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Neural, Psychophysiological, and Behavioral Markers of Fear Processing in PTSD: A Review of the Literature

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Abstract

As presently defined, post-traumatic stress disorder (PTSD) is an amalgam of symptoms falling into: re-experiencing of the trauma, avoidance of reminders of it, emotional numbing and hyperarousal. PTSD has a well-known proximate cause, commonly occurring after a life-threatening event that induces a response of intense fear, horror, and helplessness. Much of the advancement in understanding of the neurobiology of PTSD has emerged from conceptualizing the disorder as one that involves substantial dysfunction in fear processing. This article reviews recent knowledge of fear processing markers in PTSD. A systematic search was performed of reports within the specific three-year publication time period of January 2010 to December 2012. We identified a total of 31 studies reporting fear processing markers in PTSD. We further categorized them according to the following classification: (1) neural-activation markers (n=10), (2) psychophysiological markers (n=14), and (3) behavioral markers (n=7). Across most studies reviewed here, significant differences between individuals with PTSD and healthy controls were shown. Methodological, theoretical and clinical implications were discussed.

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Conflict of Interest Erel Shvil declares that he has no conflict of interest.

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Keywords

Posttraumatic stress disorder (PTSD); Trauma; Fear processing; Emotional regulation; ACTH; Cortisol; Electromyogram; Emotional reactivity; Fear conditioning; Fear-potentiated startle; Heart rate response; Heart rate variability; HPA; Hydrocortisone; Psychophysiological; Skin conductance response; Functional MRI (fMRI); Activation; Attentional bias; Dot-probe; Emotional stroop; Eye tracking

Introduction

A common characteristic of most anxiety disorders is an elevated fear response, which often results in increasingly avoidant behaviors and triggered fear and defensive responses to a specific or more generalized stimulus or context. Yet, despite their shared qualities, anxiety disorders differ in a number of core features. The symptom constellation of emotional numbing, hyperarousal, and hypervigilance, as well as intrusive memory phenomena such as in the forms of nightmares and flashbacks are particularly characteristic of posttraumatic stress disorder (PTSD) [1]. Conceptualizing PTSD as a disorder of the brain's fear system, with emotional processing dysregulation within its circuitry, has generated a significant body of research over the past decade that has illuminated the neurobiological and psychophysiological mechanisms that underlie this disorder. The purpose of this article is to review research from the last three years (2010–2012), focusing on the psychophysiological, behavioral, and neural markers of PTSD that are associated with fear processing. Although, this review builds to some extent on previously published reviews [2•, 3•], it is the first systematic review of literature to systematically include a wide array of fear processing markers in PTSD.

Method

Selection Criteria

Criteria for inclusion in this review were data based published articles in English language, publication dates between January 2010 and December 2012, and studies comparing adults with and without PTSD on psychophysiological, behavioral, and functional neuroimaging markers of fear processing. Review articles were excluded. Further exclusion criteria included studies in which participants suffered from additional major DSM-IV Axis I disorders (excepting major depressive disorder, MDD) or had active psychotic symptoms. Importantly, since this review is focused on fear processing circuitry, structural imaging studies (e.g., volumetric studies) are not included, whereas functional imaging studies are. We also excluded from this review studies of resting state and cognitive paradigms involving decision-making, working memory, or reward circuitry.

Search Strategy

We acquired papers for this review using a three-step procedure. First, we implemented a systematic search of the peer-reviewed literature using Academic Search Complete and Medline databases and identified potential studies for inclusion using the following keywords: 'PTSD', 'posttraumatic stress disorder', 'imaging', 'MRI', 'fMRI', 'PET', 'neurocircuitry', 'heart rate', 'HR', 'skin conductance response', 'SCR', 'startle', 'facial electromyogram', 'EMG', 'electrocephalographic event related potential', 'ERP', 'fear', 'fear conditioning', 'fear paradigm', 'behavioral paradigm', 'attention bias, and eye tracking'. Second, using the study abstracts we excluded papers that did not satisfy selection criteria. Third, using the full-texts of the remaining articles, we excluded those that did not satisfy selection criteria.

Search Results

Our search identified a total of 31 studies of functional neuroimaging, psychophysiological, or behavioral markers in PTSD. The results of this review are presented in three tables (Tables 1, 2, and 3). Each table provides a summary including lead author and year of publication, population studied (e.g., PTSD, healthy controls, trauma exposed controls), paradigm, measure (fMRI, PET, skin conductance response, heart rate response, attention bias, etc.), and main findings of the study. The review is divided into three sections. In the first section we review functional neuroimaging markers (n=10); in the second section we report psychophysiological markers of PTSD (n=14); and in the third section we report behavioral markers (n=7).

Neural-Activation Markers (n=10)

Converging results from functional neuroimaging research using position emission tomography (PET) or functional MRI (fMRI) suggest altered emotion neurocircuitry in individuals with PTSD [4]. In addition to the different scanning techniques, studies utilize trauma-related triggers (e.g., trauma-related descriptions, pictures, smells and sounds) as well as nonspecific emotional stimuli such as fearful facial expressions, and emotionally-valenced photographs in patients with PTSD compared to control subjects [4]. Emotion activation studies in these individuals have shown hyperactivation in emotion-related regions that include amygdala [5, 6], dorsal anterior cingulate cortex (dACC), and insula [6]. Hypoactivations relative to controls are also reported in emotion-regulation regions, including medial prefrontal cortex (mPFC) [7], anterior ACC, rostral anterior cingulate cortex (rACC), and ventral medial frontal gyrus [8]. Abnormal hippocampal activity has also been reported although findings across studies are highly inconsistent in whether it shows hyper or hypo-activation. Hence, overall pattern of higher amygdala activation and lower ventral medial PFC activation to negative emotionally-valences stimuli is common to most functional imaging studies.

Fearful Facial Expressions, Emotional Photographs

Most consistently, amygdala in PTSD has been shown to be hyperactivated during presentation of general emotionally laden stimuli [9]. Fonzo et al. [10] utilized an emotional face-matching task and found increased amygdala activation in response to fearful versus happy faces in women exposed to intimate partner violence (IPV) with PTSD relative to trauma-unexposed control subjects [10]. This study also reported less connectivity between the anterior insula, amygdala and anterior cingulate cortex (ACC) in PTSD for this contrast. Greater insular cortex activation during the anticipation of aversive images and in response to fearful facial expression was found in a different study involving women with PTSD related to IPV compared to non-traumatized healthy control group [11•]. In a longitudinal fMRI design study, Dickie et al. [12] investigated the neural correlates of recovery from PTSD using an emotional face memory-encoding task. The authors reported that amygdala and vmPFC activity were highly associated with current PTSD symptom severity, whereas changes in activity in the hippocampus and subgenual ACC were correlated with degree of improvement in PTSD symptoms, suggesting that activity in these areas may be associated with recovery [12]. In another recent study, Brunetti and colleagues [13] compared survivors of bank robberies with and without PTSD. They found that although both groups showed increased amygdala activation in response to negative pictures, only the PTSD group demonstrated amygdala hyperactivation in response to neutral pictures [13]. This suggests generalization of fear response to non-aversive stimuli and deficient amygdala inhibition in individuals with PTSD.

Attentional Detection of Target (DOT)

Using emotional face matching task and the DOT, El-Khoury-Malhame et al. [14] found increased amygdala activity to emotional faces in individuals with PTSD compared to non-traumatized healthy control group. The authors further report that amygdala activation was positively correlated with PTSD symptomatology as well with the disengagement index (attentional bias toward threat) [14]. In addition, a recent study examined associations between behavioral and neural correlates of attention bias for threat in a sample of trauma-exposed individuals with and without PTSD. The study found increase activation in dorsolateral prefrontal cortex (dlPFC) in response to threat cue trials in the PTSD group but not in the trauma-exposed control group [15•], suggesting this as a neural activation marker specific to PTSD.

Trauma Related Stimuli

Research has also reported amygdala responsively in PTSD using script or other trauma related stimuli [2••]. In an fMRI study, St. Jacques et al. [16] examined the effect of PTSD on brain regions involved in autobiographical memory retrieval. Subjects in the study were asked to search for autobiographical memories triggered by the auditory cue words. Strong positive association was found between vmPFC and amygdala/hippocampus region activation in the PTSD group, as well as more intense negative memories elicited in the PTSD but not in the non-traumatized healthy control group. In a recent PET study, Gold and colleagues [17••] further found decreased mPFC activation during mental imagery of traumatic events in individual with PTSD compared to non-traumatized healthy control group.

Fear-Conditioning, Extinction, and Recall Paradigm

Fear conditioning and extinction paradigms in humans during functional imaging have identified similar brain regions with altered activity relative to controls, specifically in amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC) [18]. In using fear-conditioning paradigm developed by Milad et al. [19••], Linnman and colleagues [20] found similar responses to the conditioned stimulus in individuals with PTSD and the trauma-exposed healthy control group. However, the PTSD group exhibited hyperactivation of the amygdala, hippocampus, dACC, insula, and caudate nucleus to the unconditioned stimulus (i.e., electric shock), suggesting generalization of response to neutral and unreinforced stimuli. Furthermore, the authors report that activation in the anterior insula was positively associated with PTSD symptom severity. Using the same paradigm, Rougemount and colleagues [21] assessed brain activation to contextual information in PTSD versus trauma-exposed non-PTSD subjects. PTSD subjects showed deficiency in the processing of contextual information related to danger and safety. Specifically, compared to the control group, the PTSD group shows deactivation of vmPFC and increased activation in dACC during early extinction recall phase.

Psychophysiological Markers (n=14)

Chronic hyperarousal and excessive reactivity to trauma reminders are indicative of dysfunctional regulation of the physiological stress response system in patients with PTSD and have been confirmed in various psychophysiological studies [22]. Numerous studies have shown an elevated reactivity to auditory and visual cues associated with the trauma in individuals with PTSD in comparison with both traumatized and non-traumatized controls (e.g., for a meta-analysis see [23], also for reviews see [24, 25]). Predominantly, psychophysiological research employs a variety of physiological measures, including heart rate (HR), skin conductance (SC), and facial electromyography (EMG). Moreover, this body

of research has also examined fear processing in PTSD versus control groups employing the acoustic startle response (ASR). This is a well characterized reflexive response to a sudden acoustic stimulus mediated by a simple neural circuit and can be measured through eye-blink EMG and by electroencephalography. In fear-potential startle, this circuit is engaged by fear circuitry such that conditioned stimuli lead to enhancement of this startle response.

Cardiac Activity in PTSD

Heightened resting heart rate (HR), stimulus-triggered HR response [26] as well as non-extinction of HR response upon repeated presentation of stimuli [27, 28], are suggested to be among the most prominent abnormal psychophysiological outcomes in PTSD. Adenauer and colleagues [29••] found PTSD to be related to increased HR response to emotional stimuli, while the control groups (trauma-exposed; healthy individuals) showed non-specific undifferentiating orienting response regardless of stimuli category. Furthermore, in comparison to both the control groups, the orienting response to aversive pictures was almost absent in participants with PTSD. This suggests that the HR response to threatening stimuli is not only higher but also peaks faster in individuals with PTSD [29••]. Similarly, a recent study found subjects with PTSD to exhibit a significant increase in HR upon exposure to traumatic-related scripts [30•]. In another study of physiological responses to trauma reminders soon after the trauma; individuals with PTSD exhibit elevated HR to standardized trauma-related pictures compared with survivors without PTSD as early as 1 month after the trauma [31•, 32]. In conclusion, recent HR findings are consistent with the observation that individuals with PTSD respond to threatening cues and trauma reminders with a hypersensitive survival response [33].

Heart rate variability (HRV) is a non-invasive measure of the individual's central regulation of psychophysiological responses [34] by measuring the variable time interval between heartbeats on the electrocardiogram. This parameter reflects the individual's autonomic flexibility or ability to adjust physiological arousal on a moment-to-moment basis [35] via centrally originating sympathetic and parasympathetic input affecting heart rate. Hauschildt et al. [36•] examined HRV at rest and in response to videos of varying emotional valences in a sample of individuals with PTSD compared with both traumatized and non-traumatized controls. As expected, the PTSD group showed significant lower HRV than non-trauma-exposed controls at baseline and in response to different affective conditions. However, although the PTSD group exhibit lower HRV than the trauma exposed non PTSD group the difference between the two groups was not significant. Furthermore, lower overall HRV was associated with PTSD severity, particularly with intrusive memories and avoidance symptoms [36•]. Although HRV has not been employed often in PTSD research it represents the capacity for regulated physical and emotional responding and can be conceptualized as an important marker of emotion regulation [34, 37] in trauma.

Startle Circuitry in PTSD

The acoustic startle response is a reflexive contraction of the skeletal musculature that occurs in response to a sudden auditory stimulus [38]. An enhanced startle reflex is one of the hyperarousal symptoms constituting of PTSD. A recent meta-analysis of 25 startle studies in PTSD showed an impact with eyeblink electromyography responses to startle stimuli [2••]. McTeague et al. [39••] used an idiographic trauma imagery paradigm, where participants imagined threatening and neutral events while acoustic startle probes were presented and the eye-blink response was measured. Similar to prior studies, individuals with PTSD evinced higher startle reflex, autonomic response, and facial expressivity during idiographic trauma imagery compared with the trauma exposed non PTSD and non-trauma-exposed controls [36•]. Very recently, Kamkwalala and colleagues [40•] examined acoustic startle response in individuals with PTSD using a "dark-enhanced" startle paradigm. In the

paradigm, participants undergo the dark enhanced (total darkness) segment, which consists of two blocks each, with eight acoustic startle probes. In each block, four startle probes were delivered in the dark phase and four were delivered in the light phase [41]. The study found that only women with PTSD were associated with greater dark-enhanced startle, which potentially could be used as sex-specific marker for PTSD [40•].

In human fear conditioning models, startle response is a well-characterized reflex to a sudden intense stimulus that can be conditioned when paired with an innocuous conditioned stimulus. The startle response and fear-potentiated startle have been commonly employed in the study of PTSD [2•]. Consistently, studies, using fear-potentiated startle (FPS), have shown exaggerated startle responses and deficits in fear inhibition and fear extinction in individuals with PTSD [42•, 43•, 44•, 45, 46•, 47•, 48•]. Jovanovic et al. [44•] investigated fear inhibition differentially in PTSD and MDD using FPS. The study used a novel conditional discrimination procedure (AX+/BX-), in which one set of shapes (AX+) (the danger signal) was paired with aversive airblasts to the throat, and different shapes (BX-) (the safety signal) were presented without airblasts. The paradigm also included a transfer of fear inhibition tests (AB). Patients with PTSD, with or without comorbid depression, did not demonstrate discrimination between danger and safety cues, as evidenced by the lack of significant differences on the FPS magnitude to both cues, suggesting impaired fear inhibition [44•]. Using the same paradigm, Jovanovic and colleagues [46•] examined the relationship between hypothalamic-pituitary adrenal (HPA) axis function, FPS and inhibition of fear learning in PTSD. In addition to FPS, the dexamethasone suppression test (DEX) was also preformed, and blood cortisol and ACTH were assessed at baseline and post-DEX [46•]. The study found that a higher FPS to danger and safety cues was associated with higher baseline and post-DEX ACTH levels in PTSD. The finding suggests deficient responses to safety cues, or over generalized responding to danger cues, and might serve as an intermediate biological phenotype for PTSD [25]. In a similar study [47•] that examined the effects of DEX using a fear discrimination procedure, there were no group differences in subjects tested after dexamethasone. However, a significant treatment effect was found in PTSD subjects compared to controls, with DEX reducing FPS to danger cues. These preliminary findings suggest a possible relationship between HPA inhibition via DEX inhibition and a reduction in exaggerated fear among individuals with PTSD [47•].

Recent findings further support the hypothesis that inhibition of FPS when presented with danger reminders should be investigated as a potential marker of PTSD. Additionally, these findings support the premise that PTSD is associated with reduced responding to safety cues, or over-generalized responding to danger cues.

Behavioral Markers (n=7)

Particular behavioral symptoms of PTSD, such as avoidance of trauma-related fear-inducing stimuli and hypervigilance, have guided research on specific underlying cognitive and physiological processes potentially related to these PTSD symptoms. Two basic brain processes have been proposed that may mediate pathological hypervigilance and avoidance in PTSD [49]: attention biases to threat-related reminders [50] and abnormal fear conditioning/extinction processes [18]. With regard to the former, behavioral findings suggest that inability to disengage attention from threat relevant information may play a role in the maintenance of trauma-related ruminations, avoidance behaviors and re-experiencing symptoms. Yet, findings regarding the direction of attention bias (toward or away from) in different anxiety disorders have been mixed. Evidence for these biases has largely emerged from modified emotional Stroop, dot-probe, and eye tracking tasks (see Table 3).

The emotional Stroop studies have suggested significant disruptions during attention to trauma-related words in PTSD [51]. In this task, participants typically view words of varying emotional valence (e.g., unpleasant, neutral, and pleasant words). The words are presented in different colors, and the participants have to name the print color of each word while trying to ignore the words' meaning [52]. In a recent study, sexual trauma subjects with PTSD were significantly slower compared to non-traumatized controls in naming the color of threatening sexual violence words [52], suggesting attention bias toward aversive word cues. The study used version of the emotional Stroop that included threatening sexual violence, and non-threatening sexual words. In a similar manner, Mueller-Pfeiffer et al. [53] utilized a version of the emotional Stroop using sequences of neutral, positive and negative images. The authors compared response rate within PTSD, trauma-exposed individuals with other anxiety disorders (but no PTSD), and trauma-exposed healthy subjects. The response of individuals with PTSD were significantly slower in the presence of negative images versus neutral or positive images; yet, within the other two groups no significant variances between the different stimuli were found. In a longitudinal study El Khoury-Malhame and colleagues [54•] explored attention bias in PTSD on both emotional Stroop and the detection of target task (DOT) before and after eye movement desensitization and reprocessing (EMDR) therapy. The DOT is another stimulus-response task that examines the association between attention bias to threat and anxiety. During the tasks, two stimuli are presented side by side in a screen. The stimuli remain in the screen for a specified duration of time, after which a dot appears in the screen, replacing one of the two stimuli. The participant presses a button that corresponds to the relative position of the dot on the screen. If the participant has a bias of attending to threat stimuli, s/he should respond faster when the dot appears in space where the threat stimuli were previously [55]. In both of the tasks, emotionally negative versus neutral words were employed as distracting stimuli. In the pre-treatment evaluation, individuals with PTSD found it difficult to disengage their attention from aversive cues, suggesting attention bias toward threat. Yet, attention bias toward threat cues was significantly diminished during post-EMDR treatment. Furthermore, this improvement was highly correlated with PTSD symptom reduction. Kleim and colleagues found a similar pattern of attention bias using a different task. In their study, both individuals with acute stress disorder (ASD) and individuals with PTSD performed better in a task involving identification of trauma-related pictures (v. neutral pictures) presented in a novel blurred picture [56].

Recently, several versions of the dot-probe task have been used to explore attention bias processes in PTSD, yielding inconsistent results regarding direction of attention bias toward or away from the threat. A number of studies [57•, 58•, 59•] probing attentional bias under life-threatening circumstances (e.g., rocket attacks; war trauma) showed attentional *avoidance* of threat-related words to be associated with acute proximal stress and stress-related psychopathology (PTSD and depression). Using a longitudinal design, [59•] attentional avoidance during threat predicted higher rates of PTSD symptoms at 1-year follow-up. Yet, other studies [55, 60•] have found attentional bias *toward* general threat images to be correlated with greater severity of posttraumatic stress symptoms. With particular relevance to this problem, studies that used eye tracking [61], a measure of attentional bias that does not require verbal or non-ocular motor responses, showed increased number of initial fixations to trauma-related words in PTSD compared to trauma exposed non-PTSD subjects, suggesting attentional bias toward aversive cues is likely to be PTSD specific rather than a result of trauma per se [62•, 63]. Overall, it appears that attention bias abnormalities related to PTSD-prediction depend in part on the specific task and the studies' environment (i.e., laboratory versus naturalistic set-up. Yet, predominately, when assessing PTSD individuals versus non-PTSD control group, PTSD patients exhibited significant vigilant attention bias *toward* threat cues.

Conclusions

The overarching goal of this review was to present and discuss recent efforts to investigate psychophysiological, behavioral and neural mechanisms underlying fear processing in PTSD. An impressive body of research from the past three years (2010–2012) represents an increasing effort to identify key biomarkers of pathophysiology and maintenance of PTSD. Importantly, most laboratory measures of psychophysiology are noninvasive, enabling real-time recording of separate psychophysiology processes. Markers to date are expected to show elevation under conditions of intense distress. Indeed, most studies found a high association between PTSD and the biological system that is consistent with physiological recovery from adversity [23].

Research on attention bias in PTSD using dot-probe, and emotional Stroop tasks to assess either vigilance or avoidance of threat, uncover uncertainty to whether tasks should be specific to trauma-related cues or generalizes to a range of emotional material. Furthermore, little work has focused on the degree to which attention biases are specific to PTSD or related to secondary factors, such as depressive symptoms [64, 65]. Finally, the current fear processing neurocircuitry model of PTSD suggests lower activation in medial prefrontal regions and hyperactivation of the amygdala in response to negative emotionally laden stimuli. “Emerging evidence suggests that the dACC and insula may also be hyperresponsive in PTSD” [2]. However some of these abnormalities have also been found in other anxiety disorders such as obsessive-compulsive and panic disorders [4, 7]. Findings in hippocampus activity tend to vary, and this may suggest that direction and intensity of hippocampal activity may depend more on the methods used [4, 7].

As reviewed above, studies have demonstrated that a variety of biological and behavioral markers have shown to be significantly different among individuals with PTSD compared with non-PTSD control groups. Importantly, the cross-sectional design used in most of these studies does not allow determination of whether the irregularities in PTSD should be considered state markers (markers of the disorder itself rather than of vulnerability for the disorder) or trait markers (pre-morbid vulnerability). Further studies utilizing longitudinal designs are needed in order to address this gap. An important direction for future research would be to use several types of markers to predict treatment response in PTSD. For example, Neria and colleagues [66] are currently assessing the neurobiological effect of prolonged exposure therapy (a type of therapy that encourages re-experiencing the trauma through recalling and reengaging with it) in PTSD by utilizing the neuroscience model of Pavlovian fear conditioning and extinction [19••] and measuring both neural (fMRI) activation and SCR. This model can clarify how fear learning may be involved in the occurrence of PTSD symptoms and how persistence of symptoms over time potentially involves a failure of basic extinction processes of learned fear memory [67]. Preliminary findings imply greater fear neurocircuitry regulation as a result of prolonged exposure therapy, suggesting a strong association between normalizing neurological activity and symptoms reduction [66]. Other treatments for PTSD, such as attention bias modification treatment (ABMT) (see [68] for review), suggest that such treatments may be clinically useful in PTSD symptom reduction. More research is still needed on ABMT’s effects on both brain and psychophysiological activation. The quest for an objective, gold standard biomarker as a diagnostic tool for PTSD should focus on understanding how the different markers influence each other and/or operate together. Research that measures such markers simultaneously and under the same experimental conditions is highly recommended, along with attention to the type(s) of comparison groups (e.g., trauma exposed or unexposed control groups), as studies with unexposed trauma controls may not conclude with certainty whether the identified abnormalities are related to PTSD or to the trauma exposure per se.

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•• Of major importance

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Table 1

Neural activation markers of fear processing in PTSD

First author, year	Sample	Paradigm	Measure	Results
Brunetti et al. [13], 2010	PTSD (n=10)	A visio-attentional task (emotionally negative or neutral pictures)	fMRI	Amygdala responses and emotional response to neutral stimuli are elevated as a function of severity in PTSD symptoms
Felmingham et al. [9], 2010	PTSD (n=23)	Masked facial expression of fear	fMRI	Amygdala hyperactivation in response to masked fearful faces in PTSD
Fonzo et al. [10], 2010	PTSD (n=12)	Emotional face matching task	fMRI	Amygdala hyperactivation in PTSD during presentation of fearful faces
Dickie et al. [12], 2011	Time 1 PTSD (n=27)	Face recognition memory Task	fMRI	Severity of symptoms is positively correlated with Amygdala and vmPFC activation. Level of activation change in the hippocampus and sgACC was associated with symptom improvement
Linnman et al. [20], 2011	PTSD (n=19)	Fear conditioning procedure with electric shock	fMRI	Amygdala, Hippocampus, dACC, Insula, and caudate nucleus hyperactivation in PTSD Unconditional stimulus response
Rougemont-Bücking et al. [21], 2011	PTSD (n=18)	Two-Day Fear Conditioning & Extinction Paradigm	fMRI	PTSD exhibited hypoactivation of the vmPFC and hyperactivation of the dACC in response to the context
Gold et al. [17•], 2011	PTSD (n=17)	Script- driven imagery	PET	Decrease mPFC activity during mental imagery of traumatic event in PTSD
St. Jacques et al. [16], 2011	PTSD (n =15)	Emotional intense autobiographical memory (AM)	fMRI	Greater activation in the PTSD group during the retrieval of negatively intense AM in the vmPFC, Amygdala, and Hippocampus
Aupperle et al. [11•], 2012	PTSD (n=37)	Anticipation of negative and positive emotional images	fMRI	Greater anterior insula and during emotional anticipation in PTSD
Fani et al. [15•], 2012	PTSD (n=18)	Dot probe task	fMRI	Increase activation in dlPFC in response to threat cue trials in the PTSD group but not in the control

ACC; sgACC: Subgenual Anterior cingulate cortex; PFC: medial prefrontal cortex [dlPFC: dorsolateral; vmPFC: Ventral medial; vIPFC: ventrolateral]; OFC: Orbitofrontal cortex

Table 2

Psychophysiological studies of fear processing in PTSD

First Author, Year	Sample	Paradigm	Measure	Results
Adenauer et al. [29•], 2010	Torture-Related PTSD (n=39)	Torture-Exposed (n=20) Non-Trauma-Exposed (n=19)	Heart Rate Response (HR)	HR response was significantly greater in PTSD
Suendermann et al. [31•], 2010	PTSD (n=56)	Trauma-Exposed (n=110)	HR Skin Conductance Response (SCR)	HR response higher in PTSD and predictive of PTSD severity
McTeague et al. [39•], 2010	Multiple Trauma PTSD (n=27)	Trauma-Exposed (n=30)	HR	PTSD showed greater startle reflex during idiographic trauma imagery
Ehlers et al. [32], 2010	Single Trauma PTSD (n=22)	Non-Trauma-Exposed (n=46)	Startle Response	
Hauschildt et al. [36•], 2011	PTSD (n=66)	Trauma-Exposed (n=96)	HR	HR to trauma related pictures was significantly greater in PTSD
Barkay et al. [30•], 2012	Interpersonal Trauma-Related PTSD (n=26)	Trauma-Exposed (n=26) Non-Trauma-Exposed (n=18)	HR Heart Rate Variability (HRV)	PTSD had lower HRV, HRV was negatively related to PTSD severity
Jovanovic et al. [46•], 2010	Accident-Related PTSD (n=6)	Trauma-Exposed (n=9)	HR	HR response was elevated in PTSD
Jovanovic et al. [44•], 2010	PTSD (n=29)	Trauma-Exposed (n=61)	Startle Response ACTH & Plasma Cortisol	PTSD had a positive relation to ACTH levels and FPS and a negative association with cortisol
Norholm et al. [43•], 2011	PTSD (n=14) PTSD & MDD (n=22)	MDD (n=17) Trauma-Exposed (n=53)	Startle Response	PTSD and comorbid PTSD/MDD subjects had higher FPS to the safety cue
Glover et al. [42•], 2011	PTSD (n=41)	Trauma-Exposed (n=70)	Startle Response SCR	FPS was greater in PTSD to danger cue and safety cue; FPS also predicted symptom severity
Jovanovic et al. [47•], 2011	PTSD (n=16) PTSD DST (n=17)	Trauma-Exposed (n=38) Trauma-Exposed DST (n=29)	Startle Response ACTH & Plasma Cortisol	FPS increased to danger and safety cue in PTSD and predicted symptoms
Miller et al. [48•], 2011	PTSD Male Veteran (n=32)	Trauma-Exposed (n=31)	Startle Response Salivary Cortisol	PTSD showed greater FPS to the danger cue
				PTSD subjects had greater FPS, which diminished after hydrocortisone administration

First Author, Year	Sample	Paradigm	Measure	Results
Jovanovic et al. [45], 2012	PTSD (n=24)	Acute stress disorder (ASD) (n=27) Non-Trauma-Exposed (n=27)	Fear-Potentiated Startle (AX+/BX-)	Startle Response
Kamkwalala et al. [40•], 2012	PTSD (n=47)	Trauma-Exposed (n=94)	Dark-Enhanced Startle	PTSD was associated with greater dark-enhanced startle in women and greater HRV in men

ACTH: adrenocorticotrophic hormone; HRV: heart rate variability; DST: dexamethasone suppression test; MDD: major depressive disorder; FPS: fear-potentiated startle; SCR: skin conductance response

Table 3

Behavioral studies of fear processing in PTSD

First Author, Year	Sample	Paradigm	Measure	Results
El Khoury-Malhame et al. [54•], 2011	PTSD (n=19)	Control (n=19)	Target Detection Emotional Stroop task	In both tasks PTSD exhibited attentional bias toward emotional negative stimuli
Fani et al. [60•], 2012	PTSD (n=25)	Trauma-Exposed (n=39)	Dot Probe Fear-Potentiated Startle (CS+, CS-, NA)	Participants with PTSD demonstrated attentional bias toward threat and exaggerated startle response
Fleurkens et al. [52], 2011	PTSD (n=14)	Control (n=24)	Emotional Stroop task	PTSD exhibited an attentional bias towards threatening sexual violence words
Mueller-Pfeiffer et al. [53], 2010	PTSD (n=14)	Trauma Exposed (n=12) Non-Trauma Exposed (n=19)	Emotional Stroop task	PTSD group where significant slower in the presence of negative images compare to the other groups
Felmingham et al. [62•], 2011	PTSD (n=11)	Trauma Exposed (n=10)	Trauma-relevant words vs. neutral words	PTSD had greater number of initial fixations to trauma words
Lee & Lee [63], 2012	Females PTSD (n=14)	Females Trauma Exposed (n=14) Females Control (n=15)	Eye Tracking, Eye Fixation, Pupil Dilation	Both PTSD and trauma-exposed allocated more time to the dysphoric images than non-exposed controls
Kleim et al. [56], 2012	PTSD (n=22) (3–12 month after the accident) ASD (n=36) (2 weeks after the trauma)	No PTSD (n=77) (3–12 month after the accident) No ASD (n=185) (2 weeks after the trauma)	Blurred Picture identification task (Pictures were trauma related, general threat related, or neutral)	Both PTSD and ASD patients identified trauma related pictures better than neutral pictures