Extreme Male Brain Theory of Autism

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Résumé :

(traduction)

Les troubles du spectre autistique (TSA) sont une catégorie de troubles de la neurologie du développement présentant des symptômes de dégradation sociale et des communications, ainsi que des comportements restrictifs et répétitifs. Ils sont davantage présents chez les hommes que chez les femmes, et cette différence entre les sexes a beaucoup influencé les hypothèses au sujet de leur étiologie. La théorie du cerveau mâle extrême (CME) est un modèle cognitif proposé par Simon Baron-Cohen pour expliquer les différences entre les sexes et les causes potentielles des TSA susmentionnés. Elle repose sur sa théorie d'empathisation-systématisation, qui consiste à classer les sujets dans cinq profils cognitifs (Type S, Type E, Type B, Type S extrême et Type E extrême). Ces profils cognitifs déterminent la capacité du sujet de systématiser et d'être en empathie avec. La systématisation est la capacité de comprendre un système et d'en déduire les règles. Elle exige des capacités de déduction et d'analyse. L'empathie a trait à la compréhension des émotions et des comportements humains, ce qui exige des capacités sociales et de communication. Les hommes ont tendance à mieux systématiser, tandis que les femmes présentent le profil opposé. Selon la théorie du CME, les autistes auraient un profil de Type S extrême, car on peut expliquer leurs troubles de communication sociale par leur déficit d'empathie, alors qu'on peut relier à leur fort niveau de systématisation leur préoccupation au sujet des patrons et leur comportement axé sur les détails. Ensemble, ces modèles cognitifs ont conduit à la théorie de la testostérone fœtale (Tf), qui stipule qu'un niveau élevé de testostérone prénatale est un facteur de risque pour le profil cognitif hypermasculinisé des sujets atteints de TSA. Dans cet article, les auteurs évaluent la validité des théories du CME et de la Tf, en étudiant la documentation portant sur la Tf avec des caractéristiques autistes dans l'ensemble de la population. Ces sept études ont confirmé une corrélation entre des niveaux élevés de Tf et une augmentation des caractéristiques autistes, mais il faut envisager d'y mettre des limites au moment de généraliser ces informations à un échantillon de sujets atteints de TSA.

Mots-clés :

Troubles du spectre autistique, théorie du cerveau mâle extrême, théorie d'empathisationsystématisation, théorie de la testostérone fœtale

Abstract:

Autism spectrum conditions (ASCs) are a category of neurodevelopmental disorders with symptoms of communication and social impairment, and the exhibition of restrictive and repetitive behaviours. Their occurrence is greater in males than females and this sex difference has played an important part in hypothesizing their etiology. The Extreme Male Brain (EMB) theory is a cognitive model proposed by Simon Baron-Cohen to explain the aforementioned sex differences and potential cause of ASCs. It is based upon his Empathizing -Systemizing theory, which classifies individuals into one of five cognitive profiles (Type S, Type E, Type B, Extreme Type S and Extreme Type E). These cognitive profiles determine an individual's ability to systemize and empathize. Systemizing is the ability to understand and derive the rules of a system, and requires deductive and analytical skills. Empathizing relates to understanding human emotion and behaviour, thus requires social and communication skills. Males tend to systemize better than empathize while females have an opposite profile. Based upon the EMB theory, autistic individuals would possess an Extreme Type S profile as their impairments in social communication can be explained by a deficit in empathizing, while their preoccupation with patterns and detail-oriented behaviour can be related to their high systemizing. Together, these cognitive models have resulted in the Foetal Testosterone (fT) Theory, which implicates high prenatal testosterone as a risk factor for the associated hypermasculinized cognitive profile of individuals with ASCs. This review paper assesses the validity of the EMB and fT theories by reviewing the literature relating fT with autistic traits in the general population. The seven studies confirmed a correlation between higher fT levels and an increase in autistic traits, but limitations need to be considered when generalizing this information to an ASC sample.

Keywords:

Autism spectrum disorders, extreme male brain theory, systemizing– empathizing theory, foetal testosterone Theory

Introduction

Autism spectrum conditions (ASCs) or autism spectrum disorders (ASDs) are a category of neurodevelopmental conditions characterized by impairments in the domains of communication, social interaction, and repetitive behaviours and interests (Faras, Al Ateeqi, & Tidmarsh, 2010; Hill & Frith, 2003; Knickmeyer & Baron-Cohen, 2006). Classical autism, Asperger Syndrome (AS) and Pervasive developmental disorder-not otherwise specified (PDD-NOS) are the three main types of ASCs and they differ in their number and severity of symptoms from each of the three domains (Hughes, 2008; Jones, Cork, & Chowdhury, 2006) Specific features of each type of ASC are described in Table 1.

The incidence of autism is greater in males than females (4:1) with an even greater sex difference for AS (10:1 males to females) (Baron-Cohen, 2009; Manson, 2008). Earlier reports showed a prevalence of 0.4/1000 in the general population, but recent rates for these disorders now range from 1-6/1000 (Marco & Skuse, 2006). Although ASCs appear to be on the rise, many attribute this phenomenon to improved diagnostic methods or expanded diagnostic criteria (Hughes, 2008; Jones et al., 2006; Marco & Skuse, 2006; Baron-Cohen, Knickmeyer, & Belmonte, 2005). However with little known about the etiology of these disorders, it is difficult to make this conclusion with any certainty. Changes in maternal and neonatal exposure to important environmental factors cannot be excluded from consideration. There appears to be a genetic component to these disorders as exemplified by the higher recurrence rate in siblings (2-8%) and twins (10-90%) (Marco & Skuse, 2006). And, while the spectrum of disorders is not directly heritable, recent molecular genetics studies have implicated multiple chromosomal loci (specifically chromosomes 15, 16, and 17) in their etiology (reviewed in (Hughes, 2008)). Thus, a multifactorial explanation involving both the environment and genetics contribute to the complex neurological mechanisms underlying ASCs (Faras et al., 2010; Hughes, 2008).

A variety of theories have been put forth that attempt to relate the symptoms of autism to existing cognitive concepts, such as the Theory of Mind Deficit, Executive Dysfunction, and Weak Central Coherence Theory (Hill & Frith, 2003). Others have taken these a step further by overlaying biologically relevant changes and exploring how these relate to cognitive deficits observed in autism and how together they might explain the important sexual dimorphism in the incidence rate. One such theory is the Foetal Testosterone (fT) Theory proposed by Simon Baron-Cohen (Baron-Cohen et al., 2009; Manning, Baron-Cohen, Wheelwright, & Sanders, 2001). It derives from the Ex-

Table 1 Characteristics of three main Autism Spectrum Conditions

Type of ASC	*Symptoms*
Classical autism	• deficits in social abilities and empathizing • deficits in communicative language • cognitive impairment (usually lower than average IQ) • delay of speech development • restrictive interests and behaviours • detectable before the age of 3
Asperger Syndrome	• poor social skills and lack of insight • restrictive interests and behaviours • IQ over 70 • no delay in speech
PDD-NOS	• individuals who do not meet the criteria of autism or AS, although still displaying symptoms in the 3 domains

(Adapted from: Jones A, Cork C, Chowdhury U. (2006). AUTISTIC SPECTRUM DISORDERS: Presentation and assessment. Community Pract. 2006 Mar;79(3):97-8)

treme Male Brain (EMB) theory that relates to the Empathizing-Systemizing (E-S) theory (Baron-Cohen, 2009; Baron-Cohen, 2002; Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003). The goal of this work is to review the Foetal Testosterone Theory of autism by delving into the cognitive models that define it; a review of the Empathizing-Systemizing and Extreme Male Brain theories will first be presented.

The Empathizing-Systemizing Theory

The premise of the Empathizing-Systematizing Theory (E-S) is that within the population, there are generally five brain types: Type S, Type E, Type B (balanced brain), and the Extreme Type S and E brains. Table 2 shows the cognitive profile of individuals with each brain type. A higher proportion of males tend to have a Type S brain as compared to other types and thus Type S brains can be considered a "male brain" whereas a higher proportion of females have Type E, which signifies a "female brain" (Baron-Cohen, 2009; Baron-Cohen et al., 2003; Goldenfeld, Baron -Cohen, & Wheelwright, 2005).

Males tend to systemize better than empathize, which relates to their Type S brains whereas females are superior at empathizing compared to systemizing (Baron-Cohen, 2002; Baron-Cohen et al., 2003). Systemizing is the ability to generate rules for a system and understand the processes underlying those rules. Individuals who can systemize tend to be very detail-oriented, understand patterns and thus can predict input and output relationships (ie: variable A correlates with outcome B). Such examples include memorizing the patterns of a train timetable (numerical system), understanding how to operate a video recorder (mechanical system), understanding a computer logarithm (abstract systems) or differentiating between types of stones (collectible system) (Baron-Cohen, 2009). Stronger systemizing in males may also relate to their appeared superior spatial abilities, specifically those of 2D and 3D mental rotation tasks and targeting (Voyer, Voyer, & Bryden, 1995; Collins & Kimura, 1997). For contextual-based systems such as social interactions, systemizing cannot be easily applied, as human emotions and behaviour tends to be highly variable. Empathizing is in opposition to systemizing with females tending to outperform males in this domain. A Type E brain appears to impart the ability to understand others via interpretation of their mental states and requires skills in empathy and communication in order to respond appropriately (Baron-Cohen, 2009; Baron-Cohen et al., 2005). Females tend to possess better social skills, language abilities, and verbal fluency as compared to males (Hines et al., 2003; Knickmeyer et al., 2006a) which may be related to their capacity to better understand and predict human behaviour (Baron-Cohen, 2009; Baron-Cohen, 2002; Knickmeyer, Baron-Cohen, Raggatt, Taylor, & Hackett, 2006b). Studies using the Empathizing and Systemizing Quotients (the EQ and SQ) have shown that in a sample of 114 males from the United Kingdom and Canada, the Type S profile was most prominent at 53.5% followed by Type B at 23.7%, Type E at 16.7%, Extreme Type S at 6.1% and no males displaying Extreme Type E profiles. In a related sample of 164 females, 44.2% of females had a

Table 2 Cognitive profiles and attributes that best describe them according to the Empathizing-Systemizing theory

Type of Cognitive Profile	*Attribute*
Type E (E > S)	Individuals who have stronger empathizing than systemizing abilities
Type S (S > E)	Individuals whose systemizing is stronger than their empathizing
Type B (S = E)	Individuals whose empathy is as good (or as bad) as their systemizing (B stands for "balanced")
Extreme Type E (E >> S)	Individuals whose empathy is above average, but who are challenged when it comes to systemizing
Extreme Type S (S >>E)	Individuals whose systemizing is above average, but who are challenged when it comes to empathy

(Adapted from: Baron-Cohen S. Autism: the empathizing-systemizing (E-S) theory. Ann N Y Acad Sci. 2009 Mar;1156:68-80)
S= systemizing ability; E= empathizing ability

Type E profile, 35% with Type B, 16.5% with Type S, 4.3% with Extreme Type E and none having an Extreme Type S profile (Baron-Cohen et al., 2003; Goldenfeld et al., 2005). Although individual variations are apparent, there is still a strong sex difference in systemizing and empathizing abilities.

The Extreme Male Brain Theory

Baron-Cohen's Extreme Male Brain (EMB) theory of autism is an extension of his E-S theory. It contends that individuals with ASCs have an Extreme Type S cognitive profile which results in higher than average systemizing with impaired empathizing (Baron-Cohen, 2009; Baron-Cohen et al., 2009). Lowered empathizing would then be responsible for their social and communication deficits, exemplified by the difficulties these individuals have in understanding and responding to others, while superior systemizing abilities would be attributed to their detailed and pattern-oriented behaviour and inability to predict human emotions and behaviours (Baron-Cohen, 2009). Results of a Japanese study showed that from a sample of 38 males and 10 females, 31.6% of ASC individuals have an Extreme S type brain, whereas 36.8% had a Type S brain, 28.9% a Type B, 2.6% a Type E and none had Extreme Type E (Wakabayashi et al., 2007). Similar results were found in a separate sample of high functioning autistic individuals (33 males, 14 females): 46.8% had an Extreme Type S brain and 40.4% had a Type S profile (Baron-Cohen et al., 2003; Goldenfeld et al., 2005). Note, however, that ASC individuals in these studies were predominantly male, a caveat typical of this work given the higher incidence rate of these disorders in males. Taken together the results of these studies further support the EMB theory (Baron-Cohen, 2009;Wakabayashi et al., 2007; Goldenfeld et al., 2005) in that a large proportion of autistic individuals fall within the range of Extreme Type S to Type S cognitive profiles, indicative of even higher systemizing ability than the typical male profile.

The Foetal Testosterone Theory of Autism

The Foetal Testosterone (fT) theory of autism is rooted in the sex difference that exists in ASCs. It relates to the EMB and E-S theories because androgens are hypothesized to play a role in foetal brain development (Geschwind & Behan, 1982; Geschwind & Galaburda, 1985; Pomerantz, Fox, School, Vito, & Goy, 1985; Chura et al., 2010) and high fT might thus be a risk factor for the hypermasculinized cognitive profile (Extreme Type S brain) in ASC individuals (Knickmeyer & Baron-Cohen, 2006). In animal studies, changes in prenatal testosterone have been shown to influence neuronal differentiation and postnatal cognitive behaviour (Phoenix, Goy, Gerall, & Young, 1959; Goy & McEwen, 1980). The results of studies with rodents and non-human primates show that the removal or addition of testosterone in males and females in utero during androgen-sensitive critical periods leads to changes in sexually dimorphic behaviour such as spatial abilities, play patterns, grooming, and sexual behaviours (Phoenix et al., 1959; Goy & McEwen, 1980; Wallen, 2005; Goy, Bercovitch, & McBrair, 1988; Casto, Ward, & Bartke, 2003). Indirect evidence stems from observations of androgen receptor binding in key areas of the foetal primate brain such as the hypothalamus, the amygdala, the cerebral cortex, the corpus callosum and the cerebellum (reviewed in 9). Thus, it is proposed that if levels of testosterone change significantly during critical periods, development of these key brain areas would be altered as would be the behaviours they underlie (Baron-Cohen et al., 2009; Hines, 2006). Animal work has shown modulation in the levels of circulating testosterone by maternal stress or alcohol consumption in male offspring (Skuse, 2009; Ward et al., 2003) and in fact, recent work has shown an important positive correlation between cortisol and plasma testosterone levels in the fetus (Chakrabarti et al., 2009; Gitau, Adams, Fisk, & Glover, 2005), further supporting environmental factors as capable of altering circulating testosterone during development.

The organizational effects of testosterone are found within critical periods. The current literature defines one of these periods between weeks 8 and 24 of gestation given that this is when the sex difference in fT is the greatest (Finegan, Bartleman, & Wong, 1989). Some implicate postnatal testosterone in influencing neural development, since there is a surge that occurs immediately after birth. However, no link has yet been reported between postnatal testosterone and sexual dimorphism in behaviour (Wallen, Maestripieri, & Mann, 1995). Part of the difficulty in assessing which behaviours are impacted by changes in foetal testosterone is our inability to alter foetal testosterone levels for ethical reasons. Therefore research with humans consists of evaluating the normal variations in fT levels in the general population and relating these to specific behavioural phenotypes. The direct method of assessing the relationship between fT and autistic traits is to measure fT in

umbilical cord blood, maternal blood, or amniotic fluid in a sample of children and to determine if androgen levels positively correlate with certain male-typical behaviours also seen in ASCs. If ASCs are an extreme of the male-typical brain, and this effect is influenced by surges in prenatal testosterone, then one would expect individuals with higher than average fT to have more male-typical traits and cognitive abilities. For example, males tend to excel at spatial abilities and studies have shown a high male dominance in tasks such as targeting and mental rotation. Females have better social skills, language abilities, and verbal fluency as compared to their male counterparts (Hines et al., 2003; Knickmeyer et al., 2006a). Thus, studies assessing the relationship between fT and cognition would be expected to reveal that individuals with high levels of testosterone would be superior at mental rotation and targeting tasks, while more impaired at empathizing and language abilities (Knickmeyer & Baron-Cohen, 2006). Those individuals with higher fT levels would also demonstrate more autistic traits, such as having problems in social interaction as well as impairments at verbal and non-verbal communication, as compared to people with lower fT levels (Baron-Cohen, 2009; Baron-Cohen et al., 2009).

Most of the studies assessing fT and autistic traits were from the Cambridge Foetal Testosterone Project, which used amniotic fluid samples from 235 women who underwent routine amniocentesis during their second trimester of pregnancy (Auyeung, 2009). This time period represents weeks 14-20 of gestation, which encompasses the critical period mentioned above when surges in fT are reportedly observed (Manson, 2008; Ward et al., 2003). Testosterone levels were analyzed by radioimmunoassay and participants were excluded from the study if the amniocentesis carried chromosomal abnormalities, if twins were the outcome, if the pregnancy led to birth defects, or if medical information was missing (Auyeung, 2009). The healthy children born to these women were enrolled in various studies to evaluate the presence of autistic traits and/or systemizing and/or empathizing traits at different stages of postnatal development. Descriptions and summaries of the results from these studies are detailed below.

When 129 typically developing toddlers aged 18-24 months from the Cambridge Foetal Testosterone Project were assessed using the Checklist for Autism in Toddlers (Q-CHAT) as an outcome measure of autistic traits, the authors found a positive correlation between fT levels and Q-CHAT scores (higher scores indicate more autistic traits), with a significant difference in scores between the males and females (males: 28.09 ± 7.30, females: 24.94 ± 6.52, $p < 0.05$ Cohen's $d = 0.46$, Appendix A, 36). While both foetal oestrogen and testosterone were assessed in their amniotic fluid samples, no relationship with oestrogen was observed (Auyeung, Taylor, Hackett, & Baron-Cohen, 2010).

In another study, a sample of 4-year-olds (24 males, 14 females) was assessed for a relationship between fT and skills of empathy and social interaction – animations of geometric figures were used to assess their ability to understand intentional human interactions. No correlation was found between fT and rates of mental or affective state, whereas fT was negatively correlated with intentional propositions and positively correlated with frequency of neutral propositions (Appendix A, Knickmeyer et al., 2006b). Sex differences in these results were also observed, but no correlation was present when sexes were analyzed separately (Knickmeyer et al., 2006b).

Using the Child's Communication Checklist (CCC), 35 males and 23 females aged 4 years were tested to explore the relationship between fT and quality of social relationships, communication skills, and presence of restricted interests in children of the same age. The results show a negative correlation between fT and scores for quality of social relationships and a positive correlation for restricted interests (Knickmeyer, Baron-Cohen, Raggatt, & Taylor, 2005). Males scored higher on the restricted interests subscale (Cohen's $d = 0.64$), whereas females scored higher for quality of social relationships (Cohen's $d = 0.47$; Appendix A, Knickmeyer, 2005). Further probing reveals no relationship between fT and quality of social relationships for each sex evaluated separately, whereas a correlation between fT and restricted interests was found exclusively in males. Subscales assessing speech, syntax, and pragmatics scores did not show sex differences or a correlation with fT (Knickmeyer, 2005).

In children 6-8 years of age, Chapman et al (2006) evaluated capacity to empathize using one of two tasks; study 1 used an Empathy Quotient (EQ) whereas study 2 used the Reading the mind in the eyes task (Eyes-C). The Eyes-C test involves looking at photos of eye regions, while the remaining facial features are covered, and discerning the emotional state of the photo's subject. In the first study, males scored lower than females on the EQ, interpreted to demonstrate poorer empathizing abilities (mean males' score: 32.62 ± 9.57, females' score: 39.12 ± 7.44, $p<0.01$); Cohen's $d = 0.76$; Appendix A, 38) and fT was negatively correlated with EQ scores ($r = -0.28$, $p< 0.01$). To exclude

sex as a potential confound, the scores for males and females were evaluated separately and the correlation between fT and EQ scores remained in males but was no longer apparent in female subjects.

A negative correlation between fT and Eyes-C scores was reported in the second study (Chapman et al., 2006), thus suggesting that individuals with higher fT levels had more difficulty correctly identifying emotions on the Eyes-C test. This effect remained when analyzing data from males ($r = -0.42$, $p<0.01$) and females ($r = -0.29$, $p<0.05$) separately, further supporting the notion that these differences are due to fT levels and not sex (Chapman et al., 2006).

The relationship between fT levels and sex-typical play was assessed in children aged 6-10 years in the Auyeung et al study (2009). Using the Pre-school Activities Inventory (PSAI), where higher scores reflect male-typical behaviour, the authors found a positive correlation between fT and sex-typical play behaviour in both males ($r = 0.20$, $p<0.05$) and females ($r = 0.42$, $p<0.001$) (Appendix A, Auyeung et al., 2009).

In another study from the Cambridge Foetal Testosterone Project, the authors employed the Childhood Autism Spectrum Test (CAST) and the Child Autism Spectrum Quotient (AQ-CHILD) to assess for autistic traits in 6-10 year-old children. Both instruments are parent-report questionnaires and higher scores translate to increased presence of autistic traits. The results found fT levels to be correlated with CAST ($r = 0.25$, $p < 0.01$) and AQ-Child scores ($r = 0.41$, $p < 0.01$). Males scored higher than females for the combined AQ-Child score (male mean score: 48.75 ± 17.96, female mean score: 34.42 ± 15.01, $t233 = 6.64$, $p < 0.01$) and the CAST score (male mean score: 5.22 ± 4.35, female mean score: 4.65 ± 3.87, $t226.25 = 2.12$, $p < 0.05$; Appendix A, Auyeung, 2009). When analyzing male and female scores separately to determine the correlation between fT and test scores, only the AQ-Child was found to correlate with fT. The CAST was positively correlated with fT in males but not in females (Auyeung, 2009). The authors attributed the negative finding in females to the narrower range in CAST scores and fT levels.

The results of a recent study by an unrelated group using data from the Western Australian Pregnancy Cohort showed a positive correlation between free fT levels (measured from umbilical cord serum) and Pragmatic Language Scores (PLS) ($r = 0.3$, $p < 0.01$) (Appendix A, Whitehouse et al., 2010). Note that higher PLS scores indicate greater difficulty in social communication, a trait typically associated with ASD individuals (Whitehouse et al., 2010). Further details of the six studies from the Cambridge Foetal Testosterone Project and the study from the Western Australian Pregnancy Cohort are presented in Appendix A.

Overall, the results of these studies show a positive correlation between fT levels and autistic traits. The outcome measures assessed different domains of autistic traits such as social skills, attention switching, attention to detail, communication and imagination, thus increasing the comprehensiveness of the findings. Instruments used to measure autistic traits included the Childhood Autism Spectrum Test (CAST), the Autism Spectrum Quotient-Child Version (AQ-Child) and the Checklist for Autism in Toddlers (Q-Chat), which are questionnaires that detect the amount and intensity of autistic traits in a general population (Auyeung, 2009; Auyeung et al., 2010). Note that test-retest reliability and validity studies for these instruments are currently ongoing. Also used was the Pragmatic Language Score (PLS), as verbal communication is known to be affected in ASC individuals (Whitehouse et al., 2010). Social interaction, including quality of social relationships, and presence of restricted interests were also assessed in age appropriate children (Knickmeyer et al., 2006b; Knickmeyer, 2005). Two studies focused on sextypical play (Auyeung et al., 2009) and empathizing (Chapman et al., 2006), both known
to be somewhat sexually dimorphic in children. Thus, the male-typical and autistic traits that were found to correlate with fT levels, such as reduced verbal communication, reduced social interaction, increased restricted interests, male-typical play, and reduced empathizing abilities lend further support to the EMB theory.

Limitations/Evaluation of the Foetal testosterone theory

The fT studies reviewed above appear to strengthen the fT theory of autism. However, an important limitation requiring consideration is that the studies did not assess fT in an ASC sample. Although fT levels were normally distributed and were shown to correlate with autistic traits, the sample was from the general population and not an autistic one. The ideal next step for this group would be to look specifically at children from their population for whom fT was assessed but who now have a diagnosis of ASC to compare to children without this diagnosis or even to children with

a diagnosis of another neurodevelopmental disorder. In fact, Baron-Cohen and his colleagues are currently using the Danish Biobank, where a large number of amniotic fluid samples were collected from pregnant women, in order to evaluate fT levels that they will compare to clinical cases of ASCs within the offspring of the mothers from whom fluid was collected (Baron-Cohen, Auyeung, Ashwin, & Knickmeyer, 2009). The results of this work are highly anticipated.

Another important limitation is that results are correlational, thus fT levels may not directly cause autistic traits, nor does it necessarily account for all of the variability observed. Other researchers suggest that there may be a third unknown factor responsible for both the effects of fT as well as the autistic traits (Barbeau, Mendrek, & Mottron, 2009). For example, Skuse (2009) notes that the fT theory cannot explain whether high fT levels cause ASCs or whether these increase susceptibility to ASCs via genetic factors. Recently, an association between clinical cases of AS, autistic traits, and genes that regulate sex steroids was reported (Chakrabarti et al., 2009). The present data are promising but are, as of yet, inconclusive as the etiological basis of ASCs.

Further criticism of the Cambridge group studies is the single assessment of fT levels and whether they were taken at the same time during development in all individuals (weeks 8-24 being a large range); thus, it is difficult to deem these levels as representative of foetal levels as hormone levels fluctuate over foetal development. Similarly, amniocentesis is generally carried out in women who are older and thus the foetus may be at risk for multiple insults during development. Maternal age, however, was controlled for in all amniotic fluid studies, and there was no correlation between age and outcome measures. Thus, despite its limitations, amniotic fluid is still a valid and the most ethical method for obtaining measures of fT, and may be superior to other methods such as using umbilical cord serum. Umbilical cord testosterone may contain maternal testosterone (as it contains maternal blood), thus may not reflect an accurate measure of fT (Auyeung et al., 2010).

Conclusion

The studies presented herein using direct measurements of fT yielded consistent correlations between higher fT levels and increased ASC characteristics, with effects being more prominent in males, thus supporting the EMB theory. While recognizing that most studies were conducted by a single group as part of the Cambridge Foetal Testosterone Project and that the psychometric properties of the evaluation instruments have been a point of contention for some researchers in this field (Skuse, 2009), these studies are nonetheless an important first step in exploring how biology can affect cognition. Future studies of the EMB theory may help us better understand how biologically relevant events underlie important sex differences in neurodevelopment and behaviour and why one sex appears to be more vulnerable to insults during this critical developmental period.

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Appendix 1: Studies Assessing Foetal Testosterone and Autistic Traits

Study	Sample	Outcome variables	Outcome Measures	Results
Auyeung, B., 2010	N = 66 N = 63	Q-CHAT, amniotic fT and fE levels	fT vs autistic traits in toddlers 18-24 months	Males: fT = (0.80 ± 0.36), Q-CHAT = (28.09 ± 7.30/ for a max. of 100 points) Females: fT = (0.34 ± 0.23), Q-CHAT = (24.94 ± 6.52 for max. of 100 points) Sex-difference effect size: fT (d = 1.36), Q-CHAT (d = 0.46), no effect of fE
Whitehouse, A. J., 2009	N = 78	PLS, fT in umbilical cord serum	TT vs free testosterone and pragmatic language ability in 10 year old females	PLS: mean = 1.06 (SD = 1.72, range: 0–7 out of max of 20 points) FAI = 7850.73 (SD = 22.05, range =6.93–123.53) Free testosterone, but not TT was positively correlated with PLS (R = 0.3, p = 0.009)
Auyeung, B…. Hines, M., 2009	N = 112 N = 100	PSAI, amniotic fT	fT vs sex-typical play in children aged 6-10	Males: fT (m = 0.83, SD = 0.83), PSAI scores (m = 68.95, SD = 10.73 Females: fT (m= 0.33, SD = 0.32), PSAI scores (m = 34.95, SD = 12.48) fT correlated positively with PSAI scores for both girls (r = .42, p < .001) and boys (r = .20, p < .05).
Auyeung, B….Hackett, G., 2009	N = 118 N = 117	CAST, AQ-CHILD, amniotic fT	fT vs empathizing in children aged 6-8	Males: fT (m=0.84, SD=0.41), AQ-CHILD (m=48.75, SD=17.96), CAST (m=2.36, SD=0.82); within sex, positive correlation between fT and AQ-Child and CAST scores Females: fT(m=0.32, SD=0.20), AQ-CHILD (m=34.42, SD=15.01), CAST (m=2.15, SD=0.69); within sex, positive correlation between fT and AQ-Child (no correlation with CAST scores) Between sexes: positive correlation of fT and AQ-Child and CAST scores
Chapman, E., 2006	N = 100 N = 93	EQ-C, Eyes-C Task (N = 40 males, N = 38 females), Amniotic fT	fT vs empathizing in children aged 6-8	Experiment 1: fT vs EQ scores • Males: fT (m=0.81 SD =0.37), EQ (m=32.62 SD =9.57) • Females: fT (m=0.31 SD=0.18), EQ (m=39.12, SD =7.44) • Effect size of sex differences, fT: d = 1.85, EQ scores, d = 0.76 Experiment 2: fT vs Eyes-C task • Males: fT (m=0.79 SD =0.41), Eyes-C (m=15.23, SD = 3.5) • Females: fT (m =0.38 SD =0.27), Eyes-C (m=16.29 SD =3.29) • Effect size of sex differences, fT: d=1.21, Eyes-C: 0.31
Knickmeyer, R., 2006	N = 24 N = 14	Animations showing social interactions (measures empathy) amniotic fT and fE	fT vs ability to disseminate visual stimuli in intentional and human terms in children aged 4	Sex differences: • Males = more neutral propositions (d =0.63) • Females = more affective state terms (d = 0.82), intentional propositions (d = 0.62), more mental state terms (d= 0.49) fT Correlations: fT not associated with mental or affective state terms (within or between sexes), negatively correlated with intentional propositions (between sexes and within sexes for males only), negatively correlated with neutral propositions (between sexes only) No sex differences in fE

Appendix 1 continued: Studies Assessing Foetal Teststerone and Autistic Traits

Study	Sample	Outcome variables	Outcome Measures	Results
Knickmeyer, R., 2005	N = 35 N = 23	CCC, amniotic fT	fT vs quality of social relationships and restricted interests in children aged 4	Sex differences: • Males: fT (m= 1.04 SD = 0.4) • Females: fT (m= 0.40 SD =0.19) Sex differences in effect size: • fT: d = 2.0 CCC subscale on quality of social relationships: Females > Males, d = 0.47 CCC subscale on restricted interests: Males > Females, d= 0.64 for males fT = positively correlated with restricted interests between and within sexes, negatively correlated with quality of social relationships between sexes only

*TD = typically developing, fT = foetal testosterone (measured in nmol/L), fE = foetal oestrogen, Q-CHAT =checklist for autism in toddlers (revised), m = mean, SD = standard deviation, d = Cohen's d, PLS = pragmatic language score (higher scores = more difficulty), FAI = free androgen index (pmol/l), TT = total testosterone, PSAI = Pre-school activities inventory (higher score = more male-typical behavior), CAST = Childhood Autism Spectrum Test, AQ-CHILD = Child Autism Spectrum Quotient, ASC = Autism Spectrum Condition, CPQ = Child's Play Questionnaire, CM = control males, CF = control females, EQ-C = Empathy quotient, Eyes-C task = Reading the mind in the eyes task, CCC = Child's Communication Checklist