Review article

Can Traumatic Stress Alter the Brain? Understanding the Implications of Early Trauma on Brain Development and Learning

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ABSTRACT

Background: Youth who experience traumatic stress and develop post-traumatic symptoms secrete higher levels of the glucocorticoid cortisol than youth with no trauma history. Animal research suggests that excess corticosterone secretion can lead to neurotoxicity in areas of the brain rich in glucocorticoid receptors such as the hippocampus and the prefrontal cortex (PFC). These two areas of the brain are involved in memory processing and executive function, both critical functions of learning.

Methods: In this article, we summarize findings presented at the National Summit for Stress and the Brain conducted at Johns Hopkins University's Department of Public Health in April 2011. The presentation highlighted structural and functional imaging findings in the hippocampus and PFC of youth with post-traumatic stress symptoms (PTSS).

Results: Youth with PTSS have higher levels of cortisol. Prebedtime cortisol levels predict decreases in hippocampal volume longitudinally. Cortisol levels are negatively correlated with volume in the PFC. Functional imaging studies demonstrate reduced hippocampal and PFC activities on tasks of memory and executive function in youth with PTSS when compared with control subjects.

Conclusions: Effective interventions for youth with PTSS should target improved function of frontolimbic networks. Treatment outcome research using these potential markers can help develop more focused interventions that target the impaired learning of vulnerable youth experiencing traumatic stress.

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Our inner cities are plagued by an epidemic of interpersonal violence and trauma that affects our nation's children on a daily basis. If traumatic stress damages the developing brain and impairs the ability for children to learn, this could have important public health and education implications. Studies have shown that children exposed to traumatic stress are more likely to have poorer school performance [1,2], lower reading achievement [3], decreased verbal IQ [4], and more days of school absence [5]. Furthermore, childhood trauma has an impact over the entire lifespan. Although youth exposed to adverse childhood experi-

ences are at greater risk for learning and behavior disorders, adults with a history of adverse childhood experiences have a higher risk for various health issues, including depression, substance use, and suicidality [6,7].

Trauma acts as a threat to an individual's well-being, thereby activating a neurobiological stress response. Although necessary for survival, chronic and frequent physiological stress responses can alter brain development, leading to dysregulation of neural circuitry. Children exposed to traumatic stress may develop post-traumatic stress disorder (PTSD) or its symptoms (PTSS). PTSD is characterized by three clusters of symptoms: re-experiencing symptoms, such as flashback memories; avoidance and emotional numbing symptoms, such as inability to recall the trauma; and hyperarousal symptoms, such as difficulties with concentration. Neuroimaging studies of PTSD in adults have demonstrated the involvement of two key structures in the
pathophysiology of this syndrome: the prefrontal cortex (PFC) and the hippocampus [8].

The Hippocampus

The hippocampus is a medial temporal brain structure in the limbic system that plays an essential role in new learning and memory formation [9]. In healthy individuals, the hippocampus is engaged during encoding and retrieval of information [10]. However, during and after exposure to a traumatic experience, physiological hyperarousal may make memories difficult to regulate. The memories may be processed abnormally, leading to both overrepresentation, such as intrusive thoughts and nightmares, or suppression, inability to recall memories, or selective amnesia. These cognitive manifestations suggest involvement of the hippocampus in the pathophysiology of PTSS, specifically as they relate to learning from previous experience.

Animal research has shown that one potential mechanism of damage to the hippocampus is through corticosterone, the animal analog to cortisol in humans, which can be neurotoxic if secreted in high levels [11]. In studies involving rodents, the number of damaged cells in the hippocampus because of corticosterone exposure was associated with the magnitude of deficits in learning [12].

In human studies of patients with Cushing’s disease, characterized by excessive release of cortisol over long periods, hippocampal volume reductions on neuroimaging have been demonstrated and correlated to deficits in verbal declarative memory [13]. Similarly, in patients with epilepsy who underwent surgical resection of the hippocampus, the reduction in left hippocampal volume correlated with deficits in verbal and visual memory performance [14].

The Prefrontal Cortex

The PFC is an anterior frontal lobe structure that plays an essential role in shifting attention and forming stimuli–response associations, both of which are fundamental cognitive processes that contribute to learning. In healthy individuals, the PFC supports cognitive control—the ability to filter and suppress information and actions in favor of shifting attention to relevant information and responses [15]. The PFC is also important for making the association between stimuli and its rewards, thus contributing to the formation of response–reinforcement associations and guiding goal-directed actions [16].

However, individuals with PTSS may experience difficulties in sustaining attention and can be easily distracted. They may also have difficulties suppressing intrusive memories of the trauma (e.g., flashbacks, nightmares) and extinguishing fear responses. These behavioral manifestations of PFC overlap with the function of PFC, implicating the involvement of PFC in the pathophysiology of PTSD and associated learning impairments.

In support of this hypothesis, animal studies have shown that rats with PFC lesions were unable to extinguish fear responses after fear conditioning, whereas this fear response was easily extinguished when there was no damage to the PFC [17]. Consistent with these animal studies, human imaging studies have shown that PFC is preferentially active during extinction of fear [18]. Similarly, human studies have shown that individuals with lesions to the PFC have deficits in shifting attention and reversal of stimulus–reward associations, cognitive tasks fundamental to academic learning [19,20].

Methods

Magnetic resonance imaging (MRI) studies offer a method of interest to developmental neuroscientists because of their benefits of no radiation exposure and no requirement for contrast. In this article, we present a review of studies presented at the National Summit for Stress and the Brain at Johns Hopkins University’s Department of Public Health in April 2011. Results from studies involving youth with PTSS from our research group that highlight frontolimbic network deficits were presented. A total independent sample of 40 youth with PTSS and 38 age- and gender-matched healthy children was studied across the neuroimaging studies, with 30 of the youth with PTSS and 15 of the healthy children participating in the study on cortisol. Relevant research from other investigators is also highlighted to provide context for interpreting our findings, particularly as to how such deficits may underlie symptomatology and learning difficulties. The Discussion section presents the implications of such findings on the directions for future neuroimaging research in pediatric PTSD.

Results

Table 1 presents a summary of hippocampal and PFC structural and functional imaging findings in youth with PTSS.

The hippocampus

We conducted a longitudinal study to investigate the changes in hippocampus volume and its relationship to cortisol in children who had been exposed to trauma [21]. In a group of 15 children aged between 8 and 14 years who presented with PTSS and a history of trauma exposure, we evaluated their initial PTSS severity and cortisol levels and the changes in their hippocampal volume over a 12- to 18-month interval. We found that greater PTSS severity and prebedtime cortisol levels at baseline predicted greater reduction in hippocampal volume, while controlling for pubertal maturation and gender. This was the first longitudinal study on PTSD to document an association between hippocampal changes with PTSS and with a biological marker of stress.

A later study by our group further investigated differences in the hippocampus functioning during a memory task in traumatized children [22]. We studied a group of 16 youth aged between 10 and 17 years with PTSS and a history of interpersonal trauma in comparison with a group of 11 age- and gender-matched healthy youth, on a Verbal Declarative Memory Task. The memory task requires encoding 40 unique visually presented nouns and retrieving 32 of them 5–10 minutes later. Controlling for IQ, we found that children with PTSS showed reduced activation of the right hippocampus during memory retrieval compared with healthy children, as well as decreased retrieval accuracy on the verbal declarative memory task. Within the PTSS group, the severity of avoidance and emotional numbing symptoms correlated with reduced left hippocampal activation during retrieval. These results suggest that difficulties in memory processing by youth with PTSS may be related to activation deficits of the right hippocampus. Furthermore, our findings implicate the functional disturbance of the hippocampus in the manifestation of avoidance and numbing symptoms, which may include the inability to recall important aspects of the trauma and a restricted range of affect.
<table>
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<td>Hippocampus</td>
<td>Carrion et al [21]</td>
<td>Stress predicts brain changes in children: A pilot longitudinal study on youth stress, PTSD, and the hippocampus</td>
<td>Fifteen children aged between 8 and 14 years with PTSS and a history of trauma exposure</td>
<td>None</td>
<td>Longitudinal study involving clinical evaluation for PTSD, salivary cortisol levels, and structural MRI; analysis of brain volume changes controlled for pubertal maturation and gender</td>
<td>Greater PTSS severity and prebedtime cortisol levels at baseline predicted greater reduction in hippocampal volume over an ensuing 12- to 18-month interval</td>
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<td>Functional</td>
<td>Carrion et al [22]</td>
<td>Reduced hippocampal activity in youth with PTSS: An fMRI study</td>
<td>Sixteen children aged between 10 and 17 years with PTSS and history of interpersonal trauma</td>
<td>Eleven age-matched healthy children with similar gender distribution</td>
<td>An fMRI study comparing the PTSS group with healthy control subjects on brain activation during the Verbal Declarative Memory Task (encoding and retrieving of visually presented nouns) with correlation to PTSD symptoms; analysis controlled for IQ</td>
<td>Children with PTSS showed reduced activation of the right hippocampus during memory retrieval compared with healthy children. Within the PTSS group, the severity of avoidance and emotional-numbing symptoms correlated with reduced left hippocampal activation during retrieval</td>
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<td>Prefrontal cortex</td>
<td>Carrion et al [23]</td>
<td>Attenuation of frontal asymmetry in pediatric PTSS</td>
<td>Twenty four children aged between 7 and 14 years with PTSS and a history of trauma exposure</td>
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<td>MRI study comparing PTSS group with healthy control subjects, with focused analysis of amygdala and hippocampus volumes, controlling for total brain volume</td>
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<td>Structural</td>
<td>Carrion et al [24]</td>
<td>Regional differences of the PFC in pediatric PTSD: An MRI study</td>
<td>Twenty three children aged between 7 and 14 years with PTSS and a history of interpersonal trauma</td>
<td>Twenty four age- and gender-matched healthy children</td>
<td>MRI study comparing regional PFC volumes of PTSS group with healthy control subjects, with correlation to PTSD symptomatology and functional impairment. Analysis controlled for total cranial gray matter volume and comorbid major depressive disorder and ADHD</td>
<td>Children with PTSS showed a larger volume of gray matter in the delineated middle-inferior and ventral regions of the PFC compared with healthy control subjects. Within the PTSS group, greater functional impairment scores were associated with reduced dorsal PFC gray matter volume</td>
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<tr>
<td>Structural</td>
<td>Carrion et al [25]</td>
<td>Decreased prefrontal cortical volume associated with increased bedtime cortisol levels in traumatized youth</td>
<td>Thirty children aged between 10 and 16 years with PTSS and a history of interpersonal trauma</td>
<td>Fifteen age- and gender-matched healthy children</td>
<td>MRI study comparing PTSS group with healthy control subjects on total brain tissue volume and regional PFC volumes areas, with correlation to diurnal cortisol secretion. Analysis controlled for age and IQ</td>
<td>Children with PTSS showed reduced total brain tissue, reduced total cerebral gray volume, and decreased left ventral and left inferior prefrontal gray volumes compared with healthy children. Within the PTSS group, the high prebedtime cortisol levels were associated with reduced left ventral PFC gray volume</td>
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<td>Functional</td>
<td>Carrion et al [26]</td>
<td>PTSS and brain function during a response-inhibition task: An fMRI study in youth</td>
<td>Sixteen medication-naive children with PTSS between 10 and 16 years</td>
<td>Fourteen age- and gender-matched healthy children</td>
<td>fMRI study comparing PTSS group with healthy control subjects on the go/no-go (response-inhibition) task, while controlling for IQ</td>
<td>Children with PTSS showed reduced middle frontal cortical and increased left medial frontal gyrus and anterior cingulate gyrus activation compared with healthy control subjects during response-inhibition. Within the PTSS group, children with self-injurious behaviors had increased insula and orbitofrontal activation compared with children without self-injurious behaviors, with greater insula activation correlated to greater PTSS severity</td>
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PFC = prefrontal cortex; PTSS = post-traumatic stress symptoms; PTSD = post-traumatic stress disorder; fMRI = functional magnetic resonance.
In adults with PTSS, including those with a childhood history of abuse, studies have similarly demonstrated volume reductions and hypoactivation in the hippocampus associated with deficits in memory performance [8,27,28]. However, pediatric studies limited to structural neuroimaging and cross-sectional design have not replicated findings of smaller hippocampus among children [29]. The discrepancy between the longitudinal finding of reduced hippocampus in our recent study and unremarkable cross-sectional studies implicates neurodevelopmental processes that are not observed in the hippocampus early in the course of PTSS. For example, a study of rats exposed to early stress and killed at different ages showed that differences in the hippocampus only emerge after young adulthood [30]. Cortisol likely plays a key role because elevated salivary cortisol levels have been found in maltreated children with PTSD [31], and cortisol can be neurotoxic if secreted in high levels [11]. Indeed, cortisol level differences in individuals with PTSS persist through adulthood with abnormal declines in the context of hypothalamic–pituitary–adrenal axis alterations [32]. Thus, reductions in hippocampus volume secondary to cortisol neurotoxicity may be found only after years of chronic PTSS. In the larger context of hippocampus research in PTSS, our findings suggest that youth with PTSS have deficits in hippocampus structure and functioning, which are associated with impairments in memory processing that may underlie learning difficulties and PTSS associated with maladaptive processing of traumatic memories.

**The prefrontal cortex**

In an early study, we investigated the hypothesis of brain volume differences in children with PTSS [23]. In a group of 24 children between the ages of 7 and 14 years with PTSS and a history of trauma exposure, compared with 24-age- and gender-matched healthy youth, we found that children with PTSS showed attenuation of frontal lobe asymmetry and smaller total brain and cerebral volumes compared with healthy control subjects. Specifically, children in the control group showed significant right more than left differences across the hemispheres, whereas no significant asymmetry in frontal hemisphere volumes was detected for the PTSS subjects.

In a later study assessing 23 children with PTSS and a history of interpersonal trauma, we found that children with PTSS showed a larger volume of gray matter in the delineated middle inferior and ventral regions of the PFC compared with healthy control subjects [24]. Within the PTSS group, greater functional impairment scores were associated with reduced dorsal PFC gray matter volume. This suggests that the neuroanatomy of the dorsal PFC may influence some of the symptoms experienced by children with PTSS.

Having identified frontal structural differences, we sought to understand the functional significance of such findings. In a functional study (functional MRI [fMRI]) of brain activation during a response-inhibition task, we studied 16 children with PTSS in comparison with 14 healthy children [26]. We found that children with PTSS showed reduced middle frontal cortex and increased left medial frontal gyrus and anterior cingulate gyrus activation compared with healthy control subjects during a response-inhibition task. Notably, this region overlaps with the ventromedial PFC, which plays a role in the extinction of a conditioned fear response [33]. This suggests that diminished middle frontal activity and enhanced medial frontal activity during response-inhibition tasks may represent both a neurofunctional marker and a pathophysiological mechanism of development for PTSS. Furthermore, we also found that within the group of children with PTSS, children with self-injurious behaviors had increased insula and orbitofrontal activation compared with children without self-injurious behaviors, with greater insula activation correlated to greater PTSS severity [26]. By implicating a self-injurious subtype of PTSD that may represent a failure of response inhibition associated with more severe PTSS and greater insula activation, this finding suggests that neuroimaging may further our understanding of the heterogeneity in PTSD by identifying clinically relevant biological subtypes.

In a follow-up study, we investigated the relationship of cortisol to PFC function among 30 children with PTSS and a history of interpersonal trauma, in comparison with 15 age- and gender-matched healthy control subjects [25]. We found that children with PTSS showed reduced total brain tissue, reduced total cerebral gray volume, and decreased left ventral and left inferior prefrontal gray volumes compared with healthy children. Furthermore, in the full sample including both PTSS and healthy children, high prebedtime cortisol levels were associated with reduced left ventral PFC gray volume. These findings suggest another link between cortisol secretion after traumatic stress and its neurotoxic effect on brain development, this time in the PFC.

Structural neuroimaging of the PFC among youth with PTSS has repeatedly demonstrated abnormalities, but the direction of regional volume change is inconsistent across studies. As with the association of cortisol with PTSS, time since trauma may moderate the direction of developmental differences. In addition to time-related factors, the inconsistent findings across studies may be related to variations across studies in methodology for volumetric imaging and analysis, in sample demographics of age, developmental stage, and gender, or in clinical history of abuse subtype and PTSS severity. Specifically, in comparing a more recent structural imaging study with an early study, we acquired imaging with a 3.0-T MRI compared with 1.5-T MRI, analyzed volumes using eight PFC subdivisions compared with two, had a demographic sample with a higher ratio of females, greater average age, and Tanner stage, and had a clinical sample with a higher ratio of subthreshold PTSD and physical abuse compared with other trauma subtypes [24,25].

Neuroimaging studies of children with PTSS by other investigators have replicated our findings of abnormalities in PFC structure among children with PTSS. For example, De Bellis et al [34] found reduced white matter volume in the PFC among children with a history of maltreatment. Furthermore, brain abnormalities in the PFC have been consistently demonstrated in studies of adults with PTSS, including reduced volume and hypoactivation during tasks of attention, memory, and emotional cognition [8,35]. Taken together, these findings suggest that youth with PTSS have deficits in key areas of the PFC responsible for cognitive control attention, memory, response inhibition, and emotional reasoning—cognitive tools that may be necessary for learning and therapeutic processing of trauma.

**Discussion**

We presented data supporting anatomical and neurofunctional differences between youth with PTSS secondary to interpersonal trauma and healthy youth. One important question is whether brain abnormalities found in youth with PTSD represent pre-existing risk factors for PTSS, or the consequences of traumatic stress. We found that more severe PTSS and higher cortisol
levels in maltreated children predicted greater hippocampal volume reduction over time [21]. In contrast, Gilbertson et al [36] found that twins of veterans with PTSS, but not exposed to combat trauma, had a reduced hippocampal volume. These studies suggest that a decreased hippocampal volume may be both a risk factor and a consequence of PTSS. This highlights the importance of longitudinal studies that can investigate developmental changes. Furthermore, although research may inform clinical practice more directly in the future, the uncertain significance of neuroimaging markers dictates that current interventions for pediatric trauma should remain targeted toward youth with clinical symptomatology impairing function, rather than youth with particular biological markers.

However, neuroimaging research investigating biological markers may inform clinical practice by promoting development of evidence-based interventions. More specifically, individual interventions can gain empirical evidence by demonstrating an effect on putative biological markers—markers that may represent not only reversible functional impairments but also subtypes of PTSD or predictors of specific treatment response. Notably, using an animal model of PTSD, Hendriksen et al [37] demonstrated that recovery from trauma-induced impairments is associated with cell growth in the hippocampus and alterations in neurotransmitter activity in the PFC and hippocampus. Furthermore, recent studies incorporating neuroimaging in adult PTSD treatment research showed that psychotherapy can modify brain activity in the PFC and associated neural circuits responsible for cognitive control of attention, memory retrieval, and emotional reasoning [38–40]. This small, but growing, body of research suggests that the impact of neuroimaging on treatment—outcome research is promising, by potentially strengthening empirical evidence of treatment efficacy.

In this review, we have identified biological markers of pediatric PTSS including structural and functional abnormalities in the PFC and hippocampus, further associated with abnormal cortisol levels. Such findings suggest that interventions that effectively reduce cortisol levels early in development and improve frontal and limbic function may be particularly effective at facilitating recovery from PTSS and enhance resilience to learning impairments. For example, identifying gaps in a child’s trauma narrative as he or she integrates the experience into history may improve hippocampus function and memory, whereas behavioral interventions that develop cognitive control of attention may enhance prefrontal activity and executive functioning.

Limitations of the current research include a predominance of correlational studies that cannot disentangle causality, and the small sample sizes, although these are representative of neuroimaging studies. Given the few longitudinal and functional imaging studies of youth with PTSS, there is a need for replication of our findings in future research. Further research will need to elucidate whether interventions that improve frontal and limbic activity will translate to improvements in the learning difficulties and symptoms of pediatric PTSD.

References


