaptive behavior (e.g., Silton et al., 2011).

Studies reviewed below have found evidence for reliable biomarkers that are indicative of anxious apprehension and anxious arousal. However, only a few studies have confirmed that these dimensions of anxiety predict behavioral performance in the context of mildly arousing affective distractors and cognitive load during executive function tasks. Future studies should investigate these constructs in clinical neuroscience paradigms that use more arousing affective contexts or more challenging executive function tasks. Current models suggest that measures of these transdiagnostic anxiety dimensions would correlate with behavioral errors in ecologically-valid, sufficiently arousing experimental contexts. For example, mechanisms supporting compensatory responses to initial failures in top-down control of attention for those high in anxious apprehension are posited to break down in more challenging tasks that include higher cognitive load and/or more arousing affective distractors (Moser et al., 2013; Silton et al., 2011).

Studies reviewed below manipulate variables that some may categorize as either affective (e.g., valence of word stimuli) or cognitive (e.g., inhibiting a prepotent response on a Stroop task). Although many consider these terms (affective, cognitive) useful to distinguish psychological and biological phenomena, this review remains agnostic about the ontology or utility of this distinction psychologically and biologically, in line with available literature in clinical neuroscience and psychology (Barrett and Russell, 2015; Duncan and Barrett, 2007; Miller, 1996, 2010; Miller and Keller, 2000; Pessoa, 2008; Russell, 2003). In the context of negatively-valenced stimuli, the psychological processing that is instantiated in the biology is likely a combination of traditionally-defined affective changes (change in core affect) and traditionally-defined cognitive changes (re-orientation of current goals and subsequent allocation of attentional resources).

5.1. Neural correlates of anxious apprehension

Anxious apprehension is marked by a persistent pattern of negative, repetitive thinking about perceived threats that can be proximal or distal in time (Engels et al., 2007). Evidence suggests that anxious apprehension is primarily implemented in neural circuits that specialize in language production and verbal working memory (e.g., Nitschke et al., 1999, 2000; Engels et al., 2007, 2010).

Anxious apprehension was first found to have a distinct neurobiological signature using EEG (Heller et al., 1997). An fMRI study was able to localize this left-lateralized activity more specifically to the left inferior frontal gyrus (Broca's area, related to speech production, Engels et al., 2007). In this between-subjects design, a significant difference in left IFG activation occurred only when comparing negatively valenced stimuli to neutral stimuli. This aligns with an a priori hypothesis that anxious apprehensive individuals have automatic biases toward negative stimuli and would be more likely to process negative words despite their irrelevance to the task.

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A limitation of Engels et al. (2007) that is yet to be resolved (though see discussion below of Spielberg et al., 2013) is the lack of experimental manipulation of worry, which could elucidate whether hyperactivity in Broca's area reflects maladaptive processing of task-irrelevant information. An alternative psychological function that could be implemented by Broca's area during this executive function task is the articulatory rehearsal of task rules, which has been shown to increase activity in Broca's area during verbal working memory tasks (Paulesu et al., 1993). Both are task-relevant processes that are difficult to distinguish on the basis of behavioral performance. Future studies are needed to clarify this interpretation issue, to ensure that studies of anxious apprehension are not equating data (neural hyperactivity) with construct (worry) (Kozak and Miller, 1982). This may be resolved by assessing self-reported worry *during* tasks, or inducing worry during an executive function task and examining its interactive effects with self-reported anxious apprehension. Additionally, resting-state functional MRI may shed light on the tendency for individuals high in anxious apprehension to have increased functional connectivity between Broca's area and the default-mode network, bolstering confidence that this hyperactivity is in fact reflective of worrying (Burdwood et al., in revision). Future studies should also assess anxious apprehension in the context of more challenging executive function tasks and/or more arousing, threatening stimuli. If activation in Broca's area is predictive of behavioral performance in these paradigms, one could be more confident that this hyperactivity reflects dysfunctional processing of task-irrelevant information.

Studies investigating error-related negativity (ERN) in EEG studies have also found that specifying transdiagnostic dimensions of anxiety supports a priori psychological models of anxiety and executive dysfunction and results in stronger correlations with psychophysiological data. Compared to the relationship between anxiety broadly defined as a unitary construct and executive function performance, anxious apprehension resulted in an ERN effect size three times larger in executive function tasks (Moser et al., 2013). An aberrantly high ERN suggests processing inefficiency. The compensatory error monitoring theory (Moser et al., 2013) explains these data by suggesting that high anxious apprehension is associated with an initial failure of goal maintenance due to worry co-opting working memory, which is compensated for by temporary reactivation (manifested in high ERN) of task rules. This borrows from previous theoretical work in which worry impairs processing efficiency, not performance effectiveness, via distraction and/or impaired inhibition (Attentional control theory; Eysenck et al., 2007).

Anxious apprehension has also been associated with unique impairments in the executive function network defined in the cascade-of-control model (Banich, 2009). For example, anxious apprehension was associated with unique impairments in a frontocingulate network that includes left DLPFC and dACC during a color–word Stroop task using multi-modal imaging combining ERP and fMRI methods (Silton et al., 2011). Much like the ERN studies of Moser and colleagues, this study posited that anxious apprehension would show hyperactivity in dACC (considered the source of the ERN; Hochman et al., 2014; Miltner et al., 2003; van Veen and Carter, 2002). ERP source analysis validated the temporal cascade predicted by Banich (2009) of DLPFC activation preceding dACC activation, and fMRI results indicated an association between high anxious apprehension and increased dACC activity during incongruent trials. Importantly, anhedonic depression was not shown to have a moderating effect on dACC activity, further substantiating anxious apprehension as a unique contributor to the cascade circuit.

High dACC activity was interpreted to reflect a compensatory mechanism for an initial failure in top-down control of attention in the temporal cascade described by Banich (2009). Although the source-localization paradigm did not allow for investigation of inferior left IFG activity (Broca's area, associated with worry), it was presumably hyperactive in individuals with high levels of anxious apprehension and likely affected the relationship between dACC and DLPFC, reflective of inefficient processing (initial failure of and subsequent compensation for top-down control).

The preceding account coheres with Warren et al. (2013), who found increased posterior left DLPFC activity for participants with high anxious apprehension who were low in anxious arousal, interpreted as increased top-down control to mitigate the distracting effect of worry. In both cases, worry is presumed to interfere with top-down control, which in turn engages a concomitant compensatory process in one or more brain regions.

Anxious apprehension may also serve to mitigate the deleterious effects of other transdiagnostic dimensions of psychopathology, acting singly or in conjunction, on brain activity and cognition. For example, when anhedonic depression and anxious arousal were both high, co-occurring anxious apprehension seemed to lessen their impact on activity in left DLPFC (Engels et al., 2010; see Section 5.3 for further discussion).

More work is needed to refine how hyperactivity in Broca's area (instantiating worry) affects dACC and DLPFC (both implementing top-down control) in a mechanistic neural model (perhaps using functional connectivity fMRI analysis and/or EEG/MEG source-localization during executive function tasks).

5.2. Neural correlates of anxious arousal

Anxious arousal is associated with sympathetic hyperarousal and hypervigilance in the presence of mild stressors (Heller et al., 1997; Nitschke et al., 2000; Watson et al., 1995). Initially, anxious arousal was treated as being synonymous with fear, a state construct. In Heller et al. (1997), fear was experimentally manipulated in a within-groups design and shown to be associated with right posterior hemisphere activity that was interpreted to reflect the engagement of regions involved in monitoring and responding to threatening stimuli (Heller, 1993; Keller et al., 2000). In a subsequent between-group study of resting-state EEG, anxious arousal as measured by the Mood and Anxiety Symptom Questionnaire Anxious Arousal subscale (MASQ-AA; Watson and Clark, 1991; Watson et al., 1995) was characterized by greater right hemisphere activity, primarily in lateral frontal areas (Nitschke et al., 1999). In addition to supporting the notion that anxious arousal would be distinguished from anxious apprehension in terms of neural mechanisms, these findings suggest that fear (state) and anxious arousal (trait) involve distinct patterns of regional brain activity. Fear engages right posterior regions and networks specialized for monitoring the environment and responding to threat. In contrast, anxious arousal may involve frontal, temporal, and parietal regions, including processes involved in hypervigilance, attentional biases, and dispositional tendencies (Burdwood et al., in revision; Compton et al., 2003; Engels et al., 2007; Nitschke et al., 1999).

Subsequent studies have replicated these findings, identifying more specific brain regions implicated in anxious arousal using EEG (e.g., O'Hare and Dien, 2008) and fMRI (e.g., Engels et al., 2007). Anxious arousal was associated with activity in right inferior temporal gyrus (ITG) and middle temporal gyrus (MTG), which are two nodes in a neural system thought to instantiate threat detection (Engels et al., 2007; Nitschke et al., 2000; Spielberg et al., 2013). These studies used Stroop-type paradigms, in which anxious arousal groups showed hyperactivity in these temporal regions while attempting to ignore negatively-valenced words. Such findings lend support to the argument that anxious arousal as measured by the MASQ-AA is a trait marked by a lower threshold to engage a (state) fear response when exposed to mildly threatening stimuli.

A recent study expanding on these findings found that anxious apprehension and anxious arousal are associated with different patterns of habituation to task-irrelevant threat stimuli (Spielberg et al., 2013). The paradigm's hypotheses were informed by two models: (1) the psychological Avoidance Model of Worry (AMW; Borkovec et al., 2004) which suggests that worry is a cognitive avoidance strategy that

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mitigates the somatic and emotional intensity of fear (Bergman and Craske, 2000), and (2) a proposed neural model of attention that is engaged during a threat response (Corbetta and Shulman, 2002; Corbetta et al., 2008; Nitschke et al., 2000). Results were consistent with hypotheses that those high in anxious apprehension would immediately engage areas thought to instantiate worry, leading to a reduced initial threat response. As worry, thought to be cognitively taxing, diminished (evidenced by decreased activity in Broca's area over time), threat response increased (as evidence by increased activity in right superior frontal gyrus: SFG), and more top-down control was required for the individual to stay on task (as evidenced by increased activity in dACC). Thus, it was inferred that normal habituation to fearful stimuli was disrupted in those with high anxious apprehension.

Alternatively, those with high anxious arousal displayed early engagement of a threat response system (as evidenced by activity in SFG, inferior temporal gyrus, and middle temporal gyrus) that decreased (habituated) over the course of the experiment, consistent with normative habituation to fearful stimuli. These findings are consistent with theory and evidence suggesting that anxious arousal engages a fear response more easily to mildly threatening stimuli (e.g., Engels et al., 2007). However, it also appears that anxious arousal is ultimately associated with a more adaptive response than anxious apprehension in this context.

Identifying differential profiles of habituation to fearful stimuli may have significant translational significance for clinical diagnosis and treatment of anxiety disorders. Habituation to fearful stimuli is a key aspect of exposure therapy (e.g., Craske et al., 2014; Foa and Kozak, 1986; Fanselow and Sterlace, 2014), an empirically-supported and efficacious treatment for many anxiety disorders. Spielberg et al. (2013) provided evidence that those high in anxious arousal engage neural mechanisms that implement bottom-up attention more easily to mildly threatening stimuli, a putative endophenotype for later emerging pathological panic/fear disorders. The opposite profile was observed in those high in anxious apprehension, which demonstrates a potential impediment (worry) to mechanisms of change involved in exposure therapy (habituation). This may inform more targeted therapies for those who have high levels of anxious apprehension and/or anxious arousal. Exposure treatment may work better if strategies target mitigating worry first, which has been shown here to interfere with habituation to feared stimuli.

5.3. Co-occurring depression constructs

Accounting for co-occurring dimensions of depression when studying these dimensions of anxiety has helped to clarify the distinct circuitry involved in each and the relationships among them (Engels et al., 2010; Heller et al., 1995; Keller et al., 2000; Bruder et al., 1997; Reid, Duke, & Allen, 1998). Similar to studying anxiety as a unitary construct, clinical neuroscience paradigms that studied depression as a single category had mixed and often contradictory findings. Taken together, EEG findings have been supportive of left-hemisphere hypoactivity in depressed individuals (for reviews, see Coan and Allen, 2004; Davidson, 1992). However, fMRI findings have been inconsistent, with left DLPFC being hypoactive (Elliott et al., 1997), hyperactive (Hugdahl et al., 2004), or insignificantly different from its right-hemisphere homologue (Barch et al., 2003) as a function of depression. This problem was resolved by Herrington et al. (2010), who found diminished activity for depressed individuals compared to controls in both left DLPFC and amygdala when controlling for high anxious apprehension and high anxious arousal, specifically when exposed to negative stimuli. Additional though less direct support came from Herrington et al. (2005), who found that lateralization of frontal activation as a function of stimulus valence differed in different frontal subregions, a distinction the (mostly low-density) EEG literature had not been able to address.

The Herrington et al. (2010) finding has been extended to evaluate how anxiety dimensions interact with anhedonic depression, a transdiagnostic dimension that has been shown to predict DSM diagnoses of depression (Bredemeier et al., 2010; Buckby et al., 2007). Anhedonic depression has been described as characterized by low positive affect and has been hypothesized to be unique to clinical depression as explicated in the influential tripartite model (Clark and Watson, 1991; also see Nitschke et al., 2000).

Importantly, whereas Herrington et al. (2010) used a group analysis (high depression with low anxiety vs. controls), Engels et al. (2010) examined the complex interactions among anxiety dimensions and anhedonic depression as continuous variables using regression analyses and found similar results. When anxious apprehension was low, the interaction of anxious arousal and anhedonic depression was associated with diminished activation in left DLPFC and higher activation in right DLPFC, a pattern that was not present when anxious apprehension was high These findings imply that higher levels of anxious apprehension counteract a tendency to suppress top-down control in favor of threat-related responding as reflected by modulation of left and right DLPFC activity (e.g., Nitschke et al., 2000). In other words, anxious apprehension could be an adaptive strategy to counteract negative effects of depression on cognition as proposed by Borkovec et al. (2004) and Bergman and Craske (2000).

Thus, investigations of neural mechanisms associated with depression should take into account anxious apprehension and anxious arousal and vice versa, as these anxiety dimensions affect neural activity associated with anhedonic depression. This is not only important for building neural models but for improving nomological networks that relate depression and anxiety constructs to each other.

5.4. Conclusions regarding psychological relationships

Several psychological theories have informed models of neural mechanisms implementing anxious apprehension and anxious arousal. With regard to anxious apprehension, attentional control theory (ACT; Eysenck et al., 2007) posits two possible contexts (that may not be mutually exclusive) in which worry has been shown to disrupt goal-directed, executive processes. Anxious apprehension may impinge on top-down attentional control via worry (1) in the context of negative affective distractors (as reported by Engels et al., 2007; Herrington et al., 2010) and/or (2) in the context of irrelevant stimuli in Stroop paradigms without affective distractors, suggesting a more general impairment in executive function (as reported by O'Hare et al., 2014; Silton et al., 2011). ACT, however, does not explicate a causal mechanism explaining *how* worry impinges on attentional functions. Theoretical progress in conceptualizing attentional processes will aid the effort to empirically test how dimensions of anxiety impinge on executive function.

With regard to anxious arousal, Spielberg et al. (2013) provided evidence that this dimension of anxiety also affects attentional networks in specific ways. Anxious arousal was associated with greater sensitivity to distracting and mildly threatening stimuli as inferred from greater activity in a ventral attentional network thought to implement threat detection (Corbetta and Shulman, 2002; Nitschke et al., 2000). Although ACT posits that worry is indicative of a similar pattern, results suggest that sensitization to threatening stimuli in this ventral network is unique to anxious arousal. This pattern of brain activity has also been linked to worse Stroop task performance, consistent with an override of a dorsal, goal-oriented system (Finy et al., 2014; Warren et al., 2013). Since there have been mixed findings regarding how impairing these dysfunctional mechanisms in anxious arousal are of task performance, future studies should assess how anxious arousal correlates with behavior in the context of more threatening stimuli (perhaps an electric-shock paradigm) that would elicit acute fear responses in control groups as well.

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6. Avoiding reification of anxious apprehension and anxious arousal

Although empirical evidence from clinical neuroscience suggests that anxious apprehension and anxious arousal are useful constructs in explaining phenomena that occur across several DSM anxiety disorders, other work parsing anxiety symptoms has found alternative constructs to explicate the latent structure of anxiety (e.g., Watson et al., 2007). In these factor analyses of several anxiety and depression self-report measures, worry (state counterpart of anxious apprehension) does not emerge as an explanatory factor. Instead, worry is subsumed under a general dysphoria factor that includes symptoms of excessive fear, depressed mood, anhedonia, psychomotor agitation, and other major criteria of major depressive disorder. This work has been vital to refining self-report measures of anxiety and provides valuable constructs to examine with the tools of clinical neuroscience.

Despite a discrepancy between these two separate lines of research on anxiety, anxious apprehension and anxious arousal remain useful constructs in explaining meaningfully different dimensions of anxiety. Discrepancies between psychometric evaluations of self-reported anxiety and clinical neuroscientific studies may be explained by differences in what is actually being measured. The aforementioned factor analyses rely on correlations among responses of what is consciously available to participants filling out questionnaires at the time of measurement. Although worry was highly correlated with other constructs such as fear, low mood, and anhedonia, these results may be a function of people not having discrete meanings readily available for these features of affective experience. In other words, subjects may categorize such experiences (e.g., fear vs. worry) as very similar and therefore may rate such experiences similarly during self-report, even if psychologically or biologically distinct. Additionally, even if items are highly correlated in a given sample, they may still be meaningfully different constructs. From a theoretical perspective, smoothing the differences between depressed mood and worry by subsuming them under a single dysphoria scale may be useful for certain purposes (e.g., investigating antecedent, genetic correlates) and inappropriate for others (e.g., identifying distinct neural systems) (Pickles and Angold, 2003).

In any case, individuals lack awareness of much of their psychological processing, just as they are not aware of how visual stimuli are processed along the cascade of activity from the retina through the visual cortices and beyond. It is not surprising that the dimensional structure of self-report misses some distinctions that exist in other psychological or biological phenomena. Results reviewed above distinguishing anxious apprehension and anxious arousal emerged from testing specific a priori hypotheses about neural systems that likely implement protracted verbal processing of negative information and sympathetic hyperarousal, respectively.

Quantitative analyses of self-report data and clinical neuroscientific investigations have not resolved how constructs of interest should be placed along etiological timelines. Anxious apprehension and anxious arousal may be endophenotypes (Miller and Rockstroh, 2013, in press) that emerge during adolescence (given that work on these constructs has been done primarily with college-age populations), whereas other constructs that come out of factor analytic work may uncover common propensities (e.g., internalizing vs. externalizing constructs; Krueger and Markon, 2006) that are more strongly related to genetically predisposing factors, or later-emerging phenomena (anxious symptoms: panic, anxious mood) that are more relevant for already-morbid individuals. Without sufficient theory concerning how constructs from clinical neuroscience and psychometrics inform etiological models of anxiety disorders, researchers should not assume that disagreement in mapping of relevant constructs across these approaches indicates that one set of constructs is more or less explanatory.

Given alternative models of the structure of internalizing symptoms, it would be timely to test models of anxiety that emerge from recent factor-analytic work of self-report data using clinical neuroscience paradigms and vice versa (Ofrat and Krueger, 2012). This will help elucidate which constructs are more useful to explaining things such as etiological factors in the development of anxiety and taxonomic criteria for anxiety disorders.

7. Mapping transdiagnostic anxiety constructs onto the RDoC matrix

There are a number of places that anxious apprehension and anxious arousal could fit within the domain of negative valence in the RDoC matrix. For anxious apprehension, the most obvious place is under the construct "potential threat". If one conceptualizes anxious apprehension as a type of negative repetitive thinking, then anxious apprehension could be offered as a subconstruct of potential threat (on the NIMH website there are no subconstructs offered for any constructs within the negative valence domain in the matrix). Within potential threat, several indicators (neurobiological, psychological) of this latent, psychological trait could fall under different units of analysis. There is no consensus regarding which indicator and/or set of observables best measures anxious apprehension, so it is not yet clear under which unit(s) of analysis to place anxious apprehension.

As the psychological and biological mechanisms of anxious apprehension become clearer, its placement within the RDoC matrix may change. For example, if a mechanistic model of anxious apprehension includes negative repetitive thinking and a breakdown in executive flexibility (see description of this model above) as two interacting, constituent states, then anxious apprehension may also belong under the cognitive systems domain, specifically to the flexible updating subconstruct (see Fig. 2).

This example highlights the potential to argue for changes in the RDoC matrix (which NIMH offered only as an example, not as a finished plan). Although much evidence suggests that cognitive and positive/negative valence domains are separable, many constructs relevant to psychopathology may be best characterized by interactions among multiple domains. Thus, it remains to be seen how the RDoC matrix evolves to accommodate such trans-domain constructs.

For anxious arousal, the placement in the RDoC matrix is less clear. In the examples of RDoC matrix entries on the NIMH website, anxious arousal is listed under the construct of "sustained threat" in the negative valence domain. Anxious arousal is often defined as the unique symptom profile that distinguishes anxiety from depression (e.g., Watson et al., 1995; Somerville et al., 2013) and relies primarily on sympathetic hyperarousal in its definition. However, based on previous research (Engels et al., 2007; Spielberg et al., 2013) and current theorizing, the present review now explicitly defines anxious arousal as a neuropsychological trait comprised of component psychological states such as hypervigilance and defensive preparedness in addition to sympathetic hyperarousal. Based on this definition, anxious arousal would also fit under potential threat (defensive preparedness) and acute threat (excessive fear to mild stressors) in addition to sustained threat (hypervigilance). Given that constituent psychological components of anxious arousal fit differentially across RDoC constructs, anxious arousal is likely best characterized by a pattern of multiple constructs (see new column furthest to the left in Fig. 2). Thus, the RDoC matrix may expand to accommodate these and similar superordinate constructs (e.g., traits), which are broader than constructs but narrower than domains in the RDoC matrix hierarchy.

Additionally, it should be noted that it is unclear why some psychological constructs in the RDoC Matrix are sometimes denoted as subconstructs (e.g., effort valuation) and others as behavioral units of analysis (e.g., rumination). This is problematic for two reasons: (1) there are no specified criteria for denoting psychological constructs as either subconstructs vs. behavioral units of analysis, and (2) there is a tacit conceptualization that certain psychological constructs are synonymous with behavior. The latter issue is more problematic, in that it reduces psychological constructs to observable behavior, which is logically flawed (Kozak and Miller, 1982; Miller, 2010) and lacks theory and empirical work to justify this conceptualization. Although we have

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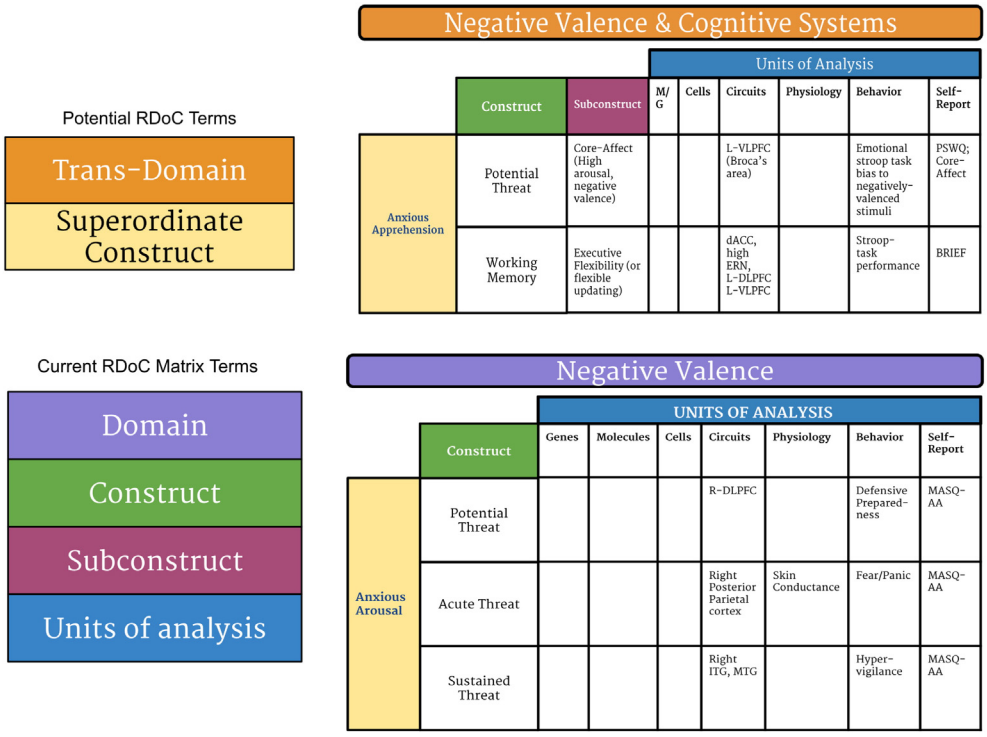

Fig. 2. Examples of RDoC matrix entries. In these hypothetical RDoC matrices, an entry for anxious apprehension is the top matrix and the bottom matrix is for anxious arousal. The top matrix conceptualizes anxious apprehension in line with our mechanistic description, in which constituent psychological states from both the negative valence domain (core affect, offered as a subconstruct) and cognitive systems domain (flexible updating, an existing RDoC subconstruct) are components. We've termed the highest-level in this hypothetical RDoC matrix entry a "trans-domain" in that it spans multiple domains: potential threat exists currently in the negative valence domain and working memory in the cognitive systems domain. Alternatively, anxious arousal is placed solely in the negative valence domain, which includes several constructs (including potential threat, acute threat, sustained threat as depicted here), of which each is subdivided into biological, behavioral, and self-report units of analysis. Anxious arousal is best characterized by a pattern of multiple RDoC-defined constructs (potential threat, acute threat, sustained threat), each of which includes indicators of anxious arousal across units of analysis (e.g., for acute threat: reported state fear/panic and heightened right posterior parietal activity). The diagram on the bottom left conveys the RDoC matrix hierarchy, starting from the broadest level of categorization (domain) to the most specific level of categorization (units of analysis). There is no subconstruct column in the anxious arousal matrix entry illustrated here, because there are presently no subconstructs for any construct in the negative valence domain on the NIMH website. The diagram on the upper left includes hypothetical RDoC matrix categories that we feel fit aspects of anxious apprehension and anxious arousal better than existing RDoC matrix categories. Trans-domain entries may best suit constructs that do not respect the dichotomy between cognition and emotion, and superordinate constructs may be best suited for psychological traits.

also placed psychological constructs (e.g., defensive preparedness) under the behavioral unit of analysis in the diagram above, it could be argued that these constructs are more appropriately subconstructs in the RDoC matrix hierarchy.

8. DSM-defined anxiety disorders and executive function impairments

Although this article advances a transdiagnostic, dimensional framework for conceptualizing dimensions of anxiety and their interactions with executive function, many well-established categorically conceived anxiety disorders have been shown to involve executive dysfunction. DSM-defined disorders are related to poor executive function including obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and panic disorder (PD). Findings illustrate that executive function deficits can be risk factors, maintaining components, and impairing outcomes of several psychopathologies (for reviews see Crocker et al., 2013; Snyder, 2013; Snyder et al., 2015; also Crocker et al., 2012; Letkiewicz et al., 2014).

Studies differ in their results regarding the relationship between anxiety disorders and executive function deficits. Whereas OCD (Snyder et al., 2014) and PTSD (Olff et al., 2014) were associated with pervasive executive function deficits, generalized anxiety disorder (GAD) findings have been mixed. Executive function deficits were linked to GAD in a young population (Tempesta et al., 2013) but had no association with GAD in clinical psychiatric samples (Airaksinen et al., 2005; Smitherman et al., 2007).

The discrepancies in these results may be partly explained by the heterogeneity of transdiagnostic components within DSM disorders that remain unaccounted for in most studies investigating the association of executive function impairments and psychopathology. In the case of anxiety, if a study examining executive function in GAD finds no association, the data could be confounded by differences in dimensions of anxiety across individuals. In any given sample, certain individuals may be differentially high in anxious apprehension and/or anxious arousal, and such a distinction may relate to unique profiles of executive function impairments (e.g., Crocker et al., 2013). Conversely, because executive function is not a unitary construct (for review see Snyder et al., 2014), if a study assesses only a limited number of executive function components, and finds no association, the null results could be explained by a failure to measure the relevant correlate with a specific anxiety disorder or type of anxiety.

9. Implications for prevention, diagnosis, and treatment of psychopathology

In a review of the shortcomings of the DSM, Hyman (2010) expressed concern that its categorical approach "denies an appropriate clinical status to early or milder symptom presentations, thus impeding preventive interventions." Clinicians may eventually use transdiagnostic, dimensional anxiety constructs in prevention, diagnosis, and treatment. To determine how the use of these constructs can improve clinical practice, research is needed to determine which clinical interventions are most appropriate for individuals with differing degrees of dimensional components of psychopathology. For example, someone who scores one standard deviation above the mean on anxious apprehension may benefit more from a given treatment than someone who is two standard

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deviations above the mean. In medical practice, dimensionally-measured phenomena such as hypertension and hypercholesterolemia have multiple, industry-wide accepted thresholds (depending on level of severity) that call for specific treatment response (Hyman, 2010).

Attention to transdiagnostic anxiety phenomena may be especially relevant for preventing the onset of psychopathology. The research needed to optimize this opportunity faces the same competing economic incentives and ethical imperatives as health care in general:

> Economic incentives encourage overuse of services by favoring procedural over cognitive tasks (e.g., surgery versus behavior-change counseling) and specialty over primary care. The current model largely ignores subclinical disease unless risk factors are "medicalized" and asymptomatic persons are redefined as "diseased" to facilitate drug treatment. These mismatched economic incentives effectively preclude successful prevention through health maintenance.
>
> [Marvasti and Stafford (2012, p. 890)]

The categorical diagnostic system forces clinicians "to make subthreshold or atypical diagnoses (Jackson et al., 2007), which are not likely to be covered by insurance, or to engage in diagnostic "bracket creep" in order to gain reimbursement for treatment" (Hyman, 2010, p. 166). Anxious apprehension, anxious arousal, and anhedonic depression represent three interacting factors that occur in at-risk populations and which, if studied further, may elucidate mechanisms of dysfunction that occur before symptom severity passes thresholds as currently defined in the DSM.

Despite the potential benefits of using a multidimensional conceptualization of anxiety to inform the prevention, diagnosis, and treatment of psychopathology, there are a few significant limitations. If these constructs were to permeate clinical practice, there would likely be de facto cutoffs along these continua that would have implications for diagnosis and intervention. These cut-offs may be based on (non-exhaustive) population estimates, may be determined on a case-by-case basis by clinical experts, or may be assessed using algorithms that integrate several observable indicators of the constructs (self-report, neuroimaging, peripheral physiology). Medical practitioners face the same dilemma for dimensional, biological constructs such as hypertension (Hyman, 2010).

Additionally, these dimensions of anxiety will likely have to be evaluated within an array of other clinical tests that will assess relevant, co-occurring constructs in order to determine treatment plans. Most psychological dysfunctions and many medical diseases are multidetermined across different units of analysis (Sartorius, 2014), and different constellations of etiological factors across individuals may influence clinical decisions. Clinicians are already using targeted therapies in physical medicine for diseases that vary across individuals (Insel and Cuthbert, 2015). Such precise treatments are derived from research that has begun to delineate multifactorial etiological pathways for certain pathologies. Future work needs to be done to explicate how a variety of etiological factors involved in the pathogenesis of anxiety relate to anxious apprehension and anxious arousal to help inform clinical diagnosis and treatment.

10. Future directions

More work is needed to understand how best to measure these psychological constructs, how they are instantiated in neural networks, how they relate to diverse emotional phenomena and executive functions, and what role they play in the etiology of psychopathology.

10.1. Measuring anxious apprehension and anxious arousal

Theory proposed here and elsewhere should be tested to advance an understanding of the psychological mechanisms of anxious apprehension and anxious arousal. To this end, future research should address how these constructs are measured, and how they can be improved as the conceptualizations of these constructs change.

We proposed above that negative-valence/high-arousal affect and executive inflexibility may interact and give rise to anxious apprehension. Thus, future questionnaires may want to include questions that characterize such interactions between worry and executive inflexibility. For example, an item could be, "When I worry it's hard to concentrate on anything else" or "If something important comes up, it's easy for me to stop worrying." These items are not included on the questionnaire most commonly used to measure anxious apprehension, the 16-item PSWQ (Meyer et al., 1990). It measures how frequent and overwhelming one's experience of worry is, without explicitly addressing the connection between worry and executive function.

Constructs were advanced above that are likely indicative of anxious arousal but are not measured in current questionnaires. Anxious arousal has typically been measured with the MASQ-AA (Watson et al., 1995), which is designed to gauge the intensity of peripheral hyperarousal an individual tends to experience (e.g., "Had pain in my chest" and "Hands were cold or sweaty"). The Beck Anxiety Inventory is also geared toward symptoms of sympathetic hyperarousal (Beck et al., 1988). Since the instructions are to report one's experience during the past week or two, the responses may detect transient and aberrant patterns of sympathetic hyperarousal that could be due to a variety of causes (e.g., physical illness). The popular State–Trait Anxiety Inventory (Spielberger et al., 1970) makes almost no reference to somatic or physiological phenomena and thus is relatively remote from anxious arousal (and suffers from a confound with depression, problematic if one wishes to distinguish the two experimentally; Nitschke et al., 1999).

Measures need to be developed that test whether the present proposed psychological components (defensive preparedness, hypervigilance) reliably and validly indicate anxious arousal. Potential new questions may include, "I consider many situations dangerous that others would not" or "I am quick to assess risk in any situation". These future versions should also expand the time frame in the self-report instructions to at least the past month, if not during the past year, or provide a composite score of several measurements taken over several weeks or months.

It may be invaluable to complement self-report measures with behavioral performance tasks that measure correlates of anxious arousal that operate below conscious thresholds. Many people are likely not aware of their level of hypervigilance to mildly threatening stressors. For example, using a Stroop task or dot-probe task with varying levels of threatening stimuli may distinguish those who evaluate such stimuli (e.g., as inferred from aberrant neural correlates or eye-tracking) as more threatening than the average individual and may behave differently (e.g., as inferred from reaction time/decision errors) in sufficiently arousing contexts.

10.2. Building mechanistic neural models

Research has demonstrated that there are distinct neural circuits involved in implementing anxious apprehension and anxious arousal, but there also may be shared neural mechanisms that serve a common anxiety function. More work is also needed to investigate how these neural mechanisms putatively implementing dimensions of anxiety are functionally connected to other systems across different contexts. Some neuroscientists argue that the brain has domain-general mechanisms that interact with highly specific contexts to construct mental phenomena (Conceptual Act Theory: Barrett, 2014; Adaptive–Constructive Processes: Schacter et al., 2012). This perspective need not contradict "essentialist" theories that seek to identify unique neural mechanisms implementing psychological constructs, but it urges researchers to measure psychological phenomena across different contexts (to cover within-construct variability) and delineate both shared and unique neural mechanisms.

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Examining anxiety dimensions across a range of paradigms with evolving methods (e.g., neural connectivity) may be able to further refine the mechanistic neural models associated with them. For example, to further advance theory regarding how those high in anxious arousal differentially process threatening stimuli, clinical neuroscience paradigms can leverage multivoxel pattern analysis of fMRI data to investigate whether anxious arousal scores predict neural coding of varying levels of threatening stimuli. If individuals high in anxious arousal display less distinct patterns of neural encoding for mildly vs. highly threatening stimuli, such data would refine our understanding of the neural mechanisms (neural population coding of threat) and of the psychological mechanisms (lower-order categorization of threat) that are involved in a reduced threshold to experience fear.

Emerging, basic-science theories should also inform future clinical neuroscience paradigms investigating anxiety dimensions, a central principle of the RDoC initiative (Insel and Cuthbert, 2015). Neuroscientists have argued that predictive coding is a basic function of the brain, which essentially means that conceptual expectations drive perceptions of new, incoming stimuli (e.g., Clark, 2013; Shipp et al., 2013). Such theory may be brought to bear in effective connectivity paradigms, which are designed to test causal models of how activity unfolds in a priori defined neural systems.

10.3. Anxiety dimensions and executive functions

Although research has explored the relationship between these anxiety dimensions and some aspects of executive function (e.g., inhibition of distracting information as measured by the Stroop task), much more should be done to clarify their relationship to other specific constructs of executive function (e.g., updating, shifting), and other ways of conceptualizing executive function (e.g., maintenance vs. flexibility: Dosenbach et al., 2008; Snyder et al., 2015). Progress also depends on more basic research on cognitive components of and neural mechanisms associated with attention to move beyond relying on broad constructs (e.g., a "central executive") involved in attention that are difficult to operationally define (Eysenck et al., 2007).

Psychological constructionist theories (e.g., Barrett, 2014) consider executive function processes as basic, psychological ingredients that interact with other basic functions to give rise to most psychological phenomena. Anxious apprehension, then, could be viewed as an emergent phenomenon that arises out of interactions of core affect and executive inflexibility (as proposed above). Such a conceptualization may shed light on mechanisms contributing to a sustained pattern of negative, repetitive thinking, which may improve the identification and treatment of this form of psychopathology.

10.4. Anxiety dimensions and affective phenomena

In addition, future studies should investigate the differential relationships anxious apprehension and anxious arousal may have with broad emotional constructs such as negative affect as well as with more specific emotional categories such as guilt and shame. Indeed, Watson and Tellegen (1985) argued that general and specific emotion categories are useful, complementary models of emotion:

> Positive and Negative Affect, although accounting for about one half to three quarters of the common variance [in self-reported emotion], do not exclude the operation of additional systematic sources of variance. The two-dimensional framework, in other words, is complementary to, rather than competitive with, multifactorial structures. In fact, we show that Positive and Negative Affect are hierarchically related to the more numerous and circumscribed "discrete-emotion" factors posited by other investigators.(p. 220)

Both negative affect and discrete emotion categories may be differentially associated with anxious apprehension and anxious arousal and implemented via both shared and distinct neural mechanisms. Techniques such as representational similarity analysis have recently been used to investigate how the brain represents emotional valence. Findings point to a population coding of valence that is both sensory-specific and sensory-independent across different brain regions (Chikazoe et al., 2014; Kriegeskorte and Kievit, 2013). These methods may be able to differentiate how basic dimensions of emotion (valence and arousal), and discrete categories of emotion (guilt, shame, fear) are differentially represented in neural circuitry across anxiety dimensions.

10.5. Testing trait models of anxious apprehension and anxious arousal

Finally, clarifying the constructs and separating state (worry/panic) and trait (anxious apprehension/anxious arousal) effects of anxiety in future studies can help elucidate how trait anxiety dimensions relate to cognitive processes, neural mechanisms, and risk for psychopathology. The present review has offered working definitions of anxious apprehension and anxious arousal as traits, based on available theory and data that warrant further empirical testing. Novel subordinate constructs of interest for anxious apprehension include core affect and executive inflexibility and for anxious arousal include vigilance and defensive preparedness.[3] The present discussion clarifying distinctions between constructs of state affect and trait anxiety dimensions addresses previous confusions in the literature and may provide future studies with improved tools to more accurately conceptualize constructs and develop sensitive paradigms with which to examine mechanisms and relationships. A more precise explication of anxious apprehension and anxious arousal phenomena promises to reduce the gap between biological and psychological conceptualizations of anxiety and to refine theoretical frameworks describing how these domains causally relate to each other (if causation is the right way to think of their relationship) and influence the etiology of psychopathology.

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[3] Although not discussed in the present review, anxious arousal could be described mechanistically similar to the proposed generative mechanistic description for anxious apprehension. In such a description, core affect would also be a constituent element, along with other processes involved in hypervigilance and defensive preparedness.

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