Psychophysiology in the Study of Psychological Trauma: Where Are We Now and Where Do We Need to Be?

D.T. Acheson, M.A. Geyer and V.B. Risbrough

Abstract Posttraumatic stress disorder (PTSD) is a major public health concern, which has been seeing increased recent attention partly due to the wars in Iraq and Afghanistan. Historically, research attempting to understand the etiology and treatment of PTSD has made frequent use of psychophysiological measures of arousal as they provide a number of advantages in providing objective, non-self-report outcomes that are closely related to proposed neurobiological mechanisms and provide opportunity for cross-species translation. Further, the ongoing shift in classification of psychiatric illness based on symptom clusters to specific biological, physiological, and behavioral constructs, as outlined in the US National Institute of Mental Health (NIMH) Research Domain Criteria project (RDoC), promises that psychophysiological research will continue to play a prominent role in research on trauma-related illnesses. This review focuses on the current state of the knowledge regarding psychophysiological measures and PTSD with a focus on physiological markers associated with current PTSD symptoms, as well as markers of constructs thought to be relevant to PTSD symptomatology (safety signal learning, fear extinction), and psychophysiological markers of risk for developing PTSD following trauma. Future directions and issues for the psychophysiological study of trauma including traumatic brain injury (TBI), treatment outcome studies, and new wearable physiological monitoring technologies are also discussed.

Keywords Psychophysiology · PTSD · Startle · Heart rate variability · Electrodermal response · TBI

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1 Introduction

Posttraumatic stress disorder (PTSD) is a major public health concern with lifetime prevalence rates in the USA estimated to be 6.8–12.2 %, and 12-month prevalence rates estimated to be 3.5 % (Breslau 2009). Due to the wars in Iraq and Afghanistan, PTSD has received significant attention in the past 10–13 years, in terms of both popular media coverage and funds directed toward its research. This attention is warranted, given that rates of PTSD have increased in service members by 656 % since 2001 and the cost to the US Department of Defense (DoD) for treating these service members doubled between 2007 and 2012 (Blakeley and Jansen 2013 Congressional Research Service Report). In addition, it is important to note that PTSD affects more than just combat veterans and occurs in civilians following physical and sexual assaults, forced captivity, muggings/robberies, motor vehicle accidents, natural disaster, and life-threatening illness among other events (Breslau 2009). The DSM-IV classification of PTSD consisted in exposure to the traumatic event, as well as 3 clusters of symptoms: re-experiencing, avoidance and numbing, and hyperarousal. With the recent publication of DSM-5, the definition has expanded into 4 symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. This expansion recognizes broader, more heterogeneous symptom expressions (such as dysphoria and anger) while allowing for more dynamic changes in arousal and reactivity. Current treatments for PTSD are mainly psychotherapy based (e.g., exposure therapy and cognitive therapy). Pharmacological treatments, such as serotonin-selective and serotonin-norepinephrine reuptake inhibitors (SSRI/SNRIs), have also achieved modest efficacy (Committee on treatment of posttraumatic stress disorder IoMotNA 2007).

There is a clear need for the development of novel preventive and therapeutic treatment strategies for PTSD via increased understanding of etiological and maintaining factors of the disorder (Baker et al. 2009). To this end, there is a new focus on utilization of biological, physiological, and behavioral tools to enable a

"paradigm shift" from sole reliance on self-report measures to assess symptom status and diagnosis for psychiatric disorders such as PTSD. The US National Institute of Mental Health (NIMH) Research Domain Criteria project (RDoC) represents a framework for research in this area, with an emphasis on developing a diagnostic classification scheme based upon valid observable markers of common biological processes across the range of currently identified diagnostic categories. The negative valence system (NVS) domain suggested by the NIMH contains the constructs of acute threat of "fear," potential harm or "anxiety," and sustained threat. The 2011 NVS working group meeting identified many of the physiological measures reviewed below as important research tools for understanding these constructs. Psychophysiological measures may have utility as static markers of these constructs, as well as dynamic markers of change enabling the elucidation of the roles of learning and memory processes in the expression of these constructs. Thus, psychophysiological measures are poised to play an important role in the future understanding of mental illness generally, and traumatic stress-related disorder characterized by negative valence states more specifically.

Psychophysiological outcome measures have a number of advantages in neuropsychiatric research. (1) Psychophysiological measures provide objective, non-self-report outcomes and thus are less subject to bias by the subject and/or researcher. (2) Physiological measures are quantifiable. (3) Compared to self-report symptom scales, physiological measures may represent more discrete symptom domains that probe specific neurobiological pathways enabling mechanistic study of neurobiological abnormalities underlying symptoms. (4) Physiological measures enable cross-species translation to examine causal mechanisms of psychophysiological abnormalities linked to trauma exposure that cannot be achieved with self-report measures. The current manuscript will review the current state of knowledge on psychophysiological outcomes in PTSD with attention to their use as markers of current symptoms as well as markers of PTSD-related processes. We will also discuss these variables in terms of their sensitivity and selectivity for PTSD symptoms versus other anxiety and mood disorders and comorbid disorders such as traumatic brain injury (TBI). Further, we will discuss potential future avenues for integrating psychophysiology into emerging areas of PTSD research. We have limited our review to relatively common psychophysiological measures of arousal/threat, including cardiovascular, electromyographic, and electrodermal measures.

2 Psychophysiological Markers of Current PTSD Symptoms

2.1 Cardiovascular Activity

Baseline: Current conceptualizations of PTSD, reflected in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM 5; APA 2014) criteria, recognize that PTSD has a complex phenomenology expressed not just as

fear-based hyperarousal, but also as anhedonic and dysphoric emotional states. In contrast, earlier conceptualizations of the disorder, reflected in DSM-III through IV criteria, placed a larger emphasis on fear-related arousal. Given the past emphasis on arousal-related symptoms, research has long focused on identifying and understanding the psychophysiological basis of elevated arousal. Though studies have assessed the construct of arousal across a number of psychophysiological measures, an extensive body of work has focused on the cardiovascular system. Cardiovascular physiology is a convenient domain to focus on since it can be measured relatively easily using a number of different methods and equipment typically present in an emergency department or urgent care clinic. Further, some elements of cardiac physiology can be interpreted as a readout of sympathetic/parasympathetic balance, which has long been theorized to be disrupted in PTSD (see below).

Blanchard et al. (1982) observed that Vietnam veterans with PTSD had higher resting baseline heart rate (HR) and blood pressure (BP) than Vietnam veterans without PTSD. These initial observations were later largely confirmed in a meta-analysis by Buckley and Kaloupek (2001), which reviewed 34 studies of resting cardiovascular activity in PTSD conducted up to that time. This meta-analysis found support for elevated resting HR and diastolic blood pressure (BP), though systolic BP levels were similar across PTSD subjects and healthy controls. A more recent meta-analysis of psychophysiological studies in PTSD (Pole 2007) reviewed 55 studies conducted until that time and also supported increased resting HR in PTSD relative to healthy controls. However, elevations in systolic and diastolic BP were only present under relaxed criteria for statistical significance.

While the evidence for altered cardiovascular activity at rest in PTSD appears fairly strong, some researchers have suggested a more nuanced relationship. First, some studies (i.e., Shalev et al. 1992) have failed to find HR differences in new-onset PTSD. Further, Buckley and Kaloupek (2001) showed a greater effect size for HR in patients with chronic PTSD (>13 years). Taken together, these findings suggest that elevated HR may be a consequence of physiological changes driven by long-term PTSD. Second, studies monitoring cardiovascular activity over 24-h periods have suggested that HR and BP may fluctuate widely across the day, complicating previous studies (Muraoka et al. 1998; Buckley et al. 2004). One study using 24-h HR monitoring did, however, confirm increased HR in veterans with PTSD, with more pronounced effects during the night, perhaps related to the sleep disturbances commonly associated with PTSD (Agorastos et al. 2013). Third, there is disagreement among researchers regarding whether resting state activity is actually being measured in these studies, or if what is actually being captured are cardiovascular responses to a stressful situation/challenge induced by the testing environment (see below; Zoladz and Diamond 2013). Other studies suggest that PTSD subjects are hyperresponsive to stress or threat across a number of physiological markers, including HR, startle, and skin conductance (see below). Further, increased HR is not specific to PTSD, but is also reported in panic disorder and depression (Cohen et al. 2000; Blechert et al. 2007; Kamphuis et al. 2007).

An additional marker of resting-state cardiovascular activity that is altered in PTSD is heart rate variability (HRV). HRV is a measure of the variation in time between heart beats, which indicates autonomic flexibility (the higher the variation, the more flexibility). HRV is most accurately measured via electrocardiogram; however, photoplethysmography is also utilized. HRV is measured as time-domain variables (e.g., changes in the standard deviation of beat–beat interval) and frequency domains using power spectral density analysis methods. Frequency components are thought to represent sympathetic and parasympathetic control over HR, with the high frequency domain (HF; 0.15–0.4 Hz) representing parasympathetic or vagal tone, while the low frequency (LF; 0.04–0.15 Hz) is comprised of both parasympathetic and some sympathetic elements (see Heathers 2014; Berntson et al. 1997 for review). Finally, respiratory sinus arrhythmia, HRV due to respiration, is another measure of vagal control of autonomic activity. Reduced HRV is associated with mortality and cardiovascular symptoms in patients with PTSD, highlighting the clinical importance of these measures (Kubzansky et al. 2007). There is growing evidence that both LF and HF are reduced in PTSD patients, which may be suggestive of an imbalance between sympathetic and parasympathetic drive on cardiovascular output (Cohen et al. 2000; Blechert et al. 2007; Jovanovic et al. 2009), though exceptions have been reported (Sahar et al. 2001). In a recent twin study of combat-related PTSD in Vietnam era veterans, Shah et al. (2013) found that HRV abnormalities (lower LF and HF) were present only in the twin with PTSD, suggesting that reduced HRV is an acquired consequence of the disorder. They also suggested that HRV abnormalities were not present in subjects with remitted PTSD, suggesting HRV reductions are indicative of symptom state. We have recently shown that HRV reductions (reduced HF) are also associated with new-onset PTSD symptoms in active duty marines who served in Iraq/Afghanistan, suggesting that reduced HRV is not related to age or chronicity of PTSD (Minassian et al. 2014). These studies have also shown that reductions in HRV in these populations are not due to depression or TBI, nor are they related to degree of combat exposure or deployment history per se (Shah et al. 2013; Minassian et al. 2014). Finally, reduced HRV is reported in untreated subjects (Minassian et al. 2014; Chang et al. 2013), indicating that this phenotype is not due simply to medication side effects. Although HRV measures appear to be sensitive to PTSD symptoms, they are not specific to PTSD. Indeed, reduced HRV, in particular HF, may be a more general marker of anxiety disorders (Pittig et al. 2013) or even mental illness, as it is reduced across multiple disorders including anxiety, depression, bipolar disorder, and schizophrenia (Moon et al. 2013). It is possible that multiple mechanisms underlie the reductions in HRV across these diverse patient groups, or that reductions in HRV are due to the higher stress or allostatic load experienced by those with neuropsychiatric illness (McEwen 2000).

Response to Challenge: In contrast to resting-state cardiovascular markers, several studies have assessed cardiovascular activity in response to challenges from either loud acoustic stimuli (startle) or trauma-related cues. A large body of literature documents larger HR reactivity to startling sounds in PTSD patients (Pallmeyer et al. 1986; Shalev et al. 1992; Orr et al. 2002). Pole (2007) investigated 10 studies

measuring HR response to loud acoustic stimuli and found that elevated HR response was among the most robust effects found using this paradigm. Pitman et al. (2006) examined elevated HR reactivity to sudden loud tone presentation in a twin sample of Vietnam veterans. They found elevated HR reactivity only in the twin with PTSD, indicating HR response is an acquired consequence of the disorder rather than a predisposing trait.

HR response to trauma-related reminder cues has also been examined, which may probe biological mechanisms relevant to fear memory processes. These studies typically involve either "standardized" cues, such as combat sounds (Liberzon et al. 1999) that are held constant across the sample being studied, or "ideographic" cues which are tailored to be specific to each subject's traumatic experience. Pole (2007) reviewed 16 studies investigating HR response to standardized trauma cues and another 22 investigating HR response to ideographic trauma-related cues. Elevated HR response to standardized cues in PTSD emerged as one of the more robust effects in these paradigms. Support for increased HR responses to ideographic trauma cues was also found, though less robust than that for standardized cues. Recent studies have also supported these findings in both standardized (Adenauer et al. 2010; Suendermann et al. 2010; Ehlers et al. 2010) and ideographic trauma cues (Barkay et al. 2012). Barkay et al. (2012) have investigated the neurobiological correlates of this effect using PET imaging and found correlations between HR and rCBF in the orbitofrontal, precentral, and occipital regions of the cortex only in patients with PTSD and not in trauma-exposed non-PTSD subjects. These findings are suggestive that increased HR responses to trauma reminders may overlap in neural substrates (orbitofrontal cortex) with the reduced ability to inhibit fear responses (Shin et al. 2006). In PTSD, there are correlations between HR response to trauma and norepinephrine concentrations in cerebrospinal fluid (Geracioti et al. 2008), suggesting that central noradrenergic hypersignaling could play a role in this phenotype. It is unclear whether increased HR or other cardiovascular abnormalities are ameliorated by treatment, however, despite the use of noradrenergic reuptake inhibitors (Hoge et al. 2012) as well as clinical trials of the alpha 1 receptor antagonist prazosin (Raskind et al. 2013). Whether increases in HR are an epiphenomenon of increased centrally mediated fear responses, or are a core feature of PTSD pathology is unclear. One intriguing recent finding suggests that inhibitors of angiotensin I signaling, commonly given for hypertension, are associated with fewer PTSD symptoms in a cross-sectional sample of highly traumatized civilian populations (Khoury et al. 2012). Other common hypertension medications were not associated with fewer symptoms, suggesting that the angiotensin pathway may play a role in PTSD-related pathology. Thus, more research is clearly needed to further elucidate pathways involved in elevated cardiovascular responses in PTSD.

Summary of Cardiovascular Markers of PTSD Symptom State: Cardiovascular physiology is an active and important area of research in PTSD, especially given reported links between PTSD and increased incidence of cardiovascular disease (Wentworth et al. 2013). While there is strong evidence that resting-state cardiovascular activity, as well as HR response to standardized and ideographic trauma cues, is altered in PTSD, this is still an active area of research that is not without

controversy. Specifically, the degree to which the testing situation contributes to findings of elevated HR in PTSD is unclear. The extent to which elevated HR is a feature of core PTSD pathology versus simply a consequence of chronic stress is also unknown. Some studies have suggested that HR soon after trauma may predict development of PTSD, suggestive of HR being a proxy for biological risk factors for PTSD (see below). However, a recent study suggests that HR is not altered in relatively "recent" PTSD cases after combat (Minassian et al. 2014), arguing against elevated HR as a risk factor. HR increases are also not specific to PTSD, but are increased in other anxiety disorders more generally. Research investigating the time course and neurobiological correlates of altered cardiovascular activity in PTSD is needed to further clarify these issues.

Many questions still remain for the association of HRV with PTSD symptoms. Although twin studies suggest that altered HRV is specific to PTSD symptom state, prospective studies are needed to confirm HRV measures as symptom dependent or markers of risk for PTSD (Baker et al. 2012). Similarly, although there is some evidence from cross-sectional analysis in small samples for symptom remission to be associated with normalization of HRV (Shah et al. 2013), longitudinal treatment studies are required to best address this question. The biological mechanisms responsible for HRV reductions in PTSD are also unclear. However, dysregulated sympathetic output (e.g., via increased noradrenergic tone, Geracioti et al. 2001, 2008; Pietrzak et al. 2013) and abnormalities in stress and immune systems have been identified as candidate mediators (Risbrough and Stein 2006; Eraly et al. 2014).

2.2 Exaggerated Startle Response

Baseline: The startle response is a sensitive, noninvasive measure of central nervous system activity that is typically accessed via electromyographic (EMG) measurement of strength of contraction of the *orbicularis oculi* muscle controlling eyeblink in response to a sudden acoustic or tactile stimulus (Blumenthal et al. 2005). Exaggerated startle is a symptom of PTSD according to the DSM 5 (APA 2014). Thus, it follows that larger baseline startle responding should be detectable in PTSD. However, evidence for increased startle reactivity under "baseline" conditions in PTSD is mixed, with some studies finding evidence for increased startle in PTSD relative to healthy controls and others finding equivalent startle responses (see Zoladz and Diamond 2013 for a recent review of this literature). There are also some suggestions that increases in baseline startle may only occur in chronic PTSD patients or following certain forms of trauma, such as combat (Grillon and Baas 2003). A significant problem with assessments of "baseline" startle is that it is very difficult to accurately assess this phenomenon. Startle reactivity is extremely plastic, and it is sensitive to many rapid and dynamic modes of inhibition such as habituation and sensorimotor gating, to emotional valence or experimental context, and of course is extremely sensitive to stimulus parameters such as intensity and duration of the startling stimulus, all of which will influence the detection of putative differences.

For example, startle is higher in PTSD patients under low-intensity startle stimuli but not high intensity (Butler et al. 1990), which may reflect a lowering of startle thresholds rather than an exaggeration of startle responses elicited by supra-threshold stimuli. Thus, more robust and reliable startle phenotypes in PTSD and other disorders are measured when comparing startle across multiple stimulus conditions and emotional contexts. Startle has also generally only been explored in terms of magnitude of the response (muscle contraction) compared to controls. However, self-reports of "increased startle" from patients may not simply reflect magnitude, but *the probability* of a response under subthreshold conditions, which has yet to be explored.

In Response to Challenge: Given the inconsistency of baseline startle changes in PTSD, it has been suggested that startle reactivity is higher in PTSD patients only when under threat; thus, this phenomenon is indicative of mechanisms related to increased stress responding rather than disruption of baseline arousal (Grillon and Baas 2003). Grillon et al. (1998) reported normal baseline but increased startle magnitude in Vietnam combat veterans with PTSD during anticipation of experimental electrical shock relative to non-PTSD veterans, demonstrating a higher response in situations of threat or stress in PTSD. Startle is also elevated in response to trauma reminders (imagery, trauma scripts) in PTSD patients (e.g., Cuthbert et al. 2003; McTeague et al. 2010); however, these tasks are relatively unique to individual laboratories and more difficult to generalize across studies. As a whole, these studies suggest that exaggerated startle in PTSD is not indicative of increased arousal at baseline, but is a physiological marker of heightened response to threat and heightened fear responses in the presence of trauma cues. Thus, startle is increasingly used as a quantitative measure of fear responding that complements self-report data on anxiety and stress to identify biological mechanisms underlying PTSD symptoms.

Studies have recently suggested that elevated startle to challenge in PTSD may be subject to gender differences. Kamkwalala et al. (2012) showed that women with PTSD had higher startle in a dark environment relative to a light environment than men and women without PTSD. However, this elevated "dark-enhanced" startle was not present in male subjects with PTSD. Further, dark-enhanced startle has been shown to be associated with pituitary adenylate cyclase-activating polypeptide receptor (PAC1) genotypes in females, a gene that interacts with estrogen and has also been associated with PTSD in females (Ressler et al. 2011). These studies represent a new avenue of PTSD research that is just coming to fruition in utilizing physiological markers as intermediate phenotypes to identify biological pathways related to PSTD risk.

Startle Habituation: Habituation is a non-associative learning process whereby an organism displays a reduction in some innate orienting or defensive response following repeated presentation of a stimulus (Halberstadt and Geyer 2009). Shalev et al. (2000) examined habituation of the startle and electrodermal response to loud acoustic stimulus in a sample of traumatized Israeli civilians tested at 1 week and 1 and 4 months following the traumatic event. Those who developed PTSD began to show reduced habituation in both measures beginning 1 month post-trauma, suggesting that reduced habituation may be an acquired sign of PTSD. The reduced

startle habituation finding is confounded, however, as the methodology used to detect startle was flawed, with sample rates that were much too slow (50 Hz) to visualize the very fast on and off rate of a startle response which is typically measured with 1,000 Hz sampling rates. The reduced electrodermal habituation, however, supported earlier findings by this group (Shalev et al. 1992). Other studies had failed to detect reduced startle habituation in PTSD but were compromised by their use of inappropriately slow sampling rates (Pitman et al. 1987, 1993; Orr and Pitman 1993). A more recent study in Croatian combat veterans found that PTSD and control groups did not differ in startle habituation as assessed by quantitative analysis of EMG reduction across trial; however, there was a reduction in PTSD subjects compared to controls when using nonparametric comparisons of a number of subjects who met criteria for habituation (lowest responding at the last trial) (Jovanovic et al. 2009). This study also did not replicate habituation of the electrodermal response, a physiological marker of sympathetic nervous system arousal based on electrical conductivity across the skin due to sweat (see below). Thus, taken together across studies, evidence for differences in startle habituation in PTSD subjects is weak. PTSD subjects may exhibit reduced habituation of fear-potentiated startle during fear association training (Ressler et al. 2011). However, it is unclear whether this effect reflects reduced habituation to startling sounds or increased reactivity to the aversive stimuli used during fear conditioning. Reductions in habituation have been detected in other neuropsychiatric disorders (schizophrenia, panic disorder); thus, it is possible that reductions in habituation of the response may represent a pathology in a subset of patients across disorders, as such a phenotype would have substantial consequences for multiple behavioral functions (Geyer and Braff 1982; Ludewig et al. 2002a, b, 2003, 2005). Habituation is another "intermediate phenotype" that is being used to identify potential gene pathways disrupted in these disorders (Greenwood et al. 2012, 2013).

Prepulse Inhibition of the Startle Response: Prepulse inhibition (PPI), the unlearned suppression of the startle reflex to an intense acoustic stimulus when immediately preceded by a weaker acoustic prepulse, is an operational measure of sensorimotor gating (Geyer et al. 1990; Geyer and Braff 1987). PPI has been shown to be a robust but non-specific biomarker of psychiatric diagnosis. PPI performance is reduced compared to healthy controls in a number of neuropsychiatric disorders including panic disorder, obsessive compulsive disorder, schizophrenia, bipolar disorder, Tourette's disorder, and Huntington's disorder (Braff et al. 2001; Swerdlow et al. 2006; Castellanos et al. 1996; Perry et al. 2001; Ahmari et al. 2012; Ludewig et al. 2002a, b). Many of these disorders are linked to cortico-limbic circuit abnormalities (Kohl et al. 2013). Given the evidence for PTSD to have disruptions in this circuit (Shin et al. 2006), PPI in PTSD subjects has also been examined. However, PPI associations with PTSD are inconsistent, with some studies showing significantly reduced PPI in PTSD patients (Ornitz and Pynoos 1989; Grillon et al. 1996, 1998), while others detected no differences or only marginal differences (Butler et al. 1990; Morgan et al. 1997; Lipschitz et al. 2005; Holstein et al. 2010; Vrana et al. 2013). Thus, additional research is needed to clarify or refute the presence of PPI deficits in PTSD.

Summary of altered startle plasticity in PTSD: Exaggerated startle responding in PTSD patients is seen fairly consistently, most predominantly under conditions of challenge or threat. Pole (2007) conducted a meta-analysis of 20 studies measuring startle response via *orbicularis oculi* EMG both at baseline and after manipulation of contextual threat. This analysis supported a significant increase in startle responses in PTSD; however, this effect was not as robust as elevated cardiovascular responses. Furthermore, increased startle response to threat is also not specific to PTSD, but is also reported in other disorders that are characterized by high physiological arousal and fear (e.g., panic disorder) but not generalized anxiety disorder (Grillon et al. 2009; Grillon 2008). These findings suggest that disorders characterized by exaggerated startle may share an overlapping biological pathway. It is not clear, however, whether these effects are due to increased fear responses per se (e.g., via increased amygdala and/or insula circuit activation), or reduced ability to inhibit or modulate these responses appropriately (e.g., reduced modulation of amygdala output by hippocampal and cortical circuits; see below; Acheson et al. 2012; Klumpers et al. 2007).

Habituation and PPI are both measures of fundamental aspects of information processing that are disrupted in a number of psychiatric disorders and are to some degree heritable (Greenwood et al. 2007). However, there is relatively weak evidence at present for disruptions in PTSD. It is possible that disruption in these processes may indicate one of potentially many biological risk traits for neuropsychiatric disorders. Hence, further understanding of the genetic and neurobiological mechanisms underlying these phenotypes and their relationship to PTSD risk is worth further investigation. Indeed, PTSD is thought to share polygenic risk with other disorders that exhibit information processing deficits, such as bipolar disorder and schizophrenia (Nievergelt et al. in review; Solovieff et al. 2014).

While exaggerated startle per se is not unique to PTSD, it nonetheless represents a powerful method for exploring mechanisms underlying the development of PTSD symptoms. In animals, exaggerated startle phenotypes have long been utilized to test causal hypotheses of potential mechanisms underlying development of anxiety and fear-related behaviors after severe stress, including corticotropin-releasing factor and noradrenergic abnormalities (e.g., Risbrough and Stein 2006; Davis et al. 2010; Grillon et al. 2009). In humans, utilization of startle plasticity as an intermediate phenotype is just now beginning to be exploited (Greenwood et al. 2012). Further, questions of exaggerated startle magnitude versus reduced startle threshold in PTSD remain to be answered (Butler et al. 1990). Finally, surprisingly few pharmacological studies have thus far utilized startle to examine potential biological mechanisms of increased physiological responses in PTSD. Using a pharmacological challenge with the alpha 2 antagonist yohimbine, Morgan et al. (1995) showed that startle reactivity in PTSD patients may be via increased sensitivity to noradrenergic signaling.

2.3 Other Physiological Measures

Electrodermal Level/Response: In addition to HR and startle, researchers have examined electrodermal levels in PTSD both at resting baseline and in response to challenge. Electrodermal response, or the increase in electrical conductivity across the skin due to sweat, is a physiological marker of sympathetic nervous system arousal. A meta-analysis by Pole (2007) looked across 31 studies that measured resting electrodermal levels in subjects with PTSD versus controls and found support for significantly higher levels associated with PTSD, although the effect size was small. Blechert et al. (2007) found that PTSD subjects had higher resting baseline electrodermal level relative to both healthy controls and subjects with panic disorder, suggesting some diagnostic specificity. Resting electrodermal level has historically been reported to be reduced in subjects with depression versus healthy controls (Argyle 1991), further suggesting that this measure may hold some diagnostic specificity.

Electrodermal response to challenge by standardized and ideographic trauma cues has also been examined in relation to PTSD. Pole (2007) looked across 22 studies and found medium effect sizes for elevated electrodermal response to both standard and ideographic cues in PTSD versus controls. Interestingly, Blechert et al. (2007) found blunted electrodermal response in PTSD when subjects were under threat of electrical shock, suggesting that there may be a difference in effect between challenge by reminder cue versus challenge by contextual threat (experimental shock). Similarly, McTeague et al. (2010) found that PTSD subjects with multiple traumas and more severe, chronic PTSD showed blunted defensive responses to ideographic imagery. More recently, Glover et al. (2011) showed overall elevations in fear-potentiated startle in a classical conditioning paradigm in PTSD subjects relative to controls; however, no differences were found in electrodermal responses. It is possible that startle reactivity measures may offer a wider measurable range to detect increased reactivity than skin conductance measures because startle baseline can be controlled by the experimenter (i.e., via adjustments of the intensity of acoustic pulse). Thus, it is possible that startle may be more sensitive to detecting differences in responses even under relatively high arousal states (e.g., under threat). Skin conductance, however, offers other significant advantages over startle, since it does not require a relatively invasive stimulus (e.g., acoustic pulse) for measurement. The passive nature of this measurement has also supported its use as a complementary tool in imaging studies in which subject movement must be severely limited (i.e., startle response movement can disrupt image processing).

Facial EMG: Facial EMG has been used as a physiological measure of emotional response and typically involves measurement of activity in the frontalis, corrugator, and zygomaticus major muscles involved in emotional facial expressions such as smiling and frowning. Pole (2007) found support for increased frontalis and corrugator EMG activity while viewing ideographic trauma cues (12 and 5 studies, respectively). Pole (2007) found no support for altered facial EMG activity at resting baseline, or in response to standardized trauma cues (12 and 6 studies, respectively).

Because these measures are (1) more sensitive to artifact (e.g., non-specific facial and head movements, talking) and (2) are not easily controlled or evoked parametrically compared to reflexive responses such as changes in HR, skin conductance, and startle, they have not been utilized widely. They do not offer cross-species translation nor have well-defined circuits; thus, they may have less utility in understanding biological mechanisms of PTSD.

Summary of Other Physiological Measures Associated with PSTD: Elevated resting-state electrodermal level may be a psychophysiological measure that is relatively specific to PTSD. However, this measure is susceptible to the same methodological difficulties as resting HR or baseline startle response, namely that it is difficult to eliminate contextual factors that may influence stress and thus electrodermal activity. Electrodermal response to challenge presents a complicated picture with findings varying dependent upon both subject-specific and testing protocol variables. There is support for an association between increased facial EMG reactivity specifically in response to idiographic trauma cues; however, the utility of this measure for further biological research is limited.

3 Psychophysiological Markers of PTSD-Relevant Constructs: Fear and Sustained Anxiety

Safety Signal Learning: Safety signal learning is the process by which an individual learns to inhibit a learned fear response in the presence of a cue signaling absence of danger. This process is directly relevant to PTSD phenomenology insofar as PTSD is in part characterized by altered reactivity to trauma-related cues even in "safe" environments. Safety signal learning can be measured by assessing responses to a CS− that is never associated with an aversive event versus a CS+ that is contiguous with an aversive event, or via a specific CS that predicts absence of the aversive event when given in conjunction with the CS+. Using the latter paradigm, Jovanovic et al. (2010) recently tested this process in a sample of trauma-exposed civilians who were healthy, had PTSD, had major depression, or had comorbid PTSD and major depression with fear-potentiated startle as the primary outcome variable. Subjects learned that a cue predicted a blast of air to the throat, but that when this cue was presented along with another cue (the safety signal), the blast of air would not occur. Subjects with PTSD and comorbid PTSD/major depression failed to show inhibition of the potentiated startle response in the presence of the safety cue. Inability of subjects with PTSD to inhibit responding to a safety signal was also confirmed in the former paradigm, a simple CS+/CS− discrimination learning task (Jovanovic et al. 2013). Andero et al. (2013) found associations between the ability to learn to discriminate between the CS+ (danger) and CS− (safety) are impaired in subjects with a single nucleotide polymorphism (SNP) on the opioid receptor 1-like gene which encodes for the amygdala nociception/orphanin FQ receptor involved in pain processing. This SNP was also associated with greater PTSD symptoms, providing

further evidence for impaired safety signal processing in PTSD as well as a putative biological pathway for this effect. These results, though preliminary and in need of replication, suggest that failure to learn to distinguish between environmental cues signaling danger versus safety may be an important process that is impaired in PTSD.

Fear Extinction: Fear extinction is the process by which an organism learns that a cue that once signaled threat no longer does so, thus resulting in a progressive reduction in defensive physiological responding in the presence of this cue. Extinction of psychophysiological fear responding has long been considered a putative model of PTSD process due to its similarity to naturalistic recovery from trauma experience. Orr et al. (2000) and Peri et al. (2000) showed that PTSD patients failed to extinguish a conditioned electrodermal response to a cue signaling electrical shock or loud acoustic stimuli, respectively. Subsequent studies using electrodermal responses as the dependent variable have largely supported these original findings (e.g., Wessa and Flor 2007; Blechert et al. 2007). Norrholm et al. (2011) examined fear extinction in PTSD using fear-potentiated startle to a cue signaling an aversive air puff to the throat and found that PTSD patients showed greater potentiated startle in the early and middle portions of extinction training. This finding suggests that enhanced initial fear conditioning produced a greater "fear load" that the PTSD patients had to extinguish. This increased fear responding is also associated with specific symptom clusters of PTSD, re-experiencing (Glover et al. 2011), indicating this paradigm likely probes neural mechanisms of trauma memory.

Not all studies have found evidence for delay of fear extinction learning in PTSD. Milad et al. (2008) found equal levels of extinction performance, as measured by electrodermal response, in combat-related PTSD compared to combat-exposed monozygotic twins without PTSD and controls. However, the PTSD twins failed to recall this fear extinction learning when tested 24 h later. These results suggest that PTSD is not associated with a fear extinction learning deficit, but rather a fear extinction memory deficit. Further, this deficit appears to be an acquired sign of PTSD rather than an inherited trait. This difference in within-session learning results across these studies may be due to the physiological measures of fear used, startle versus skin conductance. The higher magnitude of the startle response to the conditioned cue in PTSD patients is providing a behavioral window to detect reduced/delayed extinction within session, which is not detectable via skin conductance responses (Glover et al. 2011). Taken together, these data suggest overall that there is higher fear responding in PTSD patients, which subsequently takes longer to extinguish fully and is less likely to be fully extinguished upon retesting. Additional research will be needed to determine the time point at which extinction deficits may occur, the most effective method for capturing such deficits, and the specific role these deficits play in PTSD symptomatology.

Summary of Psychophysiological Markers of PTSD-relevant Constructs: Psychophysiological markers have emerged as critical measures of unbiased fear responding to understand fear and anxiety domains disrupted in PTSD. These markers provide quantifiable assessments of autonomic processes that may not be adequately probed by self-report. They have been critical behavioral measures that

complement studies of the neural circuits underlying PTSD pathology, such as cortico-hippocampal–amygdala circuit function (Quirk et al. 2006), that can be translated across species for further study of causal factors for PTSD symptoms or PTSD risk. The intriguing preliminary evidence for safety signal learning to be disrupted specifically in PTSD versus depression patients may indicate this is a potential "biomarker" of PTSD, but needs further research and replication. Extinction has shown to be impaired in a number of neuropsychiatric disorders as well as PTSD, including obsessive–compulsive disorder and schizophrenia (Holt et al. 2009; Milad et al. 2013), suggesting that extinction learning may probe common pathological circuits across these disorders. Impairment in these processes is further supported by imaging research showing impaired function and structure of the ventromedial prefrontal/orbitofrontal cortex in PTSD subjects, which are structures known to be central to fear extinction learning and memory (Shin et al. 2006). Recent research suggests involvement of these areas in safety signal learning as well (Jovanovic et al. 2013). Finally, more recently, these paradigms have been utilized in healthy controls or PTSD patients to serve as proof of concept tests for novel treatments for fear-related disorders such as PTSD, with recent or ongoing tests of cannabinoid agonists (Rabinak et al. 2013), oxytocin (Acheson et al. 2013), glucocorticoids (de Quervain et al. 2011), and dopamine agonists (Haaker et al. 2013), among others. It remains to be determined how predictive these paradigms will be for treatment efficacy; however, this is an exciting avenue for PTSD drug discovery.

4 Psychophysiological Markers of Risk for Developing PTSD Following Trauma

Trait Markers: Given that elevated physiological reactivity is a common finding in those with current PTSD, researchers have explored the possibility that this elevated reactivity might serve as a marker of risk prior to or immediately following the traumatic experience. Several studies examined the relationship between HR shortly following trauma and later development of PTSD and found that elevated HR following trauma predicted development of PTSD symptoms (Bryant et al. 2000; Kassam-Adams et al. 2005; Shalev et al. 1998; Zatzick et al. 2005; Kuhn et al. 2006; Gould et al. 2011). Though numerous exceptions have been reported (Blanchard et al. 2002; Buckley et al. 2004; Ehring et al. 2008; Roitman et al. 2013; Price et al. 2014). In a related study, Suendermann et al. (2010) found that HR response to trauma-related images in motor vehicle accident survivors 1 month after trauma predicted PTSD severity at 6 months after trauma. The inconsistency in these findings may be due to the fact that cardiovascular activity assessed immediately post-trauma in the ambulance or emergency department may be subject to too many contextual variables, methodological inconsistencies, or ceiling effects that may limit reproducibility of findings. Newer technology allowing for ambulatory monitoring in the days following trauma (see below) may prove more useful

in determining at which time points and under what circumstances post-trauma HR may be most predictive of future PTSD.

While these studies of peri-traumatic HR suggest potential clinical utility as a marker of risk in traumatized individuals, they tell us little about who might be at risk for trauma before the event happens. Toward answering this question, Pitman et al. (2006) examined HR responses to a series of loud tones in Vietnam veterans with PTSD and their non-combat-exposed monozygotic twins. Only the twin with PTSD showed elevated HR response relative to combat-exposed veterans without PTSD and their non-exposed twins, suggesting that elevated HR response is an acquired sign of PTSD rather than a risk factor. However, further longitudinal studies where HR response is measured prior to trauma will be necessary to definitively rule out HR as a prospective marker of risk for PTSD. Pole et al. (2009) measured a number of physiological indices (startle, electrodermal response, HR) in response to startling tones under conditions of varying contextual threat (low, medium, and high threat of electrical shock) in new police academy cadets. These cadets were then later assessed for PTSD symptoms following one year of police work. They found that elevated startle measured by eyeblink EMG (with appropriate sampling rate), elevated electrodermal response, and slower habituation of the electrodermal response predicted PTSD symptom severity, but that HR response did not. Further, the associations between physiological reactivity and PTSD severity varied as a condition of the contextual threat: Greater electrodermal response was associated with PTSD symptom severity under low and high threat, and eyeblink EMG under medium threat was associated with symptom severity. These findings support the hypothesis that increased physiological reactivity to threat may be a useful marker for understanding biological mechanisms of PTSD risk.

Markers of Fear and Anxiety Constructs: Little is known about how abnormalities in safety learning and fear extinction may function as preexisting markers of risk for PTSD. A recent study found that impaired ability to inhibit fear-potentiated startle responding in the presence of a safety cue was associated with PTSD symptoms 2 and 9 months after combat-related trauma (Sijbrandij et al. 2013). These findings suggest that impaired safety signal learning may be important in predicting the maintenance of PTSD symptoms over time. It is not clear, however, whether reductions in safety signal learning predict PTSD prospectively. Investigators have also begun to look at impaired fear extinction processes as risk factors for developing PTSD following trauma. A twin study of combat-related PTSD by Milad et al. (2008) suggested that reduced recall of fear extinction memory is an acquired sign of PTSD rather than a preexisting risk factor. Guthrie and Bryant (2006) examined initial fear extinction learning of an aversively conditioned corrugator EMG response in a sample of firefighter trainees. They found that slower extinction while in training predicted PTSD severity after later exposure to trauma. Lommen et al. (2013) showed similar effects in a sample of Dutch combat veterans, though they only assessed explicit contingency awareness rather than physiological response. Further prospective–longitudinal studies assessing both habituation and extinction prior to trauma are needed to confirm whether or not these are robust markers of PTSD risk.

Summary of Risk Markers: While peri-traumatic physiological response may provide some information regarding who is at risk for developing chronic PTSD, more research is needed to solidify the extant findings and to link elevated physiology following trauma to specific biological changes underlying chronic disorder. Much less is known about using physiological markers to predict risk for PTSD prior to traumatic experience, though the results of Pole et al. (2009) provide promising avenues for future research in this area and suggest the possibility of achieving superior prediction by the integration of multiple psychophysiological domains into a single marker for risk. Knowing who is at risk for PTSD prior to trauma may have utility for screening of soldiers and first responders such as firefighters and police officers. Identification of pretrauma risk factors that are modifiable can inform prevention efforts in these and other populations at high risk for trauma exposure and may also point toward fruitful targets for novel treatment efforts.

5 Future Areas of Application for Psychophysiological Research

Psychophysiological Markers of Treatment Response: Beyond serving as markers of PTSD state or risk for developing the disorder, psychophysiological outcomes may have potential to provide objective markers of treatment response. This utility is particularly relevant as the NIMH now requires treatment studies to include biological and/or physiological markers along with standard symptom scales. To date, however, relatively few studies have made use of physiological outcome measures. To our knowledge, there are no reports of psychophysiological responses in PTSD patients during standard pharmacotherapies, e.g., serotonin reuptake inhibitors. Two recent studies using psychotherapy have included physiological markers. Robinson-Andrew et al. (2014) assessed potentiated startle responding in the presence of trauma-related visual cues in a small number of combat veterans with PTSD before, during, and after either prolonged exposure or "present-centered therapy" treatment. Treatment responders showed a dynamic pattern of increasing and then decreasing startle potentiation across treatment, while non-responders did not change. In another recent study, Rothbaum et al. (2014) compared the effects of d-cycloserine, alprazolam, and placebo on response to 5 sessions of prolonged exposure therapy for PTSD. Outcomes consisted of both self-reported diagnostic assessments as well as potentiated startle response to trauma-related images. The patients receiving d-cycloserine showed significantly lower startle potentiation post-treatment, and magnitude of startle reduction was associated with self-reported treatment response in this group only. However, groups did not differ on self-reported response to the treatment overall. There is no research yet on treatment effects on PTSD-related constructs of fear extinction or safety signal learning.

One earlier area of study where psychophysiological outcomes appeared promising was in predicting potential prophylactic efficacy of propranolol, a beta-adrenergic receptor antagonist. Pitman et al. (2002) originally showed that propranolol given immediately after trauma reduced physiological arousal (HR, electrodermal response, facial EMG) to script-driven traumatic imagery 3 months later, as well as showing a nonsignificant trend toward reduced PTSD symptom severity 1 month following trauma. In a larger study, Hoge et al. (2012) showed mixed results when propranolol or placebo was given to emergency department patients for 19 days following trauma. In "high-medication adherence" subjects, those who took the active drug showed reduced physiological reactivity to trauma imagery across three domains (electrodermal response, HR, lateral frontalis EMG) at 1 month following trauma relative to those who received placebo. However, this difference was not found at 3 months post-trauma, nor was there an effect of treatment on PTSD symptoms. Given the very mixed literature for treatment efficacy of propranolol as a prophylactic treatment for PTSD (Vaiva et al. 2003; Stein et al. 2007; McGhee et al. 2009), the predictive validity of psychophysiological measures for propranolol prevention of PTSD symptoms is inconclusive. Current studies have now shifted to examination of propranolol effects on memory reconsolidation in PTSD patients (www.clinicaltrials.gov), based in part on recent findings that propranolol given immediately after reactivation of the trauma memory via script preparation reduces physiological responding to the same script one week later (Brunet et al. 2009).

Psychophysiological outcomes have also seen limited use in studies investigating potential novel treatments. Jovanovic et al. (2011) showed that dexamethasone treatment reduces fear-potentiated startle in PTSD patients, suggesting that this treatment could reduce physiological symptoms of fear in these patients. These results provide preliminary support for the predictive validity of fear-potentiated startle in PTSD, since glucocorticoid agonists may reduce PTSD symptoms (Aerni et al. 2004; Steckler and Risbrough 2012). An ongoing study is also assessing the efficacy of corticotropin-releasing factor receptor antagonist treatment on both PTSD symptoms and fear-potentiated startle (Dunlop et al. 2014). We expect that more studies will utilize this complementary approach of physiological and self-report measures to assess treatment efficacy in the future.

Overall, psychophysiological outcomes have not been utilized in treatment studies and thus remain largely untested for sensitivity to treatment effects for PTSD. An important caveat is that some studies have shown a pattern of treatment-induced reductions in psychophysiological arousal, but not in self-reported PTSD symptom severity. This pattern of findings suggests several possibilities. First, psychophysiological alterations may not be powerful enough to generalize into symptom change per se (e.g., Hoge et al. 2012). Second, psychophysiological alterations may be one of the several potential mechanisms of change occurring within the same treatment protocol (e.g., Rothbaum et al. 2014). These conclusions suggest that psychophysiological assessment may be used as an objective marker of treatment response and have utility in elucidating mechanism/process of change that may vary across subjects being treated with the same protocol. Further, psychophysiological

assessment may have utility for understanding which patients may benefit from among several treatment modalities aimed at the same overt condition (Aikens et al. 2011). More research is required before this approach can be considered a realistic possibility in the near term.

Consideration of Mild Traumatic Brain Injury (mTBI) in Psychophysiological Investigations of Trauma-related Pathology: Many of the traumatic experiences that might result in development of PTSD (motor vehicle accident, physical assault, combat) also involve potential for physical harm. The large numbers of blast-related injuries coming out of the wars in Iraq and Afghanistan (Hoge et al. 2008) have brought into recent focus the potential relationship between mTBI and PTSD. A prospective study of service members deployed in these conflicts suggests a strong association between deployment-related mTBI and post-deployment PTSD symptoms (Yurgil et al. 2014). These findings suggest that mTBI may need to be considered as an important factor in assessing psychophysiological outcomes in PTSD, similar to its potential effects on neurocognitive symptoms in PTSD (Vasterling et al. 2009, 2012). Little research has been conducted on how mTBI affects the physiological markers discussed here, with the exception of HRV. HRV is reduced in some TBI patients, with alterations related to time since injury and injury severity (Keren et al. 2005; Baguley et al. 2006). One study in active duty marines with PTSD suggests that HRV is reduced in PTSD subjects even when controlling for TBI although TBI was also independently associated with reduced HRV (Minassian et al. 2014). Williamson et al. (2013) have suggested that in cases of mTBI-induced damage to white matter tracts involved in emotional behavior (e.g., uncinate fasciculus and the anterior limb of the internal capsule) may cause disruption of top-down control of autonomic nervous system activity reflected in psychophysiological measurements. These forms of disruption could also explain the higher risk for development of PTSD in individuals exhibiting mTBI (Yurgil et al. 2014). Interestingly, recent animal studies have also supported that mild TBI could result in sensitization of fear learning processes (Heldt et al. 2014). Thus, mTBI should be carefully considered in future assessments of PTSD-related physiology, particularly in abnormalities of cortical-mediated inhibitory processes and fear learning constructs, to understand its modulating or mediating role in psychophysiological abnormalities in PTSD.

Wearable Physiological Monitoring Technology: Although the specific physiological abnormalities linked to trauma symptoms are becoming more clear as reviewed above, one of the next steps for the field is to determine whether these measures can translate to clinical applications, such as prediction of symptom development, symptom class, and/or treatment response. Moving these measures to clinical applications faces significant hurdles, one of which is the development of more usable devices that are not dependent on narrow laboratory-specific parameters or expensive and complicated hardware. One potential area for psychophysiology variables in mental health in the future is use of "wearable" devices in subjects that have experienced, or at risk for, trauma (Darwish and Hassanien 2011).

There is a strong push both in private and academic medical sectors to implement wearable devices for a host of medical purposes including diabetes, cardiovascular disease management, cognitive therapy aids, and other lifestyle aids for better wellness. Predictive psychophysiological variables relevant to PTSD phenotypes that may be conducive to wearable technology are measures of physical activity via accelerometers (e.g., Fukukawa et al. 2004), sleep (Suzuki et al. 2014), skin conductance (Rajan et al. 2012), HR and HRV (Billeci et al. 2014), EMG (Grenier et al. 2012), and EEG (Zao et al. 2014). The development of these wearables will enable assessment of dynamics of physiology in naturalist settings, at rest (i.e., sleep) as well as during stress. These devices may help answer the question of which physiological variable, or combination of variables, might be able to predict development of PTSD symptoms after trauma exposure (e.g., after discharge from the ER/hospital). Another question is if physiological markers are sensitive to treatment, and when in the recovery process does this happen (i.e., could these markers serve as early predictors of treatment response?). Many of these variables are not "static," for example, longer-term assessment of sleep variance across multiple nights will enable a much more comprehensive picture than can feasibly be obtained in laboratory settings. Similarly, HRV over long time periods will provide greater fidelity in the assessment of cardiovascular changes after trauma. Some wearable devices may also be utilized in "at-risk" populations, such as rescue service and military personnel, to develop algorithms of risk based on physiological response and recovery after trauma exposure. This approach is currently being examined in the military (Tharion et al. 2013). However, a number of hurdles must be considered in terms of feasibility/practicality of the technology, the data quality, storage capacity, and of course the ethical component of resulting data being used or stored improperly.

One example of current status of technology is assessment of continuous HR. HRV can now be obtained via sophisticated wearable devices (e.g., pulse oximeter introduced into a wrist watch) over long periods of time with little burden to the subject. However, technical challenges must be addressed, including the high sampling rate needed for HRV assessments that can produce power and data storage limitations for continuous monitoring. Data quality is also affected significantly by movement artifact for many of these devices. Thus, despite significant promise, many technical limitations must be addressed before these devices will produce reliable physiological assessments for utility in prediction and intervention.

6 Conclusion

As discussed above, there are now a number of well-validated physiological phenotypes that are reliable across multiple studies/laboratories, including increased and poorly inhibited physiological responses to threat (electrodermal and EMG), as well as altered HRV. We are just now beginning to understand these measures in a larger context of symptom domains, as well as comorbid symptoms (depression, TBI, etc.).

Much more work is needed, however, to refine these phenotypes in terms of specific associations with PTSD symptoms versus other anxiety disorders and comorbid symptoms (depression, TBI). Importantly, many of these phenotypes are now well mapped to circuitry that supports translational research across species for mechanisms driving these phenotypes, which will support development of novel treatment targets. To this end, psychophysiological measures are increasingly being used as complementary measures for integration with both self-report and other biological assessments (e.g., blood-based or genetic markers). We expect much more research in the years to come with these tools for objective assessment of treatment outcome. Finally, in the long term, wearable technology could accelerate the feasibility of these markers as tools to identify risk and symptom development in clinical settings.

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