



Genetically based correlates of serum oxytocin and testosterone in autism and schizotypy



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ABSTRACT

The hormones oxytocin and testosterone have been implicated in autism spectrum and schizophrenia-spectrum cognition and disorders, but their roles in mediating these psychological phenotypes remain largely unknown. We genotyped a large set of healthy individuals for loci that represent established genetic indicators of serum testosterone and oxytocin levels, and tested for associations of these genetic indices of hormone levels with self-report measures of autistic and schizotypal cognition. A low genetic index of testosterone, a high genetic index of oxytocin, and/or a low ratio of testosterone to oxytocin indices were positively correlated with high imagination (by the Autism Quotient) and high positive and total schizotypy (by the Schizotypal Personality Questionnaire). The genetic indices for oxytocin, and testosterone relative to oxytocin, also showed significant correlations with a metric of positive schizotypy relative to autism, implicating higher oxytocin and lower testosterone in increased positively-schizotypal traits combined with decreased autism-associated traits. These results link genetic indicators of serum hormone levels with measures of schizotypy and autism among healthy individuals.

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1. Introduction

Autism and schizophrenia are primarily defined by alterations to aspects of human social cognition, affect and behavior. These disorders represent paradigmatic psychiatric conditions, but their phenotypes grade continuously into those of psychologically healthy populations (Baron-Cohen, Weelwright, Skinner, Martin, & Clubley, 2001; Raine & Benishay, 1995; van Os, 2009). Both autism and schizophrenia have been associated with variation in levels of two hormones, testosterone and oxytocin, that modulate aspects of human sociality. For example, higher testosterone levels have been associated with increased liability to autism through some combination of prenatal and postnatal effects (Auyeung, Lombardo, & Baron-Cohen, 2013), and lower testosterone levels have been linked with symptoms of schizophrenia in multiple previous studies (Markham, 2012). Despite such findings, the roles of oxytocin and testosterone in mediating social cognition along the autism spectrum, and the schizophrenia spectrum, remain incompletely understood, especially with regard to their joint effects and how they contribute to cognitive alterations in these two spectra of psychological and psychiatric conditions. Such effects are espe-

cially important given emerging treatments of autism and schizophrenia with intranasal oxytocin administration, which demonstrate both positive and problematic influences on symptoms (e.g., De Berardis et al., 2013; Gordon et al., 2013; Preti et al., 2014).

Of particular interest with regard to effects of oxytocin and testosterone in psychiatric conditions related to human sociality is that these two hormones exhibit evidence of opposite effects on a broad range of human phenotypes, including trust (Bos, Panksepp, Bluthé, & van Honk, 2012; Bos, Terburg, & van Honk, 2010; Van Ijzendoorn & Bakermans-Kranenburg, 2012), cognitive empathy (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; van Honk, Montoya, Bos, van Vugt, & Terburg, 2012), parental behavior (Feldman et al., 2012; Gettler, McDade, Feranil, & Kuzawa, 2011; Okabe, Kitano, Nagasawa, Mogi, & Kikusui, 2013; Weisman, Zagoory-Sharon, & Feldman, 2014), and amygdala connectivity with social-brain regions of the cortex (Bos, van Honk, Ramsey, Stein, & Hermans, 2013; Sripatha et al., 2013; Van Wingen, Mattern, Verkes, Buitelaar, & Fernández, 2010; Volman, Toni, Verhagen, & Roelofs, 2011). As such, analyses of the effects of these two hormones may provide especially useful information concerning the endocrinological bases of human social cognition (Auyeung et al., 2013), the relationship of autism with schizophrenia (Crespi & Badcock, 2008), and the uses of such hormones in therapeutic interventions (e.g., Gordon et al., 2013).

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Most studies of oxytocin and testosterone in human sociality have conducted intranasal administration (Bos et al., 2012), or single-point measures of serum hormone levels (Koven & Max, 2014). A complementary approach is to use genetic indicators of serum hormone levels (Feldman et al., 2012). Two advantages of such measures are first, that they provide, in principle, indices of relative hormone levels relevant across the lifespan, and second, that directions of causation can be inferred because the indices are genetically based.

In this study, we tested for associations of genetically-based indicators of serum oxytocin, and serum testosterone, with measures of autism-spectrum and schizophrenia-spectrum cognition in healthy individuals. We predicted in particular that high serum testosterone indices, and lower oxytocin indices, would be associated with higher scores on autism-spectrum cognitive phenotypes. Moreover, based on a model of autism spectrum and schizophrenia spectrum conditions as diametric disorders (Crespi & Badcock, 2008), recent findings that oxytocin mediates “holistic processing, divergent thinking, and creative performance” but reduced analytic reasoning (De Dreu et al., 2014), positive association of serum oxytocin levels with delusional ideation in schizophrenia patients (Walss-Bass et al., 2013), and the opposite cognitive effects of testosterone and oxytocin described above, we also predicted that lower serum testosterone indices, and higher oxytocin indices, would be associated with higher scores on schizotypal cognitive phenotypes, especially those involving ‘positive’ schizotypal traits such as perceptual alterations, delusions, altered self-referential beliefs, and magical thinking. Specific *a priori* predictions, with regard to the autism and schizotypy subscales measured here, are presented below.

2. Materials and methods

2.1. Populations and sampling

Questionnaire data and DNA samples (from mouthwash, which yields lymphocyte cells) were collected from Caucasian undergraduate students (175 males and 309 females) at the University of Alberta and Simon Fraser University (recruited from psychology classes), and protocols were carried out according to guidelines established by ethics boards of the both universities.

2.2. Psychometric data

Schizotypy was measured using the Schizotypal Personality Questionnaire-Brief Revised (SPQ-B) (Raine & Benishay, 1995), and autistic phenotypes were measured using the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001). PC2 is computed from SPQ-B and AQ and represents a scale from positive schizotypy to autism, such that individuals with higher values exhibit relatively-high positive schizotypy scores combined with relatively-low autism scores, on the SPQ-B and AQ (Dinsdale, Hurd, Wakabayashi, Elliot, & Crespi, 2013). Details concerning mean values and sex differences for these metrics, and their subscales, in this population can be found in Dinsdale et al. (2013).

2.3. SNP genotype data

Genotyping was performed on two SNPs in OXTR (rs1042778 and rs2254298) and one in CD38 (rs3796863) that have each been linked with plasma oxytocin and measures of empathy (Feldman et al., 2012; Schneiderman, Kanat-Maymon, Ebstein, & Feldman, 2014), and on three SNPs in HSD17B1 (rs12602084), HSD17B2 (rs1424151), and HSD17B3 (rs9409407) that have been linked with serum testosterone (Sun et al., 2011). We constructed oxyto-

cin genetic indices, derived from summing the number of high-oxytocin alleles (G for rs1042778, A for rs2254298, A for rs3796863) (additive model), or by summing the number of high oxytocin genotypes (GG and GT for rs1042778, AA and AG for rs2254298, and AA and AC rs3796863) (dominant model). The dominant index is based directly on previous work (Feldman et al., 2012) and the additive index is based on the linear association of OXTR genotype (for rs2254298) with amygdala size (Furman, Chen, & Gotlib, 2011; Inoue et al., 2010), which is indicative of additive functional effects. An index of serum testosterone was likewise constructed from the three SNPs in rs12602084 (high-testosterone genotype, AA), rs1424151 (high-testosterone genotype, GG) and rs9409407 (high-testosterone genotypes, CC and CT) (Sun et al., 2011). Indices of testosterone relative to oxytocin were also constructed by reversing the values of the additive, or dominant, oxytocin indices and adding them to the testosterone index, such that high values on these indices represent high testosterone combined with low oxytocin, and low values represent the reverse. Genotyping was performed by Genome Québec (Montréal, Canada) using the Sequenom Mass-ARRAY iPLEX platform, and loci were in Hardy–Weinberg equilibrium.

2.4. Predictions and analyses

We predicted that a higher testosterone index, lower oxytocin index, and higher index of high testosterone relative to oxytocin, would be associated with (1) higher scores on the AQ for the main social-behavior subscales (Social and Communication), (2) higher scores on the AQ for the Imagination subscale (higher scores indicating reduced imagination), (3) higher total autism score, (4) lower positive schizotypy on the SPQ-B (measured by the Cognitive-Perceptual subscale), (5) lower total schizotypy on the SPQ-B, and (6) lower scores on PC2, the index of high positive schizotypy relative to autism.

3. Results

The serum testosterone index was negatively associated with Cognitive-Perceptual positive schizotypy scores among females (Table 1), but was not significantly correlated with any of the analyzed subscales on the AQ. Negative associations of the testosterone index with Total Schizotypy, and PC2 (positively-schizotypal traits relative to autism traits), were borderline non-significant, among females ($p = 0.056$ and 0.096 , respectively). These findings thus fit partially with predictions regarding negative associations of schizotypy with the serum testosterone index, but predictions regarding association with autism subscales and total AQ were not met.

The serum oxytocin index was positively correlated with PC2, and negatively correlated with the AQ Imagination subscale (such that higher oxytocin index was associated with better imagination, since a higher AQ Imagination score indicates reduced imagination). The serum oxytocin index was uncorrelated with the autism subscales Social and Communication, and total AQ autism score. Again, these results partially support predictions regarding positive associations of the oxytocin index with measures of schizotypy, although not for autism scales other than Imagination.

The index of testosterone relative to oxytocin was negatively correlated with PC2, strongly negatively associated with the SPQ Cognitive-Perceptual subscale in females (for both models), and positively associated with the AQ Imagination subscale (for the additive model). This index was also negatively associated with Total Schizotypy in females, but was uncorrelated with the AQ scales. These findings suggest that the index of testosterone relative to oxytocin shows stronger and more consistent associations

Table 1
Correlations between hormone indices and psychological variables.

Hormone index	Gender, N	AQ-social		AQ-commun.		AQ-imagination		AQ-autism total		SPQ-cognitive perceptual		SPQ-schizotypy		PC2	
		r	p	r	p	r	p	r	p	r	p	r	p	r	p
Testosterone (T)	Both 484	−0.03	0.57	−0.02	0.63	−0.01	0.75	−0.02	0.61	−0.06	0.22	−0.03	0.57	−0.05	0.25
	♂ 175	0.06	0.42	−0.00	0.96	−0.01	0.89	0.03	0.67	0.15	0.054	0.12	0.12	0.05	0.53
	♀ 309	−0.07	0.19	−0.05	0.42	−0.03	0.55	−0.07	0.19	−0.15	0.008	−0.11	0.056	−0.09	0.096
Oxytocin (O): additive model	Both 479	−0.03	0.45	−0.03	0.50	−0.13	0.004	−0.07	0.15	0.06	0.19	0.03	0.50	0.10	0.027
	♂ 172	−0.07	0.38	−0.09	0.23	−0.15	0.057	−0.10	0.17	−0.04	0.65	−0.05	0.55	0.09	0.25
	♀ 307	−0.01	0.82	0.02	0.77	−0.11	0.049	−0.03	0.60	0.11	0.053	0.08	0.18	0.10	0.08
Oxytocin: dominant model	Both 479	−0.02	0.61	−0.03	0.57	−0.10	0.029	−0.06	0.17	0.06	0.18	0.03	0.51	0.09	0.041
	♂ 172	−0.03	0.67	−0.10	0.19	−0.15	0.044	−0.07	0.35	−0.01	0.89	−0.04	0.62	0.10	0.20
	♀ 307	−0.02	0.79	0.03	0.62	−0.06	0.33	−0.05	0.42	0.10	0.087	0.08	0.18	0.08	0.15
T/O: additive model	Both 475	0.02	0.68	0.02	0.74	0.11	0.02	0.04	0.33	−0.07	0.11	−0.03	0.45	−0.11	0.020
	♂ 170	0.10	0.20	0.08	0.32	0.13	0.10	0.11	0.16	0.10	0.20	0.10	0.21	−0.06	0.44
	♀ 305	−0.03	0.60	−0.04	0.51	0.08	0.18	−0.01	0.81	−0.16	0.005	−0.12	0.035	−0.12	0.032
T/O: dominant model	Both 475	0.01	0.88	0.01	0.87	0.07	0.12	0.04	0.43	−0.08	0.10	−0.03	0.45	−0.10	0.03
	♂ 170	0.08	0.30	0.08	0.33	0.12	0.12	0.08	0.32	0.10	0.20	0.10	0.18	−0.05	0.49
	♀ 305	−0.04	0.52	−0.05	0.39	0.02	0.70	−0.01	0.89	−0.16	0.005	−0.12	0.031	−0.11	0.049

with schizotypy, and positive schizotypy relative to autism (PC2), than does either hormonal index considered separately.

4. Discussion

Our results provide evidence that a low testosterone genetic index, a high oxytocin index, and a low index of testosterone relative to oxytocin, are each associated with one or more measures of relatively-schizotypal cognition, including high positive schizotypy (as measured by the Cognitive-Perceptual subscale of the SPQ), high PC2 (which quantifies positive schizotypy relative to autism), and high imagination. The associations of oxytocin, and testosterone relative to oxytocin, with PC2 also provides evidence supporting a hormonal dimension to a hypothesized psychological axis from positive schizotypy, to normality, to autism-spectrum cognition (Crespi & Badcock, 2008; Dinsdale et al., 2013). By contrast, the lack of associations of the testosterone (or oxytocin) indices with the autism Social and Communication subscales, or total Autism score, remains unclear, although it may be related to the nature of the genetic markers used as indicating post-natal adult hormone levels, which may not reflect prenatal or childhood levels.

Low serum testosterone has been reported among patients in most studies of schizophrenia (Markham, 2012), with negative associations between serum testosterone levels and symptoms of schizophrenia (Goyal, Sagar, Ammini, Khurana, & Alias, 2004; Ramsey et al., 2013), and evidence of lower prenatal testosterone in schizotypy and schizophrenia (Walder, Andersson, McMillan, Breedlove, & Walker, 2006). However, experimental testosterone administration studies and direct measures of plasma testosterone are needed to further elucidate the effects of testosterone levels on schizotypal cognition. Our results predict in particular that low serum testosterone and high oxytocin will be associated with increased levels of positive schizotypy, especially among females.

Rosenfeld, Lieberman, and Jarskog (2011) reported that most studies of oxytocin in schizophrenia report higher baseline levels of this hormone or its binding partner (compared to controls), but other reviews emphasize that results remain mixed (Macdonald & Feifel, 2012). Rubin et al. (2014) found no differences between schizophrenia patients and controls in plasma oxytocin, but reported a significant positive correlation between oxytocin levels and positive symptom severity among patients, which they suggested may be due to beneficial effects in the low range of oxytocin levels, but deleterious effects at high levels. Tseng et al. (2014) found that plasma oxytocin levels were positively associated with total schizotypy, and the interpersonal subscale (using the SPQ), among healthy females but not healthy males.

Intranasal oxytocin administration to individuals with schizophrenia (or autism), or healthy individuals with relatively-low social-cognitive abilities, increases performance on tasks of social cognition across most studies conducted to date (e.g., Bakermans-Kranenburg & van IJzendoorn, 2013; Domes et al., 2007; Guastella et al., 2010; Leknes et al., 2013; Luminet, Grynberg, Ruzette, & Mikolajczak, 2011; Rosenfeld et al., 2011). However, several recent reports have also found that oxytocin administration to healthy individuals may sometimes result in impaired and biased social-cognitive performance (Cardoso, Ellenbogen, & Linnen, 2014; Groppe et al., 2013; Voorthuis, Riem, Van IJzendoorn, & Bakermans-Kranenburg, 2014; Walss-Bass et al., 2013), apparently due in part to ‘over-sensitivity’ and ‘over-interpretation’ regarding social cues (Cardoso et al., 2014; Walss-Bass et al., 2013). Such alterations involve features of positive schizotypy (Crespi & Badcock, 2008) and may be related to forms of dysregulated social salience as found in extreme form in schizophrenia (van Os, 2009).

Taken together, these findings, our results, and evidence from De Dreu et al. (2014) that individuals with high-oxytocin genotypes of OXTR rs1042778, or treated with intranasal oxytocin, exhibit higher scores on metrics of divergent thinking and creativity (which have been notably associated with positive schizotypy (Acar & Sen, 2013)), suggest that relatively-high oxytocin levels may in some circumstances mediate the expression of positively-schizotypal phenotypes. The lack of association in our results of indices of testosterone or oxytocin with autism spectrum Social and Communication subscales on the AQ, but the association of the oxytocin index with the subscale Imagination (such that a higher oxytocin index is associated with better imagination), is intriguing in this context, and suggests that this hormone may play a role in social behavior, and risk of autism spectrum disorders, in part via effects on imaginative, social scenario-building (Craig & Baron-Cohen, 1999, 2000; Scott & Baron-Cohen, 1996). The Imagination subscale of the Autism Spectrum Quotient indeed measures aspects of social imagination that overlap with theory of mind and other mentalistic forms of cognition, that have been linked with oxytocin in many previous studies (e.g., Leknes et al., 2013; Van IJzendoorn et al., 2012).

The hypotheses raised here can be tested most directly by evaluating the effects of varying dosages of intranasally-administered oxytocin, and the effects of serum oxytocin measured directly, on performance in tests of imagination and social cognition, and scores for questionnaire-based metrics of schizotypal and autism spectrum traits, and by evaluating links of oxytocin with the dopaminergic pathways that mediate schizophrenia risk and expression

(Groppe et al., 2013; Rosenfeld et al., 2011). Our results also suggest that joint measurements of oxytocin and testosterone levels (and genetic indices thereof) may be especially useful, given the apparent opposite effects of the hormones discussed above, and the observation that in our results associations between hormonal indices and some psychological traits were more pronounced when both hormones were considered. An advantage of healthy populations in this context is that any associations should not be confounded by alterations due to psychiatric conditions themselves. An advantage of data from genetic indices of serum hormone levels, in comparison to direct measurements and administration, is that such indices may be associated with hormone levels across long time periods, including early development, although any such associations require empirical assessment. A limitation of our study in this context is the lack of direct measurements of serum oxytocin and testosterone, which would have allowed testing for validation of our genetic indices, beyond that provided by Sun et al. (2011), Feldman et al. (2012), Schneiderman et al. (2014).

The correlation coefficients reported here are generally low, as expected from effects of genetic variation in a small number of single nucleotide polymorphisms, although our large sample sizes generated sufficient power for robust tests. The magnitudes of these associations indicate that about 1–2% of the variation in the significantly-associated psychological variables can be explained by variation in three to six genetic markers, which represents a notable proportion for genetically-based psychological or psychiatric studies of highly-polygenic phenotypes (e.g., Manolio et al., 2009). Most generally, our results provide novel evidence that genetic indicators of serum hormone levels represent useful and complementary sources of information regarding the roles of endocrine systems in social cognition and disorders of social behavior, especially autism and schizophrenia.

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