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Article

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Abstract

Objective: People with autism spectrum disorders (ASD) often have comorbid ADHD symptoms. ASD and ADHD are both associated with high intrauterine testosterone (T) levels. This study aims to investigate whether masculinization predicts inattention symptoms in parents, and in their ASD-affected offspring. **Method:** The sample consisted of 32 parents with ASD-affected children (13 male, 19 female) and 32 offspring individuals (28 male, 4 female). Masculinization of parents was measured by 2D:4D finger ratio, and current T levels. Inattention in both parents and in their offspring was measured with behavior questionnaires. **Results:** The results indicated that masculinized 2D:4D explains inattentive ADHD symptoms in ASD parents and in their offspring. These predictions are mediated by T and inattention symptoms of ASD parents, respectively. **Conclusion:** These findings suggest the existence of a masculinized endophenotype in ASD parents, which may be characterized by high attentional sensitivity to T effects. *(J. of Att. Dis. 2017; 21(11) 938-943)*

Keywords

autism spectrum disorders, ADHD, testosterone, 2D:4D ratio

Introduction

A considerable percentage of children with autism spectrum disorder (ASD) also present ADHD-related symptoms (Sucksmith, Roth, & Hoekstra, 2011). Both disorders exhibit male-biased prevalence rates (Ames & White, 2010), and a plausible biological risk factor for both disorders may be elevated testosterone (T) levels. Indeed, it was reported that high intrauterine T levels may be partially involved in the development of both disorders (James, 2008). For ASD in particular, it was suggested that T may contribute to develop an "extreme male brain" (Auyeung, Taylor, Hackett, & Baron-Cohen, 2010). A study by De Bruin, Verhiej, Weigman, and Ferdinand (2006) showed that high prenatal T (defined as a smaller 2D:4D ratio) was more often present in children diagnosed with ADHD compared with those diagnosed with anxiety disorders. Also, animal research showed that early exposure to high T during the development is related to impairments in cognitive function (King, Barkley, Delville, & Ferris, 2000; Li & Huang, 2006).

A peripheral indicator of the exposure to prenatal T in the central nervous system (CNS) is the 2D:4D finger ratio—the quotient between the lengths of the second and the fourth digits. Accordingly, the greater the exposure and sensitivity to prenatal T and corresponding reductions in estrogens, the greater the likelihood of developing a lower 2D:4D ratio (Breedlove, 2010). Interestingly, a smaller or masculinized 2D:4D ratio has been related to ASD and ADHD disorders (Manning, Baron-Cohen, Wheelwright, & Sanders, 2001; Martel, 2009). Thus, it might be that families with high masculinization, and consequently low 2D:4D ratio, show greater likelihood toward developing autistic symptoms (Manning et al., 2001). Indeed, parents and siblings of people with ASD and ADHD usually show slightly autistic or ADHD traits, which may point to shared endophenotypes (Bernier, Gerdts, Munson, Dawson, & Estes, 2012; Trujillo-Orrego, 2011). A previous study revealed that 2D:4D ratio of ASD parents predicted the degree of autistic traits of their offspring (Romero-Martínez et al., 2013).

The current study examined the involvement of masculinization in the development of ADHD comorbid symptoms in offspring of a carefully selected sample of parents of people with ASD. Masculinization was operationalized by the

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2D:4D finger ratio, as well as by salivary T levels in the parents, while inattention was measured with behavior questionnaires. We propose a theoretic model that includes the mediation between all these variables. A masculinized 2D:4D ratio has been related to high current T levels in a clinical population (infertile men; Manning, Scutt, Wilson, & Lewis-Jones, 1998). Also, high sensitivity to current T levels has been associated with social cognition (van-Honk et al., 2011) and ADHD symptoms (De Bruin et al., 2006). Thus, we examined whether salivary T levels in ASD parents might mediate the relationship between a masculinized 2D:4D ratio and inattentive symptoms of ASD parents. As ADHD is highly heritable (Polderman et al., 2007), we also analyzed whether inattentive symptoms of ASD parents might mediate the relationship between the 2D:4D ratio of ASD parents and ADHD symptoms in their offspring. We hypothesized that T of ASD parents would mediate the relationships between a masculinized 2D:4D ratio of ASD parents and ADHD symptoms of themselves and their offspring, respectively. Hence, high current T levels will be related with a masculinized 2D:4D ratio and more inattentive symptoms in ASD parents. And finally, high inattentive symptom scores in ASD parents will be related to a masculinized 2D:4D ratio and increased ADHD symptoms in their offspring. Moreover, the relationship between masculinization and ADHD symptoms will be stronger with inattentive than hyperactivity symptoms as revealed by previous research (McFadden, Westhafer, Pasanen, Carlson, & Tucker, 2005).

Method

Participants

The sample consisted of 32 participants, all fathers ($n = 13$) and mothers ($n = 19$) of offspring with ASD, aged between 33 and 63 years (45.00 ± 5.9). They participated voluntarily in the study and signed an informed consent in accordance with ethical standards for human research. Anthropometrical and demographical variables of ASD parents are summarized in Table 1. The ages of the offspring with ASD ranged from 5 to 30 years (13.60 ± 5.46), with a gender distribution of 28 men and 4 women, in accordance with the expected gender distribution in this disorder. The inclusion criteria for participating in the study were as follows: being a first-degree family of an ASD patient with a clinical diagnosis, living at home with the patient, and being the main provider of first-needs for at least 2 years before the study.

Table 1. Anthropological and Sociodemographical Variables of ASD Parents.

	ASD parents	
	Men ($n = 13$)	Women ($n = 19$)
Age (years)	44.85 ± 4.47	45.16 ± 6.96
BMI ($Kg/m^{2)}$	29.43 ± 5.75	25.99 ± 4.82
Right 2D:4D ratio	0.96 ± 0.04	0.99 ± 0.03
T levels (pmol/L)	65.21 ± 22.00	22.87 ± 17.53
Phases of the menstrual cycle		
Luteal (1-14)	—	7 (36.8%)
Follicular (15-menstrual period)	—	9 (47.4%)
Amenorrhea (>6 months)	—	3 (15.8%)
Marital status		
Single	—	—
Married	13 (100%)	17 (89.5%)
Divorced	—	2 (10.5%)
Widowed	—	—
Others	—	—
Educational level		
None	—	—
Basics	3 (23.0%)	4 (21.1%)
Advanced	4 (30.8%)	2 (10.5%)
University	6 (46.2%)	13 (68.4%)
Others	—	—
Source of income		
Job	1 (7.7%)	1 (5.3%)
Unemployment	11 (84.6%)	16 (84.2%)
Others	1 (7.7%)	2 (10.5%)
Number of children		
1	8 (30.8%)	4 (21.0%)
2	4 (61.5%)	12 (63.2%)
3	1 (7.7%)	3 (15.8%)
4 or more	—	—

Note. ASD = autism spectrum disorders; BMI = body mass index.

Procedure

Participants visited the laboratories of the psychology faculty at the University of Valencia, without having food or drinks (except water, brushing teeth, or chewing gum) during the 2 hr period before arrival at the laboratory. The experimental sessions lasted approximately an hour and were carried out between 4:00 and 7:00 p.m. After arrival in the laboratory, participants were taken to a room with a constant temperature (22°C ± 1°C) where weight, height, 2D:4D ratio, and demographic variables were recorded. Two samples of saliva were collected for determining T; the first sample was taken at the end of the collection of anthropometric data and the second sample was taken 20 min after the first. Participants then completed three questionnaires: one self-report and two assessing hyperactivity and/or inattention symptoms in their offspring.

2D:4D Ratio

To calculate the 2D:4D ratio, three separate measurements of the length of the index finger (2D) and the ring finger (4D) of the right hand were made (Martel, 2009). Measurements

were made on the ventral side of the hand. The length of the finger was taken from the proximal fold at the base of the finger to the tip thereof. For this purpose, we used digital calipers with an accuracy of 0.01 mm. Two of the three measurements were made directly by two investigators, while the third was performed using a scanner for subsequent measurement. The value of the 2D:4D ratio was obtained by calculating the average of three measurements, as has been done in a previous study (Schneider, Pickel, & Stalla, 2006). The interobserver reliability was 0.98, and the reliability between the average of direct and scanned measure was 0.99.

Inattention Measures for ASD Parents

Attention Switching Subscale of the Autism Spectrum Quotient (AQ) for Adults. For this study, the "Attention Switching" subscale of the AQ for adults (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) was used as a measure of difficulty in attention switching or deficient inhibitory processing (Polderman et al., 2012). We will refer to this measure as AQ-Switch of Parents. It consists of 10 items that are rated on a 4-point scale with *definitely agree, slightly agree, slightly disagree*, and *definitely disagree*. Ratings were recoded as 1 if the person reports inattentive symptoms and as 0 if they do not show any symptom. So scores could range from 0 to 10, obtained by adding the frequency of inattentive symptoms, with a high score corresponding to more symptoms.

ADHD and Autistic Symptoms Questionnaires for Offspring

The SNAP-IV "Teacher and Parent Rating Scale" is an adapted Spanish revision of the original questionnaire (Swanson, Sandman, Deutsch, & Baren, 1983). Parents completed this questionnaire. Items from the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) for ADHD are used to measure symptoms of inattention (Items 1-9) and symptoms of hyperactivity/impulsivity (Items 10-18). There are four response options: "not at all" = 0, "just a little" = 1, "often" = 2, and "very often" = 3. Subscale scores (inattention and hyperactivity) on the SNAP-IV are calculated by summing the scores of a subscale and dividing this sum by the number of items in the subscale. We will refer to these measures as SNAP-IV Inattention of Offspring and SNAP-IV Hyperactivity of Offspring.

We used the Attention Switching subscale of the AQ for adolescents as a measure of difficulty in attention switching or deficient inhibitory processing in offspring. This is an adapted version of the AQ for children and adolescents aged 9 to 16, although it is also valid for older people (Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006) and is designed to be completed by parents or caretakers. The interpretation is the same as in the Attention Switching subscale for adults. We will refer to this measure as AQ-Switch of Offspring.

T Analyses

Basal levels of T were obtained from two samples of saliva, directly collected by salivation through a glass tube. However, as far as spurious alterations in salivary T levels have been reported using the salivette method of collection (Granger, Schwartz, Booth, & Arentz, 1999), direct and spontaneous salivation was preferred for salivary collection in the present study. The samples were frozen at −20°C until analysis by enzyme-linked immunosorbent assay (ELISA). The reactive used for the T was the "saliva testosterone ELISA Kit" (Diagnostics Biochem Canada Inc.). Assay sensitivity was 1 pg/ml. The coefficients of variation intra- and interassay were 3.98% and 7.98%, respectively. All values are shown in pmol/L Cronbach's alpha for the two T measures was 0.75.

Data Analysis

It was tested whether data were normally distributed (using the Kolmogorov–Smirnov statistic). To analyze gender differences for anthropometric (age and body mass index [BMI]), psychological (AQ adults), and hormonal (T) variables, *t* tests were performed. Cohen's *d* for independent groups was calculated to estimate the effect size of the different measures (Cohen, 1988). For the analysis of the frequencies of the demographics, chi-square statistics were used. All posterior analyses were conducted with and without including gender as a covariate.

We used linear regression models to investigate whether the 2D:4D ratio of the right hand predicted inattention (AQ adults) and circulating T of ASD parents. Subsequently, it was tested whether the 2D:4D ratio of ASD parents predicted ADHD symptoms (SNAP-IV and AQ adolescents) of their offspring. As recommend by Preacher, Rucker, and Hayes (2007), we confirmed the association between the mediation variable (T) and the independent variable (2D:4D ratio of ASD parents), and inattentive symptoms in ASD parents (dependent variable). Second, we investigated the relationship between the mediation variable (AQ-Switch of Parents) and the independent variable (2D:4D ratio of ASD parents), and ADHD symptoms in their offspring (AQ-Switch of Offspring and SNAP-IV measures of Offspring).

Data analyses were carried out using SPSS 17.0 software (SPSS Statistics). Statistical significance was accepted for p values $< .05$.

Results

Descriptive Characteristics

Values ($M \pm SD$) for T levels, and the anthropometric and demographic variables for males and females are

Table 2. *M* ± *SD* for the SNAP-IV Measures of Offspring, AQ-Switch of Offspring, and AQ-Switch of Parents.

	M + *SD*	Skewness	Kurtosis
Offspring (*n* = 32)			
Inattention (SNAP-IV)	0.34 + 0.29	0.17	−0.46
Hyperactivity (SNAP-IV)	0.37 + 0.28	0.55	−0.39
AQ-Switch of Offspring	7.21 + 2.08	0.59	0.50
ASD parents (*n* = 32)			
AQ-Switch of Parents	4.56 + 2.23	0.47	0.50

Note. AQ = autism spectrum quotient; ASD = autism spectrum disorders.

summarized in Table 1. There were no gender differences in BMI, age and demographic variables, and AQ adult scores. However, as expected, men had higher T and smaller right 2D:4D ratio than women, $t(21.93) = 5.79$, $p < .01$; $t(30) = -2.47$, $p < .05$, respectively, with high effect sizes ($d = 2.12$; $d = 0.90$, respectively). Descriptives of SNAP-IV Offspring measures and AQ-Switch measures of parents and offspring are presented in Table 2.

Masculinized 2D:4D Ratio of ASD Parents As a Predictor of ADHD Symptoms in Parents and in Their Offspring

Question 1: Is a more masculinized right 2D:4D of ASD parents associated with (a) more inattentive symptoms and (b) high T levels in ASD parents?

The 2D:4D ratio of the right hand of ASD parents predicted 18.3% of AQ-Switch of Parents (β = −.457, $p < .01$) and 14.3% of the basal T levels (β = −.413, $p < .05$).

Question 2: Is a more masculinized right 2D:4D of ASD parents associated with (a) more ADHD symptoms in their offspring?

The 2D:4D ratio of the right hand of ASD parents predicted 8.9% of SNAP-IV Inattention of Offspring (β = −.345, $p < .05$) and 7.2% of AQ-Switch of Offspring (β = −.320, $p < .05$). The 2D:4D ratio of ASD parents did not predict SNAP-IV Hyperactivity of Offspring (β = −.229, $p > .05$).

Question 3: Are high current T levels of ASD parents associated with more inattentive symptoms in ASD parents?

The current T levels of ASD parents predicted 6.5% of the AQ-Switch scores of parents (β = .308, $p < .05$)

Question 4: Are high inattentive symptoms of ASD parents associated with more ADHD symptoms in their offspring?

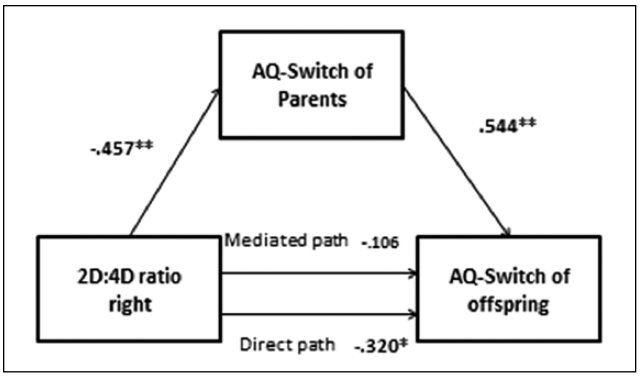

Figure 1. T mediates the relationship between masculinized 2D:4D ratio and AQ-Switch of ASD parents.
Note. AQ = autism spectrum quotient; ASD = autism spectrum disorders.

The AQ-Switch of Parents predicted 32.7% of the AQ-Switch of Offspring (β = .592, $p < .01$). However, AQ-Switch of Parents did not predict SNAP-IV Inattention of Offspring (β = .155, $p > .05$) or SNAP-IV Hyperactivity of Offspring (β = .125, $p > .05$).

Mediation Models

Model 1: Does high T mediate the association between more masculinized right 2D:4D and inattentive symptoms in ASD parents?

Current T levels emerged as a possible mediator of both 2D:4D ratio and AQ-Switch of Parents. This was tested with a mediation model in which the 2D:4D ratio and T were both entered as predictors of AQ-Switch of Parents. The results showed that 2D:4D ratio no longer significantly predicted AQ-Switch of Parents (β = −.143, $p > .05$), but T remained a significant predictor (β = .398, R^2 for full model = .32, $p < .05$). Thus, high T mediated the relationship between 2D:4D ratio and AQ-Switch of Parents (Figure 1).

Model 2: Does AQ inattention in ASD parents mediate the association between more masculinized right 2D:4D of ASD parents and ADHD symptoms of their offspring?

When the 2D:4D ratio and AQ-Switch of Parents were both entered as predictors, 2D:4D ratio no longer significantly predicted AQ-Switch of Offspring (β = −.106, $p > .05$). However, AQ-Switch of Parents remained a significant predictor (β = .544, R^2 for the full model = .33, $p < .01$). Thus, high AQ inattention symptoms in ASD parents mediated the relationship between 2D:4D ratio and AQ-Switch of Offspring (Figure 2).

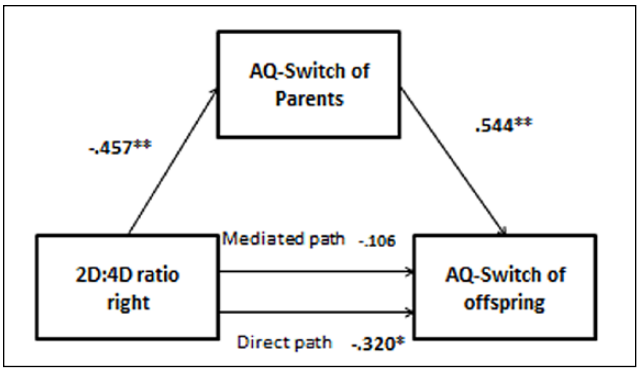

Figure 2. AQ-Switch of Parents mediates the relationship between a masculinized 2D:4D ratio and AQ-Switch of their offspring.
Note. AQ = autism spectrum quotient.

When gender of ASD parents and their offspring were entered as a covariate, the same results were obtained.

Conclusion

This study examined in a carefully selected clinical sample the effects of direct and indirect T levels on attention deficits in parents of ASD-affected children. Furthermore, indirect effects of T levels (via the parents) on attention deficits and hyperactivity in their offspring were investigated. Our results revealed that a masculinized 2D:4D ratio of the right hand of ASD parents is associated with inattention symptoms in ASD parents, and with inattentive symptoms but not hyperactive symptoms in their offspring. However, in ASD parents, current T levels mediated the association between a masculinized 2D:4D ratio and AQ inattention symptoms, while inattention symptoms in ASD parents mediated the association between the 2D:4D ratio of ASD parents and inattentive symptoms in offspring. Thus, our results confirmed that masculinization is related to ADHD symptoms (De Bruin et al., 2006) and that the involvement is stronger in inattentive ADHD symptoms than hyperactivity symptoms (McFadden et al., 2005). However, a population-based study of dizygotic female twins reported opposite findings (Attermann et al., 2012). That study examined the hypothesis that sex of the co-twin influences the level of fetal exposure to T, and may therefore relate to ADHD symptoms (evaluated by means of the Attention Problem scale of the Child Behavior Checklist, a questionnaire complemented by parents). They found that girls with a twin brother (i.e., high prenatal T levels) had lower ADHD trait scores than those with a twin sister (i.e., low prenatal T levels). However, in this study, ADHD traits in clinically diagnosed ADHD girls were examined, whereas our study explored cognitive and hormonal characteristics of parents of offspring (both girls and boys) with ASD.

A masculinized 2D:4D ratio may point to the influence of prenatal T exposure (Manning, Bundred, Newton, & Flanagan, 2003). Given the presence of slightly (nonclinical) autistic traits in parents of ASD-affected children (Sucksmith et al., 2011), and our current findings of attention deficits in the parents, our results may indicate a shared genetic liability, associated with (prenatal) T levels to develop autistic disorders and comorbid ADHD symptoms.

A limitation of our study is the cross-sectional and nonexperimental design with which causality could not be addressed. Moreover, "AQ-Switch" was used as a measure of inattentive ADHD symptoms, while it is developed as an ASD measure. In addition, our relatively small sample had limited statistical power; future work might replicate these findings in a larger sample. Another limitation is that the masculinization of parents may have influenced their self-reports and the way they reported on their children. Multiple informants would have optimized our study design. Moreover, as masculinization may affect parenting style, descendants of people with ASD could also partially learn this cognitive style from their progenitors, which, in turn, may reinforce the development of those disorders.

The present study focused on biological factors related to comorbid ASD and ADHD symptoms, but further studies should also consider other educative and social aspects such as parenting styles. Future research could also include additional variables such as neuropsychological tests related to multiple domains of executive functions, or other sex hormones such as estrogens. Our data are relevant and novel as no laboratory studies have analyzed masculinization in ASD parents and its involvement in their offspring disorders. Further analyses are required to determine its involvement and its relationship with other important parameters for ASD and ADHD.

Declaration of Conflicting Interests

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