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Social cognition, face processing, and oxytocin receptor single nucleotide polymorphisms in typically developing children

Mylissa M. Slane[a,1,2], Laina G. Lusk[a,1], K.B. Boomer[b], Abby E. Hare[c], Margaret K. King[c], David W. Evans[a,*,1,2]

[a] Bucknell University, Department of Psychology, Program in Neuroscience, 701 Moore Avenue, Lewisburg, PA 17837, USA
[b] Bucknell University, Department of Mathematics, 701 Moore Avenue, Lewisburg, PA 17837, USA
[c] Geisinger-Bucknell Autism and Developmental Medicine Center, 120 Hamm Drive, Suite 2, Lewisburg, PA 17837, USA

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ABSTRACT

Recent research has provided evidence of a link between behavioral measures of social cognition (SC) and neural and genetic correlates. Differences in face processing and variations in the oxytocin receptor (*OXTR*) gene have been associated with SC deficits and autism spectrum disorder (ASD) traits. Much work has examined the qualitative differences between those with ASD and typically developing (TD) individuals, but very little has been done to quantify the natural variation in ASD-like traits in the typical population. The present study examines this variation in TD children using a multidimensional perspective involving behavior assessment, neural electroencephalogram (EEG) testing, and *OXTR* genotyping. Children completed a series of neurocognitive assessments, provided saliva samples for sequencing, and completed a face processing task while connected to an EEG. No clear pattern emerged for EEG covariates or genotypes for individual *OXTR* single nucleotide polymorphisms (SNPs). However, SNPs rs2254298 and rs53576 consistently interacted such that the AG/GG allele combination of these SNPs was associated with poorer performance on neurocognitive measures. These results suggest that neither SNP in isolation is risk-conferring, but rather that the combination of rs2254298(A/G) and rs53576(G/G) confers a deleterious effect on SC across several neurocognitive measures.

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1. Introduction

There is growing recognition that traits traditionally associated with neurodevelopmental disorders (NDDs) manifest as quantitative traits in the typical population (Constantino, 2011; Gillberg, 2010; Moreno-De-Luca et al., 2013). In this study, we examined quantitative behavioral and social-cognitive traits associated with NDDs and neuropsychiatric disorders (NPDs; e.g., autism spectrum disorder (ASD) and schizophrenia) in typically developing (TD) children and their parents. We correlated these quantitative traits with neural biomarkers of face processing and genetic variability in the oxytocin receptor gene (*OXTR*). Through this method, we extended the observed gene-brain-behavior links in ASD to the typical range of development, highlighting the continuities between clinical and normally distributed traits.

Social cognition (SC) is a broad, adaptive, developmental process that reflects an understanding of the actions,

* Corresponding author. Tel.: +1 570 522 9404.
E-mail address: dwevans@bucknell.edu (D.W. Evans).
[1] Present address: Geisinger-Bucknell Autism and Developmental Medicine Center, 120 Hamm Drive, Suite 2, Lewisburg, PA 17837, USA.
[2] These two authors contributed equally to this manuscript.

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emotions, and intentions of oneself and others (Brothers, 1990; Frith and Frith, 2007, 2012; Pinkham et al., 2008). Deficits and delays in SC are common in ASD, even when accounting for overall cognitive ability (Baron-Cohen et al., 1997; Brent et al., 2004; Chan et al., 2011; Klin, 2000). Persons with ASD are more likely to misinterpret mental states, use fewer internal state terms when describing events (Beaumont and Newcombe, 2006; Brent et al., 2004; Castelli et al., 2002; Chan et al., 2011; Shimoni et al., 2012), and are delayed on tasks assessing the ability to impute mental states from images of human eyes (Baron-Cohen et al., 2001a). Subjects with ASD anthropomorphize moving geometric shapes less than TD subjects, most of whom readily infer social meaning based on the movement of these shapes (Klin, 2000). These reduced abilities also exist in other disorders such as schizophrenia (Bell et al., 2010), suggesting that difficulty inferring social meaning is symptomatic of a range of NDDs and NPDs.

SC has also been linked to functional neural correlates. Face perception tasks have been robustly linked to the activation of inferior temporal brain regions, specifically, the fusiform gyrus, which is less active in individuals with ASD during face perception tasks (Schultz et al., 2000; Schultz, 2005). Event-related potential (ERP) studies reveal that relative to TD subjects, individuals with ASD often produce a delayed N170 response to faces (McPartland et al., 2004) and a faster precursor N170 response to objects (Webb et al., 2006). Individuals with ASD also exhibit a muted inversion effect, as evidenced by little or no differences in N170 latencies to upright relative to inverted faces (McPartland et al., 2004). Even in individuals with no family history of ASD, increased atypical social behaviors are associated with reduced N170 amplitudes (Hileman et al., 2011). Similarly, adults that are classified as "introverted" failed to exhibit the inversion effect, whereas "extroverted" individuals demonstrated an inversion effect (Cheung et al., 2010). These findings suggest continuity between atypical social development and typical social processes, thereby highlighting the importance of examining a broader phenotype that extends to unaffected relatives of ASD probands, as well as to the general population.

Some symptoms associated with ASD are ameliorated by administration of oxytocin. Oxytocin is a hormone that is produced by the hypothalamus and acts as a neuromodulator in the brain by activating its receptor, OXTR, in neurons (Anagnostou et al., 2014). Continuous oxytocin infusion decreases the number and severity of repetitive behaviors in adults diagnosed with ASD (Hollander et al., 2003). Intranasal administration of oxytocin increases empathizing ability in males with low levels of social functioning (Bartz et al., 2010) and increases attention paid to the eyes in typical adult males (Guastella et al., 2008). Similarly, following inhalation of oxytocin, adults with ASD exhibited increased social reciprocity and trust and increased their total looking time at facial stimuli, specifically the eyes (Andari et al., 2010). Adults with ASD also exhibited increased ability to comprehend affective speech when given an infusion of oxytocin (Hollander et al., 2007). In children with ASD, intranasal administration of oxytocin has been found to significantly improve emotion recognition on the Reading the Mind in the Eyes Test-Revised (RMET) (Guastella et al., 2010). In addition, intranasal oxytocin in children and adolescents with ASD has been shown to differentially affect brain activity in regions associated with reward and face perception, increasing activity during socially relevant judgments and decreasing activity during nonsocial judgments (Gordon et al., 2013).

While these social deficits are characteristic of ASD, it is important to note that much of the individual variation in social ability may be accounted for by subtle variations in single nucleotide polymorphisms (SNPs) within the *OXTR* gene. Given that several SNPs within *OXTR* correlate to pair-bonding in humans (Walum et al., 2012) and attachment security in infants (Chen et al., 2011), it is not surprising that they have also been implicated in ASD (Campbell et al., 2011; Jacob et al., 2007; Liu et al., 2010; Wu et al., 2005). Of the thirty SNPs identified in *OXTR*, rs53576, rs237897, rs1042778, and rs2254298 have been most consistently associated with a variety of traits linked with ASD. In addition, these SNPs are common enough to be found in TD populations, making them an ideal choice for analysis (Bookheimer, 2012). Rs53576 has been associated with the functional connectivity of the hypothalamus (Tost et al., 2010; Wang et al., 2013), differences in maternal and empathic behavior (Bakermans-Kranenburg and van IJzendoorn, 2008; Rodrigues et al., 2009), decreases in optimism, self-esteem (Saphire-Bernstein et al., 2011), positive affect, non-verbal intelligence (Lucht et al., 2009), and empathy (Rodrigues et al., 2009). Rs237897 is strongly associated with facial recognition memory in families with a single child with ASD (Skuse et al., 2014) and rs2254298 is associated with ASD (Jacob et al., 2007), depression (Costa et al., 2009), and social anxiety (Thompson et al., 2011). Positive parenting and functional responses to child stimuli in the orbitofrontal cortex, anterior cingulate cortex, and hippocampus are associated with rs1042778 (Michalska et al., 2014).

Although these SNPs have been shown to be associated with SC, the risk alleles vary due to differing study designs, including variability in measuring social behavior, focus on adults rather than children, variability in the diagnostic status of participants, and the designation of heterozygous individuals as part of the "risk" or "no risk" groups. A recent, large-scale, meta-analysis (Bakermans-Kranenburg and van IJzendoorn, 2014) found no evidence for association of rs2254298 or rs53576 with social behavior or autism, casting even more doubt on the link between these SNPs and SC. The links between *OXTR*, the brain, and behavior in SC during childhood are complex and far from unequivocal. Despite some convergence in the literature, much remains to be known about the association of *OXTR* risk alleles with SC and other ASD-associated behaviors, as well as neural function. In the present study, the genetics-brain-behavior links observed in NDDs are extended to TD children. First, we evaluated multiple ASD traits reflecting adaptive and maladaptive social behavior and repetitive behaviors using dimensional, quantitative scales and subscales that are sensitive to these traits in TD children. We then evaluate these traits relative to the neural processing of face perception and to four *OXTR* SNPs (rs2254298, rs53576, rs1042778, rs237897). We hypothesize that presence/absence of *OXTR* risk alleles and the neural processing

of face perception will predict performance on behavioral measures of SC.

2. Methods

2.1. Subjects

Sixty-six children were recruited from local public schools in rural central Pennsylvania and from the Bucknell University Message Center. Each family received monetary compensation for their participation. Experimental procedures were approved by the Bucknell University IRB. Written consent was obtained from parents and verbal assent was obtained from children. Parents completed several parent-report forms on their children using the online survey tool, Qualtrics® (Provo, Utah). These measures included a demographics form, the Social Responsiveness Scale 2 (SRS-2): School Age (Constantino and Gruber, 2012), and the Adaptive Behavior Assessment System 2nd edition ABAS 2 Parent Form: Ages 5–21 (Harrison and Oakland, 2003). The SRS-2 served as a parent-reported, quantitative measure of ASD-like traits, whereas the ABAS 2 assessed a range of adaptive behaviors.

In the lab, parents completed a paper form of the Child Behavior Checklist 4–18 (CBCL) (Achenbach and Rescorla, 2001), a parent-report checklist of maladaptive behaviors. Cognitive levels were assessed for the first three children with the Kaufman Brief Intelligence Test 2 (KBIT-2) and with the Shipley Institute of Living Scale 2 (SILS 2) (Shipley et al., 2009) for all other children. The SILS 2 is a valid and reliable measure of IQ designed to assess crystalized knowledge and fluid reasoning. Administration of the SILS 2 in this study included two sections: a vocabulary questionnaire and a series of mental rotation tasks. This measure was chosen for its brief administration time (about 25 min). Children completed a paper version of this measure in the lab. In addition, children completed the Children's RMET (Baron-Cohen et al., 2001b). In this task, they were presented with a series of pictures on the computer featuring only an individual's eyes and were asked to determine what the person is thinking or feeling by selecting one of four possible answers. Children also completed the Social Attribution Task Multiple Choice Version (SAT-MC) (Klin and Jones, 2006), a task that presents a 61 s video of three geometric shapes in dynamic movement that generally elicits anthropomorphic social attributions. This measure of theory of mind and social attribution correlates with ASD social deficits (Klin, 2000).

In order to ensure the non-clinical status of the sample, all children ($n = 5$) and parents ($n = 3$) who were taking medication for psychiatric conditions at the time of testing were removed from analysis. Additionally, any child or parent with a family history of autism or Asperger's syndrome was removed from analysis ($n = 3$). One child was removed from analysis due to an abnormally high SRS-2 score (>3 SDs above the mean). During analysis, three children who were heterozygous (A/G) for rs53576 and rs2254298 were removed from analysis due to the small sample size and insufficient power. Forty-eight children (23 female) between the ages of 6 and 15 were included in the study analysis after exclusions. The sample was largely Caucasian (95.8%). Participants were of average or above average intelligence with average scores on the SRS-2, ABAS 2 composites, and CBCL (Table 1).

Table 1
Means and standard deviations of sample characteristics.

	N	Mean (SD)
Demographic characteristics		
Parent age	24	40.79 (5.62)
Child age	48	10.04 (2.50)
IQ		
Parent verbal IQ	24	110.58 (10.30)
Child verbal IQ	48	118.71 (12.33)
Parent nonverbal IQ	24	113.42 (13.43)
Child nonverbal IQ	48	115.06 (12.16)
Parent FSIQ	24	114.50 (10.92)
Child FSIQ	48	120.46 (12.77)
Measures of ASD-traits and social functioning		
Parent SRS-2 score	24	44.67 (4.62)
Child SRS-2 score	48	46.56 (6.63)
RMET total	45	18.25 (3.59)
SAT-MC total	48	12.96 (3.63)
Measures of adaptive/maladaptive functioning		
CBCL anxious depressed	43	53.88 (5.93)
CBCL withdrawn depressed	43	53.30 (5.59)
CBCL somatic complaints	43	53.14 (4.99)
CBCL social problems	43	51.56 (2.50)
CBCL thought problems	43	52.74 (3.75)
CBCL attention problems	43	53.40 (4.73)
CBCL rule breaking	43	52.12 (3.25)
CBCL aggressive behavior	43	52.40 (3.57)
CBCL internalizing total	43	48.28 (9.58)
CBCL externalizing total	43	45.84 (8.97)
CBCL total	43	46.70 (7.91)
ABAS general adaptive composite	41	102.46 (16.24)
ABAS conceptual composite	43	103.95 (14.56)
ABAS social composite	46	107.61 (12.21)
ABAS practical composite	42	99.10 (16.17)

Note. *N*s vary due to missing/incomplete data for one or more participants or incomplete individual items required for composite calculation and/or too many "guess" indications.

2.2. Electroencephalogram (EEG)

Children were fitted with a 32 channel Ag-AgCl electrode fabric cap arranged in the international 10–20 system, grounded at site AFz (ANT, Enschede, Netherlands). Stimuli were presented on a Dell computer monitor (16 in.) and consisted of 100 images of upright and inverted faces (50 each) and 200 images of upright faces and houses (100 each) (Herrington et al., 2011). All images were presented individually in grayscale in the center of the screen, and all faces were depicted with a neutral expression. Each image was presented for 500 ms with a 1000 ms inter-stimulus interval, creating a total stimulus length of 2.50 min for the upright-inverted paradigm and 5.00 min for the houses-faces paradigm.

ERP data were analyzed with ASA (Advanced Source Analysis) version 4.7.3. Signals were recorded at a sampling rate of 512 Hz, filtered continuously with a low cutoff frequency of 0.3 and a high cutoff frequency of 30 Hz. Averaging epochs were set to −100 ms before to 250 ms after stimulus presentation and impedances were maintained below 10 kΩ. Baseline correction was applied with

a sample baseline duration of 100 ms and a 0 ms offset before event; time interval for correction was set to event duration. ASA's artifact detection removed any artifacts that were outside of the accepted range of −70 to 70 μV. DC correction was also applied. Data were analyzed using both positive and negative amplitudes and latencies of N170 occurring between 150 ms and 245 ms after stimulus presentation. Electrode sites P7 and P8 were used for analysis. To safeguard against unreliable data due to increased movement in children, an inclusion criterion of at least 50% valid events for the upright-inverted and houses-faces paradigms was established. Participants had to have at least 25/50 valid events for both upright and inverted faces and at least 50/100 valid events for both faces and houses to be included in the respective analyses. If reaching the criterion number of events required deactivation of more than five electrodes, the data were considered unreliable given that all electrodes are used as reference points to one another.

Normal or enhanced face perception is measured by larger amplitudes, and in the case of the N170, a larger amplitude is expressed by more negative values (−μV). Faster response time (shorter latencies of the N170) is also a marker of enhanced face processing, so both amplitudes and latencies are expected to predict social behavior. Conversely, images of houses elicit a slower, less negative N170 relative to images of faces in individuals with normal or enhanced face perception. Finally, images of inverted faces tend to elicit a slower but more negative N170 relative to images of upright faces. It is expected in this study that N170 responses characteristic of typical or enhanced face perception for each stimulus type will also be indicative of increased SC as measured by behavioral tasks and parent-report measures.

2.3. DNA collection and genotyping

Saliva samples were collected using Oragene DISCOVER (OGR-500) collection kits (DNA Genotek Inc., Kanata, Canada). DNA was extracted using QIAsymphony (QIAGEN, Duesseldorf, Germany) with protocol CF1000, CR2276 ID366 V1 and DSP Virus/Pathogen Midi Kit Version 1 (Ref 937055, 2013-07). The DNA was eluted in 120 μl water, and the concentration and purity ratios were assessed using the NanoDrop 2000 UV-Vis Spectrophotometer (Thermo-Scientific, Wilmington, DE). Genotyping was performed on the following SNPs: rs53576, rs237897, rs1042778, and rs2254298, using the Applied Biosystems 7500 Fast Real-time PCR System (Life Technologies Corp., Grand Island, NY; V 2.0.5) and the standard cycling protocol for the 96-well reaction plate format. Briefly, each 10 μl reaction consisted of TaqMan Genotyping Master Mix, a TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA), 10 ng of genomic DNA, and DNase-free water, leaving a minimum of 2 wells as no-template controls.

2.4. Statistical analysis

Grand averaging was conducted for all EEG data, which were then mean-centered so that each slope could be interpreted independently of the other covariates. The data were modeled using a univariate linear mixed model (LMM) controlling for within family covariance (with a compound symmetric covariance structure) with backwards elimination using an elimination criterion of $p > .200$; the repeated component was included to control for the covariance between siblings. The following dependent variables were modeled separately: SRS-2 Social Avoidance subscale score (SRS-2-SA), SRS-2 Emotion Recognition subscale score (SRS-2-ER), SRS-2 Interpersonal Relatedness subscale score (SRS-2-IR), SRS-2 Insistence on Sameness subscale score (SRS-2-IS), SRS-2 Repetitive Mannerisms subscale score (SRS-2-RM), ABAS 2 Social Composite score, CBCL Social Problems score, RMET total score, and SAT-MC total score. EEG amplitude and latency independent variables were modeled separately due to differences in scaling, so that each model began with 8 covariates: P7 and P8 minimum amplitude (or latency) for houses and for faces, and P7 and P8 minimum amplitude (or latency) for upright faces and for inverted faces. The four SNP variables were entered as factors (rs1042778, rs2254298, rs53576, rs237897) along with sex. Significance levels were adjusted by the Bonferroni method to account for multiple comparisons.

If sex was found to be significant after completion of a model, sex differences in EEG measures were examined by adding the interactions of each remaining EEG component and sex as additional covariates in the model. Modeling then continued with backwards elimination using an elimination criterion of $p > .200$. When modeling was complete, any significant interactions between EEG components and sex were reported and sex differences were examined.

During initial analysis, an interaction between rs2254298 and rs53576 was discovered for several DVs. Thus an interaction variable was created and the data were re-modeled with the interaction variable, rs237897, and rs1042778 serving as factors. If the interaction was not significant at the end of the modeling process, the data were re-modeled. The same procedure was used, but the interaction was removed and rs2254298 and rs53576 were entered as factors to allow for the expression of main effects. In order to account for a strong correlation between children's age and both SAT-MC scores ($r = .563$, $p < .001$) and RMET scores ($r = .518$, $p < .001$), age was entered as a covariate for all models involving these two measures.

2.5. Parent data

A subset of data was also collected on parents. Social behavior was assessed using the SRS-2: Adult Self-Report and IQ was assessed using the SILS 2. Saliva samples were collected and analyzed using the same methods outlined above for children. Only parents of children who were included in the child analysis were included in the adult analysis. Similar to children, any parent who was using psychotropic mediation or had a family history of autism or Asperger's Syndrome was eliminated from analysis. Additionally, three parents were removed due to missing SRS-2 data. Finally, parents with rs2254298 and rs53576 (AA/GG and AG/AG) genotypes were removed from analysis due to insufficient sample size. Parent SRS-2 and SNP data were analyzed separately from child data using similar univariate LMM methods. The following dependent variables were

modeled separately: SRS-2-SA, SRS-2-ER, SRS-2-IR, SRS-2-IS, and SRS-2-RM. The SNP variables rs237897, rs1042778, and the interaction between rs2254298 and rs53576 were entered as factors along with sex.

3. Results

3.1. OXTR SNPs

In the children, genotype frequencies ($n = 48$) for each SNP were as follows: rs1042778: TT:9, GT:28, GG:11; rs2254298: AA:0, AG:8, GG:40; rs53576: AA:4, AG:21 GG:23; rs237897: AA:11, AG:18, GG:19. No SNPs were removed due to departures from Hardy Weinberg Equilibrium (HWE) ($p < .01$). No SNPs indicated linkage disequilibrium using an r^2 cutoff of 0.8.

A significant and consistent interaction occurred between rs2254298 and rs53576. When EEG amplitude variables were entered as covariates, the combination of rs2254298(A/G) and rs53576(G/G) was associated with the worst CBCL Social Problems subscale scores, SRS-2-SA, SRS-2-ER, and SRS-2-IR scores. When EEG latency variables were entered as covariates, the presence of rs2254298(A/G) and rs53576(G/G) was associated with the worst RMET, SRS-2-SA, SRS-2-ER, and SRS-2-IR scores. In the only exceptions to the pattern, children with rs2254298(A/G) and rs53576(G/G) had the second worst scores on the RMET with amplitude covariates and the second worst scores on the SAT-MC with latency covariates. See Table 2 for significance values and Table 3 for full details on pairwise comparisons.

Children with rs2254298(A/G) and rs53576(G/G) scored significantly worse on the SRS-2-SA (amplitude and latency covariates), SRS-2-IR (amplitude covariates) and the CBCL Social Problems subscale (amplitude covariates) than children with rs2254298(G/G) and rs53576(G/G or A/G) combinations. They also scored significantly worse on the SRS-2-ER (latency covariates) than children with rs2254298(G/G) and rs53576(G/G or A/A) combinations. Similarly, children with an rs2254298(A/G) and rs53576(G/G) combination scored significantly worse on the RMET (latency covariates) than those with an rs2254298(G/G) and rs53576(A/A) combination. Finally, children with the AG/GG genotype also scored significantly worse on the SRS-2-ER (amplitude covariates) and SRS-2-IR (latency covariates) than children with an rs2254298(G/G) and rs53576(G/G) combination. Interactions are plotted in Fig. 1.

In addition to the interaction effects of rs2254298 and rs53576, a main effect emerged indicating that children with an rs2254298(A/G) combination received significantly worse scores on the SRS-2-IS (latency covariates) than those with the rs2254298(G/G) combination. Main effects also emerged for rs1042778 and rs237897. When both EEG amplitudes and latencies were entered as covariates, results were mixed, with the poorest performing genotype for rs1042778 varying between SC measures. In contrast, children with the rs237897(G/G) combination received significantly worse scores on the SRS-2-RM with both amplitude and latency EEG covariates. For full details, see Tables 2 and 4.

3.2. EEG

Whereas the genetic findings of this study – that the rs53576 and rs2254298 SNPs interact to predict adaptive and maladaptive social behavior – were clear and consistent, the EEG findings were varied and equivocal. Although nearly all of the EEG variables predicted scores on measures of social cognition, no consistent pattern emerged as to the directions of these predictions. As Table 5 indicates, approximately half of the significant EEG covariates predicted SC in the expected direction (green): increased face sensitivity in the neural measures predicted better social cognition. This pattern persisted even among the covariates with higher beta values (bold).

The most consistent pattern emerging from the EEG data involved a significant interaction between sex and three EEG amplitude covariates (upright faces at electrode P8, and inverted faces at electrodes P7 and P8) when SRS-2-IS was the dependent variable. At all three of these sites, females exhibited a stronger correlation between the EEG covariate and SRS-2-IS scores than males. In addition, the beta values for females reached significance while those for males did not. Although the direction of the relationship differed among the three EEG covariates (negative or unexpected for inverted faces at P8 and positive or expected for the others), the beta values were consistently stronger in females than in males. This suggests that the SRS-2-IS subscale, measuring an insistence on sameness and order, is predicted by the identified EEG correlates in females but not in males.

3.3. Parents

In the parents, genotype frequencies were as follows: rs1042778: TT:6, GT:13, GG:5; rs2254298: AA:0, AG:4, GG:20; rs53576: AA:3, AG:14, GG:7; rs237897: AA:6, AG:11, GG:7. Although only significant for the IR subscale ($p = .019$), all subscales of the SRS-2 (IR, SA, IS, RM, ER) showed a trend in which a genotype of AG for rs2254298 and GG for rs53576 had the highest scores. The lack of significance may be explained by the small sample size for parents ($n = 24$ overall and $n = 4$ for the AG/GG genotype in these two SNPs). However, it should be noted that the trends seen in the parent data correspond to the significant findings in the child data.

4. Discussion

The present study examined SC in TD children using multiple quantitative trait measures and several methodological approaches including parent report, performance-based tasks, neural response, and genotype analysis. We found a clear association between rs2254298, rs53576, and several measures of SC, including the CBCL Social Problems subscale, RMET, SAT-MC, and several subscales of the SRS-2 (SA, ER, and IR).

A significant and consistent interaction arose between rs53576 and rs2254298 such that children with

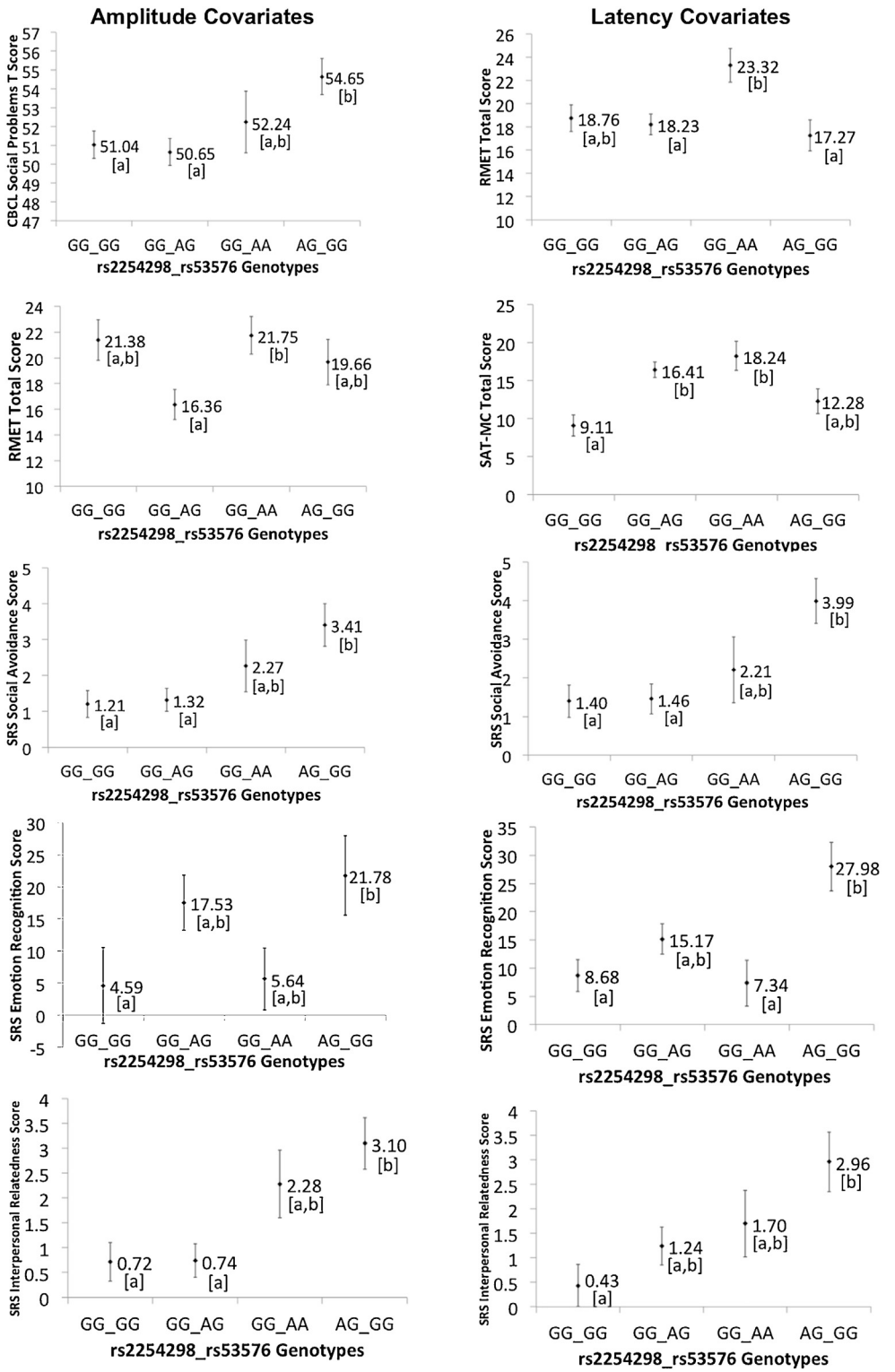

Fig. 1. Summary of significant interactions between rs53576 and rs2254298. This figure depicts the 10 interactions for which individuals with an rs2254298(A/G) and rs53576(G/G) combination received the poorest scores. The *y*-axis represents estimated marginal means for various measures of SC and the *x*-axis represents the genotype combinations for rs2254298/rs53576. Values with the same superscript are not significantly different from one another and vertical lines represent standard errors. Interactions modeled with amplitude covariates are presented on the left and interactions modeled with latency covariates are presented on the right.

Table 2
Significant SNP covariates by dependent variables.

SNP factors	Dependent variables								
	ABAS social	CBCL social	RMET total	SAT-MC	SRS-SA	SRS-ER	SRS-IR	SRS-RM	SRS-IS
Amplitude covariates									
rs1042778	.004	ns	ns	.002	.013	.010	ns	ns	ns
rs237897	ns	ns	ns	ns	ns	ns	ns	.019	ns
rs2254298*rs53576	ns	.022	.002	ns	.016	.004	.003	ns	ns
Latency covariates									
rs1042778	ns	ns	ns	.015	.003	ns	ns	ns	.008
rs2254298	ns	ns	ns	ns	ns	ns	ns	ns	.006
rs237897	ns	ns	ns	ns	ns	ns	ns	.001	ns
rs2254298*rs53576	ns	ns	.006	.012	.003	.010	.020	ns	ns

Note. Table includes *p* values for all significant SNP factors. SNPs modeled with amplitude covariates are presented in the top half of the table and SNPs modeled with latency covariates are presented in the bottom half of the table. ABAS social = Adaptive Behavior Assessment System 2 Social Composite score; CBCL social = Child Behavior Checklist Social Problems score; RMET = Reading the Mind in the Eyes Test-Revised score; SAT-MC = Social Attribution Task Multiple Choice version total score; SRS = Social Responsiveness Scale 2; SRS-SA = SRS-2 Social Avoidance score; SRS-ER = SRS-2 Emotion Recognition score; SRS-IR = SRS-2 Interpersonal Relatedness score; SRS-RM = SRS-2 Repetitive Mannerisms score; SRS-IS = SRS-2 Insistence on Sameness score. * = interaction. ns = not significant, $p > .05$.

rs2254298(A/G) and rs53576(G/G) received the worst scores (i.e. those reflecting decreased social cognition) on several measures of SC, including the CBCL Social Problems subscale, RMET (latency covariates), SRS-2-SA, SRS-2-ER, and SRS-2-IR. Several interactions were significant for both amplitude and latency (RMET, SRS-2-SA and SRS-2-IR), while the CBCL Social Problems subscale was only significant with amplitude covariates and the SAT-MC was only significant with latency covariates. In addition, children with rs2254298(A/G) and rs53576(G/G) also received the second lowest scores on the RMET (amplitude covariates) and the SAT-MC (latency covariates), indicating more ASD-like performance. Though only significant for scores on the IR subscale of the SRS-2, parents showed a similar pattern in which those with rs2254298(A/G) and rs53576(G/G) had the highest or most ASD-like scores for all subscales of the SRS-2.

These findings complement a recent meta-analysis study (Bakermans-Kranenburg and van IJzendoorn, 2014) that examined the associations between social behavior/autism status and rs2254298 or rs53576, independently, and found no significant association between any outcome measure and these SNPs across approximately 18,000 participants for rs53576 and 13,000 participants for rs2254298. Our results suggest that it is the combination and interaction of rs2254298(A/G) and rs53576(G/G) that predisposes an individual to a risk for poorer SC and increased ASD-like tendencies, not a single SNP. Thus, our results extend those reported by the meta-analysis and indicate that the combination of rs2254298(A/G) and rs53576(G/G), and not either SNP in isolation, poses the greatest risk for poorer SC. To our knowledge, the present study is the first to provide evidence of this interaction, and this finding merits further exploration on larger samples.

In addition to the interaction, a main effect emerged for rs2254298 such that the AG combination is associated with significantly more ASD-like behavior than the GG combination. Previous studies have had mixed findings regarding the "risk" allele of rs2254298. Some studies have found the A allele to be associated with ASD (Liu et al., 2010; Wu et al., 2005) and higher Autism Quotient scores in males (Chen and Johnson, 2012). Furthermore, the A allele is associated with greater levels of depression, attachment anxiety (Chen and Johnson, 2012), and exacerbated physical and social

Table 3
Estimated model adjusted means and standard errors of significant rs2254298 and rs53576 interactions.

SNP rs22554298/rs53576	CBCL social	RMET total	SAT-MC	SRS-SA	SRS-ER	SRS-IR
Amplitude covariates						
GG_GG	51.04 (0.72)^{a}	21.38 (1.58)^{ab}	ns	1.21 (0.38)^{a}	4.59 (5.93)^{a}	0.72 (0.39)^{a}
GG_AG	50.65 (0.71)^{a}	16.36 (1.17)^{a}	ns	1.32 (0.32)^{a}	17.53 (4.28)^{ab}	0.74 (0.34)^{a}
GG_AA	52.24 (1.64)^{ab}	21.75 (1.47)^{b}	ns	2.27 (0.72)^{ab}	5.64 (4.85)^{ab}	2.28 (0.68)^{ab}
AG_GG	54.65 (0.95)^{b}	19.66 (1.76)^{ab}	ns	3.41 (0.60)^{b}	21.78 (6.19)^{b}	3.10 (0.52)^{b}
Latency covariates						
GG_GG	ns	18.76 (1.15)^{ab}	9.11 (1.40)^{a}	1.40 (0.42)^{a}	8.68 (2.86)^{a}	0.43 (0.43)^{a}
GG_AG	ns	18.23 (0.89)^{a}	16.41 (1.02)^{b}	1.46 (0.39)^{a}	15.17 (2.71)^{ab}	1.24 (0.39)^{ab}
GG_AA	ns	23.32 (1.46)^{b}	18.24 (1.92)^{b}	2.21 (0.85)^{ab}	7.34 (4.08)^{a}	1.70 (0.68)^{ab}
AG_GG	ns	17.27 (1.33)^{a}	12.28 (1.62)^{ab}	3.99 (0.58)^{b}	27.98 (4.28)^{b}	2.96 (0.61)^{b}

Note. Table presents genotype estimated model adjusted means and standard errors for significant rs2254298/rs53576 interactions. Values that share the same superscript are not significantly different from one another. Interactions with amplitude covariates are presented in the top half of the table and interactions with latency covariates are presented in the bottom half of the table. CBCL social = Child Behavior Checklist Social Problems score; RMET = Reading the Mind in the Eyes Test-Revised score; SAT-MC = Social Attribution Task Multiple Choice version total score; SRS = Social Responsiveness Scale 2; SRS SA = SRS-2 Social Avoidance score; SRS-ER = SRS-2 Emotion Recognition score; SRS-IR = SRS-2 Interpersonal Relatedness score.

Table 4
SNP allele estimated model adjusted means and standard errors for significant dependent variables.

SNP	ABAS social	SAT-MC	SRS-SA	SRS-ER	SRS-RM	SRS-IS
Amplitude covariates						
rs1042778						
GG	105.58 (2.87)[a]	17.19 (1.28)[a]	2.93 (0.58)[a]	5.69 (3.02)[a]	ns	ns
GT	103.82 (2.75)[a]	13.34 (0.69)[b]	1.15 (0.27)[b]	13.85 (2.62)[b]	ns	ns
TT	115.42 (3.23)[b]	15.45 (1.31)[ab]	2.07 (0.55)[ab]	17.62 (3.80)[b]	ns	ns
rs237897						
GG	ns	ns	ns	ns	2.46 (0.39)[a]	ns
AG	ns	ns	ns	ns	0.81 (0.40)[b]	ns
AA	ns	ns	ns	ns	0.92 (0.49)[ab]	ns
Latency covariates						
rs1042778						
GG	ns	13.45 (1.16)[ab]	3.10 (0.53)[a]	ns	ns	6.07 (1.32)[ab]
GT	ns	12.27 (0.60)[a]	1.18 (0.31)[b]	ns	ns	5.51 (0.81)[a]
TT	ns	16.32 (1.20)[b]	2.52 (0.62)[ab]	ns	ns	10.57 (1.42)[b]
rs237897						
GG	ns	ns	ns	ns	2.61 (0.39)[a]	ns
AG	ns	ns	ns	ns	0.73 (0.41)[b]	ns
AA	ns	ns	ns	ns	0.41 (0.51)[b]	ns
rs2254298						
GG	ns	ns	ns	ns	ns	5.06 (0.65)[a]
AG	ns	ns	ns	ns	ns	9.71 (1.47)[b]

Note. Table presents genotype estimated model adjusted means and standard errors for significant SNP factors. Values that share the same superscript are not significantly different from one another. Interactions with amplitude covariates are presented in the top half of the table and interactions with latency covariates are presented in the bottom half of the table. ABAS Social = Adaptive Behavior Assessment System 2 Social Composite score; SAT-MC = Social Attribution Task-Multiple Choice version total score; SRS = Social Responsiveness Scale 2; SRS-SA = SRS-2 Social Avoidance score; SRS-ER = SRS-2 Emotion Recognition score; SRS-RM = SRS-2 Repetitive Mannerisms score; SRS-IS = SRS-2 Insistence on Sameness score.

anxiety in girls who experience increased early adversity (Thompson et al., 2011). However, other studies have found the G allele of rs2254298 to be associated with ASD (Jacob et al., 2007; Lerer et al., 2008) and lower empathic concern in children with schizophrenia (Montag et al., 2012). Thus, no true "risk" allele can be ascertained from the literature, but in this study the A/G genotype for rs2254298 was associated with poorer SC.

In contrast, no main effects emerged for rs53576 on the measures of SC. Other studies examining the association of rs53576 with SC have produced mixed results, with some studies suggesting that lower SC is associated with the A allele and other studies suggesting it is associated with the G allele. For example, studies have shown the A allele of rs53576 to be associated with ASD (Wu et al., 2005), lower sensitive responsiveness (Bakermans-Kranenburg and van IJzendoorn, 2008), lower positive affect (Lucht et al., 2009), lower scores on the RMET (Rodrigues et al., 2009), higher emotional suppression (Kim et al., 2011), less affiliative nonverbal cues (Kogan et al., 2011), less optimism and self-esteem (Saphire-Bernstein et al., 2011), less emotional support seeking in highly distressed Americans (Kim et al., 2010), and less trusting behavior (Krueger et al., 2012). However, other studies have shown the G allele of rs53576 to be associated with unipolar depression (Costa et al., 2009), poorer social cognitive ability (Park et al., 2010), and higher satisfaction after betrayal (Tabak et al., 2013). Here, we found no such link. More importantly, our results indicate that it is not a particular genotype for a single SNP in isolation that poses the greatest risk for poorer SC but rather the combination of rs2254298(A/G) and rs53576(G/G).

4.1. Conclusions and future directions

We have demonstrated significant associations between quantitative measures of SC and ASD-like traits, neurological measures of face perception abilities, and two *OXTR* SNPs in TD children. Through the use of a multi-dimensional approach, we have shown that behaviors and *OXTR* SNPs associated with ASD are present in TD children. Similar to previous literature, we have shown that no one genotype for any of the four SNPs sequenced can truly be designated as a risk for poorer SC in isolation. Rather we have shown that the AG/GG genotype combination for rs2254298 and rs53576 confers the greatest risk for social impairments in TD children. These findings corroborate previous work implicating these SNPs in social behavior, empathy, and social anxiety that are governed by a host of neural substrates (i.e., the hypothalamus, orbitofrontal cortex, anterior cingulum and the hippocampus; see Bakermans-Kranenburg and van IJzendoorn, 2008; Michalska et al., 2014; Rodrigues et al., 2009; Thompson et al., 2011; Tost et al., 2010; Wang et al., 2013). However, given our small sample sizes and restriction of our sample to children, the generalizability of these findings is limited. Thus, this finding will need to be replicated and expanded in future studies.

ASD is a complex, multi-faceted disorder and only through equally complex and multi-faceted approaches can we hope to understand the full nature of the disorder. The quantitative nature of our measures made it possible to detect individual differences in SC, making them useful tools for ASD research given the wide range

of abilities in both those who are diagnosed and those who are considered TD. There is a large degree of overlap between various neurodevelopmental disorders, and in many cases, there are more similarities than differences. Even the previously "distinct" genetic markers of disorders have been found to overlap within differing conditions (Moreno-De-Luca et al., 2013). Thus, given the extensive overlap between disorders neurologically, phenotypically, and genetically, it seems logical that the field should shift toward a theoretical structure that allows for the expression and identification of these similarities using the previously proposed paradigm of developmental brain dysfunction (Moreno-De-Luca et al., 2013). This concept has been proposed as an overarching framework that encompasses all neurodevelopmental disorders with various etiologies and manifestations (Moreno-De-Luca et al., 2013). The use of this broad and flexible model allows for a more comprehensive assessment of an individual's needs and the institution of a treatment plan designed to emphasize his/her strengths while improving deficits manifested not only through primary diagnoses, but through any comorbid conditions or symptoms as well.

Given that non-clinical variations of ASD exist within the typical population and are manifest in multiple domains of functioning, it is logical to move toward the direction of spectrums for neurodevelopmental disorders. If a multi-dimensional assessment technique can identify such a large degree of variability within TD individuals, it stands to reason that it could be a useful tool for the treatment of various forms of neurodevelopmental disorders when viewed through the framework of developmental brain dysfunction.

Table 5
Significant EEG covariates by dependent variables.

Cell contents: Beta (Std Err) p value	**Dependent Variables**								
EEG Amplitude Covariates	ABAS Social	CBCL Social	RMET Total	SAT-MC	SRS SA	SRS ER	SRS IR	SRS RM	SRS IS
P7 Faces Min Amp	**0.74 (0.11) .001**	ns	ns	-0.31 (0.11) .008	ns	**0.42 (0.17) .037**	-0.10 (0.04) .030	ns	ns
P8 Faces Min Amp	ns	ns	-0.37 (0.16) .028	ns	ns	ns	ns	0.11 (0.04) .021	ns
P7 Houses Min Amp	**-0.56 (0.12) .007**	ns	ns	ns	ns	ns	ns	ns	0.17 (0.08) .036
P8 Houses Min Amp	**0.74 (0.10) <.001**	ns	ns	-0.28 (0.13) .048	ns	ns	ns	ns	ns
P7 Upright Min Amp	ns	ns	ns	ns	-0.17 (0.07) .016	**-0.74 (0.25) .020**	ns	-0.20 (0.06) .005	**-0.79 (0.14) <.001**
P8 Upright Min Amp	**-0.64 (0.17) .009**	0.23 (0.10) .035	ns	0.33 (0.10) .009	ns	**0.55 (0.21) .043**	ns	ns	
Males									ns
Females									**0.67 (0.15) .001**
P7 Inverted Min Amp	**-0.58 (0.15) .010**	ns	ns	ns	ns	ns	ns	0.21 (0.07) .009	
Males									ns
Females									**0.63 (0.15) .001**
P8 Inverted Min Amp	ns	-0.02 (<0.01) .023	ns	ns	ns	ns	ns	ns	
Males									ns
Females									**-0.49 (0.15) .005**

Table 5 (*Continued*)

EEG Latency Covariates	ABAS Social	CBCL Social	RMET Total	SAT-MC	SRS SA	SRS ER	SRS IR	SRS RM	SRS IS
P7 Faces Min Lat	-0.07 (0.02) .025	0.04 (0.02) .040	0.04 (0.02) .020	ns	ns	ns	ns	ns	ns
P8 Faces Min Lat	ns	ns	ns	ns	ns	ns	ns	ns	0.10 (0.03) .008
P7 Houses Min Lat	0.21 (0.04) <.001	ns	ns	ns	ns	-0.18 (0.07) .017	ns	ns	ns
P8 Houses Min Lat	ns	ns	-0.05 (0.02) .028	ns	ns	ns	ns	0.02 (0.01) .025	ns
P7 Upright Min Lat		-0.05 (0.02) .018	ns	ns	ns	ns	ns	ns	ns
Males	-0.17 (0.43) .002								
Females	ns								
P8 Upright Min Lat	ns	ns	ns	ns	ns	ns	ns	ns	ns
P7 Inverted Min Lat	ns	ns	ns	ns	ns	ns	ns	ns	ns
P8 Inverted Min Lat	-0.12 (0.03) .004	0.01 (<0.01) .042	0.06 (0.02) .011	-0.08 (0.02) .002	ns	ns	ns	ns	ns

Note. SNPs modeled with amplitude covariates are presented in the top half of the table and SNPs modeled with latency covariates are presented in the bottom half of the table. Male and female values are reported separately for significant EEG*Sex interactions. ABAS Social = Adaptive Behavior Assessment System 2 Social Composite score; CBCL Social = Child Behavior Checklist Social Problems score; RMET = Reading the Mind in the Eyes Test-Revised total score; SAT-MC = Social Attribution Task Multiple Choice version total score; SRS = Social Responsiveness Scale 2; SRS-SA = SRS-2 Social Avoidance score; SRS-ER = SRS-2 Emotion Recognition score; SRS-IR = SRS-2 Interpersonal Relatedness score; SRS-RM = SRS-2 Repetitive Mannerisms score; SRS-IS = SRS-2 Insistence on Sameness score. * = interaction. ns = not significant, $p > .05$. Bold = beta > 0.4.

4.2. Limitations

As this study was drawn from a small geographic region, it may not be representative of the population and should be replicated in a larger sample in the future. Many of the behavioral measures relied upon parent reports, which may introduce bias. However, these parent-report measures are normed, standardized, and are assessed based on performance relative to age-matched peers, and offer an important perspective on behavioral profiles. The study also involved a relatively small sample size of 48 TD children, which became smaller when they were divided into the appropriate interaction subgroups (rs2254298/rs53576: AG/GG = 8; GG/AA = 4; GG/AG = 21; GG/GG = 15). While the sample sizes were large enough to detect differences, they warrant caution in terms of interpreting and generalizing these findings.

The participants were selected because they were considered to be TD and thus none of their scores were expected to fall within the clinical range. Despite this, we found a large degree of variation in scores on SC measures and have demonstrated that those individuals with an rs2254298(A/G) and rs53576(G/G) combination received the lowest scores on four unique (6 total when the SRS-2 subscales are considered separately) measures of SC. These children are not at risk for developing autism or other social problems, but through the use of quantitative measures sensitive enough to detect individual differences, we have demonstrated that these children exhibit poorer SC phenotypes than their peers. It is important to note, however, that the models linking cortical function during face perception tasks to other measures of SC produced mixed results, possibly owing to the relatively small sample size. But it may also be that the mixed findings are due to real differences in the clinical manifestation of ASD and the milder range of social deficits that are observed in the general population. Thus, while we advocate a quantitative approach, more research is needed to examine the continuities and discontinuities in the clinical presentation of ASD and the normal range of ASD-like behaviors found in non-clinical populations.

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Conflicts of interest statement

We declare no conflicts of interest for this work.

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