HIGH SCHOOL EDITION
Journal of Student Research
Volume 14 Issue 1 (2025)

# Biological Clues to Mental Health Disorders in Children

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## ABSTRACT

Mental health disorders are becoming increasingly prevalent in the population. Anxiety, depression, ADHD, and autism levels have been increasing in children in the last decade. This has raised concerns and has emphasized the need for understanding the different biological factors that impact mental health in children. This paper investigates the relationship between biological indicators and mental health disorders in children. The conditions have been found to be associated with three main areas: hormonal dysregulation (particularly cortisol); inflammatory markers (interleukin-6 (IL-6) C-reactive protein (CRP)); changes in genetic and epigenetic factors.

## Introduction

Mental health disorders have been an increasing concern among the population as numbers are increasing as the years go by. These include depression, anxiety, and autism. Worldwide, approximately 10-20% of children have been diagnosed with these disorders particularly in their early childhood [1]. Conditions like these are life changing, impacting not only your relationships with others, but also your social, emotional, cognitive, and behavioral development. Educational systems are stressed as well as different fields in healthcare. Before, studies in pediatrics focused more on the behavioral and emotional aspects but now, studies about biological markers/processes and their impacts have come to rise. These markers are tools that professionals use to diagnose children and measure the different processes (physiological and pathological). The measurements taken with these are critical when it comes to treatment plans and identifying weaknesses in children. Studies have discovered that mental health disorders are a combination of different biological factors such as hormones, immune functions, and genetics instead of just changes in behavioral and emotional processes. Understanding the different factors is crucial for early diagnosis, prevention, and treatment.

This paper examines how biomarkers, including cortisol, IL-6, and CRP, contribute to understanding and managing mental health disorders. By exploring hormonal dysregulation, inflammation, and genetic influences, this research provides a foundation for early diagnosis and intervention.

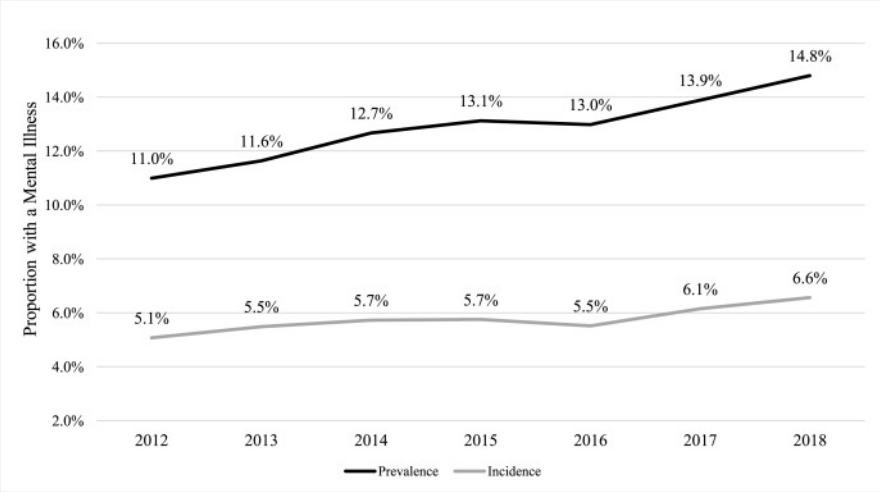


**Figure 1.** Increase in Mental Health Disorders in Children
Source: Public Health Practice

This graph shows the increase in mental health illnesses over the span of six years. These numbers only include children. The prevalence has gone up almost 4% in six years which is a huge amount of the population. Incidence has also gone up about 1.5% meaning that the number of cases each year is going up. The fact that there has been only increase and no decrease as demonstrated in the graph above proves that mental health disorders in children are becoming a serious issue.

## Biomarkers in Mental Health

### *Biological Markers*

Biomarkers are bioindicators that can be measured. These include hormones, variations in genetic encoding, and immune system responses. They help dive deeper into the reasons and processes causing different conditions [2].

*Biomarkers and the Physiological Processes they Measure*

1. Stress Response: Cortisol levels (hormone) are used to help measure abnormalities along the hypothalamic-pituitary-adrenal (HPA) axis. This is a communication system between different 3 different parts of the brain: the hypothalamus, the pituitary gland, and the adrenal glands. These are found in the endocrine system and help create a feedback loop of hormones that regulate the body's stress reaction [3]. When abnormalities are found on this axis, it usually means an increase in responses due to chronic stress. It impacts the hippocampus and the amygdala.
2. Inflammatory Pathways: The biomarkers in these are IL-6 and CRP. They help scientists measure how inflated a system is. If these levels are high, there will be problems with balancing neurotransmitters, disrupting synaptic plasticity, and neurogenesis.
3. Epigenetics and Genetics: Mood and behavior are impacted by external, environmental processes, and hereditary. Biomarkers help with the measurement of the extent to which these two factors contribute to impacting neurodevelopmental pathways connected to that mood and behavior.

Hormonal Impacts on Children's Mental Health

## *Hypothalamic-Pituitary-Adrenal (HPA) Axis and Cortisol*

Cortisol is a stress hormone which is regulated by the HPA axis. When a person is stressed, the pituitary glands are signaled by the hypothalamus to release adrenocorticotropic hormone (ACTH). This hormone is what stimulates cortisol production, and it occurs in the adrenal glands of the body.

### *Cortisol*

Cortisol has many different functions. It regulates the body's stress response by using it to stay on high alert after the *fight or flight* response has worn off. It can do this by releasing glucose from the liver to help energize one during times of stress. It suppresses inflammation which helped boost one's immunity. On the other hand, too much of it can increase inflammation leading to a weak immune system. It also impacts one's sleep cycle. Before going to sleep, cortisol levels are low suggesting that in the morning, cortisol helps one wake up playing a part in the circadian rhythm [4].

The body has a lot of system to control the levels of cortisol. The hypothalamus and the pituitary gland are some of these systems, and they regulate the levels of cortisol produced by the adrenal glands which are located above the kidneys. The hypothalamus releases corticotrophin-releasing hormone (CRH) in response to levels of cortisol falling. This then signals the production of adrenocorticotrophic hormone (ACTH) in the pituitary glands which then leads to the adrenal glands releasing cortisol [4].

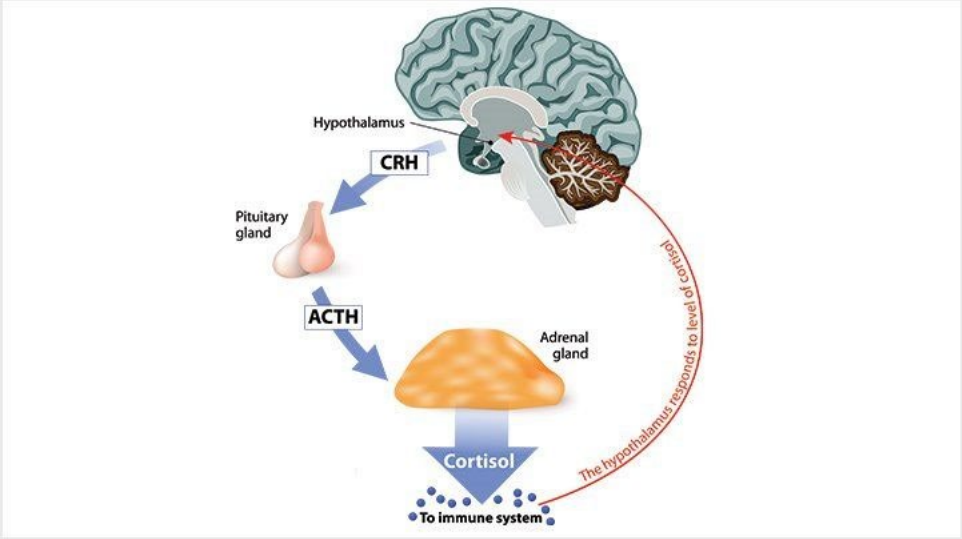


**Figure 2.** Cortisol Regulations and the Steps that Lead Up to It
Source: Everyday Health, Cortisol the Stress Hormone

As talked about before, the image displays the steps involved in production and regulation of cortisol.

Cortisol is a stress hormone induces multiple types of stress. These include acute stress and chronic stress. Acute stress is what happens when someone is in danger for a short period of time. It is stress that causes one to react to dangerous situations immediately. Chronic stress is long term. When someone is constantly frustrated or consistently anxious, chronic stress is the result [5].

*Impact on Regions of the Brain*

- Chronic cortisol has negative impacts on the hippocampus of the brain. It causes disfunction in neurogenesis (new neurons forming) which is very important when it comes to storing long term memories and learning new concepts and ideas. The volume of the hippocampus shrinks when cortisol levels increase abnormally, disrupting its ability to control and regulate the HPA axis. Dysregulation in this axis increases stress levels due to the feedback loop formed. Children who experience chronic cortisol become highly susceptible to mental health conditions such as depression [6].
- Chronic stress also impacts the prefrontal cortex. The prefrontal cortex is in charge planning and decision making. Stress leads to functional and structural impairments in this part of the brain. Cognitive flexibility and attention are reduced due to the deregulation of cortisol weaking the synaptic connections in the PFC. Children experience trouble regulating emotion in response to this [6].
- When the amygdala experiences higher levels of cortisol sensitivity, it becomes extremely reactive to stress stimuli. This extreme reactivity results in anxiety contributing to heightened emotions. If the amygdala stays this way, over time, children become more susceptible to anxiety disorders such as post-traumatic stress disorders (PTSD) and different phobias [6].

*Cortisol Levels Rising in Children*

Children these days experience higher levels of chronic stress. In this case, chronic stress entails neglect, family dis-function, and abuse. Chronic stress causes dysregulation in the HPA-axis which is what regulates cortisol production leading to negative side effects (mental health disorders and conditions) [7].

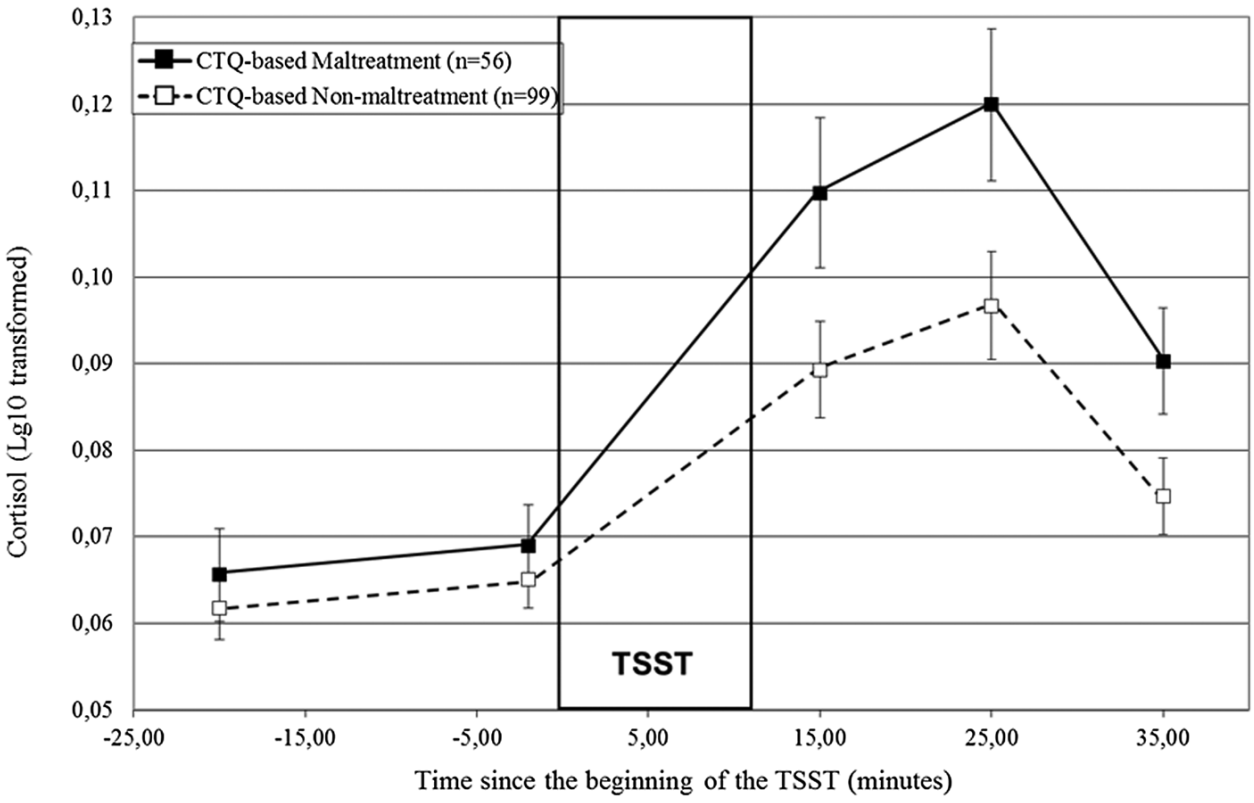


**Figure 3.** Cortisol Levels in Relation with Maltreatment of Children and Non-maltreatment of Children
Source: Enduring effect of childhood maltreatment on cortisol and heart rate responses to stress: The moderating role of severity of experiences

Children who face maltreatment such as abuse, and instability often have higher levels of cortisol as shown in the graph above. Higher levels of cortisol are associated with increased stress and increased susceptibility to mental health disorders such as anxiety and depression.

Another reason for higher levels of cortisol is economic stress. Poverty, housing instability, and food insecurity levels are increasing. These are factors associated with higher levels of cortisol as all of these induce higher levels of stress [7].

Children whose parents experience chronic stress are often burdened with chronic stress themselves. This causes dysregulation in levels of cortisol which impacts the physiological processes going on in the body [7].

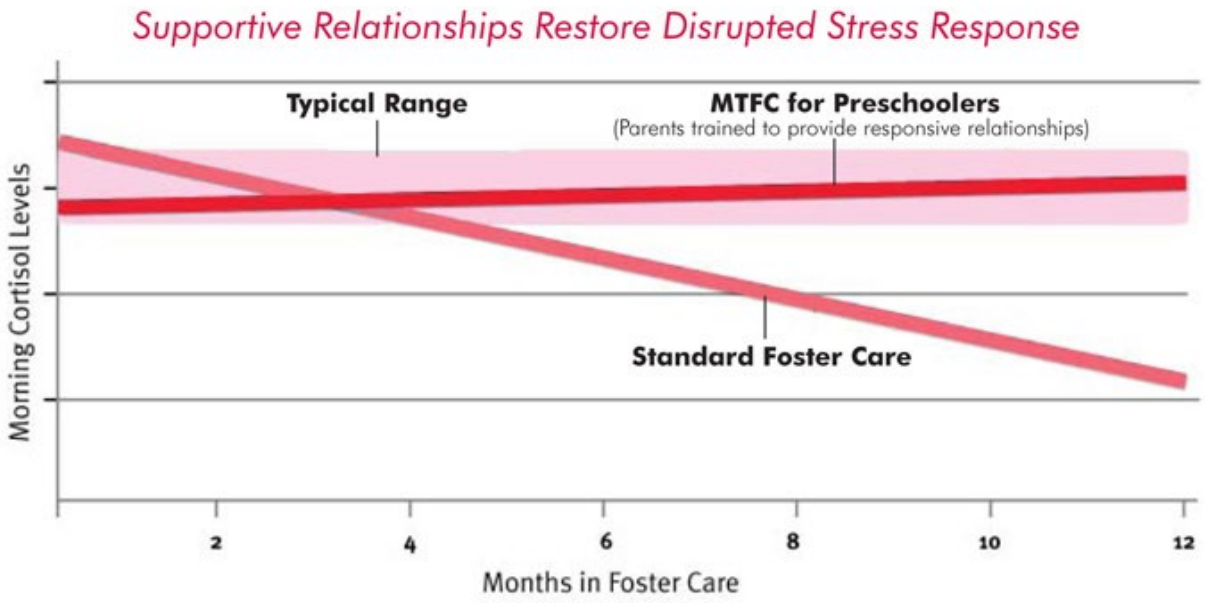


**Figure 4.** Supported Relationships vs Instability and Cortisol Levels in Children
Source: MTFC-P: An Evidence-Based Intervention for Child Neglect

Children who live with parents who support them and foster positive relationships with them experience higher, normal levels of cortisol in the morning. Children who face instability in the foster care system wake up in the morning with lower levels of cortisol, decreasing with the time they spend there. Higher levels of cortisol in the morning are important because of its importance in someone's circadian rhythm. It increases alertness, preparing the body for the activities that await them for the rest of the day. The high morning levels help with the regulation of metabolism, positive immune function, and responses to stress. Disruptions to this pattern lead to dysregulation of cortisol often resulting in fatigue and increased levels of stress.

## *Mental Health Disorders and Cortisol*

1. Cortisol and depression: Major Depressive Disorder (MDD) is often associated with elevated cortisol levels. As talked about previously, dysregulation of the HPA axis is caused by chronic stress which results in the hypersecretion of cortisol. This damages the neurons in the hippocampus, which controls emotions and encodes memories. If dysregulation persists for a long period of time, the brain will no longer be able to respond to stress resulting in symptoms of hopelessness and cognitive malfunction. This exposes children to depression and makes them more prone to developing it. Patients who have MDD experience a jump upwards in levels of cortisol which exacerbates the disorder [8].

2. Cortisol and anxiety: When the amygdala is hypersensitive to stress it results in cortisol hyperactivity which are key contributors to mental health disorders. The amygdala controls how one reacts to fear, and it helps regulate emotions. When chronic cortisol levels are increased, the connections between the prefrontal cortex and the amygdala are stronger, meaning the brain reinforces fear responses and can no longer smother memories that induce anxiety. Post traumatic stress disorder (PTSD) and general anxiety disorder (GAD) are often results of the phenomenon described above. Increased activity in the HPA axis also results in restlessness which is another symptom of anxiety [8].

## Sex Hormones and Mental Health Disorders

Sex hormones play a key role when it comes to the development and the progression of mental health disorders in children. They impact the function and the structure of the brain while it is developing. When going through puberty, children are more likely to develop depression or anxiety because it is a vulnerable period for them. Mood and behavior are greatly impacted because sex hormones like estrogen and testosterone interact with neurotransmitters like dopamine and serotonin (happiness and emotions). When these hormones are imbalanced or deregulated, mood swings become more prevalent [9].

## Inflammation and Dysregulation in The Immune System

### *Immune System Dysregulation and Inflammation*

When the body is unable to maintain a balanced immune response (hyperactivity or underactivity), it is called immune system dysregulation. The imbalance serves as a trigger for chronic inflammation which is a state when the immune system is always active and never stops working. When children are going through important developmental phases, they are more susceptible to this as chronic inflammation disrupts neural pathways and causes changes in the brain. The constant activation of the immune system results in neural damage and damaged brain plasticity causing trouble with development emotionally, cognitively, and socially [10].

### *Biomarker of Inflammation: CRP and IL-6*

C-reactive protein is produced by the liver and serves as a biomarker of inflammation. Increased stress exposure led to in an increase in pro-inflammatory cytokines, and therefore an increase in C-reactive protein. Increased CRP levels are often associated with mood disorders in children as well [10].

Interleukin-6 (IL-6) is a cytokine and is a part of immune signaling and pro-inflammatory and anti-inflammatory pathways. High chronic stress as a strong association with high levels of IL-6. Due to this, they serve as an indicator when it comes to determining levels of mental health disorders such as anxiety and depression. IL-6 plays a huge role in the inflammation of neural pathways which impair emotional regulation by changing synaptic connections and disrupting the repair of neural pathways [10].

#### *Impact on Mental Health Disorders in Children*

CRP and IL-6 directly impact emotional regulation and mood. High levels of these immune biomarkers correlate with chronic inflammation which result in increased susceptibility to depression and anxiety. Children are in the process of developing and going through critical changes that will stay with them for the rest of their life. Inflammatory processes have negative effects on the especially vulnerable amygdala and prefrontal cortex–stress and emotions–including memory problems and cognitive function. Increased inflammation also means a hypersensitive HPA axis leading to chronic stress and dysregulation of cortisol. When these symptoms stay for longer periods of time, children become predisposed to mental health disorders like major depressive disorder (MDD) and generalized anxiety disorder (GAD) [10].

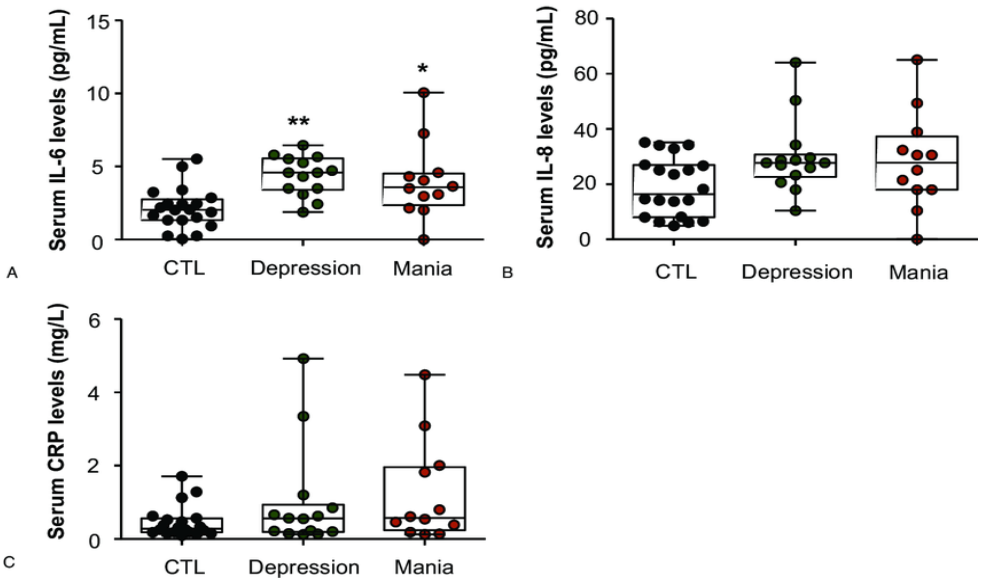


**Figure 5.** Levels of IL-6 and CRP in Control vs. Levels in People with Depression
Source: Research Gate

IL-6 levels and CRP levels in people who are experiencing are higher as shown in the graph above. While the control for IL-6 is in the range of 2-2.5 pg/ml, the level of depression reaches 6.5 pg/ml. For c-reactive protein, the control is about 1.5 mg/L, but the depression is about 3 pg/mL some even reaching 5 pg/mL. The IL-8 won't be considered as of now as it is not discussed in the paper.

## Genetics and Epigenetics with Mental Health Disorders

### *Genetic Risk Factors*

Genetics is the study of hereditary. Traits and characteristics are passed onto children from their parents through random selection and it decides the child's appearance, health conditions, and other features that make up the biology of a human. If parents have suffered from mental health disorders, children become automatically predisposed to developing one themselves. When observing mental health disorder such as schizophrenia, ADHD, depression, anxiety, and autism spectrum disorder, common genetic factors and variation have been found. An example would be changes in the CACNA1C gene, which is responsible for the encoding of a calcium channel that is very important for neurons to communicate. Genetic variations also have significant impacts on the transmission of neurons which affects mood, cognitive thinking, and emotions [11].

Another example of a genetic factor altering to increase risk of mental health disorders in children is the DISC1 gene. This gene aids the formation of synapses and plasticity of the brain. Mutations and variation found in this gene have been associated with mental health disorders such as schizophrenia, depression, and anxiety due the impairment it causes emotional regulation and cognitive thinking. Genetic variation can couple with environmental factors as well which increases a child's risk for developing a mental health disorder [11].

### Epigenetic Variations

Predisposition due to genetics and environmental factors are linked through changes because of epigenetic factors. Epigenetics can alter the expression of a gene without changing the DNA sequence. The modifications are ever changing and respond to stress and trauma.

*DNA Methylation*

Methyl groups need to be delivered to different and specific DNA regions to turn genes on and off. They regulate the protein production therefore deciding whether a certain trait is expressed or not. Methyl groups generally attach to cytosine bases in CpG islands (regions of DNA with a lot of cytosine and guanine). DNA methylations is the process that adds these methyl groups to those regions. This usually reduces the expression of certain regions because it blocks transcription factors from binding to the gene preventing the formation of a protein. It also recruits proteins so that they can inhibit transcription, also preventing the formation of a protein. Children who face difficulty during their childhood have been seen with increased methylation of the NR3C1 gene which encodes the glucocorticoid receptor. The receptor plays a role in stress control and regulation because it directly aids the regulation of the HPA axis [12].

Increased methylation of the NR3C1 gene means less of the protein that the gene encodes, leading to impaired feedback inhibition of cortisol release. Increased risk of mental health disorders is caused by this as increased cortisol and stress is a result. Brain structures like the amygdala and the prefrontal cortex can experience changes in structure and function if this deregulation continues over time [12].

*Histone Modifications*

Histones are proteins that bind to DNA, shaping it into a chromosome shape, and help DNA fit into the cell nucleus. They are rich in the amino acids lysine and arginine which allows them to associate themselves with DNA's negative charge. They can go through many different modifications: acetylation, deacetylation, phosphorylation, and methylation which influence if a gene can be transcribed into a protein. Acetylation for example relaxes the structure of a protein but deacetylation causes the histones to wind up tight and prevents transcription of genes. Children who have experienced trauma in their life often face dysregulation of these processes [12].

When histone deacetylation is forced due to trauma in a child's past, the silenced genes can result in problems with memories and neural plasticity. This phenomenon consequences inhibit the brain's ability to recover from stress. Children already have trouble with their emotions, seeing as they are constantly developing, so when this happens coping mechanisms and emotion processing gets impaired. Adding on to this, dysregulation of histones in the amygdala and the hippocampus has a direct correlation with behavioral instability and increased emotional activity – symptoms associated with mental health disorders [12].

These findings prove that histone dysregulation is largely caused by external, environmental factors.

## Conclusion

This study underscores the significant role of biomarkers in understanding and managing childhood mental health disorders. By identifying hormonal, immune, and genetic influences, targeted interventions can be developed to address the root causes of these conditions. Future research should focus on longitudinal studies to establish causality and explore therapeutic strategies, particularly for high-risk populations.

## Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

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