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Neurobiology of PTSD in Adults and Children: The Impact of Stress-Induced Brain Abnormalities Across the Lifespan

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Abstract

In the scholarly community, there is disagreement about the effects of PTSD or chronic stress on the brain of adults and children. Though PTSD or chronic stress are known to negatively affect neurobiological structures, specifically due to prolonged glucocorticoid excess, volumetric discrepancies between traumatized and control groups are not unanimously confirmed. This review sought to address the common understandings in academia of the effects of PTSD on the brains of adults and children. Literature on this topic indicated that, in adults, the hippocampus, cingulate gyrus, and prefrontal cortex bilaterally appeared to decrease in gray matter volume and the corpus callosum decreased in white matter volume, while the amygdala bilaterally increased in gray matter volume. In children, however, volumetric differences are generally not present. PTSD and chronic stress has further effects on the body, with immunological, cardiovascular, and behavioral differences appearing in traumatized individuals as opposed to healthy controls. Potential genetic or neurochemical treatments are also hypothesized, with specific emphasis being placed on demethylation of the NR3C1 gene and increase of reelin or cypin production. Implications of this review are also given, regarding the importance of interdisciplinary research and how future research must be conducted.

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The Neurobiology of Developmental PTSD: How the Body and Mind Cope with and Heal from Trauma

1. Introduction

Though the United States has emerged as an international economic and social leader during the 20th and 21st centuries, the U.S. has one of the lowest childhood safety scores compared to other developed Western countries (Shinkman, 2018). The Centers for Disease Control and Prevention (CDC) explains that, at minimum, 1 in 7 children in the United States have experienced some form of child abuse or neglect (2022). Moreover, this level of abuse is costly to taxpayers, for, as of 2018, approximately $592 billion total were spent by the United States in addressing this issue, with similar amounts being spent on addressing heart disease or diabetes (CDC, 2022). Such statistics connote the existence of an epidemic that, as Bessel A. van der Kolk says in his book, *The Body Keeps the Score*, is "…the gravest and most costly public health issue in the United States" (2014, p. 150) The effects of trauma or chronic stressful or abusive situations, furthermore, are numerous, with many individuals who endure this trauma developing Post-Traumatic Stress Disorder (PTSD) and other psychological and physical ailments.

The newest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), fifth text-revised edition (DSM-V-TR), released in March 2022, encompasses the most up-to-date understanding and research on the appropriate diagnosis of PTSD in both children and adults. There is a critical distinction between the DSM-IV and the DSM-V-TR; the DSM-V-TR now includes criteria on diagnosing PTSD in children who are under the age of six, an endeavor that had previously been overlooked due to the complexity of diagnosing an individual who is unable to verbally describe their experiences and emotions. Across the four pages of possible

symptoms and criteria for diagnosing PTSD in adults alone, the DSM-V-TR states that one must have been exposed "to actual or threatened death, serious injury, or sexual violence" in any number of manners, along with intrusive and avoidant symptoms (p. 271). Diverging from these criteria, the manual explains that, for children under six, there must be "negative alterations in cognitions," along with intrusive memories that are commonly exhibited as play-reenactment of the trauma (p. 272). A developmental regression in children subjected to trauma and subsequent PTSD can also occur, along with difficulty regulating one's emotions. PTSD can appear as soon as the first year of a child's life, though there has been evidence of "delayed expression" of PTSD symptomology for months or years after the trauma occurred (American Psychiatric Association, 2013, p. 273).

Though a great deal of research has been conducted regarding the state and treatment of PTSD in adulthood, only in recent years has research on childhood PTSD come about, with most results being inconclusive and unable to be irrefutably replicated. This literature review will first synthesize and compare known information about the neurobiological changes associated with PTSD or chronic stress diagnoses in adults and children to outline all current data on the topic. Next, this review will give a comprehensive analysis of the immunological, physiological, and behavioral effects of PTSD or chronic stress, all in order to analyze how treatments addressing trauma and PTSD must differ between adults and children. Thus, the goal of this review is to hypothesize new avenues for research, with most revolving around glucocorticoid-focused treatments, in order to underscore the importance of PTSD-related studies and illustrate necessary and crucial changes in psychological research.

2. Outline of Neuroanatomical Structures and Neurochemicals

Limbic System

The limbic system is comprised of many key structures, most notably the hippocampus, the amygdala, the corpus callosum, the cingulate gyrus, and the hypothalamus. Located medial to the cerebral cortex or lobes of the brain and superior to the brain stem, the primary role of the limbic system is to process one's memories and emotions (Guy-Evans, 2021). Presented below are explanations of each portion of the limbic system.

Hippocampus. Named after the Greek word for "seahorse" (Ho and Ross, 2016) due to its curved shape, the hippocampus is the most well-understood and researched part of the limbic system (Knierim, 2015). This part of the brain, which sits posterior to the amygdala and directly on top of the brain stem, contributes to initial memory processing prior to long-term storage (Tsien & Wittenberg, 2002) and regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis (Jacobson & Sapolsky, 1991). The hippocampus is able to modulate the HPA axis by expressing glucocorticoids (Smith & Vale, 2006), the role of which is described below. Because of the hippocampus' malleable, ever-changing structure, glucocorticoids also have been hypothesized to affect its formation (Conrad, 2011; Anand & Dhikav, 2012).

Glucocorticoids. This steroid hormone is classified as a catabolic hormone and originates in the adrenal gland (Conrad, 2011), with the purpose of breaking down molecular bonds to produce energy in a negative feedback loop with the HPA axis (Herman & Jankord, 2009). A negative feedback loop is a homeostasis-regulatory mechanism, meaning that it helps maintain a healthy resting state for the body, in which the amount of chemicals in the bloodstream affects

the quantity of the same chemical produced. Such a regulation occurs through an inverse relationship, meaning that, as levels of a certain chemical increase in the bloodstream, the release of the chemical into the bloodstream decreases, and vice versa (Boskey, 2023). Regarding glucocorticoids, the negative feedback loop allows for safe levels of glucocorticoids to be in the body by ensuring that high levels of glucocorticoids are not present in the blood for too long (Sauro, 2017).

Thus, glucocorticoids are hormones that aid in maintaining homeostasis or consistent and safe molecular levels of stress hormones in the body (Yang & Yingyan, 2021) and help to immediately mobilize energy in high-stress situations (Conrad, 2011). Examples of commonly understood glucocorticoids include cortisol, which is naturally occurring, as well as prednisone and hydrocortisone, which are generally synthetically made. Glucocorticoids, along with other steroid hormones that are produced outside of the brain, which become neurotransmitters as they enter the brain, are able to cross the blood-brain barrier (BBB), which protects the brain from harmful substances (Banks, 2012; National Cancer Institute, n. d.). This protective mechanism occurs through transmembrane diffusion, wherein only certain hormones or chemicals are moved across the membrane barrier of the brain by means of carrier proteins (Hall, 2021).

Amygdala. The amygdala, originating from the Greek word for "almond" (Salzman, 2019, para. 1), is an oval-shaped structure located anteriorly to the hippocampus and is known to detect threats in the environment by controlling defensive responses to possibly threatening situations (Vasterling & Brewin, 2005). Such responses are elicited by the release of catecholamines, which are described below; moreover, serotonin also participates in the expression of the HPA axis and the expression of emotional appraisal in the amygdala, in a

similar fashion to the control through stress that the hippocampus has over the HPA axis, which is also explained below (Feldman et al., 1998).

Catecholamines. Like glucocorticoids, catecholamines are produced by the adrenal glands and are released in response to a given stressor (Smith, 2020), making catecholamines concentrations positively correlated to glucocorticoid concentrations. Examples of catecholamines include dopamine, norepinephrine, and epinephrine (Vasterling & Brewin, 2005). Known to act both as neurotransmitters and hormones, the role of catecholamines in the brain is to activate an emotional or instinctual response to a perceived threatening situation (Paravati et al., 2021). Silberman and Winder (2013) made similar conclusions, finding that catecholamine signaling is a key factor in modulating amygdala activity by controlling circulatory glutamate, an excitatory neurotransmitter (Silberman & Winder, 2013; Zhou & Danbolt, 2014).

Serotonin. This hormone, which becomes a neurotransmitter as it enters the brain, is found in the bloodstream (American Chemical Society, 2013) and constricts blood vessels in response to stress (Cleveland Clinic [CC], 2022b). Created primarily in the gastrointestinal tract, though it is also found in the midline of the brainstem, serotonin plays a vital role in mood, sleep, digestion, and recovery from illness (CC, 2022b). Amygdalae functioning and concentration of serotonin in the amygdala are inversely related; as serotonin levels decrease, activation or functionality of amygdalae increases (Vasterling & Brewin, 2005).

Corpus Callosum. A core component of the brain, the corpus callosum connects the two hemispheres of the brain together by a thick collection of axons or nerve fibers (Queensland Brain Institute, 2017). The corpus callosum is located under the lobes of the brain, partially enveloped by the hippocampus and above the amygdala. This portion of the brain is key to the functionality of and communication between the left and right hemispheres because it attaches both hemispheres through myelinated axons (Luders et al., 2010). The corpus callosum is thought to be influenced negatively by glucocorticoids, the details of which are described further in this review (Huang et al., 2001).

Cingulate Gyrus. Located above the hippocampus and directly beneath the temporal lobe, the cingulate gyrus assists in the regulation of emotions, behaviors, and pain, as well as helping control autonomic motor functions, a term used to describe rate of breathing, heartbeat, and other bodily functions that are not consciously controlled (Guy-Evans, 2021). This part of the brain is also involved in foreseeing and subsequently avoiding possible negative outcomes in a person's life (Cold Spring Harbor, 2020). Like the hippocampus, the cingulate gyrus helps regulate of the expression of glucocorticoids from the HPA axis and is affected by glucocorticoid amounts in the brain (Diorio et al., 1993; Lu et al., 2013).

Hypothalamus and HPA axis. The hypothalamus, similar in size to the amygdala (CC, 2022a), sits superior to the amygdala and is spatially close to the prefrontal cortex than the amygdala. The role of the hypothalamus is primarily to maintain the body's homeostasis or resting state at all times (Guy-Evans, 2021). Because of this, the hypothalamus controls levels of hunger, thirst, one's body temperature, and other autonomic functions (Guy-Evans, 2021),

making it an important connection between the endocrine system, the hormone system (United States Environmental Protection Agency, 2022), and the nervous system (CC, 2022a). Moreover, the HPA axis is integral in the stress response, as the hypothalamus signals the pituitary gland to produce a hormone, which then signals the adrenal glands to increase glucocorticoid production (American Psychological Association, 2018). The hypothalamus itself will not be the focus of this review; however, the HPA axis is means by which glucocorticoids enter into the system, making it crucial to stress expression and PTSD development.

Prefrontal Cortex

Separate from the limbic system, the prefrontal cortex (PFC) further regulates stress-responses and memory, and it is thought to be negatively affected by trauma or PTSD. Located anteriorly to the frontal lobe (Queensland Health, 2022), the PFC is known as important to working memory, which is used to focus on tasks, self-regulatory behaviors, and executive functioning, how one can plan and control behaviors (McEwen et al., 2016). Glucocorticoids and catecholamines are all to have an effect on PFC development and function, as the PFC is very sensitive to the concentrations of these chemicals (Aburada et al., 2004; McGaugh et al., 2004).

3. Overview of Neurobiological Differences in Adults

Changes in the Hippocampus

Scientists, such as Von Ziegler et al. (2022), have found that mammals can have short-term negative outcomes from acutely stressful situations. Here, researchers conducted preclinical studies in the forced swim stress model, wherein there are two groups of mice, one group of mice swimming in a pool for six minutes with no apparent escape and another group being able to

swim to a ledge. These scientists discovered many chemical changes in the hippocampi of mice who had no visible escape, the first of which was the phosphorylation or addition of a phosphate group of proteins in the hippocampus, which researchers identified as the earliest intracellular signal of change caused by stress. Moreover, these scientists found transcriptomic changes, alterations in the rat's gene expression, both in general and in specific cell types, such as astrocytes, neurons, vascular cells, and oligodendrocytes. Nonetheless, these changes were entirely reversed by the fourth hour after the experiment, as the rats were able to return to homeostasis after the stressful event (Von Ziegler et al., 2022).

Many studies during the 21st century have focused on the theoretical point at which the level of stress and concentration of glucocorticoids exceeds the levels the body can manage while maintaining homeostasis. Depending on both the high concentration and prevalence of glucocorticoids in the limbic system, hippocampal volume and shape can be altered, most commonly between the CA3 region of the hippocampus and the dentate gyrus gland, located in the innermost region of the hippocampus (Conrad, 2011). This change is thought to occur because of a decrease in cell proliferation, differentiation, and the branching out of dendrites, the end of neurons that allows for further connection to other neurons (Conrad, 2011). Further, brain-derived neurotropic factor (BDNF), in opposition to glucocorticoids, aid in the differentiation and growth of neurons and maintain neuronal circuitry over time (Bekinschtein et al., 2008). Because of the inverse functionality of BDNF and glucocorticoids, BDNF levels appear to decrease when stress and glucocorticoid levels increase (Kozlovsky et al., 2007). Thus, because decreased BDNF levels lead to an inability to maintain existing neurons and increased glucocorticoid levels lead to a decline in neuronal connectivity, hippocampal volume, in the face of extreme or prolonged stress, may be lessened.

PTSD and chronic stress, therefore, can greatly affect the size and neuronal makeup of the hippocampus. In order to understand the general conception of changes in hippocampal volume seen in victims of trauma and diagnosed with PTSD, Woon and Hedges (2008) conducted a meta-analysis of 21 studies between 1997 and 2007. Researchers here found that there was a significant decrease in bilateral hippocampal volume in adults with PTSD, as the difference in left and right hippocampal volumes was statistically significant (Woon & Hedges, 2008). The pair explain their findings further, saying that higher chronic glucocorticoid levels, which come with an increase in perpetual stress, can decrease hippocampal volume significantly, for reasons explained previously. Similarly, Woon et al. (2010) found that bilateral hippocampal volumes in those who had been exposed to trauma were notably smaller than that of others who were not exposed to trauma.

Moreover, Zhang et al. (2011) found that, in 22 survivors of a coal mine flood disaster who had a subsequent onset of PTSD and who underwent MRI scanning, gray matter hippocampal volume appeared significantly smaller. Notably, however, researchers in this study found no change in white hippocampal volume. This decrease in the size of gray matter in the hippocampus is key to understanding the implications of smaller hippocampus size. Gray matter contains dendrites and synapses, consisting of local neuronal networks without myelination, while white matter contains neuronal networks that allow for proper communication between parts of the brain through myelinated axons (Wen & Chklovskii, 2005). The disparity between gray matter decreasing and white matter being constant in the hippocampus can be understood thusly: Because gray matter is comprised of mostly dendritic branches or synapses, and because glucocorticoids have been shown to decrease dendritic branching, it can be estimated that gray

matter reductions in the hippocampus occur through excess glucocorticoid concentrations that decrease the content of the gray matter itself.

Despite the seemingly unanimous and convincing results of the previous studies, O'Doherty et al. (2015), upon conducting their meta-analysis of 59 volumetric analyses, found that results of hippocampal volume decreases are not consistent. For example, Yehuda et al. (2005) assessed the volume of gray and white matter in the hippocampus in 33 male combat veterans with and without PTSD who were given a trauma history questionnaire and a Childhood Trauma Questionnaire (CTQ). These participants were also given two cognitive tests, the Wechsler Adult Intelligence Scale (WAIS-III) that assessed verbal and nonverbal intelligence, along with the Wechsler Memory Scale-III (WMS-III), a logical memory test. First, scientists here found a significant mean increase in urinary cortisol excretion per day (p=.03) and a significantly weaker performance on memory tests for those with PTSD.

This, researchers believe, illustrates an inverse relationship between glucocorticoids and memory, as there is an increase in glucocorticoid levels in the urine for those with decreased memory capacities. However, the MRI scans were unable to statistically prove that veterans with diagnosed PTSD had smaller hippocampi (Yehuda et al., 2005). The results of this study and others of the sort that find no significant hippocampal volume differences could be inaccurate due to small sample sizes and the subjects being of an older age (Jatko et al., 2006). Thus, more research with a larger number of subjects and less confounding variables must be conducted to affirm or deny conclusions on decreases in hippocampal volume and PTSD diagnoses.

Changes in the Amygdala

Unlike hippocampal research, the amygdala has been much less investigated, making conclusions on this topic particularly hard to reach. Hölzel et al. (2009) conducted a study to examine the correlation between perceived stress and gray matter volume changes in the amygdala. Similar to hippocampal volume changes, these researchers found that increases in amygdalae gray matter volumes were related to self-reported perceived stress scale (PSS) numbers. From this correlation, researchers proposed that increases in amygdalae volumes, specifically in the right, bottom corner of the gray matter in this structure were significantly associated with an increase in stress. Researchers in this study also found that the right portion of the amygdala being implicated was critical to understanding the effects of volumetric increases in amygdala, as this portion of the amygdala is where sensory information is relayed from cortical areas of the brain to the central areas of the amygdala (Hölzel et al., 2009; Caetano et al., 2021). This gray volume increase, scientists found, was due to an increase in dendrite length and the general number of dendrites in the amygdala (Caetano et al., 2021). Such increases in volume, it is hypothesized, increase hyperactivity of the amygdala, which can lead to intrusive thoughts, memories, and flashbacks (Pitman et al., 2006).

Pieper et al. (2020), moreover, investigated amygdalae volume changes associated with PTSD in 89 combat veterans who had a comorbid traumatic brain injury (TBI). Here, researchers found that, upon viewing MRI scans from each participant to compare amygdalae volumes to general brain volume, those with comorbid PTSD and TBI had significantly larger amygdalae in comparison to those who only had a TBI. Bae et al. (2019) concurred with these results, finding that, though there was no significant difference volumetrically in those who had PTSD and those who did not have PTSD but had a TBI, there was a trend of left amygdalae volumes being larger

(p=0.06) in those with PTSD and TBI compared to right amygdalae volumes in the same group. However, researchers did find a significant correlation, though small, between HAM-D scores, a test for depression, and left amygdalae volumes (r = -.28, p = .04). With this data in mind, scientists hypothesized that combat veterans who have PTSD and a traumatic brain injury are more likely to have volumetric increases in the left amygdalae, as opposed to control groups without PTSD or TBI and to veterans with TBI and not PTSD (Bae et al., 2019). Nevertheless, more research must be conducted to confirm these results on a larger scale, apart from combat PTSD and TBI comorbidity.

Due to sparse research on amygdala volume increases in subjects with PTSD, there has yet to be any definitive determinations concerning volumetric changes in those with PTSD. Pitman et al. (2006) detailed five neuroimaging studies in which amygdala activation, though expected, did not appear in those who were experiencing symptoms of PTSD; these studies are reported here for referencing purposes (Bremner et al., 1997; Shin et al., 1999; Bremner et al., 1999a; Bremner et al., 1999b; Lanius et al., 2001). Conversely, Karl et al. (2006), in a meta-analysis of 48 studies, found that amygdala volumes were significantly smaller bilaterally in those with PTSD compared to healthy controls. And, in this study, left amygdala volumes in adults with PTSD were statistically smaller in comparison to the healthy control group. Findings of a smaller left amygdala were also found by Beall et al. (2012), wherein 200 combat veterans were located between 2006 and 2010 and split into groups, with one group having PTSD and the other being subjected to war violence but not having diagnosed PTSD. Upon obtaining MRI scans of each participant, these researchers concluded that there was an association between smaller left amygdala volume and PTSD diagnoses. Thus, conclusive volumetric amygdalae results are not available, which gives way to the need for most controlled studies on this topic.

Changes in the Corpus Callosum

Goldstein et al. (2022) explain how the corpus callosum is comprised solely of white matter, comprised of a total of 200 million myelinated axons. Unfortunately, there are significantly less studies focused on corpus callosum and PTSD correlation than the amygdala and hippocampus, making analysis of PTSD-specific effects on the corpus callosum more difficult to discern; nevertheless, current and available information on adult corpus callosum volumetric abnormalities will be outlined.

The majority of studies regarding volumetric changes in the corpus callosum after chronic stress or PTSD show that there is a general reduction in the white matter of the corpus callosum; specifically, Siehl et al. (2018) found that, in adults with late-onset PTSD, there were volumetric decreases, though slight, in the corpus callosum. Moreover, Brooks et al. (2004) conducted a study, wherein ten women with PTSD of various origins were given MRI scans. Here, scientists found significant volumetric decreases in many subregions of the corpus callosum in those with severe and chronic PTSD.

Another group found dissimilar results, however; Graziano et al. (2019) found no significant volumetric changes in the corpus callosum. The composition of the corpus callosum is notable, as, up until this point, the only volumetric changes that have been found has been in the gray matter of the hippocampus and amygdala. Nevertheless, there now appears to be changes in the white matter, in the axon bundles as opposed to the neuronal centers. The question arises as to why the white matter comprising the corpus callosum is affected, while the gray matter of the hippocampus and amygdala is affected, which will require further research to address.

Changes in the Cingulate Gyrus

The focus of this cingulate gyrus review will be on the anterior cingulate gyrus (ACG), which contributes most to the control of conditional or learned fear responses (Mahmutyazıcıoğlu et al., 2005), as it is the most researched and well-understood portion of the cingulate gyrus. Shin et al. (2001) found that combat veterans with PTSD had lower functioning ACGs compared to combat veterans without PTSD, an understanding which is generally agreed upon scientifically. Kasai et al. (2008) concurred, finding a decrease in the gray matter of the anterior cingulate cortex (ACC), which encompasses more than the cingulate gyrus alone, in combat-exposed twins with PTSD compared to those without PTSD. Notably, Mahmutyazicioğlu et al. (2005), upon conducting a study with ten subjects who have diagnosed PTSD and six healthy controls, found a decrease in ACG volume. These researchers hypothesized that this volume decrease was due to the loss seen in the hippocampus, which, theoretically, implicates glucocorticoids as decreasing the size of the ACG, though researchers have yet to confirm this theory. O'Doherty et al. (2015) add to this conclusion, describing how atrophy of the ACG is scientifically more conclusive than that of the hippocampus, as they found numerous studies from 1999 to 2008 that determined as such.

Despite the results of these studies, some scientists have failed to replicate the results concerning gray matter volume decreases ACG/ACC. For example, Labonte et al. (2012) found no significant differences in volume in the ACGs between those with PTSD and without PTSD. Moreover, Lanius et al. (2004), upon researching found hyperactivation of the ACC in 11 subjects who had developed PTSD after sexual abuse, which contradicts previous findings. Such results reveal a need for more in-depth analyses of the cingulate cortex and cingulate gyrus and its implications in the outward expression of PTSD symptomology.

Changes in the Prefrontal Cortex

As Arnsten and Li (2005) explain, catecholamines are critical to PFC function, for they explain that depletion of catecholamines can be as harmful to PFC performance as if the PFC were entirely removed. Moreover, increased levels of catecholamines during stressful events impair executive functions, such as inhibiting inappropriate behaviors and thoughts and planning for the future (Arnsten and Li, 2005; Arnsten, 2011). Few studies, however, have addressed the role of the PFC in stress modulation and PTSD symptoms. To identify how the PFC influences PTSD symptomology in mammals, Almeida et al. (2011) conducted a preclinical study that began when male Wistar rats were two months old. Upon subjecting the rats to chronic stress in the form of a water-maze task, these researchers found that long-term stressors can severely affect and change behavioral flexibility and working memory. These scientists confirmed that such changes were due to plasticity or malleability differences in the hippocampus-to-PFC synapses and specific volumetric reduction of the uppermost PFC. The importance of hippocampus-to-PFC synapses is further revealed in this study, as researchers explain how the medial PFC (mPFC) is stimulated and influenced by hippocampal activity. However, these researchers were unable to conclusively find volumetric changes in the PFC. Likewise, Akerib et al. (2011) found that ventral-medial PFC (vmPFC) activity positively correlated with PTSD symptom severity and activation.

However, some researchers have found volumetric changes in the PFC that mirror the changes of the hippocampus. PFC volume has been shown to decrease after traumatic exposure (Kredlow et al., 2022), with the most common reduction occurring in the gray matter of the PFC (Holmes et al., 2018). Geuze et al. (2008), furthermore, conducted a study of 25 male veterans to identify a hypothesized change in the cortical thickness, the outer layer of gray matter, of the

PFC after combat-induced PTSD. Here, researchers found that there was a thinning of the cortical layer of the PFC, with subsequent PFC functioning being proportionality compromised. Studies on PFC volumetric changes, though, are sparse, with more placed on the hypoactivation of the mPFC in subjects with PTSD instead of concrete volumetric abnormalities (Patel et al., 2012). Because chronic stress, trauma, and PTSD appear to impact executive controls in the PFC, volume differences may also be present and, thus, must be studied further.

4. Neurobiological Differences in Developmental PTSD

Regardless of the devastating consequences of chronic stress and PTSD on the adult brain, such stressors in childhood have consequences beyond previous neurobiological abnormalities in adults. Thus, it is crucial to examine trauma through the lens of the children and adolescents in order to have a fuller scope of the evolution that chronic stress, trauma, and PTSD have on the developing brain that would, therefore, impact them in adulthood. The change in DSM-V criteria to include diagnostic criteria for children under six-years-old is key here, as clinicians now have the proper measures to successfully identify and treat prepubescent PTSD symptoms that were previously beyond their reach.

The scientific consensus referring to why children have the capacity to maintain statistically similar limbic system volumes, which is further described below, is due to the increased plasticity or malleability of developing brains. Dennis et al. (2013) define plasticity as the brain's ability to return to homeostasis after some neuronal change by adapting to the changed conditions and being relatively unharmed. The advantage for children appears to be that their neuronal composition generally allows for better acclamation to new stressors, because developing brains are thought to be more plastic than matured brains.

Nevertheless, changes in the brain, to some extent, occur in the developing limbic system of children who have experience chronic stress or trauma as the brain matures, primarily due to the chemical shifts that were caused by the trauma or abuse. Some neuronal differences between children with PTSD or chronic stress and healthy children are similar to that of adults; there are alterations in the HPA axis function and, thus, chronic glucocorticoid concentration increases (Parade et al., 2016). However, volume changes in children's brains do not occur immediately as a result of these chemical changes, which is conversely observed in adulthood. Regardless, there are both similarities and differences regarding volume changes in the brain as a result of chronic stress or PTSD in adults and children.

Changes in the Hippocampus

As is true for developmental PTSD research in children and adolescents, there is a lack of information and, thus, many differing views as to hippocampal dysfunction in maltreated children. Unlike research concerning hippocampi in adults with PTSD, studies regarding hippocampi in children with PTSD are weaker and sparser, with more emphasis being placed on general symptoms of developmental PTSD instead of specific neurobiological correlations to PTSD in children. Woon and Hedges (2008) conducted an in-depth analysis and comparison of the hippocampus of children and adulthoods who were maltreated in childhood. This study found information concerning general volumetric and symmetry changes; hippocampal volumes between the PTSD group and the control group, both of which were comprised of children, were statistically similar, with the size of both hippocampi being statistically symmetrical. However, adults with PTSD had a significant reduction in hippocampal volume compared to healthy controls, with a greater reduction observed in the left hippocampi than the right, meaning that the

asymmetry normally seen in healthy adults was not present in those with PTSD. Hart and Rubia (2012) concur with these results, as they observe that initial responses to child abuse do not cause volumetric changes in the hippocampus until the individual matures.

Disagreement about hippocampal volume in children with PTSD, however, is readily apparent, with some studies suggesting an increase in hippocampal volume in children and adolescents with PTSD. De Bellis and Tupler (2006) found that bilateral hippocampal volume was higher in children with PTSD than those without when examining MRI scans of 61 maltreated children. Scientists suggest that this increase is due to a drastic increase in cortisol, which may cause the hippocampus to initially increase in size then decrease as the child matures (Hart & Rubia, 2012). Moreover, De Bellis (1999) did not find any significant volumetric differences in developing hippocampi.

Regardless of various statistical volumetric findings on the hippocampus, researchers found that PTSD appears to substantially affect memories of maltreated children. For example, children with PTSD performed statistically worse on orientation and prospective memory tasks than children in a control group, with prospective memories ideas of what must be completed in the future and orientation memory being memory of oneself, time, and location (Moradi et al., 1999; Wilson, 2010). Such memory-related deficiencies in children with PTSD are similarly observed in adults with PTSD; however, the cause of memory deficits in children specifically has not been identified.

Some evidence suggests developmental memory deficits may occur due to an increase in glucocorticoid levels that have yet to impact neurostructural volumes, yet more research is needed to confirm this theory. Despite inconclusive evidence regarding volumetric changes in the developing hippocampus of those with PTSD, Chen et al. (2019) explain how chronically

heightened levels of glucocorticoids, in altering hippocampal functioning, impair memory functions that were observed by Moradi et al. (1999), which could also give a viable explanation for childhood memory loss. Thus, further research investigating correlational relationships between memory deficits and hippocampal abnormalities in children with PTSD must be conducted.

A question that arises from the differences in the hippocampi of adults with PTSD and children with PTSD is the origin of causation, whether hippocampal volume affects PTSD development, or vice versa (Woon & Hedges, 2008). An answer to this question has not yet been conclusively determined, though many believe volumetric reductions to reflect PTSD symptomology, thereby asserting that volumetric decreases are caused by chronic stress or PTSD. Nevertheless, more research must be conducted to confirm or deny this conclusion to see whether chronic stress and PTSD cause volumetric changes in hippocampi or smaller hippocampi increase the likelihood of developing PTSD.

Changes in the Amygdala

Van der Kolk (2003) discusses a developmental difference between the hippocampus and the amygdala that could give a valid theory for the differences that are seen volumetrically between the hippocampus and the amygdala. He explains how the amygdala starts functioning very quickly after birth in order to analyze possible fearful situations necessary for survival, while the hippocampus can take up to five years to fully function; this understanding of developmental differences could give scientists more understanding as to why hippocampal volumes do not appear to be impacted until later in the child's life and why the amygdala

responds to glucocorticoid increases by increasing responsiveness to stimuli instead of decreasing sensitivity, which will be explained further.

In a comprehensive review of previous research, Cohen et al. (2002) discussed differences between normal neural functions in children compared to that in children with diagnosed PTSD. Here, scientists found that the effects of chronic stress or PTSD on children's brains potentially activates a hyperresponsiveness of the amygdala, as the negative feedback loop that is intended to maintain homeostasis in the child's brain does not function properly. This negative feedback loop is intended to occur when the release of neurotransmitters, most notably gamma-aminobutyric acid (GABA), from the mPFC signals less of this same neurotransmitter to be released (Sun et al., 2018). Cohen et al. (2002) explain how amygdala overactivity can have detrimental impacts on PTSD symptomology by describing hyperactivity both as the cause of intrusive, recurring traumatic memories and the fear that follows from these memories, both of which are common PTSD symptoms in children.

Similar to findings concerning the developing hippocampus, volumetric analyses of the amygdala are inconclusive. Woon and Hedges (2008) found that bilateral amygdalae volumes were not statistically different between children with PTSD and children without. Notably, in children in general, the right amygdalae were greater than the left, which was also true for the adult control and experimental groups; however, more research would need to be conducted to confirm these findings. Likewise, Herringa (2017), in conducting a review of relevant volumetric analyses of developing limbic systems, found that amygdala volume was most significantly altered when the trauma occurred before the age of ten or eleven. Notably, the most crucial period of development for amygdala functioning occurs during Piaget's concrete operational stage, in which problem-solving abilities sharpen and puberty begins (Nortje, 2021). Though not

scientifically confirmed, developing amygdalae being more detrimentally impacted when trauma occurs during the concrete operational stage may affect a child's ability to problem-solve or see other outcomes to a given event.

Moreover, Herringa (2017) addresses one of the believed neurobiological difference between mentally "weak" and "strong" individuals: Increased prefrontal-amygdala coupling appears to reflect "strong" minded children's ability to be resilient, with the opposite being true for "weak" minded or high internalized adolescents. With this information, further research is necessary to quantifiably understand resilience and its relationship to the communicative abilities parts of the brain have with one another. Other research is also necessary in this field to resolve disagreements in volumetric and neuronal changes in the amygdala, as well as to functionally understand why the developing amygdala does not exhibit more statistically conclusive results as those seen in adults.

Changes in the Corpus Callosum

Similar to studies focused on the corpus callosum in adults, many studies of neurobiological manifestations of developmental PTSD report changes in the amount of white matter present in the corpus callosum. Jackowski et al. (2007) used diffusion tensor imaging, the use of MRI technology to microscopically visualize tissue in white matter portions of the brain (Alexander et al., 2007), to investigate corpus callosum size both in children who had been reported to child protective services for maltreatment and in a healthy control group. Results from this study revealed that maltreated children had reduced fractional anisotropy, a way in which the rate of molecular diffusion in the brain is measured, in the posterior and medial regions of the corpus callosum. Rinne-Albers et al. (2016) took these findings a step further,

addressing a correlation between abnormalities in the white matter in the left body of the corpus callosum and anger presentation in adolescents with PTSD, which brings into question how molecular diffusion in the corpus callosum affects emotion regulation. Interestingly, researchers hypothesize a cause for the reduction in molecular diffusion, explaining that there may be a decrease in developmental-expected myelination of axons in the corpus callosum (Jackowski et al., 2007; Rinne-Albers et al., 2016).

This proposition has interesting implications in the understanding of long-lasting effects of PTSD on the developing brain. The volumetric aspects of the corpus callosum did not appear to change in the presented studies; however, the individual axonal integrity within the medial and posterior corpus callosum did change. This conclusion can lead scientists to investigate specifically how to myelinate axons that have not properly myelinated themselves, a process which could aid in the decrease of the long-term effects of chronic stress or PTSD. Nevertheless, there must be continued study of how the corpus callosum alters developmentally in children and adolescents with PTSD, as studies of this sort are sparse in number and entirely correlational in nature, thus not being able to confirm causality in any regard.

Changes in the Cingulate Gyrus

Studies conducted about the cingulate gyrus in children with chronic stress or PTSD, though few, address four main areas of the cingulate gyrus, the ACC, the frontal pole (FP), inferior frontal cortex (IFC), and the posterior cingulate cortex (PCC). Sun et al. (2018) tested three experimental groups, 57 non-maltreated or healthy controls, 32 maltreated children without diagnosed PTSD, and 31 maltreated children with PTSD. Through the use of MRI comparisons, these researchers found significant functional differences in the ACC, FP, IFC, and PCC between

all three experimental groups. Notably, volumetric changes associated with the cingulate gyrus were not found; the presented changes are more associated with the way in which cortical thickness in one area facilitates proper brain functioning in another area is decreased (Sun et al., 2018). Volumetric changes, in and of themselves, do not appear to be responsible for behavioral and cognitive changes associated with PTSD in this study, for it is the relationship between sections in the cingulate gyrus that have deteriorated.

Other studies generally concur with this conclusion, commenting on the change in functional connectivity in the cingulate gyrus. Milani et al. (2016) add further research to this understanding of the cingulate gyrus, saying that those with acute stress syndrome (ASD), understood as the formation of PTSD symptoms in less than a 30-day time span, exhibited an increase in the activation of the frontal, anterior, and medial portions of the cingulate gyrus. Apart from these discoveries, not much else in the literature or research has been presented regarding the cingulate gyrus; thus, more studies concerning cingulate gyrus deficits in children and adolescents must be conducted, specifically regarding neuronal malformities within the connections between the different portions of the cingulate gyrus.

Changes in the Prefrontal Cortex

Similar to volumetric changes seen in the developing and matured amygdala, the PFC has been shown to generally increase in volume, specifically in the gray matter of bilateral inferior and superior, or top and bottom, sections of the PFC (Carrion et al., 2009). Moreover, the axonal density, or number of axons in a given area, in children in this study who had experienced interpersonal trauma was increased, especially in the ventral PFC (vPFC), when compared to children who had not experienced trauma. These results are supported by a comprehensive study

conducted by Richert et al. (2006), as this investigation was the first of its kind to compare specific structures within the PFC in children with and without PTSD symptoms. These researchers, in evaluating the MRI data from 23 children who expressed PTSD symptomology and scored highly on the Clinician-Administered PTSD Scale (CAPS-CA) and 24 children who were healthy controls, found a positive correlation between PTSD symptomology and an increase in gray matter volume in the middle-inferior PFC (miPFC) and the vPFC. Conversely, these scientists also found a decrease in gray matter volume in the dorsal PFC (dPFC), to which researchers attribute a negative correlation between dPFC volume and functional impairment.

Further, many studies regarding the PFC and pediatric PTSD focus primarily on the vmPFC, a focus that reflects research in adults with PTSD. As such, Morey et al. (2016), in a cross-sectional study of maltreated youth with and without PTSD and healthy, non-maltreated controls, found that maltreated children with PTSD generally displayed a volumetric decrease in the right vmPFC compared to the other two experimental groups. Interestingly, researchers in this study suggest that the volumetric changes seen in the vmPFC could explain why PTSD is so often present with other mental health conditions.

Limitations

A critical discrepancy regarding child and adolescent research of correlations between chronic stress or PTSD and other neurobiological malformities exists and must be understood to address necessary avenues of pediatric trauma research. Many of the aforementioned studies, which have been noted accordingly, analyze neurobiological differences between maltreated and non-maltreated youth. Though such an investigation certainly is of great importance, as seen in other studies presented in this review, there is a neurobiological difference between maltreated

youth who are diagnosed with PTSD and those who were not diagnosed or presenting with PTSD symptoms. As such, it is the duty of current researchers to investigate reasons for why some children respond neurobiologically differently than other children might respond.

5. Physiological and Behavioral Manifestations of PTSD in Adults and Children

Proper analysis of the difficulties for individuals that experience PTSD and chronic stress must expand beyond the brain and address the entirety of the body for adults and children alike. Before further elaboration on these topics of physical manifestations of PTSD, it must be emphasized that an individual exhibiting physical symptoms similar to that described in the following sections does not imply that their symptoms are caused by PTSD or chronic stress, nor does it mean that a person who has PTSD or chronic stress will encounter such physical or behavioral abnormalities. As such, though research will be addressed in this section, in no way is information on this particular section indicative of the definitive behaviors or physiological characteristics of a population of people; it is merely to show the long-lasting, life-altering impacts PTSD can have on the body when left untreated over time. Thus, there will be little focus on physiological reactions that are a byproduct of the behavior itself, thereby making the focus of this section the direct physiological and behavioral changes that occur as a byproduct of PTSD or chronic stress.

PTSD and the Immune System

Recent research has identified a potent link between immune dysfunction and the presence of PTSD in adults. Research on biological malformities in adults with PTSD generally focus on two hormone-circulating systems, the HPA axis and the sympathetic-adrenal-medullary

(SAM) system (Pace & Heim, 2011), the latter of which is beyond the scope of this review. As previously discussed, the HPA axis releases glucocorticoids, categorized as steroid hormone. Scholars have observed a deficiency in cortisol circulation that appears more commonly in adults with PTSD rather than healthy controls, thereby leading poor circulation of glucocorticoids to be a possible cause for immune dysfunction (Neigh & Ali, 2016). Individuals with PTSD have commonly been shown to have decreased rhythmic cortisol spiking compared to healthy controls, which is thought to be correlated to chronic illnesses such as cardiovascular disease and insulin resistance (Wessa & Rohleder, 2014). Mechanistic causes for the link between immune system and PTSD, however, have been hypothesized but not definitively identified, including a reduced circulation of cortisol and a premature shortening of telomeres or the end of chromosomes that slowly shorten during replication, among others (Neigh & Ali, 2016).

Regardless of possible structural causes for immune deficiencies resulting from chronic trauma exposure or PTSD, scientists generally agree that the immune response of an individual with PTSD is statistically different compared to a healthy control, with great emphasis being placed on the common increase in inflammatory responses and decrease in anti-inflammatory responses (Sun et al., 2021). Katrinli et al. (2022) address immune inflammation, which originates in the immune system, directly by investigating possible immunological discrepancies in patients with PTSD. In doing so, these researchers found that participants with diagnosed PTSD exhibited a higher rate of abnormal alterations in monocytes, a type of white blood cell, in the immune system, which can lead to increased inflammation in the body (Katrinli et al., 2022).

Notably, Wang et al. (2017) discuss a potential reversal of the relationship between PTSD and the immune system, illustrating theories about the role of the immune system in causing the development in PTSD. These researchers explain the mechanism by which

individuals can become more susceptible to PTSD if there are certain differences in immune regulation dictated by certain genes. Deslauriers et al. (2017) elaborate on this idea, explaining that, despite a lack of causal evidence on whether PTSD causes changes in genetic biomarker in the immune system or vice versa, there is scientific evidence that increase in internal inflammation and changes in gene expression both correlate to PTSD symptomology. Such evidence of immunological correlations with PTSD gives credence to the supposition that PTSD negatively affects the body; however, more research is needed to identify a causal relationship, if any, between the immune response and PTSD or to pinpoint a potential third variable that is causing a correlation between PTSD symptomology and immunological abnormalities. Based on available data, proper research should seek to identify possible precursors to PTSD development or, conversely, how to prevent the development of immunological disorders that result from chronic trauma exposure or PTSD.

Any association or correlation between immunological disorders and chronic stress or PTSD in children, however, has yet to be clinically identified. Cohen et al. (2002) address the complexities of studying immune responses in children. Here, researchers found that children with acute traumatic exposure, characterized by at least six months since the abuse occurred, exhibited increased production of cortisol, which leads to irregularities in the negative feedback loop of the HPA axis. However, Kaufman et al. (2007) observed that children experiencing ongoing trauma or a more complex history of maltreatment appeared to have normal levels of cortisol, thereby revealing a discrepancy in the effects of trauma on children's bodies depending on duration and consistency of abuse or stress exposure.

PTSD and the Cardiovascular System

Alterations in the cardiovascular system as a result of chronic stress and PTSD, are relatively unanimously understood by scholars. In fact, in order to be diagnosed with PTSD, one must have certain cardiovascular symptoms, such as an increased resting heart rate and blood pressure when being reminded visually of the traumatic situation (Bedi & Arora). These minor changes tend to occur due to experiencing heightened levels of adrenaline from increased activation of the sympathetic nervous system due to an increased perception of danger in a stable environment (Sherin & Nemeroff, 2011). However, of more interest in this section are the facets of the cardiovascular system that are permanently or fatally altered as a result of PTSD.

Ahmadi et al. (2011) conducted an experiment to identify if a correlation existed between levels of coronary artery calcium (CAC), a prominent indicator for CAD, death rates, and PTSD. These researchers found that PTSD was more commonly seen in those with moderate to severe CAC; likewise, this study discovered that PTSD, in conjunction with the presence of CAC, was a predictor for mortality, increasing one's relative and expected risks of mortality. Though CAD was not directly diagnosed in these individuals, this study reveals an increase in CAC, which can lead to diagnosable CAD and possible death. The data here, therefore, reveals an apparent correlation between the presence of PTSD and the development or presence of CAC and subsequent CAD. However, further research to confirm causality is required to make definitive conclusions on the topic.

Other studies discuss the comorbidity of cardiovascular disease (CVD) and PTSD. Sibai et al. (2001) sought to identify if there was a relationship between an individual's exposure to traumatic events of war, CVD, and mortality, specifically during the Lebanese civil war. These scientists located a group of 1,786 male and female participants who originally took part in a

community-based survey in 1983 and asked them to answer follow-up questions regarding PTSD symptomology in 1993, all in order to track their physical and mental conditions longitudinally or over time. These researchers found that chronic stressors, as opposed to a single traumatic event, led to an increased likelihood of CVD and mortality rates (Sibai et al., 2001). Notably, these researchers also found specific gender-based differences in mortality rates in those with CVD, finding that women were more likely to die from CVD when traumas occurred against them or their families. Such a distinction brings about questions regarding the presence of gender-based differences in relation to the internalization of traumatic experiences, as were mentioned previously; it can be hypothesized that women, feeling their role to be homemaker and caregiver for the children, would feel more personally at fault in response to losing their home or the harm of themselves or their children, but such underlying discrepancies between males and females would need to be investigated further to confirm.

Research addressing cardiovascular malfunctions in children and adolescents with PTSD is practically nonexistent, though many studies do link childhood trauma and CVD occurrences in adulthood (Goodwin & Stein, 2004; Galli et al., 2021). As such, evidence regarding cardiovascular issues in children with concurrent PTSD is nonexistent; it should, therefore, be the intention of future researchers to identify what changes in the cardiovascular systems of children exposed to chronic stress or trauma so as to properly prevent future cardiovascular problems. Further, oxytocin, which has been recently identified as a means by which the heart reduces inflammation (Jankowski et al., 2020), ought to be investigated further in order to illuminate any potential benefit external, synthetic administration of oxytocin could bring to trauma victims.

In order for the aforementioned research regarding cardiovascular health to be scientifically valid, one must understand that there are extraneous, confounding variables that could be affecting the analyses and making inaccurate any suppositions of causation. For example, when someone undergoes a traumatic experience of any kind, they may be more likely to attempt to avoid their feelings of depression, regret, guilt, etc. This shift to avoidance, further, could lead an individual to eating more than usual and altering their diet in a negative manner, which could inherently cause increased calcification of arteries in the heart, high blood pressure, and things of the sort. This is not to deny that PTSD may causes increases in CAC and possible CAD or general CVD; rather, the lack of definitive causality uncovers holes in current research that could have implications in how cardiologists or other medical doctors diagnose and treat cardiovascular disorders.

PTSD and Chronic Pain

Those who suffer from PTSD or chronic stress often discuss symptoms of chronic pain, with the U.S. Department of Veterans explaining how 98% of diagnosed patients with PTSD have concurrent chronic pain (2022). Some proffer that chronic pain comes from an immunological deficiency resulting in increased internal inflammation. However, studies occurring as of late have sought to identify differences in pain perception between those with PTSD and healthy controls so as to explore why those who suffer from chronic stress or PTSD are more likely to experience persistent pain. This supposed change in perception between sufferers of PTSD and healthy controls will be the focus of this section, as immune inflammation and its effects has been discussed previously.

First, Defrin et al. (2008) sampled 32 outpatient individuals who had combat or terror-related PTSD and conducted somatosensory testing to identify any differences in sensational responses between PTSD victims and healthy controls. This study concluded that patients with PTSD had a significant increase in the rate of chronic pain prevalence compared to the control group, with the pain itself being perceived as more intense and widespread and being correlated to intensity of PTSD symptomology (Defrin et al., 2008). These researchers found evidence that patients with PTSD have a higher threshold for pain from heat or mechanical stimuli; however, subjects with PTSD were less sensitive to other physical pain stimuli. Thus, the conclusion drawn was that those with PTSD are more likely to be hypersensitive to pain with an increased threshold for this same pain; as such, scientists here concluded that patients with PTSD may be abnormally processing sensory information that affects how individuals interpret and manage pain.

Other studies indicate possible factors for this concurrence by investigating a difference between physically present pain and perceived pain. Defrin et al. (2015) describe how perceptions and symptomology of PTSD, specifically anxiety and dissociation, can alter the interpretation of physical pain, causing people to be hypersensitive or hyposensitive depending on their levels of anxiety and dissociation. Studies also advocate for the possibility of general perception discrepancies between subjects with PTSD and healthy controls, with one study suggesting that those with PTSD are more likely to be conditioned to expect painful stimuli compared to healthy controls (Jenewein et al., 2016). It must be noted, however, that a meta-analysis of 21 studies, conducted by Tesarz et al. (2020), found no significant correlations between PTSD prevalence and sensory pain perception dysfunction, thereby showing a need for further and more conclusive data.

Chronic pain in pediatric cases of PTSD appears to be equally as prevalent in children and adults, making this topic different from PTSD comorbidity with immunological or cardiovascular deficiencies. Seng et al. (2005) found, through a cross-sectional analysis of epidemiological data from female pediatric populations, that chronic pain conditions, such as irritable bowel syndrome or fibromyalgia, were strongly correlated to PTSD symptomology. Nevertheless, data of this sort regarding pediatric populations is sparse, with literature on the topic generally being a review of past research with no conclusive evidence of any relation between PTSD occurrence and chronic pain in children (Kao et al., 2018; Janssen et al., 2022).

From these studies, there certainly appears to be a comorbid relationship between PTSD and chronic pain in pediatric and adult cases, with evidence supporting both perceptual and sensitivity changes between PTSD subjects and healthy controls. Further research on the topic should focus more on the extent to which both perceptual and pain sensitivity changes affect pain perception in those with PTSD, as both understandings of perceptual abnormalities and hypersensitivity to pain are likely working with one another to create complex pain-processing differences in subjects with PTSD.

PTSD and Behavioral Abnormalities

Literature regarding behavioral difference between those with PTSD and those without is broad yet inconclusive, as a direct identification of chronic stress or PTSD-influenced behaviors is difficult because such matters differ from person to person. To understand the extent to which PTSD influences certain behaviors, the distinction between trauma survivors who have PTSD and who do not have PTSD must be addressed. The DSM-5 states that, on top of the experience of a traumatic event, one who is diagnosed with PTSD must exhibit intrusive symptoms of

recurrent, distressing memories of the trauma, dissociative reactions to a potentially threatening situation, avoidance behaviors, and memory deficiencies related to the event (American Psychiatric Association, 2013). It can seem that, with these diagnostic criteria, there is a fine line between a reaction to a traumatic event and a diagnosis of PTSD; it is for this reason that PTSD symptoms are delineated from other trauma responses by occurring consistently past one month after the event and by interfering with the individual's quality of life (Taylor-Desir, 2022).

Nevertheless, there are behavioral signs that an individual is being affected by PTSD or chronic stress. Most commonly and publicly understood as a symptom of PTSD, many individuals re-experience symptoms from their traumatic event (Lancaster, 2016); in the scientific community, researchers generally agree that the proper cause for these flashbacks can be understood through the dual representation theory (DRT). Brewin et al. (1996) founded this theory, describing how triggers of a traumatic event are stored in one's situationally accessible memory, that which can only be accessed unconsciously when encountering triggering stimuli. However, in processing the traumatic events in a conscious manner, the triggering sensations are moved to one's verbally accessible memory. As such, without conscious processing of the traumatic memory, the triggering sensations can remain in the situationally accessible memory, which leads to flashbacks (Brewin et al., 1996).

Likewise, another common behavioral shift that can occur with a PTSD diagnosis is a change in cognitive patterns after the traumatic event has occurred. In order to assess these changes, Kimble et al. (2018) conducted a study of 46 males and females who reported at least one traumatic event in their lives. Upon finding which participants had internal and external negative, pessimistic views of the world using the Posttraumatic Cognitions Inventory (PTCI), these researchers found that those with negative world views were more likely to finish a

sentence in a pessimistic manner. Dekel et al. (2013) expound on this sentiment, finding in a 17-year longitudinal study that severity levels of PTSD symptomology were an accurate predictor of internal and external negative cognitions after the traumatic event. Interestingly, this behavioral shift, characterized by inherent negativity about all aspects of life, is also distinctive in individuals who have borderline personality disorder (BPD), which has led to a great amount of overlap between BPD and PTSD diagnoses (Golier et al., 2003).

Moreover, research finding a presence of dissociative symptoms in those with PTSD diagnoses or traumatic exposure is plentiful, with many addressing possible correlations between the two. Wolf et al. (2012) found, upon analyzing dissociative symptoms in 644 individuals with war-related PTSD, that PTSD severity was not directly correlated to dissociative symptomology. However, these researchers discovered that an individual was more likely to have dissociative symptoms if they both had high PTSD severity and scored highly on a depersonalization and derealization questionnaire. From this information, it can be understood that PTSD is not a direct predictor of dissociative symptoms, meaning that there must be another aspect of an individual's personality or, possibly, the length of the traumatic exposure, that causes dissociative symptoms. As such, researchers must seek further knowledge on the nature and cause of dissociative symptoms in order to address methods of preventing dissociation that can arise with chronic stress or PTSD. These behavioral shifts that are characteristic of those with PTSD are the most common markers of a PTSD diagnosis in adults and, further, are the behavioral changes which tend to affect the individual most in daily life. Nevertheless, there are many other common behavioral abnormalities that can be present in those with PTSD, the most common of which are persistent anxiety or depression symptoms and use of substances (National Institute of Health, 2020).

Behavioral problems in children with PTSD are complex, as symptoms are not as scientifically understood and recognized in younger populations as those in adult populations. Despite this problem, DSM-V-TR diagnostic criteria for all children elaborates on the possible presence of flashbacks as well as dissociative reactions, avoidance behaviors, and negative changes in behavioral patterns (McLaughlin, 2022; Cohen & Scheeringa, 2009). From this description, the comparative similarities between childhood and adulthood manifestations of PTSD appear to be great; however, the differences appear when one has to delineate between typical childhood behaviors and PTSD-related behaviors, such as a child being aggressive because they do not understand boundaries or because they are reacting negatively to trauma. As such, of importance for study in pediatric PTSD is not exact identification of behaviors seen in all children with PTSD; rather, it is the presence of abnormal, atypical behaviors in children that must be considered as potentially serious.

6. Necessary Treatment Differences Between Adult and Pediatric PTSD Cases

The culmination of this literature review necessitates the assessment and synthesis of these various studies so as to highlight potentially essential treatment differences between adult and pediatric cases of PTSD and chronic stress. It must be understood upfront that, because these conclusions are based off somewhat inconclusive data, further research is necessary to confirm or deny any of these conclusions. Thus, these ideas will be further discussed in the following section of this review in addressing what further research must be done in this field.

Treatments: Adults

The most scientifically conclusive data regarding the correlation between volumetric brain abnormalities and PTSD or chronic stress are in reference to hippocampi irregularities. It must be noted, however, that studies have unanimously found statistically significant memory decreases in those with PTSD and chronic stress compared to healthy controls. Various studies address hypotheses for why the hippocampal volume is statistically different than healthy controls, with most studies finding decreases in hippocampal volume. These studies unanimously state that these changes occur due to excess and persistent elevation in glucocorticoid levels, with Conrad (2011) explaining that these increased glucocorticoid levels decrease cell differentiation, proliferation, and dendritic branching. Volumetric changes most commonly occur in the gray matter regions of the hippocampus, the location of the dendritic branches (Wen & Chklovskii, 2005). Thus, the theoretical treatment goal for hippocampal memory and volumetric changes is to increase dendrite branching to better the functioning of the memory-storage processing in the hippocampus, which would possibly be reflected volumetrically.

There are two particular biochemicals that Arikkath (2012) describes as increasing dendrite formation in hippocampi, reelin and cypin. Reelin is known to increase dendrite branching and growth (Jossin, 2020), with Pesold et al. (1998) finding reeling in rat hippocampi across the lifespan. Cypin, moreover, acts to promote dendritic branching through affecting the formation of microtubules or skeletal formation of the cells in the hippocampus (Rodríguez et al., 2018). Therefore, reelin and cypin appear to be naturally released in mammalian brains to increase dendritic branching and plasticity; however, these experiments are preclinical, using rats as the subjects of study instead of humans, which insinuates a need for human-based studies of reelin and cypin in the brain.

Notably, Kwon et al. (2011) found that BDNF mediates the release of cypin in the brain; BDNF levels, as discussed previously, decrease at the increase of glucocorticoid levels (Kozlovsky et al., 2007). Thus, a logical conclusion follows from these data: if reelin and cypin increase dendritic branching, glucocorticoid excess may diminish the effects or presence of reelin and cypin either directly or indirectly (Lussier et al., 2011; Kwon et al., 2011). If the former is true, then hippocampal-based memory loss or volumetric decreases could be mitigated by increasing reelin and cypin concentrations in the brain. Reelin and cypin, therefore, could be critical in increasing dendritic branching, thereby negating the effects of PTSD and chronic stress on the hippocampus of adult brains. Human studies of reelin and cypin in the brains of those with PTSD or chronic stress are necessary to confirm or deny this hypothesis, however, as the hypothesis itself is currently unsupported.

Unlike decreased dendrite branching seen in the hippocampus as a result of chronic glucocorticoid exposure, changes in amygdala volume act in the opposite manner in adults. As a result of chronic glucocorticoid exposure seen in PTSD diagnoses or cases of consistent stress, dendrites in the amygdala are thought to proliferate (Vyas et al., 2002), with some scholars finding that this increase in dendrite quantities leads to an increase in amygdala volume (Caetano et al., 2021). Notably, research about volumetric changes in the amygdala is not entirely conclusive, with some researchers finding that chronic glucocorticoid exposure led to decreased bilateral amygdala volume (Karl et al., 2006; Rogers et al., 2009). If one is to assume that the former theory of increased amygdala volume is true, the treatment for dendritic hyperproliferation would, theoretically, be to decrease dendritic branching, but only in the proper areas. This specific, location-based chemical process, however, would be impossible to administer chemicals like those proposed in hippocampal treatments, as synthetic chemicals that

are ingested in pill form cannot be centralized on one area. Moreover, questions concerning the corpus callosum appear, specifically regarding volumetric changes in the white matter of the corpus callosum. Because white matter decreases are believed to be caused by a loss in in axonal bundles, the reasoning for why white matter volumes in the corpus callosum are decreased may be due to a loss of axon fibers in the corpus callosum from increased concentrations of glucocorticoids (Huang et al., 2001). This theory is not yet proven, revealing a need to address the root cause of brain abnormalities, specifically glucocorticoid excess, in treatments.

In order to decrease glucocorticoid excess, scientists must be able to identify from where these heightened glucocorticoid levels originate. Perroud et al. (2011), in conducting a study of 200 subjects with BPD and major depressive disorder (MDD) where various childhood trauma-related questionnaires were administered, found that childhood sexual abuse severity was positively correlated to increased methylation of the NR3C1, a glucocorticoid receptor gene. Methylation occurs when enzymes, known as methyltransferases, remove a methyl group (CH_3) from an S-Adenosyl methionine molecule, created in the body from the amino acid methionine, and attach the methyl group to the fifth carbon of a cytosine (Moore et al., 2013). One of the four key compounds used to create DNA, cytosine is thought to be where genetic data in the DNA is stored, as it is commonly the group on which methylation and subsequent gene expression occurs (Nabel et al., 2012). Methylation of NR3C1 could alter the transcription or building of the glucocorticoid receptors from this gene, which would alter the glucocorticoid negative feedback loop (Sauro, 2017). As such, glucocorticoids remaining in the bloodstream and not being attached to receptors can cause higher levels of glucocorticoids to continue to be produced. Thus, theoretical NR3C1 methylation could increase chronic glucocorticoid levels.

The following conclusion from this information would be that treatments to decrease hyperproduction of glucocorticoids have to reverse the epigenetic methylation of NR3C1. Wolffe et al. (1999) discuss the difficult process by which active DNA demethylation, the removal of a methyl group, would theoretically occur, illustrating how breaking carbon bonds to remove the methyl group is necessary yet complex. Most research regarding DNA demethylation focuses on cancerous growths, as treatments for cancer are being developed with the idea that tumor-suppressor genes can be demethylated and begin to function properly (Szyf et al., 2004). However, little research is available regarding the validity or proof of PTSD-induced methylation of the NR3C1 gene, with most scholars noting the importance of this topic rather than researching the topic directly. Thus, it is imperative for scientists to identify if a strong correlational relationship between PTSD or chronic stress and methylation of the NR3C1 gene occurs. If these necessary investigations found a correlational relationship between PTSD symptomology and methylation of the NR3C1 gene, researchers would need to attempt to prove causality, specifically that PTSD causes methylation of NR3C1. Scientists would then need to identify if it is possible to demethylate specific genes so as to preserve the integrity of other uninvolved genes.

Treatments: Children

Conclusive answers for all hippocampal abnormalities in pediatric individuals are impossible to obtain in the current state of the field, primarily because studies on this topic are inconclusive and inconsistent. On the whole, scientists agree that there are no significant volumetric differences in the bilateral hippocampus between children with PTSD and healthy controls. Nevertheless, there appears to be decreased memory functionality in children with

PTSD or chronically high levels of stress when compared to healthy controls, are a more consistent and, therefore, statistically significant finding in the community. Thus, no cause for these memory differences has, as of yet, been identified, as inconclusive evidence on the existence of limbic system abnormalities leads to a decrease in initiative for scientists to find answers.

As previously stated, the main difference volumetrically between adult and pediatric cases of PTSD is that children with PTSD do not appear to have significant changes in bilateral hippocampal volume, while adults with PTSD are more likely to have significant volumetric changes. Both age groups do, however, have statistically significant memory deficiencies; the logical conclusion from this being that, somehow, the volume of the hippocampus does not inherently reflect memory-storage abilities. Previous studies have hypothesized a reason for hippocampal volumetric differences, as they address how gray matter, the part of the hippocampus most commonly affected by glucocorticoid excess, is comprised of dendritic branches. Moreover, reelin and cypin are known to act in the creation of dendritic branches, with the concentration of only reelin known to be higher in childhood (Despotovski et al., 2021) and with the concentration of cypin being inconclusive.

From understanding how dendritic branching, reelin or cypin, and hippocampal functionality are interrelated, a possible theory appears: hippocampal volumetric changes may not occur in childhood because the heightened level of reelin counteracts the effects of glucocorticoid levels (Lussier et al., 2011) and, thus, protects the volume of the hippocampus for a time. The decreased memory capacities of children with PTSD, being seen only qualitatively, not quantitatively, compared to healthy controls could potentially be due to a decrease in cell proliferation or differentiation, something which would not affect the volume of the

hippocampus as dendritic branching does but still impacts hippocampal functioning. Thus, a possible hypothesis arises that synthetic reelin, given to the client consistently, could counteract the future effects chronic glucocorticoid exposure has on the brain. It becomes clear from these sentiments that treatments for PTSD in adults and children coincide at a point, for possibly giving individuals synthetic or external reelin or cypin could increase dendritic branching in the gray matter of the hippocampus for adults and prevent volumetric losses in the hippocampus for children. Differences occur in that, for pediatric cases, neurogenesis must be focused on as well as increasing dendritic branching.

Apart from symptom-focused neurochemical treatments for the effects of PTSD or chronic stress symptomology, as stated in treatments for adults, demethylation of the NR3C1 gene would, theoretically, decrease the overproduction of glucocorticoids and prevent any brain-related volumetric abnormalities from occurring later in life. As such, the necessary treatment for children who experience PTSD or chronic stress symptoms would inherently depend on the severity of the trauma and the age of the child so as to identify whether volumetric changes in the brain have already occurred. If they have not, then targeted treatment to demethylate the NR3C1 gene would be appropriate, with other treatments regarding reelin or cypin being initially unnecessary. However, if the individual is in adolescence, and the trauma they experienced occurred further in the past, then epigenetic methylation of NR3C1 may have occurred, making reuptake of glucocorticoids more likely to be decreased, thereby necessitating both demethylation and possible reelin or cypin treatments.

7. Options for Further Research

Due to the broad and in-depth nature of this review, there are multiple options for further research, many of which have been established throughout the paper. The most critical next steps for research will be the focus of this section, giving options to work on ridding the field of research flaws, inconclusive results, and finding various age-related treatment options. First, as is common in many of the studies regarding adults and children with PTSD or chronic stress, the low number of participants leads to difficulties finding statistical significance, especially if generalizations are trying to be made. Moreover, equally as challenging for researchers is to account for all extraneous variables in experiments in order to identify true relationships between variables. Even though causation can never be proven through correlation, extraneous variables must be controlled and factored out as much as possible to yield better results, which means there must be a more intricate and extensive process of identifying and classifying subjects. Age, specifically, must be controlled, as the developing brain is affected drastically differently than the mature brain, along with other confounding variables, such as familial upbringing. Therefore, in this field of study, more care must be taken to statistically account for confounding variables and confirm that the given number of participants will yield scientifically valid results. Other research flaws are also seen in these performed analyses. For example, many studies sought to identify if two variables had a linear correlational relationship; though such an analysis could be telling, it excludes any possibility of there being possible exponential or curved correlations. Because a linear correlation can only identify if the variables consistently related, any other form of correlation is unidentifiable from this test, thereby increasing the need for more diverse forms of correlational analyses to rule out all possible associations.

Likewise, further research must be conducted regarding differences between left and right brain structures. Most commonly seen in results for the hippocampus, amygdala, and the corpus callosum in adults, some studies address more severe volumetric differences from healthy controls on the left side of the brain compared to the right side of the brain for all ages. Because of this discrepancy, more thorough and statistically significant research must be conducted to confirm or deny these results, as differences from one side to the other instead of bilaterally can have implications for treatment and effects on a person's functionality. With the understanding of inconclusive results plaguing this field, there are necessary steps that must be taken to conduct volumetric analyses of the brain, especially in the limbic system, mainly relating to how the volume of these structures is measured and analyzed. Components cannot and should not be analyzed separately, because, for example, the hippocampus processes episodic memory and the amygdala processes emotions related to memories, thereby presenting the need for them to be studied as pair, not independently from one another.

Regarding further, direct focuses in experiments for those of all ages with PTSD or chronic stress, researchers must first push to conduct more longitudinal studies. Instead of cross-sectionally investigating a population at one point in time, it is crucial to analyze the evolution of neurostructural volume as the subject ages, as it may lead to an understanding of the point at which excess glucocorticoid concentrations cause limbic system volumetric changes. Furthermore, researchers must continue to investigate what differentiates maltreated youth who have diagnosed PTSD from those who are maltreated but do not have diagnosed PTSD: Is there a neurobiological reason for why resilience in maltreated youth decreases the likelihood of neurological malformities, which could be a neurochemical or biological predecessor to a treatment for the permanent effects of pediatric PTSD? Likewise, if a child's interpretation of a

traumatic event affects how the volume of certain brain structures change, how can educators or counselors teach children how to adopt a resilient mindset in order to prevent neurobiological malformations?

Lastly, there are many avenues for which further studies and experiments are required. First and foremost, avenues of selectively demethylating genes must be examined to see if active and specific demethylation is possible in order to increase glucocorticoid reuptake and reregulate the glucocorticoid negative feedback loop. Further, because the addition of removal of a methyl group occurs due to environmental factors, NR3C1 could, theoretically, be demethylated through different psychotherapeutic or environmental measures. However, if these hypotheses do not prove true, then the viability of reelin or cypin as effective components to increase dendritic branching must also be tested. Such an investigation is of the utmost importance so as to mitigate the effects that excess glucocorticoid exposure has on dendritic branching and neuron proliferation in the brain and subsequent neurobiological functions. Through these two key experiments, scientists will effectively be capable of halting or reversing the effects that PTSD, trauma, or chronic stress has on both the developing and matured brain.

8. General Implications

In studying the neurobiological and physiological manifestations of chronic stress and PTSD, there appears a great setback. Despite the reality that childhood abuse and trauma are detrimentally rampant in the United States, the two key fields of study in relation to this topic, psychology and biology, work distinctly apart from one another. The various studies presented in this review show the stark divide between psychological, counseling-based research and biological, chemical-based research; none of the presented studies are successfully able to

synthesize both academic fields in achieving their common goal. Apart from the goal of furthering research possibilities in the neurobiology and PTSD community, this review has effectively outlined the faults of the sciences as a whole: To delineate between natural and social sciences supposes an inability to combine the two fields and make effective changes to both the body and mind. Researchers have a unique and crucial duty to perpetuate inclusivity in research, allowing participants in various fields to contribute to a common goal of bettering lives.

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