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

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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, physical, or emotional trauma.

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 conditioned 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. |
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. Connectivit y 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.
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 (vPFC) 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].

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**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 predisposes to 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 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.
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 hyperresponsivity 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 neural 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 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 \times environment interaction

The significance of gene \times environment (G\times 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\times E interaction in PTSD is mediated by specific DNA demethylations affecting gene expression levels [62,63]. Another relevant G\times 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 hyper-sensitivity 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Scientific approach</th>
<th>Subjects (gender, N)</th>
<th>Imaging method</th>
<th>Task</th>
<th>Predisposed vulnerability</th>
<th>Acquired deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>[39]</td>
<td>Genetic</td>
<td>War veterans (M+F; 51, 48)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>ACC volume*</td>
</tr>
<tr>
<td>[41]</td>
<td>Genetic</td>
<td>Post-9/11 veterans (M+F; 22, 20)</td>
<td>fMRI</td>
<td>Trauma-related distractors</td>
<td>Amy and vlPFC function¹</td>
<td>N/A</td>
</tr>
<tr>
<td>[50]</td>
<td>Environmental</td>
<td>Adolescents who experienced orphanage rearing (M+F; 14, 11)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>Amy volume</td>
</tr>
<tr>
<td>[51]</td>
<td>Environmental</td>
<td>Children who experienced orphanage rearing (M+F; 34, 28)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>Amy volume</td>
</tr>
<tr>
<td>[52]</td>
<td>Environmental</td>
<td>Children exposed to maternal depressive symptomatology (M+F; 17, 21)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>Amy volume</td>
</tr>
<tr>
<td>[53]</td>
<td>Environmental</td>
<td>Healthy youths with a history of caregiver deprivation and emotional neglect (M+F;11, 19)</td>
<td>fMRI</td>
<td>Viewing neutral and emotional faces</td>
<td>Amy and HC function</td>
<td>N/A</td>
</tr>
<tr>
<td>[54]</td>
<td>Environmental</td>
<td>Healthy youths who experienced orphanage rearing (M+F; 28, 27)</td>
<td>fMRI</td>
<td>Go/No-go task with fearful and neutral faces</td>
<td>Amy function</td>
<td>N/A</td>
</tr>
<tr>
<td>[60]</td>
<td>Environmental</td>
<td>Healthy adults exposed to various childhood maltreatments (M+F; 145)</td>
<td>MRI and fMRI</td>
<td>Matching threatening angry and fearful faces to a target face</td>
<td>Amy function</td>
<td>HC gray matter volume</td>
</tr>
<tr>
<td>[61]</td>
<td>Environmental</td>
<td>Healthy adults exposed to various childhood maltreatments (M+F; 150)</td>
<td>fMRI</td>
<td>Viewing masked neutral and emotional faces</td>
<td>Amy function</td>
<td>N/A</td>
</tr>
<tr>
<td>[67]</td>
<td>Twin pairs</td>
<td>Vietnam veterans (M; 17, 23)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>HC volume</td>
</tr>
<tr>
<td>[68]</td>
<td>Twin pairs</td>
<td>Vietnam veterans (M; 18,23)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>rACC gray matter density</td>
</tr>
<tr>
<td>[69]</td>
<td>Twin pairs</td>
<td>Vietnam veterans (M; 14, 19)</td>
<td>PET</td>
<td>Rest</td>
<td>dACC function</td>
<td></td>
</tr>
<tr>
<td>[70]</td>
<td>Twin pairs</td>
<td>Vietnam veterans (M; 12, 14)</td>
<td>fMRI</td>
<td>Multi-source interference (cognitive)</td>
<td>dACC function</td>
<td></td>
</tr>
<tr>
<td>[75]</td>
<td>Prospective</td>
<td>IDF soldiers (M+F; 24)</td>
<td>fMRI</td>
<td>Playing a game with threatening and rewarding intervals</td>
<td>Amy function</td>
<td>HC function</td>
</tr>
<tr>
<td>[76]</td>
<td>Prospective</td>
<td>IDF soldiers (M+F; 37)</td>
<td>fMRI</td>
<td>Viewing masked neutral and stress-related pictures</td>
<td>Amy function</td>
<td>HC–vmPFC functional connectivity</td>
</tr>
<tr>
<td>[77]</td>
<td>Prospective</td>
<td>IDF soldiers (M+F; 33)</td>
<td>MRI &amp; DTI</td>
<td>–</td>
<td></td>
<td>HC volume</td>
</tr>
<tr>
<td>[78]</td>
<td>Prospective</td>
<td>Healthy adolescents (M+F; 42)</td>
<td>MRI</td>
<td>–</td>
<td></td>
<td>OPC gray matter volume</td>
</tr>
<tr>
<td>[79]</td>
<td>Prospective</td>
<td>UN soldiers (M+F; 33)</td>
<td>fMRI</td>
<td>Viewing angry and fearful faces</td>
<td>Amy and insula function⁹</td>
<td>Amy–dACC connectivity⁹</td>
</tr>
<tr>
<td>[80]</td>
<td>Prospective</td>
<td>UN soldiers (M+F; 23)</td>
<td>fMRI</td>
<td>Viewing angry and fearful faces</td>
<td>Amy–dACC connectivity⁹</td>
<td></td>
</tr>
</tbody>
</table>

*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.

EIn interaction with dopaminergic polymorphism.

¹In interaction with serotonin transporter polymorphism.

²Not 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
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 3](image-url)  
**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 (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.

![Figure 4](image-url)  
**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 lines), 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 example 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.

**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 appears 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 conditions.
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.

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