Prenatal testosterone and theory of mind development: Findings from disorders of sex development

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Abstract

Women on average perform better than men on the “Reading the Mind in the Eyes” test (RMET) which is a measure of Theory of Mind (ToM). The aim of this study was to assess whether these sex differences are influenced by differences in prenatal testosterone levels through a study on individuals with Disorders of Sex Development and matched controls. ToM performance was examined using the RMET in female-assigned-at-birth individuals with increased prenatal testosterone exposure (Congenital Adrenal Hyperplasia (CAH) and 5α-Reductase type-2 Deficiency (5α-RD-2)), female-assigned-at-birth individuals with testosterone insensitivity (Complete Androgen Insensitivity Syndrome (CAIS)), and their age-matched unaffected male and female relatives. A total number of 158 individuals participated in the study; 19 with 5α-RD-2, 17 with CAH, 18 women with CAIS, 52 matched unaffected men and 52 matched unaffected women. All subgroups were around 20 years of age. Women with CAH scored significantly lower on RMET than control women and CAIS individuals. CAIS individuals scored significantly higher than control men and participants with 5α-RD. Statistically, CAIS individuals’ performance on RMET was similar to control women’s, women with CAH did not differ significantly from control men and 5α-RD-2 individuals scored significantly lower than control men. These results, which are in line with previous theories, illustrate that performance on the RMET, as an index of ToM, may be influenced by variations in prenatal androgens levels.

Keywords:
Disorders of sex development
Prenatal testosterone
Congenital adrenal hyperplasia
Complete androgen insensitivity syndrome
S-alpha reductase deficiency

1. Introduction

The ability to attribute mental states to others, to make sense of and predict other’s behavior is commonly called ‘mindreading’ or ‘theory of mind’ (ToM). ToM has been shown to be impaired in several conditions such as autism spectrum disorders (Miranda et al., 2017), schizophrenia (Langdon et al., 2017), depression, and bipolar disorder (Tay et al., 2017). Despite the scientific focus on ToM, as a cognitive ability whose impairment may have crucial consequences for mental health and social functioning, a clear understanding of the origin of its variation is yet to be obtained.

One consistent finding in studies on ToM is the sex difference; women on average perform better on ToM measures (Baron-Cohen et al., 2001; Rutherford et al., 2012; Schiffer et al., 2013). A meta-analysis found statistically significant differences ($g = 0.177–0.206$) between adult females and males, with females performing better on several ToM measures (Khorashad et al., 2015; Kirkland et al., 2013). In order to understand these sex differences, the impact of sex steroid hormone levels has been studied on ToM abilities (Baron-Cohen et al., 2011). Studies have generally highlighted the influence of prenatal (Auyeung et al., 2009) and pubertal (Celec et al., 2015) testosterone exposure on the development of ToM. Testosterone, progesterone and estradiol influence the activity of brain areas involved in signal interpretation (Lombardo et al., 2012; van Wingen et al., 2011). A unique study measured ToM among children between 6 and 8 years old and focused on their scores in association with their prenatal testosterone levels obtained through amniocentesis. It turned out that prenatal androgen levels are negatively correlated to children’s ToM performance.
(Chapman et al., 2006). In addition, it has been found that prenatatal testosterone levels are positively associated with a number of autistic traits, a condition in which ToM is impaired (Auyeung et al., 2009; Baron-Cohen et al., 2015).

Intersex conditions or Disorders of Sex Development (DSD) are congenital conditions in which the chromosomal, gonadal, and/or anatomical sex develops atypically. Some of the DSD conditions are accompanied by hormonal imbalances, including elevated levels of testosterone in-utero or insensitivity of its receptors. Due to the atypical combination of sex chromosomes, hormones and phenotypes, people with DSD have been invaluable sources for studying the origins of sex differences (Hines, 2009). Yet, to our knowledge, no study has been performed on ToM among individuals with DSD. Moreover, most of the studies on sex differences have taken place in Western industrialized societies. Considering the cultural embeddedness of human psychosexual development, studies from non-Western countries are valuable to this field (Henrich et al., 2010).

In this study we aim to investigate the effects of testosterone exposure on the development of ToM in a non-Western setting. In order to isolate the effects of testosterone, ToM was studied in three groups of people each with a particular DSD condition and their age-matched unaffected male and female relatives as controls. Participants with three clinical conditions were studied, including individuals diagnosed with 46,XX classic Congenital Adrenal Hyperplasia (CAH); 46,XY 5α-Reductase Deficiency (5α-RD-2) and 46,XY Complete Androgen Insensitivity Syndrome (CAIS) who were female-assigned at birth.

Due to an adrenal up-regulation, girls with CAH are exposed to similar levels of androgens in-utero as typical boys. However, girls with CAH have a 46,XX karyotype and mostly identify as a female. Due to a mutation in the gene encoding for 5α-reductase, the enzyme that converts testosterone into dihydrotestosterone (DHT), individuals with 5α-RD-2 are exposed to male-typical levels of prenatal testosterone yet low levels of DHT. During embryogenesis, DHT plays a crucial role in sexual differentiation of the male genitalia, and in later life, in the development of facial, body, and pubic male-pattern hair growth (amongst other functions). Depending on the level of DHT, consequent to how much 5α-reductase function is deraigned, genital phenotype may show various degrees of ambiguity somewhere in between typical masculine and feminine. Newborns of this group are mostly assigned female at birth. In case the condition remains undiagnosed, they may virilize at puberty due to increased testosterone production whence a considerable proportion of this group may seek sex realignment treatments (Khorashad et al., 2016). Lastly, individuals with CAIS hold 46,XY chromosomes but since their androgen receptors are mostly insensitive, they undergo no masculinizing effect of testosterone. Most individuals diagnosed with CAIS will identify as females. Although individuals with CAIS have a much higher circulating levels of testosterone compared to unaffected females, considering their insensitivity to androgens it can be assumed that in effect they experience a similar hormonal milieu as typical females. It should be restated, however, that typical females are exposed to low levels of testosterone. A brief summary of these conditions is provided in Table 1.

### 2. Hypotheses

In case fetal androgens play a pivotal role in ToM development (hypothesis 1), we expect to observe the following results: CAIS and control women perform similarly (both experience limited testosterone effects during their prenatal period); participants with CAH and 5α-RD-2 perform similar to control men (all of them experience high levels of prenatal testosterone); male controls, participants with CAH and 5α-RD-2 score lower than women with CAIS and women with typical sex development.

In case the assigned gender is the main determinant in ToM development (hypothesis 2), we expect to see: participants with CAH, CAIS and 5α-RD-2 perform similar to control women (all of them are assigned as female at birth); male controls score lower compared to all other participants.

Finally, if sex chromosomes are the distinguishing factor (hypothesis 3), we expect to see: participants with 46,XX karyotype, i.e. women with CAH and women with typical sex development score similarly; and participants with 46,XY karyotype, i.e. participants with CAIS, 5α-RD-2 and men with typical sex development score the same; participants with 46,XX perform better compared to those with 46,XY karyotype.

### 3. Methods and materials

#### 3.1. Participants and procedure

Participants were recruited from the referrals to Mashhad University of Medical Sciences’ gender clinic, which is the biggest tertiary medical center in Eastern Iran, from January 2013 through December 2016. All individuals diagnosed with any form of DSD are routinely referred to the gender clinic for psychoeducation and psychological evaluation based on the World Professional Association for Transgender Health’s Standards of Care, edition 7 (Coleman et al., 2011). All individuals were interviewed by at least two experienced psychiatrists according to the Structured Clinical Interview based on DSM-IV-TR (SCID-clinical version) for psychiatric conditions. Applicants were also evaluated according to DSM-5 criteria for Gender Dysphoria (American Psychiatric Association, 2013). Participants were excluded if they were diagnosed with a major psychiatric condition such as psychosis (n = 1), had intellectual disabilities (n = 2), were under 18 years of age (n = 25), illiterate (n = 1) or unwilling to join the study (n = 4). In total, 87 individuals were considered to participate, of whom 54 were included (62%; mean age = 20.96, SD = 4.28). The study sample included 17 individuals with CAH (mean age = 19.47, SD = 3.82), 18 individuals with CAIS (mean age = 21.39, SD = 3.56) and 19 individuals with 5α-RD-2 (mean age = 21.89, SD = 5.08).

To ensure proper matching on socioeconomic status and reduce confounding biases, controls were recruited from those accompanying the participants during their clinical visits. Controls included siblings, relatives, friends, or partners. Exclusion criteria for controls included a history of gender incongruence or DSD. A total of 52 male (mean age = 20.62, SD = 3.28) and 52 female controls (mean age = 20.94, SD = 3.61) consented to participate as well. For each participant, one unaffected female and one unaffected male of a similar age were recruited. The study was approved by the ethical committee of Mashhad University of Medical Sciences.

### Table 1

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Hormonal Sex</th>
<th>Assigned Sex At Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male controls</td>
<td>46,XY</td>
<td>Male levels of FT, male-typical levels of fDHT</td>
</tr>
<tr>
<td>Female controls</td>
<td>46,XX</td>
<td>Female levels of FT, female-typical levels of fDHT</td>
</tr>
<tr>
<td>CAH</td>
<td>46,XX</td>
<td>Male-typical levels of FT, Male typical levels of fDHT</td>
</tr>
<tr>
<td>5α-RD-2</td>
<td>46,XY</td>
<td>Male-typical levels of FT but female-typical levels of fDHT</td>
</tr>
<tr>
<td>CAIS</td>
<td>46,XY</td>
<td>Male-typical levels of FT but insensitive, Male-typical levels of fDHT but insensitive</td>
</tr>
</tbody>
</table>

FT: Fetal Testosterone; fDHT: Fetal Dihydro-Testosterone; CAIS, Complete Androgen Insensitivity Syndrome; CAH, Congenital Adrenal Hyperplasia; 5α-RD-2, 5 Alpha Reductase Type 2 Deficiency.
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