Integrating Threat Conditioning and the Hierarchical Taxonomy of Psychopathology (HiTOP) to Advance the Study of Anxiety-Related Psychopathology

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Abstract. Theoretical and methodological research on threat conditioning provides important neuroscience-informed approaches to studying fear and anxiety. The conditioning framework is at the vanguard of physiological and neurobiological research into core mechanistic symptoms of anxiety-related psychopathology, providing detailed models of neural circuitry underlying variability in clinically-relevant behaviors (e.g., decreased extinction, heightened generalization) and heterogeneity in clinical anxiety presentations. Despite the strengths of the threat conditioning approach in explaining symptom-level variability and syndromal heterogeneity, the vast majority of psychopathology-oriented threat conditioning work has been conducted using the Diagnostic and Statistical Manual (DSM) paradigm. Unfortunately, DSM categorizations fail to capture symptom-level resolution afforded by threat conditioning indices. Further, relations between fine-grained neurobehavioral measures of threat conditioning and specific anxiety symptoms are substantially attenuated by within-category heterogeneity, arbitrary boundaries, comorbidity, and limited reliability of the DSM. Conversely, the Hierarchical Taxonomy of Psychopathology (HiTOP) is a promising approach for modeling anxiety symptoms studied by threat conditioning work and for relating threat conditioning to broader anxiety-related constructs. To date, HiTOP has had a minimal impact on the threat conditioning field. Here, we propose that combining the HiTOP and neurobehavioral threat conditioning approaches is an important next step in studying anxiety-related pathology. We provide a brief review of prominent DSM critiques and how they affect threat conditioning studies and suggest solutions and recommendations that flow from the HiTOP perspective. Our hope is that this effort serves as both an inflection point and practical primer for HiTOP-aligned threat conditioning research that benefits both fields.

Threat conditioning models are among the most informative experimental paradigms employed in psychology and neuroscience and have yielded fundamental knowledge of the mechanisms that guide how humans learn and regulate fear and anxiety in response to threat (Ojala & Bach, 2020; Vervliet & Boddez, 2020). Based on the successful translation of animal neurobiological research (Fullana et al., 2020), threat conditioning models constitute an elegant and testable explanatory framework for the biology and behavior of anxiety-related psychopathology (Abend, 2023; Beckers et al., 2023), with clear relevance to explaining variability in anxiety symptoms. Further, threat conditioning and extinction are the theoretical bedrock of exposure therapy, a gold standard treatment for anxiety-related psychopathology, and threat conditioning research continues to contribute to neuroscience-informed efforts to address limitations of current exposure-based therapies (Craske et al., 2018, 2023; Fullana et al., 2020).

Despite clinical promise and recent advances in the neuroscience of threat conditioning, empirical evidence linking threat conditioning to anxiety-related psychopathology is inconsistent and frequently contradictory (Beckers et al., 2023; Lonsdorf & Merz, 2017). Part of the solution is refining the threat conditioning paradigm (see Beckers et al., 2013; Dunsmoor et al., 2015; Lonsdorf et al., 2017). Here, we propose a parallel avenue for advancement: reforming the operationalization of anxiety-related psychopathology in the threat conditioning model to maximally contribute to clinically-relevant efforts. We start with a brief definition of anxiety-related psychopathology and approaches to its classification. Next, we expand on the advantages of using threat conditioning to study anxiety-related psychopathology. We then briefly review the relevant literature linking threat conditioning to disorders represented in the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) and highlight the limitations of this approach. We next introduce the Hierarchical Taxonomy of

Psychopathology (HiTOP), an empirical nosological framework that organizes psychopathology hierarchically, from individual behaviors and symptoms to broad spectra (Kotov et al., 2017; Ringwald et al., 2023). We emphasize the strengths of HiTOP and provide practical recommendations for threat conditioning researchers transitioning from DSM to HiTOP. Finally, we consider the synergy between threat conditioning and HiTOP, particularly for incorporating neuroscience-informed fear and anxiety mechanisms into the HiTOP framework.

What is Anxiety-Related Psychopathology?

After centuries of inquiry into maladaptive fear and anxiety, there are almost as many definitions of these constructs as there are people studying them (Grogans et al., 2023; Mobbs et al., 2019). Here, we use the term "anxiety-related psychopathology" to refer to subjective symptoms, states, and traits that relate to anticipating (real or not) future threats and that result in distress and/or impairment. For the present purposes, we do not differentiate between fear and anxiety as neurobiological or subjective constructs (for related discussion, see Fox & Shackman, 2017; Watson, Clark, et al., 2022).

The DSM (currently DSM-5; APA, 2013) is the most widely used system for classifying anxiety-related psychopathology in the United States. Mental illnesses in the DSM are defined based on clinical consensus and classified as polythetic dichotomies that are inherently categorical and assume a natural divide between health and disorder (Kotov et al., 2017). DSM anxiety-related disorders (Asmundson, 2019) are found in three chapters: Anxiety Disorders, Obsessive-Compulsive and Related Disorders, and Trauma- and Stressor-Related Disorders. Anxiety-related symptoms are also included as criteria for disorders in other chapters.

Importantly, the DSM and its diagnostic criteria are not synonymous with psychopathology. The DSM is an attempt to describe and classify psychopathology for the

purposes of practical application. However, over time, it has been reified and imposed critically flawed limits on how psychopathology is conceptualized (e.g., Carson, 1991; Kotov et al., 2017; Millon, 1991). Modern empirical efforts have focused on moving from DSM's clinician-expert categorical system to a more reliable and valid data-driven dimensional system, typified by the still-evolving HiTOP framework (Forbes, Ringwald, et al., 2023). Anxiety-related psychopathology is evident at the lowest level of the HiTOP framework in individual symptoms and maladaptive behaviors (e.g., hypervigilance to threat). Moving up the hierarchy, these basic building blocks are grouped into homogenous symptom components (e.g., "anxious hyperarousal"), which are further combined into higher-order dimensional syndromes (e.g., "post-traumatic responses"), and then sub-factors that describe closely associated groups of symptoms (e.g., "fear" and "distress"). Above sub-factors are spectra, which broadly encompass groups of commonly covarying syndromes. The internalizing spectrum includes anxiety-related psychopathology (Watson, Clark, et al., 2022; Watson, Levin-Aspenson, et al., 2022) as well as related symptoms and syndromes such as depression, emotional lability, and interpersonal dysfunction. In this way, HiTOP provides a system for understanding not only anxiety-related psychopathology itself but also its commonalities with and distinctions from other forms of psychopathology, both within and beyond the internalizing spectrum.

Threat Conditioning and Its Value for Understanding Anxiety-Related Psychopathology

Conditioning refers to both an experimental paradigm and a learning process. Threat conditioning models of psychopathology describe a system of interrelated processes that map onto both normative and maladaptive learning and regulation of threat and safety. The two most basic of these processes are threat acquisition and extinction (Pavlov, 1927), which are commonly measured in the laboratory using the differential conditioning task. In a typical human differential

conditioning preparation, acquisition involves pairing an inherently aversive unconditioned stimulus (US), such as mild shock, with a neutral conditioned stimulus (CS) that predicts delivery of the US. The previously neutral stimulus begins to elicit a conditioned response (CR, e.g., fear) even in the absence of the US, becoming a conditioned threat stimulus (CS+). In most human conditioning preparations, another neutral stimulus is never paired with the US to serve as a within-subjects control (CS-) for non-associative factors, such as sensitization toward any cue delivered around the time of an aversive US. The extinction procedure, in which the CS+ is repeatedly presented without the US, reduces the CR. Conditioning has strong face and construct validity to model how animals learn to discriminate between dangerous and benign environmental cues and then inhibit defensive responses through new extinction learning processes that, if deficient, result in pervasive anxiety, or the "return of fear" (Dunsmoor & Paz, 2015; Mineka & Zinbarg, 2006). Specifically, laboratory conditioning yields parametric indices of maladaptive learning and regulation that parallel the development and maintenance of anxiety-related psychopathology. Elevated physiological arousal or threat expectations to the unpaired CS- during acquisition or sustained CRs to the CS+ during or after extinction are theoretically analogous to the pervasive and refractory anxiety responses seen in many forms of psychopathology (Beckers et al., 2023). These basic protocols can also be extended to align more closely with the everyday reality of clinical anxiety. For example, threat uncertainty, a fundamental element of anxiety (Grupe & Nitschke, 2013), can be experimentally manipulated by including stimuli with uncertain threat value that resemble the CS+ (i.e., generalization; e.g., Dunsmoor & Paz, 2015) or by reintroducing the CS+ without US reinforcement in a novel context (i.e., contextual renewal; e.g., (Vervliet et al., 2013).

Threat conditioning is also widely used to study the neurobehavioral substrates of anxiety-related psychopathology. A major strength is that it facilitates translation of the wealth of non-human animal research. These studies use extensively validated behavioral paradigms and invasive techniques (e.g., single-cell recordings, optogenetics) that cannot be applied in humans. Such studies yield precise knowledge of the neural circuitry and biological systems governing threat processes (Johansen et al., 2012; Maren, 2001), many of which are relatively well-conserved in humans. This work provides a translational framework for human experimental paradigms to facilitate precise hypotheses regarding specific neural mechanisms (Haaker et al., 2019; Milad & Quirk, 2012), and provides targets for the underlying neurobiology supporting behavioral symptoms of excessive fear, anxiety, or deficits in implicit forms of emotion regulation (such as extinction). Key differences between the methods used to study rodent/non-human primates compared with human brains limit the direct translatability of animal findings. Fortunately, a large human threat conditioning literature using functional magnetic resonance imaging (fMRI) has emerged in recent decades (Fullana et al., 2016, 2018; Webler et al., 2021). This literature continues to grow and to leverage advances in human behavioral (Beckers et al., 2013; Dunsmoor et al., 2015; Lonsdorf et al., 2017) and neural measurement and analysis (e.g., computationally informed multi-variate analyses: Cisler et al., 2015; Hennings et al., 2022; Zhou et al., 2021; brain stimulation approaches: Webler et al., 2023. Another strength is that threat conditioning can provide multidimensional output, where different processes can be compared to each other and across units of analysis, from different measures of brain structure and function to various physiological and cognitive components affected by negatively-valenced emotions (Beckers et al., 2023). All of this supports the ability of conditioning paradigms to detect meaningful variation

between individuals and relations amongst neurobehavioral processes in anxiety-related psychopathology[1].

Threat Conditioning and the DSM

The utility of a laboratory model to understand psychopathology is predicated on a system to reliably define and quantify psychopathology. The majority of threat conditioning studies of anxiety-related psychopathology have been under the umbrella of the DSM system (Duits et al., 2015). Accordingly, investigations of anxiety-related psychopathology and threat conditioning deficits have hinged on "patient-control" designs with the assumed validity of a diagnostic boundary between diagnostic categories. Common practices in these designs include use of "pure" disorder groups (i.e., those without any other comorbid DSM conditions) or strict exclusion of specific conditions, most commonly psychosis and problematic substance use. A lack of current DSM disorders typically determines inclusion in "control" comparison groups.

Some of the most-cited theoretical works on threat conditioning in anxiety-related psychopathology are centered on patient-control investigations and specific anxiety-related disorders (Bouton et al., 2001; Charney et al., 1993; Mineka & Zinbarg, 2006), and the resulting empirical research has largely adhered to the DSM approach. However, the evidence for threat conditioning as a core component of anxiety-related DSM disorders is mixed. Although meta-analyses indicate that threat conditioning indices differentiate anxiety-related disorder groups from control groups (Cooper, van Dis, et al., 2022; Duits et al., 2015; Suarez-Jimenez et al., 2019), effect sizes are modest. Notably, most meta-analytic effects are seen at the transdiagnostic level, with minimal support for unique patterns of threat conditioning in particular disorders. Larger

[1]Although, it should be noted that whether animal models can be relied on to model the construct of emotions such as "fear," rather than a more specific and operationalized model of defensive survival circuits, remains controversial (see LeDoux & Pine, 2016; Mobbs et al., 2019).

studies comparing transdiagnostic anxiety-related disorder groups to non-psychiatric groups also fail to find some or all of the hypothesized acquisition and extinction deficits in the disorder group (e.g., Fyer et al., 2020; Pöhlchen et al., 2020), indicating that the solution is not to simply combine DSM disorders. That said, disorder-specific results are also largely contradictory. Posttraumatic stress disorder (PTSD) is frequently studied with threat conditioning techniques, both in humans and non-human animal models (Bienvenu et al., 2021), yet decreased extinction is not reliably detected across studies (Dunsmoor et al., 2022; Lissek & van Meurs, 2014; Zuj et al., 2016). This inconsistency is especially notable given the prominence of extinction theories in the development of widely used exposure therapies for PTSD (Foa & Kozak, 1986; Zuj & Norrholm, 2019). Similar inconsistency arises for other anxiety-related disorders. Obsessive-compulsive disorder (OCD) is also commonly treated with exposure techniques, but conditioning deficits are inconsistent, and extinction results vary widely by protocol and sample (Cooper & Dunsmoor, 2021; Steuber & McGuire, 2022). There is also evidence both for and against heightened fear generalization in generalized anxiety disorder (GAD; (Lissek et al., 2014; Tinoco-González et al., 2015). Further, direct comparisons between disorders to clarify disorder-specific conditioning processes are hampered by discordance across measures and weak statistical evidence (e.g., Cooper et al., 2018; Rabinak et al., 2017).

Neuroimaging research has also yielded inconsistent results regarding the neural regions or circuits associated with threat conditioning processes in anxiety-related psychopathology. For example, a recent fMRI study of multiple anxiety-related disorders tested putative threat and safety brain regions during initial conditioning and immediate and delayed extinction (Marin et al., 2020). This study found relatively consistent evidence for impaired safety processing in ventromedial prefrontal cortex across anxiety-related disorders, yet failed to identify any disorder-specific neural

correlates of threat learning or extinction in canonical threat circuits (e.g., amygdala, insula, anterior cingulate). Other fMRI studies focusing on single disorders also yielded contradictory results (e.g., Fricke et al., 2023; Lange et al., 2019; Schwarzmeier et al., 2019).

Of course, there are many plausible reasons for inconsistent results, especially given the known methodological variability across different conditioning studies (Beckers et al., 2013; Lonsdorf et al., 2017, 2019) and experimenter degrees-of-freedom in neuroimaging analyses (Carp, 2012). Certainly, continued innovation in threat conditioning research is needed to improve reliability (Cooper et al., 2023; Klingelhöfer-Jens et al., 2022) and external validity (Beckers et al., 2013; Krypotos et al., 2018). Still, given inconsistent results and ongoing critiques of the DSM in both experimental psychopathology and clinical practice, it is time to consider whether the DSM system is hindering progress in understanding psychopathology using threat conditioning.

Critiques of the DSM Approach and the HiTOP Alternative

HiTOP emerged as a data-driven response to a variety of DSM critiques. We focus on the most common ones: heterogeneity, dichotomization ("the boundary problem"), comorbidity, and reliability. In the following subsections, we describe these key criticisms in relation to threat conditioning studies of anxiety-related psychopathology and how HiTOP-aligned approaches might resolve these issues. Table 1 summarizes these critiques, examples, and solutions, and an online repository for this effort (https://osf.io/maqnj/) contains HiTOP-related tutorials and resources. For critiques of the DSM beyond those most germane to experimental psychopathology and neuroscience, we refer the reader to Kotov et al. (2022) and Lahey et al. (2022).

Table 1. Overview of key DSM issues, their relation to threat conditioning, and HiTOP-aligned alternatives

DSM Limitation	**The Critique**	**DSM Disorder Example**	**Effect on Threat Conditioning**	**How HiTOP Can Help**
Heterogeneity	DSM categories use arbitrary thresholds that lead to large between-person variation in symptom profiles, such that two people with the same disorder can endorse entirely different sets of symptoms.	*PTSD:* criteria for diagnosis can be satisfied without manifest anxiety symptoms.	• Threat conditioning assumes anxiety-related disorders characterized by fear and anxiety symptoms, but heterogeneity means some with a disorder will have little to no anxiety symptoms. • Fear conditioning is mechanistic in nature, DSM obscures functional associations between symptoms that might be amenable to mechanistic accounts.	• Heterogeneity assumed and explicitly modeled in HiTOP and can be accounted for at different construct levels. • Structural modeling allows testing of specific mechanistic relationships between symptoms and threat conditioning processes.
Artificial dichotomization ("Boundary Problem")	DSM categories artificially bifurcate naturally dimensional psychopathological constructs, resulting in information loss and reifying an unsupported distinction between "illness" and "health".	*Panic Disorder:* panic attacks and related symptoms are distributed throughout the population.	• Threat conditioning processes are naturally dimensional and neuroscience-based models assume dimensionality. • Patient-control design results in information loss and truncated or incomplete distributions of psychological variables of interest.	• Dimensional scales negate need for categories and artificial boundaries. • Interpretation becomes more intuitive, based on quantitative relationships, and does not rely on vague qualifiers (e.g., "good" vs. "poor" extinction).

Comorbidity	Comorbidity is extremely common, and the DSM erroneously assumes each disorder is a distinct pathology.	*OCD:* psychosis-related problems identified in OCD, but any psychosis is excluded in most studies.	• Ubiquitous comorbidity, but inconsistent inclusion/exclusion criteria, creates difficulties in interpreting threat conditioning results. • Removes relevant variance from psychopathology not commonly considered as related to threat conditioning (e.g., depression, psychoticism), reducing generalizability.	• Many HiTOP-recommended scales are multidimensional measures with content that covers a broad range of psychopathology. • Removes need for (frequently idiosyncratic) inclusion/exclusion criteria.
Reliability	Many DSM disorders show poor reliability, especially when compared to strong reliability for dimensional approaches.	*GAD:* poor reliability for GAD diagnosis, stemming from substantial overlap with MDD.	• DSM disorder reliability limits use of DSM categories as outcomes for establishing criterion validity of threat conditioning.	• Dimensional psychopathology scales have excellent reliability • Can account for relatively poorer reliability for some constructs using appropriate modeling techniques.
Abbreviations. DSM = Diagnostic and Statistical Manual; GAD = generalized anxiety disorder; HiTOP = Hierarchical Taxonomy of Psychopathology; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; MDD = major depressive disorder.				

Heterogeneity

The critique. The symptoms that constitute DSM disorders reflect a mix of clinical observations and data constrained by the DSM's categorical paradigm. Further, the thresholds for a diagnosis are arbitrary. Consequently, two people diagnosed with the same disorder can have markedly different symptoms with varying degrees of interrelatedness and concordance with etiologic models, reducing the usefulness of the diagnostic label as both predictor and criterion.

Anxiety-related DSM disorders are not necessarily primarily characterized by fear and anxiety. Threat conditioning models assume that maladaptive fear and anxiety are the defining

characteristics of anxiety-related psychopathology (Dunsmoor et al., 2022; Zinbarg et al., 2022) and, therefore, that observed relations between threat conditioning indices and anxiety-related disorders supply meaningful information about learning and regulating fear and anxiety. However, fear and anxiety might not be the primary features for many with anxiety-related diagnoses. For example, under DSM-5 criteria, PTSD can be diagnosed without any manifest anxiety by endorsing primarily dysphoria and externalizing symptoms. Indeed, structural analyses show that PTSD coheres more closely with a distress factor characterized by depression and dysphoria rather than a purely fear-related factor (Watson, Clark et al., 2022), suggesting that across individuals, DSM-defined PTSD might not be consistently a disturbance of fear and anxiety. Practically, any relation between threat conditioning indices and PTSD is contaminated to some degree by dysphoria-related variance, and this variance is inconsistent across samples. Overall, the fundamental assumption that threat conditioning metrics covary with increases in anxiety symptoms is obfuscated when anxiety is operationalized as a DSM disorder.

Threat conditioning is concerned with mechanistic associations amongst symptoms that are obscured by DSM diagnostic criteria. Many etiological accounts of anxiety-related psychopathology emphasize the role of internal states or memories that prompt negative emotions or motivate external behaviors, such as avoidance. Conditioning theory has historically served as a leading experimental model for tests of such causal interrelations (e.g., concordance between subjective and neural threat indices; Taschereau-Dumouchel et al., 2020; fear leading to avoidance; Pittig et al., 2018). When applying the patient-control design to threat conditioning, an assumption is that the disorder group contains people who all display the same threat-related mechanistic relationship between particular symptoms. Following this logic, any differences between disorder and comparison groups on a threat conditioning index can be putatively linked

to a specific mechanism. For example, one could assume that all people with panic disorder avoid places associated with panic attacks, or that all people with PTSD avoid cues that remind them of a trauma, and then attribute performance on a threat conditioning task to these mechanistic relationships. This assumption would be workable if the DSM required the presence of these types of relationships for diagnosis, but that is not the case. Instead, there is no requirement for the emotional distress and avoidance symptoms to logically align with each other (e.g., one can meet PTSD criteria by endorsing emotional distress to internal cues but avoiding only external cues). A major strength of threat conditioning experiments is the flexibility they afford in creatively parameterizing real-world situations and dynamics, and one can generate many novel techniques to test the interplay of threat learning and avoidance, or extinction of emotional responding leading to corresponding physiological decreases. This flexibility is squandered with reliance on DSM diagnostic criteria and their de-prioritization of mechanistic links among symptoms.

How HiTOP can help. Heterogeneity in psychopathology is inherent to the theoretical and statistical underpinnings of the HiTOP model; it is a feature, not a bug (Conway et al., 2022). Modern statistical approaches (e.g., structural equation modeling; SEM) can simultaneously parameterize different independent and dependent psychopathology variables and their relationships with each other and with experimental threat conditioning indices (Sadikaj et al., 2021). Tests of significant bivariate relationships or more complex chains of relationships (paths) can evaluate different hypotheses related to threat conditioning and one or more psychopathology variables. A particularly appealing aspect of this approach is that in HiTOP, different threat conditioning processes can be simultaneously tested in relation to different symptoms from across the entire structure, not just DSM-siloed categories, to determine patterns that are not easily revealed in more traditional analyses. For example, impaired extinction learning and increased

contextual renewal likely both relate to symptom-level intrusive memories and more general hyperarousal, but to different degrees (Dunsmoor et al., 2022; Lissek & van Meurs, 2014). These types of complex relationships can be easily tested within the HiTOP model.

Dichotomization and the Boundary Problem

The critique. DSM disorders represent arbitrary boundaries, as there is no empirical basis for classifying a person meeting minimum criteria as "disordered" and one with all but one required criterion as "healthy" (i.e., the boundary problem; Kotov et al., 2017). Instead, extensive research establishes that psychopathology is dimensional in nature (Markon et al., 2011) and varies from the statistically normative range to the maladaptive extremes that are typically thought of as "illness."

Threat conditioning is dimensional, not categorical, and is poorly suited to categorical models of psychopathology. Inherent to neural threat conditioning models is that potential abnormalities in learning, retrieval, and regulation are a matter of degree, not kind. Modern human neuroscience does not posit that congenital malformations, encephalopathies, viral infections, or any other forms of cerebral insult are the root of (or even relevant to) maladaptive fear and anxiety. Instead, maladaptive threat conditioning is perhaps best conceptualized as the product of relatively stable characteristics and learning experiences that parametrically modulate the expression of fear and anxiety to problematic levels (e.g., Lonsdorf & Merz, 2017; Pittig et al., 2018). There is no inflection point or boundary demarcating "good" from "bad" threat learning, yet the DSM dichotomy encourages these distinctions.

Artificial dichotomization results in information loss. Because of the binary nature of DSM disorders, experimental between-subjects designs frequently employ a "healthy control" comparison. As previously discussed, this distinction is arbitrary and misrepresents mental illness

as a discrete disease state. We note two primary consequences of employing these boundaries. First, a tremendous amount of information is lost when reducing complex psychopathology data to a binary diagnosis. For example, DSM criteria for PTSD include 20 possible symptoms. Consider the information loss encountered when distilling 20 dimensional symptoms (e.g., very/somewhat/a little/not at all hypervigilant to threat) into a single binary (presence/absence of diagnosis), particularly given the sheer number of symptom combinations possible (Bryant et al., 2023; Galatzer-Levy & Bryant, 2013). From a statistical point of view, there is a dramatic decrease in variance, which leads to decreased precision when relating psychopathology and threat conditioning data. Second, a practical ramification of using DSM binaries concerns the control group. Information loss also occurs in these groups, as individual variability on psychopathology scales (i.e., small but non-zero responses) in the comparison group is lost and, problematically, assumed to be zero within the DSM model. Again, considering PTSD, evidence shows that PTSD symptoms are distributed throughout the entire population, often at subthreshold levels that would not meet DSM diagnostic criteria (Nelson et al., 2018). Additionally, many "control" participants are close to the diagnostic boundary and thus are more similar to "patients" than not (Kotov et al., 2017). As such, purported "control" groups are certainly not free of psychopathology variance and are better conceptualized as uncontrolled comparison groups (Lilienfeld et al., 2015). Further compounding this issue are inconsistencies in how patient-control groupings are formed. For neuroscience work, including or excluding psychotropic medication use in the control group in some studies, but not others, can considerably interfere with cross-study interpretations (Fullana & Simpson, 2016).

How HiTOP can help. HiTOP conceptualizes psychopathology as dimensional, removing the boundary problem as a concern and the need to construct problematic patient-control groups

(Kotov et al., 2017). Dimensional psychopathology data are also inherently compatible with threat conditioning data, as both comprise a set of continuous variables that are purportedly similar in distribution across the population (Lonsdorf & Merz, 2017). In terms of neuroimaging, complex circuit interactions are more readily conceptualized as covarying with a psychopathology dimension than as being qualitatively different when observed in a DSM disorder relative to the absence of psychopathology (e.g., Marin et al., 2020).

Comorbidity

The critique. In many cases, a single DSM disorder is insufficient to describe an individual's psychopathology (Krueger, 1999). Comorbidity, the co-occurrence of multiple disorders within the same person, is common for anxiety-related psychopathology. The ubiquity of comorbidity indicates that diagnostic categories might be too narrow and might not "carve nature at its joints." There is also no formal system for indicating etiological or functional relationships between disorders in the DSM, creating additional uncertainty around the practical meaning of co-occurring disorders.

Ubiquitous comorbidity of DSM diagnoses obfuscates interpretation of threat conditioning studies. As noted in previous commentary (Fullana et al., 2020), variation in handling comorbidity obscures the interpretation of threat conditioning processes in relation to psychopathology. A recent meta-analysis of threat generalization reported that the majority of analyzed studies included participants with comorbid diagnoses (Cooper, van Dis, et al., 2022). Additionally, some of the most highly-cited threat conditioning studies of DSM disorders included multiple comorbid conditions in the target disorder group (e.g., Blechert et al., 2007; Milad et al., 2009, 2013; Orr et al., 2000). The issue is that there is substantial variability in which comorbid conditions are allowable. Not only is diagnostic heterogeneity exacerbated within each study due

to these inconsistencies, but across-study heterogeneity and comparability are negatively impacted. From a mechanistic perspective, some frequently comorbid disorders are likely to relate to threat conditioning processes in opposite directions, presenting an unaccounted-for confounding factor. For example, GAD and major depressive disorder (MDD) are frequently comorbid, and both fall under a "distress" factor with substantial overlapping variance (Watson, 2005; Watson, Levin-Aspenson, et al., 2022). These presentations thus appear to reflect two facets of a higher-level classification rather than separate disorders, explaining their high comorbidity and shared genetic variance when classified categorically (e.g., Kendler et al., 2007). Despite this substantial overlap, the nonoverlapping (unique) aspects of GAD and MDD are likely to relate to threat conditioning measures of sympathetic arousal in opposing directions. The anxiety-relevant elements of GAD that are not shared with MDD might relate to more dysregulated threat conditioning (Lissek et al., 2014, but see Tinoco-González et al., 2015). However, meta-analytic evidence shows that sympathetic arousal is blunted in MDD, which could lead to confounding effects in common physiological measures (Bylsma et al., 2008). This creates major issues in interpreting patient-control differences if some or all individuals in a GAD patient group have comorbid MDD, and cross-study synthesis is even noisier if some patient groups exclude MDD comorbidities and some do not.

Attempts to control for categorical-diagnostic comorbidity limit the generalizability of threat conditioning work. The practice of disallowing any or certain comorbidities also has consequences. For most anxiety-related psychopathology, single-disorder presentations are rarely observed naturalistically; therefore, any study disallowing comorbidity has limited generalizability. For example, about 50% of people meeting criteria for PTSD also meet criteria for substance use disorder (SUD; Najavits et al., 2020). A common practice in DSM-oriented

research, including threat conditioning, is to exclude participants with SUD (Leeman et al., 2017). Even relatively consistent results, such as delayed threat extinction deficits in PTSD (Dunsmoor et al., 2022), must be considered in this context. Can we really conclude impaired extinction is characteristic of PTSD if the results are not necessarily relevant for half of people meeting PTSD criteria? Further, substance use often serves an avoidance function in PTSD (Weathers et al., 2018), and acute anxiety is strongly linked to avoidant substance use (Hawn et al., 2022). When those with SUD are excluded from study samples, variability in anxiety and avoidance is capped, limiting possible associations with threat conditioning. Similarly, psychosis (including mania) is often an exclusionary criterion in conditioning research. Yet, some of the most severe obsessions and compulsions found in OCD can be considered delusional (Cederlöf et al., 2015), severe OCD is commonly comorbid with psychosis (Cederlöf et al., 2015), and OCD loads strongly onto a psychoticism factor in structural modeling (Cooper, Hunt, et al., 2022; Faure & Forbes, 2021). Excluding psychosis therefore likely curtails the distribution of OCD severity in threat conditioning studies, which reduces generalizability. It also creates conundrums for bench-to-bedside research, as threat conditioning results might not be appropriate to inform improved treatments for OCD if said results do not apply to severe and difficult-to-treat cases. Relatedly, schizophrenia has been associated with differences in threat conditioning processes (e.g., Holt et al., 2009; Tuominen et al., 2021), further emphasizing the pitfalls of excluding psychosis-variance from future research on anxiety-related psychopathology.

How HiTOP can help. In HiTOP, the relationships between anxiety-related constructs of interest to threat conditioning researchers and other psychopathology constructs can be incorporated as known parameters. Therefore, to establish specificity of threat conditioning effects on anxiety-related constructs, it is beneficial to include and assess a wide range of forms of

psychopathology (per recommendations, see Ringwald et al., 2023). Importantly, sampling does not need to be based on group designations and instead can include a broader swath of the population (Kotov et al., 2017). Another benefit is that auxiliary hypotheses or alternative explanations regarding other forms of psychopathology can be tested. For example, assessing psychopathology more comprehensively can help neuroimaging researchers answer research questions about neural regions that are less involved in threat conditioning but have strong conceptual and empirical links to anxiety-related psychopathology, such as reward-related regions implicated in depression (Young et al., 2021).

Reliability

The critique. Many DSM anxiety-related disorders have poor interrater reliability (i.e., two clinicians disagreeing on a diagnosis), and reliability varies across anxiety-related disorders. DSM-5 field trials found unacceptable to questionable reliability for GAD and MDD, questionable reliability for OCD, but good reliability for PTSD (Regier et al., 2013); panic disorder also shows inconsistent reliability (Craske et al., 2010). Internal consistency (i.e., degree to which each item measures the same construct) is also limited for these categorical diagnoses (Shankman et al., 2018). Across all areas of psychopathology, dimensional assessments consistently outperform DSM dichotomies on reliability measures (Markon et al., 2011; Shankman et al., 2018).

DSM disorders are not reliable enough to consistently show robust associations with threat conditioning. Threat conditioning, as with most experimental approaches, is largely concerned with mean differences between manipulated conditions, which are under experimental control and thus have essentially perfect reliability. For example, if assigning one participant to a "stress" condition and another to a "control" condition, there is no uncertainty on the assignment

and the objective differences between conditions. These are true categorical variables and are appropriately modeled as such. DSM disorders, on the other hand, are not under experimental control and are thus quasi-experimental categorical variables. Unfortunately, threat conditioning work has largely relied on categorical-by-categorical interactions in analysis of variance (ANOVA) and similar models to identify diagnosis-related differences in conditioning indices (e.g., Experimental-condition x Disorder, as meta-analyzed by Duits et al., 2015). DSM disorder reliability limits the reliability of this interaction, yet this is not reflected in the model and rarely, if ever, discussed at the conceptual level. To put this in perspective, consider a scenario in which the analyst was uncertain if a particular participant had been assigned to the "stress" or "control" condition and applied a checklist of indirect indicators to make decisions. Experimental researchers would never accept anything close to this level of uncertainty in their analyses. Yet, this is exactly the situation when applying the DSM paradigm: for many disorders, there is a meaningful chance that the participant is "assigned to the wrong group," to the extent that such groups even exist (see above).

How HiTOP can help. Reliability for HiTOP-aligned measures are typically in the good to excellent range (e.g., Lebeau et al., 2012; Markon et al., 2011). Further, if reliability is a concern for a given investigation, structural models commonly applied to HiTOP variables can quantify and adjust for this issue (e.g., Yang & Green, 2010) and provide options other than assuming groups are perfectly reliable.

Obstacles in Implementing HiTOP Within Threat Conditioning Research

To facilitate the uniting of threat conditioning and HiTOP, we consider current barriers to its adoption in research, particularly those affecting threat conditioning researchers who typically study DSM-defined groups.

Integrating Two Streams of Research

One issue challenging the integration of threat conditioning and HiTOP is their derivation from distinct "streams" of psychological science (Cronbach, 1957) characterized by differing research questions, methods, and statistics. HiTOP is a part of the *correlational* stream, focused on description of the nature and covariance of traits using techniques such as regression and factor analysis. Threat conditioning comes from the *experimental* stream, which emphasizes mean differences between circumscribed and well-controlled experimental conditions using *t*-tests and ANOVAs. Cronbach (1957) hoped that the complementary strengths of these streams would someday merge, allowing for the experimental study of individual differences (e.g., psychopathology). For this merge to occur in threat conditioning, our theories and statistical methods must be adapted to account for individual differences, which are considered the outcome of interest in correlational research but unwanted error variance in experimental research.

Considering distribution. Instead of focusing exclusively on mean differences between conditions (e.g., CS+ vs CS-), we suggest greater emphasis on the data's *distribution*. For example, consider two threat-related experimental conditions yielding identical mean responses but notably differing variances. The "noisier" variable will have a smaller test statistic and larger *p*-value when compared to the control condition but might contain systematic variance related to individual differences on a psychopathology dimension (Hedge et al., 2018). When deciding which conditions are worthy of further exploration, the "noisy" one might be more relevant for psychopathology work.

Choosing optimal statistical tests. Experimental research typically uses tests of mean differences (e.g., repeated-measures ANOVA). Continuous variables are incorporated into such models using covariance subtraction methods (i.e., analysis of covariance; ANCOVA) or are

analyzed in relation to a threat conditioning composite (e.g., CS+ minus CS-) using simple bivariate correlation or multiple regression. However, this repertoire of statistical methods is inadequate for testing associations between threat conditioning and dimensional psychopathology variables. Regarding threat conditioning variables, experimental tasks are frequently clustered, repeated-measures designs that yield multiple indices, and processes of interest are often characterized by interactions between different conditions (Lonsdorf et al., 2017). Standard correlations or linear regression are not appropriate to model these designs and repeated-measures ANOVA cannot, in most cases, model continuous independent predictors without violating statistical assumptions (Field & Wilcox, 2017; Field & Wright, 2011). Moreover, the hierarchical structure of HiTOP cannot be easily incorporated into such models. Attempts to manipulate threat conditioning or psychopathology variables to suit these models (e.g., creating experimental difference score composites; artificially dividing psychopathology dimensions into groups) have significant drawbacks (Castro-Schilo & Grimm, 2018). Not only do such approaches harm reliability and validity, as discussed above, but they also artificially reduce variance, which in turn attenuates associations between neurobehavioral conditioning and psychopathology variables (Meyer et al., 2017).

Fortunately, appropriate models for these questions exist, as do resources that make them more approachable to researchers. For more flexible modeling of threat conditioning data that permits testing continuous psychopathology indicators while properly modeling the repeated-measures aspect of the data, resources include tutorials on mixed effects regression (i.e., multilevel or random-effects regression) (Field & Wright, 2011; Vanbrabant et al., 2015), Bayesian regression (Krypotos et al., 2017), and “multiverse” approaches that simultaneously consider more flexible and more limited statistical approaches (Lonsdorf et al., 2022). For modeling the (latent)

structure of psychopathology and refining the psychopathology indicators linked to threat conditioning, (multilevel) SEM is recommended; both HiTOP-specific (Conway et al., 2021; Tiego et al., 2023) and more general tutorials are available (Sadikaj et al., 2021).

Sample sizes for psychopathology research. Relatedly, well-powered individual-difference studies of psychopathology require larger samples than those typical of experimental research, including threat conditioning. Average sample sizes of N~65 in threat conditioning work (see Lonsdorf & Merz, 2017) are well below the minimum N~200 needed for modest correlations to stabilize (Kretzschmar & Gignac, 2019; Schönbrodt & Perugini, 2013). We recognize that vastly increasing sample size incurs substantial time and resource burdens, particularly for MRI research, but it is likely necessary for clinically-relevant progress (Marek et al., 2022). To lessen the load, we recommend borrowing techniques already established in personality and psychopathology neuroscience, such as collecting multiple neural and behavioral indicators, oversampling from the higher end of psychopathology dimensions of interest, and administering a standard set of psychopathology questionnaires across similar studies to facilitate multi-study analyses (Latzman & DeYoung, 2020; Mar et al., 2013). Consortium-level and open-science efforts to pool similar data (e.g., Bas-Hoogendam et al., 2022; Ehlers & Lonsdorf, 2022; Forbes, Fried, et al., 2023) and to collect new multi-site data (e.g., Bach et al., 2023) will also be crucial for amassing datasets with sufficient power.

Avoiding Pitfalls of Psychopathology Conceptualization and Measurement

Notably and admirably, many threat conditioning researchers are trying to move away from studying specific DSM diagnoses. Here, we detail some commonly used but potentially problematic approaches to this goal and explain why a HiTOP-aligned strategy is preferable.

Transdiagnostic lumping. Recent threat conditioning work has compared a transdiagnostic group with any anxiety-related disorder to non-psychiatric controls (e.g., Fyer et al., 2020; Marin et al., 2020). This conceptual rationale aligns with the notion of higher-order commonalities among manifestations of anxiety, in keeping with HiTOP. However, it is still hamstrung by reliance on (a set of) DSM diagnoses for grouping — meaning the above-noted criticisms of DSM still apply, particularly the issue of excessive heterogeneity. In addition to basic distinctions in presentation, there are considerable differences in average distress and impairment across anxiety-related disorders (e.g., Naragon-Gainey et al., 2014). Therefore, transdiagnostic lumping introduces another confounding dimension that is not typically addressed conceptually or statistically. The HiTOP approach does not have these limitations, as it allows the analyst to simultaneously test which threat conditioning indices relate to higher-level anxiety constructs (e.g., spectra, subfactors) compared with lower-level constructs (e.g., symptoms, behaviors), both of which benefit from stronger reliability compared with lumped DSM disorders (Markon et al., 2011). This approach thus broadens the set of hypotheses that can be tested in a rigorous manner.

Assumption that dimensional measures only capture psychopathology in specific samples. The growing number of threat conditioning investigations using dimensional anxiety and psychopathology scales, some of which are testing much larger sample sizes than previously seen, is an encouraging sign. One obstacle is that even when collecting dimensional data, many studies tend to conceptualize psychopathology itself as binary (present vs. absent). A common framework is that, when assessed in community samples, higher scores on dimensional anxiety-related traits are conceptualized as conferring *risk* for developing (binary) psychopathology (e.g., Beckers et al., 2023; Lonsdorf & Merz, 2017; Sep et al., 2019; Zinbarg et al., 2022). In other words, a dimensional index of anxiety-related traits — yielding scores reflecting a wide range of severity,

including the "extreme range" — is incorrectly assumed to reflect risk and *not psychopathology itself* when administered to an unselected community sample, in comparison to one explicitly recruited for psychopathology. Despite using a dimensional measure, this approach implicitly subscribes to an artificially dichotomized notion of psychopathology as present or absent rather than being able to vary continuously in the general population. The same logical misstep also encourages dichotomization of naturally continuous threat conditioning processes and shifts descriptions from measurable covariation between psychopathology and threat conditioning (e.g., decreased extinction learning as psychopathology increases) to arbitrary categorical definitions of both psychopathology and maladaptive threat conditioning when no actual boundary exists (e.g., poor extinction or overgeneralization). Finally, it inherently devalues traits not represented in the DSM nor traditionally used to define "clinical" populations but have strong conceptual and empirical relations to pathological anxiety and threat conditioning (e.g., intolerance of uncertainty, see Morriss, Wake, et al., 2021; Morriss, Zuj, et al., 2021). This is a non-issue with HiTOP, as its constructs explicitly apply across purported clinical and non-clinical boundaries, and common HiTOP-aligned measures capture the full range of individual variation.

Undue focus on siloed psychopathology constructs. DSM diagnoses are embedded in many research traditions and appear to linger even when studies have shifted to non-DSM dimensional approaches. A primary example here is that the DSM's artificial framework is implicitly reified when threat conditioning studies include only a narrow set of anxiety-related variables and do not consider other related constructs, such as mood and problematic substance use. Essentially, this mirrors the issues in attempting to study "pure" DSM disorders and excluding any comorbidities. A narrow focus on a particular construct, even when measured dimensionally, is unlikely to be productive, given empirical consensus that psychopathology is multidimensional

and interrelated (Kotov et al., 2017). To circumvent this issue and better align with the clinical reality of anxiety-related psychopathology, we recommend that researchers consider the full HiTOP structure when planning study measures and analyses.

Using the the Research Domain Criteria (RDoC) to conceptualize psychopathology. There have been some attempts to formally integrate the RDoC system (Cuthbert & Insel, 2013) with threat conditioning, including a handful of conditioning investigations framed as RDoC-inspired or -compliant (e.g., Briscione et al., 2014; Marin et al., 2020). These are important intermediary steps to dimensional psychopathology analyses in the threat conditioning field. However, we note that while RDoC moves away from DSM disorders, it is not itself a psychopathology classification system; it is a collection of neurobehavioral dimensions and operationalizations with inconsistent coverage of the full range of psychopathology (e.g., trauma-related symptoms; see Hawn et al., 2022). Instead of a target for future research, we see RDoC as a valuable framework to conceptualize narrow psychobiological constructs (specific symptoms and behaviors) within the HiTOP structure and as a common language across experimental paradigms (e.g., Michelini et al., 2021). In short, we propose that RDoC has an important role as an interface between the heavily self-report- and interview-based HiTOP structure and the neurobehavioral framework of threat conditioning.

How Threat Conditioning Can Benefit HiTOP

As noted above, we contend that HiTOP will improve threat conditioning research on anxiety-related psychopathology by providing a hierarchical-dimensional model of clinical symptoms. Reciprocally, we also note that threat conditioning research itself can inform the ongoing evolution of HiTOP in several ways.

Refining the HiTOP Structure

On a basic level, threat conditioning metrics could serve as a reference point for iterative refinement of report-based scales (see Joyner & Perkins, 2023) to ensure they reflect the foundational psychobiological construct of interest (e.g., ensuring self-reported hypervigilance taps into threat generalization). This approach would help ensure that RDoC constructs, as evident within threat conditioning paradigms, are infused into HiTOP-aligned assessments, preventing these measures from becoming contaminated with excessive method-specific variance.

In addition, we contend that threat conditioning is well suited to advancing the HiTOP model as a criterion validator. The current model is derived from patterns of co-occurrence among report-based symptoms; importantly, however, the HiTOP initiative explicitly calls for external validation using variables from other measurement modalities (e.g., Perkins et al., 2020). As such, threat conditioning studies of HiTOP dimensions can provide crucial information about the validity of the existing structure, lending credence to (or raising questions about) the placement of constructs based on their relative coherence with neurobehavioral indices of threat conditioning. For example, increased difficulty extinguishing threat might strongly covary with both behavioral avoidance and negative emotionality traits, which are currently placed in different subfactors of the model (Watson, Levin-Aspenson, et al., 2022). This information could contribute to the ongoing refinement of the HiTOP model to better represent the nature of psychopathology and its constituent neural substrates.

Facilitating Integration of HiTOP with Neuroscience-Informed Intervention Research

HiTOP offers new opportunities for innovative treatment research (Hopwood et al., 2020), including neuroscience-informed interventions (Latzman & DeYoung, 2020). Threat conditioning can provide an interface between the two. Specifically, neurobiologically-characterized conditioning processes provide intermediary targets for precision interventions (e.g., improved

extinction) that are then directly related to the behavioral and subjective processes of interest for treatment. For example, psychopharmacological techniques to enhance extinction learning can then be related to the HiTOP structure to determine the influence of these strategies on different levels of psychopathology. A particularly intriguing avenue for future work is causal brain manipulations that induce larger neurobehavioral effects than seen in other intervention areas (see Webler et al., 2023). These include focal brain stimulation techniques such as transcranial magnetic stimulation (TMS) that can elucidate whether a given brain area, circuit, or network is causally linked to a candidate behavior. These techniques are used to map psychopathology-symptom networks (e.g., Siddiqi et al., 2021) and conditioning-related circuits (e.g., Raij et al., 2018), but have not yet been used in the context of empirical psychopathology structures. Accordingly, future multimodal threat conditioning studies that leverage causal methods to intervene on HiTOP constructs might represent an exciting next step in improving precision, neuroscience-guided intervention.

Conclusions

Threat conditioning models provide mechanistic insights into anxiety-relevant threat learning and regulation and can be operationalized with multiple neurobehavioral indices. Using threat conditioning to study anxiety-related psychopathology has been hampered by the limitations of the DSM system, limitations that modern dimensional models address. Integrating HiTOP – an empirically derived, hierarchical, dimensional nosology – with threat conditioning could assist in clarifying an inconsistent literature and reveal heretofore obscured links between conditioning mechanisms and anxiety-relevant constructs measured at narrow to general levels of abstraction (i.e., symptoms to spectra). Such links could improve our knowledge of the neurobehavioral substrates of variation in anxiety-related psychopathology variation while supporting the

generation of novel, mechanistically informed intervention efforts that leverage HiTOP measures to inform patient selection and that target specific conditioning processes (i.e., at the behavioral or neural level) and their interactions with HiTOP constructs.

Overall, we support a unified HiTOP-threat conditioning framework that extracts maximal value from and builds on the existing DSM-based literature. An ideal transition to HiTOP will involve harnessing the insights generated from the large DSM-aligned threat conditioning literature, which has illuminated tentative relationships (albeit inconsistent) between threat conditioning and anxiety-relevant psychopathology. These relationships will inform hypotheses that can be tested using reliable, valid, and comprehensive HiTOP measures. Leveraging HiTOP measures while also continuing to assess DSM diagnostic criteria will also support backward translation to the DSM-based literature (Ringwald et al., 2023). Finally, we want to emphasize that the present effort (1) focuses on only one potential solution to individual differences and variance in threat conditioning work and (2) that this solution can be applied to other experimental models of psychopathology, not just threat conditioning. We hope that the critiques, discussion, and recommendations here will provide a reference for broader conversations on integrating HiTOP with experimental psychopathology and neuroscience traditions.

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