Berkeley Pharma Tech
Journal of Medicine

Adolescent Brain Development Under Stress and Trauma: Evidence-Based Treatments

By: Isabelle Pappas, Tzung Yu, Olivia Liu and Nainika Srinivasan

Correspondence:
isabelle.pappas02@gmail.com

Keywords:
PTSD
Brain Development
Stress
Trauma
Adolescents
Neurodevelopment Neuroimaging
Youth

Published July 31, 2025

Full Open Access

Abstract

The developing adolescent brain is particularly susceptible to the effects of stress and trauma which can result in long-lasting morphological and psychological effects. This review paper aims to highlight the important changes caused by childhood stress and trauma, outline current treatments, and provide insight into future research directions. Studies suggest that exposure to stressors and traumatic events at a young age increases overall volume in the amygdala while decreasing volume in the hippocampus and frontocortical regions. However, due to a discrepancy in results, there is a need for future studies to control for age-based and trauma differences. Additionally, analysis of commonly used treatments reveals that a combination of therapeutic approaches, hormonal treatments, and lifestyle changes is generally most effective to address both underlying mechanisms and psychological effects. Ultimately, studies show that adolescent stress and trauma leads to significant hormonal and morphological changes in the brain that result in psychological changes such as anxiety and depressive symptoms.

1. Introduction

Trauma is defined as an experience that triggers intense physical and psychological stress reactions, including heightened arousal, intrusive thoughts, and emotional numbness. The stress induced by trauma releases hormones like cortisol which can disrupt bodily systems and is associated with increased risk of anxiety, depression, and Post-Traumatic Stress Disorder (PTSD).[1] Researchers often model trauma in test subjects using chronic variable or restraint stress, enabling the study of these impacts.[2]

A severe outcome of trauma is PTSD, characterized by abnormalities in frontolimbic circuitry that result in increased threat sensitivity and reduced emotional regulation.[3] PTSD is linked to poor academic performance, higher rates of depression, suicide attempts, and substance abuse.[3] In adults, PTSD manifests through symptoms like flashbacks, avoidance, hyperarousal, and mood changes.[4]

Adolescent development is a time of significant psychological and physiological vulnerabilities. For instance, there are significant volumetric increases in the hippocampus and amygdala in the early stages of puberty.[2] Furthermore, there are periods of cortical thinning in the frontal and temporal cortical volumes during adolescence following the initial increase in volume during childhood.[2] These are regions intimately involved in emotional and cognitive processes, and it can be inferred that alterations to the developmental process of these brain regions would affect the emotional and cognitive abilities of the individual; however, the precise nature of this structure-function relationship in the adolescent brain is unclear. [5]

In animal models, particularly mouse models, adolescence is also marked by increased hippocampal volume and vulnerability to stress, making this period of development particularly vulnerable to the morphological changes that result from stress and trauma. Mouse models are particularly useful because of their genetic similarity to humans and the ability to control their environmental factors. Exposure to stressful stimuli in adolescent mice (between 5 and 7 weeks old) results in short term as well as long term morphological changes in their brains, suggesting similar results for

adolescent humans.[6] Behaviorally, mice exhibit impaired cognitive functions and social withdrawal, which mirror the psychological effects of stress in adolescent humans. Thus, mouse models can allow researchers to identify biological indicators of disorders caused by stress. Additionally, the mouse models can aid physician scientists in developing the most effective treatment plans to mitigate the adverse effects of stress and trauma.

The impact of trauma is most pronounced during adolescence, affecting critical brain regions at specific ages: the hippocampus at 14, the amygdala between 10 and 11, and the prefrontal cortex between 14 and 16.[3] Adolescents exhibit higher stress reactivity, with stress hormones like ACTH and corticosterone taking longer to normalize post-stress compared to adults.[2] This necessitates study and prevention of abuse and trauma for adolescents due to the vulnerable nature of that time period and the long term effects these changes can have on the psychology of these individuals.

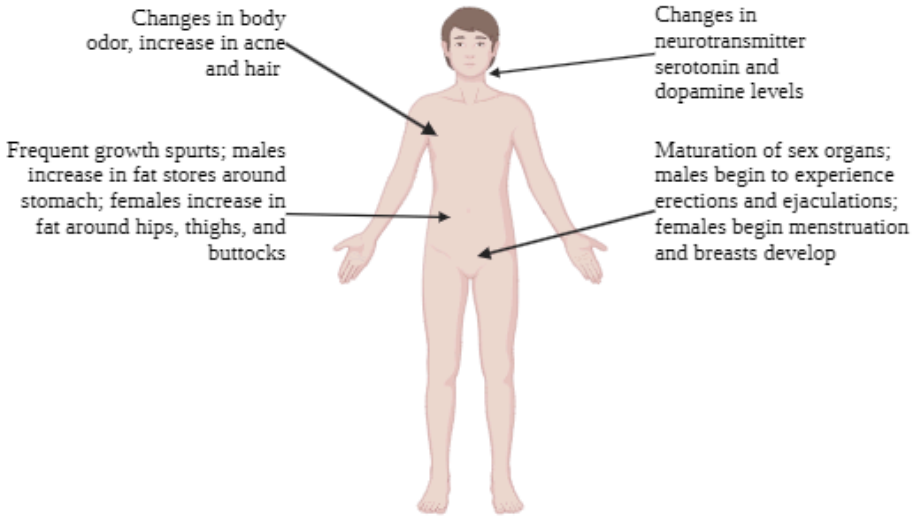


Figure 1. Physical changes characteristic of adolescence in humans.

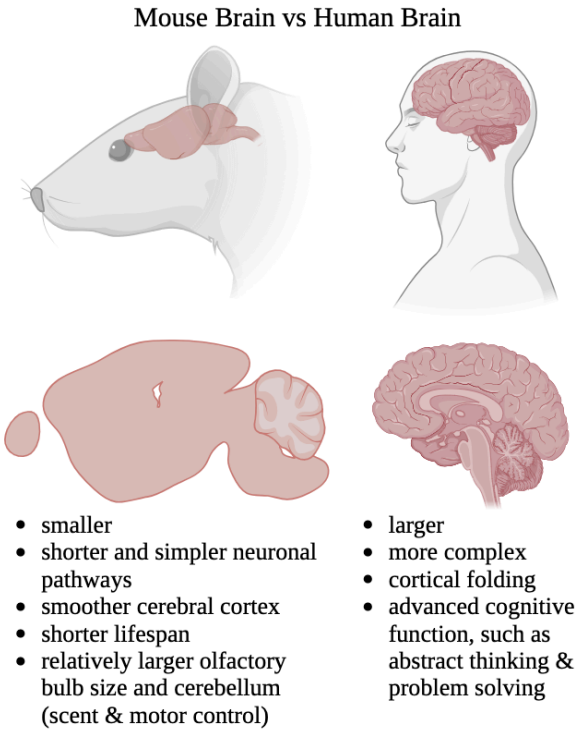


Figure 2. Physical characteristics of mice (left) vs. human (right) brains. Mice models are commonly used for the studies reviewed in this paper.

2. Morphological and Psychological Effects

2.1 Amygdala

The amygdala, critical for emotional reactivity and cognitive processes such as memory, possesses a high concentration of glucocorticoid receptors that causes it to be susceptible to stress.[7,8] During postnatal development, the amygdala undergoes a period of rapid growth which peaks during ages 9-11 and diminishes.[9] These changes highlight the importance of the amygdala in studies regarding adolescent stress and trauma.

Childhood trauma and adversity have been found to be correlated with heightened amygdala reactivity to negative stimuli in functional magnetic resonance imaging (fMRI) studies of both healthy and psychiatric youth.[10–12] In addition, amygdala hyperactivation in youth with PTSD compared to healthy youth has also been reported, similar to the hyperactivation in adult PTSD.[11,13–15] On the other hand, many studies also

report no difference in amygdala hyperactivation.[16–18] This contrast in findings may be due to a delayed expression of amygdala hyperactivation until adulthood, as shown when analyzing amygdala activation using age-related differences demonstrates that typically developing youth show decreased activation with age whereas youth with PTSD have increased activation with age.[19] The same authors established that amygdala activation in youth with PTSD was lower at ages below 15 years compared to healthy youth, possibly due to younger children compensating for stress by downregulating amygdala activity, but this becomes less effective as they age.

Amygdala hypertrophy caused by childhood trauma is expressed in adulthood. In a longitudinal sample, adult subjects exposed to maltreatment had higher right and left amygdala volumes than healthy controls.[20] Furthermore, by using the Maltreatment and Abuse Chronology of Exposure Scale, it was revealed that the right amygdala undergoes a sensitive period during 10-11 years, becoming prone to enlargement from exposure to maltreatment.[21] Interestingly, even small amounts of maltreatment in healthy controls triggered hypertrophy during this sensitive period, despite not meeting the threshold for moderate exposure. Left amygdala volume was also shown to be correlated to attachment disruption at 18 months.[1] This underscores the susceptibility of the amygdala to stress and trauma during youth development and highlights the need for further understanding in this topic.

In rats, early life stress exposure led to increased amygdala volume and reactivity for prolonged periods of time.[22–24] Developing rats exposed to restraint stress exhibited an increase in dendrite complexity and frequent, spontaneous neuron firing in the basolateral amygdala which resulted in amygdala hypertrophy.[25,26] Further studies found that exposure to psychological stress or stress hormone lead to increased excitability and spine formation on pyramidal cells, a basis for exhibiting anxiety-like behaviors.[27–29] Additionally, studies have shown that development of threat learning occurred earlier in rodents exposed to early life stress compared to the controls.[30] This evidence supports previous trials indicating an association with early life stress and enhanced threat bias in youth.[23] These findings suggest that hyperreactive amygdala in adolescents exposed to

trauma and stress may be of evolutionary advantage to detect threat. Similarly, chronic restraint stress during adolescence also resulted in short-term difficulties unlearning fear responses, such as freezing, which disappeared in the long term.[26,31] However, when adolescent and adult rats were exposed to corticosterone as a chronic stressor, only adolescents had impaired extinction retention, showing the importance of sensitive periods during development.[32]

2.2 Hippocampus

The hippocampus, which plays key roles in memory, learning, and emotion, grows rapidly during adolescence.[33] Additionally, this region is densely populated with glucocorticoid receptors, causing it to be highly susceptible to the increased levels of glucocorticoids due to childhood maltreatment.[34] Studies have shown that high exposure to glucocorticoids can lead to changes in hippocampus regions, such as reversible atrophy of dendritic processes in the cornu ammonis and suppression of neurogenesis in the dentate gyrus.[35] Due to the rapid development and sensitivity to stress hormones of the hippocampus, this region is important in our understanding of the effects of childhood trauma and stress.

Current literature proposes that childhood stress and trauma are associated with lower volume of the hippocampus, aligning with the reduced hippocampal volume present in adult PTSD.[36] One study on patients with childhood PTSD concluded a significant 12% reduction in left hippocampal volume compared with typically developing controls.[37] Another paper analyzing structural MRI images determined that childhood trauma was associated with less gray matter in the hippocampus.[38] However, some report that hippocampal volume is not altered between youth with PTSD and typically developing youth. For example, multiple studies have found no significant reduction in hippocampal volume in children with PTSD.[39–41] One possible explanation for the discrepancy between these studies is that, similar to the amygdala, the hippocampus has delayed onset of reduced volume. For instance, analyses show that subjects in studies reporting no significant reduction had a mean age of 11.26 years whereas studies reporting significant hippocampus reduction had a mean age of

12.65 years, suggesting that there is a silent period between maltreatment and neurobiological effects.[42] Additionally, when analyzing differences using age-related differences, hippocampal volume increased in typically developing youth but decreased in PTSD youth with age.[3]

Rodent studies have also shown impaired hippocampus growth. One study reported that chronic restraint stress on both male and female adolescent rats resulted in lowered dendrite complexity of pyramidal neurons in the hippocampus compared to controls.[25] Rats exposed to stress also exhibited depressive behaviors. In another study, male rats that were exposed to chronic stress during adolescence exhibited short-term increase in hippocampal growth in the CA1 region only.[43] However, a later examination revealed a significant long-term decrease in CA1 and DG regions and CA3 growth arrested. These structural changes correlated with impaired abilities in navigation which demonstrates that adolescent stress can significantly change brain structure and function in the long-term.

2.3 Frontocortical Regions

2.3.1 Prefrontal Cortex

The prefrontal cortex (PFC) is a region of the brain that controls complex processes such as emotion, thought, and actions. Studies have analyzed MRI images and found that gray matter in the frontal lobe increased during adolescence.[44] Growth peaked at 12.1 years for males and 11.0 years for females then decreased during post-adolescence. Additionally, past literature has stated that the PFC is particularly vulnerable to stress-induced morphological changes which makes it important to understand changes in the PFC from stress and trauma in developing youth.[45]

Youth with PTSD have shown a decreased volume in the PFC compared to typically developing youth. For example, multiple articles found decreased gray matter volume in the right ventromedial prefrontal cortex (vmPFC), bilateral ventrolateral prefrontal cortex (vlPFC), dorsomedial prefrontal cortex (dmPFC), and dorsolateral prefrontal cortex (dlPFC)[11,46,47] while other studies report increased gray matter in the vmPFC, vlPFC, dmPFC, and dlPFC in individuals with childhood trauma.[16,17,19,38,48] One possible explanation for this disparity could be differences in sample PTSD severity,

trauma-related factors, or age-related differences. Studies that report a decrease in gray volume also note that lower left ventral and left inferior prefrontal matter are associated with higher cortisol levels.[49] Additionally, childhood PTSD was found to be associated with loss of neuronal integrity in the PFC.[47] These results demonstrate the need to further investigate the underlying mechanisms and contributing factors to better understand the impact of PTSD on brain development and to develop targeted intervention strategies.

Studies using rodent models have achieved similar results. When chronic restraint stress is applied to adolescent rats, those exposed to stress had reduced PFC dendrite complexity in pyramidal neurons.[25] The same protocol combined with early weaning caused rats to show decreased PFC neuronal activity in stress-inducing environments.[50] Furthermore, social isolation rearing led to decreased spine density, dendritic branching in pyramidal neurons, and volume in the PFC.[51–54] Exposure to isolation stress also resulted in lasting lower concentrations of proteins spinophilin, synaptophysin, and myelin basic protein in the PFC of adolescent rats.[55] Post-adolescent rats that were exposed to isolation stress in childhood exhibited down-regulation of immediate early genes and genes that regulate differentiation and apoptosis in the medial PFC.[56] These genetic changes were associated with the degree of hyperlocomotion and social isolation in stressed rats which offers a molecular basis for anxiety-like behaviors expressed in individuals exposed to stress and trauma.

2.3.2 Anterior Cingulate Cortex

The anterior cingulate cortex (ACC) regulates emotions, motivation, cognition, and motor abilities during conflict. Due to the importance of the ACC in body processes, it is crucial for us to further understand the effects of stress and trauma on its development during adolescence. Previous studies have found that the dorsal ACC becomes hyperactivated when exposed to threat and emotional pictures in youth with PTSD.[18,19] However, this contrasts with dorsal ACC becoming hypoactivated in adults with PTSD which could be due to overcompensating for emotional regulation during adolescence which fades with age.[57] Moreover, reduced gray matter in the ACC has been associated with maltreatment during

adolescence.[58] Since ACC volume has been correlated with depressive symptoms, there is an urgent need for more understanding of trauma effects on this region of the brain.[59]

2.4 Corpus Callosum

The corpus callosum connects the left and right brain hemispheres and allows them to communicate and coordinate actions. Studies show that children who have PTSD or suffered abuse have a smaller corpus callosum than controls.[4] For example, multiple studies have reported an association between maltreatment and a significant reduction in corpus callosum volume, specifically higher in adolescent male samples than females.[39,60–63] This may be due to males having a larger sensitive period lasting throughout infancy and early childhood. Notably, one study reported that at corpus callosum segments II and III, adolescents with low risk of mental disorders had the greatest fractional anisotropy followed by controls then adolescents with high risk.[64] These results demonstrate the possibility that corpus callosum size may indicate vulnerability to mental disorders. However, analysis on the Bucharest Early Intervention Project demonstrated that significant reductions in the corpus callosum were mitigated when orphans were placed in foster care compared to those who remained in institutions.[65] These findings are particularly impactful since they demonstrate the potential irreversibility of the damage to the corpus callosum caused by stress and trauma.

2.5 Larger Scale Effects

2.5.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis

During adolescence, the Hypothalamic-Pituitary-Adrenal (HPA) axis undergoes significant growth and developmental changes. The HPA axis is intricately intertwined with the hypothalamic-pituitary-gonadal (HPG) axis which releases more gonadal steroids, triggering the onset of puberty. HPA activity is influenced by the HPG Axis, resulting in heightened activity along with an increase in mineralocorticoid and glucocorticoid receptors in the hippocampus during this particular period of development.[66] Basal activity of the HPA axis, characterized as the resting rate of hormones associated with this axis, increases during adolescence. This increase in basal

activity results in hypersensitivity and reactivity to stimuli, which can make adolescents particularly vulnerable to traumatic experiences.[67]

In rodent models, stress results in higher levels of adrenocorticotropic hormone (ACTH) and cortisone which last longer during periods of adolescence than during adulthood. Studies have revealed sex-specific changes in the HPA axis due to stress in adolescent rodent models. For example, "males that have been subjected to adolescent isolation have lower corticosterone responses to restraint stress compared with controls, whereas females develop greater restraint-induced corticosterone responses."[67] Additionally, rats that are exposed to repeated stressful environments, such as prolonged isolation, exhibit an increase in hormonal reactivity after being paired with a foreign cagemate. Prolonged exposure to stress can also lead to habituation or desensitization of the HPA axis in rodent models, which suggests that the same can occur in adolescent humans under conditions of chronic stress and trauma. Maladaptive changes, such as hyperactivity or subdued activity of the HPA axis, can make adolescents more vulnerable to mental health disorders, such as anxiety and depression.

2.5.2 The Dopaminergic System

The dopaminergic system is involved in the regulation of motor, cognitive, and motivational brain regions.[68] Furthermore, dopamine (DA) modulates emotional processing at multiple levels, which affects the amygdala, medial temporal lobe, and prefrontal cortex.[69] The dopaminergic system has three main dopaminergic pathways, affecting regions of the brain spanning the prefrontal cortex and midbrain.[70] In rats, the development of this system has several maturation steps. Firstly, the activity and levels of DA and 3,4-dihydroxyphenylacetic acid rises in the nucleus accumbens and striatum at postnatal day (PD) 28, which remains constant until adulthood [71]. DA synthesis and turnover increases in the PFC at approximately PD 30 but decreases after several days.[72–75] DA fibers mature earlier in the striatum and nucleus accumbens (~PD 35) compared to projections in the PFC.[76–78] D1 and D2 receptor densities peak at PD 28 in the nucleus accumbens and striatum, and peak in the PFC at around PD 40-60.[78–83]

There are changes to the DA system during adolescence that make it particularly sensitive to the effects of stress.[67] For example, extracellular DA levels in the dorsal and ventral striatum are lower during adolescence, while DA activity in the PFC peaks during adolescence.[84] This can also be seen when rats were subjected to social isolation rearing, where several effects on the DA system were observed. There was an increase in the in vivo firing rate and burst-like activity of putative DA neurons in the ventral tegmental area (PD 25-90),[85] DA release and DA transporter activity was increased in the nucleus accumbens and dorsomedial striatum (PD 28-77),[86] and DA innervation and turnover decreased in the mPFC (starting from PD 21-28).[76,87,88]

Furthermore, during adolescent social isolation rearing, DA activity and turnover increased in the nucleus accumbens.[76,77,89,90] DA levels declined in the PFC in adulthood after repeated prolonged social isolation episodes in periadolescent mice (PD 15-21).[91] The predator odor model in adolescent mice also showed decreased levels of D2 receptors in the mPFC.[92] There was also lower basal tissue and extracellular DA levels and upregulated DA transporters in the PFC as a result of social defeat stress.[93–96] Restraint stress and footshock increased responsivity of VTA DA neurons in adults when adolescent rats (PD 31-40) were exposed to these stressors.[97] Lastly, DA levels in the mPFC were elevated in adulthood as a result of chronic variable physical stressors during adolescence (PD 27-33).[98]

2.5.3 Default Mode, Salience, and Central Executive Networks

Recent research has highlighted the significant impact of larger brain networks in PTSD, extending the frontolimbic model to include key networks such as the default mode network (DMN) for self-referential thought, the salience network (SN) for detecting relevant cues, and the central executive network (CEN) for goal-directed behavior and emotion regulation.[99] Typically, the DMN and CEN function in opposition, switching between internal processing and external tasks.

In adult PTSD, studies show increased SN activity, decreased DMN and CEN activity, and poor regulation between the CEN and DMN, which may explain symptoms like hypervigilance and poor emotion regulation.[100]

Pediatric PTSD research suggests a hyperactive SN and decreased CEN engagement as children age, though large-scale network function studies in this group are limited. Initial research in youth with PTSD indicates increased DMN connectivity and greater anti-correlation between the DMN and CEN/SN compared to adults.[101] Stronger CEN/SN connectivity correlates with fewer re-experiencing symptoms, suggesting compensatory use of executive control systems, which might also contribute to dissociative symptoms. However, additional research is required to understand network function in pediatric PTSD and its development over time.

During acute stress, connectivity increases between DMN and CEN regions while decreasing between the SN and both DMN and CEN.[102] Greater polyvictimization is associated with reduced connectivity between the DMN and the left insula of the SN, potentially disrupting emotion regulation. Further studies are necessary to clarify these dynamics and their impact on PTSD symptoms in youth.

2.6 Brain Region Connectivity

2.6.1 Changes and importance of neuroplasticity

Neuroplasticity is the ability for the brain to form and reorganize synaptic connections following learning, experience, or injury. This is particularly important during development since stress strongly impacts social interactions and behaviors in developing adolescents, magnifying negative effects on neuroplasticity due to social isolation.[103] Studies have found stress to impact the ability to develop neurons during adolescence. In two experiments, female rats exposed to chronic restraint stress or social instability during adolescence exhibited lower levels of neurogenesis in contrast to another study that reported increased neurogenesis in males.[104–106] Interestingly, levels of brain-derived neurotrophic factor as well as neurogenesis was reduced in mildly-stressed adult animals but increased in adolescents.[106] Due to this discrepancy, more studies are needed to determine the short and long-term effects of stress and trauma on neuroplasticity in male and female adolescents.

2.6.2 Alterations in brain region connectivity

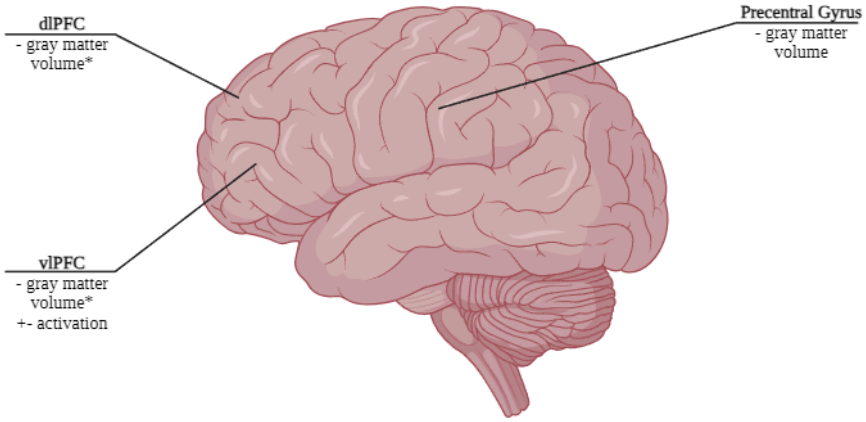
Previous studies have found changes in connectivity between various brain regions in adolescents exposed to stress and trauma.

For example, less coupling occurred between the amygdala and the ACC/dmPFC in youth with PTSD, which is also inversely associated with the severity of PTSD.[18,19,101] These results are of interest because adolescents exposed to adversity that downregulate amygdala and ACC/dmPFC coupling exhibit depressive and anxiety symptoms during late adolescence.[57] Furthermore, coupling between the amygdala and the vmPFC decreased in youth with PTSD in contrast to increases shown in typically developing youth.[18] However, similar to discrepancies discussed previously, age-related differences can also be seen. Compared to typically developing youth, younger adolescents with PTSD show greater connectivity between the amygdala and vmPFC which reverses as they age.[18] Overall, when accounting for age differences, amygdala and ACC/PFC connectivity has been shown to decrease in adolescents exposed to stress and trauma.

Additionally, studies have shown that adolescent PTSD patients have decreased connectivity between the vmPFC to amygdala and vlPFC to hippocampus during development compared to healthy youth.[47]

In the posterior cingulate cortex (PCC) of healthy individuals, activity was correlated with activity in regions of the default network such as the mPFC, precuneus, lateral parietal cortices, inferior and middle temporal cortices, thalamus, and cerebellum.[107] However, patients with early life trauma expressed only correlation between the PCC and right superior frontal gyrus and left ventrolateral thalamus. Additionally, connectivity between the PCC and precuneus, right amygdala, right hippocampus, mPFC, right insula, and bilateral lateral parietal cortex was higher in healthy controls than those with early life trauma. These results suggest that early life trauma may strongly impact development of the right hemisphere and the default network.

(A)



(B)

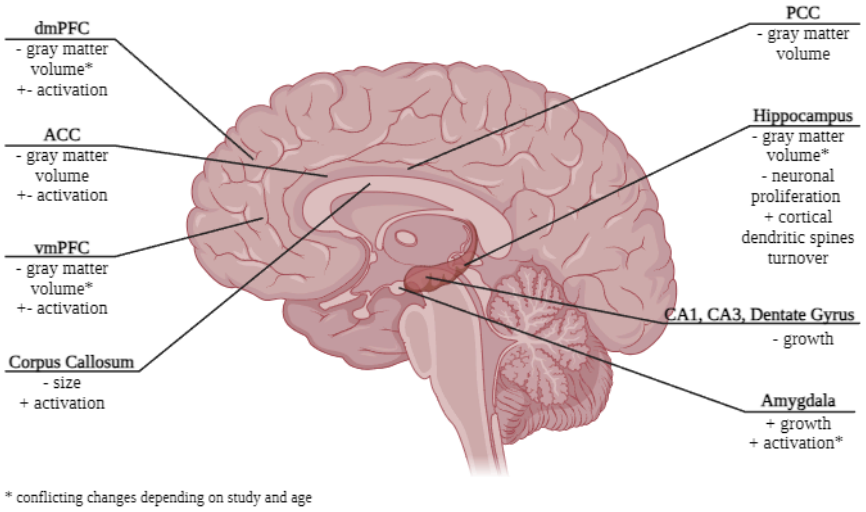


Figure 3. Morphological effects of stress and trauma on the adolescent (A) outer brain regions and (B) inner brain regions.

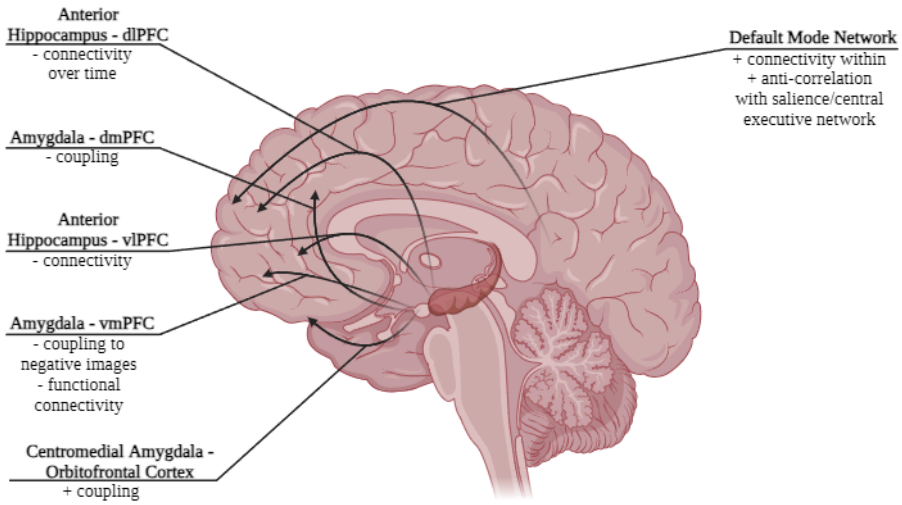


Figure 4. Physiological effects of stress and trauma on adolescent brain connections.

3. Discussion

3.1 Overall Effects

Adolescence is a period of significant volumetric increases in the hippocampus and amygdala, cortical thinning in the frontal and temporal lobe, as well as heightened sensitivity to stress. This is mirrored by the time periods in which different parts of the brain are the most vulnerable to change due to abuse as mentioned above, exacerbating the importance of the study, prevention, and treatment of trauma and PTSD of adolescents.

The physiological changes to the brain caused by trauma present differently depending on parts of the brain, but they largely affect neural networks that are related to emotional processing and memory. It is worth noting that many of the studies investigating this topic have been unable to differentiate the effects of different kinds of trauma on the developing brain, as it is often the case that youth with PTSD are subject to multiple and repeated traumas instead.[3] Furthermore, many symptoms common to adults with PTSD like reduced hippocampal volume and hyperactivity of the amygdala and insula do not consistently present themselves in adolescents with PTSD. This is due to the increased stress sensitivity of the developing neural system, as well as delayed developmental effects.[3]

PTSD in youth exhibits changes to the frontolimbic circuits that contribute to the psychological changes like increased threat reactivity and reduced emotion regulation capacity as they age, which can persist well into adulthood.[2,3] It has commonly been speculated that these changes to the brain caused by trauma and PTSD are adaptations to aversive and threatening environments, as the neural circuits affected by trauma in adolescents affect the brain's capacity to detect threat, threat extinction, and threat reactivity.[3,47] In particular, the increased volume and activity of the amygdala, as well as the abnormal connectivity between the amygdala and different parts of the prefrontal cortex are indicative of early maturation of these processes, at the potential cost of sustained hypervigilance and an inability inhibiting threat responses. This ultimately leads to an improved automatic detection of threat, increased responsivity of the hypothalamic-pituitary axis stress response, impaired threat regulation, etc.[3]

There are many parts of the PFC that get affected as a result of early life stress and trauma, including the dorsolateral PFC, ventrolateral PFC, ventromedial PFC, precentral gyrus, and dorsomedial PFC. As stated above, there are discrepancies in how trauma affects gray matter volume in these areas, which seem to be due to differences in age-related factors and trauma/PTSD severity. The abnormal development of the PFC also showed evidence of decreased intrinsic connectivity with the amygdala and hippocampus over time. Furthermore, there has been mixed evidence on the activation of these parts as a result of PTSD, including the ventrolateral PFC, ventromedialPFC/rostral ACC, and dorsomedial PFC. There are many possible reasons for this, including task differences, trauma-related factors, sex differences, and age differences in the studies.

A particularly important region of the PFC for emotional processing is the ventromedial PFC. The ventromedial PFC has been associated with the top down modulation of the amygdala responses and threat response inhibition. Abnormal development of the ventromedial PFC and reduced ventromedial PFC-amygdala coupling we've seen in both youth and adults with PTSD contributes to the reduced threat extinction and negative emotional processing capabilities of these youth.[3,47]

Adult PTSD is characterized in the hippocampus with reduced volumes. However, this is not consistently found in youth with PTSD.[47] A possible reason for this is the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of PTSD, which has been shown to increase hippocampal neurogenesis and increase hippocampal gray matter volume in adults with PTSD.[47] This suggests that the use of SSRIs can counteract the effects of trauma on the hippocampus by preventing the reduction of hippocampal volume. Another reason is the delayed developmental effect mentioned above, where the physiological effects of trauma take time to present themselves.

Both the ventrolateral PFC and dorsolateral PFC have shown decreased connectivity with the anterior hippocampus in adolescents with PTSD. This is significant as the anterior hippocampus has many projections into the amygdala, and is involved in unconditioned threat responses. Both of these PFC regions are heavily involved in emotional processes; the ventrolateral PFC is associated with selection and inhibition of cognitive appraisals, while the dorsolateral PFC is associated with explicit emotion regulation through cognitive reappraisal.[47] It can be hypothesized that this reduction in connectivity between the two parts of the PFC and the anterior hippocampus can result in a loss of inhibitory control of unconditioned threat responses, increased threat acquisition, and impaired threat extinction. However, the study by Heyn et al. was unable to confirm this, and further study including threat learning and emotion regulation is required.[47]

The physiological changes in the hippocampus as a result of stress doesn't just affect the emotional and threat responses of the individual, but spatial memory and navigation as well. This is evident by the reduced spatial navigation capabilities in rats tested using the Morris Water Maze, which coincides with reduced volumes of the cornu ammonis 1, 3, and dentate gyrus.[2] These reductions in volume in different parts of the hippocampus as a result of stressors shows that early life trauma does not just affect the emotional and threat responses of individuals, but other parts of mental capacity as well, such as spatial navigation and memory.

Overall, the physiological changes in adolescent brains caused by trauma contribute to the symptoms of PTSD that persist through adulthood, such as improved threat detection, impaired threat extinction, and reduced negative emotion regulation. These changes include abnormal gray matter volumes and connectivities throughout different parts of the PFC, amygdala, and hippocampus. These changes do not immediately present themselves, however, and can take many years to appear. Furthermore, these changes affect not only the emotional and threat processing circuits, but other brain regions responsible for thinking and memory as well. These effects of these physiological changes on the brain and emotional capabilities on the individuals highlight the importance of studying, treating, and prevention of trauma in adolescents.

3.2 Therapeutic Treatments

The most effective treatments for adolescents who have experienced stress and trauma include a combination of therapeutic, hormonal, and lifestyle changes. Medication alone may not be effective in treating a patient with severe psychological illness, but medication combined with therapy may be.

Cognitive behavioral therapy (CBT) is one of the most effective methods for helping individuals cope with trauma. CBT focuses on the interplay between thoughts, feelings, and behaviors. This therapy helps individuals challenge negative thought patterns and develop problem-solving skills. CBT is particularly desirable for adolescents because it equips them with the skills to manage distressing behaviors and emotional reactions. Trauma-focused cognitive behavior therapy (TF-CBT) is a subset of CBT designed to help those who have experienced significant trauma in their lives. This form of therapy often focuses on controlled exposure to emotions associated with the trauma, the creation of a trauma narrative, and relaxation techniques.[108] TF-CBT is a short-term treatment, lasting up to 16 sessions of this type of therapy, and its main focus is to address post traumatic stress. TF-CBT relies on the individual's ability to master the therapeutic techniques learned during the session in order to practice them routinely after the sessions have ended.[109] A meta-analysis of published and

unpublished data regarding the efficacy of CBT for PTSD in adolescents found that "participants who received CBTs-TF had lower mean post-traumatic stress symptoms after treatment than those who received the control conditions, after adjusting for post-traumatic stress systems before treatment."[110] According to an article by Evgenia Gkintoni et al. assessing the efficacy of different therapeutic interventions for PTSD in adolescents: "Among the array of therapeutic interventions analyzed, CBT and specifically TF-CBT emerge as the most effective and extensively employed methodologies for addressing PTSD in children and adolescents."[111]

Eye movement desensitization and reprocessing (EMDR) is another popular form of therapy used to treat post traumatic stress. EMDR is based on the Adaptive Information Process (AIP) model of storing memories, which suggests that some traumatic events can remain "unprocessed" by the brain and stay "stuck" in the body, resulting in negative emotions and adverse responses to similar situations as the traumatic event. By having the individual "focus on external stimuli" while recalling these traumatic events, EMDR aims to desensitize the individual to their own traumatic experiences.[112] EMDR helps to mitigate the effects of stress and trauma on the brain by using bilateral stimulation, in the form of guided eye movements, while the brain recalls traumatic events. The eye movements are thought to stimulate the information processing region of the brain, which enables the reprocessing of traumatic memories into less distressing ones. Bilateral stimulation allows the participant to reconstruct a more coherent traumatic narrative, reducing the emotional impact of the event itself.[113] Significant research suggests that EMDR is beneficial for minimizing the effects of PTSD by desensitizing the participant, allowing the individual to think about their traumatic event without inciting an intense emotional response.[114] While EMDR was originally meant to be used on adults, the therapy has been relatively recently extended to help children of all ages. EMDR would be beneficial for adolescents who have experienced any sort of trauma because it is a holistic approach to healing and provides them with the tools to manage distressing emotions that may arise in their future.

3.3 Hormonal Treatments

In addition to employing a myriad of therapeutic treatments, adolescent trauma survivors can also take medication to alleviate the psychological symptoms of PTSD. The hormonal treatments focus on addressing the dysregulation of the HPA axis which is often disrupted in adolescents who have experienced stress and trauma. Most recently, glucocorticoid-therapy based treatments have become popular for treating PTSD in individuals of all ages.[115] The glucocorticoids are used to normalize levels of cortisol, commonly known as the stress hormone, in order to mitigate the physiological and psychological effects of stress on the individual. Glucocorticoids are thought to prevent the overactivation of the HPA axis which is commonly seen in individuals suffering from PTSD.[116] Glucocorticoids impair memory consolidation and impairs the retrieval of adverse memories. Glucocorticoids have been used both as a treatment and preventative method for individuals that may be more susceptible to developing PTSD.[115] Although the use of glucocorticoids presents promising results, there are some negative side effects that should be taken into consideration when choosing the most effective treatment plan for the patient. Some side effects of glucocorticoid use are insomnia, edema, and hypomania. These side effects, coupled with the daily struggles of adolescence, may make this relatively new form of therapy not entirely desirable for this age group. It may be a few years before biochemists and physician-scientists refine the treatment approach for this therapeutic drug, but the potential for glucocorticoids to prevent and treat PTSD is there.[117]

Psychedelic drugs, such as ketamine and MDMA, are being used as alternative hormonal therapies to treat PTSD and other stress-related disorders. Ketamine is a dissociative anesthetic which acts on the brain's N-methyl-D-aspartate (NMDA) receptors involved in mood regulation and synaptic plasticity. Ketamine infusions are intravenous and have been most widely used to treat major depressive and anxiety disorders, specifically in previously treatment-resistant patients.[118] There is a current clinical trial entitled "Ketamine-Assisted Psychotherapy for Adolescents PTSD (KAP)" that aims to investigate the efficacy of ketamine infusions for adolescents diagnosed with PTSD. The study is set to commence in August 2024 and conclude a year later. Participants will receive three intravenous ketamine administrations before receiving psychotherapy sessions over a six week

course. Then, participants' sleep will be monitored using SmartSleep EEG recording headset for seven consecutive days. The researchers hypothesize that, following the ketamine infusion therapy, the participants' PTSD symptom severity will decrease.[119]

As opposed to psychedelics, selective serotonin reuptake inhibitors (SSRIs) are more widely accepted drugs that have been used since the late 1980s to treat major depressive disorders and anxiety, which can result from complex trauma and stress in adolescents. SSRIs function by increasing the amount of serotonin in the brain, a neurotransmitter responsible for feelings of happiness and mood regulation. SSRIs can often mitigate the symptoms of depression and anxiety by reducing the intensity of emotions and emotional responses.[120] Some SSRIs include sertraline (Zoloft), paroxetine (Paxil), and fluoxetine, but only sertraline and paroxetine are currently FDA approved as treatments for PTSD.[121,122] SSRIs are most effective when used alongside other therapeutic treatment methods, like CBT or EMDR. Additionally, this hormonal treatment is appealing to adolescents suffering from PTSD because it stabilizes mood and regulates complex emotions that arise from traumatic experiences. That being said, SSRIs can also have adverse side effects, such as significant weight gain and changes in appetite which can be particularly harmful to adolescents who already struggle with body dysmorphia and/ or disordered eating as a result of the stress and trauma. Finally, the use of SSRIs can result in dependency, which makes tapering off them an added challenge for adolescents who may not want to take them long term.[123]

In addition to SSRIs, alpha-adrenergic blockers (Prazosin) is also an effective hormonal treatment for PTSD in adolescents. Alpha-adrenergic blockers, also known as alpha-1 adrenergic receptor antagonists, block alpha-receptors on cells within the body, which can be used to treat high blood pressure and stress-related disorders like PTSD. Within the scope of this article, alpha-adrenergic blockers limit adrenergic activity which reduces the body's stress response. Research suggests that alpha-adrenergic blockers are effective at minimizing hyperarousal symptoms associated with PTSD which can manifest in adolescents as extreme moodiness and heightened anxiety. By blocking the alpha-1 adrenergic receptor, the body decreases its

parasympathetic and sympathetic responses, which are responsible for activating the "fight or flight" feelings.[124] Finally, PTSD can disrupt particular stages of the sleep cycle, like the rapid eye movement (REM) stage, and these alpha-adrenergic blockers are known to restore this sleep stage. While alpha-adrenergic blockers have been most suitable for treating PTSD in war veterans due to the high incidence of sleep disturbances and night terrors in this population, studies suggest that it may also be used for treating PTSD and other stress-related disorders in other groups as well.[125] Maintaining proper sleep quality is essential for adolescents in particular as sleep regulates emotions and determines cognitive functioning during the day. The negative side effects of Prazosin include dizziness and headaches due to slight hypotension.[125] Just as with other hormonal treatments, alpha-adrenergic blockers are most effective when used in combination with other therapeutic treatments discussed above.

An ongoing clinical trial entitled "Sleep and Emotion Processing in Adolescent Post Traumatic Stress Disorder" explores the role of sleep in emotional processing and reactivity in adolescents with PTSD. Subject ages from 12 to 17 years old, and all have been previously diagnosed with PTSD. The researchers plan to use electroencephalogram (EEG) tests to determine the quality of sleep in their subjects. Using sleep enhancement algorithms, researchers hope to investigate if the deepest sleep, non-rapid-eye-movement (NREM), can be clinically enhanced in adolescents suffering from sleep disturbances due to PTSD.[126] This study could potentially lead to targeted interventions for improving sleep and mitigating the effects of PTSD in adolescents.

3.4 Lifestyle Changes

In addition to biochemical and therapeutic treatments, adolescents can also make lifestyle changes that may mitigate the effects of stress and trauma on the body and the brain. Perhaps the most important lifestyle change for treating PTSD is to engage in physical activity. Exercising releases endorphins, which reduce symptoms of anxiety and depression and is known to stabilize mood. Research suggests that "aerobic exercise, which improves cardiorespiratory fitness, is an effective treatment for depression,

anxiety, and schizophrenia through both physiological and psychological mechanisms, and may be comparable or superior to other common treatments, such as psychotherapy and pharmacology."[127] Additionally, a balanced diet plays an important role in maintaining emotional wellbeing. A diet rich in whole grains, vitamin D and B12, and lean proteins can minimize physiological and psychological effects of stress on the brain as well as regulate mood and emotions. In an article recently published by Harvard T.H. Chan School of Public Health, a study suggests that a mediterranean diet may help to mitigate the symptoms of PTSD.[128] Additionally, caffeine in chocolate, coffee and other fountain drinks act as a stimulant, enhancing the body's stress response and ultimately exacerbating PTSD symptoms. This is particularly important for this age group, as coffee and energy drinks are popular beverages among middle and high school students.

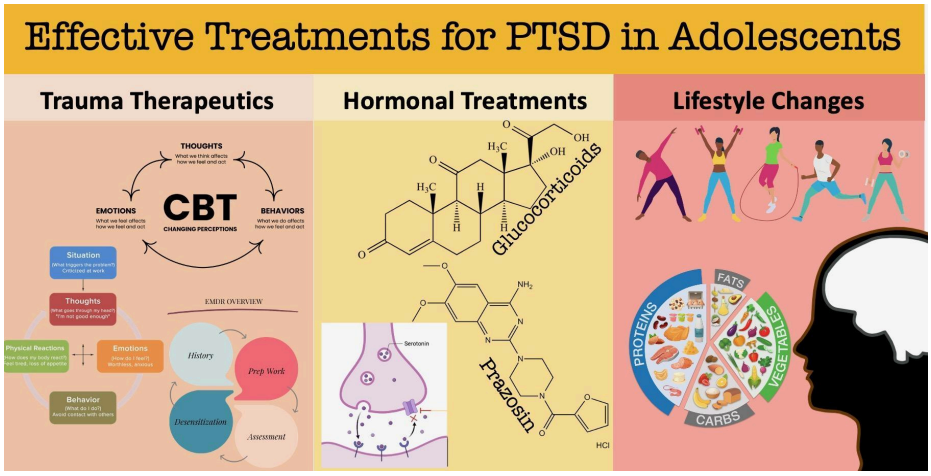


Figure 5. Infographic for Effective Treatments for PTSD in Adolescents - *Some effective therapeutic treatments for PTSD in adolescents include CBT, TF-CBT, and EMDR. Additionally, hormonal treatments, such as glucocorticoids and SSRIs can be used to mitigate symptoms from stress-related disorders. Finally, lifestyle changes like maintaining a well-balanced diet and a routine sleep schedule can help to normalize cortisol levels in the body.*[129–136]

3.5 Future Research

Future research on the effects of stress and trauma on adolescent brain development should focus on several key areas to enhance our understanding and ultimately improve health outcomes. For one,

physician-scientists could conduct long-term research that follows subjects from childhood, through adolescence, and into adulthood to investigate the long term effects of trauma on the mind and body. Additionally, these studies could investigate which period of development interventions are most effective. It would also be beneficial to explore resilience factors that may affect how trauma manifests itself in the body as well as the healing process. Factors like social support, coping mechanisms, and genetic predispositions all play significant roles in the body's response to stress and trauma. Since this article is geared towards adolescents, it would be important to investigate how the use of social media might reduce or exacerbate the effects of stress and trauma on the brain. Additionally, there needs to be more research done on the socio-economic and cultural factors that might influence how adolescents process trauma and ultimately heal from it as well. Access to mental health resources may mitigate the effects of trauma on the adolescent brain, so this would be an important area to explore when determining health outcomes. Finally, it would be interesting to investigate how collective traumas like cultural diasporas and natural disasters affect the brain, morphologically and psychologically. This information could provide a point of comparison to how individual traumas, like experiences in childhood, affect the adolescent brain.

4. Conclusion

4.1 Summary of Main Ideas

Adolescent trauma has been shown to induce severe physiological and psychological stress, including disorders such as PTSD, anxiety, and depression. Some regions in the adolescent brain have also been shown to be in a sensitive period during that time and are particularly vulnerable to stress and trauma. Studies in both animal and human models reflect this sensitivity since exposure to stressors during adolescence results in lasting brain changes and impaired cognitive function. This underscores the need for more research and treatment efforts to address stress and trauma in adolescents.

Clinical trials as well as rodent studies have mapped the effects of stress and trauma on adolescent brain development. Most notably, individuals with exposure to stress or trauma exhibited altered volume in brain regions with increased volume in the amygdala, reduced volume in the hippocampus, and various changes in PFC matter according to specific location. Additionally, studies have shown reduction in corpus callosum volume, decreased brain connectivity, and changes in the HPA axis, DA levels, and larger brain networks. It is important to mention that many studies reported conflicting results; however, many of these discrepancies were eliminated when analyzing based on age-related effects.

The most effective treatments for adolescent PTSD often combine hormonal, therapeutic, and lifestyle treatments. CBT, specifically TF-CBT, addresses negative thought patterns associated with PTSD and is one of the most common treatments for adolescents. Another therapeutic option, EMDR, helps those with PTSD process memories. Therapeutic treatments, which mitigate psychological symptoms, are often combined with hormonal treatments, including glucocorticoids, ketamine, SSRIs, and alpha-adrenergic blockers which target underlying biological processes. Additionally, lifestyle changes such as exercise, a balanced diet, and limited caffeine intake are commonly recommended.

4.2 Practical Applications

This research article has several practical applications that may impact mental health treatment and public health policies. Understanding how stress and trauma affect the brain as well as how these morphological changes manifest themselves as emotional and behavioral changes is important for early detection of PTSD and other stress-related disorders. Early identification is necessary for timely intervention, which significantly improves health outcomes. Therefore, this article can be used as an informational guide for those who care for and work closely with adolescents, such as parents, pediatricians, and educators. In school settings, teachers can be trained to recognize the signs of trauma in their students, which would help early detection and prevention. Along with teachers, students could attend required educational sessions on trauma so that they, themselves, are aware of the effects of trauma and can spot warning signs

well in advance of symptoms worsening. Finally, this review article could be used for the development of new and effective mental health treatments and policy advocacy. Public health policies could leverage the insights gained from this article to advocate for community-based initiatives that address several systemic causes of stress and trauma such as poverty and familial violence.

4.3 Acknowledgements

We would like to thank Ms. Vanloan Nguyen for her guidance and support throughout the writing process of this paper. We would also like to thank Hayden Loc-Jun Wong, Aditi Shankar and Luke Wang for feedback on our manuscript. Figures were created with BioRender.com.

References

1. Teicher MH, Samson JA. Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect. *J Child Psychol Psychiatry.* 2016;57(3):241-266. doi:10.1111/jcpp.12507

2. Eiland L, Romeo RD. Stress and the Developing Adolescent Brain. *Neuroscience.* 2013;249:162-171. doi:10.1016/j.neuroscience.2012.10.048

3. Herringa RJ. Trauma, PTSD, and the Developing Brain. *Curr Psychiatry Rep.* 2017;19(10):69. doi:10.1007/s11920-017-0825-3

4. Bremner JD. Traumatic stress: effects on the brain. *Dialogues Clin Neurosci.* 2006;8(4):445-461. doi:10.31887/DCNS.2006.8.4/jbremner

5. Pfeifer JH, Allen NB. Arrested development? Reconsidering dual-systems models of brain function in adolescence and disorders. *Trends Cogn Sci.* 2012;16(6):322-329. doi:10.1016/j.tics.2012.04.011

6. Zimmermann KS, Richardson R, Baker KD. Maturational Changes in Prefrontal and Amygdala Circuits in Adolescence: Implications for Understanding Fear Inhibition during a Vulnerable Period of Development. *Brain Sci.* 2019;9(3):65. doi:10.3390/brainsci9030065

7. Gallagher M, Chiba AA. The amygdala and emotion. *Curr Opin Neurobiol.* 1996;6(2):221-227. doi:10.1016/s0959-4388(96)80076-6

8. Sarrieau A, Dussaillant M, Agid F, Philibert D, Agid Y, Rostene W. Autoradiographic localization of glucocorticosteroid and progesterone binding sites in the human post-mortem brain. *J Steroid Biochem.* 1986;25(5B):717-721. doi:10.1016/0022-4731(86)90300-6

9. Uematsu A, Matsui M, Tanaka C, et al. Developmental Trajectories of Amygdala and Hippocampus from Infancy to Early Adulthood in Healthy Individuals. *PLoS ONE.* 2012;7(10):e46970. doi:10.1371/journal.pone.0046970

10. Hein TC, Monk CS. Research Review: Neural response to threat in children, adolescents, and adults after child maltreatment - a quantitative meta-analysis. *J Child Psychol Psychiatry.* 2017;58(3):222-230. doi:10.1111/jcpp.12651

11. Garrett AS, Carrion V, Kletter H, Karchemskiy A, Weems CF, Reiss A. BRAIN ACTIVATION TO FACIAL EXPRESSIONS IN YOUTH WITH PTSD SYMPTOMS. *Depress Anxiety.* 2012;29(5):449-459. doi:10.1002/da.21892

12. Herringa RJ, Burghy CA, Stodola DE, Fox ME, Davidson RJ, Essex MJ. Enhanced prefrontal-amygdala connectivity following childhood adversity as a protective mechanism against internalizing in adolescence. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2016;1(4):326-334. doi:10.1016/j.bpsc.2016.03.003

13. Patel R, Spreng RN, Shin LM, Girard TA. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev.* 2012;36(9):2130-2142. doi:10.1016/j.neubiorev.2012.06.003

14. Etkin A, Wager TD. Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia. *Am J Psychiatry.* 2007;164(10):1476-1488. doi:10.1176/appi.ajp.2007.07030504

15. Hayes JP, Hayes SM, Mikedis AM. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biol Mood Anxiety Disord.* 2012;2:9. doi:10.1186/2045-5380-2-9

16. Crozier JC, Wang L, Huettel SA, De Bellis MD. Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: Does gender matter? *Dev Psychopathol.* 2014;26(2):491-513. doi:10.1017/S095457941400008X

17. Yang P, Wu MT, Hsu CC, Ker JH. Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: a functional MRI study. *Neurosci Lett.* 2004;370(1):13-18. doi:10.1016/j.neulet.2004.07.033

18. Wolf RC, Herringa RJ. Prefrontal–Amygdala Dysregulation to Threat in Pediatric Posttraumatic Stress Disorder. *Neuropsychopharmacology.* 2016;41(3):822-831. doi:10.1038/npp.2015.209

19. Keding TJ, Herringa RJ. Paradoxical Prefrontal–Amygdala Recruitment to Angry and Happy Expressions in Pediatric Posttraumatic Stress Disorder. *Neuropsychopharmacology.* 2016;41(12):2903-2912. doi:10.1038/npp.2016.104

20. Pechtel P, Lyons-Ruth K, Anderson CM, Teicher MH. Sensitive periods of amygdala development: The role of maltreatment in preadolescence. *NeuroImage.* 2014;97:236-244. doi:10.1016/j.neuroimage.2014.04.025

21. Teicher MH, Parigger A. The 'Maltreatment and Abuse Chronology of Exposure' (MACE) Scale for the Retrospective Assessment of Abuse and Neglect During Development. *PLoS ONE.* 2015;10(2):e0117423. doi:10.1371/journal.pone.0117423

22. Vyas A, Pillai AG, Chattarji S. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience.* 2004;128(4):667-673. doi:10.1016/j.neuroscience.2004.07.013

23. Malter Cohen M, Jing D, Yang RR, Tottenham N, Lee FS, Casey BJ. Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proc Natl Acad Sci U S A.* 2013;110(45):18274-18278. doi:10.1073/pnas.1310163110

24. Howell BR, Grand AP, McCormack KM, et al. Early Adverse Experience Increases Emotional Reactivity in Juvenile Rhesus Macaques: Relation to Amygdala Volume. *Dev Psychobiol.* 2014;56(8):1735-1746. doi:10.1002/dev.21237

25. Eiland L, Ramroop J, Hill MN, Manley J, McEwen BS. Chronic juvenile stress produces corticolimbic dendritic architectural remodeling and modulates emotional behavior in male and female rats. *Psychoneuroendocrinology.* 2012;37(1):39-47. doi:10.1016/j.psyneuen.2011.04.015

26. Zhang W, Rosenkranz JA. Repeated restraint stress increases basolateral amygdala neuronal activity in an age-dependent manner. *Neuroscience.* 2012;226:459-474. doi:10.1016/j.neuroscience.2012.08.051

27. Mitra R, Jadhav S, McEwen BS, Vyas A, Chattarji S. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proc Natl Acad Sci U S A.* 2005;102(26):9371-9376. doi:10.1073/pnas.0504011102

28. Rau AR, Chappell AM, Butler TR, Ariwodola OJ, Weiner JL. Increased Basolateral Amygdala Pyramidal Cell Excitability May Contribute to the

Anxiogenic Phenotype Induced by Chronic Early-Life Stress. *J Neurosci.* 2015;35(26):9730-9740. doi:10.1523/JNEUROSCI.0384-15.2015

29. Rau AR, Ariwodola OJ, Weiner JL. Postsynaptic Adenosine A2A Receptors Modulate Intrinsic Excitability of Pyramidal Cells in the Rat Basolateral Amygdala. *Int J Neuropsychopharmacol.* 2015;18(6):pyv017. doi:10.1093/ijnp/pyv017

30. Callaghan BL, Richardson R. Early experiences and the development of emotional learning systems in rats. *Biol Mood Anxiety Disord.* 2013;3:8. doi:10.1186/2045-5380-3-8

31. Negrón-Oyarzo I, Pérez MÁ, Terreros G, Muñoz P, Dagnino-Subiabre A. Effects of chronic stress in adolescence on learned fear, anxiety, and synaptic transmission in the rat prelimbic cortex. *Behav Brain Res.* 2014;259:342-353. doi:10.1016/j.bbr.2013.11.001

32. Den ML, Altmann SR, Richardson R. A comparison of the short- and long-term effects of corticosterone exposure on extinction in adolescence versus adulthood. *Behav Neurosci.* 2014;128(6):722-735. doi:10.1037/bne0000022

33. Tamnes CK, Bos MGN, van de Kamp FC, Peters S, Crone EA. Longitudinal development of hippocampal subregions from childhood to adulthood. *Dev Cogn Neurosci.* 2018;30:212-222. doi:10.1016/j.dcn.2018.03.009

34. Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. *Neurosci Res.* 1996;26(3):235-269. doi:10.1016/s0168-0102(96)01105-4

35. Sapolsky RM. Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion. *Stress Amst Neth.* 1996;1(1):1-19. doi:10.3109/10253899609001092

36. Kühn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. *Biol Psychiatry.* 2013;73(1):70-74. doi:10.1016/j.biopsych.2012.06.029

37. Bremner JD, Randall P, Vermetten E, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. *Biol Psychiatry.* 1997;41(1):23-32. doi:10.1016/s0006-3223(96)00162-x

38. Paquola C, Bennett MR, Lagopoulos J. Understanding heterogeneity in grey matter research of adults with childhood maltreatment-A meta-analysis and review. *Neurosci Biobehav Rev.* 2016;69:299-312. doi:10.1016/j.neubiorev.2016.08.011

39. De Bellis MD, Keshavan MS, Clark DB, et al. A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biol Psychiatry.* 1999;45(10):1271-1284. doi:10.1016/s0006-3223(99)00045-1

40. Carrion VG, Weems CF, Eliez S, et al. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry.* 2001;50(12):943-951. doi:10.1016/s0006-3223(01)01218-5

41. De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry.* 2001;50(4):305-309. doi:10.1016/s0006-3223(01)01105-2

42. Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. Neuropsychopharmacol Off Publ Am Coll *Neuropsychopharmacol.* 2004;29(11):1988-1993. doi:10.1038/sj.npp.1300528

43. Isgor C, Kabbaj M, Akil H, Watson SJ. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus.* 2004;14(5):636-648. doi:10.1002/hipo.10207

44. Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci.* 1999;2(10):861-863. doi:10.1038/13158

45. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci.* 2009;10(6):410-422. doi:10.1038/nrn2648

46. Morey RA, Haswell CC, Hooper SR, De Bellis MD. Amygdala, Hippocampus, and Ventral Medial Prefrontal Cortex Volumes Differ in Maltreated Youth with and without Chronic Posttraumatic Stress Disorder. *Neuropsychopharmacology.* 2016;41(3):791-801. doi:10.1038/npp.2015.205

47. Heyn SA, Keding TJ, Ross MC, Cisler JM, Mumford JA, Herringa RJ. Abnormal prefrontal development in pediatric posttraumatic stress disorder: a longitudinal structural and functional magnetic resonance imaging study. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2019;4(2):171-179. doi:10.1016/j.bpsc.2018.07.013

48. Carrion VG, Weems CF, Watson C, Eliez S, Menon V, Reiss AL. Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric PTSD: an MRI study. *Psychiatry Res.* 2009;172(3):226-234. doi:10.1016/j.pscychresns.2008.07.008

49. Carrion VG, Weems CF, Richert K, Hoffman BC, Reiss AL. Decreased Prefrontal Cortical Volume Associated with Increased Bedtime Cortisol in Traumatized Youth. *Biol Psychiatry.* 2010;68(5):491-493. doi:10.1016/j.biopsych.2010.05.010

50. Ishikawa J, Nishimura R, Ishikawa A. Early-life stress induces anxiety-like behaviors and activity imbalances in the medial prefrontal cortex and amygdala in adult rats. *Eur J Neurosci.* 2015;41(4):442-453. doi:10.1111/ejn.12825

51. Silva-Gómez AB, Rojas D, Juárez I, Flores G. Decreased dendritic spine density on prefrontal cortical and hippocampal pyramidal neurons in postweaning social isolation rats. *Brain Res.* 2003;983(1):128-136. doi:10.1016/S0006-8993(03)03042-7

52. Day-Wilson KM, Jones DNC, Southam E, Cilia J, Totterdell S. Medial prefrontal cortex volume loss in rats with isolation rearing-induced deficits in prepulse inhibition of acoustic startle. *Neuroscience.* 2006;141(3):1113-1121. doi:10.1016/j.neuroscience.2006.04.048

53. Hellemans KGC, Benge LC, Olmstead MC. Adolescent enrichment partially reverses the social isolation syndrome. *Dev Brain Res.* 2004;150(2):103-115. doi:10.1016/j.devbrainres.2004.03.003

54. Schubert MI, Porkess MV, Dashdorj N, Fone KCF, Auer DP. Effects of social isolation rearing on the limbic brain: A combined behavioral and magnetic resonance imaging volumetry study in rats. *Neuroscience.* 2009;159(1):21-30. doi:10.1016/j.neuroscience.2008.12.019

55. Leussis M, Lawson K, Stone K, Andersen S. The enduring effects of an adolescent social stressor on synaptic density, part II: Poststress reversal of synaptic loss in the cortex by adinazolam and MK-801. *Synap N Y N.* 2008;62:185-192. doi:10.1002/syn.20483

56. Levine JB, Youngs RM, MacDonald ML, et al. Isolation rearing and hyperlocomotion are associated with reduced immediate early gene expression levels in the medial prefrontal cortex. *Neuroscience.* 2007;145(1):42-55. doi:10.1016/j.neuroscience.2006.11.063

57. Kalisch R, Gerlicher AMV. Making a mountain out of a molehill: on the role of the rostral dorsal anterior cingulate and dorsomedial prefrontal cortex in conscious threat appraisal, catastrophizing, and worrying. *Neurosci Biobehav Rev.* 2014;42:1-8. doi:10.1016/j.neubiorev.2014.02.002

58. Chaney A, Carballedo A, Amico F, et al. Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. *J Psychiatry Neurosci JPN.* 2014;39(1):50-59. doi:10.1503/jpn.120208

59. Webb CA, Weber M, Mundy EA, Killgore WDS. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of mild depressive symptoms: a voxel-based morphometric analysis. *Psychol Med.* 2014;44(13):2833-2843. doi:10.1017/S0033291714000348

60. Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E. Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Ann N Y Acad Sci.* 1997;821:160-175. doi:10.1111/j.1749-6632.1997.tb48277.x

61. Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. *Biol Psychiatry.* 2004;56(2):80-85. doi:10.1016/j.biopsych.2004.03.016

62. De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry.* 2002;52(11):1066-1078. doi:10.1016/s0006-3223(02)01459-2

63. De Bellis MD, Keshavan MS. Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. *Neurosci Biobehav Rev.* 2003;27(1-2):103-117. doi:10.1016/s0149-7634(03)00013-7

64. Galinowski A, Miranda R, Lemaitre H, et al. Resilience and corpus callosum microstructure in adolescence. *Psychol Med.* 2015;45(11):2285-2294. doi:10.1017/S0033291715000239

65. Sheridan MA, Fox NA, Zeanah CH, McLaughlin KA, Nelson CA. Variation in neural development as a result of exposure to institutionalization early in childhood. *Proc Natl Acad Sci U S A.* 2012;109(32):12927-12932. doi:10.1073/pnas.1200041109

66. Malinowski JT, St. Jean DJ. Next-generation small molecule therapies for heart failure: 2015 and beyond. *Bioorg Med Chem Lett.* 2018;28(9):1429-1435. doi:10.1016/j.bmcl.2018.03.064

67. Lo Iacono L, Carola V. The impact of adolescent stress experiences on neurobiological development. *Semin Cell Dev Biol.* 2018;77:93-103. doi:10.1016/j.semcdb.2017.09.040

68. Lindsey KP, Gatley SJ. Applications of Clinical Dopamine Imaging. *PET Clin.* 2007;2(1):45-65. doi:10.1016/j.cpet.2007.09.005

69. Badgaiyan RD, Fischman AJ, Alpert NM. Dopamine Release During Human Emotional Processing. *NeuroImage.* 2009;47(4):2041-2045. doi:10.1016/j.neuroimage.2009.06.008

70. Bronfeld M, Israelashvili M, Bar-Gad I. Pharmacological animal models of Tourette syndrome. *Neurosci Biobehav Rev.* 2013;37(6):1101-1119. doi:10.1016/j.neubiorev.2012.09.010

71. Burke AR, Miczek KA. Stress in adolescence and drugs of abuse in rodent models: Role of dopamine, CRF, and HPA axis. *Psychopharmacology (Berl).* 2014;231(8):1557-1580. doi:10.1007/s00213-013-3369-1

72. Andersen SL, Gazzara RA. The Ontogeny of Apomorphine-Induced Alterations of Neostriatal Dopamine Release: Effects on Spontaneous Release. *J Neurochem.* 1993;61(6):2247-2255. doi:10.1111/j.1471-4159.1993.tb07466.x

73. Leslie CA, Robertson MW, Cutler AJ, Bennett JP. Postnatal development of D 1 dopamine receptors in the medial prefrontal cortex, striatum and nucleus accumbens of normal and neonatal 6-hydroxydopamine treated rats: a quantitative autoradiographic analysis. Dev Brain Res. 1991;62(1):109-114. doi:10.1016/0165-3806(91)90195-O

74. Andersen SL, Dumont NL, Teicher MH. Developmental differences in dopamine synthesis inhibition by (±)-7-OH-DPAT. *Naunyn Schmiedebergs Arch Pharmacol.* 1997;356(2):173-181. doi:10.1007/PL00005038

75. Teicher MH, Barber NI, Gelbard HA, et al. Developmental Differences in Acute Nigrostriatal and Mesocorticolimbic System Response to Haloperidol. *Neuropsychopharmacology.* 1993;9(2):147-156. doi:10.1038/npp.1993.53

76. Lukkes JL, Mokin MV, Scholl JL, Forster GL. Adult rats exposed to early-life social isolation exhibit increased anxiety and conditioned fear behavior, and altered hormonal stress responses. *Horm Behav.* 2009;55(1):248-256. doi:10.1016/j.yhbeh.2008.10.014

77. Lukkes JL, Watt MJ, Lowry CA, Forster GL. Consequences of post-weaning social isolation on anxiety behavior and related neural circuits in rodents. *Front Behav Neurosci.* 2009;3. doi:10.3389/neuro.08.018.2009

78. Naneix F, Marchand AR, Scala GD, Pape JR, Coutureau E. Parallel Maturation of Goal-Directed Behavior and Dopaminergic Systems during Adolescence. *J Neurosci.* 2012;32(46):16223-16232. doi:10.1523/JNEUROSCI.3080-12.2012

79. Tarazi FI, Campbell A, Yeghiayan SK, Baldessarini RJ. Localization of dopamine receptor subtypes in corpus striatum and nucleus accumbens septi of rat brain: comparison of D1-, D2- and D4-like receptors. *Neuroscience.* 1998;83(1):169-176. doi:10.1016/S0306-4522(97)00386-2

80. Tarazi FI, Tomasini EC, Baldessarini RJ. Postnatal development of dopamine D4-like receptors in rat forebrain regions: comparison with D2-like receptors. *Dev Brain Res.* 1998;110(2):227-233. doi:10.1016/S0165-3806(98)00111-4

81. Tarazi FI, Tomasini EC, Baldessarini RossJ. Postnatal Development of Dopamine D1-Like

Receptors in Rat Cortical and Striatolimbic Brain Regions: An Autoradiographic Study. *Dev Neurosci.* 1999;21(1):43-49. doi:10.1159/000017365

82. Andersen SL, Thompson AT, Rutstein M, Hostetter JC, Teicher MH. Dopamine receptor pruning in prefrontal cortex during the periadolescent period in rats. *Synapse.* 2000;37(2):167-169. doi:10.1002/1098-2396(200008)37:2<167::AID-SYN11>3.0.CO;2-B

83. Tarazi FI, Baldessarini RJ. Comparative postnatal development of dopamine D1, D2 and D4 receptors in rat forebrain. *Int J Dev Neurosci.* 2000;18(1):29-37. doi:10.1016/S0736-5748(99)00108-2

84. Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. *Trends Neurosci.* 2008;31(4):183-191. doi:10.1016/j.tins.2008.01.004

85. Fabricius K, Helboe L, Fink-Jensen A, Wörtwein G, Steiniger-Brach B, Sotty F. Increased dopaminergic activity in socially isolated rats: An electrophysiological study. *Neurosci Lett.* 2010;482(2):117-122. doi:10.1016/j.neulet.2010.07.014

86. Enduring increases in anxiety-like behavior and rapid nucleus accumbens dopamine signaling in socially isolated rats - Yorgason - 2013 - European Journal of Neuroscience - Wiley Online Library. Accessed August 9, 2024. https://onlinelibrary.wiley.com/doi/abs/10.1111/ejn.12113

87. Winterfeld KT, Teuchert-Noodt G, Dawirs RR. Social environment alters both ontogeny of dopamine innervation of the medial prefrontal cortex and maturation of working memory in gerbils (Meriones unguiculatus). *J Neurosci Res.* 1998;52(2):201-209. doi:10.1002/(SICI)1097-4547(19980415)52:2<201::AID-JNR8>3.0.CO;2-E

88. Neddens J, Brandenburg K, Teuchert-Noodt G, Dawirs RR. Differential environment alters ontogeny of dopamine innervation of the orbital prefrontal cortex in gerbils. *J Neurosci Res.* 2001;63(2):209-213. doi:10.1002/1097-4547(20010115)63:2<209::AID-JNR1013>3.0.CO;2-E

89. Miura H, Qiao H, Ohta T. Influence of aging and social isolation on changes in brain monoamine turnover and biosynthesis of rats elicited by novelty stress. *Synap N Y N.* 2002;46(2):116-124. doi:10.1002/syn.10133

90. Heidbreder CA, Weiss IC, Domeney AM, et al. Behavioral, neurochemical and endocrinological characterization of the early social isolation syndrome. *Neuroscience.* 2000;100(4):749-768. doi:10.1016/S0306-4522(00)00336-5

91. Niwa M, Matsumoto Y, Mouri A, Ozaki N, Nabeshima T. Vulnerability in early life to changes in the rearing environment plays a crucial role in the aetiopathology of psychiatric disorders. *Int J Neuropsychopharmacol.* 2011;14(4):459-477. doi:10.1017/S1461145710001239

92. Wright LD, Hébert KE, Perrot-Sinal TS. Periadolescent stress exposure exerts long-term effects on adult stress responding and expression of prefrontal dopamine receptors in male and female rats. *Psychoneuroendocrinology.* 2008;33(2):130-142. doi:10.1016/j.psyneuen.2007.10.009

93. Burke AR, Forster GL, Novick AM, Roberts CL, Watt MJ. Effects of adolescent social defeat on adult amphetamine-induced locomotion and

corticoaccumbal dopamine release in male rats. *Neuropharmacology.* 2013;67:359-369. doi:10.1016/j.neuropharm.2012.11.013

94. Burke AR, Renner KJ, Forster GL, Watt MJ. Adolescent social defeat alters neural, endocrine and behavioral responses to amphetamine in adult male rats. *Brain Res.* 2010;1352:147-156. doi:10.1016/j.brainres.2010.06.062

95. Watt MJ, Burke AR, Renner KJ, Forster GL. Adolescent male rats exposed to social defeat exhibit altered anxiety behavior and limbic monoamines as adults. *Behav Neurosci.* 2009;123(3):564-576. doi:10.1037/a0015752

96. Novick AM, Forster GL, Tejani-Butt SM, Watt MJ. Adolescent social defeat alters markers of adult dopaminergic function. *Brain Res Bull.* 2011;86(1):123-128. doi:10.1016/j.brainresbull.2011.06.009

97. Gomes FV, Grace AA. Prefrontal Cortex Dysfunction Increases Susceptibility to Schizophrenia-Like Changes Induced by Adolescent Stress Exposure. *Schizophr Bull.* 2017;43(3):592-600. doi:10.1093/schbul/sbw156

98. Luo XM, Yuan SN, Guan XT, Xie X, Shao F, Wang WW. Juvenile stress affects anxiety-like behavior and limbic monoamines in adult rats. *Physiol Behav.* 2014;135:7-16. doi:10.1016/j.physbeh.2014.05.035

99. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci.* 2011;15(10):483-506. doi:10.1016/j.tics.2011.08.003

100. Akiki TJ, Averill CL, Abdallah CG. A Network-Based Neurobiological Model of PTSD: Evidence from Structural and Functional Neuroimaging Studies. *Curr Psychiatry Rep.* 2017;19(11):81. doi:10.1007/s11920-017-0840-4

101. Cisler JM, Steele JS, Smitherman S, Lenow JK, Kilts CD. Neural Processing Correlates of Assaultive Violence Exposure and PTSD Symptoms during Implicit Threat Processing: A Network Level Analysis among Adolescent Girls. *Psychiatry Res.* 2013;214(3):10.1016/j.pscychresns.2013.06.003. doi:10.1016/j.pscychresns.2013.06.003

102. Corr R, Glier S, Bizzell J, et al. Triple Network Functional Connectivity During Acute Stress in Adolescents and the Influence of Polyvictimization. *Biol Psychiatry Cogn Neurosci Neuroimaging.* Published online March 12, 2022:S2451-9022(22)00069-6. doi:10.1016/j.bpsc.2022.03.003

103. Klein ZA, Padow VA, Romeo RD. The effects of stress on play and home cage behaviors in adolescent male rats. *Dev Psychobiol.* 2010;52(1):62-70. doi:10.1002/dev.20413

104. Barha CK, Brummelte S, Lieblich SE, Galea LAM. Chronic restraint stress in adolescence differentially influences hypothalamic-pituitary-adrenal axis function and adult hippocampal neurogenesis in male and female rats. *Hippocampus.* 2011;21(11):1216-1227. doi:10.1002/hipo.20829

105. McCormick CM, Nixon F, Thomas C, Lowie B, Dyck J. Hippocampal cell proliferation and spatial memory performance after social instability stress in adolescence in female rats. *Behav Brain Res.* 2010;208(1):23-29. doi:10.1016/j.bbr.2009.11.003

106. Toth E, Gersner R, Wilf-Yarkoni A, et al. Age-dependent effects of chronic stress on brain plasticity and depressive behavior. *J Neurochem.* 2008;107(2):522-532.

doi:10.1111/j.1471-4159.2008.05642.x

107. Bluhm RL, Williamson PC, Osuch EA, et al. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *J Psychiatry Neurosci JPN.* 2009;34(3):187-194.

108. Cognitive Behavioral Therapy (CBT) for Treatment of PTSD. https://www.apa.org. Accessed August 9, 2024. https://www.apa.org/ptsd-guideline/treatments/cognitive-behavioral-therapy

109. Trauma–Focused Cognitive Behavioral Therapy. March 8, 2018. Accessed August 9, 2024. https://www.goodtherapy.org/learn-about-therapy/types/trauma-focused-cognitive-behavioral-therapy

110. de Haan A, Meiser-Stedman R, Landolt MA, et al. Efficacy and moderators of efficacy of cognitive behavioural therapies with a trauma focus in children and adolescents: an individual participant data meta-analysis of randomised trials. *Lancet Child Adolesc Health.* 2024;8(1):28-39. doi:10.1016/S2352-4642(23)00253-5

111. Gkintoni E, Kourkoutas E, Yotsidi V, Stavrou PD, Prinianaki D. Clinical Efficacy of Psychotherapeutic Interventions for Post-Traumatic Stress Disorder in Children and Adolescents: A Systematic Review and Analysis. *Child Basel Switz.* 2024;11(5):579. doi:10.3390/children11050579

112. Eye Movement Desensitization and Reprocessing Therapy (EMDR). November 28, 2017. Accessed August 9, 2024. https://www.goodtherapy.org/learn-about-therapy/types/eye-movement-desensitization-and-reprocessing

113. EMDR Therapy: What It Is, Procedure & Effectiveness. Cleveland Clinic. March 29, 2022. Accessed August 9, 2024. https://my.clevelandclinic.org/health/treatments/22641-emdr-therapy

114. Greyber LR, Dulmus CN, Cristalli ME. Eye Movement Desensitization Reprocessing, Posttraumatic Stress Disorder, and Trauma: A Review of Randomized Controlled Trials with Children and Adolescents. *Child Adolesc Soc Work J.* 2012;29(5):409-425. doi:10.1007/s10560-012-0266-0

115. Florido A, Velasco ER, Monari S, et al. Glucocorticoid-based pharmacotherapies preventing PTSD. *Neuropharmacology.* 2023;224:109344. doi:10.1016/j.neuropharm.2022.109344

116. de Quervain DJF. Glucocorticoid-induced reduction of traumatic memories: implications for the treatment of PTSD. *Prog Brain Res.* 2008;167:239-247. doi:10.1016/S0079-6123(07)67017-4

117. Bisson JI, Baker A, Dekker W, Hoskins MD. Evidence-based prescribing for post-traumatic stress disorder. *Br J Psychiatry.* 2020;216(3):125-126. doi:10.1192/bjp.2020.40

118. Stein MB, Simon NM. Ketamine for PTSD: Well, Isn't That Special. *Am J Psychiatry.* 2021;178(2):116-118. doi:10.1176/appi.ajp.2020.20121677

119. Ketamine-assisted Psychotherapy for Adolescent PTSD (KAP). ClinicalTrials.gov. April 22, 2024. Accessed August 9, 2024. https://clinicaltrials.gov/study/NCT06378528?cond=Psychotherapy&term=PTSD&intr=Ketamine&rank=4

120. Bajor LA, Balsara C, Osser DN. An evidence-based approach to psychopharmacology for posttraumatic stress disorder (PTSD) - 2022 update. *Psychiatry Res.* 2022;317:114840. doi:10.1016/j.psychres.2022.114840

121. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and Safety of Sertraline Treatment of Posttraumatic Stress Disorder: A Randomized Controlled Trial. *JAMA.* 2000;283(14):1837-1844. doi:10.1001/jama.283.14.1837

122. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry.* 2001;158(12):1982-1988. doi:10.1176/appi.ajp.158.12.1982

123. Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev.* 2022;2022(3):CD002795. doi:10.1002/14651858.CD002795.pub3

124. Azevedo H, Ferreira M, Mascarello A, Osten P, Werneck Guimarães CR. The serotonergic and alpha-1 adrenergic receptor modulator ACH-000029 ameliorates anxiety-like behavior in a post-traumatic stress disorder model. *Neuropharmacology.* 2020;164:107912. doi:10.1016/j.neuropharm.2019.107912

125. Paiva HS, Filho IJZ, Cais CF da S. Using Prazosin to Treat Posttraumatic Stress Disorder and Associations: A Systematic Review. *Psychiatry Investig.* 2021;18(5):365-372. doi:10.30773/pi.2020.0411

126. Sleep and Emotion Processing in Adolescent Post-traumatic Stress Disorder. ClinicalTrials.gov. July 31, 2024. Accessed August 9, 2024. https://clinicaltrials.gov/study/NCT06341413?aggFilters=ages:child,status:act%20rec%20not&term=stress,%20trauma,%20ptsd,%20adolescent,%20teen&page=2&rank=17

127. Hegberg NJ, Hayes JP, Hayes SM. Exercise Intervention in PTSD: A Narrative Review and Rationale for Implementation. *Front Psychiatry.* 2019;10:133. doi:10.3389/fpsyt.2019.00133

128. Brownstein M. Researchers discover associations among PTSD, diet, and the gut microbiome. Hervard School of Public Health. October 19, 2023. Accessed August 9, 2024. https://www.hsph.harvard.edu/news/press-releases/researchers-discover-associations-among-ptsd-diet-and-the-gut-microbiome/

129. Silhouette Brain Clip Art at Clker.com - vector clip art online, royalty free & public domain. Accessed August 9, 2024. http://www.clker.com/clipart-silhouette-brain.html

130. Cognitive Behavioral Therapy. Inspire Malibu. Accessed August 9, 2024. https://www.inspiremalibu.com/cognitive-behavioral-therapy-cbt/

131. Eye Movement Desensitization and Reprocessing Therapy. Health and Healing Therapy. Accessed August 9, 2024. https://www.healthandhealingtherapy.com/mental-health/approach/eye-movement-desensitization-reprocessing/

132. (CBT) Cognitive Behavioral Therapy. Abalance Client-Centered Counseling. Accessed August 9, 2024. https://abalancecounseling.com/services/cognitive-behavioral-therapy-cbt/

133. Glucocorticoid. Illustrated Glossary of Organic Chemistry. Accessed August 9, 2024.

https://www.chem.ucla.edu/~harding/IGOC/G/glucocorticoid.html

134. Prazosin HCl. Good Laboratory Practice Bioscience. Accessed August 9, 2024. https://www.glpbio.com/prazosin-hcl.html

135. Selective Serotonin Reuptake Inhibitor (SSRI) Mechanism of Action. BioRender. Accessed August 9, 2024. https://www.biorender.com/template/selective-serotonin-reuptake-inhibitor-ssri-mechanism-of-action

136. Page S. 17 Health Benefits of Exercise That May Surprise You. TotalWellness. September 16, 2021. Accessed August 9, 2024. https://info.totalwellnesshealth.com/blog/health-benefits-of-exercise