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UNDERSTANDING HETEROGENEITY IN PTSD: FEAR, DYSPHORIA, AND DISTRESS

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Abstract

Fear, dysphoria, and distress are prominent components in the conceptualization of posttraumatic stress disorder (PTSD). However, because our diagnostic categories are open concepts, relying on observed patterns of symptoms for classification, it is unclear whether these components represent core or auxiliary features of the disorder. Convergence across multiple indices is critical for this understanding. In this paper, we examine these components of PTSD across observed symptom patterns, broader theoretical conceptualizations, underlying information processing mechanisms of attention and memory, and underlying learning and neurobiological mechanisms. For each, evidence for similarity or distinctiveness of PTSD with other anxiety disorders and depression is examined. Throughout the review, key points of similarity to the anxiety disorders and divergence with depression argue for a distinction between core fear symptoms and auxiliary dysphoria and distress symptoms. Implications are discussed, noting that, as heterogeneity increases, core characteristics will become more diffused and ancillary constructs will gain an inflated degree of importance.

Keywords

PTSD; Fear; Depression; Dysphoria; Distress; Anxious-Misery

INTRODUCTION

Psychiatric diagnostic categories commonly exhibit considerable symptom heterogeneity. Posttraumatic stress disorder (PTSD) is no exception, with some symptoms being similar to “distress” disorders, such as generalized anxiety disorder (GAD) and major depressive disorder (MDD), and others being similar to fear and anxiety disorders, such as panic disorder, social anxiety disorder, and specific phobias. Three recent developments in our field highlight the necessity to better understand the observed heterogeneity in PTSD. First, understanding the commonalities across diagnostic categories underlies the National Institute of Mental Health’s (NIMH) Research Domain Criteria (RDoC).^[1] RDoC seeks to define basic transdiagnostic constructs across multiple units of analysis from genes to neural circuits to behaviors in order to rapidly develop an integrative understanding of psychopathology and improve treatment development. Second, although PTSD criteria in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV-TR)^[2] have been criticized for being too heterogeneous,^[3] the revisions in DSM-5 increases the number of symptoms from 17 to 20, increasing its heterogeneity. Further, DSM-5 reconceptualizes PTSD as a “trauma and stressor-related disorder” instead of an anxiety

disorder, shifting the focus away from fear and anxiety. Third, the highly debated^[4] proposed disorder of complex PTSD seeks to capture symptoms observed in survivors of prolonged trauma that differ from “simple” PTSD. Understanding the heterogeneity within PTSD will help in clarifying whether complex PTSD fits inside and outside PTSD boundaries. Taken together, each of these developments depends, in part, upon having a clear understanding of PTSD’s similarities and differences across diagnostic categories.

In this paper, we examine three components of heterogeneity in PTSD that are shared with other disorders: fear, dysphoria, and distress. These terms are defined in a variety of ways that are often overlapping and add to confusion within the field. We roughly adopt the convention of Clark and Watson^[5, 6] examining specific (e.g. fear, dysphoria) and nonspecific (e.g. distress) components. Fear refers to an alarm response to present or imminent danger that is real or perceived.^[7] It has better specificity to the anxiety disorders and includes such symptoms as marked physiological hyperarousal and fear-specific avoidance. Dysphoria refers to an absence of positive mood and pleasurable experiences. It has better specificity to depression and is related to symptoms such as hopelessness, extreme fatigue, anhedonia, and psychomotor retardation. Finally, distress refers to a nonspecific factor, reflecting general anxious, and depressed mood. It is often labeled as neuroticism, general maladjustment, negative emotionality, or negative trait affect. When discussing study results throughout the manuscript, we utilize the author’s original terminology and shift back to the terms fear, dysphoria, and distress when synthesizing the material.

Because our diagnostic categories are open concepts,^[8] relying on observed patterns of symptoms for classification rather than both observed and underlying processes, it is unclear whether observed symptoms represent specific or nonspecific features of a disorder. Although important to understand their presence, the inclusion of nonspecific symptoms may increase the heterogeneity of the disorder, interfere with identification of comorbid disorders, and obscure the understanding of core underlying disease processes. Convergence across observed and underlying processes and in comparison with anxiety and depressive disorders is critical for better understanding PTSD. Accordingly, in this paper, we will examine fear, dysphoria, and distress components of PTSD across observed symptom patterns, broader theoretical conceptualizations, underlying information processing mechanisms of attention and memory, and underlying learning and neurobiological mechanisms. These areas were chosen in that they reflect an emerging evidence base to explore similarity or distinctiveness of PTSD to other anxiety disorders and depression. If the observed heterogeneity is more consistent with the distress rather than fear disorders, individuals with PTSD should be more similar to depression and GAD than to the anxiety disorders across these indices.

STRUCTURAL AND SYMPTOM ANALYSES

We initially start by examining the associations among diagnosed mental disorders and among symptoms. These studies, based on patient-report and clinician-rated symptoms, focus on observed patterns of association but do not address underlying processes.

Comorbidity occurs frequently among mental disorders, and PTSD is no exception.^[9] Unlike other anxiety disorders, with the exception of GAD, PTSD shares diagnostic symptoms with MDD, including anhedonia, difficulty sleeping, irritability, and difficulty concentrating. Not surprisingly, epidemiological data show that between 48 and 55% of people with PTSD have comorbid MDD.^[10, 11] Using tetrachoric correlations, PTSD and MDD are significantly associated with one another (.50), showing a similar degree of association to other anxiety disorders with MDD (.42–.60).^[9]

Some have suggested that PTSD and cooccurring PTSD and MDD after trauma exposure may be the same construct and that their separation may be arbitrary.^[12] Indeed, when exploring predictors of chronic PTSD versus cooccurring PTSD and MDD, O'Donnell et al.^[12] found nearly identical sets of predictor variables. Accordingly, removing nonspecific symptoms of distress from PTSD may help improve its validity.^[13–16] However, several studies have shown that this does not substantially affect PTSD prevalence or comorbidity with MDD.^[10, 17–19] Instead, other factors may account for their high comorbidity.^[20, 21]

Negative affect^[22, 23] is a dimension of emotional experience that may help account for the high rates of comorbidity seen in PTSD. In the well-replicated tripartite model,^[24, 25] a negative affect factor, consisting of general subjective distress and dissatisfaction, and two lower order factors of anxiety (anxious arousal) and depression (low positive affect) emerge. These three factors are relatively stable temperamental traits. Negative affect has a substantial genetic loading and functions as a shared vulnerability factor across anxiety disorders and depression.^[26] This negative affect factor may be largely responsible for the high comorbidity rates of anxiety and depression^[20] and may account for the high comorbidity rates of PTSD with depression. Consistent with this, Post et al.^[27] found that in comparison to PTSD alone, individuals with PTSD and cooccurring MDD reported elevated dysphoria, higher levels of negative affect, and lower positive affect.

Structural evidence examining the associations among mental disorders is generally consistent with the tripartite model, with confirmatory factor analyses (CFA) supporting externalizing and internalizing factors.^[28–32] These studies suggest that fear disorders involve high fearfulness to specific stimuli whereas distress disorders are characterized by elevated negative affectivity.^[20, 25, 26] CFAs specifically including PTSD have been equivocal.^[28, 31] Cox et al.^[28] found that PTSD had a significantly smaller loading on a distress factor than other distress disorders; whereas, Slade and Watson^[31] found that factor loadings for PTSD were consistent with other distress disorders. This discrepancy may be explained in that Cox et al. used the International Classification of Diseases (ICD-10) criteria for PTSD, which contains fewer dysphoria symptoms than DSM-IV. Ultimately, structural analyses of associations among disorders are dependent on any hierarchical structure created by the overarching system and the symptoms chosen to be included for any disorder. Nevertheless, these analyses point to a separation between fear and distress disorders, with a lack of clarity on where PTSD belongs.

Symptom-level analyses point to a significant nonspecific component of subjective distress in PTSD. These analyses have disconfirmed the three-cluster DSM-IV model of PTSD in favor of four-factor models.^[33] One of two additional factors emerge: either a “dysphoria” factor corresponding to DSM-IV avoidance symptoms C3–C7^[34] or an “emotional numbing” factor, including the same avoidance symptoms with two hyperarousal symptoms (D1–D2).^[35] Several lines of evidence strongly suggest that symptoms included in these factors actually index high subjective distress and lack specificity to PTSD.^[21] First, dysphoria is correlated with depression more than with general anxiety,^[34] GAD,^[36] and other PTSD symptoms.^[34] Second, when comorbid MDD is present, dysphoria-related symptoms tend to be elevated to a greater degree than other PTSD factors.^[21] Third, the inclusion of self-reported depression significantly attenuates factor loadings for dysphoria symptoms but not as much for other PTSD factors.^[34] These findings call into question the utility of including nonspecific distress symptoms.^[16] As Watson^[21] stated, “...it is not clear that it is necessary—or even desirable—to build such a strong distress component into the diagnosis of PTSD” (p. 242).

But to what extent does PTSD contain a fear component? PTSD was originally conceptualized as an initial intense fear reaction followed by fear-related intrusions and both

cognitive and behavioral avoidance of fear-eliciting stimuli.^[37, 38] Fear has received less attention than distress within the structural modeling approach despite the fact that the remaining factors of the Simms et al.^[34] model of DSM-IV PTSD, specifically reexperiencing (criteria B1–B5), active avoidance (C1–C2), and hypervigilance/startle (D4–D5), are not shared with MDD.^[20, 39, 40] Forbes et al.,^[40] in a large prospective study, found that these PTSD-specific symptoms loaded more highly onto the fear than distress factor, whereas PTSD-nonspecific symptoms (dysphoria) loaded more highly onto the distress factor. This study argues for an increased emphasis on fear symptoms and de-emphasis on dysphoria in PTSD.

Taken together, based on structural and symptom findings, distress, dysphoria, and fear components of PTSD consistently emerge. CFAs will continue to yield these components as long as nonspecific distress and dysphoria symptoms are prominently represented in the PTSD diagnostic criteria. This is in contrast to other anxiety disorders, where, although often present, these symptoms are often not included in the diagnostic criteria. Ultimately, convergence between these observed structure of symptoms and other levels of analysis, reviewed below, is necessary to move toward understanding underlying disease processes.^[41, 42]

THEORETICAL CONCEPTUALIZATIONS OF PTSD

In contrast to the atheoretical approach used with observable symptoms, theoretical conceptualizations take largely a top-down approach for understanding PTSD. In this section, we will briefly discuss basic PTSD and depression models, examining associative, evolutionary, and cognitive theories.

As with the other anxiety disorders, fear plays a central role in major theoretical models of PTSD. Fear is a highly adaptive response of the mammalian defensive motivational system to perceived environmental threats, involving the coordinated engagement of physiological, behavioral, and, in humans, verbal responses.^[17] Through basic associative learning processes, these responses become associated with both the fear-eliciting stimulus and incidental neutral stimuli present at the time of the event. In humans, the association between stimulus information and behavioral response is also thought to include the meaning of this association to the individual. This meaning element serves to further strengthen the relationship between stimulus and response elements and determines the contexts in which this association will become activated.^[43] This may represent a universal process that allows an individual to learn from experience, adapt to the environment, and ultimately increase survival. However, pathological anxiety, such as in PTSD, is thought to develop when this meaning element becomes catastrophic (suggesting current threat or danger), the response becomes exaggerated, and the stimuli that activate this fear network becomes overgeneralized.^[43] These pathogenic processes are thought to be associated with a failure to inhibit fear in objectively safe situations, deficits in responding appropriately to safety cues, an overgeneralization of the fear response, and a failure of normal extinction processes.^[44] Evolutionarily, the signs and symptoms of PTSD are thought to involve a self-preservation function,^[38, 45] akin to other anxiety disorders. In contrast, the main associative learning models of depression, though implicated in animal models of PTSD,^[46] emphasize both a lack of positive reinforcement for adaptive behavior and exposure to inescapable chronic stressors, including models of conditioned defeat and learned helplessness.^[47] Evolutionary models for depression are less straightforward than ones for fear. They suggest that depression confers evolutionary benefit by enhancing some forms of in-depth analytical processing or the ability to fight infection.^[48]

Heightened conditioning and failure of extinction processes may not be sufficient to account for the persistence of fear beyond initial conditioning, including conditioning following traumatic events. Other processes, such as personality, genetics, interpersonal factors, cognition, and verbal behavior, operate in tandem with the basic learning processes, informing expectancies about both conditioned and unconditioned stimuli.^[49, 50] The nature of these expectancies form the basis for cognitive theories. In the anxiety disorders, these processes often affect an individual's worldview, including perceptions of uncontrollability and unpredictability.^[51] Both uncontrollability and unpredictability are core constructs across fear and anxiety^[49, 52] and are thought to produce strong feelings of impending danger, threat, and doom.^[53] Indeed, the sense of an uncontrollable and unpredictable future, particularly in terms of threat, is thought to be important for the maintenance of PTSD symptoms.^[54] These beliefs serve as a means to filter, code, and evaluate information.^[55] In contrast, cognitive theories of depression, including hopelessness theory^[56] and Beck's cognitive theory,^[57] also emphasize uncontrollability, but highlight beliefs that highly desirable outcomes will not occur and that adverse outcomes will occur. Notably, related themes are of loss, inadequacy, failure, hopelessness, and worthlessness. Anxious themes, however, involve the inability to control or cope with negative future events.

In summary, associative, evolutionary, and cognitive models of PTSD and depression diverge, with ongoing threat being implicated in PTSD and learned helplessness, conditioned defeat, and hopelessness implicated in depression. These theories help set up divergent expectations regarding underlying attention, memory, learning, psychophysiology, and neurobiological processes.

INFORMATION PROCESSING

In this next section, both attention and memory processes in PTSD will be examined and contrasted with depression and anxiety disorders. Attention enables the detection and selection of stimuli, and memory helps determine what information is salient or worthy of attention.^[58]

When attending to nonemotional stimuli, individuals with PTSD generally show normal attentional processing but show some possible impairment in sustaining attention over time.^[67] In monozygotic twin pairs discordant for trauma exposure, this impairment for nonemotional stimuli appears not to be a consequence of PTSD but rather a familial risk factor.^[60] Comparing trauma- or threat-relevant to neutral stimuli, individuals with PTSD consistently exhibit an attentional bias toward threat.^[61, 62] This pattern is consistent with overgeneralization of fear responding.^[59, 63] Individuals with severe PTSD also exhibit delayed disengagement of attention from trauma-relevant information compared to low-PTSD controls.^[64] These attentional processing deficits in PTSD are broadly consistent with findings in individuals with panic disorder, social phobia, and specific phobia.^[65]

Clinically depressed individuals show several attentional abnormalities that are distinct from those observed in PTSD and other anxiety disorders. In the limited studies examining simple or sustained attention in individuals with depression, impairments are slightly greater than in nondepressed controls.^[66] These depression-linked deficits exist in attentional processing of both nonemotional^[59] and emotional information.^[80] Specifically, clinically depressed individuals are slower to disengage attention from negative cues,^[81] more susceptible to attentional interference by negative information,^[108] and less successful in inhibiting task-irrelevant negative information relative to nondepressed individuals.^[69] This attentional bias is most evident on tasks that have longer response times (1,000 ms or more), encourage elaborative processing of self-relevant content or socially relevant content, and involve

negative stimuli.^[70] By comparison, in anxiety disorders, including PTSD, attentional bias can be detected at 500 ms or less in response to threat-relevant stimuli.^[68] Thus, depressed individuals exhibit abnormal attention involving slower, more elaborative processing across a broader range of stimulus contents. Individuals with PTSD show relatively fast, automatic attentional abnormalities involving specificity to threat.

Memory is implicated in the intrusive, involuntary retrieval of traumatic memories, and their associated avoidance in PTSD.^[71] Because attention is a necessary component of many memory processes, it is difficult to obtain evidence of memory deficits that cannot also be explained by attentional abnormalities.^[72] Research on memory biases in PTSD has primarily examined cued autobiographical recall, general memory, and episodic memory for trauma-relevant stimuli. Compared to healthy controls, individuals with PTSD recall less specific autobiographic memories in response to trauma-relevant memory cues than neutral memory cues.^[73] In two metaanalyses, PTSD has been associated with a small- to medium-effect-size impairment in memory for neutral information, particularly for verbal but not visual information.^[74, 75] In monozygotic twin pairs discordant for trauma exposure, this impairment of verbal but not visual memory for neutral information appears not to be a consequence of trauma exposure and PTSD but rather a familial risk factor.^[60] Although enhanced memory for threat-relevant material is often observed, individuals with PTSD do not recall threatening or negative stimuli more than nonanxious individuals within studies that account for attentional bias during encoding.^[72] However, deficient executive control for trauma-relevant information is implicated in PTSD, including encoding deficits on working memory tasks.^[76] Individuals with PTSD also show deficits in the ability to “forget” newly studied trauma-relevant words compared to healthy controls on memory-interference tasks.^[86] Thus, individuals with PTSD may recall overgeneral, trauma-relevant autobiographical memories and retain trauma-relevant information longer than nonanxious individuals. Other anxiety disorders have shown similar patterns of autobiographical memory deficits (e.g. social phobia, panic disorder^[77]), enhanced memory for threat-relevant stimuli (e.g. panic disorder^[78]), and deficits in inhibitory control for threat-relevant information (e.g. OCD,^[79] panic disorder^[80]).

Memory processes may be central to clinical depression in ways that are both similar to and different from PTSD. Several neuropsychological studies in depression show impairment on working memory tasks, including both verbal and visual stimuli.^[81–84] As in PTSD, clinically depressed individuals recall less specific autobiographical memories in response to negative, compared to neutral or positive, memory cues.^[85] However, whereas PTSD has been associated with impaired forgetting of trauma-relevant words, data from similar paradigms in clinical depression have been less clear.^[80, 86] Depressed individuals may be able to intentionally forget negative information at the expense of to-be-forgotten information.^[86] These findings suggest more general inhibitory memory impairments in depression than seen in PTSD.

In summary, many abnormalities in attention and memory in PTSD^[66, 67] are similar to those seen in other anxiety disorders^[87] and distinguishable from those in MDD.^[88] Consistent with an emphasis on fear in PTSD, threat or trauma information elicits the greatest and fastest attentional disruption among individuals with PTSD, similar to panic disorder, social phobia, and specific phobia; whereas, depression is associated with difficulty inhibiting negative information, especially over the longer intervals necessary for elaborative processing.

LEARNING, PHYSIOLOGICAL, AND NEUROBIOLOGICAL PROCESSES

Underlying processes of learning, physiology, and neurobiology in PTSD will next be examined and contrasted with depression and anxiety disorders.

As discussed above, fear conditioning and a failure of extinction are theoretically implicated in the pathogenesis of anxiety disorders. Classical conditioning research in individuals with PTSD is broadly consistent with this view. Relative to non-PTSD controls, individuals with PTSD show an enhanced conditioned fear response that remains elevated during extinction.^[89, 90] Notably, in a study of monozygotic twins discordant for trauma exposure, this extinction deficit is linked specifically to trauma exposure resulting in PTSD.^[89] This may suggest that elevated anxiety during extinction is a specific rather than general marker of PTSD. Individuals with PTSD also consistently show greater difficulty inhibiting fear in response to safety cues than those without PTSD.^[90, 91] Although enhanced fear acquisition, contextual cue discrimination problems, and stronger conditioned responding during extinction often characterize other anxiety disorders, such as panic disorder,^[92] they do not characterize responding in depression^[93] or GAD.^[63] Indeed, impaired safety signal processing has been put forth as a potential biomarker, having specificity for PTSD but not depression.^[91]

PTSD is also consistently characterized by physiological arousal. Metaanalyses suggest that elevated physiological responding is frequent among individuals with PTSD.^[94, 95] Pole^[94] noted that the most consistent findings for individuals with PTSD, compared to those without PTSD, include elevated heart rate across all types of physiological studies, greater facial muscle tension during personally relevant trauma scripts, and slower reduction of skin conductance during habituation. The effect sizes reported by Pole^[94] are comparable to the strongest psychosocial predictors of PTSD reported in metaanalyses,^[96, 97] suggesting that these effects are as central as any self-reported predictor. These effects are also comparable to threat-cue physiological reactivity in specific phobias^[98] and may be an underestimate of physiological responding due to competing trauma-related avoidance.^[99] Elevated physiological responding is consistent with panic disorder^[100] but is not as consistent with GAD^[101] and is not apparent in depression.^[102]

Fear-potentiated startle provides a neurobiologically instantiated indicator of defensive motivational system activity^[103] with phasic responses to explicit threat, mediated by the central nucleus of the amygdala, and tonic negative arousal, mediated by structures in the extended amygdala, particularly the bed nucleus of the stria terminalis (BNST). In their review, Grillon and Baas^[104] suggest that enhanced startle reactivity in PTSD is particularly evident in stressful or aversive contexts. A more recent review suggests that this may occur pervasively across broader contexts.^[105] Panic disorder is similarly more strongly associated with context than cue-specific conditioning,^[105] though one panic study^[106] showed that those without cooccurring depression show cue-specific potentiation of startle. Depression, on the other hand, is generally associated with a lack of valence modulation of startle reflex for both pleasant and unpleasant stimuli.^[105, 107] Furthermore, the dampening effect of depression on startle modulation may be independent of the startle-potentiating effect of fear,^[104, 108] suggesting that dysphoria and fear components are physiologically separable.

Neuroimaging methods in PTSD have primarily focused on regions of the brain most strongly implicated in fear: the sensory cortex, dorsal thalamus, lateral and central nucleus of the amygdala, and structures in the medial prefrontal cortex (mPFC), including the anterior cingulate cortex.^[109] Two recurrent findings in individuals with PTSD are decreased mPFC activation and increased amygdala activation.^[110] Similar functional differences in the mPFC-amygdala circuit have been found across the anxiety disorders,^[111]

including OCD,^[112] panic disorder,^[113] and generalized social phobia.^[114] Similarly, in depression, consistent findings have included hypermetabolism of the amygdala and hypometabolism of the left dorsal lateral prefrontal cortex; however, in contrast to PTSD, depression has also been reliably associated with increased metabolism in the orbital frontal cortex (OFC) and subgenual anterior cingulate cortex (sgACC).^[115, 116] In the neurocircuitry of depression, Brodmann Area 25 may be a key node in a network of brain regions involved with mood regulation and increased activity during a sad mood.^[117] Further, in depression, there is also consistent evidence for lower volume in the orbital and ventral prefrontal cortex. Other structures, such as the hippocampus and parahippocampal gyrus, may differ between PTSD and depression.^[118] These regions have been targeted for their involvement in spatial and episodic memory, stress, emotion regulation, and novelty processing. Specifically, research has widely reported reduced hippocampal volume in depression^[119] but has been inconclusive regarding the role of the hippocampus and parahippocampal gyrus in PTSD.^[110] Thus, although neuroimaging research points to some similarities between PTSD and depression, there are notable points of demarcation. Even when observing some similarities, such as affective dys-regulation and poor emotional clarity, these similarities may reflect common processes associated with negative affect or distress across disorders.^[120, 121] Indeed, the BNST has been implicated in these shared processes, with animal data suggesting that its activity is both necessary and sufficient for the development of learned helplessness.^[46]

In summary, elevated fear acquisition, conditioning, and impaired extinction responding appear to be consistent markers associated with PTSD. These phenomena do not consistently appear in GAD and depression. Heightened physiological reactivity is also characteristic of PTSD, observed across fear-potentiated startle data, contextual reactivity, and general heightened level of arousal. This pattern is similar in the anxiety disorders;^[122] whereas GAD and depression show blunted responding. Finally, although the ventromedial “emotion” circuit is clearly implicated in both fear and dysphoria, emerging evidence points to potential differences seen in major depression both in hyperactivation (OFC, sgACC) and decreased volume (hippocampus, OFC, ventral prefrontal cortex).

CONCLUSION

Heterogeneity is commonly observed in PTSD. Fear, dysphoria, and distress are undoubtedly present in individuals with PTSD, but each component may not contribute proportionately to its core pathology. Based on observed symptoms, factor analytic studies point to the presence of all three, largely reflecting the current DSM-IV conceptualization of PTSD. However, these studies question the need for a sizeable distress component in PTSD. Theoretical models diverge with ongoing threat being implicated in PTSD and learned helplessness, conditioned defeat, and hopelessness implicated in depression. Information-processing research shows consistent attentional biases toward threat in PTSD, similar to other anxiety disorders, and broader general elaborative processing and memory deficits in depression but not as prominent in PTSD. Conditioning studies provide consistent evidence for exaggerated fear conditioning, impaired safety signal and extinction learning, and enhanced physiological cue reactivity in PTSD, similar to other anxiety disorders but not distress disorders. Brain systems implicated in fear, dysphoria, and distress also point to distinct fear-related processes and shared general processes. Taken together, because underlying processes in PTSD are generally more similar to those in anxiety than distress disorders and link clearly to specific observed symptoms, dysphoria, and distress are best considered to be auxiliary rather than central to the conceptualization of PTSD.

This specificity suggests the importance of fear-specific components in PTSD. Some have suggested that the mechanisms underlying fear extinction, but not fear conditioning, and

depression-related behaviors show genetic, molecular, and neuroanatomical overlap.^[123] This type of further understanding of distinct (e.g. fear conditioning) and shared processes (e.g. fear and mood regulation) is critical. Given its heterogeneity, it may make sense not to view PTSD itself as a phenotype but rather to focus on symptoms dimensions (e.g. hyperarousal) and link those to intermediate phenotypes (e.g. impaired safety signal learning).

Examining fear and dysphoria components in PTSD fits easily within the proposed RDoC negative and positive valence systems. Progress within PTSD will advance more rapidly with this type of transdiagnostic, multiple levels of analysis approach. Further, general distress variance is often overlooked. When examining symptoms dimensions, their properties need to be measured at both the level of specificity to the disorder and the magnitude of general distress variance.^[21] In DSM-5, categorizing PTSD separately from other anxiety disorders may create an artificial emphasis of how PTSD differs (e.g. linked to traumatic stressor) and may disregard the similarities PTSD shares with other anxiety disorders (e.g. avoidance learning, threat vigilance, etc.). Increasing the emphasis on fear-based symptoms may help improve specificity.^[40] Increasing fear-based requirements beyond active avoidance to include physiological reactivity to trauma reminders, hypervigilance, and startle symptoms is more in line with the observed findings and closer to PTSD's original conceptualization as a pathological response to traumatic threat.^[40] At present and with DSM-5, an individual can meet PTSD criteria without any of these specific fear symptoms. Finally, with the increasing clinical impetus toward the development of a complex PTSD diagnosis, specific criteria need to be put forth.^[124] Points of commonality and demarcation, as suggested in this synthesis, need to be empirically examined between complex PTSD and other disorders, most notably borderline personality disorder (BPD), MDD, and PTSD.

Clinically, understanding the heterogeneity in PTSD may improve differential diagnosis and treatment planning. With its existing heterogeneity, clinicians run the risk of making an "attribution bias" error. Namely, the presence of any traumatic event, which is ubiquitous based on epidemiological data, shifts the diagnostic focus to PTSD and makes it less likely that other disorders such as MDD, BPD, and GAD will be considered and more likely that PTSD will be given inappropriately. This also potentially inflates rates of comorbidity and clinical perceptions of complexity. Further, understanding the components of heterogeneity in PTSD has the potential to enhance the development and utilization of more targeted, principle-specific interventions that better match underlying pathology and maximize clinical gains.

Ultimately, heterogeneity in PTSD is not bad. It reflects the clinical reality seen in most mental disorders. The nature of this heterogeneity and its pattern across levels of analysis are critical to understand. The emerging pattern seen in PTSD suggests that dysphoria and distress components of PTSD are most discernable in observable symptoms and more fear-specific components are apparent in both observable symptoms and underlying processes of information processing, learning, physiological, and neurobiological responding.

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