

NEUROBIOLOGICAL PROCESSES INVOLVED IN THE STRESS RESPONSE

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Research regarding the neurobiological aspects of PTSD and its development from single and/or multiple traumatic event(s) in childhood is limited to date. Initial findings appear to reflect PTSD in childhood as a different developmental process compared to PTSD in adults. These differences may be reflected in the finding that children appear to be less resilient to trauma than adults. Results of a meta-analysis demonstrated children and adolescents who have experienced trauma are approximately 1.5 times more likely to be diagnosed with PTSD compared to adults (2).

Traumatic stress activates the catecholamine system, i.e. the sympathetic nervous system, leading to increases in heart rate, blood pressure, metabolic rate, and alertness. In addition, during a stress response, corticotropin-releasing hormone (CRH) is released from the hypothalamus, thereby activating the hypothalamic-pituitary-adrenal (HPA) axis by stimulating secretion of adrenocorticotropin (ACTH) from the pituitary. Cortisol is then released from the adrenal glands, further stimulating the sympathetic nervous system during stress. These biological processes are consistent with the “fight-or-flight” response evolutionarily adapted to protect the individual from danger and potential harm but in chronic experience may become counterproductive. HPA regulation eventually leads to restoration of basal cortisol levels via negative feedback inhibition. It is hypothesized that dysregulation of the catecholamine system

and HPA axis in response to stress and trauma may significantly contribute to the negative symptoms of PTSD.

It has generally been hypothesized that early stress on brain development could exert only deleterious effects on neural development. An alternative hypothesis has been proposed, suggesting early stressors can create new developmental pathways, allowing the brain to adapt itself for continued survival and reproduction, despite existence in a stressful environment (1). Nonetheless, elevated levels of catecholamines and dysregulation of the HPA axis associated with stress and trauma appears to lead to adverse neuronal development through a variety of mechanisms. There is evidence of accelerated loss of neurons (3-5), delays in myelination (6), decreased number and length of dendritic processes (7), disruptions in neural pruning (8), inhibition of neurogenesis (9, 10), and decreases in brain-derived neurotrophic factor expression (11). Early stressful experiences have also been shown to have neurobiological structural consequences, such as reduced corpus callosum size, attenuated development of the left neocortex, hippocampus and amygdala, enhanced electrical irritability in limbic structures, and reduced functional activity of the cerebellar vermis (1). Loss of the corpus callosum volume can lead to reduced communication between the hemispheres, and has been shown to produce lateralization that can lead to catecholamine dysregulation. The brain regions effected during stressful experiences appear to have one or more of the following features: a) a prolonged postnatal development, b) a high density of glucocorticoid receptors, and c) some degree of postnatal neurogenesis (1). While the picture at this point is still preliminary, there appears to be increasing evidence that collectively damage to these areas of the brain

can lead to difficulties in social integration, attachment and bonding, as well as mood and anxiety disorders. These features suggest there are potential on-going, developmental consequences to traumatic stress. In order to better understand the neurobiological and psychological sequelae of trauma, it is worthwhile to review neurobiological findings in children at varying developmental stages into adulthood.

THE CATECHOLAMINE SYSTEM AND TRAUMA

There has been significant evidence to suggest maltreated children and adolescents with mood and anxiety symptoms have altered catecholamine levels. Maltreated children with PTSD have been shown to have elevated concentrations of urinary norepinephrine and dopamine over 24 hours compared to non-traumatized children diagnosed with over-anxious disorder and healthy controls, with a significant positive correlation between urinary catecholamine levels and duration of trauma and severity of PTSD symptoms (12). Increased 24-hour urinary norepinephrine concentrations in neglected depressed male children has been reported (13), as well as greater 24-hour urinary catecholamine and catecholamine metabolite concentrations in dysthymic, sexually abused girls (14). This is a consistent finding in adult populations, as adult patients with chronic PTSD have been shown to have increased circulating levels of norepinephrine (15) and increased reactivity of α_2 -adrenergic receptors (16).

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND TRAUMA

The HPA axis has also been implicated in the pathophysiology of PTSD, although current PTSD research reflects conflicting theories regarding the regulation of

the HPA axis in PTSD, both in child and adult populations. Still, it appears some trends in HPA axis research have been identified. For example, most studies of traumatized pediatric populations have found increased basal levels of cortisol, whereas cortisol levels in adult populations with PTSD are generally decreased.

The theory that adults with PTSD have low basal cortisol levels is supported by evidence of lower plasma cortisol levels in adult combat veteran populations with PTSD compared to controls without PTSD (17), and findings of low urinary cortisol excretion in adult holocaust survivor with PTSD compared to holocaust survivors without PTSD (18). It is hypothesized that cortisol levels in adults with chronic PTSD are decreased compared to non-traumatized control subjects due to a down-regulation of anterior pituitary CRH receptors secondary to chronic elevations in CRH levels and also due to an enhanced negative feedback inhibition of cortisol at the level of the pituitary (19). This down-regulation may be an adaptive response, as chronically elevated cortisol levels are potentially neurotoxic. This theory is supported by studies by Yehuda et al. demonstrating combat veterans with PTSD have an exaggerated cortisol suppression following the administration of low dose dexamethasone (an analog of cortisol) and an exaggerated decline of cytosolic lymphocyte glucocorticoid receptors compared to those without PTSD (20). Also compatible with this hypothesis are the findings that individuals with PTSD have high levels of corticotropin-releasing factor (CRF) in their CSF (21), a blunted adrenocorticotrophic hormone (ACTH) response to corticotropin-releasing hormone (CRH) (22), and an enhanced ACTH response to doses of metyrapone suppressing cortisol production (23).

Other studies have not been compatible with the above-mentioned theory regarding PTSD in adults. Specifically, three studies reported elevated 24-hour urinary cortisol excretion in adult patients with PTSD (24-26). In addition, a greater ACTH response to CRF in PTSD compared to control subjects has been reported (27), as well as greater ACTH responses to current psychosocial stress among women with histories of childhood physical and sexual abuse compared to women with no such histories (28). These studies postulate an alternative theory explaining baseline low cortisol levels; such being a chronically low adrenal output of cortisol, or rather, adrenal insufficiency (29). These discrepant findings may be associated with the confounding effects of assay methodology as well as potential current life stressors influencing the regulation of the HPA axis.

Studies of the HPA axis and its regulation following trauma in children have generally demonstrated elevated cortisol levels, suggesting different biological consequences to traumatic stress compared to adult populations. De Bellis et al. reported maltreated prepubertal children diagnosed with PTSD have increased 24-hour urinary cortisol levels compared to matched control subjects (12). Carrion et al. demonstrated significantly elevated salivary cortisol levels in children with trauma exposure histories and PTSD symptoms when compared with control groups (30). Gunnar et al. demonstrated elevated salivary cortisol levels in 6-12 year old children raised in Romanian orphanages for eight months of their lives compared with early adopted and Canadian born children tested at 6.5 years after adoption (31). In a relatively large study, Hart et al. demonstrated depressed maltreated children had

elevated afternoon salivary cortisol levels compared to depressed non-maltreated children (32).

Table 1: Recent HPA Studies of PTSD and Trauma in Children

Study	N	Location	Population	DSM Diagnosis	Findings
Goenjian et al 1996	37 Trauma exposed from 1988 Armenia earthquake (5 years after event)	Armenia	Adolescents	PTSD symptoms	Lower morning salivary cortisol, and greater suppression with dexamethasone challenge
De Bellis et al 1999	18 PTSD 10 Overanxious Disorder (OAD) 24 Control	United States	Ages 8-12 mixed gender	PTSD diagnosis	Urine catecholamines PTSD>OAD=Control
Gunnar et al 2001	18 Romanian orphans (adopted at 8 months) 15 Early adopted (prior to 4 months) 27 Canadian born	Canada / Romania	Ages 6-12	None	Salivary cortisol greater in 8 month institutionalized infants
King et al 2001	— girls with sexual abused histories	United States	Ages 5-7, girls	None	Lower basal cortisol levels than controls
Carrion et al 2002	51 PTSD symptoms 31 Control	United States	Ages 7-14 mixed gender	PTSD symptoms	Salivary cortisol elevated in PTSD>control

In contrast, Goenjian et al. studied adolescents 5 years after the 1988 Armenian earthquake and reported reduced levels of cortisol in children in closest proximity to the disaster (33). Also King et al. found that girls with a history of sexual abuse within the last 2 months had lower cortisol in comparison to control subjects (34). Comparing and interpreting the results of these studies in children, as well as in adult PTSD studies, is limited by varying methodological approaches and differing population samples. While there is no absolute consensus on whether cortisol levels in children with PTSD are elevated or decreased, most studies show an elevation in cortisol levels in children diagnosed with PTSD.

It is possible that some variations in study results could also be explained by examining the developmental stage when trauma occurred as well as the duration of

time elapsed since exposure to trauma in children as well as adults. One could postulate CRH and cortisol levels are elevated acutely after a trauma. Long-term, or rather, developmental effects of trauma could eventually lead to decreased levels of cortisol due to chronic elevations in CRH and the enhanced negative feedback on the HPA axis. This hypothesis is supported by a study comparing pituitary volume differences using magnetic resonance imaging (MRI) in children of varying ages with PTSD and non-traumatized healthy comparison subjects (35). Although there were no differences seen in pituitary volumes between PTSD and control subjects, there was a significant age-by-group effect for PTSD subjects showing greater differences in pituitary volume with age compared to control subjects. Post hoc analyses revealed pituitary volumes were significantly larger in pubertal and post pubertal maltreated subjects with PTSD compared to control subjects, but were similar in prepubertal maltreated subjects with PTSD and control subjects. Pituitary volumes changes in response to stress and dysregulation of the HPA axis have already been demonstrated in various research models. Chronically administering CRH to rats shows an increase in the number and size of pituitary corticotroph cells (36, 37). Also, suicide victims have been shown to have larger pituitary corticotroph cells (38).

Clearly, neurobiological research regarding PTSD in children is only beginning to elucidate the biological effects of trauma. While preliminary data and developing theory regarding HPA regulation in children with PTSD is provocative, it is still with incomplete evidence to date. Further research is needed to clarify HPA regulation in PTSD in children at varying developmental stages.

NEUROANATOMICAL FINDINGS ASSOCIATED WITH TRAUMATIC STRESS

A growing body of evidence is reflecting significant involvement of glucocorticoids (cortisol) and their impact on the hippocampus in a stress response (9). There is significant evidence for hippocampal atrophy in adult populations with PTSD (40-43), Cushing syndrome (characterized by a pathologic oversecretion of glucocorticoids) (44, 45), and recurrent major depressive disorder (46, 47) also frequently associated with oversecretion of glucocorticoids. There is also significant evidence that glucocorticoid toxicity may, in part, be mediated by prolonged elevations in excitatory amino acids such as glutamate (48).

With the use of high-resolution magnetic resonance imaging (MRI), significant hippocampal atrophy has been demonstrated in adult combat veterans with the diagnosis of PTSD compared to control subjects (40, 41). In addition, studies have reported significant left hippocampal volume reduction in adult populations with histories of childhood trauma and a current diagnosis of PTSD (42, 43).

In contrast, studies of children with PTSD have not demonstrated any significant differences in hippocampal volumes compared to normal controls. Carrion et al. did not observe any significant differences in hippocampal volumes between abused children with the diagnosis of PTSD and subthreshold diagnosis of PTSD compared to normal control subjects (49). De Bellis et al. (1999) and in a subsequent study studied hippocampal volumes by MRI in maltreated children with PTSD and healthy controls, finding no significant differences in volume (50, 51). Rather, it was reported subjects with PTSD had smaller intracranial, cerebral, and prefrontal cortex, prefrontal cortical white matter, right temporal lobe volumes, and smaller areas of the corpus callosum.

Teicher et al. found a marked reduction in the middle portions of the corpus callosum in child psychiatric inpatients with a substantiated history of abuse or neglect versus control subjects (52). De Bellis et al. also reported reduced corpus callosum size in children with a history of abuse and PTSD with more notable volume changes in males versus females. This neurobiological finding may be associated with decreased communication between the cortical hemispheres, which may be related to memories difficulties and dissociative disorders, both of which are often found to be co-morbid with PTSD.

There are several possible explanations for the differences in neuroanatomical findings between adult and child populations with diagnoses of PTSD. One possibility may be associated with the fact that many adults with PTSD have comorbid substance use disorders and reduced hippocampal volumes may be associated with this alcohol and/or drug use. De Bellis et al has demonstrated a decrease in hippocampal volumes in adolescent-onset alcohol abuse (53). Yet neuroimaging studies described in adults have continued to reflect significant hippocampal volume changes even after matching controls for years of substance use (41, 42) or adjusting volume changes for cumulative alcohol exposure (40, 43).

Another possible cause of these discrepancies could be that neurobiological findings may take time to present, suggesting the stress response is gradual and progressive in nature. The hippocampus, as well as other brain structures, is known to have continued neurogenesis postnatally. In addition, the hippocampus has been shown to have an overproduction of axonal and dendritic arborization, as well as synapses and receptors, which are not pruned and eliminated until the postpubertal

period (54-56). Animal models suggest that psychological and physical stress produce measurable changes in brain-derived neurotrophic factor (BDNF) which has effects on neurogenesis and prevention of apoptosis (57). Cumulatively, these findings suggest that the effects of childhood trauma could have ongoing developmental implications on brain structure and function. Traumatic injury could therefore be partially dependent on the individual's stage of postnatal neural development.

A third possibility may be that the neurobiological finding of a smaller hippocampal volume is actually not a result of chronic stress, but rather is a predisposition for the development of PTSD. This is supported by a study comparing monozygotic twin veterans and normal control subjects. It was found that combat veterans with PTSD, as well as their identical twin without exposure to trauma, both had smaller hippocampi compared to normal, non-traumatized controls. In addition, veterans with PTSD had significantly smaller hippocampal volumes compared to their non-traumatized twins (58). This may suggest smaller hippocampal volumes may be a both predisposition to the development of PTSD as well as an effect of trauma in adults.

The majority of research involving metabolic activity of the brain in PTSD has been conducted in adult populations although there are a few recent studies in children as well. Positron-emission tomography and functional magnetic resonance imaging have shown increased reactivity in the amygdala and anterior paralimbic region (59, 60) and decreased reactivity in the anterior cingulate and orbitofrontal areas in adults who have experienced childhood sexual abuse while reading trauma-related scripts (61). Preliminary studies in child populations with PTSD have reported some similar metabolic activity, implicating specific brain areas as metabolically affected in PTSD.

Using proton magnetic resonance spectroscopy, De Bellis et al. found a decreased ratio of N-acetylaspartate to creatine in the anterior cingulate in 11 maltreated children and adolescents with PTSD compared to control subjects, suggesting the anterior cingulate's metabolism is altered in childhood PTSD (62). Of note, these brain areas described have been implicated in the fear response.

One caveat to these studies must be noted. Functional imaging studies are labor intensive to produce, and have yield interesting preliminary data, but to this point the sample sizes are generally small, number less than twenty in the best studies. The data emerging must therefore be interpreted with caution, and clinicians are strongly discouraged at this point from using imaging techniques as the sole or primary basis for diagnosis. Expense, expertise and the need to interpret images very carefully are cautionary flags for the practicing clinician. In contrast, these cautions need not extend to the endocrine literature that is much better established, and represent a long history of research with some degree of clinical correlation. But here again, the diagnostic value of this information still remains in doubt and only further studies will shed light on these complex pathways and their utility in practice.

Research on the neurobiological and neuroanatomical effects of PTSD from single and/or multiple traumatic event(s) in childhood is limited to date. Initial findings may appear to demonstrate PTSD in childhood as a different developmental process compared to PTSD in adults with potentially evolving neurobiological consequences during the course of an individual's early life. It is important to consider the likelihood of prolonged effects from childhood trauma, not only impacting the development of coping strategies, impact on interpersonal relationships and academic performance, but also

the neurobiological effects in children and adolescent populations. These neurobiological effects may indeed demonstrate significant impact on behavior and cognition, and may in part be influenced by the neurobiological developmental stages in children and adolescents. Further research is needed to clarify these complexities in PTSD development in childhood through adolescence and into young adulthood.

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