The Neurological consequences of Early Life Stress

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Abstract:

Early life stress can be defined as extreme stress or trauma experienced by a child during developmental stages. This type of chronic stress can cause far reaching consequences well into adulthood. The following literature review will focus on the neurological consequences from ELS exposure. Studies show that ELS exposure can be linked to decreased hippocampus volume and blunted mesolimbic pathway, potentially increasing the risk of depression. ELS is also associated with increased amygdala volume and increased attention bias to negative cues, which might increase susceptibility to anxiety. Furthermore, insults during early childhood stages can affect the functioning and development of cognitive circuits, resulting in impaired learning and memory as evidenced by human and rodent studies. Epigenetic studies indicate that DNA methylation and BDNF expression can be altered by ELS. Fortunately, some epigenetic modulations can be targeted for therapeutic purposes.

Key words: Early life stress (ELS), hippocampus, amygdala, cognitive circuits, epigenetics

Early life stress (ELS) can be any extreme stress experienced by a developing child, including physical, sexual or emotional abuse or neglect that go on to cause molecular, physiological, and psychological effects well into adulthood [1]. Data analysis shows that there are approximately 44,063 reported cases of child abuse in Pennsylvania, with Philadelphia having 5,909, the highest among other cities [2]. Given the high prevalence of early life stress, it is critical to examine its consequences on a vulnerable population.

The severity of stress determines the ultimate outcome for the individual. Some clinicians suggest that stress in early life can be considered a "double-edge sword" - while mild stress early in life can be beneficial, chronic and severe stress can have massive repercussions on brain development and behavioral trajectory of an individual [3]. Early Life Stress is associated with morphological and circuit wide consequences in the brain that translate to distinct behavioral and psychiatric conditions.

SNS and the HPA axis: acute and chronic stress

The nervous system structures involved and reactions elicited by acute stress can be impacted by early life stress (ELS). In fact, these specific markers and physiological reactions can be assessed to understand the impact of ELS. Acute stress can trigger a set of physiological responses between the sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis [1]. However, there is inconsistent research on how ELS can affect stress pathology.

Previous studies have shown that the relationship between ELS and cardiovascular health is affected through the HPA axis. For instance, Dong et al. found that there is a direct relationship between adverse childhood experiences and the risk of developing ischemic heart disease [4]. Furthermore, the number of ELS events seem to be correlated with higher resting and activated heart rates [5]. Researchers in the field aimed to address a potential dysfunction between the HPA axis, assed by cortisol levels, and ELS [6] There are conflicting results on whether ELS can attenuate or diminish cortisol levels. For instance, some scientists conclude that ELS can heighten cortisol reactivity. In contrast, others say that ELS is associated with blunted cortisol, which translates to decreased levels of the hormone and increased threshold to activate the HPA axis and stress response. In order to reconcile this discrepancy, reviewers conducted an overarching meta-analysis of ELS studies only to find that cortisol awakening response, baseline cortisol, and cortisol reactivity is not significantly associated with ELS [6]. That said, the type of stressor is critical in determining its impact on cortisol pathology. For instance, data suggests that the cortisol awakening response (CAR), corticol concentration during the first hour of sleep, is heighted for those who experience sexual, physical, or emotional abusive early on in childhood [7, 1]. As such, following the meta analysis results, researchers conclude that some forms of childhood hardship can be much more impactful and

severe than others. ELS can also moderate the immune system by increasing inflammatory responses [6]. A longitudinal study has shown that ELS is linked to more sensitive c-reactive protein levels. The C-reactive protein (CRP) is a biological marker of inflammation in the body and clinicians use its measurements to examine the risk of coronary disease for a patient [8]. In corroboration with the previous discussion, ELS seems to be associated with poor cardiovascular health by increasing sensitivity to CRP inflammatory markers.

Altogether, it has been proposed that ELS acts upon the interplay between SNS, HPA axis, and the immune system. The activation of the sympathetic nervous system coupled with abnormal cortisol levels can result in low-grade inflammation over time [9]. In line with this logic, it has been suggested that ELS can prime neurocircuitry to elicit a heightened response between SNS, HPA axis, and immune system. In summary, there are quite a few consequences of ELS on the HPA axis and cardiovascular system, which seem to be contingent on the type, condition, or severity of childhood events.

Impact on hippocampus and mesolimbic dopaminergic pathway

Literature supports the fact that early life stress can interact with brain structures to increase vulnerability to depression. Importantly, the hippocampus, a brain region critical for learning and memory, is critical in inhibiting the activity of the HPA axis [10]. Furthermore, the hippocampus is implicated in major depressive disorder, such that many studies have shown that decreasing volumes of the structure can correlate to increased instances of depression [11]. A plethora of research suggests that stress affects hippocampal integrity and function [12]. Notably, in human studies, early-life adversity is associated with small hippocampal volume and increased vulnerability to depressive disorder. In a longitudinal study, a research team examined whether hippocampal changes can affect the relationship between early life adversity and depression [13]. To do so, adolescents with clinical depression, parental depression (high-risk of developing clinical depression), and control subjects were examined through magnetic resonance imaging studies. There were follow-ups up to 5 years of the onset of and clinical course of depression. Results show that depressed and high-risk groups have significantly smaller left and right hippocampal volumes compared to control subjects [13]. Higher levels of early adversity are shown to be linked to smaller hippocampal volumes as well [13]. Therefore, researchers concluded that early life adversity can interact with genetic vulnerability to induce hippocampal changes and increase the risk of depressive disorder [13].

More research corroborates the negative impact of stressful experiences during periods of rapid hippocampal development [14]. In another study, clinicians examined 178 early adolescents regarding

their stress exposure and conducted structural magnetic resonance imaging. Results show that there is a moderate significant association between stress onset and hippocampal volume [14]. This would translate to increasing stress levels relating to lower hippocampal volume during early childhood. Interestingly, there was no association between stress severity and hippocampal volumes at later ages. This result allowed researchers to conclude that there is a critical sensitive period in early childhood in which life stress can alter the volume of the hippocampus [14].

Additionally, the mesolimbic pathway, critical for reward processing, is reported to be affected by ELS and increase vulnerability to depression, as well. Animal studies have shown that ELS can affect the mechanism in which rewards are processed in the brain and ultimately increase the risk of depression. Affective or emotional processing is associated with the mesolimbic dopaminergic pathway and is critical for reward processing. Key brain structures such as the dopaminergic cell body interacts with the ventral tegmental area and nucleus accumbens in response to rewards [3]. Essentially, a blunted mesolimbic DA transmission is shown to be involved in depression. Animal studies have shown that chronic and persistent stressors lead to anhedonia-like behavior (defined as lack of pleasure) and irregular mesolimbic dopamine pathways in adulthood [3] Translationally speaking, ELS exposure among children can present the risk factors associated with depression.

In summary, ELS exposure has been linked to decreased hippocampus volume and blunted the mesolimbic pathway. While changes to both are implicated in depression, ELS seems to increase one's vulnerability to developing the condition. Preclinical and clinical studies have shown that these robust neurological changes can correlate with the development of psychiatric conditions, such as depression.

Impact on amygdala and affective processing:

Early Life Stress impacts the structure and modernates the function of the amygdala, a brain structure that regulates human emotion, particularly that of fear and aggression. The amygdala continues to develop through birth, especially with it reaching its peak volume in early childhood. As such, perturbations during early years as a result of ELS can disrupt the amygdala's development [3]. Interestingly, a seminal body of work has examined the consequence of ELS on the morphological changes of the amygdala and the behavioral responses [15]. The research team studied a sample of institutionalized, but later adopted children, for morphological changes to the limbic system and behavioral response states. Using magnetic resonance imaging (MRI), researchers noted that early postnatal stress can lead to larger amygdala volume. Further data analysis indicates that this larger amygdala volume can be indicative of higher ratings of internalized behavior and higher number of anxiety symptoms [15, 3]. Behavioral data shows

that, among other results, previously institutionalized children had slower response times to neutral stimuli in positive contexts and faster response times to neutral stimuli in negative contexts [15, 3]. It is important to note that the larger amygdala volume can signify increased and robust connectivity across the cortex that could translate to a heightened sensitivity to environmental stimuli. Unfortunately, ELS can be correlated with anxiety symptoms well into adulthood [16]. In a study with 1872 participants from the Helsinki Birth Cohort Study, researchers examined the relationship between ELS and self-reported anxiety symptoms at the age of 65-77 years [16]. Results indicate that people experiencing low socioeconomic status, emotional trauma, or physical trauma during the early developmental stages are linked to increased anxiety symptoms in late adulthood compared to the control group (people with no physical or emotional trauma or trauma in adulthood) [16].

In line with emotional processing, children who have experienced ELS have a distinct attentional bias when it comes to identifying negative emotions [3]. Event related potential (ERP) studies show that children with a history of physical maltreatment are more likely to witness anger cues, resulting in more cognitive processes and selective attention directed to the threat [3]. Accordingly, abused children will require less visual information to detect anger in facial expressions [3]. These studies further go to show the increased sensitivity of ELS children in responding to negative stimuli. Therefore, it is quite reasonable to hypothesize that these emotional responses to cues can impact the activation of acute stress pathology.

Taken together, early life stress is shown to be linked with heightened sensitivity to environmental stimuli through morphological and functional impact to the amygdala. Event related potential studies show that given the increased exposure to negative emotions, children are more primed to direct cognitive efforts to addressing the threat. These results can demonstrate that ELS exposure can increase the risk of developing anxiety that can extend well into adulthood.

Impact on cognitive brain circuitry:

Chronic stress during early childhood can lead to insults on brain circuits and translate to deficits in cognition processing. Neural circuits consist of a set of interconnected and interrelated parts of the brain that work together to serve a specific function. These circuits can be either a cluster of neurons or a set of brain regions that integrate information from the environment and process it accordingly [17]. The brain is sensitive to environmental exposures such as stress, toxins, and illness, and nutritional deficiencies. Additionally, neurodevelopmental periods are set to a narrow temporal window and adverse events during fetal and infancy life can have massive neurocognitive and behavioral repercussions [17].

In regards to cognitive circuits, studies suggest that early life adversity negatively impacts memory retention, learning, and neural circuitry development. Many rodent studies have indicated that abusive maternal care can lead to spatial memory deficits in adult rats [18]. Decreasing nesting and bedding materials is also shown to impair spatial and recognition memory [18]. In fact, reviewers suggest that even more studies show these specific memory deficits continue well into adulthood and predispose subjects to memory senescence [18]. The circumstances of heightened anxiety, inconsistent responses to a child's behavior, and poor emotional communication can impact learning in these children [19, 20, 21]. Given the high presence of negative cues in the environment, researchers aimed to explore the impact of physical abuse on instrumental learning and cognitive flexibility [22]. In order to do so, a clinical study with fifty three 14-17 adolescents was conducted. Here, volunteers were recruited to complete an instrumental learning task that required them to pair specific stimuli to negative or positive outcomes. Results show that not only were learned associations of rewards and punishments slow for ELS individuals, their cognitive flexibility is impaired in reversing the stimulus-responding associations, compared to control non-ELS individuals. The fMRI scans show that there is abnormal activity in the putamen and anterior cingulate cortex, areas implicated in learning and attention [22]. Behavioral and imaging results seem to suggest that ELS is associated with slower learning and impaired cognitive flexibility, given its impact on key brain structures.

It is well understood that regular and patterned signals from the environment are important to develop sensory brain circuits [18]. For instance, regular sound and light stimuli during early stages of development are critical to develop auditory and visual processing in the brain. As such, disruption and inconsistent exposure can alter the way these sensory circuits are developed [18]. Extending this logic, other circuits, including cognition can be impacted by the aberrant and inconsistent insults from the environment that ELS children may experience [23]. To assess the impact of environmental insults on cognition, studies were conducted in which unpredictable and poor rat maternal care was induced to test litters on spatial memory [23]. In order to do so, dams and litters were randomly assigned to impoverished (low mesh and low bedding) or standard cages, where maternal care was unpredictable. Following this, animals underwent hippocampus-dependent spatial memory tests which indicated that unpredictable maternal behavior can be associated with poor cognitive performance [23]. These preclinical results suggest that poor and inconsistent maternal care during early childhood can cause spatial memory deficits, well into adulthood.

Studies have shown that inadequate care and neglect can affect cognitive processing. More particularly, ELS is associated with weaker spatial memory, slower learning, and impaired cognitive flexibility. In fact, some of these studies have shown that effects of chronic stress during childhood can have consequences well into adulthood. While Research in human studies might be limited due to ethical issues, preclinical models provide insight into cognitive impairments that might arise from ELS.

Molecular and Epigenetics of Early Life Stress:

The field of epigenetics is fundamentally based on the environment impacting gene expression. As such, given the nature of early life stress for developing children, it is only natural to examine epigenetics in the context of early life stress. Studies have shown a strong relationship between DNA methylation in conjunction with ELS. DNA methylation is an epigenetic mechanism that includes methyl groups binding to cytosine-guanine sites (CpG) sites and subsequently impacting gene expression [1]. For instance, formative research with rats shows that poor maternal care can increase methylation of the glucocorticoid receptor (GR) gene promoter, reduce GR expression in the hippocampus, and increase adult stress reactivity [24]. In humans, there is an increased DNA methylation and subsequent lowered GR expression in suicide victims with a history of childhood abuse, compared to suicidal victims without abuse and non-suicidal controls [25]. The glucocorticoid receptor is critical in controlling thousands of genes and has a multitude of effects on development, metabolism, stress response, and inflammation [26]. More importantly, it activates cortisol and is critical in modulating physiological reactions to acute stress response [27]. As such, increased methylation and decreased expression of the gene is fundamentally altering acute stress physiology. Perhaps, this can even be extended to say that ELS exposure can increase the threshold to activate a stress response

Examining genetic expression of candidate genes can be helpful in understanding the epigenetic modulations of early life stress. Among other genes, brain-derived neurotrophic factor (BDNF) is hypothesized to play a role in mood disorders and is linked to ELS [28]. BDNF is the most abundant neuropathic factor and has multiple functions of promoting growth, regulating synaptic transmission, and modulating pain. Disorders such as depression, autism, bipolar, schizophrenia are associated with differential BDNF neurotrophin profiles. Human studies show that lower BDNF levels is associated with memory impairment experienced by women with a past history of childhood sexual abuse [29]. That said, studies show there are differential BDNF expression profiles based on the brain region and species used in the experiments [30]. Researchers in a review suggest that these inconsistent results could arise from either limited available data sets or alternative splicing mechanisms [1]. Given the highly prevalent nature of BDNF, further research must be conducted to fully elucidate the underlying mechanisms of this

peptide's expression. However, there is general consensus in the scientific community that ELS epigenetically modulates BDNF regulation and results in psychiatric disorders like depression, anxiety, and other mental health disorders.

Treatment

Unfortunately, the phenotype and epigenetic consequences of early life stress seems to be multigenerational transmittable [31]. Therefore, research in the field of ELS therapeutics has gained momentum. Studies have been considering the role of neuroplasticity in dealing with early life stress [32]. As mentioned above, BDNF is a molecular marker that seems to be critical in neuroinflammation and plasticity. BDNF can bind to the tropomyosin receptor kinase B (TrkB) to induce cell survival, differentiation, and long term potentiation. Preclinical data has shown that antidepressants do indeed increase the expression and activate BDNF/TrkB signaling, inducing plasticity. This can allow for social circuity to be reorganized with the help of psychotherapy in a positive environment [32].

In recent years, studies into microRNAs (miRNAs) as massive regulators of neuronal plasticity and higher brian functioning have also gained traction [33]. As such, some researchers conducted a meta analysis to examine the role of noncoding RNAs in modulating epigenetic changes that can be induced by ELS. Results indicate that the miRNA linked to the HPA axis and neuroendocrine signaling systems is indeed affected [33]. The writers suggest that clinicians can select treatment options that target miRNA based on psychiatric diagnosis or blood serum levels during genetic testing. Seeing that research in ELS and miRNA is limited, advances in biotechnology makes this a promising therapeutic avenue [33].

Moreover, more research has shown that studying histone methylation in D2 medium spiny neurons of the NaC can potentially address the depression related behaviors observed in early life stress. It can also provide insight into a potential epigenetic therapeutic target [34]. Essentially, a team of researchers induced animals with ELS and noted transcriptional mechanisms changes to histones in the nucleus accumbens in mice. Dimethylation of lysine 79 of histone H3 (H3K79me2) and the enzymes (DOT1L and KDM2B) have shown to lead to ELS-induced stress susceptibility [34]. However, delivery of a small molecule inhibitor of DOT1L (enzyme) can reverse ELS-induced behavioral deficits, providing an avenue for a potential epigenetic therapeutic target [34]. In summary, moderating the expression of BDNF, miRNA, and histone 3 can address the consequences of ELS exposure. These three biological markers can induce plasticity, regulate stress physiology, and reverse ELS-induced behavioral defects. While all three provide effective therapeutic targets, research in this field is expanding.

Conclusion:

In the United States, 65% of Americans have reported undergoing traumatic childhood events and early life stress [1]. Chronic stress during early childhood is linked to perturbations in the nervous system. More notably, ELS is correlated with decreased hippocampus and increased amygdala volumes which might be associated with increased vulnerability to depression and anxiety. Furthermore, preclinical and clinical studies have shown that ELS is associated with poor spatial memory, slower learning, and impaired cognitive flexibility. The link to environmental and development of these psychiatric disorders can be the epigenetic modulations as a result of chronic childhood stress. Taken together, ELS is linked to poor mental health outcomes and can cause epigenetic changes of brain areas such as the amygdala and hippocampus, which are linked to the HPA axis. Fortunately, therapeutic developments to target epigenetic changes and markers, such as BDNF and microRNA, can enhance brain plasticity in combination with psychotherapy.

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