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Oxytocin receptor gene variants are associated with emotion recognition and resilience, but not with false-belief reasoning performance in healthy young Korean volunteers

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Summary

Aims: A growing body of literature has indicated that oxytocin is associated with several domains of social cognition and behavior. Nevertheless, the effects of oxytocin receptor gene (*OXTR*) polymorphisms on social phenotypes remain unclear. Therefore, we aimed to explore the genetic influence of *OXTR* variants on social cognition (social perception and theory of mind) and resilience in healthy individuals.

Methods: We examined the influence of 10 common *OXTR* variants on social cognitive abilities, including facial emotion recognition and theory of mind, and trait resilience in 264 unrelated, healthy participants.

Results: We found a significant association between the A-C haplotype at rs237887-rs2268490 and facial affect recognition. In addition, the single marker rs2254298 was significantly associated with participants' scores on the Connor-Davidson Resilience Scale. In contrast, variations in *OXTR* did not affect participants' performance on the false-belief reasoning task.

Conclusions: Single makers or haplotypes at *OXTR* may contribute to individual differences in facial emotion recognition and psychological resilience.

KEYWORDS

emotion recognition, false-belief reasoning, oxytocin receptor gene, resilience, theory of mind

1 | INTRODUCTION

Although substantial evidence has been accumulated on the influence of oxytocin on social cognition and behavior in humans, the results concerning the prosocial effects of oxytocin have been inconsistent.[1,2] In light of these equivocal findings, some researchers have suggested that the effects of oxytocin depend on contextual factors and/or personal factors, that is, the specific context in which oxytocin is administered and the unique attributes of the individuals to whom oxytocin is administered, respectively.[3] As social cognitive traits have been shown to be highly heritable in the general population,[4] a person's genetic makeup has been stressed as an important factor for understanding the individual variability in social phenotypes. Since the effects of the oxytocin system are principally related to the distribution and function of oxytocin receptors, previous studies have placed a strong emphasis on the gene that encodes the oxytocin receptor (*OXTR*). Hence, many studies have investigated the relationship between variations in *OXTR* and components of social cognition.

Thus far, evidence demonstrating that *OXTR* variants contribute to social cognition mostly comes from two single nucleotide polymorphisms (SNPs) located in the third intron, that is, rs53576 and rs2254298. Previous studies have identified that these SNPs are associated with several aspects of social cognition, including empathy[5] and mental-state reasoning.[6] Along with their influence on social phenotypes, rs53576 and rs2254298 have also been related to vulnerability to certain psychiatric disorders that involve social dysfunction, such as schizophrenia[7] and autism spectrum disorder.[8]

Furthermore, these SNPs have been shown to moderate the effects of early life adversities on the development of depression and anxiety[9,10] which suggests that *OXTR* variants play roles in resilience versus susceptibility in response to environmental contingencies. Collectively, these findings imply that rs53576 and rs2254298 are involved in social functioning and interact with environmental factors to modulate the risk of developing certain psychiatric conditions. However, although these two SNPs have been suggested as the most promising candidates for explaining individual differences in the oxytocin system, their associations with social cognition and behavior have not been consistently replicated in terms of the presence[11,12] or directionality of the association.[6,13] Moreover, clearer evidence of relationships between social phenotypes and *OXTR* polymorphisms other than rs53576 and rs2254298 is needed.

In the present study, we aimed to explore the genetic influence of 10 *OXTR* variants, including rs53576 and rs2254298, on two different facets of social cognition (social perception and theory of mind) in healthy individuals. As measures of social perception and theory of mind, we used a facial emotion recognition task and false-belief reasoning task, respectively. Among the various available tools for assessing theory of mind, we selected the false-belief task, because performance on this task has rarely been investigated in terms of its association with *OXTR* variants. Additionally, given the evidence supporting a relationship between *OXTR* variability and outcomes of adverse life experiences,[9,14] we sought to examine the influence these variants have on individual differences in the trait resilience level.

2 | METHODS

2.1 | Subjects

A total of 264 unrelated, healthy volunteers (127 women) were recruited through online advertisements. Our participants were adolescents and young adults between the ages of 15 and 29 years (M = 20.8 years, SD = 2.5), and their education duration varied from 10 to 17 years (M = 13.3 years, SD = 1.5). Participants with a lifetime history of psychiatric disorder, neurological illness, or traumatic brain injury were excluded. All participants were identified as ethnically Korean. The study protocol was approved by the Institutional Review Board of Severance Hospital and Severance Mental Health Hospital. Written informed consent was obtained from all participants and the parents of participants who were under 18 years of age.

2.2 | Test selection

We selected behavioral tasks that may reflect different domains of social cognition. As social cognition consists of emotional and cognitive constructs, which may have partially overlapping but not entirely identical components, measures for assessing these emotional and cognitive constructs were selected. Facial affect perception task was used to measure the capacity to identify emotional cues while false-belief reasoning task was used to assess theory of mind, which refers to ability to understand mental states of others. Since false-belief reasoning may involve higher-level processes,[15] we included an abstract reasoning task to control the effects of general intelligence when analyzing the influence of *OXTR* variants on theory of mind. Finally, according to the seminal paper by Davis,[16] in which perspective taking was negatively correlated with personal distress, resilience was hypothesized to be affected by *OXTR* genotypes associated with a better performance in theory of mind, an overlapping construct with perspective taking. Therefore, we included a measure of trait resilience.

2.3 | Measures

Participants were asked to complete tasks and scales related to facial emotion recognition, theory of mind, resilience, and abstract reasoning, as described in detail below. It should be noted that the theory of mind task was available prior to the other tasks, and thus all participants performed the theory of mind task, while only subsets of the participants completed the other tasks.

2.3.1 | Facial emotion recognition

In a subset of 230 participants, affective face perception was assessed with photographs of facial expressions depicting seven emotions (happiness, sadness, anger, fear, surprise, disgust, and contempt) and neutral faces. A total of 64 facial stimuli, eight photographs for each emotion and neutral face, were selected from among the standardized photographs within the Korean Facial Expressions of Emotion set.[17] The participants were instructed to make a forced choice regarding which of the eight emotions was displayed on the screen. The details of the task have been reported previously.[17] The outcome measure was the percentage of correct responses, calculated as follows: (number of correct responses/total number of trials) × 100. In our sample, the mean percentage of correct responses was 83.6% (SD = 9.0).

2.3.2 | Theory of mind

All participants completed the Theory of Mind Picture Sequencing Task,[18,19] which examines higher-order false-belief reasoning ability. The participants were asked to arrange six cartoon stories of four cards each in a logical order. After sequencing, a questionnaire with 23 questions about the cartoon stories was administered to assess each participant's ability to infer first- to third-order false beliefs. For sequencing scores, two points were assigned to the first and last correctly arranged cards, and one point to each of the correctly sequenced middle cards. The sequencing (0-36 points) and questionnaire (0-23 points) scores were separately analyzed in terms of their relationships with *OXTR* variants. The mean scores for the sequencing and questionnaire were 33.4 (SD = 3.3) and 21.3 (SD = 1.9), respectively.

2.3.3 | Resilience

In a subset of 260 participants, the Connor-Davidson Resilience Scale (CD-RISC)[20] was used to measure the degree to which participants had confidence in their ability to appraise and cope with stressful conditions and challenges. The CD-RISC consists of 25 items, rated on a five-point Likert scale ranging from 0 (not true at all) to 4 (true nearly all of the time). The total score ranges from 0 to 100, and higher scores indicate higher resilience. The mean score of the CD-RISC in our sample was 64.6 (SD = 12.2).

2.3.4 | Abstract reasoning

The Standard Progressive Matrices (SPM)[21] was administered in a subset of 242 participants to measure their abstract reasoning ability. The SPM is comprised of 60 patterns of increasing difficulty, all of which involve completing a missing part of the pattern with a correct piece. The score for the SPM is the number of correct matches. In our sample, the mean score was 51.5 (SD = 5.4).

2.4 | SNP selection

We selected *OXTR* SNPs based on their associations with several aspects of social cognition, as documented in the literature. The SNPs were included only if they had a verified minor allele frequency higher than 0.05 in the Japanese sample from the 1000 Genomes Project database (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/). Accordingly, the following 10 variants were included in the present study: rs1042778, rs237885, rs237887, rs2268490, rs4686301, rs2268493, rs2254298, rs13316193, rs53576, and rs2268498.

2.5 | Genotyping

In a subset of 60 participants, genomic DNA was extracted from peripheral blood samples with the QuickGene-mini80 (FUJIFILM, Tokyo, Japan). For the remaining 204 participants, DNA was prepared from saliva using the Oragene DNA collection kit (DNA Genotek, Kanata, Ontario, Canada). Genotyping was performed with the SNaPShot assay (ABI PRISM SNaPShot Multiplex kit, Foster City, CA, USA) according to the manufacturer's recommendations. Analyses were performed using the Genemapper software (version 4.0; Applied Biosystems, Foster City, CA, USA).

2.6 | Statistical Analysis

Continuous variables are expressed as the mean and standard deviation. The strengths of the associations between *OXTR* variants and facial emotion recognition, theory of mind, and resilience were examined with linear regression under an additive genetic model of inheritance. All genetic analyses were adjusted for age and sex. When assessing the relationship between *OXTR* variants and theory of mind, the SPM score was included as an additional covariate in the analysis, since false-belief reasoning may require an advanced cognitive function to understand that another's point of view may differ from one's own. Therefore, the influence of *OXTR* polymorphisms on theory of mind was analyzed in the 242 participants who performed both theory of mind task and SPM. The impact of genetic variants on SPM performance was not examined. All analyses were conducted with the R software (version 3.4.3; https://www.r-project.org) and the R package SNPassoc.[22] Deviation from the Hardy-Weinberg equilibrium was tested with the exact test implemented in the SNPassoc package. Given the number of SNPs and phenotypes (facial emotion recognition, theory of mind sequencing, theory of mind questionnaire, and resilience) analyzed, statistical significance was set at $\alpha = 0.00125$ (=0.05/(10 × 4)) with the use of Bonferroni correction.

The Haploview software (version 4.2; https://www.broad.mit.edu/mpg/haploview) was used to examine the pairwise linkage disequilibrium patterns of the genotyped SNPs. Haplotype blocks were defined by the confidence interval method and the D' threshold was 0.8. The influence of the haplotype distributions on the behavioral task performance and resilience scores was analyzed by the *haplo.score* function of the R package haplo.stats.[23] All analyses were adjusted for age and sex, and the theory of mind task was additionally adjusted for the SPM scores. Permutations (n = 100 000) were performed, and statistical significance was set at a simulated *P* value of <0.05.

2.7 | Statistical power

Statistical power was examined under an additive genetic model with the Quanto software (version 1.2.4; https://biostats.usc.edu/software) at an α level of 0.00125. For facial emotion recognition, the statistical power was calculated on the basis of a positive finding reported in a previous study,[24] although this previous study examined only rs2268498. Assuming an effect size of 0.093, given that this SNP accounted for 9.3% of the variance in Melchers et al's study, the statistical power in our study was 0.93. In terms of the association between *OXTR* and theory of mind, the only published studies were conducted in children. Based on an effect size of 0.08 in a previous study,[25] the statistical power in our sample was 0.90. For trait resilience, we referred to a study on the relationship between *OXTR* variant rs53576 and psychological resources,[26] to which trait resilience may be closely related. If this variant accounted for 3.2% of the variance, as estimated by Saphire-Bernstein et al, we had a power of 0.37 to detect an association. When α was adjusted to 0.05, the statistical power for each analysis was 0.99, 0.99, and 0.83, respectively.

3 | RESULTS

3.1 | Genotyping quality control

As seen in Table 1, the genotyping call rate reached a mean value of 99.77% in our sample. No significant deviations from the

TABLE 1 Characteristics of the *OXTR* variants

SNP	Allele[a]	Chr	Position[b]	Call rate (%)	Genotype[c]	P_{HWE}*	MAF
rs1042778	G/T	3	8794545	98.5	206/52/2	0.749	0.11
rs237885	T/G	3	8795543	100	120/125/19	0.085	0.31
rs237887	G/A	3	8797042	100	79/141/44	0.170	0.43
rs2268490	C/T	3	8797085	100	75/130/59	0.902	0.47
rs4686301	C/T	3	8798586	99.6	160/95/8	0.199	0.21
rs2268493	T/C	3	8800840	100	190/67/7	0.640	0.15
rs2254298	G/A	3	8802228	100	141/97/26	0.130	0.28
rs13316193	T/C	3	8802743	100	186/71/7	1.000	0.16
rs53576	A/G	3	8804371	99.6	116/115/32	0.681	0.34
rs2268498	T/C	3	8812411	100	140/100/24	0.359	0.28

Chr, chromosome; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; SNP, single nucleotide polymorphism.
[a]Order of alleles: D/d (lowercase *d* denotes the minor allele).
[b]Information on the chromosomal position is based on GRCh37/hg19. The locations are in reference to NM_000916.3.
[c]Order of genotypes: DD/Dd/dd (lowercase *d* denotes the minor allele).
**P* values for Hardy-Weinberg equilibrium.

TABLE 2 Associations between *OXTR* variants and behavioral task performance and resilience scores

	Facial emotion		ToM sequencing[a]		ToM questionnaire[b]		Resilience	
SNP	*B* (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*
rs1042778	−1.76 (−4.52, 1.00)	0.213	0.71 (−0.21, 1.62)	0.132	−0.19 (−0.73, 0.35)	0.486	−1.50 (−4.94, 1.94)	0.393
rs237885	1.35 (−0.54, 3.24)	0.163	0.38 (−0.29, 1.05)	0.272	0.05 (−0.34, 0.44)	0.793	0.79 (−1.58, 3.16)	0.514
rs237887	2.13 (0.42, 3.84)	0.016	0.11 (−0.51, 0.73)	0.728	0.13 (−0.22, 0.49)	0.458	1.86 (−0.31, 4.03)	0.095
rs2268490	−1.43 (−3.11, 0.25)	0.096	−0.15 (−0.74, 0.43)	0.611	−0.10 (−0.44, 0.24)	0.553	−1.29 (−3.33, 0.76)	0.220
rs4686301	−0.19 (−2.36, 1.98)	0.864	0.38 (−0.37, 1.12)	0.320	0.05 (−0.38, 0.48)	0.820	−0.25 (−2.92, 2.41)	0.852
rs2268493	−0.33 (−2.58, 1.92)	0.775	0.77 (−0.02, 1.55)	0.056	0.31 (−0.14, 0.76)	0.182	0.70 (−2.14, 3.55)	0.628
rs2254298	0.18 (−1.61, 1.97)	0.843	−0.09 (−0.71, 0.52)	0.764	0.20 (−0.16, 0.55)	0.274	−3.84 (−6.00, −1.68)	<0.001
rs13316193	−0.68 (−2.90, 1.55)	0.551	0.63 (−0.15, 1.41)	0.117	0.17 (−0.28, 0.62)	0.469	1.12 (−1.69, 3.93)	0.435
rs53576	−0.45 (−2.18, 1.29)	0.616	0.56 (−0.04, 1.16)	0.067	−0.21 (−0.56, 0.14)	0.236	−0.55 (−2.71, 1.61)	0.619
rs2268498	1.66 (−0.10, 3.41)	0.066	0.05 (−0.57, 0.68)	0.869	0.39 (0.03, 0.74)	0.036	2.56 (0.36, 4.77)	0.024

B, regression coefficient; CI, confidence interval; SNP, single nucleotide polymorphism; ToM, theory of mind.
[a]Theory of mind task sequencing scores.
[b]Theory of mind task questionnaire scores.

Hardy-Weinberg equilibrium were found (all *p*s > 0.05), and minor allele frequencies were higher than 0.1 in all SNPs. Detailed descriptions are provided in Table 1.

3.2 | Single marker association analysis

For behavioral measures of social cognition, nominally significant associations of rs237887 with facial emotion recognition ($B = -2.13$, $P = 0.016$) and of rs2268498 with resilience scores ($B = 2.56$, $P = 0.024$) were found. However, as shown in Table 2, neither of these relationships remained significant after adjusting for multiple comparisons ($P = 0.00125$). Particularly, in regard to the theory of mind task, we performed a reanalysis without adjustment for SPM scores; however, the results did not change (Table S1). On analyzing resilience, we found that the SNP rs2254298 was significantly associated with the CD-RISC scores ($B = -3.84$, $P < 0.001$), with mean values increasing in the order of AA (58.3 ± 14.4), GA (63.2 ± 11.7), and GG (66.7 ± 11.6) genotypes. The descriptive statistics for the behavioral task and resilience scores according to the *OXTR* genotypes are shown in Table S2.

3.3 | Haplotype association analysis

Figure 1 shows two linkage disequilibrium blocks identified with 10 *OXTR* markers; Block 1 contained rs237887 and rs2268490, and Block 2 contained rs2268493, rs2254298, and rs13316193. We examined the haplotype distributions in these blocks and their associations with behavioral measures and resilience.

For facial emotion recognition, A-C haplotype of block 1 was significantly associated with higher scores (haplotype-specific score = 2.41, simulated $P = 0.016$). Associations between other haplotypes and facial emotion recognition were not significant. Detailed results are presented in Table 3. In terms of theory of mind, no significant relationships were identified between the task scores and the *OXTR* haplotype distributions (Tables S3 and S4). For trait resilience, as shown in Table 4, T-A-T haplotype in block 2 was significantly associated with lower CD-RISC scores (haplotype-specific score = −3.41, simulated $P < 0.001$). The impact of other *OXTR* haplotypes on resilience scores was not significant.

4 | DISCUSSION

In this study, we explored whether variations in *OXTR* affect several aspects of social phenotypes (social perception and theory of mind) and psychological resilience in healthy individuals of Korean descent. Our findings support the involvement of *OXTR* in facial emotion recognition and trait resilience, but not in false-belief reasoning.

For facial emotion recognition, we found a significant association between the A-C haplotype at rs237887-rs2268490 and the facial emotion recognition scores; participants with the A-C haplotype were more accurate in recognizing facial emotions. Previous evidence has suggested that intranasal administration of oxytocin improves facial affect recognition,[27] but the involvement of *OXTR* variants in facial emotion perception has not been consistently replicated.[24,28] The present finding lends support to the theory that *OXTR* genetic variations play roles in the recognition of facial emotional expressions. Although rs237887 and rs2268490 do not directly affect the amino acid sequence of the protein, these intronic variants may be in linkage disequilibrium with other functionally important, but unexplored, loci. To date, research on the associations of rs237887 and/or rs2268490 with social cognition and behavior has yielded mixed results. While the A allele of rs237887 is reportedly associated with increased risk for impaired facial recognition memory[28] (but see also[29]) and autism spectrum disorder,[8] it has also been linked to better perspective taking.[30] Regarding rs2268490, the C allele was found to be associated with prosocial behavior in one study,[31] while another study found that it was associated with the callous-unemotional trait.[32] These inconsistent results might be

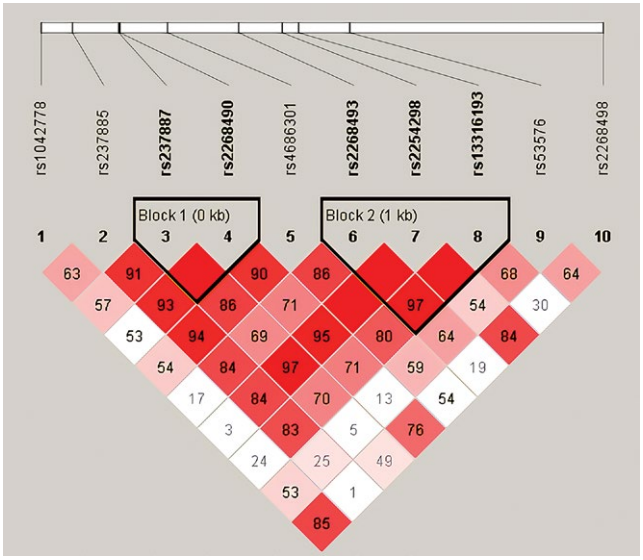

FIGURE 1 Linkage disequilibrium patterns and haplotype blocks estimated with the 10 *OXTR* markers that were examined in the present study. The numbers in squares represent the pairwise D' values as percentiles. The blank squares indicate D' values of 1

TABLE 3 The Effects of *OXTR* haplotypes on facial emotion recognition scores

Haplotype			Hap-freq[a]	Hap-score[b]	Crude P[c]	Sim P[d]
Block 1 (rs237887-rs2268490)[e]						
G	T		0.46	−1.66	0.096	0.097
G	C		0.09	−1.20	0.230	0.230
A	C		0.45	2.41	0.016	0.016
Block 2 (rs2268493-rs2254298-rs13316193)[f]						
T	G	C	0.01	−1.07	0.283	0.283
C	G	C	0.15	−0.28	0.782	0.784
T	A	T	0.27	0.20	0.842	0.842
T	G	T	0.56	0.25	0.800	0.801

[a]Estimated haplotype frequency in the 230 participants who performed the facial emotion recognition task.
[b]Haplotype-specific score.
[c]Asymptotic chi-squared P value.
[d]Simulated P value.
[e]Global-stat = 6.21, df = 2, $P = 0.045$, global simulated $P = 0.044$.
[f]Global-stat = 1.31, df = 4, $P = 0.859$, global simulated $P = 0.859$.

TABLE 4 The Effects of *OXTR* haplotypes on resilience scores

Haplotype			Hap-freq[a]	Hap-score[b]	Crude P[c]	Sim P[d]
Block 1 (rs237887-rs2268490)[e]						
G	T		0.47	−1.23	0.219	0.220
G	C		0.10	−0.60	0.549	0.552
A	C		0.43	1.67	0.095	0.095
Block 2 (rs2268493-rs2254298-rs13316193)[f]						
T	A	T	0.28	−3.41	<0.001	<0.001
C	G	C	0.15	0.56	0.574	0.575
T	G	C	0.01	0.80	0.422	0.423
T	G	T	0.56	2.54	0.011	0.010

[a]Estimated haplotype frequency in the 260 participants with a resilience scale score.
[b]Haplotype-specific score.
[c]Asymptotic chi-squared P value.
[d]Simulated P value.
[e]Global-stat = 2.87, df = 2, $P = 0.238$, global simulated $P = 0.240$.
[f]Global-stat = 12.5, df = 4, $P = 0.014$, global simulated $P = 0.014$.

explained by differences in the phenotypes of interest and/or the diverse ethnicities across study samples. To further elucidate the role of these polymorphic loci in facial emotion recognition, the underlying neural substrates and their associations with rs237887 and/or rs2268490 need to be identified.

In terms of theory of mind, no significant association was found between task performance and any of the *OXTR* variants, a finding which contrasts with the widely recognized relationship between mind-reading ability and *OXTR*. In fact, evidence from the literature has suggested that oxytocin may improve mind reading[33] and that individual differences in this ability are influenced by *OXTR* polymorphisms.[6] However, these previous studies employed the Reading the Mind in the Eyes Test,[34] which involves making inferences about what others' are thinking or feeling from viewing the eye region. As research findings have demonstrated that oxytocin enhances gaze toward the eyes,[35] it is possible that genetic variations in the oxytocin system and their effects on gaze to the eye region may have influenced performance on the Reading the Mind in the Eyes Test. By contrast, the false-belief task utilized in our study examines the ability to infer others' intentions from their behavior, which may require relatively high-level cognitive functions, including working memory and abstract reasoning. Neuroimaging studies have revealed that the temporoparietal junction and medial prefrontal cortex are particularly engaged in this mental-state reasoning process.[36] Thus far, there is limited evidence of the effects of oxytocin on these brain regions. Therefore, although speculative, the lack of an association between *OXTR* SNPs and false-belief reasoning might have resulted from the underlying neural substrates that are less likely to be influenced by *OXTR* variants. Although several previous studies also examined the relationship between *OXTR* SNPs and false-belief task performance, the results were inconsistent and participants were limited to children with mean ages varying from 4 to 7 years.[25,37,38] Hence, additional studies are needed to elucidate the role of *OXTR* variations in false-belief reasoning throughout childhood and beyond.

Our results demonstrate a dose-dependent effect of the *OXTR* variant rs2254298 on psychological resilience, as measured by a self-report questionnaire. The CD-RISC scores were highest in carriers of the GG genotype and decreased by 3.84 with a one-copy increase in the A allele, which implies that the variant A allele is associated with lower levels of resilience in this sample. Similarly, the *OXTR* haplotype containing the rs2254298 A allele was associated with lower resilience scores. Although the effect of this intronic variant on protein function has not been elucidated, previous studies have revealed that the rs2254298 A allele is associated with larger amygdala volumes,[39] as well as with enhanced amygdala activity to socially relevant face stimuli[40] and deficient deactivation of the dorsal anterior cingulate gyrus during emotion processing.[41] Considering that the amygdala and anterior cingulate gyrus are key structures in fear conditioning and extinction,[42] the observed association between the rs2254298 A allele and reduced CD-RISC scores may have been mediated by structural and functional alterations in the underlying neural correlates. Notably, the A allele of rs2254298 has also been shown to interact with mothers' depression to predict higher levels of depression and anxiety in adolescent girls,[9] which may be in line with our finding showing that this allele is associated with lower resilience, and thus increased vulnerability to psychological symptoms, in the presence of early life adversities. However, as our sample size was not large enough to have sufficient statistical power, interpretations should be made with caution. On the other hand, one study proposed that the rs2254298 A allele may confer differential susceptibility to psychiatric conditions rather than a predetermined risk of developing mental health problems, depending on the rearing conditions.[43] In that study, the author suggested that the rs2254298 A allele might yield positive results when environmental conditions are favorable. Based on this perspective, although speculative, the significant association found in our study might have been influenced by environmental factors. Since we did not obtain information on participants' early life experiences, it is difficult to determine the extent to which gene-environment interactions affected the results.

To the best of our knowledge, no study, until now, has examined the relationship between *OXTR* variants and higher-order false-belief reasoning in healthy participants, except in children. However, several caveats of our study should be noted. First, the relatively small sample size for the genetic association study may have reduced the statistical power to detect significant associations. Second, we could not control the possible confounding effects of population stratification. The considerable degree of genetic homogeneity in the Korean population[44] might have minimized the bias, but the possibility of false-positive results could not be completely eliminated. Third, as participants were restricted to adolescents and young adults, the generalizability of our results may be limited. Another limitation is that we utilized a self-report questionnaire as the only measure of resilience. Finally, environmental factors such as early life adversities were not examined, and thus widely acknowledged gene-environment interactions in the oxytocin system could not be investigated in our study.

In conclusion, we identified a significant association between the A-C haplotype at *OXTR* rs237887-rs2268490 and facial emotion perception. We also found a dose-dependent relationship between rs2254298 and a self-report measure of psychological resilience. These findings may lend further support to oxytocin's role in facial affect recognition and in moderating the effects of adverse life experiences in adolescents and young adults.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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