Review

A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities

Roee Admon[1], Mohammed R. Milad[2], and Talma Hendler[3,4]

[1] Center for Depression, Anxiety and Stress Research, McLean Hospital, Harvard Medical School, Boston, MA, USA
[2] Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA
[3] Functional Brain Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
[4] School of Psychological Sciences, Sackler Faculty of Medicine and Sagol School for Neuroscience, Tel Aviv University, Tel-Aviv, Israel

Discriminating neural abnormalities into the causes versus consequences of psychopathology would enhance the translation of neuroimaging findings into clinical practice. By regarding the traumatic encounter as a reference point for disease onset, neuroimaging studies of post-traumatic stress disorder (PTSD) can potentially allocate PTSD neural abnormalities to either predisposing (pre-exposure) or acquired (post-exposure) factors. Based on novel research strategies in PTSD neuroimaging, including genetic, environmental, twin, and prospective studies, we provide a causal model that accounts for neural abnormalities in PTSD, and outline its clinical implications. Current data suggest that abnormalities within the amygdala and dorsal anterior cingulate cortex represent predisposing risk factors for developing PTSD, whereas dysfunctional hippocampal–ventromedial prefrontal cortex (vmPFC) interactions may become evident only after having developed the disorder.

Translating neuroimaging findings into clinical practice: post-traumatic stress disorder as a unique opportunity

Extensive neuroimaging work over the past three decades has been devoted to the identification and characterization of functional and/or structural brain abnormalities of individuals with mental disorders, aiming to enhance the use of evidence-based practice in psychiatry [1]. However, given that most neuroimaging studies are conducted following the diagnosis of a given psychiatric disorder, it is impossible practically to determine whether the observed brain differences between psychiatric patients and healthy controls are causes, or consequences, of the psychopathology. In other words, it is unclear if any demonstrated between-group neural abnormalities reflect predisposing vulnerabilities to developing the disorder, or acquired deficits that represent the destructive effect of the disorder. As a result, early or even preventive treatments have rarely been implemented in psychiatry despite their potential efficacy [2].

Exposure to psychological stress plays a major role in the neurobiological manifestation of psychiatric disorders. On the one hand, exposure to stress is a trigger predicting the development or aggravation of many psychopathologies, such as anxiety, depression, and psychosis [3,4], whereas on the other hand, abundant animal and human literature has demonstrated how exposure to psychological stress can lead to long-lasting effects on brain function and structure [5]. Notably, according to epidemiological studies, approximately 50% of the individuals in the population will be exposed at least once in their lives to severe,

Glossary

Genetic polymorphism: existence of more than one form of the same gene within the population. Each of those gene forms is called an 'allele'.
Fear conditioning: laboratory fear conditioning is an experimental paradigm used to teach animals or humans to form an association between a neutral stimulus (e.g., a light or a tone) and an aversive unconditioned stimulus (US; e.g., a mild electric shock). The presentation of the now-conditioned stimulus (CS) triggers the organism to exhibit several physiological responses. Most commonly measured conditioned responses are freezing and potentiated startle in rodents, and skin conductance and potentiated startle responses in humans.
Fear extinction: a training phase in conditioning studies that occurs after fear conditioning. During fear extinction, the cue (the CS) is repeatedly presented in the absence of the US. This extinction training (or within-session extinction learning) leads to decrement of the conditioned responses over trials. Subsequent test of the extinction learning after a delay (i.e., 24 h) is referred to as an extinction recall (or retention) test.
Functional connectivity: a measure of the level of activation synchronization between two or more brain regions as inferred from common changes in their activation over time. Functional connectivity may reflect either an excitatory or inhibitory link between those brain regions in a direct or indirect pathway.
PTSD: an anxiety disorder that may develop following exposure to a traumatic event that involves actual or threatened death, serious injury, or a threat to the physical integrity of oneself or others, to which the person responded with intense fear, helplessness, or horror. Formal diagnosis of PTSD includes three symptom clusters: (i) re-experiencing the original trauma(s), such as through flashbacks or nightmares; (ii) avoidance of stimuli associated with the trauma(s); (iii) and hyperarousal in the form of irritability, hypervigilance, and exaggerated startle.

Corresponding authors: Admon, R. (radmon@mclean.harvard.edu); Hendler, T. (talma@tasmc.health.gov.il).
Keywords: stress; neuroimaging; fear extinction; risk factor; amygdala; functional connectivity; PTSD; prefrontal cortex; hippocampus.

1364-6613/$ – see front matter
 http://dx.doi.org/10.1016/j.tics.2013.05.005

Box 1. Neurocircuitry of PTSD

Early structural neuroimaging studies of PTSD focused on hippocampal volume, guided by much evidence from animal studies demonstrating in various ways how stress can have a destructive effect on the hippocampus. Indeed, human studies frequently reported reduced hippocampal volume in patients with PTSD. Considering the critical role the hippocampus is considered to play in learning and memory, abnormal hippocampus was suggested to mediate PTSD-related deficits in appreciation of safe contexts and contextual memory. The most consistent functional abnormality in human PTSD studies is a hyperactive amygdala in response to emotional stimuli, either trauma specific or not. In accordance with animal studies pointing to the pivotal role of amygdala within the fear circuit, hyperactive amygdala was associated with the heightened fear and hyperarousal of patients with PTSD. The PFC was found to display abnormal function and structure in such patients, especially in its medial sections: mPFC and ACC. Both the mPFC and ACC were repeatedly implicated in various strategies of emotional regulation and, thus, abnormal mPFC and ACC processing in PTSD was associated with patients' deficits in emotional regulation. Connectivity studies, either functional or structural, have shown deficient connectivity between the amygdala and/or the hippocampus to the frontal lobe, supporting the idea that frontal-limbic circuit failure is involved in the difficulties that patients with PTSD have in integrating cognitive control over the emotional neural system. Findings regarding the insula in PTSD are not as common as the above-mentioned brain regions, but they do suggest hyperactive insula in response to a variety of negative stimuli. The insula has a known role in monitoring internal bodily states and, thus, its abnormality in PTSD was associated with the patient's altered interoception of somatic state.

To conclude, based on extensive animal and human studies, the neural abnormalities underlying PTSD were suggested to include structure, function, and connectivity of brain regions involved in emotional expression and regulation: the amygdala, hippocampus, insula, mPFC, and ACC [11–19].

potentially traumatic, psychological stress, such as a threat to life or serious injury [6,7], with approximately 20% of exposed individuals developing the anxiety disorder PTSD (see Glossary) following such exposure [8,9]. In fact, uniquely to PTSD, the mere diagnosis of the disorder depends on the occurrence of such external traumatic events, accompanied by intense fear, helplessness, or horror [10]. Therefore, by regarding the external traumatic event as a reference point for the onset of the disorder, neuroimaging studies of PTSD have a unique opportunity to disentangle predisposing (pre-exposure) from acquired (post-exposure) neural abnormalities.

Previous work has described in great depth the neural abnormalities underlying PTSD (see, for example, [11–19]). This corpus of knowledge has been obtained mostly by conducting cross-sectional studies that compare patients with PTSD to healthy controls who were either exposed to stress but did not develop the disorder or were not exposed. Given that this is not the focus of the current review, we only briefly summarize these findings here (Box 1). At a glance, neurocircuitry models of PTSD suggest the involvement of abnormal function, structure, and connectivity of limbic, paralimbic and frontal brain regions in the disorder. These regions include the amygdala, hippocampus, insula, and various regions in the medial wall of the prefrontal lobe [including the dorsomedial prefrontal cortex (dmPFC), vmPFC, orbitofrontal cortex (OFC), rostral anterior cingulate cortex (rACC), and dorsal anterior cingulate cortex (dACC)] [11–19].

In the following sections, we account for findings from recent efforts to disentangle PTSD neural abnormalities into predisposing versus acquired neural abnormalities using novel research strategies in PTSD neuroimaging, including genetic, environmental, twin, and prospective studies (Figure 1). Although evidence from each of those independent neuroimaging approaches can initiate a knowledgeable discussion on causality in PTSD, by itself, none of these strategies can fully capture the complexity of the question in hand. For example, genetic and environmental studies can only infer predisposing elements, whereas in twin and prospective studies, a seemingly predisposing feature cannot be associated to either genetic or environmental origin. Thus, we gathered evidence here from all of the above strategies to provide a uniform causal model accounting for neural abnormalities in PTSD.

Although the data are limited in number, consistent findings across different research strategies point towards the possibility of allocating at least some PTSD neural abnormalities to either predisposed or acquired factors. Specifically, much evidence supports the abnormal structure of the amygdala and dACC, and their heightened responsivity to emotionally negative stimuli, as predisposing neural risk factors that increase PTSD likelihood following exposure to stress. By contrast, reduced volume of a mPFC structure that is more rostroventral to the dACC (i.e., rACC–vmPFC–OFC), as well as reduced vmPFC structural and functional connectivity with the hippocampus, seems to represent neural abnormalities that, if acquired following stress exposure, may lead to PTSD susceptibility. Considering the emotional-cognitive functions that these different brain circuits are suggested to sub serve [18,20,21], we further propose that hyperarousal, one of the three symptom clusters in PTSD, may represent a predisposing phenotype, whereas the other two symptom clusters (re-experiencing and avoidance) might be acquired. To conclude, we discuss the considerable clinical implications of our model as well as point towards future research directions that would be needed to validate and extend it.

Research strategies to disentangle predisposed from acquired neural abnormalities in PTSD

Studies of genetic factors

A genetic profile may appear at first glance as the hallmark of predisposing vulnerability. PTSD was indeed found to be moderately heritable, with genetic influence accounting for 30–70% of the likelihood to develop PTSD following exposure to stress [22,23]. Association studies found up to 20 different genetic polymorphisms that are evident more frequently in patients with PTSD than in healthy controls, suggesting that those genes encompass genetic stress susceptibility (reviewed in [24–27]). The most studied gene in PTSD is the serotonin transporter-linked polymorphic region gene (*5-HTTLPR*) that encodes a serotonin transporter. 5-HTTLPR relevance in the context of PTSD stems from early findings in healthy individuals showing that polymorphism of a 5-HTTLPR short (s) compared with a long (l) allele is associated with greater anxiety tendency [28,29]. Indeed, several PTSD studies found higher frequency of the (s) genotype among patients with PTSD

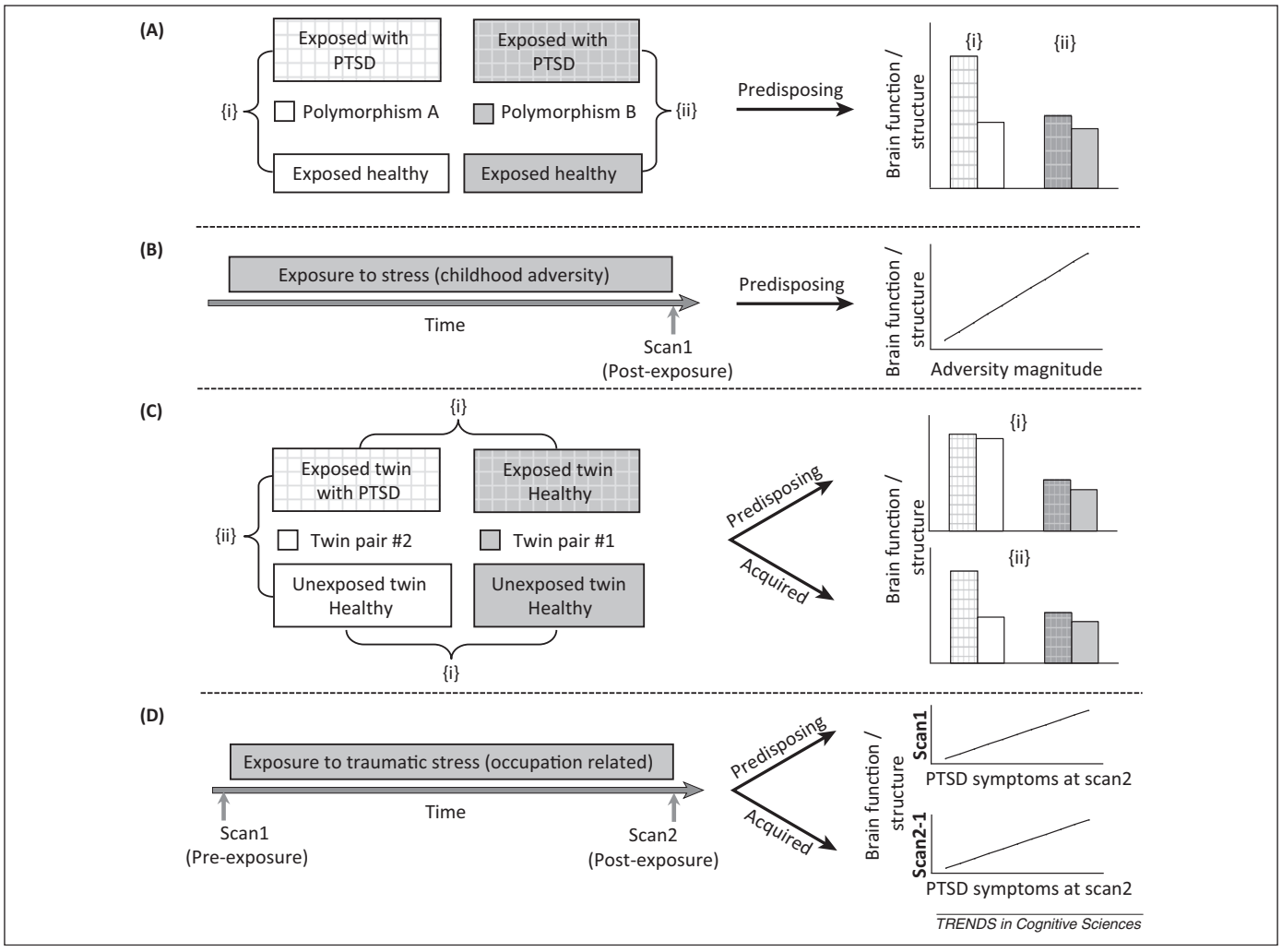

Figure 1. Research strategies to disentangle predisposed from acquired neural abnormalities in post-traumatic stress disorder (PTSD). **(A)** Studies of genetic factors can tie a specific genetic polymorphism (e.g., polymorphism A) to a localized neural abnormality in PTSD {i}, in contrast to a different polymorphism (e.g., polymorphism B) {ii}, suggesting that polymorphism A predisposingly moderates the relation between PTSD and such brain abnormality. **(B)** Studies of environmental factors examine brain abnormalities in healthy participants that were previously exposed to adversity; as such, abnormality may represent predisposed vulnerability upon re-exposure to trauma. **(C)** Studies of twin samples can identify predisposed vulnerability as brain abnormalities that are present in both the twin with stress-exposure PTSD and their unexposed identical co-twin, but not in another pair of healthy identical twins where one twin had stress-exposure {i}. Acquired neural deficits can be found by comparing the twin with stress-exposure PTSD to their own unexposed co-twin {ii}. **(D)** Prospective studies can identify predisposed vulnerability as brain abnormalities that exist pre-exposure to stress and predict PTSD post-stress exposure, whereas brain abnormalities that become evident only after having developed PTSD post-exposure may represent acquired deficits.

compared with healthy controls [30–36]. Nevertheless, contrasting evidence was also reported [37,38]. Furthermore, 5-HTTLPR polymorphism was also mentioned in regard to other anxiety disorders as well as major depression, questioning its specificity [24–27].

By tying a specific genetic polymorphism to a localized neural abnormality, imaging genetic studies enable the identification of an intermediate phenotype, thus clarifying the functional link between genes and disease. This approach may further allow the integration of candidate vulnerability genes into a neural model of the disorder. To the best of our knowledge, until now, only two pioneering studies were able to demonstrate an interaction between the presence of a specific genetic polymorphism and neural abnormality in PTSD. A structural genetic neuroimaging study found smaller ACC volume in patients with PTSD than in controls, but this difference interacted with a catechol-*O*-methyltransferase (COMT) Val158Met genetic polymorphism [39], known for its effect on dopaminergic signaling in the mPFC [40]. Patients with PTSD who carry two Val alleles compared with PTSD Met allele carriers were associated with a greater difference in ACC volume compared with the controls [39]. A functional MRI (fMRI) genetic imaging study found that post-9/11 veterans with PTSD who carry the (s) allele on the *5-HTTLPR* gene exhibited increased amygdala and ventrolateral prefrontal cortex (vlPFC) activation in response to trauma-related images compared with patients with PTSD with the (l) allele [41]. Neuroimaging studies in healthy populations further support the association between (s) allele carriers on the *5-HTTLPR* gene and increased reactivity of the amygdala to emotional stimuli [42,43]. Therefore, and considering the major role of the amygdala within the neural fear circuit [18,21,44], it has been suggested that (s) allele carriers on the 5-HTTLPR gene are prone to express enhanced fear and arousal upon stress exposure, predisposing them to increased risk of developing PTSD [45].

Studies of environmental factors

Previous stress exposure is a major risk factor for PTSD upon re-exposure to trauma [46]. For example, Vietnam veterans with PTSD had higher rates of childhood physical abuse and of total traumatic events before joining the military than did Vietnam veterans without PTSD [47]. Early adversities can thus be considered as environmental experiences that may lead to predisposed stress vulnerability upon re-exposure to trauma later on in life. In support of this notion, a large number of neuroimaging studies have demonstrated dramatic long-term effects of childhood adversity on neural function and structure and their relation to psychopathology (reviewed in [48,49]). For example, two recent structural neuroimaging studies reported increased amygdala volumes in children and adolescents who had experienced early institutionalization and subsequent adoption [50,51]. Notably, in both studies, the effects are observed years after termination of the adversity. Children exposed to adverse rearing conditions associated with maternal depressive symptoms were also shown to exhibit increased amygdala volume [52]. Two functional neuroimaging studies that investigated the effect of caregiver deprivation and emotional neglect on healthy youths found amygdala hyperactivation in response to emotional faces as a marker of childhood maltreatment [53,54]. Taken together, evidence from neuroimaging studies of environmental factors in children and adolescents suggest that childhood adversity results in increased amygdala volume and hyper-responsivity to emotional stimuli. Studies in animals have also shown that early adversity is associated with structural abnormalities in the amygdala [55], and greater amygdala response to stress [56], resulting in higher anxiety levels. Following these, and other findings, it has been suggested that stress endured in early life, a critical period in neuronal development, results in a persistent sensitization of the neural stress circuitry to even mild stress in later life, predisposing to psychopathology [57].

To investigate the effect of childhood maltreatment in an adult cohort, several neuroimaging studies compared adult patients with PTSD and childhood abuse to either patients with PTSD but without abuse or to healthy adults with childhood abuse (see, for example, [58,59]). Nevertheless, isolating the predisposing component that is contributed by the adverse environment, as is the goal of the current review, can only be achieved by comparing healthy adults with and without childhood adversity. Examining adult individuals with childhood abuse who have PTSD currently, or those who were found to have PTSD at some point in their life would not allow the desired disentanglement. Obviously, such a cohort is difficult to find, which may explain the paucity of studies.

By adopting a continuum approach towards the abuse (i.e., using the magnitude of abuse as assessed by a self-report questionnaire), two recent functional neuroimaging studies investigated a large cohort of 150 healthy adults with various degrees of childhood maltreatment. Both these studies found a positive correlation between amygdala activation in response to negative emotional faces (e.g., fearful or sad) and the magnitude of childhood maltreatment [60,61] (Figure 2). These findings not only further support

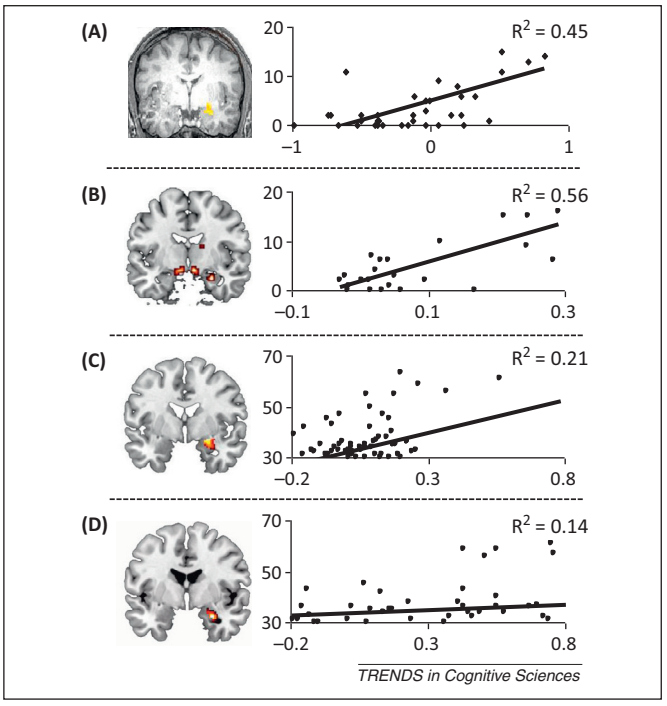

Figure 2. Amygdala as a marker for predisposing stress vulnerability. (**A–D**, left side) Coronal views of brain activation showing amygdala activation in response to diverse negatively valenced emotional tasks in healthy individuals. (A,B, right side) Scatter plots and regression lines showing the positive relation between these amygdala activations pre-exposure to stress (X-axis) and the level of post-traumatic stress disorder (PTSD) symptoms post-exposure to stress (Y-axis). (C,D, right side) Scatter plots and regression lines showing positive relation between these amygdala activations (X-axis) and the magnitude of childhood maltreatment (Y-axis). Adopted, with permission, from [60,61,75,76].

hyper amygdala activation as a marker of childhood abuse, but also suggest that such abnormality persists for prolonged periods of time, acting as a predisposing neural mediator between the experiences of adversities during childhood and the development of PTSD upon re-exposure to stress in adulthood.

Gene × environment interaction

The significance of gene × environment (G×E) interaction is well recognized. For example, (s) allele carriers on the *5-HTTLPR* polymorphism were found to be at an increased risk of PTSD only in high-risk environments (e.g., high crime, unemployment rates, natural disaster, low social support, or childhood adversity), and not in low-risk environments [33–36]. Recent evidence suggests that such G×E interaction in PTSD is mediated by specific DNA demethylations affecting gene expression levels [62,63]. Another relevant G×E interaction may stem from a familial origin (i.e., first-degree relatives of patients), because the presence of a psychopathological parent was suggested to mediate increased PTSD vulnerability in children [64]. Imaging studies attempting to explore this interaction have only been performed within the depression context [65,66], and we encourage PTSD researchers to pursue this direction.

Studies of twin samples

A unique and highly valuable sample for probing causality of PTSD neural abnormalities is represented by identical twin pairs in which one twin suffers from combat PTSD

while their co-twin had neither combat exposure nor PTSD, along with identical twin pairs where one twin had combat exposure without PTSD and their co-twin had no combat exposure or PTSD. Predisposed vulnerability may be identified as abnormalities that are present in both the twin with PTSD and their unexposed co-twin, but not in the other pair of twins. Indeed, the first neuroimaging study using such an approach demonstrated that reduced hippocampal volume, the most common structural abnormality found in patients with PTSD [14,19], might constitute such a predisposing factor [67]. A second structural study from the same research group suggested that a reduction in gray matter density of the rACC is an acquired deficit of PTSD, because it was found in combat-exposed twins with PTSD compared with their own unexposed co-twins [68]. More recently, two neuroimaging studies using PET and fMRI found increased dACC activation at rest and during a cognitive task in both patients with PTSD and their twins compared with the other pair of twins [69,70], suggesting that elevated activity of the dACC represents a predisposing risk factor. Whether twin studies support the predisposing role of hyperactive amygdala awaits the implementation of emotional tasks within this cohort.

Prospective studies

Some prospective neuroimaging studies of PTSD investigated brain structure and function immediately after stress exposure, such as in emergency rooms following car accidents, and then at follow-ups once or more for a period of up to 6 months (see, for example, [71–73]). Although insights into the peritraumatic response of the brain to trauma are valuable for predicting the development of psychopathology, such biological markers may still constitute early indicators of the emerging disorder rather than a true predisposing risk factor [74] and, thus, cannot contribute to a causal model. An alternative prospective strategy is to examine individuals before any exposure to stress and then re-examine them following stress exposure. Given that traumatic occurrences are rare and random, such prospective studies must be conducted in samples where their risk of exposure to stress is high (e.g., new military, police, or firefighter recruits). Furthermore, even within those exposed to traumatic stress, only a small subset of individuals will be found to have PTSD [8]; thus, prospective studies usually investigate interindividual variability in the magnitude of psychopathological symptoms exhibited following trauma.

A recent set of studies adopted this framework by examining new army recruits both pre- and 18 months post-deployment to combat military service in front-line combat units of the Israeli Defense Force (IDF). Importantly, because recruitment to the IDF is mandatory, the study sample did not suffer from a potential selection bias. Following stressful military service, up to 85% of the soldiers exhibited an increase in PTSD symptoms, whereas 20% developed enough symptoms to reach the threshold for mild PTSD, similar to the common ratio of vulnerability upon exposure to stress [8]. Before any exposure to stress, vulnerable individuals were characterized by heightened amygdala activation in response to two diverse negatively valenced emotional tasks [75,76] (Figure 2). Thus, these data further support the suggested predisposing role of a hyperactive amygdala.

By contrast, reduction in nucleus accumbens (Nacc) response to reward following stress [75], as well as in the functional connectivity between the hippocampus and the vmPFC [76], represented acquired neural abnormalities associated with maladaptive response to stressful military service. The acquired nature of the reduction in hippocampal–vmPFC connectivity was further supported by the finding that, following military stress, reduced hippocampal–vmPFC structural connectivity (as measured by the integrity of the fiber tract anatomically connecting the hippocampus to the vmPFC, the uncinate fasciculus) is also an acquired deficit [77].

In another structural prospective neuroimaging study, more PTSD symptoms following a severe magnitude earthquake were found to be associated with decreased gray matter volume in the ACC before the earthquake (i.e., predisposing), as well as with a reduction in gray matter volume of the OFC after versus before the earthquake (i.e., acquired) [78]. Finally, a functional prospective neuroimaging study in a group of United Nations (UN) peacekeeping force soldiers posted for 4 months to Afghanistan found increased amygdala and insula reactivity to threatening stimuli following military service as well as a perceived-threat-dependent change in amygdala connectivity with the dACC [79]. A follow-up examination of those soldiers approximately 1.5 years after they had returned from military deployment found that, in the absence of additional combat exposure, stress-induced amygdala hypersensitivity normalized to the same level as before combat service, whereas changes in amygdala connectivity persisted [80]. Notably, the UN soldiers in this sample did not display any increase in PTSD symptoms following their military service and, thus, these neural changes do not necessarily represent maladaptive patterns.

A causal model accounting for neural abnormalities in PTSD

Table 1 summarizes the results of an increasing scientific effort to allocate PTSD neural abnormalities into predisposing vulnerabilities versus acquired deficits. Figure 3 presents the results of the above functional studies overlaid on a schematic model of common hyper- and hypo-activations in PTSD. Most of the cited literature has been produced during the past 3 years and, therefore, replications will be needed before final conclusions can be reached. Nevertheless, certain trends within the dimensions of the complex issue of casualty in PTSD neural abnormality seem to appear consistently across several research disciplines. Two prospective studies in healthy soldiers found hyper amygdala responsivity to emotionally negative stimuli, the most common functional abnormality found in PTSD [17], as a predictor for more PTSD symptoms following subsequent real-life stress in the form of military service [75,76]. Exposure to childhood adversity, a major risk factor for PTSD, was repeatedly associated with elevated amygdala activation to emotionally negative stimuli in healthy youths and adults [53,54,60,61], as well as with increased amygdala volume [50–52]. Twin studies found that, even without exposure to stress, healthy identical twins of

Table 1. Causality in PTSD neural abnormalities[a]

Study	Scientific approach	Subjects (gender, N)	Imaging method	Task	Predisposed vulnerability	Acquired deficits
[39]	Genetic	War veterans (M+F; 51, 48[b])	MRI	–	↓ ACC volume[e]	N/A
[41]	Genetic	Post-9/11 veterans (M+F; 22, 20[b])	fMRI	Trauma-related distractors	↑ Amy and vlPFC function[f]	N/A
[50]	Environmental	Adolescents who experienced orphanage rearing (M+F; 14, 11[c])	MRI	–	↑ Amy volume	N/A
[51]	Environmental	Children who experienced orphanage rearing (M+F; 34, 28[c])	MRI	–	↑ Amy volume	N/A
[52]	Environmental	Children exposed to maternal depressive symptomatology (M+F; 17, 21[c])	MRI	–	↑ Amy volume	N/A
[53]	Environmental	Healthy youths with a history of caregiver deprivation and emotional neglect (M+F; 11, 19[c])	fMRI	Viewing neutral and emotional faces	↑ Amy and HC function	N/A
[54]	Environmental	Healthy youths who experienced orphanage rearing (M+F; 28, 27[c])	fMRI	Go/No-go task with fearful and neutral faces	↑ Amy function	N/A
[60]	Environmental	Healthy adults exposed to various childhood maltreatments (M+F; 145)	MRI and fMRI	Matching threatening angry and fearful faces to a target face	↑ Amy function ↓ HC gray matter volume	N/A
[61]	Environmental	Healthy adults exposed to various childhood maltreatments (M+F; 150)	fMRI	Viewing masked neutral and emotional faces	↑ Amy function	N/A
[67]	Twin pairs	Vietnam veterans (M; 17, 23[d])	MRI	–	↓ HC volume	
[68]	Twin pairs	Vietnam veterans (M; 18,23[d])	MRI	–		↓ rACC gray matter density
[69]	Twin pairs	Vietnam veterans (M; 14, 19[d])	PET	Rest	↑ dACC function	
[70]	Twin pairs	Vietnam veterans (M; 12, 14[d])	fMRI	Multi-source interference (cognitive)	↑ dACC function	
[75]	Prospective	IDF soldiers (M+F; 24)	fMRI	Playing a game with threatening and rewarding intervals	↑ Amy function	↓ Nacc function
[76]	Prospective	IDF soldiers (M+F; 37)	fMRI	Viewing masked neutral and stress-related pictures	↑ Amy function	↑ HC function ↓ HC–vmPFC functional connectivity
[77]	Prospective	IDF soldiers (M+F; 33)	MRI & DTI	–		↓ HC volume ↓ HC–vmPFC structural connectivity
[78]	Prospective	Healthy adolescents (M+F; 42)	MRI	–	↓ ACC gray matter volume	↓ OFC gray matter volume
[79]	Prospective	UN soldiers (M+F; 33)	fMRI	Viewing angry and fearful faces		↑ Amy and insula function[g] ↑ Amy–dACC connectivity[g]
[80]	Prospective	UN soldiers (M+F; 23)	fMRI	Viewing angry and fearful faces		↑ Amy–dACC connectivity[g]

[a]↓, decrease; ↑, increase.

[b]Number of patients with PTSD and healthy controls, respectively.

[c]Number of exposed and unexposed to childhood abuse, respectively.

[d]Number of PTSD twin pairs and non-PTSD twin pairs, respectively.

[e]In interaction with dopaminergic polymorphism.

[f]In interaction with serotonin transporter polymorphism.

[g]Not necessarily a maladaptive response to traumatic stress.

patients with PTSD displayed heightened dACC activation [69,70]. Some environmental and prospective evidence suggests that ACC predisposition also involves structural elements [60,78]. Finally, imaging genetic studies propose that predisposition in either or both of those brain regions is evident already at birth [39,41].

Taken together, abnormal structure of the amygdala and dACC, and their heightened responsivity to emotionally negative stimuli, may represent predisposing neural abnormalities that exist before exposure to trauma and increase the likelihood of developing PTSD following exposure. The feasibility of this proposition is supported by the vast PTSD neuroimaging literature pointing to heightened amygdala and dACC activation as highly reliable neural abnormalities in PTSD [11–19]. Even further, findings from childhood adversity studies suggest that both functional and structural abnormalities in the amygdala can be detected long after the stress has passed, supporting the stable nature of such potential predisposition. The mechanism through which such predisposing effect takes place may relate to the importance of the amygdala and dACC as mediators of fear generation and

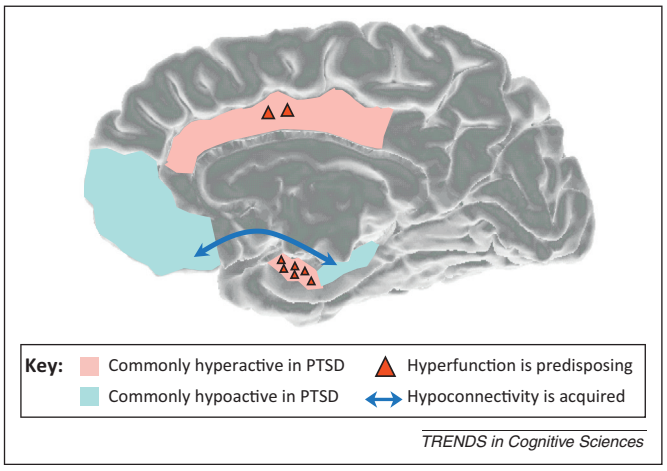

Figure 3. Neural abnormalities in post-traumatic stress disorder (PTSD). Results of functional studies discussed in this review overlaid on a schematic model of common hyper- and hypoactivations in PTSD. Light-red areas mark the amygdala and dorsal anterior cingulated cortex (dACC). Light-blue areas mark the hippocampus and medial prefrontal cortex [including the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), and orbitofrontal cortex (OFC)]. Notably, only the results of whole-brain functional studies that were not restricted to a specific brain region are presented.

expression [18,21,44]. These neural predispositions may thus make individuals prone to express heightened fear response upon stress exposure, reducing their chances to cope adequately with the experience (Figure 4).

Less evidence exists regarding the acquired side of the equation, relying solely on twin and prospective studies. The current data suggest that reduced volume of a mPFC structure that is more rostroventral to the dACC (i.e., rACC–vmPFC–OFC) [68,78], as well as reduced vmPFC structural and functional connectivity with the hippocampus [76,77], are neural abnormalities that, if acquired following traumatic exposure, may lead to PTSD susceptibility. These findings are relevant within the framework of context-dependent fear extinction, which is an essential need for adaptive recovery from traumatic experience [81], and that its impairment is a key feature of anxiety disorders, including PTSD [82]. Indeed, vmPFC and OFC gray matter thicknesses, activation levels, and connectivity strength with the hippocampus were repeatedly found to predict individuals' ability to extinguish fear [83–87]. Therefore, a thicker, more functional, and a stronger connected vmPFC to the hippocampus was suggested to confer better capacity to inhibit and maintain (i.e., retain) fear responses [44]. Compromised vmPFC structure and connectivity with the hippocampus may thus represent acquired neural abnormalities that are associated with maladaptive response to stress in the form of failure to inhibit the fear response appropriately (Figure 4). In support of the acquired nature of this deficit, a behavioral study in the twin cohort showed that reduced fear extinction was not evident in the healthy co-twins of combat veterans with PTSD [88]. Notably, the association of abnormalities within the dACC and rACC to different components of the fear response (i.e., fear expression and its inhibition, respectively), as suggested by our model, is supported by an extensive animal literature. By the use of pharmacological, electrophysiological, lesion, and molecular approaches, animal studies pointed to the prelimbic cortex, for which the dACC is a putative human homolog, as a brain region that facilitates the expression of conditioned fear, whereas to the infralimbic cortex (i.e., rACC homolog), as being crucial for fear inhibition [20].

The model presented is clearly a simplification of the complex roles of either predisposing or acquired brain abnormalities within the PTSD psychopathology. Firstly, the effects of predisposing and acquired neural abnormalities are probably not discrete but rather interrelated. For example, a neural abnormality such as reduced hippocampal

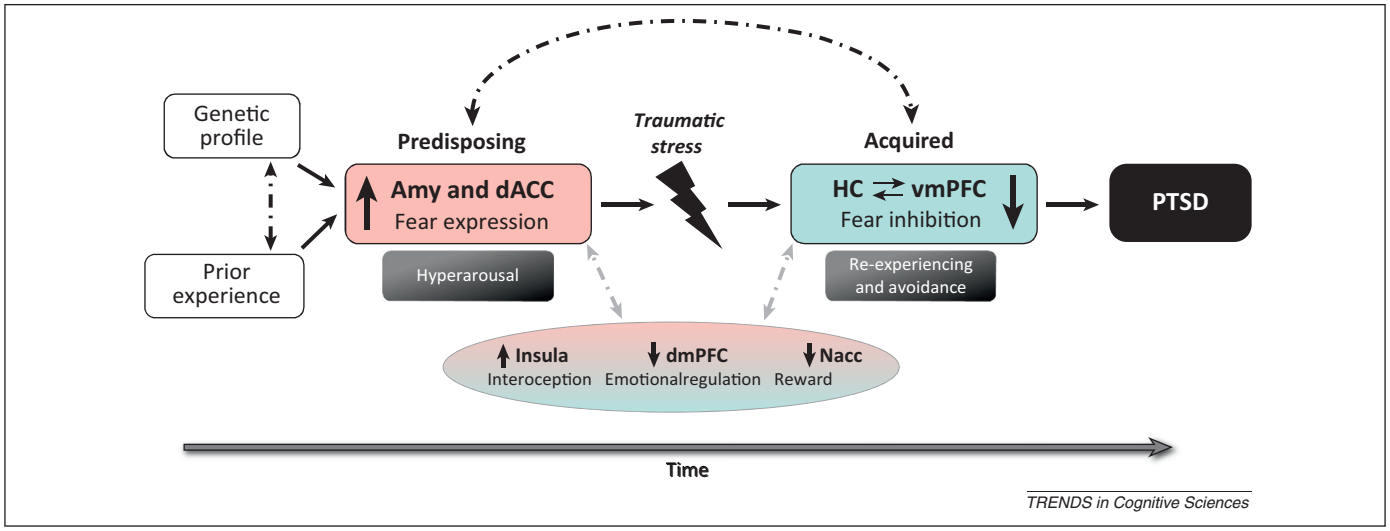

Figure 4. A causal model accounting for neural abnormalities in post-traumatic stress disorder (PTSD). The model postulates that genetic and environmental factors, as well as the interaction between them (broken black line), may lead certain individuals to display abnormal structure and hyperfunction of the amygdala (Amy) and dorsal anterior cingulated cortex (dACC). The model further suggests that such predisposition makes individuals prone to express heightened fear, manifested as PTSD hyperarousal symptoms. Following exposure to traumatic stress, a subset of those predisposingly vulnerable individuals may acquire additional neural abnormalities in the form of reduced ventromedial prefrontal cortex (vmPFC) volume, and its connectivity with the hippocampus (HC). These acquired abnormalities may contribute to impaired fear inhibition capability, thus yielding PTSD symptoms of avoidance and re-experiencing. Taken together, the model suggests that the summation of both predisposing and acquired neural abnormalities, as well as of their potential interactions (broken curved line), results in the full symptomatic phenomenon that entails clinical diagnosis of PTSD. Finally, the model recognizes the contribution of additional brain regions as potential mediators (broken gray lines). Accordingly, hypofunction of the nucleus accumbens (Nacc), and dorsomedial prefrontal cortex (dmPFC), as well as hyperfunction of the insula, may mediate PTSD through their suggested roles in reward processing, emotional regulation, and interoception, respectively.

volume may predispose to PTSD [67], yet at the same time PTSD can cause a secondary loss of volume over time [77]. This may explain why hippocampal volume is normal in children with maltreatment-related PTSD, but is reduced in adults with PTSD from childhood maltreatment [89]. Another interesting interaction may be exampled by the finding that reduced hippocampal volume following stress affects the magnitude of its connectivity with the vmPFC [77]. Even further, amygdala reactivity before stress exposure was found to predict a weaker increase of hippocampal–vmPFC functional connectivity following exposure [76]. Therefore, we can speculate that an acquired maladaptive response may interact to worsen the effect of pre-existing vulnerability (i.e., reduced ability to inhibit fear further increases the already exaggerated tendency to express fear), causing a vicious cycle that yields PTSD.

Secondly, the contribution of additional PTSD-related brain abnormalities should be considered. One such region is the Nacc, in that a reduction in its response to reward may constitute a maladaptive consequence of stress exposure, although found in only one prospective study [75]. The reward circuitry, of which the Nacc is a core element [90], has been somewhat overlooked within the PTSD neuroimaging literature, yet the few studies that did explore this domain found reduced Nacc reward responsivity in PTSD [91,92]. Furthermore, Nacc-related impaired reward processing was described as a characterizing feature of major depression [93], a psychopathology sharing high comorbidity rates with PTSD [94]. Reduced reward responsivity may contribute to PTSD symptoms of diminished motivation and restricted affect range, in particular of positive emotions. Other than the Nacc, hyperactive insula and hypo-active dmPFC may also play a mediating role within the complexity of PTSD neural abnormality, potentially due to their suggested involvement in altered interoception and emotional dysregulation in PTSD, respectively [17,95] (Figure 4).

Lastly, even the brain regions that do appear in our model, the amygdala, hippocampus, dACC, and vmPFC, were all associated with additional tasks in humans and, thus, abnormality in either one of these brain regions may extend beyond fear expression and inhibition. For example, dysfunctional hippocampus may contribute to PTSD deficits in memory modulation [96], contextual processing [18], overgeneralization of fear [97], and regulation of the neuroendocrine hypothalamic–pituitary–adrenal (HPA) axis response [98], whereas the amygdala has been linked to generalization of loss associations [99], expectation processing [100], and dealing with ambiguity [101]. Future research will determine the exact psychological sequelae of PTSD neural abnormalities and whether such deficits are acquired or predisposing factors. Box 2 details specific questions for future research.

Box 2. Outstanding questions

- What neural modifications occur during treatment of PTSD? What differentiates successful from failed treatment? Do acquired neural abnormalities exhibit more plasticity compared with predisposing abnormalities? Would successful treatment result in stronger hippocampal–vmPFC connectivity?
- Can we specifically target hippocampal–vmPFC connectivity through neuromodulation? Could such manipulation, if accompanied by treatment, improve treatment outcome?
- Considering that women are more likely than men to develop PTSD, do sex differences exist in the tendency to express fear and the capacity to inhibit fear? If so, what neural circuits mediate such sex differences?

Clinical implications

The clinical diagnosis of PTSD is dichotomous. Nevertheless, the disorder comprises a blend of several clusters of symptoms that may be experienced at varying severities across patients and time, yielding great challenges for diagnostic and therapeutic efforts. Considering the importance of the amygdala and dACC in mediating fear generation and expression [18,21,44], it has been previously suggested that their abnormality mediates the symptom cluster of hyperarousal in PTSD because it includes irritability, hypervigilance, and exaggerated startle [13]. Thus, the first clinical relevance of our model is that hyperarousal might constitute a predisposing phenotype in PTSD and, therefore, could be detected before exposure to trauma, as a vulnerability indicator. In support of that, a recent behavioral study in police academy cadets found that physiological measures of the startle response upon exposure to a threat of mild electrical shock, as well as the level of subjective fear, were predictive of PTSD symptom severity following 1 year of exposure to police-related trauma [102]. Animal studies have also shown that physiological markers of hyperarousal that are assessed before the stressful situation takes place can predict the level of PTSD-like symptoms following stress [103,104]. Notably, heightened amygdala responsivity is a common feature of many psychiatric disorders, especially within the anxiety domain [17], and thus may reflect a more general vulnerability to psychopathology upon stress. This, however, does not reduce its clinical relevance, because in most cases, PTSD is accompanied by another condition, such as major depression, other anxiety disorders, or substance abuse [105].

It is clear that not all predisposingly vulnerable individuals will develop PTSD or any psychopathology following stress. Indeed, hyperarousal, by itself, is insufficient for the full clinical diagnosis of PTSD because it also requires symptoms from the clusters of re-experiencing and avoidance [10]. This in turn supports the idea that predisposing neural abnormality may not elicit PTSD upon exposure to stress, unless accompanied by additional, potentially acquired, neural deficits. Notably, stress-induced reduction in hippocampus–vmPFC connectivity that appear as acquired abnormalities in our model may lead to failure to inhibit fear appropriately [20], which in turn has been associated with symptoms of re-experiencing and avoidance. Specifically, the tendency to avoid fear-provoking situations and stimuli was suggested to stem from diminished inhibition of the fear response [44], whereas re-experiencing was discussed within the fear extinction framework following the consideration that re-experiencing symptoms include the recurrence of fear, either spontaneously, or upon cues that have been associated with the traumatic event [15]. Therefore, the second clinical relevance of our model is that PTSD symptom clusters of re-experiencing and avoidance may represent acquired

phenotypes that mark the consequences of a maladaptive response to stress.

Taken together, the full symptomatic phenomenon that entails clinical diagnosis of PTSD is potentially underlined by a combination of predisposing and acquired elements. The above cited evidence of interactions between predisposing and acquired neural abnormalities in PTSD may be regarded as supporting such scenario. This framework, if confirmed by future evidence, may carry specific clinical implications. The current behavioral treatment of choice for PTSD is exposure therapy, which attempts to expose patients with PTSD to the feared object or context in a safe environment to extinguish their fear response [106]. A recent animal study showed that fear extinction training is highly efficient if provided in the immediate aftermath of the exposure to stress (i.e., within 1 h) because it leads to complete extinction of the fear response [107]. By contrast, extinction training provided 3 days after fear conditioning resulted in robust recovery of the fear response, either spontaneously or upon repeated exposure to the stressor [107]. Studies in humans have also raised the possibility of a 'window of opportunity' or 'golden hours' to help those who are vulnerable to develop PTSD [108]. Indeed, a recent behavioral study found that early exposure intervention initiated within hours of the trauma in the emergency department successfully reduced PTSD symptoms as measured 3 months after the trauma [109]. Accurately identifying vulnerable individuals, based on predisposing tendency such as hyperactive amygdala and dACC, could therefore enable the implementation of early clinical intervention to prevent the development of avoidance and re-experiencing symptoms and, thus, of the consequent psychopathology, potentially by avoiding the maladaptive reduction in hippocampus–vmPFC connectivity.

Concluding remarks

Based on research from four novel and independent human neuroimaging approaches, we have proposed a causal model accounting for neural abnormalities of PTSD. The model suggests that predisposing vulnerability is derived from abnormal structure and function of the amygdala and dACC. Specifically, it asserts that heightened responsivity of these regions mediates exaggerated fear generation and expression, and thus might underlie the symptom cluster of hyperarousal in PTSD. By contrast, reduced vmPFC volume, and its connectivity with the hippocampus, seems to represent neural abnormalities that, if acquired following stress exposure, may lead to impaired fear inhibition and, thus, to PTSD susceptibility due to re-experiencing and avoidance symptoms. The complexity of the PTSD phenomena requires future efforts to validate and extend the causal model proposed in this review (Box 2). It is our hope that the ability to disentangle predisposing from acquired neural abnormalities may pave the way for a better utilization of neuroimaging findings in clinical practice.

Acknowledgments

This work was supported by a grant from the U.S. Department of Defense (DoD) award number W81XWH-11-2-0008; Israel-Centers of Excellence (I-CORE) Program of the Planning and Budgeting Committee, and the Israel Science Foundation (grant no. 51/11); and Adams Super Center for Brain Studies, Tel Aviv University. We would like to thank: Dr David Papo for his fruitful comments on earlier versions; Dr Gadi Lubin and Dr Eyal Fructer from the Israel Defense Forces medical corps for their support of this work; and Mr Matan Shalita for graphical assistance.

References

1 Insel, T.R. and Wang, P.S. (2010) Rethinking mental illness. *JAMA* 303, 1970–1971
2 Yehuda, R. (2002) *Treating Trauma Survivors with PTSD*. American Psychiatric Association
3 Monroe, S.M. and Harkness, K.L. (2005) Life stress, the 'kindling' hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychol. Rev.* 112, 417–445
4 Kessler, R.C. *et al.* (1985) Social factors in psychopathology: stress, social support, and coping processes. *Annu. Rev. Psychol.* 36, 531–572
5 McEwen, B.S. (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol. Rev.* 87, 873–904
6 Norris, F.H. (1992) Epidemiology of trauma: frequency and impact of different potentially traumatic events on different demographic groups. *J. Consult. Clin. Psychol.* 60, 409–418
7 Kessler, R.C. *et al.* (1995) Posttraumatic Stress Disorder in the national comorbidity survey. *Arch. Gen. Psychiatry* 52, 1048–1060
8 Breslau, N. (1998) Epidemiology of trauma and posttraumatic stress disorder. In *Psychological Trauma* (Yehuda, R., ed.), pp. 1–29, American Psychiatric Press
9 Resnick, H.S. *et al.* (1993) Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J. Consult. Clin. Psychol.* 61, 984–991
10 DSM-IV–TR (2000) *American Psychiatric Association: Diagnostic and Statistical Manual Of Mental Disorders*. American Psychiatric Association
11 Francati, V. *et al.* (2007) Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. *Depress. Anxiety* 24, 202–218
12 Rauch, S.L. *et al.* (2006) Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research: past, present, and future. *Biol. Psychiatry* 60, 376–382
13 Liberzon, I. and Sripada, C.S. (2008) The functional neuroanatomy of PTSD: a critical review. *Prog. Brain Res.* 167, 151–169
14 Karl, A. *et al.* (2006) A meta-analysis of structural brain abnormalities in PTSD. *Neurosci. Biobehav. Rev.* 30, 1004–1031
15 Pitman, R.K. *et al.* (2012) Biological studies of post-traumatic stress disorder. *Nat. Rev. Neurosci.* 13, 769–787
16 Vermetten, E. and Lanius, R.A. (2012) Biological and clinical framework for posttraumatic stress disorder. *Handb. Clin. Neurol.* 106, 291–342
17 Etkin, A. and Wager, T.D. (2007) Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatry* 164, 1476–1488
18 Shin, L.M. and Liberzon, I. (2010) The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology* 35, 169–191
19 Smith, M.E. (2005) Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus* 15, 798–807
20 Milad, M.R. and Quirk, G.J. (2012) Fear extinction as a model for translational neuroscience: ten years of progress. *Annu. Rev. Psychol.* 63, 129–151
21 Phelps, E.A. and LeDoux, J.E. (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 48, 175–187
22 Stein, M.B. *et al.* (2002) Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. *Am. J. Psychiatry* 159, 1675–1681
23 Sartor, C.E. *et al.* (2011) Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychol. Med.* 41, 1497–1505
24 Norrholm, S.D. and Ressler, K.J. (2009) Genetics of anxiety and trauma-related disorders. *Neuroscience* 164, 272–287
25 Amstadter, A.B. *et al.* (2009) Genetics of PTSD: fear conditioning as a model for future research. *Psychiatr. Ann.* 39, 358–367
26 Broekman, B.F. *et al.* (2007) The genetic background to PTSD. *Neurosci. Biobehav. Rev.* 31, 348–362

27 Koenen, K.C. (2007) Genetics of posttraumatic stress disorder: review and recommendations for future studies. *J. Trauma. Stress* 20, 737–750
28 Lesch, K.P. *et al.* (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274, 1527–1531
29 Schinka, J.A. *et al.* (2004) A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. *Mol. Psychiatry* 9, 197–202
30 Lee, H.J. *et al.* (2005) Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. *Depress. Anxiety* 21, 135–139
31 Wang, Z. *et al.* (2011) The relationship between combat-related posttraumatic stress disorder and the 5-HTTLPR/rs25531 polymorphism. *Depress. Anxiety* 28, 1067–1073
32 Kolassa, I.T. *et al.* (2010) Association study of trauma load and SLC6A4 promoter polymorphism in posttraumatic stress disorder: evidence from survivors of the Rwandan genocide. *J. Clin. Psychiatry* 71, 543–547
33 Kilpatrick, D.G. *et al.* (2007) The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *Am. J. Psychiatry* 164, 1693–1699
34 Koenen, K.C. *et al.* (2009) Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. *Am. J. Epidemiol.* 169, 704–711
35 Xie, P. *et al.* (2009) Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. *Arch. Gen. Psychiatry* 66, 1201–1209
36 Xie, P. *et al.* (2012) Serotonin transporter 5-HTTLPR genotype moderates the effects of childhood adversity on posttraumatic stress disorder risk: a replication study. *Am. J. Med. Genet. Part B: Neuropsychiatr. Genet.* 159B, 644–652
37 Grabe, H.J. *et al.* (2009) Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population. *Am. J. Psychiatry* 166, 926–933
38 Thakur, G.A. *et al.* (2009) Development and persistence of posttraumatic stress disorder and the 5-HTTLPR polymorphism. *J. Trauma. Stress* 22, 240–243
39 Schulz-Heik, R.J. *et al.* (2011) Catechol-O-methyltransferase Val158Met polymorphism moderates anterior cingulate volume in posttraumatic stress disorder. *Biol. Psychiatry* 70, 1091–1096
40 Yavich, L. *et al.* (2007) Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J. Neurosci.* 27, 10196–10209
41 Morey, R.A. *et al.* (2011) Serotonin transporter gene polymorphisms and brain function during emotional distraction from cognitive processing in posttraumatic stress disorder. *BMC Psychiatry* 11, 76
42 Pezawas, L. *et al.* (2005) 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: a genetic susceptibility mechanism for depression. *Nat. Neurosci.* 8, 828–834
43 Hariri, A.R. *et al.* (2002) Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297, 400–403
44 Graham, B.M. and Milad, M.R. (2011) The study of fear extinction: implications for anxiety disorders. *Am. J. Psychiatry* 168, 1255–1265
45 Drabant, E.M. *et al.* (2012) Neural mechanisms underlying 5-HTTLPR-related sensitivity to acute stress. *Am. J. Psychiatry* 169, 397–405
46 Lanius, R. *et al.* (2010) *The Impact of Early Life Trauma on Health and Disease*. Cambridge University Press
47 Bremner, J.D. *et al.* (1993) Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. *Am. J. Psychiatry* 150, 235–239
48 Pechtel, P. and Pizzagalli, D.A. (2011) Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology* 214, 55–70
49 McCrory, E. *et al.* (2011) The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Front. Psychiatry* 2, 48
50 Mehta, M.A. *et al.* (2009) Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *J. Child Psychol. Psychiatry* 50, 943–951
51 Tottenham, N. *et al.* (2010) Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev. Sci.* 13, 46–61
52 Lupien, S.J. *et al.* (2011) Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proc. Natl. Acad. Sci. U.S.A.* 108, 14324–14329
53 Maheu, F.S. *et al.* (2010) A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cogn. Affect. Behav. Neurosci.* 10, 34–49
54 Tottenham, N. *et al.* (2011) Elevated amygdala response to faces following early deprivation. *Dev. Sci.* 14, 190–204
55 Ono, M. *et al.* (2008) Early weaning induces anxiety and precocious myelination in the anterior part of the basolateral amygdala of male Balb/c mice. *Neuroscience* 156, 1103–1110
56 Sanders, B.J. and Anticevic, A. (2007) Maternal separation enhances neuronal activation and cardiovascular responses to acute stress in borderline hypertensive rats. *Behav. Brain Res.* 183, 25–30
57 Heim, C. and Nemeroff, C.B. (2001) The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry* 49, 1023–1039
58 Bremner, J.D. *et al.* (1997) Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse: a preliminary report. *Biol. Psychiatry* 41, 23–32
59 Bremner, J.D. *et al.* (2003) MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am. J. Psychiatry* 160, 924–932
60 Dannlowski, U. *et al.* (2012) Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol. Psychiatry* 71, 286–293
61 Dannlowski, U. *et al.* (2012) Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. *Hum. Brain Mapp.* http://dx.doi.org/10.1002/hbm.22112
62 Ressler, K.J. *et al.* (2011) Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature* 470, 492–497
63 Klengel, T. *et al.* (2013) Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions. *Nat. Neurosci.* 16, 33–41
64 Scheeringa, M.S. *et al.* (2005) Predictive validity in a prospective follow-up of PTSD in preschool children. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 899–906
65 Frodl, T. *et al.* (2012) Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. *J. Psychiatry Neurosci.* 37, 37–45
66 Amico, F. *et al.* (2012) Functional anomalies in healthy individuals with a first degree family history of major depressive disorder. *Biol. Mood Anxiety Disord.* 2, 1
67 Gilbertson, M.W. *et al.* (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat. Neurosci.* 5, 1242–1247
68 Kasai, K. *et al.* (2008) Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biol. Psychiatry* 63, 550–556
69 Shin, L.M. *et al.* (2009) Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. *Arch. Gen. Psychiatry* 66, 1099–1107
70 Shin, L.M. *et al.* (2011) Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. *Am. J. Psychiatry* 168, 979–985
71 Daniels, J.K. *et al.* (2012) Neural and behavioral correlates of peritraumatic dissociation in an acutely traumatized sample. *J. Clin. Psychiatry* 73, 420–426
72 Daniels, J.K. *et al.* (2012) Neural correlates and predictive power of trait resilience in an acutely traumatized sample: a pilot investigation. *J. Clin. Psychiatry* 73, 327–332
73 Bonne, O. *et al.* (2001) Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am. J. Psychiatry* 158, 1248–1251

74 Kremen, W.S. *et al.* (2012) Twin studies of posttraumatic stress disorder: differentiating vulnerability factors from sequelae. *Neuropharmacology* 62, 647–653
75 Admon, R. *et al.* (2013) Imbalanced neural responsivity to risk and reward indicates stress vulnerability in humans. *Cereb. Cortex* 23, 28–35
76 Admon, R. *et al.* (2009) Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. *Proc. Natl. Acad. Sci. U.S.A.* 106, 14120–14125
77 Admon, R. *et al.* (2012) Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. *Hum. Brain Mapp.* http://dx.doi.org/10.1002/hbm.22100
78 Sekiguchi, A. *et al.* (2012) Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress. *Mol. Psychiatry* 18, 618–623
79 van Wingen, G.A. *et al.* (2011) Perceived threat predicts the neural sequelae of combat stress. *Mol. Psychiatry* 16, 664–671
80 van Wingen, G.A. *et al.* (2012) The neural consequences of combat stress: long-term follow-up. *Mol. Psychiatry* 17, 116–118
81 Rothbaum, B.O. and Davis, M. (2003) Applying learning principles to the treatment of post-trauma reactions. *Ann. N. Y. Acad. Sci.* 1008, 112–121
82 Otto, M.W. *et al.* (2004) Cognitive-behavioral therapy for the treatment of anxiety disorders. *J. Clin. Psychiatry* 65 (Suppl. 5), 34–41
83 Milad, M.R. *et al.* (2007) Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol. Psychiatry* 62, 446–454
84 Milad, M.R. *et al.* (2009) Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol. Psychiatry* 66, 1075–1082
85 Milad, M.R. *et al.* (2005) Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proc. Natl. Acad. Sci. U.S.A.* 102, 10706–10711
86 Rauch, S.L. *et al.* (2005) Orbitofrontal thickness, retention of fear extinction, and extraversion. *Neuroreport* 16, 1909–1912
87 Hartley, C.A. *et al.* (2011) Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cereb. Cortex* 21, 1954–1962
88 Milad, M.R. *et al.* (2008) Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J. Psychiatr. Res.* 42, 515–520
89 Woon, F.L. and Hedges, D.W. (2008) Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* 18, 729–773
90 Knutson, B. and Gibbs, S.E. (2007) Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology* 191, 813–822
91 Sailer, U. *et al.* (2008) Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. *Neuropsychologia* 46, 2836–2844
92 Elman, I. *et al.* (2009) Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. *Biol. Psychiatry* 66, 1083–1090
93 Pizzagalli, D.A. *et al.* (2009) Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am. J. Psychiatry* 166, 702–710
94 Bleich, A. *et al.* (1997) Post-traumatic stress disorder and depression. An analysis of comorbidity. *Br. J. Psychiatry* 170, 479–482
95 Paulus, M.P. and Stein, M.B. (2006) An insular view of anxiety. *Biol. Psychiatry* 60, 383–387
96 Parsons, R.G. and Ressler, K.J. (2013) Implications of memory modulation for post-traumatic stress and fear disorders. *Nat. Neurosci.* 16, 146–153
97 Kheirbek, M.A. *et al.* (2012) Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. *Nat. Neurosci.* 15, 1613–1620
98 de Kloet, C.S. *et al.* (2006) Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *J. Psychiatr. Res.* 40, 550–567
99 Laufer, O. and Paz, R. (2012) Monetary loss alters perceptual thresholds and compromises future decisions via amygdala and prefrontal networks. *J. Neurosci.* 32, 6304–6311
100 Belova, M.A. *et al.* (2007) Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. *Neuron* 55, 970–984
101 Zaretsky, M. *et al.* (2010) In the eye of the beholder: internally driven uncertainty of danger recruits the amygdala and dorsomedial prefrontal cortex. *J. Cogn. Neurosci.* 22, 2263–2275
102 Pole, N. *et al.* (2009) Prospective prediction of posttraumatic stress disorder symptoms using fear potentiated auditory startle responses. *Biol. Psychiatry* 65, 235–240
103 Rasmussen, D.D. *et al.* (2008) Acoustic startle amplitude predicts vulnerability to develop post-traumatic stress hyper-responsivity and associated plasma corticosterone changes in rats. *Psychoneuroendocrinology* 33, 282–291
104 Smith-Bell, C.A. *et al.* (2012) Predictors of susceptibility and resilience in an animal model of posttraumatic stress disorder. *Behav. Neurosci.* 126, 749–761
105 Zohar, J. *et al.* (2000) Update on the epidemiology, diagnosis, and treatment of posttraumatic stress disorder. *Dialogues Clin. Neurosci.* 2, 37–43
106 Foa, E.B. *et al.* (2000) *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies*. Guilford Press
107 Myers, K.M. *et al.* (2006) Different mechanisms of fear extinction dependent on length of time since fear acquisition. *Learn. Mem.* 13, 216–223
108 Zohar, J. *et al.* (2011) New insights into secondary prevention in post-traumatic stress disorder. *Dialogues Clin. Neurosci.* 13, 301–309
109 Rothbaum, B.O. *et al.* (2012) Early intervention may prevent the development of posttraumatic stress disorder: a randomized pilot civilian study with modified prolonged exposure. *Biol. Psychiatry* 72, 957–963