

Childhood Maltreatment and Depressive Symptoms: The Mediating Roles of NR3C1 Methylation and Rumination

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Date: 2026-03-04T21:05:52+00:00

Abstract

The negative effects of childhood maltreatment persist into adulthood through biological embedding, altering an individual's cognitive patterns and subsequently triggering depressive symptoms. Through a six-month longitudinal study of 593 young adult participants (mean age 19.47 years, 49.2% female), this research investigated the chain mediation mechanism of childhood maltreatment on adult depressive symptoms via NR3C1 methylation and rumination. The results indicated that: (1) different types of maltreatment all lead to increased depressive symptoms by increasing rumination; (2) compared to other types of maltreatment, only emotional neglect significantly upregulates DNA methylation levels in the NR3C1 promoter, predisposing individuals to more ruminative thinking and thereby increasing the risk of depression.

Full Text

Preamble

Childhood Maltreatment and Depressive Symptoms: The Mediating Roles of NR3C1 Methylation and Rumination

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Childhood maltreatment may indirectly influence adult depressive symptoms through rumination, or it may alter an individual's cognitive patterns via biological embedding, thereby triggering depressive symptoms. However, the specific pathways of these effects vary depending on the type of maltreatment. This study identifies epigenetic and cognitive susceptibility markers for the diagnosis

of depression. The findings emphasize that depression prevention should focus on early adverse environments; timely intervention in the family environment and cognitive processes can effectively block the proliferation and spread of the negative impacts of childhood maltreatment.

The negative effects of childhood maltreatment persist into adulthood through biological embedding, altering an individual's cognitive style and subsequently triggering depressive symptoms. This study conducted a six-month longitudinal follow-up of 593 young adults (mean age 19.47 years, 49.2% female) to investigate the chain mediation mechanism by which childhood maltreatment influences adult depressive symptoms through *NR3C1* methylation and rumination. The results indicated that: (1) different types of maltreatment all lead to increased depressive symptoms by increasing rumination; (2) compared to other types of maltreatment, only emotional neglect was found to upregulate DNA methylation levels in the *NR3C1* promoter, which predisposes individuals to more ruminative thinking and subsequently increases the risk of depression.

Keywords: depressive symptoms, childhood maltreatment, rumination, *NR3C1* methylation

CLC Number: B844

Funding: This research was supported by the National Natural Science Foundation of China (31900776), the Major Philosophy and Social Science Research Project of the Ministry of Education (2025JZDZ025), the Natural Science Foundation of Shandong Province (ZR2025MS346), the Shandong Provincial Social Science Planning Research Project (25CLJJ16), and the Humanities and Social Sciences Youth Fund of the Ministry of Education (25YJC190002).

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Childhood Maltreatment and Depressive Symptoms: Mediating Roles of Glucocorticoid Receptor Gene (*NR3C1*) Methylation and Rumination YUE Xinyi CAO Yanmiao DING Xiaofan SUN Yuhang ZHANG Wenxin (Faculty of Psychology, Shandong Normal University, Shandong Provincial Key Laboratory of Brain Science and Mental Health, Jinan 250014, China)

Abstract

Childhood maltreatment is a major global public health problem that increases the risk of depressive symptoms later in life. However, important gaps remain in our understanding of how such experiences “get under the skin”. Emerging evidence suggests that early adversity contributes to epigenetic modifications of key regulatory elements within the hypothalamic-pituitary-adrenal (HPA) axis, potentially increasing vulnerability to psychopathology. In addition, rumination—the tendency to repetitively dwell on one's problems, concerns, and distressing feelings—represents a key cognitive mechanism. Crucially, biological embedding and cognitive processes do not operate in isolation. According to transdiagnostic

models of psychopathology, distal environmental risks may heighten rumination by undermining adaptive stress responses. Moreover, because specific subtypes of childhood maltreatment may have distinct epigenetic signatures and differential contributions to depression severity, these mechanisms may vary across maltreatment subtypes.

Accordingly, this study examined whether methylation changes in the promoter region of the NR3C1 gene and rumination explain the longitudinal association between childhood maltreatment and adult depressive symptoms, and whether maltreatment subtypes differ in their predictive validity.

A total of 593 Chinese young adults (Mage = 19.47 ± 0.69 years; 49.2% female; 98.6% Han Chinese) were recruited from Shandong, China, and followed for six months. Depressive symptoms were assessed at both time points using self-report questionnaires, and childhood maltreatment was assessed retrospectively. Genomic DNA was extracted from buccal swab samples and used for DNA methylation analyses. We tested a series of serial mediation models in which childhood maltreatment predicted depressive symptoms in young adulthood through DNA methylation in the NR3C1 promoter region and rumination in sequence. We also examined whether different childhood maltreatment subtypes showed differential predictive validity.

Results showed that DNA methylation of NR3C1 and rumination mediated the longitudinal association between childhood emotional neglect and depressive symptoms in young adulthood.

Specifically, emotional neglect was associated with higher methylation levels in the NR3C1 promoter region, which in turn predicted greater rumination and higher depressive symptoms. In addition, all maltreatment subtypes were associated with depressive symptoms via elevated rumination. However, the serial mediation pathway was not observed for childhood emotional abuse, physical abuse, physical neglect, or total maltreatment. Moreover, NR3C1 promoter methylation did not significantly mediate the associations between any childhood maltreatment subtype and depressive symptoms in young adulthood.

These findings highlight the importance of epigenetic processes and cognitive vulnerability in understanding how childhood adversity increases risk for depressive symptoms across the lifespan.

Notably, this study provides further support for transdiagnostic models of psychopathology, which propose that distal environmental risks can shape individuals' stress responses, giving rise to proximal cognitive risk factors that, in turn, precipitate psychopathological symptoms. In addition, the results suggest that distinguishing among subtypes of childhood maltreatment may help clarify the pathways through which maltreatment contributes to depressive symptoms. Specifically, different maltreatment subtypes may exhibit distinct epigenetic signatures, while also sharing common mechanisms—such as rumination in the present study—in the development of depressive symptoms.

By identifying epigenetic (*NR3C1* methylation) and cognitive (rumination) vulnerability markers, as well as their roles in the development of depressive symptoms, this study has important implications for prevention and intervention. First, these vulnerability markers at the molecular and cognitive levels may facilitate early screening to identify individuals at high risk for depressive disorders. Second, this study calls for early interventions tailored to specific maltreatment subtypes.

Prioritizing early family-based programs, parenting support, and cognitive strategies to reduce rumination—and tailoring these approaches to different maltreatment experiences and pathways—may interrupt risk transmission, curb symptom escalation, and ultimately reduce the long-term burden of depression.

Depression is currently one of the most significant public health challenges worldwide, severely impacting individual health and social adaptation. The resulting health burden persists throughout the entire lifespan (WHO, 2022). Childhood maltreatment is recognized as a critical predictor of depression (Mao et al., 2023). However, understanding how the negative effects of childhood maltreatment unfold across the lifespan to increase the risk of adult depression remains a pressing issue. Research has identified physiological stress dysregulation (Nikkheslat et al., 2020) and cognitive functional deficits (Watkins & Roberts, 2020) as key pathways in this process. Transdiagnostic models of psychopathology suggest that these two pathways are not mutually exclusive but rather exhibit a serial association (Nolen-Hoeksema & Watkins, 2011). Consequently, integrating the physiological and cognitive mechanisms through which maltreatment influences depression helps explain how early experiences become embedded in the life course to trigger depressive symptoms.

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is a primary physiological pathway through which childhood maltreatment influences depression (Nikkheslat et al., 2020). Recent studies indicate that childhood maltreatment leaves long-term imprints on HPA axis genes through epigenetic modifications, increasing the risk of depression decades later (Chen & Cao, 2024; Parade et al., 2016). The *NR3C1* gene (nuclear receptor subfamily 3 group C member 1), which encodes the glucocorticoid receptor, is a vital gene for regulating HPA axis negative feedback (Berretta et al., 2021); thus, its methylation patterns have received extensive attention. Existing research has found that early adverse environments hinder the binding of transcription factors to DNA sequences by altering *NR3C1* methylation levels. This regulates *NR3C1* expression and impairs HPA axis negative feedback function, ultimately leading to depression (Chen & Cao, 2024; Parade et al., 2016). For example, maltreatment can increase methylation levels in the *NR3C1* exon 1D and 1F regions, which in turn increases internalizing problems in young children (Parade et al., 2016). More importantly, childhood maltreatment may cause lifelong epigenetic changes, increasing the risk of developing depression during adolescence and adulthood (Chen & Cao, 2024).

In addition to biological embedding, Response Style Theory (Nolen-Hoeksema

et al., 2008) suggests that childhood maltreatment triggers cognitive biases that lead to depression. Specifically, rumination—a negative cognitive style characterized by repetitive thinking about one’s negative feelings and distressing experiences—plays a mediating role between maltreatment and depression (Watkins & Roberts, 2020). Numerous studies consistently show that individuals who have experienced childhood maltreatment often adopt repetitive negative thinking as a regulatory strategy, which exacerbates their depressive symptoms (Braithwaite et al., 2017; Hoffmann et al., 2024). Recent network analyses indicate that children who suffer maltreatment exhibit ruminative thinking patterns that are closely linked to depression and its neurophysiological foundations (Hoffmann et al., 2024). This may occur because maltreatment undermines a child’s sense of self-efficacy in coping with negative events, leading the individual to interpret their difficulties in a passive, ruminative manner (Watkins & Roberts, 2020). Subsequently, rumination leads to the onset and recurrence of depression by amplifying negative emotions, impairing problem-solving abilities, and reducing contextual sensitivity (e.g., Watkins & Roberts, 2020).

The HPA axis dysfunction and rumination resulting from maltreatment do not operate in isolation. Transdiagnostic models of psychopathology propose that distal risks, such as early maltreatment, increase proximal risks like rumination by disrupting an individual’s stress system, eventually triggering psychological issues (Nolen-Hoeksema & Watkins, 2011). Although this model remains largely hypothetical, existing research provides preliminary evidence for the link between the HPA axis system and rumination. A study on schizophrenia showed that CpG sites in the *NR3C1* exon 1F region are significantly associated with both rumination and maltreatment (Piao et al., 2022), while a reduced cortisol awakening response has also been linked to self-referential rumination (Kuehner et al., 2007). Furthermore, excessive HPA axis reactivity and high cortisol awakening levels can lead to impaired prefrontal cortex function (Bertollo et al., 2025), which subsequently results in rumination (Philippi et al., 2022). Thus, HPA axis dysfunction triggered by maltreatment may foster ruminative thinking, thereby influencing depressive symptoms. In summary, the present study employs a longitudinal design to explore the biological embedding and cognitive mechanisms through which childhood maltreatment leads to adult depressive symptoms.

2.1 研究对象和程序

This study is part of a longitudinal youth project, recruiting 621 college students from Shandong Province. Follow-up assessments were conducted every six months. Among the participants, 593 individuals (19.47 ± 0.69 years old, 49.2% female, 98.6% Han ethnicity) consented to provide saliva samples. There were no significant differences in the primary research variables between participants with genetic data ($N = 593$) and those without ($N = 28$) (Gender: $\chi^2 = 1.15$, $df = 1$, $p = 0.28$; Age, rumination, childhood maltreatment, and depressive symptoms: $|t|s \leq 1.11$, $ps \geq 0.27$).

Figure 1

Figure 1: Figure 1

Figure 1

Figure 2: Figure 1

The study was reviewed and approved by the institutional ethics committee. After obtaining informed consent from both the participants and the schools, data collection was conducted in a classroom setting, with each testing session lasting approximately 30 minutes. At Time 1 (T1), participants' depressive symptoms and rumination levels were assessed, and childhood maltreatment was measured retrospectively. Under the demonstration and guidance of the researchers, participants used oral swabs to collect their own DNA samples. At Time 2 (T2), depressive symptoms and rumination were assessed again.

2.2.1 唾液采集与甲基化分析

Saliva samples were collected using oral swabs. DNA quality was assessed using a NanoDrop 2000 spectrophotometer. All samples underwent bisulfite conversion according to the protocol of the EZ DNA Methylation-Gold™ Kit. High-throughput sequencing was subsequently performed on the Illumina HiSeq platform using a 2×150 bp paired-end sequencing mode. Four target fragments within the *NR3C1* promoter region were selected for analysis (see

for details). To derive a comprehensive methylation index, principal component analysis (PCA) was performed on the average methylation levels of these four fragments, with the resulting principal component scores serving as the methylation indicators [?, ?].

2.2.2 童年虐待

CpG sites in the *NR3C1* promoter region.

Childhood maltreatment was retrospectively assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). Each dimension consists of five items (e.g., "People in my family said hurtful or insulting things to me"), scored on a five-point Likert scale (1 = never, 5 = always). Higher mean scores indicate a greater frequency of maltreatment. In the present study, the Cronbach's α coefficients for the total maltreatment score, emotional abuse, physical abuse, emotional neglect, and physical neglect were 0.85, 0.69, 0.85, 0.76, and 0.56, respectively.

2.2.3 反刍

Rumination was measured using the Children's Response Styles Questionnaire (CRSQ; Abela et al., 2004). The questionnaire consists of 13 items (e.g., "When I am sad, I think about other times when I felt sad") rated on a four-point scale (1 = *almost never*, 4 = *almost always*). Higher mean scores indicate higher levels of rumination. In the present study, the Cronbach's α coefficients for rumination at T1 and T2 were 0.87 and 0.92, respectively.

2.2.4 抑郁症状

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). This scale consists of 20 items (e.g., "I felt that my life had been a failure") rated on a four-point Likert scale ranging from 1 (*rarely or none of the time*) to 4 (*most or all of the time*). Higher mean scores indicate a greater frequency of depressive symptoms. In the present study, the Cronbach's α coefficients for depressive symptoms at T1 and T2 were 0.90 and 0.91, respectively.

2.3 共同方法偏差检验

All questionnaires in this study were administered via self-report. To assess potential common method bias, Harman's single-factor test was conducted. The results identified 10 factors with eigenvalues greater than 1. The first factor accounted for 21.17% of the total variance, which is well below the critical threshold of 40%. Therefore, no significant common method bias was present in this study.

2.4 数据处理与分析

First, correlation analysis was employed to examine the relationships between the variables. Second, the PROCESS macro for SPSS (version 26.0) was utilized to test the chain mediation model, specifically investigating the mediating roles of *NR3C1* methylation and rumination in the relationship between childhood maltreatment and depressive symptoms. To avoid multicollinearity, all predictor variables were standardized prior to analysis.

3.1 变量的描述统计和相关分析

The means, standard deviations, and correlation coefficients for all variables are presented in Table 1. With the exception of the relationships between various types of childhood abuse and *NR3C1* methylation, all other variables exhibited significant positive correlations with one another.

Table 1 Descriptive statistics and correlation analysis results .12** .14**

8 T2 抑郁症状

.80*** .66*** .84*** .77*** .19*** .36*** .58*** .52*** .46*** .23*** .34***
 .37*** .33*** .11** .12** .52*** .13** .13** .30*** .33*** .32***

Note: ** $p < 0.01$; *** $p < 0.001$.

3.2 童年虐待与成年早期抑郁症状: NR3C1 甲基化和反刍的链式中介作用

As shown in and , the sequential mediation effect involving *NR3C1* methylation and rumination on depressive symptoms was significant only for emotional neglect (see [FIGURE:2]). Specifically, higher levels of emotional neglect experienced by individuals were associated with increased *NR3C1* methylation and higher levels of rumination, which in turn led to a greater risk of depression. While the mediating pathways from various types of maltreatment to depressive symptoms via *NR3C1* methylation alone were not significant, the mediating pathways from all types of maltreatment to depressive symptoms via rumination were significant.

[FIGURE:2] Emotional neglect and depressive symptoms: The mediating roles of *NR3C1* methylation and rumination. Childhood maltreatment and depressive symptoms: Sequential mediation analysis of *NR3C1* methylation and rumination. Testing of mediating effects using Bootstrap 95% CI. Note: ** $p < 0.01$; *** $p < 0.001$. This study attempts to establish an integrated model combining physiological and cognitive perspectives to explore the potential mechanisms through which childhood maltreatment influences adult depressive symptoms. The findings suggest that childhood maltreatment may indirectly affect adult depressive symptoms through rumination, or it may alter an individual's cognitive style via biological embedding, thereby triggering depression; however, these pathways vary depending on the type of maltreatment.

In contrast to studies on children and adolescents [?, ?, ?], this study did not find a significant mediating effect of *NR3C1* methylation between maltreatment and adult depressive symptoms. Although methylation is most susceptible to environmental influences during early developmental stages, various environments encountered during the growth process may reshape methylation patterns established in childhood [?, ?]. This study focused on early adulthood, where the interval between the occurrence of maltreatment and the assessment of methylation is longer than in studies of children or adolescents. Consequently, the methylation imprints caused by childhood maltreatment might have been "overwritten" or weakened by subsequent life experiences, thereby reducing the mediating effect. Furthermore, this study focused on a non-clinical population where the prevalence and severity of maltreatment were relatively low, potentially resulting in subtle methylation changes that are difficult to capture [?, ?].

Multiple types of maltreatment increase the risk of depression in early adulthood by increasing rumination. Maltreatment may lead individuals to adopt rumination as a coping mechanism for stress by altering key physiological and

psychological mechanisms. Whether it is stress-induced physiological arousal or negative emotions, these processes consume significant physical energy or cognitive-emotional resources, making it difficult for individuals to deploy adaptive coping strategies and causing them to fall into rumination [?, ?]. Additionally, maltreatment can alter the functional connectivity of the default mode network (DMN), leading to a stronger introspective tendency during resting states [?, ?], which highly overlaps with the neural networks associated with depressive rumination [?, ?]. Engaging in rumination, in turn, reduces an individual's motivation to participate in mood-improving activities and weakens their ability to disengage attention from negative information [?, ?], ultimately leading to depression.

Consistent with the transdiagnostic model of psychopathology [?, ?], this study found that emotional neglect increased *NR3C1* methylation, and this epigenetic change triggered adult depression by shaping rumination. This suggests that “upstream” biomarkers and cognitive vulnerabilities of depression are not independent; future research should adopt an integrated perspective to focus on the complex interactions between biological, cognitive, and psychological pathways through which early adverse environments lead to depressive symptoms. More importantly, this study demonstrates that the mechanisms leading to depressive symptoms differ across types of maltreatment. Compared to other types, emotional neglect exhibits a unique “biological embedding-cognitive vulnerability” sequential mediation effect. On one hand, the impact of different types of maltreatment on *NR3C1* methylation varies [?, ?]. Meta-analyses indicate that emotional neglect is one of the most common risk factors among depressed patients [?, ?]. Meanwhile, emotional neglect uniquely predicts HPA axis function [?, ?] and depression [?, ?]. Notably, the mean score for emotional neglect in this study was higher than for other types of maltreatment, making it more likely to result in observable changes in *NR3C1* methylation levels. On the other hand, according to the dimensional model of adversity and psychopathology, deprivation-based adversities (such as neglect) are more likely to influence psychopathology through cognitive mechanisms, whereas threat-based adversities (such as physical and emotional abuse) are more likely to act through emotional mechanisms [?, ?]. Therefore, future research should incorporate multiple cognitive and emotional mechanisms to further investigate the divergent pathways of different types of maltreatment.

This study has several limitations. First, the use of retrospective reports to assess childhood maltreatment may introduce recall bias and precludes testing whether the timing or duration of maltreatment influences the “maltreatment-biological embedding-rumination-depressive symptoms” mediation mechanism. Future research should adopt a developmental perspective using longitudinal designs from early childhood to adulthood to explore how the timing and duration of maltreatment affect methylation and depressive symptoms. Second, the reliability of the physical neglect subscale in this study was low. This may be because the concept of physical neglect encompasses multiple dimensions—such as caregiving, medical care, and nutrition—leading to high heterogeneity

(i.e., low correlation) among items; additionally, the low prevalence of physical neglect in this sample contributed to the low reliability coefficient. Third, this study utilized buccal epithelial cells to detect methylation levels, but different sampling sites (such as peripheral blood) may yield inconsistent results [?, ?]. Therefore, the results of this study should be interpreted with caution until replicated. Finally, although no direct mediating effect of methylation was found between maltreatment and depressive symptoms, individual genetic variations may moderate this process. Future research should further examine allele-specific methylation [?, ?] to determine whether individual differences exist in the mediating mechanisms of methylation. In summary: (1) Different types of childhood maltreatment increase adult depressive symptoms through rumination. (2) Emotional neglect exacerbates ruminative thinking by increasing *NR3C1* gene methylation, thereby leading to adult depressive symptoms.

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