Interactive Effect of BDNF Gene rs6265 Polymorphism and Harsh Parenting on Working Memory in Preschool Children

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Abstract

Working memory is an important component of executive function. Previous studies have separately examined the influences of genetic and family environmental factors on the development of children' s working memory; however, research on how genetic and family environmental factors interactively influence the development of children' s working memory is currently lacking. The present study recruited 632 preschool children (mean age = 5.11 years, SD = 0.97) as participants, had children complete the Corsi Block Task to assess their working memory ability, extracted DNA from children' s saliva samples for genotyping to obtain the BDNF gene rs6265 polymorphism, and invited parents to complete the Parent-Child Conflict Resolution Strategies Scale to assess harsh parenting levels, thereby examining the interactive effect of BDNF gene rs6265 polymorphism and parental harsh discipline on preschool children' s working memory. The results showed a significant interactive effect of child gender and BDNF gene rs6265 polymorphism on preschool children' s working memory; BDNF gene rs6265 polymorphism could significantly predict working memory levels in boys, but did not significantly predict working memory in girls. Particularly, the study found that after controlling for age and socioeconomic status, the interactive effect of BDNF gene rs6265 polymorphism and parental harsh discipline on preschool children' s working memory was significant. Specifically, working memory performance of children carrying the CC genotype significantly decreased under high parental harsh discipline conditions, while their working memory was not affected under low parental harsh discipline conditions. For children carrying the TT/TC genotype, their working memory performance did not differ significantly across different parental harsh discipline conditions. The results support the diathesis-stress model hypothesis, indicating that the CC genotype is a vulnerability factor for negative environments.

Full Text

Preamble

Interaction Effects between BDNF Gene rs6265 Polymorphism and Parental Harsh Discipline on Preschoolers' Working Memory

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Abstract

Working memory (WM) represents a core component of executive function. While previous research has examined the independent effects of genetic and family environmental factors on children' s working memory development, how these genetic and environmental factors interact to shape working memory remains understudied. This study investigated 632 preschool children (mean age = 5.11 years, SD = 0.97) to examine the interactive effects of BDNF gene rs6265 polymorphism and parental harsh discipline on early childhood working memory. Children completed the Corsi Blocks Task to assess working memory capacity, DNA was extracted from saliva samples for genotyping of BDNF rs6265 polymorphism, and parents completed the Parent-Child Conflict Tactics Scale to evaluate harsh discipline practices.

Results revealed a significant interaction between child sex and BDNF rs6265 polymorphism in predicting preschoolers' working memory. Specifically, BDNF rs6265 polymorphism significantly predicted working memory performance in boys but not in girls. Most importantly, after controlling for age and socioeconomic status, the interaction between BDNF rs6265 polymorphism and parental harsh discipline significantly predicted working memory performance. Children carrying the CC genotype showed significantly impaired working memory under high parental harsh discipline conditions, whereas their working memory remained unaffected under low harsh discipline. For children with TT/TC genotypes, working memory performance did not differ significantly across varying levels of harsh discipline. These findings support the diathesis-stress model, indicating that the CC genotype functions as a vulnerability factor to negative environmental influences.

Keywords: BDNF gene rs6265 polymorphism, parental harsh discipline, working memory, gene-environment interaction, preschoolers

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Working memory (WM) constitutes a core component of executive function (EF), defined as a capacity-limited cognitive system responsible for the temporary storage and manipulation of information during cognitive task completion (Baddeley, 2003). As the foundation of human cognitive activity, working memory plays a crucial role in reasoning, learning, and problem-solving, undergoing rapid development during early childhood (Barrouillet et al., 2009; Gathercole

et al., 2004; Simmering, 2012). Research has demonstrated that working memory possesses a genetic basis (Nemmi et al., 2018; Vogler et al., 2014; Wang et al., 2012) while also being influenced by environmental factors (Hackman et al., 2014). However, how genetic and environmental factors interact to affect the development of children' s working memory remains insufficiently explored.

Extensive research on the genetic basis of cognitive functions, including working memory, has focused on the brain-derived neurotrophic factor (BDNF) gene. The human BDNF gene, located on chromosome 11p13 and comprising 11 exons, regulates the expression of brain-derived neurotrophic factor—a protein intimately involved in neuronal growth, development, differentiation, maintenance, injury repair, and learning and memory processes (Yamada & Nabeshima, 2003). The BDNF gene rs6265 polymorphism influences BDNF protein levels (Elfving et al., 2012). This single nucleotide polymorphism at nucleotide position 196 results in a valine (Val) to methionine (Met) substitution at codon 66, thereby affecting BDNF secretion efficiency. The Met allele is associated with reduced BDNF secretion and decreased activity. Compared to Val homozygotes, Met allele carriers exhibit lower hippocampal neuronal synaptic complexity and poorer synaptic plasticity (Savitz et al., 2006), which correlates with impaired working memory capacity (Gong et al., 2009; Rybakowski et al., 2006). Research has documented reduced hippocampal volume and prefrontal cortex gray matter volume in Met allele carriers (Bueller et al., 2006; Pezawas et al., 2004), with Val carriers outperforming Met carriers on working memory tasks involving digit span and spatial localization (Gong et al., 2009).

Despite the established genetic basis of working memory, genetic factors alone do not fully determine individual differences in cognitive function, particularly during childhood development. Theoretical models of child development—including the diathesis-stress model, differential susceptibility model, and vantage sensitivity model—posit that developmental outcomes (cognitive, emotional, and social) emerge from the interaction between biological factors such as genetics and environmental influences rather than from either factor in isolation (Wang et al., 2020). The diathesis-stress model proposes that children carrying "risk" or "vulnerability" alleles are more susceptible to negative environmental influences, leading to psychological or behavioral problems or cognitive impairments, whereas children without such vulnerability alleles remain relatively unaffected by adverse environments (Monroe & Simons, 1991; Zuckerman, 1999). The differential susceptibility model suggests that certain "plasticity" or "susceptibility" alleles render children more responsive to both negative environments (performing worse) and positive environments (performing better) (Belsky & Pluess, 2009). The vantage sensitivity model posits that children with heightened sensitivity to positive environments show more favorable responses and derive greater benefits from supportive contexts than those with vantage resistance characteristics (Pluess & Belsky, 2013).

Empirical studies have examined interactions between BDNF rs6265 polymorphism and environmental factors in relation to cognitive functions including

working memory. For instance, Gatt et al. (2009) found that adults carrying the Met allele exhibited working memory impairments under early life stress, a pattern consistent with the diathesis-stress model wherein the Met allele confers vulnerability to negative environments. Cohen-Gilbert et al. (2016) reported that Met-carrying adolescents showed poorer inhibitory control under early adverse conditions, again supporting the diathesis-stress model. However, Zhang et al. (2018) found that primary school children carrying the Val allele demonstrated lower logical thinking and spatial-visual abilities when experiencing low parental educational involvement, a result that also supports the diathesis-stress model but identifies Val as the risk allele.

These studies have preliminarily explored relationships between BDNF rs6265 polymorphism and working memory, as well as interactions with environmental factors such as early adversity and parenting styles among school-aged children, adolescents, and adults. However, research on BDNF rs6265 polymorphism and working memory in preschoolers, and how genetic and environmental factors interact to influence working memory development during the preschool period, remains scarce. First, although existing research suggests BDNF rs6265 polymorphism is closely related to working memory and represents its genetic foundation (Chen et al., 2016; Gong et al., 2009; Savitz et al., 2006), these studies have focused exclusively on adult populations. The preschool period represents a critical window of rapid working memory development (Barrouillet et al., 2009; Gathercole et al., 2004; Simmering, 2012), and investigating this relationship in preschoolers could provide novel evidence. Therefore, one objective of this study was to further examine the association between BDNF rs6265 polymorphism and working memory in preschool children.

Second, research indicates that stressful or risky environments affect BDNF activity, with chronic stress significantly reducing BDNF activity and consequently leading to negative behavioral outcomes (Hayden et al., 2010). BDNF rs6265 polymorphism moderates the relationship between early stress and individual adaptation (Cohen-Gilbert et al., 2016; Hayden et al., 2010). Parental harsh discipline constitutes a significant environmental stressor and risk factor within the family context that adversely affects children' s psychosocial development, contributing to increased internalizing and externalizing problems such as depression, anxiety, and aggression (Song et al., 2019; Xing et al., 2016), and also impairs executive functions including working memory (Xing et al., 2016). Harsh discipline refers to coercive behaviors or negative emotional expressions directed at children' s misbehavior (Erath et al., 2009), with psychological aggression and corporal punishment being the most common forms (Liu & Wang, 2018; Straus et al., 1998). Numerous studies have demonstrated negative effects of harsh discipline on children' s executive functions (Blair et al., 2011; Roskam et al., 2014; Xing et al., 2016). For example, higher frequency of corporal punishment correlates with poorer inhibitory control and working memory (Xing et al., 2016). Therefore, this study examined parental harsh discipline as an environmental risk factor and, drawing upon diathesis-stress, differential susceptibility, and vantage sensitivity models, investigated the interactive effects

of BDNF rs6265 polymorphism and harsh discipline on preschoolers' working memory.

Regarding gene-environment interactions involving BDNF rs6265, some studies have found that Met allele carriers are more environmentally sensitive (Cohen-Gilbert et al., 2016; Gatt et al., 2009; Meyer et al., 2018; Miu et al., 2016), while others support Val allele susceptibility (Chen et al., 2012; Chen et al., 2015; Felmingham, 2013). Several factors may account for these inconsistent findings. First, racial differences: most Asian samples show Val as the susceptibility factor (Chen et al., 2015; Zhang et al., 2018), whereas Caucasian samples demonstrate greater environmental sensitivity for the Met allele (Meyer et al., 2017; Miu et al., 2016). The Met allele frequency is approximately 40-50% in Asian populations but only 25-31% in Caucasian populations (Petryshen et al., 2010), which may contribute to divergent results. Second, age differences: BDNF content and function vary across developmental stages, potentially leading to different behavioral outcomes (Nederhof et al., 2010). Third, sex differences: research suggests that sex moderates the relationship between BDNF rs6265 polymorphism and individual adaptation (Verhagen et al., 2010). BDNF rs6265 polymorphism affects hippocampal function and memory capacity (Egan et al., 2003), and sex differences exist in hippocampal anatomy, neurochemistry, and stress responsivity. For instance, van Oostrom et al. (2012) found that BDNF rs6265 interacted with childhood stress events to affect affective memory bias only in Met-carrying males, not females. Therefore, sex differences should be considered when examining G×E mechanisms underlying adaptive outcomes such as working memory.

In summary, this study employed a G×E interaction design with preschool children, using BDNF rs6265 polymorphism as the genetic marker and parental harsh discipline as the environmental indicator, to investigate interactive effects on working memory. We hypothesized that: (1) BDNF rs6265 polymorphism would be associated with preschoolers' working memory; (2) BDNF rs6265 polymorphism would significantly interact with parental harsh discipline to affect preschoolers'working memory; and (3) sex would moderate both the relationship between BDNF rs6265 polymorphism and working memory and its interaction with harsh discipline.

2.1 Participants

Based on previous research, the effect size for significant gene-environment interactions typically ranges from 0.01 to 0.03. Power analysis using G*Power 3.1.9.2 indicated that a sample size of 363-1084 participants would be required to achieve 80% statistical power. We initially recruited 664 preschool children from three kindergartens in Xi' an. After excluding 32 participants due to genotyping failure or incomplete data, the final sample comprised 632 preschool children (mean age = 5.11 ± 0.97 years; 321 boys, 311 girls). Parental education levels were rated on a 7-point scale (1 = no primary school to 7 = doctoral degree), and family income was assessed on a 5-point scale (1 = $ $3000 RMB to 5

= >20,000 RMB). In this sample, 97.8% of fathers and mothers had completed undergraduate education or higher, and 81.5% of families reported monthly incomes exceeding 10,000 RMB. Given that socioeconomic status (SES) correlates with both working memory and harsh discipline (Hackman et al., 2014), we controlled for family SES by computing a composite score from standardized measures of parental education and family income (Cohen et al., 2006).

2.2.1 Harsh Discipline Questionnaire

Parental harsh discipline was assessed using the Psychological Aggression and Corporal Punishment subscales of the Parent-Child Conflict Tactics Scale (CTSPC; Straus et al., 1998). Parents reported their use of psychological aggression and corporal punishment toward their child during the past year. The original scale uses a 0-6 scoring system (0 = never, 1 = once, 2 = twice, 3 = 3-5 times, 4 = 6-10 times, 5 = 11-20 times, 6 = more than 20 times). For analysis, we converted these scores to frequency counts using the midpoint of each range: "0" = 0 times, "1" = 1 time, "2" = 2 times, "3" = 4 times, "4" = 8 times, "5" = 15 times, "6" = 25 times (Straus et al., 1998; Wang & Liu, 2018). The sum of frequencies across all items for each subscale represented the total frequency of that discipline type, with higher scores indicating more frequent harsh discipline. The combined score of both subscales represented overall harsh discipline frequency. This scale has demonstrated good reliability and validity in Chinese cultural contexts (Wang & Liu, 2018), with an internal consistency coefficient of 0.65 in the current study.

2.2.2 Working Memory Measurement

Working memory was assessed using the Corsi Blocks Task (Kessels et al., 2000). The task apparatus consisted of nine identical wooden blocks (3cm × 3cm × 3cm) arranged on a board. Numbers were affixed to one side of each block, visible only to the experimenter. The experimenter tapped a sequence of blocks at a rate of one block per second, and the child was then asked to reproduce the same sequence. Task difficulty ranged from 2 to 9 blocks across eight levels, with two trials per level. Testing was discontinued when the child failed both trials at a given level. The maximum number of blocks correctly recalled in sequence represented the child' s working memory score.

2.3 Genetic Testing

BDNF gene rs6265 polymorphism was selected as the genetic marker. SNP genotyping was performed using PCR primers designed with the MassARRAY Assay Design Suite V2.0, and SNP 分型 was completed using the MassARRAY system from Sequenom, USA.

2.4 Procedure

This study was approved by the institutional ethics committee. Informed consent was obtained from kindergartens and parents. Data collection proceeded in three stages at the classroom level. First, cognitive data were collected through one-on-one administration of the working memory task by trained graduate students in psychology. Second, questionnaires were distributed to parents via teachers and returned upon completion. Finally, saliva samples were collected from all participating children in each class by trained research assistants, with the entire sampling process taking approximately 30 minutes. Teachers instructed children to refrain from eating, drinking, or chewing gum for 30 minutes prior to sample collection. DNA extraction, purification, and genotyping were performed by a professional company.

2.5 Data Processing and Analysis

Missing data rates were low (2.1% for working memory scores, 5.8% for harsh discipline). Missing values were handled using mean substitution (Reeves et al., 2018). Descriptive statistics, correlation analyses, and hierarchical regression analyses were conducted using SPSS 21.0. Region of significance (RoS) tests (Roisman et al., 2012) were performed to examine specific interaction patterns.

3.1 Hardy-Weinberg Equilibrium Test

Hardy-Weinberg equilibrium analysis for the rs6265 locus revealed that observed genotype frequencies (CC [Val/Val] = 184, TT [Met/Met] = 139, TC [Met/Val] = 309) did not differ significantly from expected values, confirming equilibrium (^{2} = 0.08, df = 1, p = 0.96). For subsequent analyses, TT and TC genotypes were combined (CC = 184, TT/TC = 448).

3.2 Descriptive Analysis

Means, standard deviations, and correlations for all variables are presented in Table 1 . Results showed that sex was significantly positively correlated with harsh discipline. Working memory was significantly positively correlated with age and SES. Notably, rs6265 polymorphism was not significantly correlated with parental harsh discipline, ruling out gene-environment correlation.

Table 1 Descriptive Statistics and Correlations Among Variables

Note: N = 632. Sex was dummy-coded (0 = girls, 1 = boys). rs6265 was dummy-coded (0 = CC, 1 = TT/TC). $p < 0.05$, $\mathbf{p < 0.01}$, $p < 0.001$.

3.3 Interaction Effects of BDNF rs6265 Polymorphism and Harsh Discipline on Working Memory

Parental harsh discipline was standardized. Hierarchical regression analysis was conducted with working memory as the dependent variable, controlling for age

and SES, and including harsh discipline, sex, and BDNF rs6265 polymorphism as predictors. As shown in Table 2 , main effects of genotype, sex, and harsh discipline on working memory were non-significant. However, two-way interaction effects revealed that the rs6265 × harsh discipline interaction significantly predicted preschoolers' working memory (b = 0.19, p = 0.013, 95% CI [0.04, 0.35]), as did the sex × rs6265 interaction (b = -0.32, p = 0.029, 95% CI [-0.61, -0.03]). The sex × harsh discipline interaction and the three-way interaction (sex × genotype × environment) were not significant.

Table 2 Hierarchical Regression Analysis of BDNF rs6265 Polymorphism, Harsh Discipline, and Sex on Preschoolers' Working Memory

Note: $p < 0.05$, $^{**}p < 0.001$.

3.4 Region of Significance Test

Regression results indicated that BDNF rs6265 polymorphism interacted with both parental harsh discipline and child sex to predict working memory. We first employed RoS analysis to examine which theoretical model the interaction pattern supported. Simple slopes analysis revealed that harsh discipline significantly predicted working memory in CC genotype carriers (simple slope = -0.21, t = 2.71, p = 0.007) but not in TT/TC carriers (simple slope = -0.02, t = 0.27, p = 0.79). RoS analysis further demonstrated (Figure 1 [Figure 1: see original paper]) that when harsh discipline scores exceeded X = 0.76, CC carriers exhibited significantly poorer working memory performance compared to TT/TC carriers; when harsh discipline was below this threshold, no significant genotype differences emerged. The proportion of interaction (PoI) index was 0.84, supporting the diathesis-stress model. Compared to T allele carriers, CC genotype carriers were more vulnerable to negative environmental influences, resulting in poorer adaptive outcomes.

Second, the genotype × sex interaction (Figure 2 [Figure 2: see original paper]) showed a significant association between genotype and working memory in boys (simple slope = -0.23, t = -2.09, p = 0.037, 95% CI [-0.45, -0.01]) but not in girls (simple slope = 0.12, t = -1.04, p = 0.30, 95% CI [-0.11, 0.36]). Specifically, boys with the CC genotype demonstrated significantly better working memory performance than boys carrying the T allele (t = 2.52, p = 0.01) and also outperformed girls with the CC genotype (t = -2.61, p = 0.01). No significant differences emerged between girls of different genotypes (t = -1.12, p = 0.26) or between boys and girls carrying the T allele (t = 0.32, p = 0.75).

Figure 1 Interaction between BDNF rs6265 Polymorphism and Parental Harsh Discipline on Preschoolers' Working Memory

Figure 2 Interaction between BDNF rs6265 Polymorphism and Child Sex on Preschoolers' Working Memory

This study examined the interactive effects of BDNF rs6265 polymorphism, child sex, and parental harsh discipline on preschoolers' working memory. First,

we found a significant sex × genotype interaction, such that BDNF rs6265 polymorphism significantly correlated with working memory in boys but not in girls. Most importantly, the study revealed a significant interaction between BDNF rs6265 polymorphism and parental harsh discipline on working memory. Specifically, the CC genotype functioned as a vulnerability or sensitivity factor to negative environments: children with the CC genotype showed significantly impaired working memory under high harsh discipline but remained unaffected under low harsh discipline. In contrast, TT/TC genotype carriers' working memory was not influenced by harsh discipline levels. These results support the diathesis-stress model.

Although no main effect of BDNF rs6265 polymorphism on working memory was found, a significant sex × genotype interaction emerged. Boys with the CC genotype exhibited significantly better working memory than T allele carriers, whereas no such genotype differences appeared among girls. This sex-specific effect of BDNF on cognitive functions aligns with previous research (Chang et al., 2014; Shalev et al., 2009; Verhagen et al., 2014). The sex-specific influence of BDNF on working memory may stem from anatomical and organizational differences in hippocampal volume and density between males and females (Ruigrok et al., 2014), as BDNF rs6265 polymorphism affects hippocampal function and memory (Egan et al., 2003). Wierenga et al. (2018) reported greater variability in brain structures such as the hippocampus among 3-21-year-old males compared to females. Animal studies have shown that BDNF knockout male mice display hyperactivity without depressive behaviors, while females show the opposite pattern (Monteggia et al., 2007). Human neuroimaging studies have revealed sex differences in neural substrates and gene effects despite similar behavioral performance on recognition memory tasks (Van Wingen et al., 2010; Cahill, 2006). However, some sex-specific BDNF studies have only identified associations with the T allele in males (Van Oostrom et al., 2012; Van Wingen et al., 2010). Most of these studies examined adult samples, and given the developmental dynamics of BDNF expression in the cerebral cortex, age differences may produce divergent or even opposite patterns between adults and children (Hilt et al., 2007).

Although the three-way interaction (sex × genotype × environment) was not significant, BDNF rs6265 polymorphism interacted with harsh discipline to affect preschoolers' working memory, with the CC genotype functioning as a vulnerability or sensitivity factor. Compared to T allele carriers, CC genotype carriers showed poorer working memory under negative conditions (high harsh discipline) but did not differ under low harsh discipline (relatively positive conditions). These findings support the diathesis-stress model, indicating that preschoolers with the CC genotype demonstrate vulnerability to negative environments, whereas T allele carriers show greater resilience. This pattern aligns with most research on Asian populations (Chen et al., 2012; Zhang et al., 2015; Zhang et al., 2018). Researchers suggest that CC genotype environmental sensitivity may arise from altered BDNF signaling in mesolimbic dopamine circuits, whereby environmental influences affect prefrontal cortex structure and

function, subsequently impacting cognitive abilities through changes in BDNF expression in the prefrontal cortex and nucleus accumbens (Gabrys et al., 2017). The pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is implicated in reward processing, stress responses, and depression pathophysiology. Intact BDNF signaling in the VTA-NAc pathway is essential for establishing plastic neural and behavioral responses to environmental stimuli (Berton et al., 2006). The CC genotype may enhance sensitivity to negative environments by increasing neuroplasticity in mesolimbic dopamine circuits. CC carriers have shown heightened HPA axis reactivity to stress compared to T allele carriers (Alexander et al., 2010; Shalev et al., 2009), suggesting that the CC genotype may trigger excessive BDNF secretion and activity, making carriers more susceptible to environmental information.

These findings differ from most Western population studies, which typically support greater environmental susceptibility for the T allele. As noted previously, substantial racial differences exist in BDNF rs6265 allele frequencies (Petryshen et al., 2010), potentially accounting for divergent results. Research on Asian samples has revealed environmental sensitivity in CC genotype carriers, and the current study further supports the hypothesis of racial differences in G×E interactions.

This study investigated the internal mechanisms of children' s working memory development from a gene-environment interaction perspective, revealing interactive effects of BDNF rs6265 polymorphism and harsh discipline. The finding that CC genotype carriers' working memory is impaired under high harsh discipline but unaffected under low harsh discipline, while TT/TC carriers' working memory remains stable across discipline levels, identifies the CC genotype as an environmental vulnerability or sensitivity factor. Extending previous research, this study included Chinese Han children and confirmed hypotheses regarding racial differences (Petryshen et al., 2010). Additionally, given that BDNF content and function vary across developmental stages (Casey et al., 2009) and most prior research has focused on adult samples, this preschool investigation expands and enriches the existing literature.

Several limitations should be noted. First, this study examined only a single gene and single environmental factor. Individuals represent a composite of multiple susceptibility genes and are influenced by multiple environments; future research should employ candidate gene and genome-wide association approaches to investigate polygenic and multi-environment interactions in children' s cognitive functions. Second, most participants came from relatively high-SES families; future studies should increase sample diversity to examine the generalizability of findings. Third, given the developmental dynamics of BDNF expression, future research should extend across age ranges to reveal the developmental trajectory of G×E effects on working memory.

In conclusion: (1) BDNF rs6265 polymorphism significantly correlates with working memory in boys but not girls; (2) BDNF rs6265 polymorphism significantly interacts with parental harsh discipline to affect preschoolers' working

memory, with CC carriers showing impaired working memory under high harsh discipline but not under low harsh discipline, while TT/TC carriers' working memory remains unaffected by discipline levels; and (3) The interaction between BDNF rs6265 polymorphism and parental harsh discipline on working memory supports the diathesis-stress model, indicating that the CC genotype functions as a vulnerability factor to negative environments.

Author Contributions:
Zhenhong Wang: Conceptualization, study design, revision, and final approval of the manuscript.
Yuewen Zhang: Data collection, data analysis, and manuscript writing.

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Note: Figure translations are in progress. See original paper for figures.