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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.

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 especially 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; Sripada 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 oxytocin 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