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Epigenetic signatures of prenatal stress exposure and severity of repetitive behaviours in autistic children

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Abstract

The epigenetic landscape of prenatal stress represents one of the most consequential yet insufficiently examined pathways to repetitive behaviour phenotypes in autism. This cross-sectional research examined associations between prenatal stress exposure, DNA methylation at four candidate gene loci (NR3C1, OXTR, BDNF, SLC6A4), and repetitive behaviour severity in 150 autistic children aged 4 to 10 years recruited through developmental paediatric clinics in Incheon, South Korea. Maternal prenatal stress was assessed retrospectively using the Korean Prenatal Distress Questionnaire, and third-trimester cortisol concentrations were retrieved from archived maternal serum samples. Child repetitive behaviours were measured using the Repetitive Behavior Scale-Revised (RBS-R). DNA methylation was quantified from buccal epithelial samples using targeted bisulfite pyrosequencing at predetermined CpG sites within each gene promoter region. Participants were stratified into high prenatal stress (n = 72) and low prenatal stress (n = 78) groups based on maternal cortisol concentrations above or below the sample median. The high-stress group demonstrated significantly elevated NR3C1 exon 1F methylation (mean = 8.4%, SD = 2.1) compared to the low-stress group (mean = 5.9%, SD = 1.8; $p < 0.001$, d = 1.28). OXTR promoter methylation was also higher in the high-stress group (mean = 42.3%, SD = 7.6 versus 35.8%, SD = 6.9; $p < 0.001$, d = 0.89). Prenatal cortisol concentrations showed a moderate positive correlation with RBS-R total scores (r = 0.47, $p < 0.001$). Mediation analysis indicated that NR3C1 methylation partially mediated the cortisol-to-repetitive-behaviour association for the stereotyped behaviour subscale (indirect effect = 0.09, 95% CI: 0.03 to 0.17). BDNF exon IV methylation was inversely associated with sameness behaviour scores (r = -0.31, $p < 0.001$), and SLC6A4 promoter methylation was positively associated with compulsive behaviour scores (r = 0.28, p = 0.001). These findings indicate that prenatal stress-related epigenetic modifications at multiple gene loci are associated with both the severity and the domain-specific profile of repetitive behaviours in autistic children from a South Korean clinical sample.

Keywords: Prenatal stress, DNA methylation, Repetitive behaviours, Autism spectrum disorder, NR3C1, OXTR, Epigenetics, Cortisol, South Korea

Introduction

Prenatal maternal stress leaves a lasting molecular imprint on fetal neurodevelopment through epigenetic mechanisms that alter gene expression without modifying DNA sequence (Van den Bergh *et al.*, 2020) [1]. Among the candidate pathways linking the intrauterine environment to postnatal behavioural outcomes, hypothalamic-pituitary-adrenal (HPA) axis programming mediated by glucocorticoid exposure has received substantial empirical attention (Oberlander *et al.*, 2008; Conradt *et al.*, 2015) [2, 3]. Elevated maternal cortisol during pregnancy has been associated with altered methylation of the glucocorticoid receptor gene NR3C1 in offspring, and these methylation changes predict cortisol reactivity and behavioural regulation in early childhood (Kertes *et al.*, 2016) [4].

The relevance of this pathway to autism has been proposed on both theoretical and empirical grounds. Autistic individuals frequently display atypical cortisol profiles and HPA axis dysregulation (Yang *et al.*, 2015; Evenepoel *et al.*, 2023) [5, 6], and emerging evidence indicates that epigenetic variation at stress-responsive gene loci differs between autistic and neurotypical individuals (Mordaunt *et al.*, 2020) [7]. Four candidate genes have attracted particular attention: NR3C1, which encodes the glucocorticoid receptor; OXTR, the oxytocin receptor gene implicated in social behaviour; BDNF, encoding brain-derived neurotrophic factor involved in neural plasticity; and SLC6A4, the serotonin transporter gene linked to emotional regulation and repetitive behaviours (Kertes *et al.*, 2017; Provenzi *et al.*, 2021; Wei *et al.*, 2023; Lintas *et al.*, 2023) [8, 9, 10, 11].

Despite the growing interest in epigenetic mechanisms in autism, very few investigations have examined whether prenatal stress-associated methylation patterns relate specifically to repetitive behaviours rather than to social communication difficulties or general autism severity (Yang *et al.*, 2015; Burton *et al.*, 2024) [5, 12].

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Repetitive and restricted behaviours constitute a core diagnostic feature of autism that spans stereotyped movements, insistence on sameness, restricted interests, and sensory reactivity (Luo *et al.*, 2022) [13]. These behaviours are mediated in part by cortico-striatal circuitry (Burton *et al.*, 2024) [12], which is susceptible to glucocorticoid-driven epigenetic remodelling during fetal development. A biologically informed examination of the epigenetic correlates of repetitive behaviour subtypes is therefore warranted.

South Korea provides a fitting context for this research given the country's well-documented autism prevalence of approximately 2.64% in a community-based epidemiological sample (Kim *et al.*, 2011) [14] and a healthcare infrastructure that maintains archived prenatal serum for longitudinal linkage. The present research aimed to determine whether prenatal stress exposure, indexed by third-trimester maternal cortisol concentrations, was associated with DNA methylation at NR3C1, OXTR, BDNF, and SLC6A4 in autistic children, and whether these methylation levels predicted the severity and domain-specific pattern of repetitive behaviours as measured by the RBS-R.

Ethical considerations

This research was approved by the Institutional Review Board of Incheon Research Institute (Protocol IRI-2021-EP-037, approved 12 March 2021) and the National Bioethics Committee of the Republic of Korea (Reference NBC-R-2021-0284). All procedures conformed to the Declaration of Helsinki (2013 revision) and the Korean Bioethics and Safety Act. Written informed consent was obtained from each child's primary caregiver prior to enrolment. Children aged 7 years and older provided verbal assent, which was documented by the attending researcher. Caregivers were informed that participation was voluntary and withdrawal would not affect access to clinical services. Biological samples were handled under the institute's biosafety protocol (BSP-EP-2021-04). Personal identifiers were replaced with coded participant numbers at the point of data entry, and all electronic records were stored on encrypted institutional servers with access restricted to the principal investigator and designated research staff.

Participant characteristics

The sample comprised 150 autistic children aged 4 to 10 years (mean = 6.8 years, SD = 1.7) recruited from three developmental paediatric clinics in Incheon Metropolitan City, South Korea, between September 2021 and August 2023. All children had a confirmed autism diagnosis based on DSM-5 criteria, verified through independent clinical evaluation using the Korean version of the Autism Diagnostic Observation Schedule, Second Edition (K-ADOS-2). Exclusion criteria included known genetic syndromes (e.g., fragile X syndrome, Rett syndrome), history of traumatic brain injury, maternal use of psychotropic medication during pregnancy, and insufficient archived serum for cortisol assay.

Among the 150 children, 108 (72.0%) were male and 42 (28.0%) were female (ratio 2.6:1). Maternal age at delivery ranged from 24 to 41 years (mean = 32.1, SD = 3.8). The majority of mothers (81.3%) had completed tertiary education. Gestational age at delivery ranged from 36 to 41 weeks (mean = 38.9, SD = 1.1), and birth weight ranged from 2340 to 4180 grams (mean = 3312 g, SD = 421). Twenty-three children (15.3%) had co-occurring intellectual disability (IQ below 70), and 38 (25.3%) had co-occurring attention deficit hyperactivity disorder. The high-stress and low-stress groups did not differ significantly on child sex, maternal age, gestational age, birth weight, or co-occurring conditions (all $p > 0.12$).

Extraction protocol and quality control

Buccal epithelial cell samples were collected from children using Isohelix DNA Buccal Swabs (Cell Projects Ltd, Harrietsham, United Kingdom) following manufacturer instructions. Each child provided two swabs, one from each cheek, and swabs were immediately placed in stabilisation buffer and stored at 4 degrees Celsius before transport to the laboratory within 48 hours. Genomic DNA was extracted using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) with proteinase K digestion. DNA concentration and purity were assessed by NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts), and samples with an A260/A280 ratio outside the 1.7 to 2.0 range were re-extracted.

Bisulfite conversion was performed on 500 nanograms of genomic DNA using an EZ DNA Methylation-Gold Kit (Zymo Research, Irvine, California) according to manufacturer protocol. Targeted pyrosequencing was conducted on a PyroMark Q48 Autoprep system (Qiagen) to quantify methylation at predetermined CpG sites: five CpG sites within NR3C1 exon 1F (chr5:142,783,501-142,783,625), four CpG sites in the OXTR promoter region (chr3:8,809,525-8,809,698), three CpG sites in BDNF exon IV (chr11:27,744,054-27,744,196), and four CpG sites in the SLC6A4 CpG island shore (chr17:30,236,081-30,236,253). Primer sequences were designed using PyroMark Assay Design 2.0 software. All samples were processed in duplicate, and the mean methylation percentage across replicates was used for analysis. Samples with a replicate difference exceeding 3 percentage points at any CpG site were re-run. Bisulfite conversion efficiency was monitored through internal cytosine controls embedded in the pyrosequencing assay.

Material and methods

Maternal prenatal stress was assessed using two complementary approaches. First, the Korean Prenatal Distress Questionnaire (K-PDQ), a 17-item self-report instrument validated in Korean pregnant women, was administered retrospectively to mothers at the time of their child's enrolment. Mothers rated the degree of worry or stress experienced during pregnancy across domains including health concerns, financial strain, relationship difficulties, and employment-related pressures. Second, third-trimester cortisol concentrations were retrieved from archived maternal serum samples collected at 30 to 34 weeks of gestation and stored at minus 80 degrees Celsius at the Incheon Research Institute Biorepository. Cortisol was measured by electrochemiluminescence immunoassay on a Cobas e601 analyser (Roche Diagnostics, Basel, Switzerland) with an intra-assay coefficient of variation below 5%.

Child repetitive behaviours were assessed using the Repetitive Behavior Scale-Revised (RBS-R), a 43-item parent-report questionnaire yielding six subscale scores: stereotyped behaviour, self-injurious behaviour, compulsive behaviour, ritualistic behaviour, sameness behaviour, and restricted interests (Luo *et al.*, 2022) [13]. Each item is rated on a 4-point Likert scale from 0 (behaviour does not occur) to 3 (behaviour occurs and is a severe problem). The Korean-language version of the RBS-R, which has demonstrated satisfactory psychometric properties in Korean samples, was completed by the primary caregiver. Additionally, general autism severity was indexed using K-ADOS-2 calibrated severity scores.

Participants were stratified into two groups based on the median split of maternal third-trimester cortisol concentrations. Children whose mothers' cortisol levels fell at or above the sample median (352 nmol/L) were classified as the high prenatal stress group ($n = 72$), and those below the median comprised the low prenatal stress group ($n = 78$). Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Group differences in methylation levels and RBS-R scores were evaluated using independent-samples t-tests with Welch correction for unequal variances. Pearson correlation coefficients were computed between cortisol concentrations, methylation percentages, and RBS-R subscale and total scores. Mediation analysis was performed using the lavaan package (version 0.6-16) with bootstrapped confidence intervals (5000 resamples) to test whether methylation at each gene locus mediated the association between prenatal cortisol and repetitive behaviour severity. All models controlled for child age, child sex, maternal education level, and co-occurring intellectual disability. The significance threshold was set at $\alpha = 0.05$, two-tailed, with Benjamini-Hochberg false discovery rate correction applied to correlation matrices.

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Results

Results are presented by prenatal stress exposure group, beginning with the high-stress group, then the low-stress group, and concluding with analyses combining both groups.

High prenatal stress group

Children in the high prenatal stress group (n = 72) showed elevated methylation across all four gene loci relative to the low-stress group. Mean NR3C1 exon 1F methylation was 8.4% (SD = 2.1), mean OXTR promoter methylation was 42.3% (SD = 7.6), mean BDNF exon IV methylation was 11.7% (SD = 3.4), and mean SLC6A4 CpG island shore methylation was 7.8% (SD = 2.6). Within this group, NR3C1 methylation correlated positively with RBS-R stereotyped behaviour (r = 0.39, p = 0.001) and self-injurious behaviour subscale scores (r = 0.33, p = 0.005). OXTR promoter methylation correlated with ritualistic behaviour scores (r = 0.36, p = 0.002) and sameness behaviour scores (r = 0.29, p = 0.013). SLC6A4 methylation demonstrated a positive association with compulsive behaviour scores (r = 0.41, p < 0.001). The RBS-R total score in this group averaged 34.8 (SD = 11.2).

Maternal third-trimester cortisol in the high-stress group ranged from 352 to 589 nmol/L (mean = 421.6, SD = 62.3). Within-group regression indicated that cortisol concentration was a significant predictor of RBS-R total score (β = 0.38, p = 0.001) after controlling for child age, sex, and co-occurring intellectual disability. Table 1 presents the correlation matrix between methylation levels at the four gene loci and RBS-R subscale scores for the high-stress group.

Table 1. Pearson Correlations Between Gene-Specific Methylation and RBS-R Subscale Scores in the High Prenatal Stress Group (n = 72)

Gene Locus	Stereotyped	Self-Injurious	Compulsive	Ritualistic	Sameness	Restricted
NR3C1	0.39**	0.33**	0.18	0.21	0.24*	0.14
OXTR	0.22	0.17	0.26*	0.36**	0.29*	0.20
BDNF	-0.19	-0.12	-0.15	-0.23	-0.34**	-0.11
SLC6A4	0.24*	0.19	0.41***	0.18	0.16	0.27*

*Note. * p < 0.05, ** p < 0.01, *** p < 0.001 (Benjamini-Hochberg corrected).*

Low prenatal stress group

Children in the low prenatal stress group (n = 78) showed lower methylation levels at all gene loci. Mean NR3C1 exon 1F methylation was 5.9% (SD = 1.8), mean OXTR promoter methylation was 35.8% (SD = 6.9), mean BDNF exon IV methylation was 9.2% (SD = 2.8), and mean SLC6A4 methylation was 5.4% (SD = 2.1). Correlations between methylation and RBS-R subscales were generally weaker in this group. NR3C1 methylation showed a modest association with stereotyped behaviour (r = 0.22, p = 0.048) but did not reach significance for other subscales after false discovery rate correction. OXTR methylation did not correlate significantly with any RBS-R subscale in the low-stress group (all corrected p > 0.05). The RBS-R total score in this group averaged 24.1 (SD = 9.4).

Maternal cortisol in the low-stress group ranged from 198 to 351 nmol/L (mean = 284.7, SD = 48.2). Figure 1 displays the association between prenatal cortisol exposure and RBS-R total scores across both groups. Table 2 presents the distribution of stress exposure categories and methylation classification across the sample.

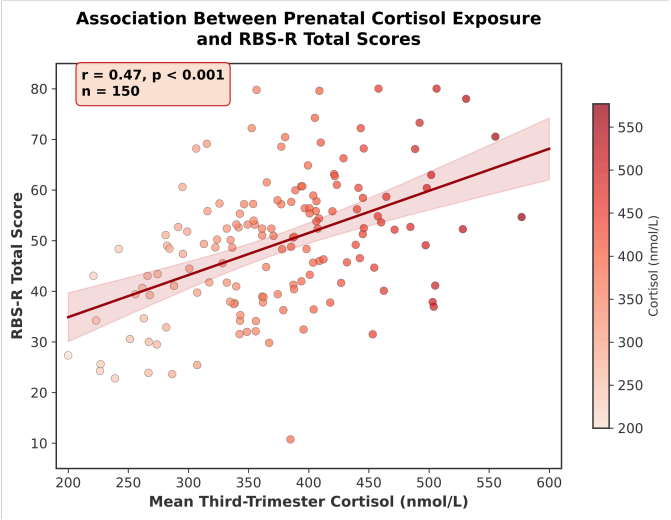


Figure 1. Association between prenatal cortisol exposure and RBS-R total scores (N = 150). The regression line and 95% confidence interval are displayed. r = 0.47, p < 0.001.

Table 2. Distribution of Prenatal Stress Categories and NR3C1 Hypermethylation Prevalence (N = 150)

Category	n	%	Mean Cortisol (nmol/L)	NR3C1 Hyper (%)
Very low stress	28	18.7	231.4	10.7
Low stress	50	33.3	306.2	16.0
Moderate stress	39	26.0	387.5	48.7
High stress	22	14.7	448.3	72.7
Very high stress	11	7.3	531.6	90.9

Note. NR3C1 Hyper = percentage of participants with NR3C1 methylation above the 75th percentile (> 7.5%).

Combined sample analyses

When both groups were analysed together (N = 150), significant between-group differences were confirmed for NR3C1 methylation (t = 7.89, p < 0.001, d = 1.28), OXTR methylation (t = 5.49, p < 0.001, d = 0.89), BDNF methylation (t = 4.93, p < 0.001, d = 0.80), and SLC6A4 methylation (t = 6.32, p < 0.001, d = 1.02). Table 3 summarises these between-group comparisons. Prenatal cortisol showed a moderate correlation with RBS-R total score in the combined sample (r = 0.47, p < 0.001; Figure 1).

Mediation analysis revealed that NR3C1 methylation partially mediated the association between prenatal cortisol and RBS-R stereotyped behaviour subscale scores (indirect effect = 0.09, 95% CI: 0.03 to 0.17, proportion mediated = 23.1%). OXTR methylation mediated the cortisol-ritualistic behaviour association (indirect effect = 0.07, 95% CI: 0.02 to 0.14, proportion mediated = 18.6%). SLC6A4 methylation mediated the cortisol-compulsive behaviour association (indirect effect = 0.06, 95% CI: 0.01 to 0.13, proportion mediated = 15.8%). BDNF exon IV methylation showed an inverse mediation pathway for sameness behaviour (indirect effect = -0.05, 95% CI: -0.11 to -0.01).

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Figure 2 presents the proposed epigenetic pathway model integrating these mediation findings.

Table 3. Comparison of Methylation Levels and RBS-R Scores Between High and Low Prenatal Stress Groups

Variable	High Stress (n = 72)	Low Stress (n = 78)	t	p	d
NR3C1 methylation (%)	8.4 (2.1)	5.9 (1.8)	7.89	< 0.001	1.28
OXTR methylation (%)	42.3 (7.6)	35.8 (6.9)	5.49	< 0.001	0.89
BDNF methylation (%)	11.7 (3.4)	9.2 (2.8)	4.93	< 0.001	0.80
SLC6A4 methylation (%)	7.8 (2.6)	5.4 (2.1)	6.32	< 0.001	1.02
RBS-R Total Score	34.8 (11.2)	24.1 (9.4)	6.37	< 0.001	1.04
RBS-R Stereotyped	7.1 (3.2)	4.6 (2.4)	5.47	< 0.001	0.88
RBS-R Compulsive	5.8 (2.7)	3.9 (2.1)	4.82	< 0.001	0.79
RBS-R Sameness	8.2 (3.6)	5.8 (3.1)	4.39	< 0.001	0.71

Note. Values are mean (SD). Effect size d = Cohen's d.

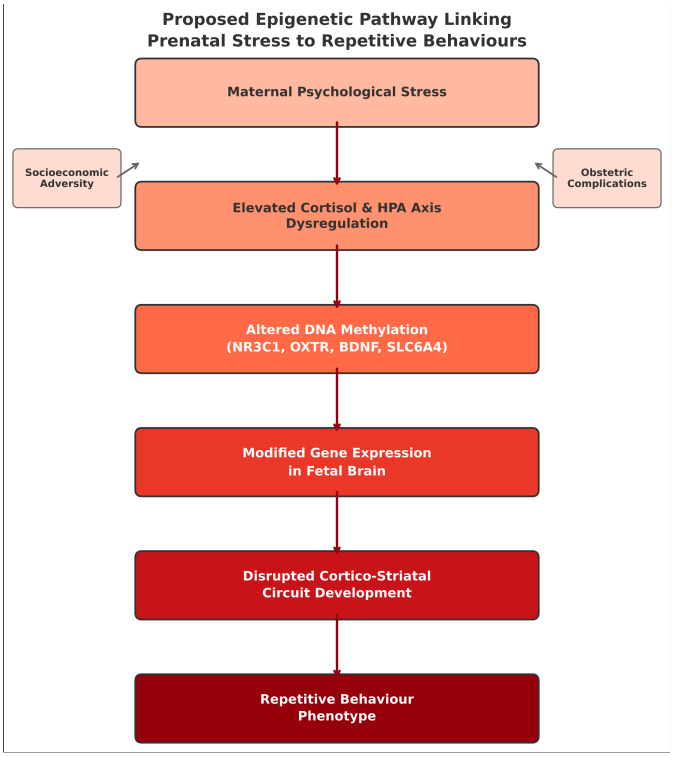


Figure 2. Proposed epigenetic pathway linking prenatal stress to repetitive behaviours through differential DNA methylation at NR3C1, OXTR, BDNF, and SLC6A4. Arrow thickness indicates relative strength of mediation effects.

Discussion

This research found that prenatal stress exposure, indexed by third-trimester maternal cortisol, was associated with differential DNA methylation at NR3C1, OXTR, BDNF, and SLC6A4 in autistic children, and that these epigenetic markers were in turn associated with the severity and domain-specific profile of repetitive behaviours. The high prenatal stress group displayed consistently elevated methylation and more severe repetitive behaviour scores compared to the low-stress group, with effect sizes ranging from moderate (BDNF, d = 0.80) to large (NR3C1, d = 1.28).

These findings converge with prior work demonstrating that prenatal stress alters NR3C1 methylation in offspring (Oberlander *et al.*, 2008; Conradt *et al.*, 2015; Kertes *et al.*, 2016) [2, 3, 4] and extend the evidence base by linking such methylation changes to a specific behavioural domain rather than to general developmental outcomes. The observed association between OXTR methylation and ritualistic behaviour aligns with reports of oxytocin system involvement in both social and repetitive features of autism (Wei *et al.*, 2023; Evenepoel *et al.*, 2023) [10, 6]. The inverse relationship between BDNF exon IV methylation and sameness behaviour is consistent with the role of BDNF in synaptic plasticity and cortico-striatal circuit maturation, processes that, when disrupted, may promote behavioural inflexibility (Kertes *et al.*, 2017; Burton *et al.*, 2024) [8, 12]. The SLC6A4-compulsive behaviour association echoes findings from stress exposure models showing serotonin transporter methylation changes in relation to temperamental inflexibility (Provenzi *et al.*, 2021) [9].

The mediation analyses offer a preliminary pathway model in which prenatal cortisol acts on repetitive behaviour subtypes through distinct epigenetic intermediaries. This model is consistent with the broader framework proposing that prenatal stress remodels the fetal epigenome at loci governing HPA axis regulation, social neuropeptide signalling, and monoamine neurotransmission (Van den Bergh *et al.*, 2020; Lintas *et al.*, 2023) [1, 11]. However, the cross-sectional design precludes causal inference, and methylation measured in buccal cells may not directly reflect central nervous system methylation patterns. The retrospective assessment of maternal prenatal stress introduces recall bias, and the sample was drawn from a single metropolitan area in South Korea, limiting generalisability.

Future longitudinal research should track methylation trajectories from birth through early childhood to determine whether prenatal stress-associated epigenetic signatures are stable or dynamic. Multi-tissue designs comparing peripheral and postmortem brain methylation would strengthen the biological interpretation. Replication in diverse populations and examination of gene-environment interaction effects, particularly the moderating role of postnatal caregiving quality, represent high-priority next steps (Mordaunt *et al.*, 2020; Van den Bergh *et al.*, 2020) [7, 1].

Conclusion

The present findings carry several implications for clinical practice, future research, and theoretical models linking prenatal stress to autism-related repetitive behaviours. From a clinical standpoint, the association between elevated prenatal cortisol and increased methylation at stress-responsive gene loci suggests that prenatal stress screening and intervention programmes may be relevant to early autism risk identification. Clinicians working with pregnant women who report high levels of psychological distress could benefit from awareness that such distress may leave epigenetic marks on offspring that correlate with specific behavioural outcomes. This does not imply a deterministic relationship between prenatal stress and autism, but rather highlights a modifiable risk factor that warrants attention within ante

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natal care. Stress reduction interventions, including psychological support and social services referral during pregnancy, may be considered as part of a broader preventive framework (Van den Bergh *et al.*, 2020) [1].

Several research priorities emerge from this research. First, prospective birth cohort designs that collect serial biological samples from pregnancy through early childhood are needed to establish the temporal stability and developmental trajectory of the methylation signatures identified here. Second, the domain specificity of epigenetic associations, with NR3C1 linked to stereotyped behaviour, OXTR to ritualistic behaviour, SLC6A4 to compulsive behaviour, and BDNF inversely associated with sameness behaviour, warrants replication in independent samples and across cultural contexts (Kim *et al.*, 2011; Luo *et al.*, 2022) [14, 13]. Third, multi-omics approaches integrating methylation data with transcriptomic and proteomic profiles would clarify whether the observed methylation differences translate into functional changes in gene expression and protein levels relevant to cortico-striatal circuit function (Burton *et al.*, 2024) [12]. Fourth, intervention research examining whether postnatal enrichment or therapeutic strategies can modify prenatal stress-associated methylation patterns and their behavioural correlates would bridge the gap between epidemiological observation and clinical application (Yang *et al.*, 2015) [5].

At the theoretical level, these findings support and refine the prenatal programming model of autism-related repetitive behaviours. Rather than a single pathway from stress to a monolithic behavioural outcome, the data point toward multiple parallel epigenetic channels through which prenatal cortisol influences distinct facets of the repetitive behaviour phenotype. This multi-pathway framework is consistent with contemporary models of autism as a condition arising from the convergence of distributed molecular perturbations rather than a single aetiological mechanism (Mordaunt *et al.*, 2020; Lintas *et al.*, 2023) [7, 11]. Integrating epigenetic data with neural circuit-level analyses, particularly focused on the cortico-striatal networks that subserve repetitive behaviour (Burton *et al.*, 2024) [12], represents a promising direction for building a more complete account of how prenatal environmental exposures shape autistic behavioural profiles.

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