

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Revisiting the Role of the Amygdala in Posttraumatic Stress Disorder

Gina L. Forster, Raluca M. Simons and Lee A. Baugh

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/67585>

Abstract

Over the past 20 years, the reactivity of amygdala to emotive stimuli has been explored by emerging neuroimaging techniques in an effort to understand the role of amygdala in the pathophysiology of posttraumatic stress disorder (PTSD). A fear neurocircuitry model, whereby the amygdala is hyperactive due to poor top-down control from the anterior cingulate and ventromedial prefrontal cortices, has been supported by numerous experimental studies and meta-analyses. However, this model has not always been upheld by experimental data and clinical observations. In particular, many neuroimaging studies find that the amygdala fails to activate in response to negative stimuli in individuals with PTSD. Several technical and design issues may explain disparate results regarding amygdala reactivity in PTSD. However, biological and symptom-based factors emerge as possible mediators of amygdala function in PTSD, leading to the conclusion that symptoms of emotional disengagement and dissociation are associated with amygdala hyporeactivity, and symptoms of hypervigilance/hyperarousal and problems with fear conditioning and extinction are reflected by amygdala hyperactivity. Therefore, treatment of PTSD should take into account the nature of amygdala dysfunction in the individual to optimize treatment outcomes.

Keywords: posttraumatic stress disorder, dissociative PTSD, fear conditioning, neuroimaging, amygdala, prefrontal cortex

1. Introduction: posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is the most prevalent psychiatric disorder, affecting one-quarter of the world's population [1]. PTSD is characterized by four clusters of symptoms that

develop in response to a traumatic event, defined as exposure to actual or threatened death, serious injury or sexual violation [1, 2]. This can be directly experienced or witnessed by the individual, or the individual may learn that the traumatic event occurred to a close family member or close friend [2]. Clinical criteria include (1) intrusive symptoms related to reexperiencing the trauma, (2) avoidance of the traumatic memory or cues, (3) negative mood and thoughts including emotional numbing and anhedonia, and (4) altered arousal including hypervigilance, irritability, aggression, and sleep disturbances [1–3]. The Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) [2] also recognizes a dissociative subtype of PTSD in which dissociative symptoms additional to those typically included in the intrusive symptoms cluster occur, including depersonalization and derealization ('this is not happening to me'). PTSD symptoms result in significant social, personal, and vocational impairment [1]. Furthermore, PTSD is commonly comorbid with other anxiety or mood disorders and is also associated with increased risk for a number of negative behavioral and health conditions, including substance use disorder, chronic pain syndromes, cardiovascular disease, type II diabetes, and Alzheimer's disease [3–9]. Therefore, PTSD has wide-ranging mental and physical health implications for the individual across their lifespan. Despite concentrated efforts in behavioral sciences, neurosciences and medicine to better understand and treat the disorder, current treatment strategies are only effective in approximately half of the PTSD population (as reviewed by [10]). One way in which current and future research may contribute to improving outcomes for those with PTSD will be to develop greater insight into the neurobiological mechanisms that relate trauma to symptoms, and how these predict symptom trajectory, associated behavioral and medical problems, and treatment outcomes.

Research suggests that the symptoms of PTSD may be associated with dysfunction in regulating responses to negative emotions, as well as attentional bias for negative stimuli, altered encoding of trauma-related memories, enhanced fear conditioning and poorer fear extinction [11–17]. Therefore, PTSD can be thought of as disorder in which emotional and cognitive dysfunction intersect, which has direct implications for future efforts to improve psychological and pharmacological therapies for PTSD [17]. In terms of the neurobiology underlying the cognitive and emotional alterations observed in PTSD, experimental and meta-analysis studies implicate cortical (anterior cingulate cortex (or ACC), ventromedial and lateral prefrontal cortex, and insula) interactions with limbic structures such as the hippocampus and amygdala [11, 14, 17–19]. The core of the traditional neurocircuitry model of PTSD is illustrated in **Figure 1**, and posits that the ventral ACC and ventromedial prefrontal cortex normally provide top-down inhibition of the amygdala, which is impaired in PTSD [17, 18, 20, 21]. This model is based on converging evidence from both animal and human studies, although some human neuroimaging findings suggest that this model should be reevaluated or expanded [14, 21, 22]. Therefore, the goals of this review are to revisit the role of the amygdala in PTSD and explain disparate findings for amygdala reactivity in PTSD across neuroimaging studies; to ultimately update the neurocircuitry model of PTSD and understand how amygdala dysfunction can be helpful in the ability to predict and/or reveal treatment outcomes.

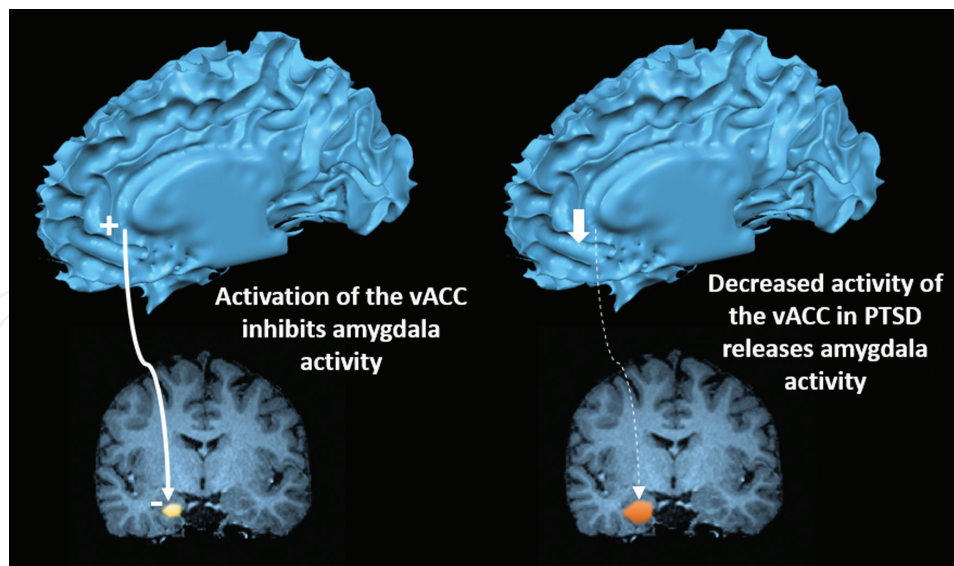


Figure 1. Fear neurocircuitry model of PTSD (based [20]). The ventral ACC and ventromedial prefrontal cortex are proposed to inhibit activity in the amygdala, and this top-down control is thought to be diminished in PTSD, leading to enhanced fear conditioning and poor fear extinction. PTSD, posttraumatic stress disorder; vACC, ventral anterior cingulate cortex.

2. Fear neurocircuitry and the amygdala in PTSD

Substantial evidence from animal experiments and human neuroimaging studies suggests that activity of the amygdala is related to the activation of fear responses and anxiety states, whereas the ventral ACC (or rodent equivalent within the medial prefrontal cortex) dampens or regulates amygdala activity and plays an important role in autonomic and behavioral inhibition [18, 20, 23–25]. Activity of specific subregions of the rat amygdala (e.g., basolateral and central nucleus) is required to respond to fearful stimuli and also to conditioned stimuli that predict or are associated with fearful stimuli [18, 20]. Similarly, the human amygdala is active during fear conditioning and this activity is positively correlated with skin conductance during conditioning [26–29], a psychophysiological index of a fear response. Projections from the rat ventral medial prefrontal cortex inhibit output from the central nucleus of the amygdala to brainstem regions involved in producing autonomic and behavioral fear responses [18, 23]. Furthermore, experimental lesions of the ventral medial prefrontal cortex of rats homologous to the primate ventral ACC prevent extinction of conditioned fear behavior while stimulation of this region promotes fear extinction [30, 31]. This, combined with observations that hypofunction or lesions of the primate ACC result in fear extinction deficits or emotional perseveration, suggests that ventral ACC inhibition of the amygdala is required for extinction of conditioned fear responses [18, 20].

In relation to the neurocircuitry model of PTSD (**Figure 1**), individuals suffering from PTSD show poor fear inhibition and reduced extinction of conditioned fear responses, indicative of disruption to ACC-amygdala circuitry [12, 13, 32, 33]. Furthermore, activity in the

ventral ACC or ventromedial prefrontal cortex within PTSD populations in response to trauma-related and nontrauma-related emotive imagery is often negatively correlated with amygdala activity [20, 34–36]. Overall, a reciprocal relationship between ventral ACC hypo-function and amygdala hyperfunction is thought to result in the inability to suppress or extinguish traumatic-related fear responses in PTSD [18, 20, 36].

The amygdala is not only critical for processes underlying fear conditioning, but also is thought to play a more general role in emotional salience and encoding emotional relevance or value, to influence attention and motivation as well as autonomic and behavioral responses [17, 22, 37]. Furthermore, it has been suggested that the amygdala may be more responsive to external threat rather than internal emotional state [38, 39]. There are numerous findings of increased amygdala activity in response to negatively valenced emotional stimuli in PTSD, and this amygdala activity is often positively correlated with the severity of PTSD symptoms [19] (**Table 1**). These findings lend support for the neurocircuitry model depicted in **Figure 1** where amygdala hyperactivity may result from poor top-down control in PTSD.

However, this model has been challenged by conflicting neuroimaging findings regarding amygdala reactivity to emotive stimuli in PTSD populations [11, 21] (**Table 1**). In particular, a meta-analysis of neuroimaging studies suggests that amygdala hyperactivity occurs more frequently in social anxiety disorder and panic disorder as compared to PTSD [11]. Although the review of relevant literature depicted in **Table 1** is not exhaustive, it is representative of amygdala-based findings in PTSD populations over the past 20 years. There are as many studies showing no effect of PTSD on amygdala reactivity as they are demonstrating hyperactivity within this region (**Table 1**). Notably, some studies actually suggest reduced amygdala activity in response to emotional stimuli in PTSD. For example, a recent study [21] shows that amygdala hyperactivity and hyporeactivity can occur within the same indi-

Population sampled	Task/stimuli	Task condition/contrasts	Amygdala activity	Reference
Civilian PTSD	Script-driven imagery	Trauma-related vs. neutral	Increased blood flow in right amygdala	[40]
Male Vietnam veterans with and without PTSD	Mental imagery	Combat-related	Increased blood flow in right amygdala in PTSD	[41]
Women abused in childhood, with and without PTSD	Script-driven imagery	Trauma-related vs. neutral	No difference in amygdala blood flow	[22]
Male Vietnam veterans with and without PTSD	Trauma-related auditory and visual stimuli	Combat-related vs. neutral	No difference in amygdala blood flow	[42]
Vietnam veterans with and without PTSD and nonveteran male controls	Trauma-related auditory stimuli	Combat sounds	Increased blood flow in left amygdala/nucleus accumbens region in PTSD group only	[43]
Women abused in childhood, with and without PTSD	Script-driven imagery	Trauma-related vs. neutral	No difference in amygdala blood flow	[44]

Population sampled	Task/stimuli	Task condition/contrasts	Amygdala activity	Reference
Male Vietnam veterans with and without PTSD	Masked faces	Fearful vs. happy	Increased BOLD signal in amygdala of PTSD vs. NoPTSD	[38]
Civilian PTSD and trauma exposed controls	Script-driven imagery	Trauma-related	No change in BOLD signal within the amygdala in any group.	[45]
Women with abuse-related PTSD—dissociative symptoms	Script-driven imagery	Imagery vs. implicit baseline	No difference in BOLD signal in the amygdala	[46]
Women with childhood-related abuse PTSD and nontraumatized controls	Declarative memory task	Emotional vs. neutral words	No difference in amygdala blood flow	[47]
Israeli Defense Forces veterans with and without PTSD	Masked pictures	Combat or noncombat	Increased BOLD signal within amygdala in PTSD vs. NoPTSD group	[48]
Women with childhood-related abuse PTSD and nontraumatized controls	Stroop task	Neutral color vs. control	Increased blood flow in right amygdala in PTSD group (did not reach significance when directly compared to NoPTSD group)	[39]
		Emotional color vs. neutral color	No difference in amygdala blood flow	
Vietnam veterans with and without PTSD	Script-driven imagery	Trauma-related vs. neutral	Increased blood flow in left amygdala—males only	[34]
		Trauma-related vs. neutral	Increased blood flow in right amygdala with increasing symptoms (males and females)	
Motor-accident related PTSD (acute phase)	Masked and Unmasked faces	Unmasked fearful vs. happy	Decreased BOLD signal in right lateral amygdala with increasing CAPS	[49]
		Masked fearful vs. happy	Increased BOLD signal in right lateral amygdala with increasing CAPS	
Vietnam veterans with and without PTSD and nonveteran controls	Script-driven imagery	Trauma-related vs. neutral	No difference in amygdala blood flow in PTSD group (noncombat controls showed an increase).	[50]
Trauma-exposed men with and without PTSD	Unmasked faces	Fearful vs. happy	Increased BOLD signal in right amygdala of PTSD vs. NoPTSD; BOLD signal did not correlate with CAPS score	[35]
Civilian PTSD and nontrauma exposed controls	Masked trauma-related images	Trauma-related vs. neutral	No difference in BOLD signal in amygdala	[51]

Population sampled	Task/stimuli	Task condition/contrasts	Amygdala activity	Reference
Vietnam veterans with and without PTSD and nonveteran male controls	Rating IAPS (noncombat related)	Aversive vs. neutral and Aversive vs. blank screen	Absence of response (rCBF) in left amygdala of PTSD vs. both combat exposed and not exposed controls (i.e., stimuli elicited increased blood flow in controls)	[52]
Civilian PTSD and nontrauma exposed controls	Unmasked faces	Fearful vs. neutral	Increased BOLD signal in left ventral amygdala in PTSD vs. controls	[53]
Civilian PTSD and nontrauma exposed controls	Masked faces	Fearful vs. happy	Increased BOLD signal in right amygdala of PTSD vs. NoPTSD	[10]
Civilian PTSD—dissociative and nondissociative	Unmasked and masked faces	Unmasked fearful vs. neutral	No difference in BOLD signal in amygdala in dissociative vs. nondissociative PTSD	[54]
		Masked fearful vs. neutral	Increased BOLD signal in bilateral amygdala of dissociative PTSD vs. nondissociative PTSD	
Civilian PTSD, trauma-exposed and nontrauma exposed controls	Masked faces	Fearful vs. neutral	Increased BOLD signal in amygdala of PTSD vs. both NoPTSD groups, no sex differences	[55]
Civilian PTSD and nontrauma exposed controls	Matching faces	Emotional (angry/fearful) vs. neutral	Increased BOLD signal in right amygdala of PTSD vs. NoPTSD; Increased BOLD signal within the right amygdala with increasing PCL scores	[15]
OEF/OIF veterans (3.5 years on average return from last deployment)	Traumatic memory encoding (visual)	Combat-related vs. neutral pictures	No difference in BOLD signal in amygdala of PTSD vs. NoPTSD	[16]
Civilian PTSD and nontrauma exposed controls	Affective Priming Task	Sad + happy + neutral faces vs. fixation	Increased BOLD signal in left amygdala in PTSD	[56]
OEF/OIF veterans within 10 years of deployment	Trauma-related and nontrauma movies.	Civilian vs. fixation	Increased BOLD signal with increasing CAPS scores	[21]
		Combat vs. fixation	Decreased BOLD signal with increasing CAPS score	
Recently (8 weeks) returned military OEF/OIF personnel, trauma exposed but did not reach score of 50 in PCL-M	Affective stroop task (IAPs)	Positive vs. neutral	Increased BOLD signal with increasing PCL scores	[57]

Population sampled	Task/stimuli	Task condition/contrasts	Amygdala activity	Reference
		Negative vs. neutral	No significant relationship between BOLD signal and PCL score	
OEF/OIF veterans with and without PTSD	Masked faces	Fearful vs. fixation and Happy vs. fixation	No difference in BOLD signal in right amygdala, failure to activate left amygdala, compared to combat-exposed NoPTSD group	Figure 2
Civilian PTSD and nontrauma exposed controls	Masked and Unmasked faces and words	Masked fearful vs. neutral faces and Masked trauma vs. neutral words and Unmasked fearful vs. neutral faces and Unmasked trauma vs. neutral words	No difference in BOLD signal in amygdala in either PTSD or controls in any contrast	[58]

BOLD, blood oxygenation level dependent; CAPS, clinician administered PTSD scale; IAPS, international affective pictures set; OEF/OIF, operation enduring freedom/operation Iraqi freedom; PCL, PTSD checklist; PTSD, posttraumatic stress disorder; rCBF, regional cerebral blood flow.

Table 1. Representative studies testing amygdala reactivity to emotive stimuli in PTSD.

vidual in response to different stimuli. Specifically, veterans within 10 years of deployment were presented with either a combat-related or civilian-related movie. The civilian movie produced greater amygdala activity with increasing PTSD symptoms, while in the same participants, the combat movie elicited *less* amygdala activity with increasing PTSD symptoms [21] (Table 1). Therefore, the authors suggest that the standard model by which PTSD is associated with hyperactivity of the amygdala needs to be reassessed. This has broader implications for furthering our understanding of biomarkers for PTSD development and treatment, and our understanding of the neurobiology of the amygdala in general.

3. Understanding inconsistent functional neuroimaging findings for amygdala function in PTSD

A variety of design, analysis, trauma-based, pharmacological and biological factors could contribute to disparate findings regarding amygdala hyperactivity in PTSD. Each will be reviewed in turn here. First, the manner in which neuroimaging data are compared to control populations may be a key in observations of amygdala hyperactivity in PTSD. To illustrate, hyperactivity of the amygdala is more likely to be revealed in a PTSD group in the absence of statistical comparison to a control group, or often when PTSD groups are compared to a nontrauma-exposed control group (Table 1). A further issue is the possibility of false positives in whole-brain analyses, given that there is a great degree of variability across studies in whether multiple statistical analyses made across the brain have been corrected for multiple

comparisons to reduce the chance of type-I error [59]. The independence of samples between studies arising from the same research group is also often not clear. Consistency and transparency in the statistical comparisons made is essential to resolving whether these design-based differences may contribute to false positive outcomes for amygdala hyperactivity in PTSD studies.

With regard to lack of effects in the amygdala, the particular characteristics of this region may play an important role in the production of null effects within some PTSD studies. As reviewed by Etkin and Wager [11], the amygdala readily habituates to emotive stimuli, which may contribute to lack of differences seen between PTSD and control groups when time course analyses are not conducted. Furthermore, the amygdala is a small volume (~1.5 cm³; [60]) region that is difficult to image largely due to its susceptibility to artifact [19, 61]. Each one of these problems singularly or combined may contribute to false negative outcomes, where hyperactivity of the amygdala in a given PTSD population is not observed.

On the other hand, a lack of an effect within the amygdala in a given PTSD study is not always due to technical difficulties associated with imaging this region. Often a null effect in the amygdala within a study is actually a failure of the PTSD group to increase activity in the amygdala in response to negative stimuli, where the control group shows amygdala activity (**Table 1; Figure 2**), and the analysis performed by Phan et al. [52] clearly illustrates this point (**Table 1**). A recent study [62] also sheds light on this issue, demonstrating that emotional numbing in PTSD results in a failure to activate the amygdala in all stimulus conditions, thus resulting in a 'null effect' when amygdala activity is compared across conditions in the experiment. This effect is also illustrated in **Figure 2**, where fearful and happy stimuli conditions result in a failure to activate the left amygdala in combat-related PTSD compared to combat-experienced controls. For the purposes of this review, the term 'hyporeactive' will be used to describe a lack of the effect in amygdala responses to emotive stimuli.

Differences in the paradigm and stimulus types can also play a role in whether the amygdala is hyperactive in PTSD. For example, amygdala hyperactivity in PTSD groups is more likely to occur with nontrauma overtrauma-related stimuli, or with masked rather than overt stimuli presentation, when these factors are compared across studies (**Table 1**). While a few studies compare these factors within-session, Armony et al. [49] show *decreased* activity in the amygdala with increasing PTSD symptoms for unmasked fearful faces but *increased* amygdala activity with increasing PTSD symptoms when that activity is elicited by masked fearful faces in the same participants. Furthermore, Brashers-Krug and Jorge [21] show a similar distinction between trauma-related and nonrelated stimuli; where *increased* amygdala activity with increasing PTSD symptoms is observed in nontrauma-related conditions but a *decrease* in amygdala activity with increasing PTSD symptoms occurs in response to trauma-related stimulus presentation in the same participants. While these conclusions will need to be confirmed with further direct within-session comparisons, it appears that hyperactivity in the amygdala following trauma may be best revealed by nontrauma-related stimuli that are presented outside the realm of the individual's conscious perception, whereas amygdala hyporeactivity is observed with overt stimuli. It has been suggested previously that amygdala hyporeactivity to overt trauma-related stimuli may be a compensatory mechanism specific

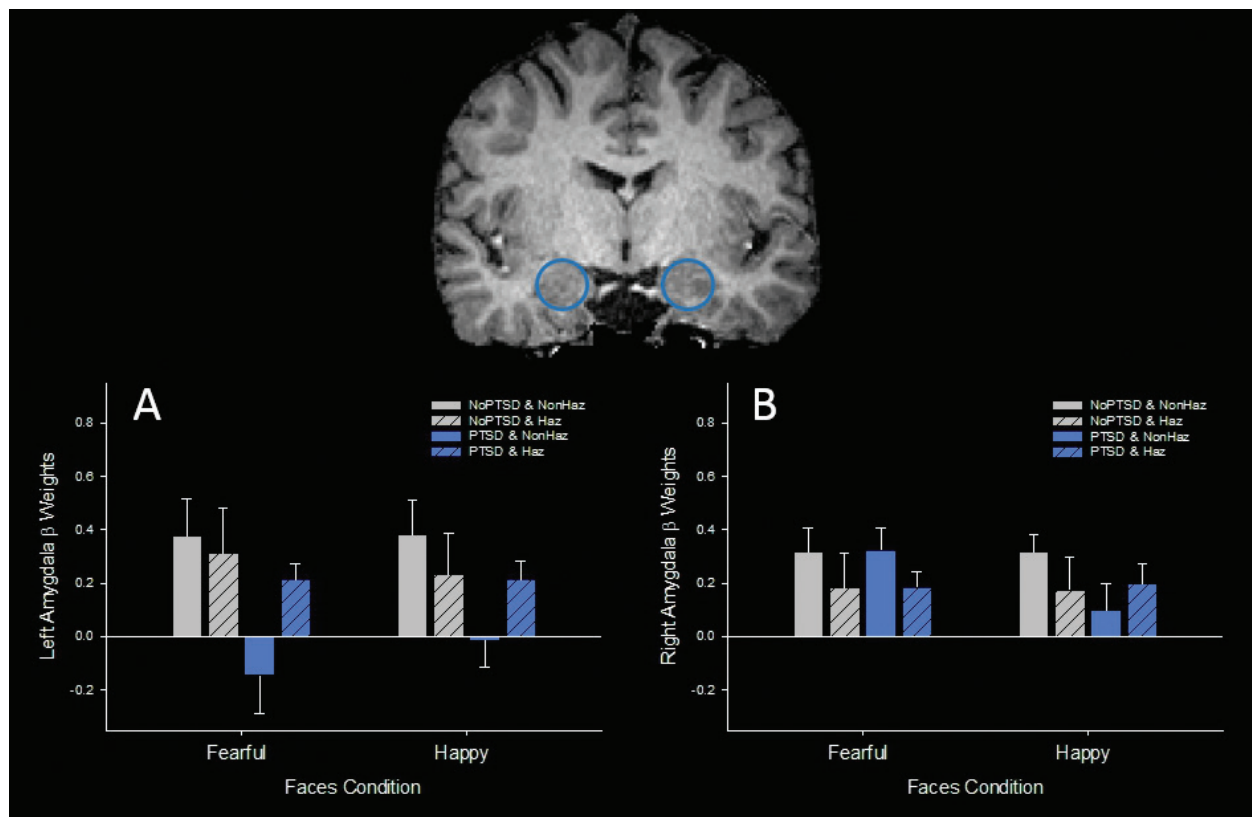


Figure 2. Activation (weights derived from BOLD signal) in the (A) left and (B) right amygdala during fearful and happy conditions of a backwards-masked faces paradigm (see [63] for full details on the paradigm and imaging parameters). One hundred and two OEF/OIF combat-exposed veterans (4.5 years from last deployment on average) were categorized by PTSD symptoms (29 or more score on PCL), and hazardous alcohol use (score of 8 or more on the AUDIT), resulting in 10–34 participants per group. (A) Three-way ANOVA revealed a significant interaction between PTSD and alcohol use in the left amygdala ($F_{(1,186)} = 4.696$; $P = 0.032$), such that the PTSD without hazardous alcohol group exhibited significantly lower activation of the left amygdala in both fearful face and happy face conditions as compared to all other groups (H-S $P = 0.006$). (B) However, there was no significant effect of PTSD or alcohol use on activation within the right amygdala in any condition. Data represented as mean \pm SEM. AUDIT, alcohol use disorders identification test; BOLD, blood oxygenation level dependent; Haz, hazardous alcohol use classification; H-S, Holm Sidak post hoc test for multiple comparisons; NonHaz, nonhazardous alcohol use classification; NoPTSD, PTSD symptoms score below 29 on PCL; OEF/OIF, operation enduring freedom/operation Iraqi freedom; PCL, PTSD checklist; PTSD, posttraumatic stress disorder.

to trauma exposure [50], which may in turn, mediate emotional disengagement or dissociation from the stimulus in PTSD reflective of emotional numbing [52]. A recent study directly testing the neurocircuitry of subliminal versus overt stimuli failed to activate the amygdala in any condition in control and PTSD groups [58], thus further research is needed to test whether stimulus type differentially activates the amygdala.

In addition to contributions made by variations in design and analysis, inconsistent findings regarding amygdala reactivity to emotive stimuli in PTSD may also result from biological phenomena or trauma characteristics that could inform our understanding of amygdala function. For example, a meta-analysis of PTSD neuroimaging studies demonstrated hyperactivity of the ventral anterior amygdala and hypoactivity of the dorsal posterior amygdala during emotional processing [11]. This suggests that the direction change in amygdala activity elicited

by emotional processing within PTSD populations could be related to the subregion of the amygdala analyzed. A second interesting biological difference within studies is presented in **Table 1**. The majority of studies that only include women fail to show changes in amygdala responsivity to emotional stimuli in PTSD, whereas the majority of studies that only include men demonstrate amygdala hyperactivity, and mixed-sex studies are mixed in their findings (either no change or increased amygdala activity with PTSD; see **Table 1**). In one of the few PTSD studies that directly compared amygdala reactivity among the sexes, increased blood flow in the amygdala in response to script-driven imagery was only noted in male Vietnam veterans [34]. However, increased amygdala activation in response to fearful masked faces was equal in male and female civilian PTSD groups in a more recent study aimed at determining potential sex differences [55]. Overall, there is mounting evidence that hyperactivity of the amygdala is more often associated with male PTSD victims.

Not surprisingly, there are sex biases in combat versus civilian PTSD prevalence, with males more likely to report combat-based PTSD and females more likely to suffer from sexual assault-related PTSD [1]. Therefore, if hyperactivity of the amygdala is more common in studies using males, amygdala hyperactivity may be more likely to be associated with combat-related PTSD. However, when comparing across studies in **Table 1**, hyperactivity of the amygdala in response to emotive stimuli is equally as likely to be found in studies of civilians, Vietnam veterans, and veterans from recent military operations. Related, participants from women-only studies are victims of childhood sexual abuse, which is associated with dissociative PTSD [14]. As discussed in detail in the next section, dissociative PTSD may be characterized by amygdala hyporeactivity to negative stimuli [14] and thus the putative sex difference in amygdala reactivity noted above may in fact be more related to differences in PTSD symptoms across those studies.

It is worth noting that the only studies to show decreased amygdala activity with PTSD were those conducted with acute civilian PTSD [49] or with veterans from recent military operations [21] (**Figure 2**). Furthermore, a recent study of OEF/OIF veterans only included participants that showed PTSD symptoms without meeting the diagnostic criteria for PTSD, who were within 8 weeks upon return from at least a 90-day deployment [57]. The rationale for this was that individuals who show significant functional impairment within 8 weeks upon return from a combat zone would provide important information as to biomarkers of a subsequent PTSD diagnosis [57], and follow-up studies of these individuals will be quite informative. In this initial study, PTSD symptom scores were not significantly related to amygdala activity elicited by the negative condition of an affective stroop task, although these scores were positively correlated with amygdala activity in the positive condition [57] (**Table 1**). While a decrease in amygdala activity was not noted, the study is supportive of a lack of hyperactivity in the amygdala to negative stimuli in individuals with preclinical acute posttraumatic stress symptoms.

Interestingly, the studies reported in **Table 1** either exclude participants based on substance/alcohol use disorder or include participants with alcohol use problems without factoring this into the analysis or conclusions. PTSD is associated with significantly elevated drinking behaviors in both men and women (range of odds ratios = 1.3–4.8) [5]. Alcohol misuse can result in

increased amygdala responsivity to emotive stimuli [64], suggesting that excessive alcohol use may, at least in some cases, underlie hyperactivity of the amygdala in PTSD. To address this hypothesis in more detail, we recently conducted a study of veterans where activity of the amygdala to masked faces was analyzed based on PTSD symptom status as well as hazardous alcohol use [63]. Activity of the left amygdala in response to fearful or happy masked faces was significantly less pronounced in individuals with PTSD symptoms but only in the absence of hazardous alcohol use, as compared to combat-exposed veterans without such symptoms (**Figure 2**). It could be speculated that hazardous alcohol use increased amygdala activity in the PTSD participants, as would be suggested by the previously noted association between alcohol misuse and amygdala hyperactivity [64], thus seemingly normalizing amygdala activity. However, hazardous alcohol use in the absence of PTSD symptoms did not have any effect on amygdala reactivity to masked faces in our study (**Figure 2**), suggestive of an interaction between PTSD symptoms and hazardous alcohol use on amygdala reactivity. Clearly, further work is needed to understand the impact of substance misuse, especially excessive alcohol consumption, on amygdala reactivity in PTSD.

Related to issues of alcohol consumption, medications taken by participants in the studies outlined by **Table 1** could also play a role in whether hyperactivity of the amygdala is observed in PTSD groups. A meta-analysis addressing this issue found that serotonin-specific reuptake inhibitors (SSRIs) and benzodiazepines may have a confounding effect on cerebral blood flow within regions commonly imaged in PTSD studies [65] but more information is necessary to determine whether medications affect amygdala hyperactivity or lack thereof. Recently, Hayes et al. [16] found that PTSD's lack of association with hyperactivity of the amygdala did not change when including medication as a covariate in the model. Due to the sparsity of research examining the effects of medication, it is recommended that investigators include both medicated but symptomatic and unmedicated participants in neuroimaging studies of PTSD to ensure generalizability of the findings [65].

In summary, there are a range of design and analysis factors that could contribute to disparate findings regarding amygdala hyperactivity in PTSD. If these potential design and analysis confounds are equally represented among the studies listed in **Table 1**, then factors such as sex, chronicity of PTSD, PTSD symptom types, and alcohol or medication use all stand out as factors that could influence amygdala reactivity to emotional stimuli. Therefore, the importance of these factors on amygdala functioning in PTSD should be systematically explored in the future to better our understanding of amygdala function and dysfunction in PTSD.

4. Functional consequences of amygdala hyporeactivity and/or hyperactivity in PTSD

Both amygdala hyperactivity and a failure to activate the amygdala (hyporeactivity) appear to be outcomes associated with PTSD, with the direction of activity dependent upon biological and stimulus factors and symptom features. Therefore, it is important to consider the functional consequences and implications of either outcome for individuals with PTSD.

As mentioned earlier, lack of activation or hypoactivation of the amygdala to emotive stimuli may mediate emotional disengagement and autonomic blunting in PTSD ultimately leading to emotional numbing and anhedonia [11, 52, 62, 66]. Furthermore, it has been suggested that the dissociative subtype of PTSD may be characterized by reduced amygdala reactivity, as a result of inhibition by midline frontal cortex structures that are often hyperactive in PTSD, such as the medial prefrontal cortex and dorsal ACC ([14]; **Figure 3**). Indeed, trait dissociation is associated with reduced amygdala activity [67], and hypnosis-induced depersonalization results in dampened amygdala activity as elicited by nociceptive stimuli [68]. Dissociative symptoms are thought to include increased pain threshold, due to an increase in stress-induced analgesia often found in PTSD [67]. Related, thermal pain stimulation resulted in amygdala hypoactivity in participants with PTSD [69]. Combined findings suggest a link between amygdala hypoactivity, disengaging and dissociative processing, and altered nociception among trauma-exposed individuals with PTSD. Reduced amygdala reactivity could also be associated with symptom maintenance. For example, hypoactivity of the amygdala and hippocampus during the encoding of trauma-related memories has been suggested to underlie distorted memory for trauma-associated events in PTSD [16]. Finally, it has been suggested that hypofunction of the amygdala may lead to failure to form associations between consumption and negative outcomes of drug or alcohol use [70]. Thus, amygdala hyporeactivity may increase the likelihood of future dependence issues. Overall, evidence suggests that hypoactivity of the amygdala during emotional processing may result in PTSD symptom development and maintenance, particularly in relation to emotional disengagement, dissociative processing, and comorbid substance use disorder.

Amygdala hyperactivity in response to emotive stimuli in PTSD may reflect an increase in activity within the amygdala itself or alternatively, a failure of the amygdala to habituate to the stimulus [71]. Regardless, the heightened activity in this region is often positively correlated with symptom severity (**Table 1**). Furthermore, negative affect in response to positive stimuli, and reexperiencing symptoms are both positively correlated with amygdala activity in PTSD participants [58, 66]. Amygdala hyperactivity is thought to facilitate acquisition and maintenance of fear responses in PTSD [11, 17, 19], in line with its critical role in fear neurocircuitry as described above. Hyperactivity of the amygdala could be associated with attentional bias often reported in PTSD, characterized by patients having difficulty disengaging from negative stimuli [15, 17]. This attentional bias is thought to occur because the amygdala is part of the limbic-cortical neurocircuitry active during tasks that assess negative attention (as reviewed by [17]), and a positive correlation exists between amygdala activity and negative attentional bias in PTSD [15]. Similarly, amygdala hyperactivity is often linked to hypervigilance in PTSD, where the heightened activity of the amygdala is thought to increase reactivity to emotional stimuli and enhance priming of emotion and emotional representations in the limbic system [72]. Therefore, like amygdala hyporeactivity, hyperactivity of this region is likely to contribute to distinct PTSD symptom development and maintenance.

In line with the above arguments, Lanius et al. [14] suggest that PTSD characterized by undermodulation of emotional responses (e.g., reexperiencing and hyperarousal) would be reflected by hyperactivity of the amygdala whereas PTSD characterized by overmodulation of emotional responses (e.g., dissociative PTSD) would be reflected by reduced activity of the

amygdala. However, it is also conceivable that a given individual with PTSD will exhibit both hyperactivation and hypoactivation of the amygdala depending on context; with attentional bias and poor fear extinction being associated with hyperactivity in the amygdala, and dissociative processes being associated with hyporeactivity of this region. Therefore, we propose that PTSD should be defined as a general dysfunction of amygdala activity rather than a directional change in activity (**Figure 3**). This is supported by findings showing both hyperactivity and hypoactivity (or lack of activity) of the amygdala in the same participants with PTSD, depending upon the stimulus presented ([21, 39, 54]; **Table 1**).

With this in mind, an important question arises—is amygdala dysfunction a consequence of trauma or a predisposing factor that converts vulnerability to PTSD? This is a critical question given that over half of the population will experience a major traumatic event in their lifetime, but the lifetime prevalence for PTSD is only 7.8% in the USA [1, 3]. There is some evidence for preexisting alterations of amygdala activity predisposing individuals to social phobia [36]. In a study of Israeli Defense Forces pre and postmilitary-based trauma, amygdala reactivity increased with increasing stress symptoms and amygdala reactivity to negative stimuli pretrauma predicted increased stress symptoms posttrauma [73]. On the other hand, studies of twins discordant for combat exposure using heart rate responses as an indirect measure of amygdala activity or resting cerebral blood flow suggest that amygdala hyperactivity may be acquired with trauma rather than a preexisting condition [74, 75]. Clearly, further longitudinal studies that capture amygdala function prior to trauma and onset of PTSD symptoms are needed to clarify whether amygdala dysfunction is acquired due to a major traumatic event or predisposes individuals to posttraumatic stress symptoms, or both as might be expected with early life trauma.

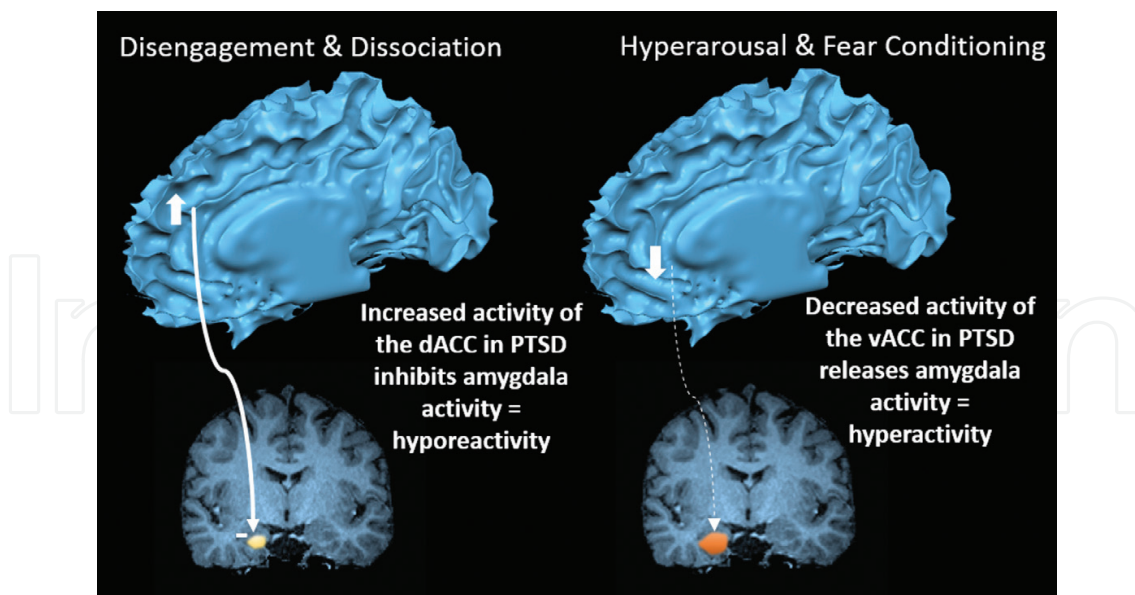


Figure 3. Refined neurocircuitry model of PTSD (based on [14]). Symptoms of emotional disengagement (emotional numbing, anhedonia) and dissociative PTSD are thought to be associated with reduced amygdala reactivity to emotional stimuli, due to increased top-down control from the medial prefrontal cortex and dorsal ACC. In contrast, hyperarousal, hypervigilance, and deficits in fear conditioning and extinction are thought to arise in part from a hyperactive amygdala, due to diminished top-down control from the ventral ACC and ventromedial prefrontal cortex are proposed. dACC, dorsal anterior cingulate cortex; PTSD, posttraumatic stress disorder; vACC = ventral anterior cingulate cortex.

A second important question arises from the conclusion that the amygdala may be dysregulated in either direction in PTSD. How does the traditional neurocircuitry model of PTSD (**Figure 1**) fit with findings that PTSD is not always characterized by amygdala hyperactivity? Many studies reported amygdala hyperactivity in PTSD also show reduced ACC or ventromedial frontal cortex activity [20, 34, 35], and a meta-analysis upholds the inverse relationship between the ventral ACC and amygdala in PTSD [11, 19]. However, it has been suggested that the 'poor top-down control of the amygdala' model of PTSD (**Figure 1**) should be reassessed, based on a failure to consistently evidence an inverse relationship between ventral ACC and amygdala activity in PTSD [21, 39, 45, 53]. Indeed, some studies show a positive association between the activity of the amygdala and ventral ACC, suggestive of either concurrent activation or positive feedback in individuals with PTSD (e.g., [21, 53]). Whether an inverse relationship between the ventral ACC/ventromedial frontal cortex and amygdala is apparent in PTSD may depend on the region of the amygdala sampled. The ventral ACC innervates the ventral amygdala to a greater degree [76] and a meta-analysis suggests that hyperactivity is more likely to be found in ventral anterior amygdala while and hypoactivity is more often observed in dorsal posterior amygdala during emotional processing in PTSD [11]. Therefore, it is plausible that the ventral amygdala is subjected to greater level of top-down control, thus becoming disinhibited with reduced cortical activity in PTSD, while the dorsal amygdala is relatively unaffected by these frontal cortex changes in PTSD. This possibility warrants further testing. Overall, an amygdala dysfunction model of PTSD would predict altered top-down control of the amygdala, with increased inhibition from dorsal ACC and medial prefrontal cortex resulting in amygdala hyperactivity accompanied by symptoms of disengagement and dissociation. Whereas decreased inhibition from ventral ACC and ventromedial prefrontal cortex would result in increased amygdala reactivity and hypervigilant and intrusive symptoms [14] (**Figure 3**).

5. The role of the amygdala in treatment of PTSD

A systematic review of amygdala function before and after psychotherapy suggests that reduced amygdala reactivity to trauma-related stimuli is associated with a decrease in symptoms in adult-acquired PTSD [77]. A similar effect has been noted in a more recent study using exposure therapy [78], and another when propranolol treatment was administered with traumatic memory reactivation [79], which the authors attribute to a norepinephrine-induced plasticity in the amygdala-cortical circuitry as outlined in **Figure 1**. Therefore, it is tempting to speculate that therapy-induced reduction in amygdala reactivity reduces symptoms of PTSD, in line with studies suggesting that hyperactivity of the amygdala is in part, responsible for symptoms of PTSD as discussed above. However, lower amygdala activity prior to treatment predicts better responses to cognitive-behavioral and trauma-focused therapy even when controlling for symptom severity [10, 80]. This suggests that reduced amygdala reactivity with decreasing PTSD symptoms after treatment may not be a direct effect of treatment on amygdala function, but instead that amygdala function prior to therapy predicts treatment efficacy. There may also be an important genetic component to this effect. Bryant et al. [81] show poorer

responses to cognitive-behavioral therapy in PTSD patients with short-form alleles (S and L_C) in the promoter region of the serotonin transporter (SERT) gene, even when pretherapy symptom severity was controlled in the analysis. The short-form alleles are associated with reduced SERT expression and function, and thus increased synaptic serotonin [82]. Of relevance is that short-form carriers have increased amygdala responses to negative stimuli [83, 84]. This, combined with the finding that short-form carriers do not respond as well to cognitive behavioral therapy [81], supports the idea that heightened amygdala activity is associated with poorer treatment outcomes. Interestingly, a recent analysis suggests that amygdala hyperactivity in short-form carriers may actually be a result of developmental effects of this polymorphism on amygdala structure and thus function, rather than current serotonergic status [85]. In addition to treatment implications, these findings suggest that differences in amygdala reactivity to emotional stimuli across PTSD studies, as discussed in detail above, could be influenced by the predominant SERT promoter polymorphism status of the study population.

The majority of longitudinal studies examining amygdala function before and after treatment have been conducted within the framework of the amygdala hyperactivity model of PTSD. It is worth noting that a recent study of adolescent sexual assault-related PTSD shows that higher amygdala reactivity to threat-based stimuli prior to trauma-focused therapy predicts *better* treatment outcomes, particularly related to emotional regulation [86]. The authors commented that those with lower amygdala reactivity prior to treatment and poorer treatment outcomes tended to have more complex symptoms with more comorbidities, although depression scores did not relate to amygdala changes over treatment [86]. Thomaes et al. [77] note that the fear neurocircuitry model of PTSD does not adequately explain dissociative PTSD that is often observed with child abuse, and as discussed earlier, the primary pathology of dissociative PTSD may be resulting from an inhibition of limbic structures like the amygdala rather than an overactivation [14] (**Figure 3**). There may be cases such as in dissociative-type PTSD, in which an increase in amygdala activity to threatening stimuli would be beneficial and therefore the goal of treatment. Thus, higher amygdala activity prior to treatment may in fact improve treatment outcomes in those cases. It is clear that future studies with large sample sizes and heterogeneous PTSD populations will allow comparison among PTSD symptom clusters, to draw conclusions about the ability of the amygdala to predict treatment efficacy. In the near future, it may be possible to utilize information about an individual's amygdala reactivity to personalize and guide their therapy, ultimately improving treatment outcomes for those with PTSD, thus reducing their risks of further health complications throughout their lifetime.

6. Summary and conclusions

A number of studies suggest that the amygdala is hyperactive in PTSD due poor top-down control from the ventral ACC and ventromedial prefrontal cortex (**Figure 1**). However, observations that the amygdala fails to activate in response to negative stimuli in individuals with PTSD in many studies (**Table 1**) suggest this model should be reevaluated. An examination of the neuroimaging literature conducted over the past 20 years suggests that technical and

design issues may explain disparate results regarding amygdala reactivity in PTSD. False positives could be a result of comparisons made in the absence of a control group, failure to correct for multiple comparisons in whole-brain analyses, and ambiguity in the independence of samples between studies. On the other hand, false negative findings could be due to rapid habituation of the amygdala to emotional stimuli, the small volume of the amygdala and its susceptibility to imaging problems. If one assumes that these issues equally affect studies over the years, several other important factors emerge as affecting amygdala function in PTSD. These include the amygdala subregion studied, sex of participants, PTSD symptoms—particularly dissociative PTSD, time between trauma and neuroimaging, substance and medicine use, and whether subliminal or overt stimuli are used to elicit amygdala function. Consideration of each one of these factors furthers our understanding of amygdala dysfunction in PTSD and leads to the model shown in **Figure 3** by which symptoms of emotional disengagement and dissociation are associated with amygdala hyporeactivity. On the other hand, symptoms of hypervigilance/hyperarousal, along with problems in fear conditioning and/or extinction, could be reflected by amygdala hyperactivity (**Figure 3**). Both amygdala states are proposed to be related to altered top-down control from the medial prefrontal cortical regions. Overall, it is unclear whether amygdala dysfunction predisposes an individual to PTSD or is acquired as a result of traumatic experiences, but clinical studies suggest that amygdala function prior to therapy can predict treatment outcomes for PTSD. Based on the refined amygdala dysfunction model of PTSD proposed here, it would be important to target amygdala function in a symptom-driven manner. That is, treatments should be designed to enhance or reduce amygdala function depending on the direction of pretreatment amygdala dysfunction in a given individual.

Acknowledgements

This work was supported by the Department of Defense grant W81XWH-10-1-0925. The authors would like to thank Vincent Magnotta PhD, Jeffrey Simons PhD, and Dawne Olson for their valuable assistance with the collection and analysis of data for **Figure 2**, and Jamie Scholl for editing assistance.

Author details

Gina L. Forster^{1,2*}, Raluca M. Simons^{1,3} and Lee A. Baugh^{1,2}

*Address all correspondence to: gforster@usd.edu

1 Center for Brain and Behavior Research, Vermillion, SD, USA

2 Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota, Vermillion, SD, USA

3 Department of Psychology, University of South Dakota, Vermillion, SD, USA

References

- [1] Jorge RE. Posttraumatic stress disorder. *Continuum*. 2015;**21**:789-805.
- [2] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 2013. Washington, DC: American Psychiatric Association.
- [3] Sareen J. Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. *Canadian J Psychiat*. 2014;**59**:460-467.
- [4] Gaher RM, Simons JS, Hahn AM, Hofman NL, Hansen J, Buchkoski J. An experience sampling study of PTSD and alcohol-related problems. *Psychol Addict Behav*. 2014;**28**:1013-1025.
- [5] Kachadourian LK, Pilver CE, Potenza MN. Trauma, PTSD, and binge and hazardous drinking among women and men: findings from a national study. *J Psychiat Res*. 2014;**55**:35-43.
- [6] Tipps ME, Raybuck JD, Lattal KM. Substance abuse, memory, and post-traumatic stress disorder. *Neurobiol Learn Mem*. 2014;**112**:87-100.
- [7] Weiner MW, Veitch DP, Hayes J, Neylan T, Grafman J, Aisen PS, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Shaw LM, Saykin AJ, Green RC, Harvey D, Toga AW, Friedl KE, Pacifico A, Sheline Y, Yaffe K, Mohlenoff B, Department of Defense Alzheimer's Disease Neuroimaging I. Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's Dementia*. 2014;**10**:S226-235.
- [8] Roberts AL, Agnew-Blais JC, Spiegelman D, Kubzansky LD, Mason SM, Galea S, Hu FB, Rich-Edwards JW, Koenen KC. Posttraumatic stress disorder and incidence of type 2 diabetes mellitus in a sample of women: a 22-year longitudinal study. *JAMA Psych*. 2015;**72**:203-210.
- [9] Simons R, Simons J, Olson D, Baugh L, Magnotta V, Forster, G. Posttraumatic stress and alcohol use among veterans: amygdala and anterior cingulate activation to emotional cues. *Psych Addict Behav*. 2016;**30**:720-732.
- [10] Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychol Med*. 2008;**38**:555-561.
- [11] Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psych*. 2007;**164**:1476-1488
- [12] Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, Pitman RK. Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J Psych Res*. 2008;**42**:515-520.

- [13] Jovanovic T, Norrholm SD, Fennell JE, Keyes M, Fiallos AM, Myers KM, Davis M, Duncan EJ. Posttraumatic stress disorder may be associated with impaired fear inhibition: relation to symptom severity. *Psych Res.* 2009;**167**:151-160.
- [14] Lanius RA, Vermetten E, Loewenstein RJ, Brand B, Schmahl C, Bremner JD, Spiegel D. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *Am J Psych.* 2010b;**167**:640-647.
- [15] El Khoury-Malhame M, Reynaud E, Soriano A, Michael K, Salgado-Pineda P, Zendjidjian X, Gellato C, Eric F, Lefebvre MN, Rouby F, Samuelian JC, Anton JL, Blin O, Khalifa S. Amygdala activity correlates with attentional bias in PTSD. *Neuropsychologia.* 2011;**49**:1969-1973.
- [16] Hayes JP, LaBar KS, McCarthy G, Selgrade E, Nasser J, Dolcos F, workgroup VM-AM, Morey RA. Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. *J Psych Res.* 2011;**45**:660-669.
- [17] Hayes JP, Vanelzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Front Integr Neurosci.* 2012;**6**:89.
- [18] Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. *Biol Psych.* 2006;**73**:61-71.
- [19] Hayes JP, Hayes SM, Mikedis AM. Quantitative meta-analysis of neural activity in post-traumatic stress disorder. *Biol Mood & Anx Disorders.* 2012;**2**:9.
- [20] Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. *Biol Psych.* 2006;**60**:376-382.
- [21] Brashers-Krug T, Jorge R. Bi-directional tuning of amygdala sensitivity in combat veterans investigated with fMRI. *PLoS One.* 2015;**10**:e0130246.
- [22] Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psych.* 1999;**156**:1787-1795.
- [23] Quirk GJ, Likhtik E, Pelletier JG, Pare D. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *J Neurosci.* 2003;**23**:8800-8807.
- [24] Liberzon I, Sripada CS, E. Ronald De Kloet MSOaEV. The functional neuroanatomy of PTSD: a critical review. *Prog Brain Res.* 2007;**167**:151-169.
- [25] Forster GL, Novick AM, Scholl JL, Watt MJ. The Role of the Amygdala in Anxiety Disorders. Rejeka, Croatia: InTech. 2012.
- [26] LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron.* 1998;**20**:937-945.
- [27] Cheng DT, Knight DC, Smith CN, Stein EA, Helmstetter FJ. Functional MRI of human amygdala activity during Pavlovian fear conditioning: stimulus processing versus response expression. *Behav Neurosci.* 2003;**117**:3-10.

- [28] Cheng DT, Knight DC, Smith CN, Helmstetter FJ. Human amygdala activity during the expression of fear responses. *Behav Neurosci.* 2006;**120**:1187-1195.
- [29] Barrett J, Armony JL. Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. *Psychol Med.* 2009;**39**:255-265.
- [30] Morgan MA, Schulkin J, LeDoux JE. Ventral medial prefrontal cortex and emotional perseveration: the memory for prior extinction training. *Behav Brain Res.* 2003;**146**:121-130.
- [31] Milad MR, Vidal-Gonzalez I, Quirk GJ. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behav Neurosci.* 2004;**118**:389-394.
- [32] Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *J Abnormal Psych.* 2000;**109**:290-298
- [33] Wessa M, Flor H. Failure of extinction of fear responses in posttraumatic stress disorder: evidence from second-order conditioning. *Am J Psych.* 2007;**164**:1684-1692.
- [34] Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, Peters PM, Metzger LJ, Dougherty DD, Cannistraro PA, Alpert NM, Fischman AJ, Pitman RK. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiat.* 2004;**61**:168-176.
- [35] Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, Rauch SL. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiat.* 2005;**62**:273-281.
- [36] Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacol.* 2010;**35**:169-191.
- [37] Weymar M, Schwabe L. Amygdala and emotion: the bright side of it. *Front Neurosci.* 2016;**10**:224.
- [38] Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psych.* 2000;**47**:769-776.
- [39] Bremner JD, Vermetten E, Vythilingam M, Afzal N, Schmahl C, Elzinga B, Charney DS. Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. *Biol Psych.* 2004;**55**:612-620.
- [40] Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiat.* 1996;**53**:380-387.
- [41] Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, Macklin ML, Pitman RK. Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. *Arch Gen Psychiat.* 1997;**54**:233-241.

- [42] Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psych*. 1999b;**45**:806-816.
- [43] Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, Koeppe RA, Fig LM. Brain activation in PTSD in response to trauma-related stimuli. *Biol Psych*. 1999;**45**:817-826.
- [44] Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, Metzger LJ, Lasko NB, Orr SP, Pitman RK. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. *Am J Psych*. 1999;**156**:575-584.
- [45] Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, Gati JS, Menon RS. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *Am J Psych*. 2001;**158**:1920-1922.
- [46] Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, Neufeld RW, Gati JS, Menon RS. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biol Psych*. 2002;**52**:305-311.
- [47] Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Staib LH, Soufer R, Charney DS. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biol Psych*. 2003;**53**:879-889.
- [48] Hendler T, Rotshtein P, Yeshurun Y, Weizmann T, Kahn I, Ben-Bashat D, Malach R, Bleich A. Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. *Neuroimage*. 2003;**19**:587-600.
- [49] Armony JL, Corbo V, Clement MH, Brunet A. Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. *Am J Psych*. 2005;**162**:1961-1963.
- [50] Britton JC, Phan KL, Taylor SF, Fig LM, Liberzon I. Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. *Biol Psych*. 2005;**57**:832-840.
- [51] Sakamoto H, Fukuda R, Okuaki T, Rogers M, Kasai K, Machida T, Shirouzu I, Yamasue H, Akiyama T, Kato N. Parahippocampal activation evoked by masked traumatic images in posttraumatic stress disorder: a functional MRI study. *Neuroimage*. 2005;**26**:813-821.
- [52] Phan KL, Britton JC, Taylor SF, Fig LM, Liberzon I. Corticolimbic blood flow during nontraumatic emotional processing in posttraumatic stress disorder. *Arch Gen Psychiat*. 2006;**63**:184-192.
- [53] Williams LM, Kemp AH, Felmingham K, Barton M, Olivieri G, Peduto A, Gordon E, Bryant RA. Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. *Neuroimage*. 2006;**29**:347-357.

- [54] Felmingham K, Kemp AH, Williams L, Falconer E, Olivieri G, Peduto A, Bryant R. Dissociative responses to conscious and non-conscious fear impact underlying brain function in post-traumatic stress disorder. *Psychol Med*. 2008;**38**:1771-1780.
- [55] Felmingham K, Williams LM, Kemp AH, Liddell B, Falconer E, Peduto A, Bryant R. Neural responses to masked fear faces: sex differences and trauma exposure in posttraumatic stress disorder. *J Abnormal Psych*. 2010;**119**:241-247.
- [56] Mazza M, Catalucci A, Mariano M, Pino MC, Tripaldi S, Roncone R, Gallucci M. Neural correlates of automatic perceptual sensitivity to facial affect in posttraumatic stress disorder subjects who survived L'Aquila earthquake of April 6, 2009. *Brain Imaging Behav*. 2012;**6**:374-386.
- [57] White SF, Costanzo ME, Blair JR, Roy MJ. PTSD symptom severity is associated with increased recruitment of top-down attentional control in a trauma-exposed sample. *Neuroimage Clin*. 2015;**7**:19-27.
- [58] Rabellino D, Densmore M, Frewen PA, Theberge J, Lanius RA. The innate alarm circuit in post-traumatic stress disorder: conscious and subconscious processing of fear- and trauma-related cues. *Psych Res*. 2016;**248**:142-150.
- [59] Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Nat Acad Sci*. 2016;**113**:7900-7905.
- [60] Brabec J, Rulseh A, Hoyt B, Vizek M, Horinek D, Hort J, Petrovicky, P. Volumetry of the human amygdala – an anatomical study. *Psych Res: Neuroimaging*. 2010;**182**:67-72.
- [61] Morey RA, Petty CM, Cooper DA, LaBar KS, McCarthy G. Neural systems for executive and emotional processing are modulated by symptoms of posttraumatic stress disorder in Iraq War veterans. *Psych Res: Neuroimaging*. 2008;**162**:59-72
- [62] Felmingham KL, Falconer EM, Williams L, Kemp AH, Allen A, Peduto A, Bryant RA. Reduced amygdala and ventral striatal activity to happy faces in PTSD is associated with emotional numbing. *PLoS One* 2014;**9**:e103653.
- [63] Simons JS, Gaher RM, Jacobs GA, Meyer D, Johnson-Jimenez E. Associations between alcohol use and PTSD symptoms among American Red Cross disaster relief workers responding to the 9/11/2001 attacks. *Am J Drug Alcohol Abuse*. 2005;**31**:285-304.
- [64] Gilman JM, Hommer DW. Modulation of brain response to emotional images by alcohol cues in alcohol-dependent patients. *Addict Biol*. 2008;**13**:423-434.
- [65] Lanius RA, Brewin CR, Bremner JD, Daniels JK, Friedman MJ, Liberzon I, McFarlane A, Schnurr PP, Shin L, Stein M, Vermetten E. Does neuroimaging research examining the pathophysiology of posttraumatic stress disorder require medication-free patients? *J Psych Neurosci*. 2010;**35**:80-89.
- [66] Frewen PA, Dozois DJ, Lanius RA. Assessment of anhedonia in psychological trauma: psychometric and neuroimaging perspectives. *Eur J Psychotraumatol*. 2012;**3**:8587.

- [67] Mickleborough MJ, Daniels JK, Coupland NJ, Kao R, Williamson PC, Lanius UF, Hegadoren K, Schore A, Densmore M, Stevens T, Lanius RA. Effects of trauma-related cues on pain processing in posttraumatic stress disorder: an fMRI investigation. *J Psych Neurosci*. 2011;**36**:6-14.
- [68] Röder CH, Michal M, Overbeck G, van de Ven VG, Linden DE. Pain response in depersonalization: a functional imaging study using hypnosis in healthy subjects. *Psychother Psychosom*. 2007;**76**:115-121.
- [69] Geuze E, Westenberg HG, Jochims A, de Kloet CS, Bohus M, Vermetten E, Schmahl C. Altered pain processing in veterans with posttraumatic stress disorder. *Arch Gen Psychiat*. 2007;**64**:76-85.
- [70] Glahn DC, Lovallo WR, Fox PT. Reduced amygdala activation in young adults at high risk of alcoholism: studies from the Oklahoma Family Health Patterns Project. *Biol Psych*. 2007;**61**:1306-1309.
- [71] Brown VM, and Morey RA. Neural systems for cognitive and emotional processing in posttraumatic stress disorder. *Front Psych*. 2012;**3**: 1-14.
- [72] Blair KS, Vythilingam M, Crowe SL, McCaffrey DE, Ng P, Wu CC, Scaramozza M, Mondillo K, Pine DS, Charney DS, Blair RJ. Cognitive control of attention is differentially affected in trauma-exposed individuals with and without post-traumatic stress disorder. *Psychol Med*. 2013;**43**:85-95.
- [73] Admon R, Lubin G, Stern O, Rosenberg K, Sela L, Ben-Ami H, Hendler T. Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. *PNAS*. 2009;**106**:14120-14125.
- [74] Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ, Shenton ME, Yehuda R, Orr SP, Harvard VAPTSI. Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. *Ann NY Acad Sci*. 2006;**1071**:242-254.
- [75] Shin LM, Lasko NB, Macklin ML, Karpf RD, Milad MR, Orr SP, Goetz JM, Fischman AJ, Rauch SL, Pitman RK. Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. *Arch Gen Psychiat*. 2009;**66**:1099-1107.
- [76] McDonald AJ. Cortical pathways to the mammalian amygdala. *Prog Neurobiol*. 1998;**55**:257-332.
- [77] Thomaes K, Dorrepaal E, Draijer N, Jansma EP, Veltman DJ, van Balkom AJ. Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. *J Psych Res*. 2014;**50**:1-15.
- [78] Roy MJ, Costanzo ME, Blair JR, Rizzo AA. Compelling evidence that exposure therapy for PTSD normalizes brain function. *Stud Health Technol. Inform*. 2014;**199**:61-65.
- [79] Mahabir M, Tucholka A, Shin LM, Etienne P, Brunet A. Emotional face processing in post-traumatic stress disorder after reconsolidation impairment using propranolol: a pilot fMRI study. *J Anxiety Disord*. 2015;**36**:127-133.

- [80] van Rooij SJ, Kennis M, Vink M, Geuze E. Predicting treatment outcome in PTSD: a longitudinal functional MRI study on trauma-unrelated emotional processing. *Neuropsychopharmacol.* 2016;**41**:1156-1165.
- [81] Bryant RA, Felmingham KL, Falconer EM, Pe Benito L, Dobson-Stone C, Pierce KD, Schofield PR. Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. *Biol Psych.* 2010;**67**:1217-1219.
- [82] Canli T, Lesch KP. Long story short: the serotonin transporter in emotion regulation and social cognition. *Nat Neurosci.* 2007;**10**:1103-1109.
- [83] Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science.* 2002;**297**:400-403.
- [84] Munafo MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biol Psych.* 2008;**63**:852-857.
- [85] Kobiella A, Reimold M, Ulshofer DE, Ikonomidou VN, Vollmert C, Vollstadt-Klein S, Rietschel M, Reischl G, Heinz A, Smolka MN. How the serotonin transporter 5-HTTLPR polymorphism influences amygdala function: the roles of in vivo serotonin transporter expression and amygdala structure. *Translational Psych.* 2011;**1**:e37.
- [86] Cisler JM, Sigel BA, Kramer TL, Smitherman S, Vanderzee K, Pemberton J, Kilts CD. Amygdala response predicts trajectory of symptom reduction during trauma-focused cognitive-behavioral therapy among adolescent girls with PTSD. *J Psych Res.* 2015;**71**:33-40.

