Prenatal testosterone exposure is associated with delay of gratification and attention problems/overactive behavior in 3-year-old boys

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ABSTRACT

Sex differences in self-control become apparent during preschool years. Girls are better able to delay their gratification and show less attention problems and overactive behavior than boys. In this context, organizational effects of gonadal steroids affecting the neural circuitry underlying self-control could be responsible for these early sex differences. In the present study testosterone levels measured in amniotic fluid (via ultra performance liquid chromatography and tandem mass spectrometry) were used to examine the role of organizational sex hormones on self-control. One hundred and twenty-two 40-month-old children participated in a delay of gratification task (DoG task) and their parents reported on their attention problems and overactive behavior. Girls waited significantly longer for their preferred reward than boys, and significantly more girls than boys waited the maximum period of time, providing evidence for sex differences in delay of gratification. Boys that were rated as suffering from more attention problems and overactive behavior waited significantly shorter in the DoG task. Amniotic testosterone measures were reliable in boys only. Most importantly, boys who waited shorter in the DoG task and boys who were reported to suffer from more attention problems and overactive behavior had higher prenatal testosterone levels. These findings extend our knowledge concerning organizational effects of testosterone on the brain circuitry underlying self-control in boys, and are of relevance for understanding how sex differences in behavioral disorders are connected with a lack of self-control.

1. Introduction

Delaying an immediate smaller reward for the sake of a later, larger one is incredibly difficult at all ages. Interestingly, the ability to show self-control by resisting predominant impulses for the pursuit of long-term goals already evolves early in life. Self-control in preschoolers is typically investigated with the delay of gratification (DoG) paradigm (Mischel and Ebbesen, 1970), which gives children the choice between an immediate smaller or less preferred reward (e.g. one marshmallow) and a later, larger or more preferred reward (e.g. two marshmallows). The relationship between delay time and parents' as well as caregivers'

ratings of self-control corroborate the validity of the DoG paradigm as a measure of self-control (Duckworth et al., 2013).

A meta-analysis consisting of 33 studies confirmed a small, but significant, female advantage in DoG, which was substantially larger when waiting time was measured continuously instead of a dichotomous measurement of choice behavior (Silverman, 2003). In line with the female advantage in the DoG paradigm, 2135 parents reported better self-control in their 3- to 6-year-old daughters in comparison with their sons on a questionnaire (Tao et al., 2014).

These sex differences fit with the finding that substantially more boys than girls are diagnosed with attention-deficit/hyperactivity

disorder (ADHD; Ramtekkar et al., 2010). Impulsive behavior (Duckworth and Steinberg, 2015) is one of the main DSM-5 (APA, 2013) diagnostic features of ADHD and is reflected by reward-delay impulsivity, defined as the choice of an immediate small reward over a delayed large reward (Patros et al., 2016). Consequently, children with ADHD differ from healthy children in their ability to delay gratification (for a meta-analysis see Patros et al., 2016). Additionally, parents' estimates of attention deficits and hyperactive behavior on questionnaires correlate with the ability to delay gratification in samples of healthy children (Duckworth et al., 2013; Paloyelis et al., 2009). Sex differences in self-control also help to explain the gender gap in school grades. While girls achieve higher grades in the major subjects, they differ from boys in measures of self-control not IQ (Duckworth and Seligman, 2006; Duckworth et al., 2015; Matthews et al., 2009; Weis et al., 2013).

Many sex differences are affected by sex hormones. Testosterone especially, has organizational and activational effects. There is little and conflicting evidence concerning activational effects of testosterone on self-control in adults (Doi et al., 2015; Ortner et al., 2013; Peper et al., 2013). Since there are little variations in circulating sex hormones before puberty, prenatal (for a review see Cohen-Bendahan et al., 2005) or early postnatal testosterone exposure (for a review see Hines et al., 2016) having organizational effects on the brain is likely to play a role in the emergence of the early evident sexual dimorphism in self-control in childhood. Nevertheless, it is indisputable that self-control is affected by the social environment to a great extent. For example, parents serve as a model in the development of self-control in their children and influence their children's self-control via caregiving behavior (for an overview see Bridgett et al., 2015). It also cannot be ruled out that boys and girls face different expectations regarding their self-control abilities (Bembenutty, 2007; Funder et al., 1983).

Supporting the hypothesis that self-control is influenced by prenatal testosterone, male rats normally make more impulsive choices than female rats in a delay-based impulsive choice task. However, these behavioral sex differences disappear when female rats are neonatally injected with testosterone (Bayless et al., 2013). In humans, there is only indirect evidence for prenatal testosterone effects on self-control from studies using the second-to-fourth-digit-ratio (2D:4D). 2D:4D is larger in females than in males early in life and is used as a marker for prenatal testosterone exposure (for a review see Breedlove, 2010). A study with preschoolers found that children who were less able to delay gratification had lower 2D:4D ratios (and supposedly higher prental testosterone levels; Da Silva et al., 2014). However, as this study did not apply separate analyses for boys and girls, the significant results might be due to the fact that both measures (2D:4D and delay of gratification) show sex differences. Another study with adults reported that women with smaller digit ratios on their right hands prefer smaller, more immediate over larger, delayed amounts of money (Lucas and Koff, 2010). Importantly, the specific relationship of 2D:4D with prenatal sex hormone levels is still under debate (Richards, 2017). Only one research group found the assumed negative relationship between 2D:4D and testosterone from amniotic fluid (a more direct measure) in girls (Ventura et al., 2013). Another report on a correlation between 2D:4D and the ratio between testosterone and estradiol from amniocentesis (Lutchmaya et al., 2004) did not separate the sexes for the correlational analyses. Clearly, evidence for an effect of prenatal steroids on self-control in children from a more direct measure of prenatal sex hormones, namely testosterone levels measured in amniotic fluid, is missing.

Amniocentesis is an invasive method of sampling amniotic fluid, normally conducted during the second trimester of pregnancy and is used only in cases of increased risk for genetic and chromosomal anomalies, like increased maternal age. Sex differences in testosterone from amniotic fluid emerge between week 8 and 24 of pregnancy peaking around week 17 (Judd et al., 1976). This corresponds quite well with the timing of amniocentesis and resembles the testosterone peak in serum (Finegan et al., 1989; although the exact relationship

between amniotic and serum testosterone is still not completely understood - for a review see Constantinescu and Hines, 2012). Other sex dimorphic behaviors in early childhood like sex-typed play behavior and empathic behavior have already been found to be associated with prenatal testosterone levels from amniotic fluid (for a review see Auyeung et al., 2013).

The present study explores, for the first time, the effects of prenatal testosterone from amniotic fluid on self-control in early childhood. Self-control behavior was measured in 40-month-old children using a modified version of the DoG task (Mischel and Ebbesen, 1970). Attention problems/overactive behavior were obtained from the parents' report in a questionnaire. Based on previous research, girls were expected to wait longer for their preferred reward than boys and boys to be reported to show more attention problems/overactive behavior than girls. According to the results from an animal study (Bayless et al., 2013) and 2D:4D studies in humans (Da Silva et al., 2014; Lucas and Koff, 2010), we expected children with higher amniotic testosterone levels to be less able to delay gratification in the DoG task and to show more attention problems/ overactive behavior. Furthermore, we expected children showing more attention problems/overactive behavior to be less able to delay gratification in the DoG task.

2. Methods

2.1. Participants

Between 2010 and 2012, a partnership of gynecologists and human geneticists in Duesseldorf, Germany, (Praenatal.de) recruited mothers who underwent amniocentesis for the present study. The children were born between January 2011 and February 2013.

One hundred and fifty-seven Caucasian children (78 female, 79 male) from Duesseldorf (Germany) and surrounding towns took part in the study at a mean age of 40.14 months (*SD* = 0.50 months). Sixteen boys and 18 girls had to be excluded from data analysis because of either refusing to participate in the delay task or the inability to understand the task instructions. Two independent raters that were blind concerning the hypotheses and the waiting time of the children rated the children's understanding of the task. The final sample for data analyses of sex differences in the delay task consisted of 60 girls (mean age: 40.15 months, *SD* = 0.63 months) and 63 boys (mean age: 40.17 months, *SD* = 0.42 months). At the time of delivery the mothers were between 25 and 44 years old (*M* = 38.37 years, *SD* = 3.55 years).

Questionnaire data for one girl was missing because the accompanying parent did not complete the *Preschool and Kindergarten Behavior Scales-II* (PKBS-II; Al Awmleh and Woll, 2013) and three amniotic fluid samples (for one boy and two girls) were missing due to problems during sample handling. All parents gave informed consent for participation, recording and storage of data and received a refund of their travel expenses. The study was approved by the local Ethics Committee of the Science Faculty of the University of Duesseldorf, Germany.

2.2. Materials and procedure

2.2.1. Prenatal testosterone concentration measurement

Prenatal testosterone levels[1] were measured in amniotic fluid from amniocentesis samples of mothers recruited from *Praenatal.de* and were carried out on average in week 14.75 of pregnancy (*SD* = 0.85 weeks). Amniotic fluid samples were analyzed with ultra-performance liquid chromatography and tandem mass spectrometry. This method allows for highly sensitive and specific simultaneous assessment of multiple biomarkers in amniotic fluid and it is not based on single-analyte

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[1] Amniotic estradiol and estriol values were also available from the sample but were used for explorative analyses only. No significant relationship to the behavioral data was found for these hormones.

Table 1
Frequencies of the chosen snacks for the DoG task for boys and girls.

		Boys	Girls
First choice	Cookie	16.9 %	13.6 %
	Cake	6.8 %	15.3 %
	Lollipop	47.5 %	49.2 %
	Yoghurt	16.9 %	8.5 %
	Cheese	6.8 %	1.7 %
	Salami	5.1 %	11.9 %
Third choice	Cookie	27.1 %	26.3 %
	Cake	35.6 %	14.0 %
	Lollipop	6.8 %	10.5 %
	Yoghurt	5.1 %	14.0 %
	Cheese	10.2 %	21.1 %
	Salami	15.3 %	14.0 %

assessments, unlike most traditional immunoassays. Previous studies already used different mass-spectrometric approaches, including gas-chromatography, mass spectrometry, and liquid-chromatography tandem mass spectrometry for the assessment of steroids in amniotic fluid (Fahlbusch et al., 2015; Hill et al., 2010; Ventura et al., 2013). The exact hormone analysis method is described by Rivet et al. (2018) reporting on the current sample. The testosterone levels of the girls were not used for subsequent statistical analyses because 57 of 58 testosterone values available fell under the limit of detection (0.02 ng/ml) or between the limit of detection and the limit of quantification (0.05 ng/ml).

2.2.2. Delay of gratification task

The children were tested independently. They were instructed by a female experimenter to choose an order of preference for six different snacks – a cookie, a small madeleine cake, a dextrose lollipop, a small yoghurt, a piece of cheese (gouda), and a salami snack – and the child's preferred snack and the third choice were used for the DoG task. For 49.2% of the girls and 47.5% of the boys the lollipop was the most preferred snack (see Table 1 for the frequencies the different snacks were used for the DoG task for boys and girls).

Sitting with the children at a children's table with two small chairs, the experimenter explained that she would leave the room and the children could either wait for the preferred reward until the experimenter comes back by herself or abandon the waiting period by ringing a bell with the consequence of receiving only the third choice. All children were allowed to try out ringing the bell. The children were not allowed to get up from the chair or unwrap the snacks which remained in front of the children on the table during the waiting period. After giving the instructions the experimenter asked the children three questions to check for their understanding – "Where am I while you are waiting?", "What do you have to do to receive your preferred choice?" and "What do you have to do if you don't want to wait any longer?". If the children were able to answer the questions correctly, the experimenter left the room for the laboratory next door and a second experimenter who monitored the cameras and instructed the parents started the time measurement. Otherwise, instructions were repeated until the children understood the rules or the task was ended due to a lack of understanding. The children were not aware of the maximum waiting period which covered 8 min. When the children rang the bell or waited the maximum time span, the experimenter returned to the laboratory to hand over the respective snack. The entire task was videotaped by two cameras from different angles of the room to identify any breaking of the rules and to later evaluate if the child understood the rules of the task.

2.2.3. Questionnaire

The German version of the *Preschool and Kindergarten Behavior Scales-II* (PKBS-II; Al Awmleh and Woll, 2013; Merrell, 2002) consists of two scales – the *Social Skills Scale* with the subscales *Social Cooperation, Social Interaction* and *Social Independence* and the *Problem Behavior Scale*

consisting of the subscales *Self-Centered/Explosive, Attention Problems/Overactive* and *Antisocial/Aggressive*. The items are answered on a 4-point-scale ranging from "0 – never" to "3 – often". The questionnaire was presented on a laptop screen with the software *Presentation* (Neurobehavioral Systems, Berkeley, USA) and completed by the accompanying parent (mostly the mother). In the present experiment, the subscale *Attention Problems/Overactive* was of interest as previous studies indicated that more attention problems and overactive behavior are associated with a lower ability to delay gratification (Duckworth et al., 2013; Paloyelis et al., 2009).

2.3. Statistical analysis

Sex differences in the waiting time in the DoG task as well as the scores in the PKBS-II scale *Attention Problems/Overactive* were analyzed with independent-sample *t*-tests. To further evaluate sex differences in DoG a chi-square test was used to test for the difference in the number of girls and boys that waited the maximum period of time.

Since the prenatal testosterone levels were not normally distributed, the values were transformed using a square root transformation for statistical analyses. Pearson correlations were used to examine the relationships between the waiting time in the DoG task and the reported attention problems/overactive behavior, the waiting time and the transformed testosterone values, as well as the reported attention problems/overactive behavior and testosterone in both sexes separately.

As stated in the introduction section, the following variables show consistent sex differences, therefore related hypotheses were formulated unidirectional and statistical tests conducted one-tailed: Girls are better able to delay gratification than boys. Boys show more attention problems/overactive behavior than girls. A worse ability to delay gratification, and more attention problems/overactive behavior are associated with higher prenatal testosterone levels.

Significance levels were set to 0.05 for all comparisons. Effect sizes *Cohen's d* and Pearson *r* are interpreted using the interval boundaries set by Cohen (1988; small effect d $\geq$ 0.20 or r $\geq$.10, medium effect d $\geq$ 0.50 or r $\geq$.30 and large effect d $\geq$ 0.80 or r $\geq$.50).

3. Results

Girls (M = 374.35 s; SD = 163.95 s) waited significantly longer than boys (M = 297.29 s; SD = 204.63 s; see Fig. 1) to receive their preferred reward (t(117.60) = 2.31, p = .012, *one-tailed, d* = 0.42, *unequal variances*; Levene's test of homogeneity of variances: F(1,121) = 13.70; p < .001) and more girls (63.3%) than boys (44.4%) delayed gratification for the maximum time span (8 min; χ^2(1) = 4.41, p = .018, *one-tailed, d* = 0.39).
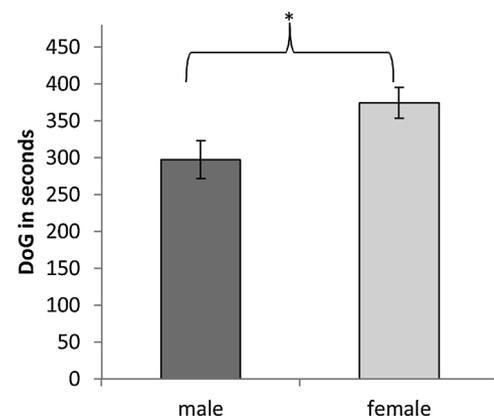
Fig. 1. Mean waiting time in the delay of gratification (DoG) task (480 s max.). Error bars represent the standard errors of the means.
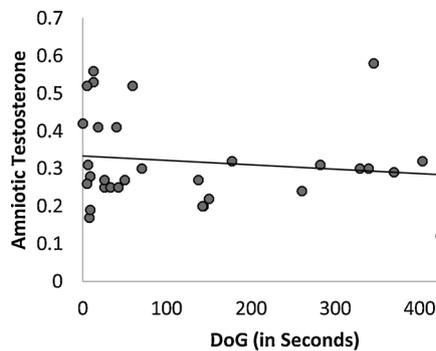* p < .05

Fig. 2. Relationship between amniotic fluid testosterone (square root transformed values) and waiting time in the DoG task (480 s max.) for boys.

Fig. 3. Relationship between amniotic fluid testosterone (square root transformed values) and parents' answers on the PKBS-II Scale "Attention problems/overactive" for boys.

According to the parents' answers on the PKBS-II Scale *Attention Problems/Overactive,* boys tended to show more attention problems and overactive behavior than girls, however there was no significant difference (boys: $M = 18.40$, $SD = 3.46$; girls: $M = 17.37$, $SD = 3.61$; t (120) = 1.60, $p = .056$, *one-tailed*, $d = 0.29$). Boys that were rated as suffering from more attention problems and overactive behavior waited significantly shorter in the DoG task ($r = -0.33$, $p = .008$) while there was no such relationship in girls ($r = -0.02$, $p = .910$).

Boys had higher amniotic testosterone levels than girls (boys: $M = 0.10$ ng/ml, $SD = 0.07$ ng/ml; girls: $M = 0.02$ ng/ml, $SD = 0.01$ ng/ml; $t(69.55) = 12.74$, $p < .001$, $d = 2.33$, unequal variances). The testosterone levels of the girls were not used for subsequent statistical analyses because 57 of 58 testosterone values available fell under the limit of detection (0.02 ng/ml) or between the limit of detection and the limit of quantification (0.05 ng/ml). For the calculation of the mean testosterone level of the girls as well as sex differences in testosterone levels the non-detectable levels of the girls were set to the square root of the minimum detectable level (0.02 ng/ml). The effectively measured testosterone levels between the limit of detection and the limit of quantification were used for these analyses although they are less reliable than the levels over the limit of quantification.

With respect to the predicted effect of prenatal testosterone on self-control, boys with higher amniotic testosterone levels waited shorter in the DoG task ($r = -0.23$, $p = .040$, *one-tailed*; see Fig. 2) and were reported to show more attention problems and overactive behavior by their parents ($r = 0.26$, $p = .021$, *one-tailed*, see Fig. 3).[2]

4. Discussion

The present research explores, for the first time, the role of prenatal sex hormones in early childhood self-control. As expected, girls outperformed boys in the ability to delay gratification. The girls waited longer than the boys to receive their preferred reward and more girls than boys waited the maximum time span. The most important finding of our study is the predicted relationship between self-control and amniotic testosterone in boys. Both self-control measures (the waiting time in the DoG task, and the parents' ratings of attention problems/overactive behavior) are significantly correlated with the prenatal testosterone levels in boys. To our knowledge, this is the first study showing that boys who are prenatally exposed to higher levels of testosterone (directly measured in amniotic fluid) are less able to delay gratification and are rated as suffering from more attention problems
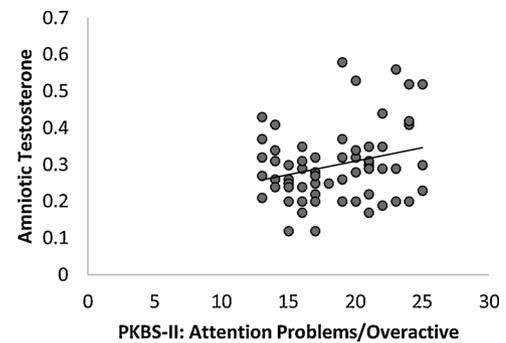
and overactive behavior by the age of three years.

The sex difference in DoG is in line with the meta-analysis by Silverman (2003). In contrast to studies that did not find a sex difference in DoG, the present study comprises a larger sample size and the children's preferences were maximized by measuring their individual liking of six different snacks. Many previous studies gave children the choice just between two rewards - an immediate small or less preferred reward and a later larger or preferred reward (e.g., Mischel and Ebbesen, 1970; Mischel et al., 1972). This approach has the disadvantage that individual differences in taste may affect the waiting time. Letting the children choose their preferred snack from a variety of different snacks increases the temptation (Duckworth et al., 2013) and may reduce interindividual variance in their preferences for the later reward. The fact that more girls than boys waited the maximum time span (and thus produced a ceiling effect) suggests that the "real" sex effect in waiting time might even be somewhat larger. That 34 children had to be excluded from the task might be attributed to the fact that the children were quite young to participate in a DoG task and understand the instructions, and to some extent they might have been afraid to be left alone in an unfamiliar room.

It further strengthens the validity of our DoG task that boys who were reported to show more attention problems and overactive behavior were less able to delay gratification. This is in line with previous research (Duckworth et al., 2013; Paloyelis et al., 2009). The non-significant relationship in girls probably arises at least partly from the more restricted variances in the girls' waiting times in comparison with the boys' (highly significant Levene's test of homogeneity of variances).

Amniotic testosterone levels of 57 girls fell under the limit of quantification and could not be used for statistical analyses. In studies that reported measurable amniotic testosterone levels of girls (Beking et al., 2018; Forest et al., 1980; Knickmeyer et al., 2006; Kung et al., 2016; Lutchmaya et al., 2004; Robinson et al., 1977) radio-immunoassays were applied as analytical method, which differs from the method we applied (Rivet et al., 2018). For example, immunoassays are prone to cross-reactivity, which may in part explain higher mean values in these publications as compared to those presented here. Other studies using gas or liquid chromatography and tandem mass spectrometry to analyze steroid concentrations in amniotic fluid have shown comparable testosterone levels (Fahlbusch et al., 2015; Wudy et al., 1999). Taking into consideration that the primary source of prenatal testosterone in male fetuses are their testes it seems plausible that female fetuses at most have very low testosterone levels produced by their adrenal glands and the mothers' adrenal glands, ovaries and fat (Gardner and Shoback, 2011; Knickmeyer and Baron-Cohen, 2006).

The relationship between self-control and amniotic testosterone in boys is likely to be established by organizational effects of prenatal testosterone on the neuronal circuitry of self-control which consists of three key areas – the prefrontal cortex, the amygdala and the ventral striatum (Casey, 2015; Luerssen et al., 2015). Regarding sex hormone

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[2] 2D:4D was also measured as a possible marker of prenatal testosterone effects at every follow-up of our longitudinal study (age: 5 months, 9 months, 20 months and 40 months). Due to drop out in the course of the longitudinal study and non-measurable hand scans, there only existed 2D:4D scores for about half of the described sample that did not show significant correlations with the DoG task or the questionnaire.

effects, the orbitofrontal cortex (OFC, as part of the prefrontal cortex) shows a high density of androgen receptors in non-human primates (Clark et al., 1988; Finley and Kritzer, 1999). Interestingly, women with complete androgen insensitivity syndrome (CAIS), who are genetically male (46,XY karyotype), but have a female phenotype in consequence of a complete androgen resistance, show a stronger functional connectivity from the amygdala to the medial prefrontal cortex (like female controls) in comparison with 46,XY males (Savic et al., 2016). This study contradicts the possible assumption that there is a direct sex chromosome-mediated effect on the neuronal structures underlying self-control. However, there is no study on CAIS women that would directly address possible sex chromosome-mediated effects on self-control. Furthermore, a study which measured prenatal testosterone levels in amniotic fluid has shown that boys (age: 8–11 years) with higher prenatal testosterone levels had lower grey matter volumes in the posterior lateral orbitofrontal cortex and that this region was larger in a female control group. Moreover, amniotic testosterone has been found to be a significant predictor of striatal sensitivity to positive facial cues (Lombardo et al., 2012). Additionally, an MRI-study on aborted fetuses during the early second trimester revealed that the frontal lobe develops quickly during this specific prenatal period (Zhan et al., 2013) which is presumed to be the most important period for organizational effects of prenatal testosterone on the developing brain (Cohen-Bendahan et al., 2005). Based on these findings it seems plausible to hypothesize that prenatal testosterone might act on the aforementioned brain areas that are associated with self-control.

The results are of relevance for understanding the roots of sex differences in the occurrence of ADHD, an illness associated with choice-impulsivity (Patros et al., 2016) that arises in childhood before the onset of puberty (ICD-10 as well as DSM-V criterion: early onset of symptoms before the age of 7; APA, 2013; WHO, 1992) and therefore before activational effects of sex hormones play a role. Furthermore, the results have implications for the understanding of sex differences in drug abuse which is also associated with poor self-control. As activational effects of gonadal steroids on drug abuse were established before (for a review see Fattore and Melis, 2016), little is known about a potential prenatal vulnerability for poor self-control following a high testosterone exposure in-utero. Our research adds to a more comprehensive knowledge of the interaction between organizational and activational effects of gonadal steroids on self-control, although much more research is needed to disentangle hormonal effects on self-control and replicate our findings. Future research should also consider the neonatal testosterone surge in boys that has been shown to be related to sex-typical play behavior (Lamminmaki et al., 2012; Pasterski et al., 2015).

5. Conclusions

This study is the first that shows a relationship between prenatal testosterone from amniocentesis and self-control for three-year-old boys. The findings extend our knowledge concerning organizational effects of testosterone on the brain circuitry underlying self-control and are of relevance for understanding how sex differences in behavioral disorders are connected with a lack of self-control.

Declarations of interest

None.

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