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Review Article

Understanding Pathways from Childhood Irritability to Psychopathology: A Scoping Study Review

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Abstract

Irritability can be a prominent characteristic of various psychopathologies, including childhood psychiatric and neurodevelopmental disorders. Genetic, environmental, and prenatal factors influence the development and progression of childhood irritability. This review aims to highlight the biological and behavioral pathways associated with childhood irritability, examine the relationship between irritability and childhood psychopathology, identify the existing gap in the literature, review these connections, and provide guidance for future research. Articles published on PubMed and Google Scholar from 2000 to 2023 were reviewed using a combination of search terms such as "childhood irritability," "maternal stress," and "prenatal stress." The literature search yielded roughly 2,800 articles using the predefined search terms, of which 65 were deemed relevant to this scoping review. The articles reviewed identified a link between prenatal stress, childhood irritability, and the development of adult psychopathology. Pathological irritability and its emerging connection to maternal stress pose a risk factor for developing neurodevelopmental disorders and psychopathology in the pediatric population. Much of the current literature addresses the biopathophysiologic pathway linking maternal stress to childhood irritability in offspring. However, no interventional research studies have reported on how to interrupt this pathway or mitigate its progression with predictable outcomes. Therefore, identifying a critical period during childhood or adolescence when the progression from childhood irritability to adult psychopathology can be recognized may reduce the risk of developing neurodevelopmental disorders or psychopathology in childhood and throughout life.

Keywords

Childhood Irritability, Maternal Stress, Neurodevelopmental Disorders, Psychopathology

1. Introduction

Irritability can be defined as a "proneness to anger, an increased sensitivity to provocation and the likelihood of behavioral outbursts with or without aggression OR a propensity to react with excessive anger, grouchiness or tantrums to a situation". [1, 2] It has also been conceptualized as a "low threshold for experiencing anger in response to frustration". [3] It comprises children's moods (e.g., grouchiness) and behaviors (e.g., anger outbursts, tantrums). [1-4] While there are normative patterns of irritability throughout childhood development, irritability can also present in externalizing (e.g., oppositional defiant disorder, conduct disorder), internalizing (e.g., anxiety, depressive disorders), as well as neurodevelopmental disorders (e.g., attention deficit hyperactivity disorder, autism spectrum disorder). [5]

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Much of the research has focused on how childhood irritability may progress to behavioral disturbances or psychiatric illness in adolescence and adulthood. However, an emerging literature focuses on bio-pathophysiologic mechanisms predisposing children to pathologic irritability. [6, 7] Given the associations between maternal stress, brain development of newborns, and the development of psychopathology in early childhood due to epigenetic changes, it is crucial to investigate and elucidate the pathway(s) that connect maternal stress and childhood irritability and, if possible, identify and mitigate contributing factors. [8-10]

The proposed pathway starts with prenatal depressive symptoms in the mother, leading to low adaptability and high intensity of temperament in the infant, which translates to childhood irritability and progresses to adult psychopathology. This review aims to provide a comprehensive literature analysis, focusing on predisposing factors and biological pathways that may lead to irritability in children. It examines the relationship between prenatal maternal stress, childhood irritability, and the later onset of psychiatric and neurodevelopmental disorders.

2. Material and Methods

A review of published articles between 2000 and 2023 was completed on PubMed and Google Scholar. Articles included those on empirical research on childhood irritability, all in English. These articles examined the association between prenatal stress, and childhood irritability and the progression to psychopathology. One study by Chess et al. was outside this timeline but was nonetheless included for historical context. Sixty-five articles met the inclusion criteria, identified in the initial search.

3. Results

A literature review on prenatal maternal stress between 2001 and 2023 revealed three main research areas. The first area involves environmental and genetic influences; the second area focuses on the positive association between prenatal maternal stress and irritable temperament in infancy and childhood; and the third area focuses on the proposed pathophysiology of irritability in relation to prenatal maternal stress. Twenty-five cross-sectional studies, 22 review articles, 4 meta-analyses, 11 longitudinal studies, and one short report. Four animal studies met the inclusion criteria. Two studies employed both cross-sectional and longitudinal study designs. [11, 12] An editorial piece was also included due to the author's expertise on the subject matter. A supplemental table categorizes studies based on the link between prenatal stress and childhood irritability; pathogenesis, pathophysiology, mechanism, and components of childhood irritability; temperament-irritability axis; early life or childhood stress/programming/epigenetics/biomarker and genetics.

4. Discussion

4.1. Background

The pathophysiology of irritability can be conceptualized as an aberrant response to threat, frustration, and oversensitivity to sensory stimuli with a lower threshold for anger. It is directly linked to physiological processes and subsequent biological changes [13]. However, there are underlying mechanisms in the published literature that explain this phenomenon as a bridge between the intrauterine experience and adult psychopathology. The specific biological mechanisms have been relatively well described without necessarily labeling it a pathway. While that is what the literature describes, it is unclear if identifiable stressors play a role in the said pathway, and if they indeed do, mitigating that to prevent progression to adult psychopathology is vital. Understanding the critical point along that pathway at which contributing factors impact outcomes could prevent the progression to childhood irritability.

4.2. Theoretical Framework for the Pathophysiology of Irritability

The primary human stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, develops prenatally and continues after birth, helping to guide adaptive responses. This system triggers the adrenal glands to release glucocorticoids essential for normal brain function and maturation; however, sustained high levels can ultimately harm brain development and function. Cortisol mediates responses within the limbic system and is critical in fear regulation, threat response, behavioral adaptation to stressful events, emotional control, cognitive development, neurodevelopment, adaptability, and self-regulation. [14-16] A “faulty” HPA axis is implicated in stress-related psychopathology due to its impact on neurodevelopment early in life. [17]

About 10%-20% of maternal cortisol passes from the mother to the fetus through the placenta, subsequently passing through the blood-brain barrier of the developing fetus. Figure 1 below illustrates the modulation and release of cortisol by placental CRH.

Studies using animal models further help with understanding the HPA axis regulatory system. They propose that the associated response by the central nervous system (CNS) regulators of the HPA axis, including the amygdala, hippocampus, and prefrontal cortex, is influenced by increased CRH signaling and impaired glucocorticoid receptor-mediated feedback, resulting in HPA axis hyper-reactivity in rodents. Thus, exposure of the developing fetus to elevated maternal cortisol levels can be considered prenatal early life stress (ELS). This phenomenon has been shown to cause the expression of genes in peripheral tissues, such as the glucocorticoid receptor (GR) and 11-beta hydroxysteroid dehydrogenase (11β-HSD1).

ELS triggers increasing levels of cortisol within the uterine environment and potentially results in an increased risk of psychopathology emerging later in life. [18] Fetal exposure to cortisol is regulated by 11beta-HSD2, a placental enzyme that transforms cortisol into an inactive metabolite known as cortisone. This enzyme protects the fetus from the harmful effects of increased circulating maternal cortisol levels during pregnancy. Furthermore, chronically elevated cortisol levels are associated with an increased risk for the onset of impaired emotional and behavioral self-regulation symptoms. [16]

Animal studies have found an association between ELS and overexpression of HPA axis regulatory hormones (CRH mRNA and glucocorticoid receptor (GR) in the amygdala and hippocampus, respectively [19, 20]. Evidence suggests that this results in decreased excitatory synaptic transmission, reduction in synaptic plasticity, and reduced expression of the N-methyl-D-aspartate (NMDA) receptor in hippocampal synapses. [21] In the prefrontal cortex (PFC), however, ELS reduces GR expression and protein levels, compromising the negative feedback function on the HPA axis, a system essential in regulating the stress response. [22, 23] These stress-related regulatory changes support a biologically plausible mechanism for the potential development of pathologic irritability. [24, 25]

4.3. Overview of Childhood Irritability

Irritable outbursts are considered a feature of typical development across childhood and adolescence. It is generally agreed that childhood irritability has tonic and phasic dimensions, with each dimension having unique implications for the development of future disorders involving either behavior regulation or psychopathology. [1, 26] The DSM-5 defines phasic irritability as developmentally inappropriate temper outbursts, while tonic irritability is the negative affect that persists between outbursts. Phasic irritability is characterized by temper tantrums or outbursts involving separate events of disproportionate temper manifested by explosions of anger and frustration with disruptive and/or disorganized behaviors, sometimes involving self-injurious behaviors, property destruction, and/or verbal or physical aggression. The duration of outburst episodes can vary, but they are generally short-lived. [27]

In contrast, tonic irritability describes a persistently angry, grouchy, negative mood state that entails an increased propensity to anger and or short temper with low frustration tolerance. This mood state continues between outbursts, with the child typically described as overly sensitive, touchy, or easily annoyed. These two patterns constitute core symptoms of many childhood psychiatric disorders. [27]

Developmentally regular irritable outbursts are often phasic, especially in preschool-aged children, and tend to decrease in later childhood and adulthood, mirroring the maturation of the prefrontal cortex. [28]

Pathologic phasic irritability is described as more heritable and more stable than tonic irritability in twin pairs between the ages of 8 and 17 years. [29] During adolescence, irrita-bility is typically linked to a small but measurable rise in irritable mood (tonic episode) and temper outbursts (phasic episode), and tonic, rather than phasic episodes, generally persist somewhat longer into adolescence. [1, 5, 6, 28, 30, 31]. Other studies describe irritability in a developmental context, where early-onset persistent irritability may be more of a neurodevelopmental origin. In contrast, later-onset irritability is more likely characteristic of an affective or depressive episode, thus with potential implications for treatment. [32]

4.4. Psychiatric and Neurodevelopmental Disorders Characterized by Childhood Irritability

Childhood irritability is a term utilized in describing a host of psychopathologic categories within the DSM, including multiple psychiatric and neurodevelopmental disorders. With data to support the natural history, course, and progression of pathological childhood irritability, it has been suggested by some that it should be categorized as an early childhood-onset neurodevelopmental disorder. [33] Irritability is common in children with neurodevelopmental disorders, including intellectual developmental disabilities (IDD), autism spectrum disorder (ASD), communication disorders, attention deficit hyperactivity disorder (ADHD), motor coordination disorder, and specific learning disorders. Furthermore, the presence of irritability is thought to contribute to the relationship between neurodevelopmental and depressive disorders, with an increased risk as high as 42% for internalizing disorders, including major depression, among adolescents with neurodevelopmental disorders. [10, 34]

After controlling for pre-existing behavioral or psychiatric disorders and associated demographic factors, it has been demonstrated that irritability in early childhood is a consistent transdiagnostic predictor of both externalizing and internalizing disorders in children and adolescents. [8, 35, 36] Research shows that chronic irritability in oppositional defiant disorder, albeit an externalizing disorder, is a strong predictor of depression and anxiety, which are internalizing disorders, later in life. [37, 38]

Mood disorders, such as depression, can have irritability as a prominent symptom, and as such, irritability is listed as one of the potential qualifying criteria for that diagnosis. A childhood-onset mood disorder called disruptive mood dysregulation disorder (DMDD) was added to the DSM-5, manifested by elevated baseline levels of persistent (tonic) irritability and anger with frequent, intense temper outbursts (phasic), thus placing this disorder at the interface of internalizing and externalizing disorders, given it has components of both emotional and behavioral dysregulation. [39, 40]

Tonic irritability has shown stronger associations with depressed mood, while the phasic dimension of irritability has more significant correlations with feelings of worthlessness,

hopelessness, and suicidality. [41] Direct associations between irritability and the risk of suicide were found for children with worsening irritability through childhood, particularly in those with disproportionate tonic and phasic episodes and an increased risk of suicidality, with phasic irritability being predictive of impulsive suicide attempts. [28, 41, 42]

4.5. Progression of Pathological Childhood Irritability to Diagnostic Disorders

Heritability and Genetic Influences

Heritability plays a significant role in the development of irritability, with genetic loading increasing the risk for both irritability and subsequent disorder severity. Twin studies have demonstrated the heritability estimate for childhood irritability ranging between 30% and 60%, with several studies finding minimal differences in heritability risk between boys and girls. [3, 28, 29, 43] The genetic association between irritability and neurodevelopmental disorders, as well as the later onset of psychopathology, has been substantiated via genome-wide association studies using polygenic risk scores (PRS), an estimate of an individual's genetic liability for a specific disorder or trait, given current knowledge of the trait's genetic architecture, particularly in attention deficit and hyperactivity disorder (ADHD) and major depressive disorder (MDD). [44]

Associations have been reported between PRS of adult traits, including internalizing, externalizing, and clinical and continuous measures of similar characteristics in children. [45] Several studies identified genetic studies that used statistical modeling to estimate the contribution of irritability to neurodevelopmental and psychiatric disorders. A large longitudinal study involving adolescent twins and siblings demonstrates irritable mood as underlying the relationship between oppositionality and depression, postulated to be the result of genetic overlap. The results suggest that genetic vulnerability to MDD significantly influences irritability in adolescence. [46]

4.6. The Intrauterine Environment as a Biological Pathway in Temperament Traits

Child Temperament, Intrauterine Cortisol Levels, and Maternal Depression

Irritability is a core dimension of temperament, which is considered a behavioral "style" or personality trait. It reflects negative affectivity (NA) and is highly associated with difficulty regulating attention and behavior [12]. This supports the thought that temperament is an early-onset variation in emotional reactivity. [47, 48] A longitudinal study by Chess et al. observed an association between baseline temperamental characteristics and psychopathology. By highlighting four attributes of temperamental functioning, including rhythmicity, adaptability, quality of mood, and intensity of reaction, the authors showed that temperament alone did not cause behavioral disturbances in children who presented with psychopathology. They showed that while irritability may play a role in clinical behavioral symptoms evidenced in temperament, it can result in an interaction between familial and environmental factors, in this case, the intrauterine environment resulting from maternal stress [49].

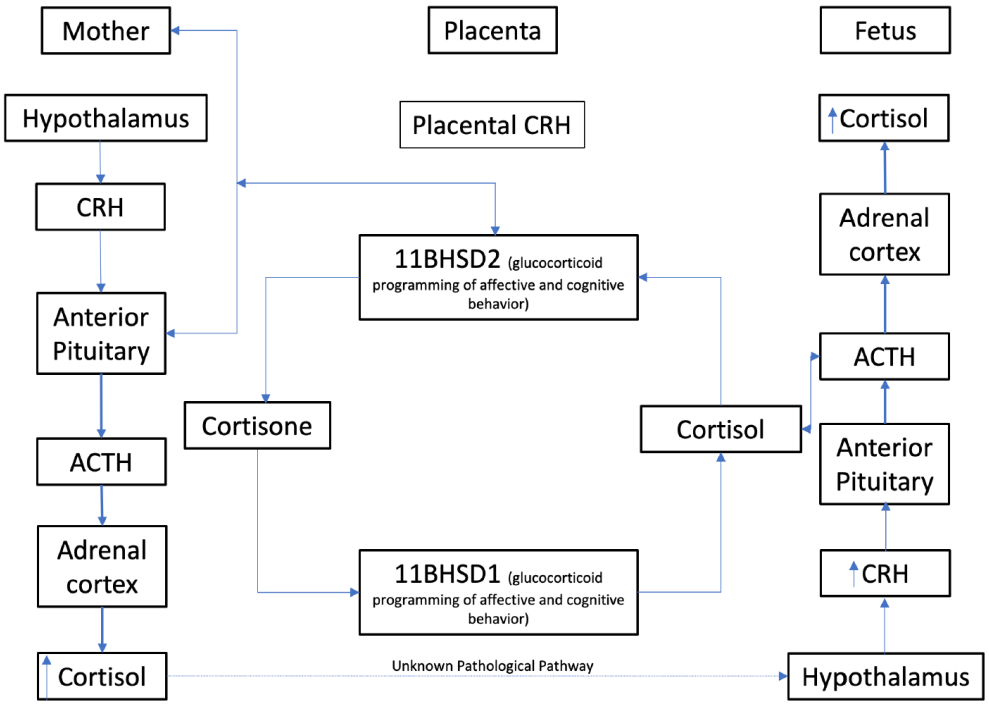

Figure 1. *Bidirectional Relationship in Cortisol Modulation Between Mother and Fetus.*

Though most previous authors primarily focus on intra-familial and extra-familial environments, more recent studies are beginning to show the intrauterine environment as an environmental factor at play in the development of behavioral disturbances that may result in the need for psychiatric care during childhood. One study examined the effects of prenatal maternal psychosocial stress indicators and cortisol levels on infant temperament in a sample of almost 250 infants. Maternal salivary cortisol and psychological states were assessed at varying weeks of gestation and 2 months postpartum, and those with high levels of cortisol at 32 weeks of gestation reported that their full-term infants demonstrated more intense negative responses, as evidenced by startled or distressed reactions to new or unusual stimuli. Infant temperament was also evaluated with a measure of negative reactivity using the fear subscale of the Infant Temperament Questionnaire at 2 months of age, finding that psychosocial stress indicators predicted infant temperament. [15] Another small longitudinal study that followed over 100 women from the 3rd trimester of pregnancy through 8 months postpartum found a strong association (after controlling for confounders) between maternal depression and childhood temperament, detectable as early as 3 to 6 months after birth. [50] See Figure 1.

4.7. Childhood Irritability to Psychopathology

Genetic and Neurobiological Underpinnings

The intrauterine environment has been said to "program" the fetus, making it vulnerable to disease as an adult. DNA methylation is one mechanism of epigenetic changes mediating stress and vulnerability leading to psychopathology. [51] Exposure of the growing fetus to excess glucocorticoids is considered a crucial mechanism in early-life disease programming. [52] The theory underlying this suggests that when the maternal HPA axis is dysregulated due to stress, fetal exposure to stress hormones triggers a response that influences susceptibility to neurodevelopmental disorders, physical illness, and psychopathology.

Higher maternal cortisol levels have been linked to offspring temperament, and cortisol measurements, especially in the third trimester, have been associated with infant emotional reactivity and neurodevelopment. [53] Given these findings, some studies have attempted to determine a "window of susceptibility," the critical point-in-time or timeframe when fetal programming starts and ends, given that cortisol levels are higher in late and not early pregnancy. [54, 55] However, no studies suggest that a minute level of programming may not have occurred earlier, right outside the window of 28-32 weeks of pregnancy.

The pathway begins with prenatal stress in the mother, resulting in biological dysregulation in the HPA axis, causing a "re-programming" resulting from a stress response in the fetus. [56]

4.8. The Pathway as Evidenced Through Population Studies

The interactions between maternal depression and childhood irritability are quite complex, given that they are not strictly linear. Maternal depression occurring as late as the third trimester has been shown to increase the risk of externalizing and/or internalizing symptoms [57-60] Postnatally, researchers were able to characterize five different irritability classes: low decreasing, moderate decreasing, high steady; initially very high, then decreasing; and high increasing, using data from The Fragile Families and Child Well-being Study (a national study of 5,000 children, ages 1-22 years and their caregivers). The authors concluded that the most severe class of irritability, high increasing, was linked to mothers with recurrent depression (assessed during 2 time points throughout the life of the child), suggesting that postnatal maternal depression is linked to childhood irritability. Furthermore, a bi-directional association between maternal depression and childhood irritability was identified. Childhood irritability during preschool age was associated with increased maternal depression by elementary school age. Conversely, maternal depression at toddler ages was also found to be associated with increased irritability at preschool ages. [61]

The role of irritability in the pathways leading from prenatal maternal depression to adolescent depression was identified in a groundbreaking study, the Avon Longitudinal Study of Parents and Children. [62] The study measured depressive symptoms in pregnant women at 18 and 32 weeks prenatally and in the postnatal period at 8 weeks, 8 months, and 21 months. Childhood factors measured included negative perceived mood (temperament), low perceived adaptability (responses to novel situations), high perceived intensity (level of emotional response) at age 24 months, irritability symptoms (temper eruption, easily annoyed, angry or offended) at age 8, 10, and 13 years, conduct (behavioral) problems, and depressive symptoms at age 16 years. [63] This study proposes a pathway from pre - and postnatal depression to irritability in childhood that is mediated by temperamental low perceived adaptability and high perceived intensity in toddler years, ultimately progressing to subsequent development of depression in adolescence. See Figure 2.

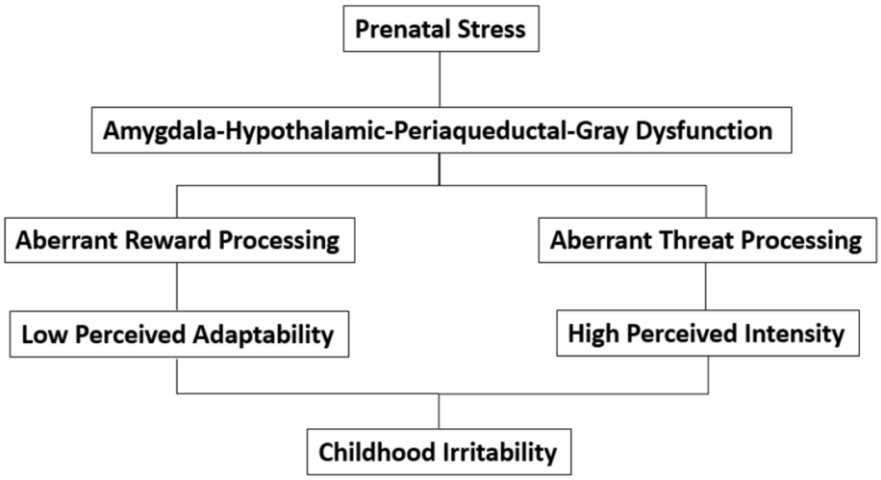

Figure 2. *Childhood Threat Response Pathway Following Maternal Stress.*

5. Evidence-based Identified Gap in the Current Literature

There is evidence to suggest that pathological childhood irritability resulting from prenatal stress is associated with the risk of psychiatric and neurodevelopmental disorders in adolescence and adulthood. While the evidence is compelling, no research supports this finding definitively. Identifying, monitoring, and intervening in the progression to pathological features should be possible. Early interventions, ideally beginning in infancy, thus capturing the critical period during the progression leading up to the presentation, could potentially reduce the subsequent risk for irritability and maladaptive behaviors, which could alter the trajectory of future psychopathology. [64]

6. Conclusion

Irritability is a common childhood feature, and mastery in regulating emotions associated with irritability is a developmentally expected milestone for children and adolescents. While irritability can be normative, it has become clear that persistent irritability can result in a disordered presentation.. The current literature suggests that cortisol levels and epigenetic changes both from within and outside the intrauterine environment play a role in the development of childhood irritability and, in turn, progression to psychopathology in adults. This review identifies gaps in the current literature that fail to adequately address the biological and genetic underpinnings of pathologic childhood irritability

Many research studies in both human and animal models provide persuasive evidence for the pathways involved in developing childhood irritability, including the impact of prenatal stress. However, more research needs to be conducted to determine the specific epigenetic pathways related to alterations in gene expression caused by environmental factors or life experiences. While this may be especially difficult to determine, identifying the timeframe within which this gene alteration occurs could provide a window of opportunity in which the progression of pathologic irritability in children to adult psychopathology could be mitigated or even halted. Specifically, identifying the critical period when cortisol modulates the intrauterine environment to provide the opportunity for early screening of childhood irritability, thus enabling the timely provision of appropriate interventions, could improve long-term outcomes.

7. Future Areas of Research

Further research could potentially establish a consensus for a battery of validated, reliable assessment tools to ensure the utility of clinicians' consistent measure of childhood irritability metrics in improving the timeliness and reliability of the screening process. [65] Established metrics could aid in providing a clear, standardized definition of pathological childhood irritability, one that could be incorporated into the DSM with distinct dimensions and objective criteria. With no consistent definition of pathological childhood irritability and difficulties in differentiating normative versus pathological irritability, building on diagnostic criteria from the DSM could be a starting point for a more unified definition of childhood irritability. [27]

8. Limitations

Limitations in reviewing the literature regarding childhood irritability include, firstly, definition and measurement challenges, given a lack of established standardized assessments, heavy reliance on subjective reporting from parents or caregivers with its associated risk of bias, and developmental considerations regarding the labeling of "irritable" behavior, which varies significantly depending on a child's age and developmental level. Secondly, there is relatively limited scientific understanding of

the underlying physiological mechanisms, neural correlates, genetic influences, and environmental factors contributing to the development of irritability. Thirdly, variability in sample heterogeneity and research methodologies, with differences in study design—involving, for example, longitudinal versus cross-sectional approaches—limits cross-study comparisons. Finally, cultural considerations come into play, as cultural norms and expectations can influence how irritability is expressed and interpreted, as well as the general lack of currently available culturally sensitive clinical assessment tools.

Abbreviations

CRH	Corticotropin-releasing Hormone
ACTH	Adrenocorticotropic Hormone
11B HSD1	11β-Hydroxysteroid Dehydrogenase Type 1
11B HSD2	11β-Hydroxysteroid Dehydrogenase Type 2
CD	Conduct Disorder
ODD	Oppositional Defiant Disorder
DMDD	Disruptive Mood Dysregulation Disorder
PTSD	Post Traumatic Stress Disorder
ASD	Autism Spectrum Disorder
ADHD	Attention Deficit Hyperactivity Disorder
IDD	Intellectual Developmental Disorder
PRS	Polygenic Risk Scores
ELS	Early Life Stress
GR	Glucocorticoid Receptor
PCIT	Parent-Child Interaction Therapy

Supplementary Material

The supplementary material can be accessed at https://doi.org/10.11648/ j.ajp.20251102.17

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Conflicts of Interest

The authors declare no conflicts of interest.

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