Review

Biological Psychiatry

# Diagnostic Biomarkers for Posttraumatic Stress Disorder: Promising Horizons from Translational Neuroscience Research

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## ABSTRACT

Posttraumatic stress disorder (PTSD) is a heterogeneous disorder that affects individuals exposed to trauma (e.g., combat, interpersonal violence, and natural disasters). Although its diagnostic features have been recently reclassified with the emergence of the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition, the disorder remains characterized by hyperarousal, intrusive reminders of the trauma, avoidance of trauma-related cues, and negative cognition and mood. This heterogeneity indicates the presence of multiple neurobiological mechanisms underlying the etiology and maintenance of PTSD. Translational research spanning the past few decades has revealed several potential avenues for the identification of diagnostic biomarkers for PTSD. These include, but are not limited to, monoaminergic transmitter systems, the hypothalamic-pituitary-adrenal axis, metabolic hormonal pathways, inflammatory mechanisms, psychophysiological reactivity, and neural circuits. The current review provides an update to the literature with regard to the most promising putative PTSD biomarkers, with specific emphasis on the interaction between neurobiological influences on disease risk and symptom progression. Such biomarkers will most likely be identified by multi-dimensional models derived from comprehensive descriptions of molecular, neurobiological, behavioral, and clinical phenotypes.

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Posttraumatic stress disorder (PTSD) is a severe psychiatric disorder that occurs after a psychological traumatic life event and increases individual vulnerability to adverse health outcomes (1). PTSD is heterogeneous, often presenting across different symptom domains, including re-experiencing, avoidance/numbing, and hyperarousal symptoms (2). While extensive work has successfully identified psychological, genomic, and biological risk factors that are associated with PTSD in trauma survivors (3–5), the identification of discrete diagnostic biomarkers for PTSD remains elusive. The lack of diagnostic biomarkers for PTSD is not due to a lack of intensive study but rather likely due to the complexity of PTSD and the complex set of rules by which we classify individuals according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as illustrated by the recent description of 636,120 different ways in which an individual can be diagnosed with PTSD (6). Furthermore, PTSD is associated with significant mental health (e.g., major depression, substance and alcohol abuse, panic disorder, suicide) and general medical (e.g., diabetes, cardiovascular disease) comorbidities (7,8), which can obscure the search for diagnostic biomarkers for PTSD. Given that DSM-5 criteria are not based on the underlying biology, PTSD research could benefit significantly from the new approach to mental health diagnoses using the Research Domain Criteria (RDoC) (9). One of the tenets of this approach is dimensional analyses of neurobiological metrics and symptoms, rather than diagnostic classification. The putative biomarkers listed in this review are reflective of the extant literature but can also serve RDoC objectives in future studies by linking PTSD symptoms to relevant biological underpinnings.

The vast heterogeneity inherent in PTSD symptom presentation makes it highly unlikely that a valid, singular biomarker will be identified for PTSD (10,11). However, comprehensive biological phenotyping of the factors associated with PTSD may yield a parsimonious diagnostic model with which to diagnose PTSD in the future. The current review will highlight several biomarkers associated with PTSD symptomatology and vulnerability, in addition to underscoring how individual factors, such as one's comorbid diagnoses and gender, must be considered, as they can profoundly influence biology and thus influence our search for true biomarkers of PTSD. Specifically, we will emphasize monoamine, neuroendocrine, inflammatory, genetic, epigenetic, psychophysiological, neuroanatomical, and neuroactivational phenotypes associated with PTSD to illustrate the potential efficacy of using multidimensional phenotypic data to characterize unique profiles of PTSD.

## MONOAMINE SYSTEMS IN PTSD

PTSD is characterized by increased sympathetic nervous system tone that is coincident with augmented levels of catecholamine secretion (12). Urinary and central levels of norepinephrine (NE) are heightened in individuals with PTSD (13) and in child trauma victims (14), and peripheral and central

 
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levels of NE in response to threatening stimuli are also elevated in PTSD (15,16). Recent evidence suggests that this increase in NE in PTSD is due to attenuated levels of the NE transporter within the brainstem locus coeruleus (17). PTSD has also been associated with decreased expression of peripheral α2-adrenergic receptors, receptors that underlie an autoreceptor-driven mechanism that serves to inhibit synaptic transmitter release (18). Further, facilitation of NE release via blockade of presynaptic α2-adrenergic receptors with the antagonist yohimbine can produce panic attacks and an increase in anxiety- and trauma-related symptoms in individuals with PTSD (19,20). A prospective study of motor vehicle accident survivors indicated that urinary levels of NE were associated with increased development of PTSD 1 month following trauma but only in men (21), indicating that gender may be important for characterizing catecholaminergic biomarkers of PTSD. Increased catecholamines, however, are also coincident with panic attacks and other fear-related psychopathology (22), indicating that increased sympathetic activation is not a specific biomarker of PTSD but rather of a common neurobiological feature of fear- and anxiety-related disorders.

Alterations in the serotonergic system have also been implicated in the pathophysiology of PTSD. Individuals with PTSD show decreased levels of paroxetine binding, suggesting that levels of the serotonin transporter are attenuated in PTSD (23) and involved in the manifestation of arousal and avoidance symptoms (24). Empirical evidence has shown that serotonin transporter expression within the amygdala is attenuated in PTSD and is significantly associated with higher anxiety and depressive symptoms (25). Brainstem and forebrain levels of the serotonin 1A receptor are higher in individuals with PTSD (26), similar to what has been described in depression (27). Likewise, reductions in central serotonin 1B receptors in trauma-exposed individuals are associated with increased PTSD and depression symptoms (25). Taken together, these data indicate that alterations within the serotonergic system could reveal putative biomarkers for depressive symptoms common to both PTSD and major depression (26). The effectiveness of selective serotonin reuptake inhibitors (e.g., sertraline) for reducing the symptoms of PTSD (28–30), major depression, and other psychiatric conditions with which PTSD is highly comorbid (2,22) further suggests that more careful examination of serotonergic phenotypes is warranted to better disentangle the specificity of biomarkers for PTSD- and depression-specific phenotypes.

One way in which to elucidate the specificity of monoaminergic biomarkers on PTSD symptomology is to concurrently characterize sympathetic and serotonergic function within the same individuals. Using a repeated-measures design, Southwick *et al.* (20) found that both yohimbine and meta-chlorophenylpiperazine treatment increased panic attacks, anxiety, and trauma-related symptoms in veterans diagnosed with PTSD in a manner that suggested at least two different biological subtypes of PTSD, thus underscoring the need for more robust phenotyping of biological factors including the monoaminergic transmitter systems.

## NEUROENDOCRINE BIOMARKERS OF PTSD

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is present in PTSD and has been extensively characterized (Figure 1) [for review see (31)]. Evidence suggests that individuals with PTSD have attenuated levels of basal cortisol (31) and that a low level of cortisol in trauma survivors is associated with increased risk for subsequent development of PTSD (32,33). However, findings on baseline cortisol levels have been mixed, and a recent meta-analysis concluded that there are no consistent differences between PTSD and control subjects (34). Similarly, equivocal results exist surrounding the cortisol response to acute cognitive stressors, as reports show heightened or no differences in cortisol response to a stressor (35,36). In part, these discordant HPA results appear to be due to different sampling methods, the diurnal rhythm of cortisol release, and confounding analyses that have disregarded the influence of sex on HPA activity (37).

Rather than focus on baseline cortisol, a more promising approach is to measure cortisol reactivity to a challenge. Blunted cortisol reactivity to acute stress exposure is associated with increased prospective risk for PTSD (38). Low cortisol levels in PTSD have been coupled to enhanced glucocorticoid negative feedback inhibition of the HPA axis as evidenced by increased suppression of cortisol levels following a dexamethasone suppression test (39). This enhanced HPA negative feedback in PTSD is coincident with 1) augmented levels of peripheral and central corticotropin-releasing hormone (40,41); 2) elevated glucocorticoid receptor (GR) levels (42); 3) increased glucocorticoid sensitivity (43); and 4) decreased levels of FKBP5 (44), a co-chaperone of GR that inhibits ligand binding and nuclear translocation of GRs. A recent prospective study indicates that augmented baseline GR levels and diminished FKBP5 messenger RNA levels are associated with increased risk for PTSD symptoms following trauma (45).

While extensive work has alluded to HPA-based biomarkers of PTSD, it is clear that additional neuroendocrine factors influence PTSD vulnerability and symptomology (Figure 1; Table 1). For example, menstrual cycle phase (46,47) and pregnancy (48) influence PTSD symptom expression profile and psychophysiology in women, suggesting that ovarian steroid hormones are important modulators of PTSD susceptibility and symptom presentation. Indeed, low levels of estradiol are associated with impaired fear extinction in PTSD (49), and high levels of pituitary adenylate cyclase-activating polypeptide, a peptide implicated in stress-related behavior and physiology (50–52), are associated with PTSD only in women (53). Furthermore, central levels of the anxiolytic neuroactive steroid allopregnanolone, a potent modulator of gamma-aminobutyric acidergic inhibition, are decreased in women with PTSD (54). Low levels of testosterone in men, on the other hand, have prospectively been associated with increased rates of PTSD (55) and increased risk for PTSD (56). These data, along with epidemiologic studies strongly suggesting that female sex is a risk factor for psychopathology (including PTSD) (57) and reinforce the need to better understand the influence of gonadal steroid hormones in men and women with PTSD.

An additional avenue of exploration with regard to PTSD and putative biomarkers is the expression and regulation of metabolic hormones in individuals with PTSD. Neuropeptide Y (NPY) is an orexigenic peptide neurotransmitter (58) that also shows anxiolytic properties via antagonism of corticotropin-releasing hormone and noradrenergic systems (59). Trauma

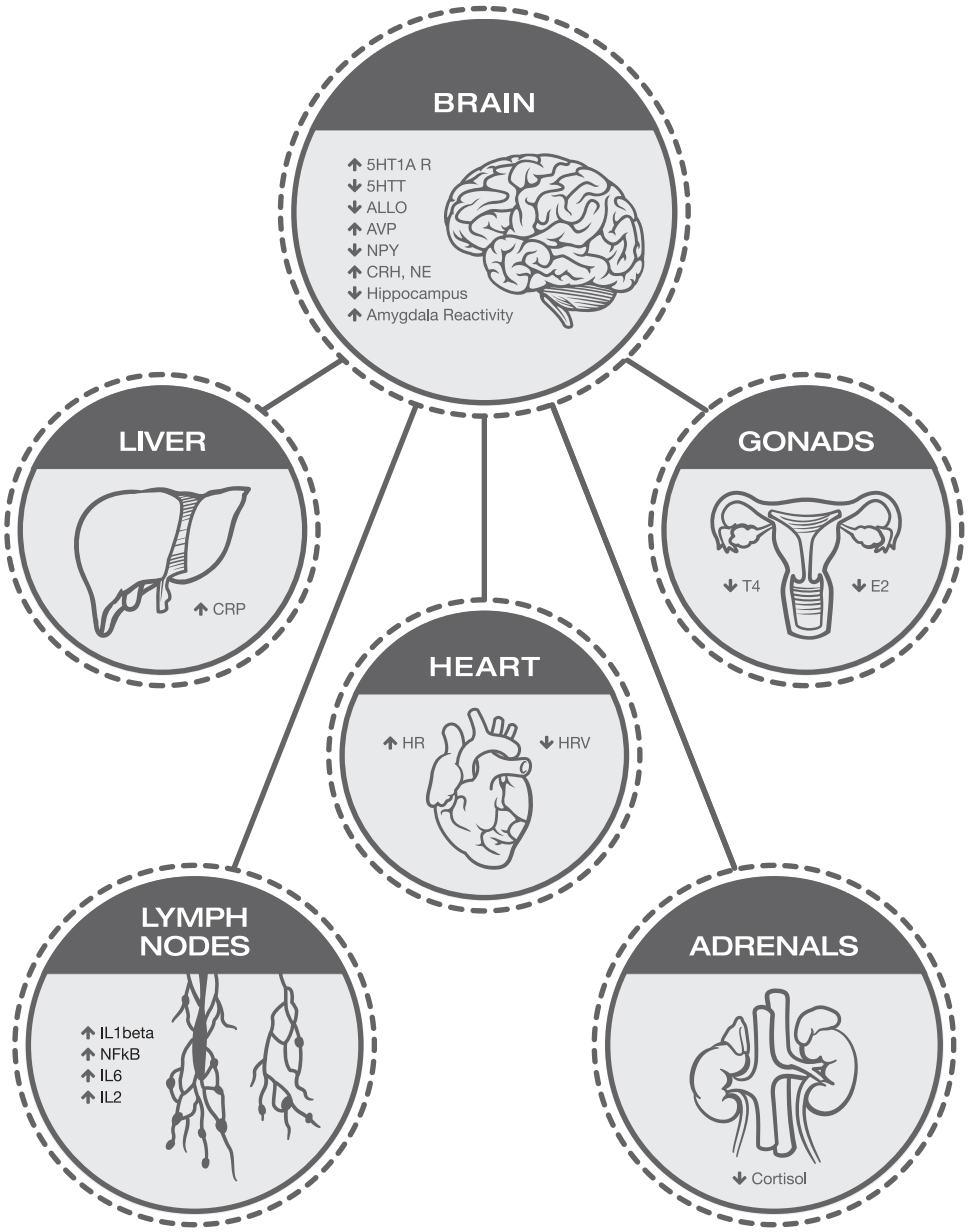


**Figure 1.** A summary of key biomarkers that are associated with posttraumatic stress disorder (PTSD), highlighting the interactions between different biological systems that influence and complicate biological phenotypes within PTSD. Gonadal steroid hormones and the hypothalamic-pituitary-adrenal (HPA) axis modulate neurotransmitter and neuropeptide systems (145), influence amygdala activity (146,147), and influence inflammatory responses (93). HPA activity, via cortisol and corticotropin-releasing hormone (CRH), alters sensitivity to gonadal hormones (148). Inflammation alters HPA activity and has adverse effects on cardiovascular function (149). Taken together, these data indicate that as a field we must begin to study these physiological systems in concert with one another to begin to characterize comprehensive biological phenotypes of PTSD. ALLO, allopregnanolone; AVP, arginine vasopressin; CRP, C-reactive protein; E2, estradiol; HR, heart rate; HRV, heart rate variability; 5HT1A R, serotonin 1A receptor; 5HTT, serotonin transporter; IL1beta, interleukin 1 beta; IL2, interleukin 2; IL6, interleukin 6; NE, norepinephrine; NFκB, nuclear factor-κB; NPY, neuropeptide Y, T4, testosterone.

exposure (60) and PTSD (59) are associated with attenuated peripheral levels of NPY, and conversely, resilience to trauma is associated with increased NPY levels (61). Ghrelin, an orexigenic peptide secreted from the stomach (58), displays fear-enhancing effects in rodents (62) and could serve as a biomarker of trauma exposure and PTSD. More recently, individuals with PTSD have shown a hyperinsulinemic response to an oral glucose challenge (63). Finally, peripheral endocannabinoid levels (64) are reduced and central cannabinoid receptor type 1 receptors (65) are increased in PTSD.

In summary, it is clear that significant progress has been made in identifying and characterizing PTSD-related neuroendocrine perturbations. However, the majority of these neuroendocrine factors have been studied in isolation in traumatized populations exhibiting PTSD signs and symptoms, and as such, it is important to characterize multilevel neuroendocrine profiles of PTSD accounting for parallel trauma-related neuroendocrinologic changes, their interaction, and the relationship to stress exposure or resilience. For example, increases in dehydroepiandrosterone and dehydroepiandrosterone-sulfate have been linked to PTSD symptom expression but are also associated with decreased levels of affective symptoms and PTSD severity (66,67). Thus, it has been suggested that the ratio of these adrenal hormones to cortisol might be important for resilience to stress and recovery from PTSD (68,69). Furthermore, elucidating the complex interaction of neuroendocrine factors (i.e., allopregnanolone/estradiol/NPY effects on cortisol) on the regulation of the HPA axis will likely expand

**Table 1. Neuroendocrine Biological Factors Associated with PTSD**

| Neuroendocrine Biomarkers | Relationship to PTSD | References |
|---|---|---|
| HPA-Axis | | |
| Glucocorticoid negative feedback | Augmented in PTSD | (39) |
| Baseline cortisol | Attenuated in PTSD | (31,32) |
| Acute cortisol following trauma | Lower levels increase risk for PTSD | (33,38) |
| Pituitary adenylate cyclase-activating polypeptide | Increased in women with PTSD | (53) |
| Steroid Hormones | | |
| Estradiol | Reduced levels increase risk for PTSD and are associated with impaired fear extinction | (49) |
| Allopregnanolone | Decreased in women with PTSD | (54) |
| Dehydroepiandrosterone | Increased in PTSD | (68) |
| Dehydroepiandrosterone sulfate | Increased in PTSD; high DHEAS increases risk for PTSD | (68) |
| Testosterone | Low levels increase risk for PTSD | (56) |
| Metabolic Hormones | | |
| NPY | Decreased in PTSD | (59) |
| Ghrelin | Increases fear in rodents | (62) |
| Insulin | Increased response to glucose in PTSD | (63) |
| Endocannabinoids | Decreased in PTSD | (64) |

DHEAS, dehydroepiandrosterone sulfate; HPA, hypothalamic-pituitary-adrenal; NPY, neuropeptide Y; PTSD, posttraumatic stress disorder.

our ability to further describe PTSD-specific and may prove beneficial in characterizing biological subprofiles of PTSD (Figure 1). For instance, avoidance symptoms in male veterans with PTSD (70) may be related to arginine vasopressin levels and, as such, may serve as a biomarker for increased aggression in men with PTSD (71).

## BIOMARKERS OF HEIGHTENED INFLAMMATION IN PTSD

The high comorbidity between PTSD, physical illness (7) , and inflammation spanning cardiovascular (72) and metabolic disease (73) has led to investigations of the relationship between inflammatory markers and PTSD symptomology (Table 2). Pro-inflammatory cytokines (i.e., proteins), including interleukin (IL)-6 (74), IL-1β (75), and IL-2 (76), are elevated in individuals with PTSD and peripheral levels of inflammatory markers correlate positively with PTSD symptomology (Figure 1) (77). C-reactive protein (CRP) levels are also elevated in individuals with PTSD (78–80). More specifically, increased CRP levels have been reported with exacerbated PTSD symptoms and impaired inhibition of fear-potentiated startle in the presence of a safety signal (79), a psychophysiological biomarker for PTSD described in a later section of this review (81).

In addition, individuals with PTSD also show altered immune cell sensitivity to glucocorticoids that results in increased inflammation (82). Lysozyme enzyme activity is more sensitive to dexamethasone in PTSD (43), indicating that innate immune efficiency is higher in individuals with PTSD. Enhanced monocyte sensitivity to glucocorticoids in individuals with PTSD is also coincident with hypocortisolemia and can lead to increased cytokine production (83). The transcriptional factor, nuclear factor-κB (NF-κB), lays upstream of cytokine activation (84) and is activated by exposure to psychosocial stress (85), as well as noradrenergic activity (85), and thus may be critically sensitive to immune changes following trauma exposure. Individuals with PTSD show augmented NF-κB gene expression (86) and NF-κB activity (87).

Overall, the cross-sectional data linking PTSD to a pro-inflammatory state further support the notion that PTSD is associated with chronic inflammation (Table 2) and suggest that inflammation may serve as a possible therapeutic target for alleviating PTSD symptoms. However, increased inflammation is a hallmark of depression (88) and other adverse health outcomes that are comorbid with PTSD (7,72,73,89), thus complicating the view that immune factors may serve as

**Table 2. Immunological Factors Associated with PTSD**

| Immune Biomarkers | Relationship to PTSD | References |
|---|---|---|
| Interleukin-6 | Increased in PTSD | (74) |
| Interleukin-1β | Increased in PTSD | (75) |
| Interleukin-2 | Increased in PTSD | (76) |
| C-Reactive Protein | Increased in PTSD; increases risk for PTSD | (78,79,94) |
| Nuclear Factor-κB | Increased in PTSD | (86,87) |
| Tumor Necrosis Factor-α | Increased in PTSD | (144) |
| Immune Cell Sensitivity to Glucocorticoids | Enhanced in PTSD | (43) |

PTSD, posttraumatic stress disorder.

diagnostic biomarkers for PTSD specifically. This point is further highlighted by other reports that have described no differences or decreases in pro-inflammatory markers, such as CRP, in individuals with PTSD (90–92). Factors such as gender should also be considered in our examination of immunological biomarkers, as there are clear sex differences in immune system function and risk for infection (93). Finally, it is still unclear whether increased inflammation is a consequence of trauma exposure and PTSD or whether a baseline pro-inflammatory state increases individual vulnerability to PTSD after trauma exposure. As such, baseline inflammation may serve as a biomarker of PTSD vulnerability, as recent evidence from a prospective study indicates that predeployment levels of CRP significantly predict postdeployment PTSD (94).

## GENETIC AND EPIGENETIC BIOMARKERS OF PTSD

Genetic loci within genes critical for the neuroendocrine regulation of the HPA axis and emotional behavior have been associated with increased risk for PTSD [see review (5)]. However, these genetic loci have been associated with other psychiatric conditions as well, indicating that these genetic polymorphisms are not specific to PTSD but rather may serve as biomarkers for stress-induced psychopathology in general or common underlying symptoms. There are several recent genomic reviews of PTSD [e.g., (95)] and the disorders with which it is comorbid and, as such, will not be discussed at length in the current review. We will simply note that the emerging genetic and epigenetic findings related to PTSD risk versus resilience have focused on modulators of HPA axis function (before and following trauma), e.g., *FKBP5, PACAP*.

## PSYCHOPHYSIOLOGICAL BIOMARKERS OF PTSD

Hyperarousal symptoms, which include some of the long-standing, hallmark symptoms of PTSD, can be strongly influenced by an individual's autonomic response following trauma; the output of the autonomic nervous system can be indexed noninvasively via psychophysiological assessments of peripheral targets, such as heart rate (HR), blood pressure, skin conductance (SC), respiration rate, muscle contractions using electromyography (EMG) (e.g., startle), and body temperature. However, the use of these psychophysiological measures as biomarkers of PTSD may rely heavily on the timing and context in which they are collected. For instance, while some reports indicate that HR in the immediate aftermath of trauma exposure is predictive of later PTSD development (96), others suggest this is not the case (97,98). These equivocal findings suggest that a more robust and controlled measurement of psychophysiological data may be necessary (99). Indeed, HR and SC changes in response to a challenge have been repeatedly associated with a diagnosis of PTSD (100–104).

Exaggerated startle response, a hyperarousal symptom that remains central to DSM-5 based PTSD diagnosis, is readily assessed by psychophysiology. Increased HR (SC and EMG less so) reactivity to startling loud tones has been found to reliably differentiate PTSD from non-PTSD (105). Heightened HR reactivity to loud tones does not appear to be pre-existing but rather is acquired with the development of PTSD (106,107). Whereas heightened HR reactivity to loud tones appears to be an acquired marker, there is accumulating evidence that heightened SC reactivity to loud tones is a pretrauma risk marker for posttraumatic stress (108,109). Exaggerated arousal can manifest as sleep disturbances, which are frequently observed in PTSD (110,111); however, the diagnostic specificity of these disturbances are not yet understood.

To examine and further explore hyperreactivity following trauma, Pitman *et al.* (112) modified an imagery procedure originally developed to study phobias (113). In this method, psychophysiological data are recorded from participants while listening to a script of their actual traumatic event. This method has been used with divergent PTSD populations, including several combat populations (114–116) and a heavily traumatized civilian population (117). In all trauma survivors, PTSD patients exhibit a stronger HR and SC response to scripts than non-PTSD trauma survivors. In studies using script-driven imagery, SC was found to be the most sensitive measure of hyperarousal in PTSD. In 1998, Keane *et al.* (101) published the results of the largest study (multisite Veterans Affairs Cooperative Study with Vietnam veterans) to date examining the utility of psychophysiological measures in diagnosing PTSD. The study employed script-driven imagery coupled with psychophysiological recordings. While this study did not find a perfect correlation between interview-based PTSD diagnosis and psychophysiological reactivity, they concluded that psychophysiological data did provide useful and objective assessment of the disorder. Recent re-analyses of script-driven imagery data collected in the 1990s have shown high specificity for PTSD (i.e., 90% of individuals without PTSD classified correctly) (102) and high concordance with subjective distress (118), but sensitivity to PTSD diagnosis remained at approximately 60% (102). Simply talking about autobiographical trauma appears to have similar effects as script-driven imagery in increasing physiological arousal (118). These methods are currently being standardized as common data elements to promote generation of large datasets using the same approach. Technological advances have afforded the opportunity to employ physiological indices that can be easily obtained in most clinical settings and may prove beneficial in the diagnosis and treatment evaluation of PTSD. A recent application of these methods using virtual reality techniques to provide immersive trauma-related imagery during recording of psychophysiological responses showed utility of this approach in tracking treatment outcomes (119).

The findings described previously support the notion that the etiology and maintenance of the fear-related symptoms of PTSD can be characterized according to the principles of fear conditioning (120,121). Given the richness of the translational literature, the neural underpinnings of fear conditioning are well understood, and PTSD research can capitalize on these findings (122). Fear conditioning is based on a simple Pavlovian conditioning model in which a neutral conditioned stimulus (CS) (for example, a light) is paired with an aversive unconditioned stimulus (US) (for example, electric shock). After a number of pairings, an association is formed such that the CS alone elicits a conditioned response (for example, a fear response). Following initial acquisition, conditioned fear is subject to consolidation, extinction, and reconsolidation, all of which may be disturbed in PTSD (123–125). Fear conditioned responses can be measured with peripheral outcomes

such as SC (123) or EMG startle responses (81). These psychophysiological measures can be used to index both the increase in fear during conditioning, as well as the reduction of fear during extinction, or the repeated presentation of the CS without the US. In addition, these measures can be used in differential conditioning studies using a CS+ cue predicting danger (US) and a CS− predicting safety from the US; these have shown that PTSD, but not depression, is associated with a reduced ability to inhibit fear-potentiated startle responses to safety signals (81). Similarly, retention of the extinction memory has been tested using SC 24 hours after fear extinction, and PTSD subjects have exhibited reduced levels of extinction recall (125). Taken together, these studies indicate the fear responses to traumatic memories may be serve as biomarkers specific for dysregulated fear in PTSD.

## NEUROANATOMICAL AND NEUROACTIVATIONAL BIOMARKERS OF PTSD

Neuroimaging data gathered during the last decade demonstrate that PTSD is associated with greater amygdala activation compared with control subjects (126). Functional magnetic resonance imaging (fMRI) studies have shown that trauma-relevant words increase amygdala activation in PTSD subjects more than in control subjects (127–130). Exaggerated fear responses observed in PTSD may be due to a weakened inhibitory control of the amygdala by the medial prefrontal cortex (mPFC). A large number of imaging studies have indicated that this inhibitory neurocircuit is dysregulated in patients with PTSD (126,128,130). A recent meta-analysis of imaging studies during emotion processing in PTSD, social anxiety, and specific phobia indicated that the rostral anterior cingulate cortex (ACC) is less active in PTSD patients relative to control subjects, an effect not found in other anxiety disorders (131).

Neuroimaging studies using fear conditioning paradigms demonstrate that fear acquisition and extinction of fear activate the prefrontal cortex, specifically the ventromedial prefrontal cortex (vmPFC) (132). For example, activation of the vmPFC (which includes the rostral ACC) is decreased in PTSD patients during an extinction recall in fMRI task (133). The vmPFC also differs in shape and size in PTSD patients (134). To date, one of the most replicated neuroanatomical findings in PTSD has been reduced hippocampal volume (135,136). Early studies of twins discordant for trauma exposure suggested that smaller hippocampal volume likely confers individual vulnerability to PTSD (137); however, a recent prospective study found that hippocampal reductions were acquired with trauma exposure (136). Finally, methods using higher resolution imaging techniques have indicated that reductions in specific subregions of the hippocampus, such as the cornu ammonis 3 and dentate gyrus, are associated with PTSD symptoms (138). Studies of neural activation have used several fMRI paradigms to activate the mPFC; the simplest and most commonly used tasks involve response inhibition. In such tasks, the participant is presented with a stimulus indicating that a response is required, for example, to press a button when a letter appears on the monitor. This is referred to as a Go signal. On a minority of trials, however, the participant is required to withhold a response during a NoGo signal (the Go/NoGo task). The Go/NoGo task has been used in subjects with PTSD with fMRI and it reliably indicates decreased activation in the rostral vmPFC and rostral ACC in PTSD subjects compared with control subjects (139,140). Weakened mPFC control of the amygdala may be a risk factor for trauma-related psychopathology: a recent study of children with depressed parents found a lack of ACC activation to the emotional Stroop, using both fear-relevant words depicting physical threat as well as social threat (141).

## SUMMARY AND CONCLUSIONS

To date, an array of putative biomarkers associated with PTSD risk and symptom progression have been identified across distinct biological domains, including, but not limited to, alterations and differences in monoaminergic systems, neuroendocrinology, inflammation, genomics, psychophysiology, and neuroanatomy. However, the heterogeneity inherent in PTSD symptom presentation and the common comorbidity with other psychiatric and general medical conditions represent formidable obstacles in the identification of valid biomarkers specifically for PTSD when considered as a diagnostic categorization (10,11). Indeed, the likelihood of characterizing one biological marker associated with the suggested 636,120 different ways in which an individual can present with PTSD (6) is vanishingly small. Rather, it is more prudent that future studies develop a cross-dimensional, comprehensive biological and psychological phenotypic profile in individuals with PTSD to 1) characterize biomarkers for specific clusters of symptoms; and/or 2) uncover divergent biological profiles of PTSD using more complex statistical techniques (142). To be compatible with the RDoC approach, biomarkers should be dimensional as well as transdiagnostic—in effect, not biomarkers specific to PTSD as a DSM-5 disorder but biomarkers of features associated with PTSD. For example, physiological measures of fear responses would be relevant to other fear-related disorders such as phobias in addition to PTSD. Similarly, deficient prefrontal activity could be associated with PTSD symptoms, as well as addiction, and could clarify common bases for comorbid disorders.

To begin collecting comprehensive phenotypes necessary for such analyses, the importance of studying the interaction between biological factors (e.g., cellular, molecular, genetic, neurotransmitter, endocrine) (Figure 1) needs to be emphasized, most notably as they relate to physiology and behaviors underlying complex biological phenotypes within PTSD. It is important to note that biology is dynamic. Thus, it is critical for the field to understand that biomarkers might be relevant at one time point (HR immediately following trauma exposure) and not at another (11). Lastly, the implications of characterizing diagnostic biomarkers for PTSD must be carefully considered to ensure that the benefits outweigh the costs (143).

In summary, the available biological and translational data point to promising new horizons for diagnostic biomarkers of PTSD symptoms. It is most likely that such biomarkers will represent a panel of several measures that will combine molecular with behavioral and clinical information to increase specificity and sensitivity of these tools.

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