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Using Experimental Methodologies to Assess Posttraumatic Stress

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Abstract

The assessment of PTSD is hindered by the absence of an objective biological measure. There is no blood test or stress test or similar objective measurement that reliably indicates the presence or absence of PTSD. In this article we focus on experimental assessments of PTSD. The focus will be on psychobiological indices that have been shown to be dysregulated in PTSD sufferers and that are responsive to treatment for PTSD. This includes psychophysiological startle, cortisol, and related assessments that will be covered succinctly below. We will end this article with future directions in the experimental assessment of PTSD that include novel measures incorporated in the immediate aftermath of trauma to assess current impact and prediction of the development of PTSD.

Current empirically supported methods for assessing PTSD

The assessment of PTSD is hindered by the absence of an objective biological measure. There is no blood test or stress test or similar objective measurement that reliably indicates the presence of PTSD. Assessment that depends on clinician or patient rated DSM PTSD symptoms is covered in an earlier article in this issue.¹ However, all of those measures ultimately depend on patient self-report.

In this article we focus on experimental assessments of PTSD. The focus will be on psychobiological indices that have been shown to be dysregulated in PTSD sufferers and that are responsive to treatment for PTSD. We will end this article with future directions in the experimental assessment of PTSD that include novel measures incorporated in the immediate aftermath of trauma to assess current impact and prediction of the development of PTSD.

Using Physiological Response to Assess PTSD

The DSM symptoms of hyperarousal and reactivity, including exaggerated startle response, implicate heightened sympathetic nervous system activity in PTSD patients. Therefore measuring physiological data such as heart rate (HR), skin conductance (SC), and acoustic startle response (ASR) offers the potential for objective assessment of PTSD symptoms. The psychophysiological evaluation of baseline startle in PTSD patients has yielded equivocal results[1,2], and therefore most assessment studies have tested reactivity using trauma-related stimuli or fear-eliciting procedures.

One of the earliest methods with trauma-related stimuli used a script-driven imagery procedure [3]. In this method, the patient describes an actual traumatic event which is then transcribed, recorded

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and played back to the individual while physiological responses are measured [4]. Among several different trauma populations [4,5][6], those with PTSD exhibited a stronger HR and SC response to scripts than non-PTSD trauma survivors. Keane and colleagues [7] conducted the largest study of script-driven imagery in veterans and concluded that it could provide objective assessment of the disorder. However, there were still false positives and false negatives in classification of PTSD, suggesting that the physiology may be influenced by other factors, such as multiple traumas [8] or dissociation [9].

A recent meta-analysis [10] of these early studies confirmed that psychophysiological responses to trauma scripts were predictive of PTSD diagnosis and were stable across time [11], and that SC was the most sensitive measure of hyperarousal. A recent application of trauma-related stimuli has been the use of virtual reality (VR), which can be used with psychophysiology to assess symptom severity. A study of active duty service members observed increased HR responses to VR scenes in soldiers with PTSD symptoms relative to non-symptomatic soldiers [12]. Psychophysiological reactions during VR can also be used to assess treatment response [13,14*]. A novel paradigm that builds on script-driven imagery and VR, but is adapted to be used in clinical settings is psychophysiological recording during a trauma interview. A recent study showed that PTSD symptom severity significantly predicted changes in HR while the patient talked about his/her trauma [15*]. SC or HR can be recorded continuously during a standardized trauma interview using mobile applications such as smartphones and tablets connected to electrodes. These new technological advances allow for low-cost and low-burden applications of psychophysiology without specialized training and easy dissemination. This method was recently used to collect SC data in the Emergency Department (ED) within hours of trauma exposure and has been found to predict later severity of PTSD symptoms [16]. One caveat is that wearable devices such as wrist watches have a significant trade-off between sampling frequency and battery life, so the data tend to be low-resolution and affected by movement artifact. However, devices with sensors that attach to the body with electrodes have been found to be reliable [16].

The acoustic startle response (ASR) can reliably be quantified using electromyography (EMG) of the eyeblink muscle contraction. The startle response is modulated by emotionally salient influences [17-19]. Several experimental paradigms have capitalized on this effect by combining fear-eliciting stimuli with a loud sound to potentiate the startle response. Early studies of Vietnam veterans with PTSD found no differences between patients and controls in the degree of startle potentiation under threat conditions [21]. However, a second set of studies that examined urban police officers found that PTSD symptom severity was positively associated with startle potentiation under the low and medium threat, but not high threat conditions [22]. Furthermore, a prospective study of police cadets indicated that higher startle to low threat prior to trauma exposure was predictive of higher PTSD symptoms a year later [23].

In a typical fear learning paradigm, a neutral cue such as a shape or tone is paired with an aversive stimulus, such as a shock or airblast [24]. After several pairings, the cue elicits a fear response; usually the experiment will include a second cue that is not paired with the aversive outcome, becoming a “safety signal”. Elevated responses to the danger signal have been repeatedly observed in individuals with PTSD, using SC, EMG, and HR [25-28], with some notable exceptions that appear to be due to divergent methodologies or physiological indices [27,29]. Over the last decade, it has become clear that PTSD is associated with heightened physiological reactivity to safety signals [30,31]; this phenotype is likely due to the inability to regulate fear. Individuals with PTSD also show exaggerated fear during extinction, an experimental paradigm in which a previously learned danger signal is repeatedly presented without the aversive outcome thereby becoming safe. The maintenance of fear responses suggests a disruption in extinction learning [25,28,32] or extinction memory [28] in PTSD compared to controls. This overexpression of fear has been termed “fear load” and appears to be related to re-experiencing symptoms of PTSD [33*].

The above described measures point to underlying biological features of PTSD symptoms that could aid in the assessment of the disorder. It is important to note that to date none have proven to have perfect specificity or sensitivity with regard to a PTSD diagnosis, which may partly be due to the heterogeneity of trauma responses and self-report bias. While novel tools are emerging that will allow for more wide-spread use of these measures, most current methods still require elaborate equipment and specialized training. However, using these methods to guide the development of more accessible tools could lead to a paradigm shift in diagnosing PTSD in the future.

Using Hypothalamic-Pituitary-Adrenal Axis Function to Assess PTSD

With recent advances hormones may serve as biomarkers of PTSD and potential tools for objective assessment. While many hormones are under study, attention has focused on the hypothalamic-pituitary-adrenal axis (HPA), including cortisol, corticotrophin releasing hormone (CRH), and adrenocorticotrophic hormone (ACTH). Under normal function, CRH is released by the hypothalamus and activates release of ACTH from the pituitary that then stimulates the release of cortisol from adrenal cortex. The system shows a diurnal pattern and is activated in response to specific types of stressors with factors such as novelty, appraisal, and perceived control influencing response [34,35]. Patients with PTSD have shown HPA axis functional abnormalities, including enhanced glucocorticoid receptor sensitivity that leads to enhanced negative feedback and hypocortisolemia [36,37] and flattened diurnal cortisol [38]. However, it remains unclear whether cortisol is a biomarker of vulnerability to PTSD that predates trauma exposure or of the disease.

There are several commonly used measures of HPA axis function. The dexamethasone suppression test (DST) examines the HPA axis response to the administration of dexamethasone that blocks the release of ACTH. Generally, the DST involves patients having saliva or blood collected on the morning of Day 1, ingesting low dose dexamethasone (0.5mg) in the evening of Day 1, and then

collection of either blood or saliva at a comparable time in the morning of Day 2. While initial studies showed enhanced suppression of cortisol following administration of DEX in PTSD [39], recent studies have also shown cortisol suppression effects in trauma exposed samples [40]. An innovative recent study showed that HPA axis dysfunction (increased cortisol in response to cosyntropin activity) was related to trauma exposure rather than specific to PTSD [41*]. Additional study is needed to clarify if this is a biomarker of PTSD or trauma exposure.

One method to overcome variability due to diurnal variation is collecting urine over a full 24-hour cycle, although it can be cumbersome for patients and study staff to collect. In a recent large epidemiological sample, current PTSD and lifetime PTSD showed lower 24-hour urinary cortisol than those who never had PTSD [42*], as did a recent meta-analysis [43]. Thus, while a measure with significant patient burden, 24-hour urinary cortisol shows promise as a reliable discriminator of PTSD.

Trauma script-driven imagery is used to examine HPA axis reactivity to trauma specific cues. The most commonly used paradigm includes brief (one to three minute) personalized trauma and neutral scripts [36] with saliva or plasma collections to examine cortisol response. While studies have demonstrated that PTSD patients show more cortisol reactivity following a personal trauma script, it is not clear if this is an effect of trauma exposure or PTSD [44]. Creating personalized scripts for each patient is burdensome and results in variability between patients in the content of their scripts. As such, additional work is needed to create a standardized, replicable paradigm that can be personalized to a specific trauma.

Cortisol awakening response (CAR) is of particular interest as a possible biomarker and tool for PTSD assessment due to ease of collection and association with perceived stress [45] and psychiatric symptoms. Patients generally receive directions and tubes for saliva collection that the patient places by their bed prior to sleep. Upon awakening and prior to any consumption, the patient collects the first

sample; samples are collected at various intervals for 1-2 hours post waking. Higher PTSD symptoms were associated with attenuated CAR in several studies [46]. Patient compliance with procedures can be an issue and samples require refrigeration prior to analysis for optimal results.

In summary, assessment of hormones as biomarkers of PTSD shows promise. At present, much additional work is needed to establish reliability and validity for utility in routine clinical assessment and diagnosis. Further, examining additional HPA axis markers or other neurosteroids, is also warranted.

Future Directions

As exemplified by the above approaches of assessing PTSD, methods continue to evolve with technological advances. This applies in terms of the direct assessment method (e.g. SC), measurement (e.g. Dex suppression), implementation abilities, as well as our ability to evaluate large datasets and complex models (e.g., machine learning methods). Experimental methods of assessing PTSD in the foreseeable future rely heavily on these ideas. For example, VR is a successful treatment modality in a multitude of disorders, including anxiety and PTSD [47]. Recent work used virtual humans to assess PTSD and depression[48*]. This cutting edge interactive program called Sim Sensei uses Microsoft Kinect to observe behavior, movement, facial expression, and verbal behavior, and is able to conduct assessments in an autonomous and automatic fashion directly from a patient [48*,49]. Results from machine-based assessments found vowel spacing, length and frequency of smiling, and other behavioral markers of psychopathology that can be recognized by this smart system and may go unnoticed by a human assessor [49,50*].

Beyond assessing the presence of PTSD or as a treatment outcome, future experimental methods of assessment include early identification of risk for and prevention of PTSD before a diagnosable disorder develops. Research indicates that this is indeed a feasible endeavor [51], with successes in implementing pilot studies of early interventions [52,53]. Given the large numbers of those

who are exposed to trauma, the need to assess risk is paramount to effective implementation of early interventions. This has led to predictive measures such as the Immediate Stress Reaction Checklist (ISRC) [54] and Predicting PTSD Questionnaire (PPQ)[55].. As technology develops, biological markers can be used in this capacity in real time, such as genetic markers, which were associated with risk, resilience, and treatment efficacy [56*], and mobile methods of collecting psychophysiology used to assess risk for PTSD and treatment response following an early intervention [57,58].

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This study used a psychophysiological fear conditioning and extinction laboratory paradigm with individuals with civilian trauma exposure and found that those with elevated re-experiencing symptoms

of PTSD had exaggerated fear responses during the early phases of fear extinction. This phenomenon was termed “fear load” and represents the high level of fear that PTSD patients must overcome in order to show normal fear extinction. Because extinction is a laboratory analogue of exposure therapy, “fear load” can model the initial levels of hyperarousal that patients may feel at the start of exposure therapy that must be overcome for successful recovery.

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The authors present findings from an innovative study working to clarify whether previous differences in adrenocortical responsivity are better accounted for by PTSD or trauma exposure. Male veterans [war zone exposed with PTSD (n = 13), War zone exposed without PTSD (n = 22) and not exposed to war zone (n = 10)] received a low dose of cosyntropin with plasma collections for cortisol and ACTH for one hour after administration. Both war exposed groups showed increased plasma cortisol level over the non-exposed group. Thus, the effect appears related to war zone exposure and not specific to PTSD. Additional research is needed to further examine this effect.

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