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Epigenetic modulation of social cognition: exploring the impact of methylation in brain-derived neurotrophic factor and oxytocin receptor genes across sex

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Social cognition, which ranges from recognizing social cues to intricate inferential reasoning, is influenced by environmental factors and epigenetic mechanisms. Notably, methylation variations in stress-related genes like brain-derived neurotrophic factor (BDNF) and the oxytocin receptor (OXTR) are linked to distinct social cognitive functions and exhibit sex-specific differences. This study investigates how these methylation differences affect social cognition across sexes, focusing on both perceptual and inferential cognitive levels. Social cognitive abilities were assessed using the Korean version of the Reading the Mind in the Eyes Test (K-RMET) and Brune's story-based Theory of Mind tasks (ToM-PST). DNA methylation levels in *BDNF* and *OXTR* were analyzed for correlations with performance on these cognitive tasks in a cohort of male and female participants. A moderation model was applied to determine if sex moderates the relationship between social cognition and DNA methylation. No significant overall correlation was found between social cognition and DNA methylation across participants. However, sex-specific correlations were identified, including a negative impact of *BDNF* methylation on K-RMET scores in males, and a similar effect of *OXTR* methylation on ToM-PST scores in females. The findings underscore the complex relationship between epigenetic modifications and social cognition, revealing sex-specific effects and highlighting the importance of considering sex in epigenetic studies of social cognition. This research contributes to understanding how epigenetic factors, influenced by sex, shape social cognitive processes and supports the need for sex-specific therapeutic approaches.

Keywords Social cognition, DNA methylation, BDNF, OXTR, Sex differences

Social cognition is a critical component of human cognitive function, involving a range of abilities and processes used to perceive, interpret, and engage with the social environment[1]. Research in social cognition has focused on analyzing the distinct sub-systems involved in processing social information. These studies typically distinguish social information processing into several categories, and the two main processes are: automatic, stimulus-driven processes that align with the perceptual level of social cognition, and strategic, context-sensitive, deliberative processes corresponding to the inferential level of social cognition[2,3]. The perceptual level of social cognition primarily involves the immediate processing of social stimuli, such as facial expressions and body language, which are critical for understanding others' emotional states and intentions at a glance[2]. Alternatively, the inferential level involves more elaborate cognitive operations, such as deducing others' beliefs, desires, and intentions through theory of mind (ToM), which requires integration of contextual information and past experiences to form judgments about the mental states of others[4].

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The range of aspects of social cognition that can be assessed include recognition of facial expressions and vocal emotion, empathy and emotion contagion, more abstract reasoning about one's own and other people's cognitive or affective mental states, identification of deception, moral judgement, and more[5]. The Reading the Mind in the Eyes Test (RMET)[6] stands out among social cognitive assessments by evaluating the ability to discern mental states from eye expressions, relying on an unconscious and automatic process of matching expressions to a mental state lexicon based on memory[7]. Story-based tasks for social cognition are designed to test more intricate ToM skills[5]. These involve stories where a character's remarks influence another's emotional state, challenging participants to discern both the mistaken beliefs and emotional responses of the characters involved.

The neurodevelopment of social information processes is significantly influenced by environmental factors[8], and epigenetic mechanisms such as DNA methylation play a pivotal role in mediating these effects[9]. Empirical research into the epigenetic bases of social cognition has highlighted two stress-related genes: brain-derived neurotrophic factor (*BDNF*)[10] and oxytocin receptor (*OXTR*)[11]. The BDNF, which is involved in neuronal development and synaptic plasticity[12], has been the focus of numerous studies aimed at understanding the relationship between stress, brain responses, and behavioral outcome[13]. Increased *BDNF* DNA methylation and decreased BDNF expression was found in prenatally stressed mice[14,15] and this was further related to hyperactivity and impaired social interaction[16]. Early-life experiences significantly promoted the empathy-like behavior of rats in adulthood which was linked by *BDNF* gene expression[17]. Oxytocin (OXT) is known to be associated with the central nervous control of stress and anxiety and with social behavior[18]. By acting in the brain via OXTR [19], which is primarily enriched in human subcortical reward and emotional regions[20], OXT affects social cognition by enhancing the salience of social cues and reward sensitivity to these cues[21,22]. Studies have shown that DNA methylation of *OXTR* can influence individual differences in social perceptiveness and prosocial behavior, suggesting that epigenetic regulation of this gene may affect social cognitive capacities[23].

Mounting evidence demonstrated sex-dimorphic differences in epigenetic mechanisms[24,25]. For instance, studies have shown that sex-specific methylation of *BDNF* may contribute to differences in brain development and psychiatric outcomes, thereby affecting behavioral and cognitive functions differently in males and females[26,27]. Additionally, sex differences in the OXTR systems have been highlighted for the regulation of distinct social behaviors[28]. These findings underscore the importance of considering sex as a critical factor in epigenetic studies of social cognition. By accounting for these differences, researchers can better understand the nuanced ways in which genetic and environmental factors converge to shape social cognition across sex. The current study aims to dissect these interactions by investigating whether the associations between DNA methylation—specifically in stress-related genes linked to social behavior, such as *BDNF* and *OXTR*—and the perceptual and inferential levels of social cognition differ by sex. By examining these relationships, this research aims to elucidate the intricate mechanisms through which epigenetic modifications, influenced by sex, contribute to the variability in social cognitive processes.

Methods

Participants

A total of 166 healthy, non-clinical young adults (81 males and 85 females) were recruited through an online advertisement. All participants were ethnically Korean. The Mini-International Neuropsychiatric Interview (MINI)[29,30] was utilized to screen out individuals with any past or current psychiatric or neurological illnesses. Blood samples and the RMET test were collected and conducted on the same day during the participants' first visit. The ToM task was administered on a separate occasion during the second visit, with a time interval between visits of 64.16 days (range: 24–126 days).

Psychometric measure

RMET

RMET[6] is a widely used tool for assessing social cognitive function. It features 36 photographs of the eye region of faces, each depicting complex mental states of the individuals shown. Surrounding each photograph are four descriptive terms. Participants are instructed to examine each set of eyes and select from four options (one target and three foils) the term that best describes what the person in the photograph is thinking or feeling. The correct choice, the target word, is awarded 1 point, while the foils receive 0 points, making the total possible score range from 0 to 36 points. For this study, a Korean-version of the RMET (K-RMET)[31] was utilized.

ToM tasks

ToM was evaluated using a series of six cartoon picture stories (ToM-PST)[32]. These cartoons illustrated various social dynamics: two scenarios depicted cooperation between two characters, two involved deceit by one character towards another, and the final two showed cooperation between two characters at the detriment of a third. Participants were given four cards per story in randomized order and were required to sequence them to accurately reflect the story's narrative. Subsequently, they answered questions designed to evaluate their grasp of the characters' mental states. The cognitive dimension of ToM involved questions regarding false beliefs, intentions, and second and third-order beliefs, while affective questions focused on the characters' emotions and feelings, especially those not clearly expressed through facial expressions. Each correctly answered cognitive question was awarded one point, with a maximum cognitive ToM score (ToM-PST-cog) of 23 points possible. The affective ToM score (ToM-PST-aff) could range from 0 to 32 points, where 2 points were given for correctly and spontaneously identifying emotions, and 1 point for correct responses following a prompt, such as distinguishing between "anger or sadness." Incorrect responses garnered no points. Because prior studies indicate that sequencing tasks gauge basic understanding of social interactions while questionnaires evaluate

more advanced ToM skills, requiring explicit articulation of mental state attributions[33,34], this study employed ToM-cog and ToM-aff specifically to assess the inferential level of social cognition.

Neurocognitive function task

While social cognitive processes are distinct from neurocognitive functions, assessments of social information processing have been shown to correlate with neurocognitive performance. Specifically, previous research has identified a link between performance on RMET and neurocognitive functions, particularly reasoning by analogy[35]. To control for the influence of neurocognitive functioning on social cognitive assessments, the Standard Progressive Matrices (SPM)[36] were employed in this study. The SPM consists of 60 non-colored diagrammatic puzzles, each with a missing segment that participants need to correctly complete from one of six choices. This test is known for its high validity and reliability across diverse cultural groups[37]. In this research, SPM scores were calculated based on the total number of correct responses from participants.

Epigenotyping procedures

Genomic DNA was extracted from the peripheral blood of 162 participants (for the detailed protocol, see the supplementary material). Methylation levels were determined by Macrogen, Inc. (Seoul, Republic of Korea) using standardized methods. Analyses targeted a CpG-rich segment of the *OXTR1* gene (chr3: 8,810,729–8,810,845; GRCh37/hg19), which includes three CpG sites[23,38]. For the *BDNF* promoter, a CpG-rich region was analyzed, spanning seven CpG sites located at chr11: 27,665,726–27,665,843 (GRCh37/hg19)[39–41]. Pearson correlation analyses revealed significant relationships between methylation values at different CpG sites within both the *OXTR1* and *BDNF* genes ($P<0.001$ for all correlations), indicating coordinated methylation across the sites. Therefore, the average vales of the percent methylation of the CpG sites were used in this study. The genome browser addresses for these regions and the correlation analyses between the CpG sites are available in the supplementary material.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 25 (IBM Corp). The independent t-test was employed to compare baseline characteristics between groups. Pearson's correlation analysis was utilized to investigate the relationships between social cognition measures (K-RMET, ToM-PST-cog, ToM-PST-aff) and DNA methylation levels. This analysis was conducted first with the entire participant pool and subsequently separately for males and females.

To assess whether sex acts as a moderator in the relationship between social cognition and DNA methylation, we applied a simple moderation model using the PROCESS macro in SPSS[42], controlling for age and SPM scores. For all tests conducted, a P-value of less than 0.05 was considered to indicate statistical significance.

Results

Participant characteristics

Table 1 outlines the demographics of the study population. The mean age of 166 healthy young adults was 23.1 years and male and female groups showed the age difference [mean(SD) = male:23.5(2.5), female: 22.6(2.6), $P=0.022$]. There were no significant differences in years of education or SPM scores between genders. The K-RMET and ToM-PST scores showed no significant differences between males and females. In terms of DNA methylation, there was no significant gender difference in *BDNF* methylation, but females exhibited higher *OXTR* methylation levels than males.

Association between Social cognition and DNA methylation

Table 2 presents the correlations between social cognition and DNA methylation. Across the entire participant group, there was no significant correlation found between social cognition and DNA methylation. However, notable exceptions include a significant correlation between *BDNF* methylation and K-RMET scores in males (β

Variable	Total (n = 166)	Male (n = 81)	Female (n = 85)	*p*-value
Age, mean (SD), y	23.1 (2.6)	23.5 (2.5)	22.6(2.6)	0.022
Education, mean (SD), y	14.4 (1.4)	14.2 (1.3)	14.6(1.5)	0.050
SPM score, mean(SD)	52.4 (5.2)	52.7 (5.7)	52.2(4.8)	0.567
K-RMET score, mean (SD)	26.9 (3.1)	26.5 (3.2)	27.2 (3.0)	0.133
ToM-PST, mean (SD)				
ToM-PST-cog score	22.0 (1.2)	21.9 (1.2)	22.0 (1.3)	0.608
ToM-PST-aff score	27.0 (2.4)	26.6 (2.6)	27.2 (2.2)	0.089
*BDNF*m[a], mean (SD), %	5.1 (1.7)	5.1 (1.7)	5.2 (1.6)	0.811
*OXTR*m[b], mean (SD), %	55.6 (6.5)	54.1 (6.5)	57.1 (6.2)	0.003

Table 1. Characteristics of the study participants. [a]*BDNF*m data were available for 80 men and 82 women. [b]*OXTR*m data were available for 79 men and 82 women. *BDNF*m, Brain-Derived Neurotrophic Factor ,methylation; *OXTR*m, OXT receptor methylation; K-RMET, Korean version of the Reading the Mind in the Eyes Test; SD, standard deviation; SPM, Standard Progressive Matrices; ToM-PST-cog, cognitive Theory of Mind Pictures Stories Test; ToM-PST-aff, affective Theory of Mind Pictures Stories Test.

	Total		Male		Female	
	*BDNF*m	*OXTR*m	*BDNF*m	*OXTR*m	*BDNF*m	*OXTR*m
K-RMET	−0.09	0.02	**−0.24**	−0.06	0.06	0.06
	(0.267)	(0.812)	**(0.034)**	(0.595)	(0.059)	(0.623)
ToM-PST-cog	0.06	−0.07	0.09	−0.15	0.03	−0.20
	(0.425)	(0.394)	(0.451)	(0.190)	(0.783)	(0.859)
ToM-PST-aff	−0.05	−0.05	0.03	0.09	−0.15	**−0.32**
	(0.564)	(0.503)	(0.805)	(0.451)	(0.193)	**(0.004)**

Table 2. Correlations of social cognition and DNA methylation. *BDNF*m, Brain-Derived Neurotrophic Factor ,methylation; *OXTR*m, OXT receptor methylation; K-RMET, Korean version of the Reading the Mind in the Eyes Test; ToM-PST-cog, cognitive Theory of Mind Pictures Stories Test; ToM-PST-aff, affective Theory of Mind Pictures Stories Test. Significant values are in [bold].

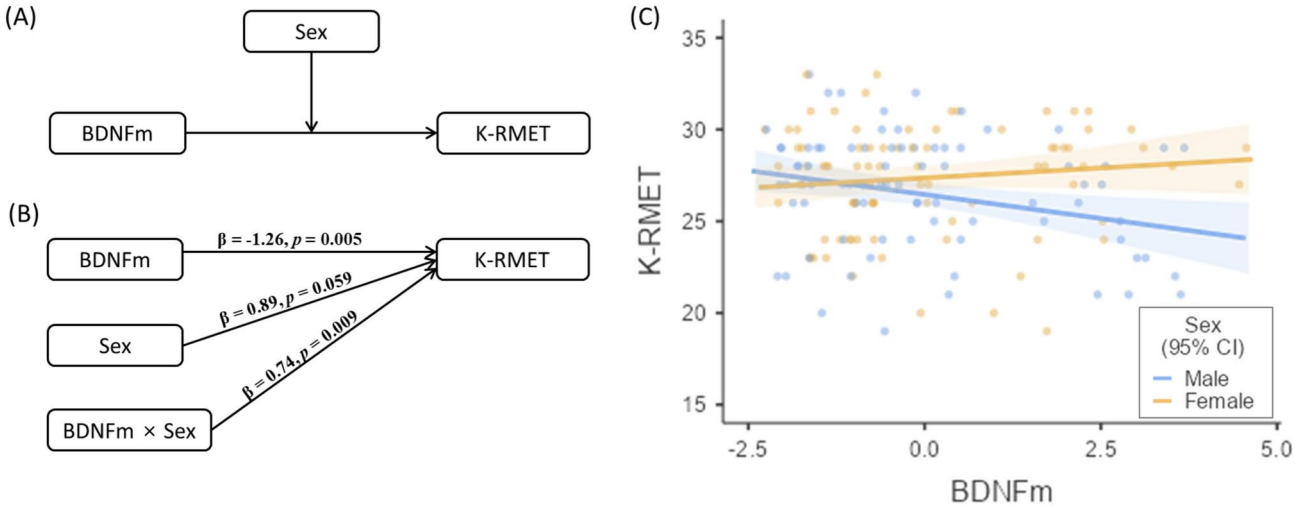

Fig. 1. (**A**) Conceptual and (**B**) statistical models and (**C**) the plot showing the simple effects with the standard errors of the estimates to visualize the association between *BDNF* methylation and K-RMET scores being moderated by sex. Regression coefficients are calculated in a moderation analysis model including age and SPM scores as covariates. Abbreviations: *BDNF*m, Brain-Derived Neurotrophic Factor ,methylation; K-RMET, Korean version of the Reading the Mind in the Eyes Test.

= −0.24, $P = 0.034$), and between *OXTR* methylation and ToM-PST-aff scores in females ($\beta = -0.32$, $P = 0.004$). No other significant correlations were observed.

Interaction between sex and DNA methylation on social cognition

Moderation of BDNF methylation and K-RMET by sex

The relationship between *BDNF* methylation and K-RMET scores was significantly influenced by sex, with adjustments made for age and SPM scores ($P = 0.009$, Fig. 1). Specifically, *BDNF* methylation negatively impacted the K-RMET scores in males ($\beta = -0.52$, $P = 0.009$), but showed no significant effect in females ($\beta = 0.22$, $P = 0.275$).

Moderation of OXTR methylation and ToM-PST by sex

Sex also moderated the relationship between *OXTR* methylation and ToM-PST-aff scores, after controlling for age and SPM scores ($P = 0.039$, Fig. 2). In females, *OXTR* methylation negatively affected the ToM-PST-aff scores ($\beta = -0.10$, $P = 0.015$), whereas in males, it showed no significant impact ($\beta = 0.02$, $P = 0.633$).

Discussion

The findings of this study underscore the intricate relationship between epigenetic modifications and social cognition, revealing both sex-specific effects and broader insights into the molecular mechanisms underpinning social cognitive processes. Notably, the observed sex-specific modulation in the correlations between *BDNF* methylation and K-RMET scores, along with *OXTR* methylation and affective ToM-PST scores, shed light on the complex biological pathways that affect social cognitive functions and their phenotypic expressions.

Relative to the more static physical environment, the social environment is significantly more intricate, unpredictable, and notably interactive in response to individual actions. Throughout evolution, social skills have

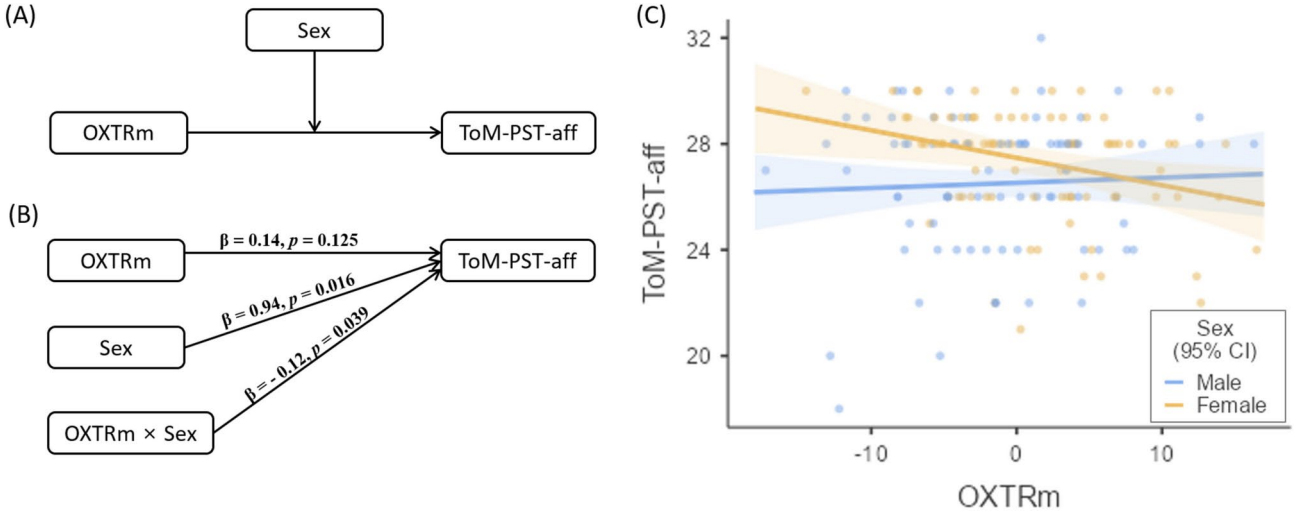

Fig. 2. (**A**) Conceptual and (**B**) statistical models and (**C**) the plot showing the simple effects with the standard errors of the estimates to visualize the association between *OXTR* methylation and ToM-PST-aff being moderated by sex. Regression coefficients are calculated in a moderation analysis model including age and SPM scores as covariates. Abbreviations: *OXTR*m, OXT receptor methylation; ToM-PST-aff, affective Theory of mind Pictures Stories Test.

therefore not only broadened in scope but also increased in complexity[8]. Brain imaging research supports the division of social cognitive abilities into various levels, showing that distinct processes in social information handling are linked to specific neural systems[43,44]. Yet, investigations into whether different social cognitive processes have distinct genetic origins are currently lacking. This research highlights that the K-RMET, representing the perceptual level of social cognition, and the ToM-PST task, indicative of the inferential level, correlate with methylation in different genes according to sex. This suggests biological distinctions between the perceptual and inferential levels of complex social cognitive abilities.

Methylation of the *BDNF* gene is influenced by a wide array of environmental factors, from early-life adversity to both acute and chronic stressors[26]. This study's observation that increased *BDNF* methylation correlates with reduced performance on the K-RMET in males implies that such environmental influences could affect social information processing, particularly at the perceptual level in males. Conversely, the lack of significant findings in females may indicate unique epigenetic regulatory processes. Research has shown that *BDNF* gene regulation and its downstream activities often vary based on sex[45,46] potentially governed by sex chromosomes and hormones[47]. This could play a role in the observed gender differences in the prevalence, severity, and response to treatment of neurodevelopmental disorders[48]. Although sex-specific effects in social cognitive processes are less studied, there is evidence suggesting that antenatal stress influences child development in a sex-dimorphic manner, particularly affecting temperament[49,50]. Furthermore, antenatal exposure to environmental toxicants has been linked to higher *BDNF* methylation in males but not in females[27]. Thus, the findings of this study not only align with previous research demonstrating the sex-dependent effects of *BDNF* methylation but also suggest that a similar sex-differentiated relationship exists between *BDNF* methylation and social perception in the realm of social cognition.

Regarding OXTR, which is well recognized to play a biological role in social bonding and empathy, mechanisms central to effective social cognition[51], the association between *OXTR* methylation and the affective component of ToM-PST performance in females highlights the role of OXT signaling in mediating social cognitive capacities, particularly in interpreting complex social cues. The current study did not find an association between *OXTR* methylation and RMET performance, a task often used to measure the perceptual, automatic level of social cognition. While this might seem inconsistent with the salience hypothesis of OXT[52], the hypothesis does not exclusively apply to automatic processes. Instead, OXT likely increases sensitivity to socially relevant cues across a range of cognitive processes, including both automatic and deliberative responses. Moreover, this finding suggests that OXT's role in enhancing social cue salience may be more prominent in tasks requiring a higher degree of emotional inference and context sensitivity. While OXT may increase sensitivity to emotionally charged, contextual information (as in affective ToM), it might not similarly affect the more basic, perceptual level of emotion recognition captured by the RMET. Future research should explore this nuanced role of OXT across different facets of social cognition. As demonstrated by Lieberz et al.[53], OXT increases the salience of social signals by enhancing sensitivity to these signals in the amygdala and striatum in women, whereas in men it primarily induces anxiolysis by reducing amygdala responses, underscoring that the effects of OXT are sex-dependent[54]. Consequently, the impact of *OXTR* methylation could also vary by sex, and the lack of this association in males may suggest different neurobiological pathways influencing social cognition. There are multiple possible OXT system alterations that could disrupt social cognition[55]. The result of this study enables a more detailed future assessment and analysis of the effects of *OXTR* methylation on social cognition than previously available. These sex-specific findings highlight the potential for tailored therapeutic interventions

targeting epigenetic modifications to improve cognitive and behavioral outcomes. Additionally, the absence of a significant correlation between overall DNA methylation and social cognition across the cohort emphasizes the specificity of epigenetic effects, supporting the need for precision medicine in neuropsychiatric and cognitive disorders.

This study is constrained by several limitations. The cross-sectional nature of the data prevents the establishment of causal relationships. Future studies should strive to replicate these findings in larger cohorts and utilize longitudinal approaches to evaluate the persistence of methylation marks and their prolonged influence on social cognition. One notable limitation of this study is the absence of a replication analysis in an independent cohort. Replication studies are crucial in epigenetic research to confirm the reliability and reproducibility of initial discoveries, reduce the likelihood of false-positive results, and assess the generalizability of findings across different populations or conditions. Future research should aim to replicate these findings in independent cohorts to strengthen the validity of our results and to better understand the robustness of the identified methylation changes across diverse samples. Although the current study utilized the MINI to exclude participants with psychiatric or neurological illnesses, autistic traits were not assessed. This is a limitation, as autistic traits are known to impact social cognition, including performance on tasks like the RMET[56] and ToM[57]. Additionally, autistic traits have been associated with *BDNF*[58] and *OXTR* methylation[59]. Considering these potential influences, future research would benefit from including measures of autistic traits to further refine the understanding of these relationships. Moreover, incorporating neuroimaging data could yield more detailed insights into the neural mechanisms underpinning these epigenetic influences, thus enriching our comprehension of the biological underpinnings of social cognition and its sex-related variations.

In conclusion, this study enhances the existing literature on the epigenetic regulation of social cognitive functions, emphasizing the necessity to account for sex differences in the molecular foundations of social cognition. By revealing the sex-specific pathways through which *BDNF* and *OXTR* methylation influence specific social cognitive abilities, this research advances our understanding of the biological underpinnings of social information processes and sets the stage for the development of more precise and impactful therapeutic interventions.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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Author contributions

H.Y.P., E.L., and S.K.A. conceived and designed the study. H.Y.P., E.S., E.L., and S.K.A. recruited the subjects. S.L., S.J.K., and Z.L. participated in data collection. H.Y.P. and S.K.A. performed the data analysis. H.Y.P., S.L.,

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
This study received approval from the Institutional Review Board at Severance Hospital (IRB No. 4–2014-0744) and was conducted in compliance with the Declaration of Helsinki.

Consent to participate
All participants provided written informed consent.

Consent for publication
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