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The association between 2D:4D ratio and cognitive empathy is contingent on a common polymorphism in the oxytocin receptor gene (*OXTR* rs53576)

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Abstract Both testosterone and oxytocin influence an individual's accuracy in inferring another's feelings and emotions. Fetal testosterone, and the second-to-forth digit ratio (2D:4D) as its proxy, plays a role in social cognitive development, often by attenuating socio-affective skill. Conversely, oxytocin generally facilitates socio-affiliative and empathic cognition and behavior. A common polymorphism in the oxytocin receptor gene, *OXTR* rs53576, has been repeatedly linked with psychosocial competence, including empathy, with individuals homozygous for the G allele typically characterized by enhanced socio-cognitive skills compared to A allele carriers. We examined the role of oxytocin and testosterone in collectively contributing to individual differences in cognitive empathy as measured by Baron-Cohen's ''Reading the Mind in the Eyes'' task (RMET). Findings are based on a large cohort of male and female students ($N = 1463$) of Han Chinese ethnicity. In line with existing literature, women outperformed men in the RMET. Men showed significantly lower 2D:4D ratio compared to women, indicating higher exposure to testosterone during the prenatal period. Interestingly, variation in the *OXTR* gene was found to interact with 2D:4D to predict men's (but not

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women's) RMET performance. Among men with GG allelic variation, those with low fetal testosterone performed better on the RMET, compared to men with GG and high fetal testosterone, suggesting greater identification of another's emotional state. Taken together, our data lend unique support to the mutual influence of the oxytocin and testosterone systems in shaping core aspect of human social cognition early in development, further suggesting that this effect is gender-specific.

1. Introduction

Humans are fundamentally social creatures, highly motivated to be with others and to form interpersonal bonds and social structures. In these contexts, the ability to infer another's feelings and emotional states is considered crucial (Frith and Frith, 1999). Both the androgen hormone testosterone and the neuropeptide oxytocin have been identified as markers for the core neuroendocrinological systems underlying our ability to understand others' emotional states, albeit in opposing ways (Bos et al., 2012; Domes et al., 2007; Hermans et al., 2006). Testosterone preprograms the brain during early development (Auyeung et al., 2013), and that programming affects socio-affective adeptness (Auyeung et al., 2009; Baron-Cohen, 2002). The involvement of the oxytocinergic system in supporting behavior, affective states, and cognitions that serve as building blocks of human socio-affiliative and empathic abilities has also been established (Ebstein et al., 2012; Feldman, 2012). Despite mounting evidence linking each of these systems to social cognition, current attempts to test their mutual influence in this respect have been limited.

Fetal testosterone is associated with an established morphological marker that can be indexed after birth: the length ratio of the right hand's second to fourth finger (2D:4D). Males on average have a significantly lower 2D:4D ratio on their right hand and fetal testosterone is thought to underlie this sex difference (Hönekopp et al., 2007; Manning et al., 2000). More so, fetal testosterone is shown to undermine the effect that exogenous testosterone has on diminishing women's cognitive empathy ability (Van Honk et al., 2011). Specifically, females with lower 2D:4D (i.e., higher early testosterone exposure) showed degraded performance on the ''Reading the Mind in the Eyes'' task (RMET), a behavioral paradigm that serves as a proxy of cognitive empathy in humans (Baron-Cohen et al., 2001).

The oxytocinergic system has also been the focus of intense research in recent years, given its role in social motivation and socio-cognitive aptitudes in both men and women (Gordon et al., 2011; McCall and Singer, 2012; Solomon et al., 2014), although often in a sexually-dimorphic manner (Apter-Levi et al., 2013; Carter, 2007; Weisman et al., 2015). Interestingly, the oxytocinergic system is a core mechanism underlying social and affiliative behaviors, including parental care, attachment relationships, and trusting behaviors (Feldman, 2007; Rilling, 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012; Weisman et al., 2012a), mediated in part by its facilitation of the ability to infer the mental state of others (Churchland and Winkielman, 2012), or by enhancing brain activity and gaze duration towards socially meaningful stimuli (Domes et al., 2014; Auyeung et al., 2015).

To examine the role of the brain oxytonergic system in social cognition, many investigations have employed a neurogenetic strategy based on the considerable heritability of the human social repertoire (e.g., Chen et al., 2011). The oxytocin receptor gene (*OXTR*) has emerged as a particularly interesting candidate in this respect. In humans, *OXTR* gene is located on chromosome 3p25, spans 17 kb, contains four exons and three introns (Inoue et al., 1994), and encodes a 389-aa polypeptide with seven transmembrane domains belonging to the class I G-protein-coupled receptor family (Gimpl and Fahrenholz, 2001). Most interestingly, common variation in one *OXTR* single nucleotide polymorphism (SNP), rs53576 G/A, has been consistently associated with individual differences in a range of socio-emotional traits and social cognition abilities (Chen et al., 2011; Lerer et al., 2008; Saphire-Bernstein et al., 2011; Smith et al., 2014; Tost et al., 2010; Wang et al., 2014). The majority of these studies suggest that individuals who are homozygous for the G allele of rs53576 (i.e., GG genotype) are characterized by increased social proficiency and enhanced empathic accuracy or emptional empathy relative to individuals with one or two copies of the A allele (Bakermans-Kranenburg and van Ijzendoorn, 2008; Bradley et al., 2013; Lucht et al., 2013; Uzefovsky et al., 2015).

For example, compared to A allele carriers, GG individuals show greater levels of empathic concern after being presented with a social interaction containing high levels of individual distress and apparent physical pain (Smith et al., 2014). In addition, mothers who carry an A-allele demonstrate lower maternal sensitivity to their child behavior relative to G-allele homozygotes (Bakermans-Kranenburg and van Ijzendoorn, 2008). GG individuals outperformed A allele carriers on the RMET (Rodrigues et al., 2009). Finally, variation in the *OXTR* rs53576 predicts individual differences in structure and function of brain regions associated with social cognitive processes (Tost et al., 2010).

Taken together, the available findings strengthen a provisional role for *OXTR* rs53576 in promoting human social cognition and, particularly, empathic abilities in both men and women. However, complex constructs such as empathy surely engage many neurochemical pathways. The oxytocin receptor likely works in concert with a number of neurobiological systems (Bos et al., 2012; Mokkonen and Crespi, 2015). Interestingly, emerging literature suggests that an interaction between the oxytocin and the testosterone systems contributes to either hypo- or hyper-socio-cognitive manifestations, displays which are commonly evident in

brain disorders such as autism and schizophrenia (Crespi, 2015).

Whereas the exact physiological mechanism by which oxytocin and testosterone ''work together'' to support these specific configurations in humans is yet to be found, indications for a ''cross-talk'' between these systems is grounded in animal research. For example, increased oxytocin binding in the hypothalamus was shown to be mediated by estradiol and testosterone in rats (Tribollet et al., 1990), and oxytocin- and oxytocin-agonist were found to stimulate testosterone production in Leydig cells isolated from the testis of male rats (Frayne and Nicholson, 1995).

In humans, Gossen et al. (2012) showed that exogenous administration of oxytocin increased circulating (plasma) testosterone levels in young men, arguably for the purpose of increasing sexual receptivity. Similarly, intranasal oxytocin has been reported to shift the individual's focus from self to group-serving cognition and decision-making as a function of fetal testosterone exposure (Kret and De Dreu, 2013). Specifically, when administered oxytocin versus placebo, men with low fetal testosterone included low-threat targets in their group more and high-threat targets moderately less. Individuals with high testosterone exposure in uterus, however, included high-threat targets more, and low-threat targets less when given oxytocin vs. placebo (Kret and De Dreu, 2013). Recently, we also showed that oxytocin administration altered father's salivary testosterone secretion during dyadic interaction with his own infant, and that this oxytocin-induced change in testosterone correlated with father—child dyadic behaviors, including positive effect, social gaze, touch, and vocal synchrony (Weisman et al., 2014).

These initial findings prompted us to further examine the role of oxytocin and testosterone in collectively contributing to individual differences in empathic ability. Specifically, we genotyped healthy Han Chinese university subjects for the *OXTR* SNP rs53576, measured subjects' right-hand 2D:4D, and assessed participants' cognitive empathy with the RMET. We hypothesized that GG allele carriers will exhibit higher cognitive empathy relative to A-allele carriers. More so, given emerging evidence for the interaction between the two systems, we expected that participants with the GG genotype and low fetal testosterone will show heightened cognitive empathy as compared to A-allele carriers with high fetal testosterone exposure.

2. Methods

One thousand four-hundred sixty three (1463) Han Chinese undergraduate students (55.6% females) at the National University of Singapore were enrolled in the study (mean age, 20.86 y; range, 18—28 y). Subjects had no self-reported history of psychiatric disorders or neurological or endocrine abnormalities, and used no medication other than contraceptive agents. The Institutional Review Board at the National University of Singapore approved the protocol of the study.

Subjects arrived at the lab according to pre-determined schedule to take part in the experiment. Visits were conducted for each subject privately, and although participants' level of English proficiency was not directly assessed, the ads publishing the study across campus were in English and subjects confirmed that they can take part in the study before starting the experiment. Adding to that, English is the official language in Singapore, and is vastly used among the local population on the island.

A computerized-version of the RMET was employed to measure variation in the ability to infer other people's mental states from the eye region of the face (Baron-Cohen et al., 2001). Of the initial cohort, the performance of 1453 subjects in the task was adequately obtained (10 subjects were automatically omitted from further analysis due to failure to record their data [less than 1% of the entire cohort]). Subjects were seated in front of a screen in a one-by-one manner and were asked to view 36 pictures of the eye region from different faces and selected one of four words (in English) that described a possible feeling or thought this person might have. Mean RMET score (% correct) for the entire sample was 71.85 (SD = 12.04, Range 13.89—97.22), and a Median of 72.22. The distribution was nearly normal with Skewness = —.97 and Kurtosis = 1.86 (Figure 1a). Given that the RMET was initially developed to test social cognition also among subjects with developmental disorders, its use of verbal descriptors is minimal and is targeting the very basic common ground, especially for typically developed individuals.

Digit ratio was adequately measured from a scan of the right hand of 1376 subjects. Digit ratio of 87 subjects was not adequately obtained mostly due to technical issues which result a drop-out of ∼5% of the initial cohort. Lengths of the second and fourth digits were measured from the ventral proximal crease of the digit to the fingertip using AutoMetric, version 2.2. When there was a band of creases at the base of the digit, measurement was taken from the most proximal crease. This was carried out by two research assistants who were trained as raters, and who remained blind to the purpose and hypotheses of the study. The 2D:4D ratios measured by the two raters were highly correlated (Pearson $r = 86$; $P < .001$), and the two measures were therefore averaged to one score. Males' median 2D:4D was .9517, and females' median 2D:4D was .9687 (Figure 1b).

Buccal epithelial cells were collected in mouthwash samples, and DNA was isolated after a standard salting out method, using the Masterpure Isolation kit (Epicentre). Genotyping of *OXTR* rs53576 was performed by 5′-nuclease assay (TaqMan SNP Genotyping Assay). PCR was conducted with Hot Start Plus DNA polymerase and Q-solution (Qiagen) in a Bio-Rad C1000 machine with a CFX96 fluorescence reading module.

2.1. Statistical analysis

First, independent t-tests and chi-square (cross-tabulation), and ANOVA analyses were used to examine gender differences in 2D:4D ratio, RMET performance, and *OXTR* genotypes. Next, independent *t*-tests were computed to check for differences in RMET score and 2D:4D ratio between homozygotes G and A-allele carriers. A dichotomous variable depicting high/low fetal testosterone (Van Honk et al., 2012) was calculated based on the median split of 2D:4D ratio of males and females, separately. A three-way interaction of Gender X high/low fetal testosterone X *OXTR* rs53576

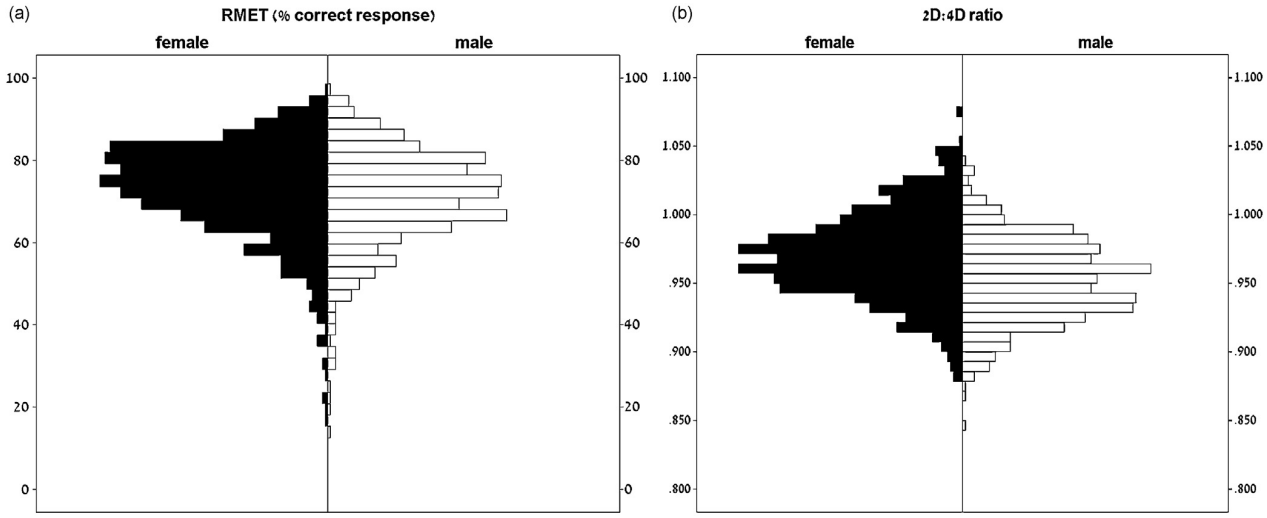

Figure 1 Graphic illustration of the distribution of RMET performance (panel *a*) and 2D:4D ratio (panel *b*) in males and females of Han Chinese ethnicity.

genotype was tested using Analysis of Variance (ANOVA). Further analysis included the stratification of the cohort by gender, in order to test a two-way interaction *of OXTR* genotype and high/low 2D:4D ratio. Post-hoc Bonferroni comparisons are specified when relevant, alongside effect sizes that better resembles the robustness of the findings reported.

3. Results

First, we examined differences between men and women with regard to performance (i.e., % of correct responses) on the RMET. As expected, women outperformed men in the task ($t_{(1,451)} = 3.44$, $P = .001$, Cohen's $d = .182$; see Table 1). The average of correct answers for males and females was 70.64% and 72.82%, respectively, paralleling the findings reported in other studies with healthy adults of European/Caucasian ethnicity (Domes et al., 2007; Vellante et al., 2013). This suggests that ethnicity (Asian background and culture, in this study) does not bias subjects' performance in the task, compared to the performance of same-age adults of different ethnic background.

Next, gender differences in 2D:4D ratio were assessed. In accordance with the existing literature, men showed significantly lower 2D:4D ratio ($n = 613$, mean = .9518) as compared to women ($n = 763$, mean = .9687), indicating higher exposure to testosterone/steroids during the prenatal period ($t_{(1,374)} = 10.85$, $P > .001$, Cohen's $d = .613$). Males in the high fetal testosterone group had mean score of .9271 (ranging between .850 and .952), and males in the low testosterone group had mean score of .9764 (range: .952—1.036). Females in the high testosterone group had mean score of .9431 (range: .880—.966), and females in the low testosterone group had mean score of .9935 (range: .966—1.077). 2D:4D was found to distribute normally in males (Skewness = —.02, Kurtosis = —.15) and in females (Skewness = .09, Kurtosis = .09). See Figure 1b for graphic illustration.

The impact of 2D:4D ratio on RMET performance across the entire sample was tested using independent t-test comparisons. No difference between high/low 2D:4D groups was found across the entire sample (high/low 2D:4D RMET score: 71.67 vs. 71.99, respectively, $P = ns$), or when the sample was stratified according to gender ($Ps = ns$).

The *OXTR* rs53576 was successfully genotyped in 1456 subjects. The distribution of genotypes for *OXTR* was 170 GGs (11.7%), 674 AGs (46.3%), and 612 AAs (42.0%). The A-allele bias is in line with previous reports of the variation in this gene in healthy Chinese Han population (Wang et al., 2014; Wu et al., 2005), and American-Asians of other or non-specified ethnicity (Kim et al., 2011, 2010; Saphire-Bernstein et al., 2011; Sasaki et al., 2011). As expected, the frequency of the A-allele in our sample was much higher than that found in Caucasian populations (Kim et al., 2010; Saphire-Bernstein et al., 2011). Neither the allele nor the genotype frequencies differed between males and females (see Table 1).

We next analyzed the impact of the *OXTR* SNP rs53576 genotype (GG, AG, AA) on RMET performance across all subjects (Table 2). Univariate ANOVA revealed a main effect for genotype, $F_{(2,1443)} = 3.21$, $P < .05$; $\text{Eta}^2 = .004$, and Tukey post hoc test showed that individuals GG homozygote (Mean = 73.94, $SD = 10.95$) scored higher on the RMET as compared to individuals with either AG or AA genotype (Mean = 71.33, $SD = 12.12$, and, Mean = 71.76, $SD = 12.14$, respectively). Based on these findings and previous literature, we stratified subjects for GG vs. A-allele carriers (Rodrigues et al., 2009). Individuals homozygous for GG showed significantly higher scores on the RMET ($t_{(1,447)} = 2.55$, $P = .011$, Cohen's $d = .214$), as compared to A-allele carriers (Figure 2a).

Further analysis conducted for men and women separately showed a difference between GG and AA/AG genotypes only for men ($t_{(637)} = 2.36$, $P = .018$, Cohen's $d = .321$; Figure 2b), albeit the pattern in women echoed that in men but did not reach statistical significance ($t_{(807)} = 1.22$,

Table 1 RMET score, 2D:4D ratio, and *OXTR* rs53576 genotypes in males and females 1b.

	n	Male	*n*	Female	*P*
RMET	644	70.64 (12.30) 809	72.83 (11.74)	.001[a]	
Mean 2D:4D	613	.9517 (.03) 763	.9701 (.03)	.000[a]	
G/G (% of 170)	69	40.58%	101	59.42%	*n.s.*[b]
A/G (% of 674)	303	44.95%	371	55.05%	*n.s.*[b]
A/A (% of 612)	271	44.28%	341	55.72%	*n.s.*[b]

Mean (SD), RMET: Read the Mind in the Eyes Task (percentage correct responses).
[a] Independent *t*-tests.
[b] Chi-square.

Table 2 RMET score stratified by *OXTR* rs53576 G/G vs. A-allele carriers and gender.

RMET	*n*	G/G genotype	*n*	A-allele carriers	*P*[a]
All subjects	169	74.03 (11.14)	1277	71.53 (12.13)	.011
Male	69	73.84 (10.18)	570	70.18 (12.50)	.018
Female	100	74.15 (11.80)	707	72.63 (11.73)	.220

Mean (SD), RMET: Read the Mind in the Eyes Task (% correct responses).
[a] Independent *t*-tests.

P = *ns*). We further tested the 'heterozygous disadvantage' model by grouping AA and GG together and comparing them to AG in terms of RMET performance. No difference emerged when the analysis was conducted for the entire sample (AA/GG: 72.23% accuracy (SD = 11.92) vs. AG: 71.33% accuracy (SD = 12.12); $t_{(1,444)} = 1.42$, *P* = *ns*), or when stratifying the sample by gender (*Ps* = *ns*).

Finally, the mutual influence of Gender, *OXTR* rs53576 genotype (GG vs. AG/AA), and 2D:4D in respect to RMET performance was tested. The ANOVA revealed a trend towards a three-way interaction ($F_{(1,1362)} = 2.87$, *P* < .10, $Eta^2 = .002$). Gender by OXTR genotype was not shown in this specific analysis ($F_{(1,1362)} < 1$, *P* = *ns*). Based on existing literature, we further stratified the sample according to participants' gender. A two-way interaction of OXTR and 2D:4D emerged for men only ($F_{(1,600)} = 4.01$, *P* < .05, $Eta^2 = .007$) but not for women ($F_{(1,762)} < 1$, *P* = *ns*), suggesting that the *OXTR* by 2D:4D interaction is sex-specific (Figure 3). Among men with GG allelic variation, those with low fetal testosterone performed better on the RMET, compared to men with GG and high fetal testosterone ($t_{(61)} = 2.40$, *P* = .019, Cohen's *d* = .594; Table 3). No difference was found between high/low fetal testosterone among men A-allele carriers (*P* = *ns*).

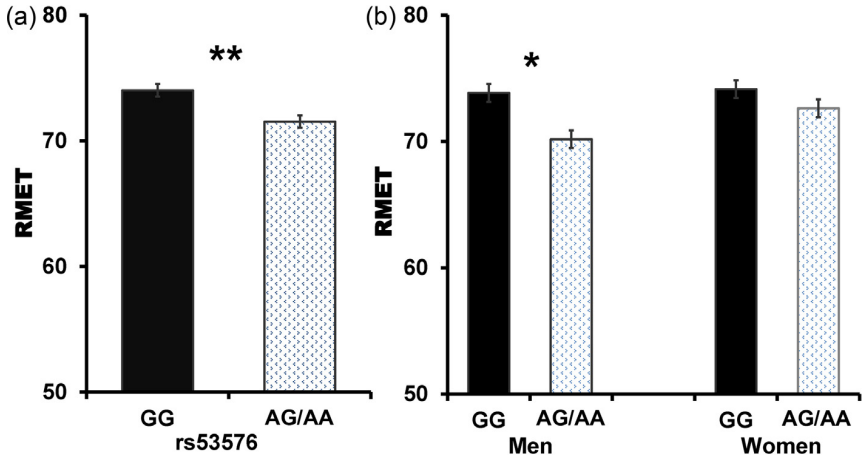

Figure 2 *OXTR* rs53576 polymorphism relates to behavioral measure of empathy. Individuals of Han Chinese ethnicity (regardless gender) with the GG genotype perform better in a task that measures cognitive empathy than individuals with the AG/AA genotypes, as measured by the ''Reading the Mind in the Eyes'' Test (panel *a*); When dividing sample according to gender, significant difference emerge in men, whereas women show a trend in the same direction (panel *b*).Error bars represent standard error of the mean. $^{*}P < .05$, $^{**}P = .01$.

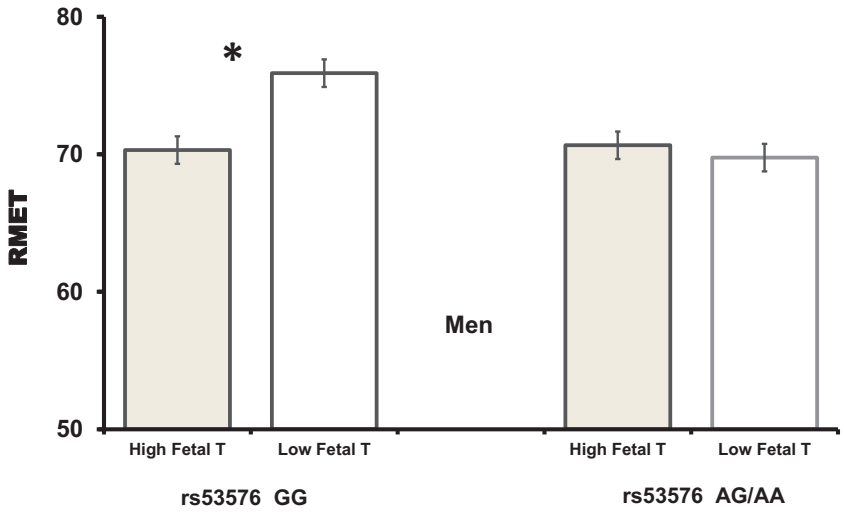

Figure 3 The association between 2D:4D and cognitive empathy is contingent on a common polymorphism in the oxytocin receptor gene. *OXTR* rs53576 genotype moderates the association between 2D:4D ratio and performance in the cognitive empathy task in men, but not in women. Error bars represent standard error of the mean. $^{*}P < .05$.

Table 3 Males' RMET score stratified by *OXTR* rs53576 G/G vs. A-allele carriers and low/high testosterone exposure.

RMET	*n*	G/G genotype	*n*	A-allele carriers	*P*[a]
Low fetal T	31	75.90 (8.19)	272	69.76 (12.10)	.018
High fetal T	32	70.31 (10.08)	269	70.66 (12.79)	.220

Mean (SD), RMET: Read the Mind in the Eyes Task (percentage correct responses), T—testosterone.
[a] Independent *t*-tests.

4. Discussion

To the best of our knowledge, this is the first study to report a moderation effect between a common polymorphism in the oxytocin receptor gene and a biomarker of early testosterone exposure with regard to social cognition in humans. We have shown that the effect of *OXTR* SNP rs53576 on men's ability to infer emotions, intentions, and other mental states from viewing the eye region of the face is significantly greater in male subjects characterized by higher 2D:4D ratios. The current findings also indicate that this effect of the two endocrine systems, oxytocin and testosterone, is sexually dimorphic.

Higher 2D:4D ratio is thought to serve as a rough measure of fetal testosterone exposure, and likely reflects the steroidogenic environment during early embryonic development as opposed to testosterone alone (Lutchmaya et al., 2002). Interestingly, the androgen theory of autism proposes that fetal programming of the brain negatively affects social intelligence (Baron-Cohen, 2002). Both cognitive empathy deficits typically seen in autism, and the male-bias of autism, provide indirect support for the theory. Recently, Baron-Cohen and colleagues reported that levels of other steroids besides testosterone, such as progesterone, 17α-hydroxy-progesterone, and androstenedione are significantly higher in individuals diagnosed with autism (Baron-Cohen et al., 2015), further substantiating the role for steroid hormones in early fetal brain development. Nevertheless, some doubt has been raised over the sensitivity of 2D:4D ratio as a marker for individual differences in prenatal androgen exposure (Berenbaum et al., 2009). Certainly there is variance in 2D:4D ratio that cannot be attributed to prenatal testosterone alone, and sex or certain phenotypes cannot be predicted from one's digit ratio (Breedlove, 2010; Hönekopp et al., 2007). Yet, 2D:4D ratio has proven useful for predicting human behavior when comparing between groups, and is still considered an established and non-invasive marker for assessing individual differences in prenatal androgen exposure (Breedlove, 2010; Hönekopp et al., 2007; Manning et al., 2000).

Our findings likely explain the lack of direct relationship between 2D:4D and cognitive empathy in adults reported to date (Sapienza et al., 2009; Van Honk et al., 2011). The relationship between digit ratio and RMET is clarified only when subjects are stratified by gender and oxytocin receptor genotype and hence the value of a neurogenetic approaches in revealing underlying neurochemical relationships at the system level.

Socio-cognitive skills are arguably heritable in the general population (Hughes and Cutting, 1999; Scourfield et al., 1999), implying that individual differences in social aptitude may be strongly influenced by corresponding differences in genetic variability (Meyer-Lindenberg et al., 2011; but see also Knafo et al., 2008 for findings that suggest a balanced contribution of genetic background and environmental factors to one's disposition towards empathy). The

present study adds to existing literature which draws a link between allelic variation in the *OXTR* SNP rs53576 and subjective differences in pro-social capabilities (Lucht et al., 2013; Saphire-Bernstein et al., 2011; Tost et al., 2010; Uzefovsky et al., 2015). Studies that report of associations between the functioning of the oxytocinergic system and socio-emotional competencies in humans continue to emerge—both in typically-developing individuals as well as in samples characterized by sub-optimal social functioning (Parker et al., 2014; Skuse et al., 2014; Weisman et al., 2015).

In addition, the finding that Han Chinese individuals with *OXTR* rs53576 GG genotype perform better on the RMET test compared to A-allele carriers (regardless of gender) complements a recent study in Caucasian men and women (Rodrigues et al., 2009). The similar pattern exhibited across Caucasians and Han Chinese populations strengthens the reliability and generalizability of the findings reported in both studies. Interestingly, cross-cultural associations between *OXTR* polymorphism and socio-cognitive abilities have been identified in several studies, including those assessing face recognition memory (Skuse and Gallagher, 2009), emotional support seeking (Chen et al., 2011), and emotion regulation strategies (Kim et al., 2011) in healthy and affected (e.g., autistic) individuals (Egawa et al., 2013; Slane et al., 2014). The results of the current study add to this ''cross-borders'' effect of *OXTR* polymorphisms on human social intelligence, by showing that allelic variation in this specific SNP is linked with social cognition in various societies of different ethnic background. Future studies that replicate the current findings in Han Chinese as well other populations across the globe are encouraged. We also suggest that a pathway approach including gene set analysis, as we have shown in a recent investigation (Set et al., 2014), will be an important next step in characterizing the human social brain at the molecular level.

Although several studies have reported associations between the rs53576 G allele and pro-social repertoire in humans, some studies have either failed to show a relationship between rs53576 genotype and social phenotypes (Apicella et al., 2010; Tabak et al., 2013), or actually reported an opposite pattern (Costa et al., 2009). While the debate about *OXTR* being the ''sociability gene'' continues (Bakermans-Kranenburg and van Ijzendoorn, 2013), its role as a central component underlying human social cognition has been adequately established.

Recently, It has been proposed that research on the implications of genetic variation in *OXTR* would benefit from considering environmental experiences and examine the association between *OXTR* and social repertoire in the context of gene-environment interaction (Tabak, 2013). Brüne (2012) has advocated for a ''differential susceptibility'' approach in explaining the link between *OXTR* and psycho-social phenotypes (Brüne, 2012), stating that specific genetic variation can be associated with either favorable or sub-optimal outcomes depending on the quality of early environmental experiences. Although the findings reported here support the dominant paradigm in the field (i.e., G homozygotes as the favorable allelic variation), we would like to take Brune's idea one step further, proposing that the relationship between oxytocin circuitry and social repertoire is often shaped by early experiences, but that the latter should not be confined to the social/environmental contexts, but be more broadly defined to include the individual's early *neuro-hormonal* environment, such as the one reflected from 2D:4D ratio marker of fetal testosterone exposure.

That being said, the considerable heritability of 2D:4D ratio (Voracek and Dressler, 2009, 2007) suggests the intriguing notion that the neuro-hormonal milieu is itself partially determined by genes. In addition, the possibility that an interaction between two or more *OXTR* SNPs will better explain variation in social cognition is gaining strength (Slane et al., 2014). Other studies suggest that different segments of the oxytocin system — including epigenetic/methylation processes, genetic polymorphisms, and circulating/peripheral levels — also take part in shaping an individual's social—emotional competence, behavioral responses and neuronal reactivity towards socially-meaningful stimuli (Puglia et al., 2015; Ziegler et al., 2015; Weisman et al., 2013a,b, 2012b), either in a idiosyncratically manner, or in conjunction with one another, or as an interaction with an individual's early life experiences (Cecil et al., 2014; Weisman and Feldman, 2013; Apter-Levy et al., 2013; Feldman et al., 2013).

To conclude, our data using a neurogenetic approach lend unique support for the mutual influence of the oxytocin and testosterone systems in shaping human social cognition early in development. Future studies should look at the interaction between these and other potential biomarkers in order to characterize their underlying contribution to individual variation in socio-cognitive dispositions (Bos et al., 2012; Crespi, 2015). Further investigations of the joint behavioral actions of the oxytocinergic and androgen systems are expected to contribute to a deeper understanding of neurodevelopmental disorders that are characterized by skewed and maladaptive social functioning, such as autism.

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Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Drs. Ebstein and Weisman have full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Authors Ebstein,

Chew, Weisman, Monhakov, Chong, and Lu designed, performed the research, and/or conducted the statistical analysis; and Authors Weisman, Ebstein, Pelphrey, Leckman, and Feldman took part in writing and revising the manuscript.

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