No difference in cognitive performance or gender role behavior between men with and without hypospadias

Anna Strandqvist[a,b,*], Lisa Örtqvist[a,f], Louise Frisén[c,d], Agneta Nordenskjöld[a,e,f], Agneta Herlitz[b], Anna Nordenström[a,g]

[a] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[b] Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[c] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[d] Child and Adolescent Psychiatry Research Center, Stockholm, Sweden
[e] Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden
[f] Department of Pediatric Surgery, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[g] Department of Pediatric Endocrinology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

ARTICLE INFO

ABSTRACT

Background: Hypospadias is a common malformation of the male external genitalia that results in urethral displacement with different levels of severity. Male genital development during the fetal period is dependent on androgen function, while the etiology of hypospadias differs and can be multifactorial. The psychosocial outcome is sometimes affected, but according to several studies acceptable. The question of whether hypospadias is associated with differences in psychosexual development has been investigated previously, with mixed results. There are no previous investigations of cognitive abilities in men with hypospadias.
Objective: The aim of this study was to investigate whether hypospadias is associated with differences in performance on cognitive tests and/or gender role behavior.
Participants: Eighty-six men with hypospadias were compared to male and female controls from the general population.
Procedure: Cognitive tasks, previously shown to yield group level sex differences and questions regarding self-reported childhood gender role behavior, were administered either at an outpatient clinic visit or via online participation.
Results: The cognitive performance of men and women in the control groups differed significantly in the expected directions. Men and women also differed on self-reported childhood gender role behavior questions. There were no significant differences between men with and without hypospadias on any of the measures. Men with proximal hypospadias performed slightly lower on many of the cognitive tasks in comparison to men with distal hypospadias and controls.
Conclusion: In general, hypospadias is not associated with differences in performance on cognitive tests that typically yield sex differences or with altered gender role behavior in childhood. Further studies on cognitive abilities in boys and men with proximal hypospadias are warranted.

1. Background

Hypospadias is a congenital malformation of male external genitalia characterized by a displacement of the urethral opening (van der Zanden et al., 2012). The severity of hypospadias ranges from the urethral opening being placed just below the glans to a situation with the meatus located under a bifid scrotum to the extent that there can be initial uncertainty about sex assignment. It is one of the more common malformations with a prevalence of 1/125 newborn boys in Sweden (Nordenvall et al., 2014). There is an increasing incidence over time, which is also observed worldwide (Springer et al., 2016). The factors contributing to the occurrence of hypospadias can be both monogenic and polygenic or multifactorial, as a result of genetic and environmental effects. In many cases, the etiology remains unknown (Bouty et al., 2016; van der Zanden et al., 2012).

Hypospadias usually presents as an isolated condition, but can be

associated with other malformations, such as cryptorchidism or inguinal hernia, and has also been described as a feature of many rare syndromes. Surgical interventions, if necessary, are usually carried out during the first or second year. In the consensus statement from 2006, severe hypospadias was classified as 46,XY DSD in the proposed nomenclature for individuals with disorders/differences of sex development (DSD) (Hughes et al., 2006).

Classification of hypospadias includes a description of the meatal position. Distal hypospadias refers to a meatus located on the glans or in the corona and is the most common presentation (60–65% of patients). A penile form indicates that the meatus is located on the penile shaft (20–30%) and proximal hypospadias refers to a meatal location in a penoscrotal, scrotal, or perineal position, which affects 10–15% of patients. The placement of the urethra in hypospadias has been proposed to correspond to the timing of developmental arrest since the fusion of the urethral folds typically occurs in a proximal to distal direction during the first trimester of gestation. In rats, this has been shown to depend on androgen action during a temporally restricted "sensitive period", corresponding to 8–14 weeks in human development (Welsh et al., 2008).

Male genital development is an androgen-driven process, which makes it sensitive to endocrine-related disruptions due to the production, availability, metabolism, or actions of sex steroids. Testosterone is produced in the Leydig cells in the testes and is converted into the more potent androgen, dihydrotestosterone, DHT, by the enzyme 5α reductase. DHT binds stronger than testosterone to the androgen receptor and is required for the formation of external genitalia (Russell and Wilson, 1994; Sharpe, 2006). Androgen insensitivity can cause or contribute to hypospadias (Kalfa et al., 2013). In complete androgen insensitivity (CAIS), individuals are born and gradually develop a female phenotype, whereas in partial AIS, hypospadias can be an obvious part of the clinical presentation. Disturbances in androgen action are thought to be one of several underlying reasons for hypospadias. Both androgen insensitivity and synthesis defects result in hypospadias in fetuses with 46, XY karyotype, which has led to the interpretation that hypospadias is a sign of deficiency of androgen action, which may not always be the case.

The literature on psychosocial adjustment in boys with hypospadias, reviewed in Schönbucher et al. (2008), describes a temporal increase of studies reporting acceptable psychosocial outcome. However psychosexual development can still be affected in terms of negative satisfaction with cosmetic results and aspects of sexual functions (Örtqvist et al., 2017).

Sex-typical gender role behavior has been shown to depend, at least to some extent, on exposure to androgens prenatally (Hines et al., 2015) and postnatally (Pasterski et al., 2015). Previous research has indicated that there is a dose-response effect, showing that exposure to higher levels of androgens prenatally affects play behavior (Nordenström et al., 2002), spare time interests (Berenbaum et al., 2012) and choice of occupation among girls with CAH (Frisén et al., 2009), a condition of cortisol deficiency leading to higher prenatal levels of androgens due to deficient regulation of the HPA axis (Speiser, 2015). Some of these girls, particularly those with severe forms of the condition prefer spare time activities and occupations in more male dominated areas. In individuals with differences in sex development, variation in gender role behavior is more common than in the general population. This is to be expected since many DSD conditions includes an atypical hormonal situation during periods of rapid brain development and sometimes atypical sex chromosomes, thereby introducing a genetic and hormonal impact that may or may not alter aspects of psychosexual development.

Whether gender role behavior is altered in boys and men with hypospadias has, however, only been investigated in a small number of previous studies which show conflicting results. One study (Sandberg et al., 1989) reported more cross-gendered behavior not related to severity, whereas another study showed small but significant increases in masculine behavior in comparison with male controls (Sandberg et al.,

1995). A study comparing boys with hypospadias with boys operated on for inguinal hernia found no differences between the two groups (Schönbucher et al., 2008). In a previous study from our group, males with distal hypospadias reported male typical gender role behavior and core gender identity in adulthood but males with proximal hypospadias were slightly less satisfied with the assigned gender and had slightly less male-typical behavior in adulthood, compared to male controls (Örtqvist et al., 2017).

Differences in gender role behavior and cognition between men and women are well documented (Miller and Halpern, 2014). Typically, men tend to outperform women on three-dimensional spatial rotation tasks, while women perform better on verbal and memory tasks (Miller and Halpern, 2014). Despite significant overlap and greater variation within than between men and women (Hyde, 2005), this is a highly replicated finding.

Gender role behavior, like preferences for spare time activities, is usually assessed through self-report. Childhood play is one way to operationalize gender role behavior. Particularly in the preschool years, play behavior in boys and girls differ regardless if direct observational methods are used (Pasterski et al., 2005) or self-report (Berenbaum, 1999).

The aim of this study was to compare performance on cognitive tasks and self-reported childhood gender role behavior between men with hypospadias and age-matched controls. In particular, we wanted to test the performance on cognitive tasks that usually show differences between men and women (Collaer and Nelson, 2002; Herlitz et al., 1997; Miller and Halpern, 2014). Hypothetically, if altered androgen action during early gestation has any effect on cognitive performance in adulthood, men with hypospadias would be expected to perform at a lower level than male controls on tasks where men typically outperform women, and at a higher level on tasks where women typically outperform men; and men with hypospadias would also be expected to report less male-typical gender role behavior. Furthermore, men with more severe forms would be more prone to report a less masculine play style.

2. Materials and methods

2.1. Participants

Patients and controls, males and females, were recruited when participating in a follow-up study of long-term surgical and psychosocial outcomes of hypospadias. The patients recruited to this study were identified through hospital records, born between 1959 and 1994, operated on for hypospadias in Stockholm and Gothenburg (Örtqvist et al., 2015). A total of 1030 men with hypospadias were invited to participate. Participation in cognitive testing was optional and of the 167 patients that completed participation in the psychosocial outcome part of the study, 83 agreed to also participate in the cognitive assessments. Of these, 73 had distal form of hypospadias and 10 had a proximal type. As controls, a total of 1000 men from the Swedish National Population Registry, matched for age, sex, and region, were invited to participate as controls in the follow-up study of long-term surgical and psychosocial outcomes of hypospadias. Of the 169 that completed participation, 89 agreed to participate in cognitive testing (Örtqvist et al., 2015).

Women participating as controls in a cross-sectional follow-up of women with DSD carried out at Karolinska University Hospital were recruited as female controls. Originally, they were selected from the National Population Registry (Engberg et al., 2015) and were matched for date of birth with the female patients participating in the follow-up. Eighty women agreed to participate.

2.2. Procedure

In the invitation letter, patients with distal hypospadias ($n = 73$) and male controls ($n = 89$) were given the opportunity to participate in

the cognitive testing online from home. Thirty patients ($n = 24$ with distal, $n = 10$ with proximal hypospadias) completed tests as part of an outpatient clinic visit and also completed the web-based battery of cognitive tests on this occasion. The remaining patients ($n = 49$) participated online. Nine male controls participated in an outpatient clinic visit and the remaining male controls ($n = 80$) participated online. Sixty-two female controls participated in an outpatient clinic visit and 18 online. After the initial invitation, patients and controls received two follow-up reminders to agree to or decline participation. The patient information was the same for patients and controls. We stated that the aim of the study was to investigate associations between cognitive performance and different hormonal or chromosomal situation in groups of patients with variation in sex development.

2.3. Cognitive test battery

A battery of tests was constructed for this study with the possibility of participation online from home or at the clinic. The tasks were chosen because they typically yield sex differences on a group level (see Strandqvist et al., 2018, for a detailed description). The tasks on which men usually outperform women were a spatial judgment task (Collaer et al., 2007) and a three-dimensional mental rotation task (Vandenberg and Kuse, 1978). The tasks on which women usually outperform men were an episodic memory task (Herlitz and Rehnman, 2008), a written verbal fluency task (FAS) and an emotion recognition test, "Reading the mind in the Eye" (Baron-Cohen et al., 2001). A multiple-choice synonym test (SRB), henceforth referred to as "Vocabulary", which usually does not yield sex differences, was also included, together with a task measuring typing speed. The instructions for the cognitive tests were identical for all participants, regardless of diagnosis and mode of participation (online from home or at the clinic).

2.4. Self-reported childhood gender role behavior

The participants completed a questionnaire containing questions about how they recalled childhood gender role behavior, including questions about the sex of their childhood friends prior to 15 years of age, during later adolescence, and in adulthood. There were also questions concerning childhood play behavior differentiating between feminine, masculine, and neutral toy/activity preferences and two questions regarding whether they perceived themselves as being girlish or boyish in childhood. The questionnaire has been developed and used in patient groups within the DSD spectrum and composite scores were calculated accordingly (Hines et al., 2003). The answers were given on a five-point Likert scale ranging from always boys, usually boys, boys and girls equally, usually girls, always girls for questions concerning the sex of friends. In the questions regarding friends in adulthood, the wording of the alternatives was changed to whether the friend was a man or a woman. The alternatives for play style and girlishness/boyishness ranged from not at all, hardly ever, a little, a lot, almost always. The questions were translated into Swedish with two parallel forward translations, which were harmonized into one version and then translated back into English and compared with the original version. Any wording that differed from the original in meaning was adjusted. The

translation was carried out by the authors, AS, AN, and LF.

Some patients ($n = 2$) and controls (women, n = 17, men n = 7) were non-native Swedish speakers and were excluded in the analysis of cognitive task performance since language proficiency could affect their understanding of online instructions and task performance. This applied to vocabulary, episodic memory, word fluency, and emotional recognition.

2.5. Statistical analysis

Age and education for the different groups were compared using a Pearson exact chi square test. Calculations were made to compare mean results on the cognitive tasks with one-way ANOVA with group (female controls/male controls/men with hypospadias) as the between factor. When significant differences arose, post hoc Tukey analyses were computed. Additional analyses to compare men with distal and proximal hypospadias were performed for hypothesis-generating purposes and effect sizes Eta squared ($\eta = \underline{SS_{effect}}/SS_{total}$) for ANOVA and Cohen's d ($M_{group1} - M_{group2}/SD_{pooled}$) for pairwise comparisons were calculated to estimate the magnitude of the difference.

In order to estimate each individual's relative cognitive strengths on the different tasks, we z-transformed the scores on spatial direction, mental rotation, episodic memory, and word fluency. Next, we computed composite scores for tasks where women perform at a higher level and where men perform at a higher level, by calculating the mean of the z-scores for spatial direction and mental rotation, and the mean of the z-scores for episodic memory and word fluency (Dekhtyar et al., 2018). To create a cognitive profile score we took the spatial direction/mental rotation score minus the verbal fluency/episodic memory score. A positive score would indicate that the individual had a relative advantage on spatial directions/mental rotations tasks over verbal fluency/episodic memory tasks whereas a negative score would indicate that the individual had a relative advantage on verbal fluency/episodic memory tasks over the spatial directions/mental rotation tasks.

For the comparisons regarding self-reported gender role behavior, a Kruskal-Wallis test was performed to compare the three groups (female controls/male controls/men with hypospadias) and a Mann-Whitney U test for post hoc comparisons of significant results. For comparisons between men with distal ($n = 73$) and proximal ($n = 10$) hypospadias, a Mann-Whitney U test was used. All statistical analyses were carried out with SPSS vs. 23.

3. Results

3.1. Demographic data

Neither age nor the level of education differed significantly between the three groups (male controls, female controls, men with hypospadias); see Table 1.

3.2. Cognitive performance

There were significant differences between groups (male controls, female controls, men with hypospadias) on all tasks: vocabulary, F (2,

Table 1
Background information on age and level of education, patient and control groups.

	Female controls	Male controls	Men with hypospadias		Distal form	Proximal form
	$n = 80$	$n = 89$	$n = 83$	p	$n = 73$	$n = 10$
Mean age at assessment	30 (20–53)	32 (18–46)	32 (19–46)	n.s.	32 (19–46)	33 (20–45)
Education						
Basic education	3 (4%)	1 (1%)	2 (3%)	n.s.	2 (3%)	0
Secondary education	27 (33%)	29 (33%)	39 (47%)	n.s.	34 (46%)	6 (60%)
Higher education	50 (63%)	59 (66%)	42 (51%)	n.s	38 (51)	4 (40%)

Table 2
Mean performances, standard deviations, p-values and effect sizes (Cohens d) for patient and controlgroups. The expected direction of sex differences is N = neutral, M = male superior, F = female superior.

Expected direction of sex difference on cognitive tasks		Female controls	Male controls	Men with hypospadias	Female vs male		Males vs hypospadias		Females vs hypospadias	
		Mean (SD)	Mean (SD)	Mean (SD)	p	d	p	d	p	d
N	Vocabulary	20.6 (4.6)	22.6 (4.3)	22.0 (4.9)	0.03	−0.45	n.s.	0.12	0.17	−0.30
M	Spatial direction	17.2 (4.2)	19.8 (3.7)	19.3 (3.9)	0.00	−0.72	n.s.	0.18	0.00	−0.54
M	Mental rotation	10.3 (4.3)	13.6 (4.2)	12.4 (5.0)	0.00	−0.75	n.s.	0.19	0.04	−0.44
F	Episodic memory	31.0 (4.1)	29.0 (3.8)	28.8 (3.6)	0.01	0.50	n.s.	−0.04	0.01	0.55
F	Word fluency	55.6 (11.0)	46.6 (11.2)	45.2 (12.1)	0.00	0.81	n.s.	0.12	0.00	0.90
N	Typing	24.9 (5.7)	23.8 (7.5)	21.6 (6.7)	n.s.	0.19	n.s.	0.31	0.02	0.36
F	Emotion recognition	28.3 (3.7)	26.5 (3.7)	26.3 (4.3)	0.03	0.48	n.s.	0.05	0.01	0.50

212) = 3.26, η^2 = 0.03, $p < .04$; spatial directions, F (2, 206) = 8.48, η^2 = 0.08, $p < .001$; mental rotation, F (2, 185) = 7.77, η^2 = 0.08, $p < .001$; episodic memory, F (2, 203) = 5.87, η^2 = 0.05, $p < .003$; typing, F (2, 197) = 3.91, η^2 = 0.04, $p = .022$; word fluency, F (2, 197) = 16.21, η^2 = 0.14 (η^2 = 0.11, corrected for effect of typing speed), $p < .001$,; emotion recognition, F (2, 203) = 4.81, η^2 = 0.05, $p = .009$.

Male and female control groups performed differently on all tasks previously shown to yield sex differences, (i.e. the spatial tasks, the memory task, verbal fluency task and the emotion recognition task). The differences were in the expected directions and effect sizes (Cohens d) ranged between 0.45 and 0.81 (see Table 2). Male controls outperformed female controls on spatial direction ($p < .001$) and mental rotation ($p < .001$), whereas female controls performed at a higher level than males on episodic memory ($p = .011$), word fluency ($p = .002$), and emotion recognition ($p = .028$). There were no significant differences in typing speed ($p = .633$). In addition, and contrary to our expectations, performance also differed significantly on the vocabulary task, demonstrating that male controls outperformed female controls ($p = .034$) (Table 2).

There were no significant differences in performance between male controls and men with hypospadias on any of the tasks (Table 2).

Men with hypospadias did not differ from female controls on vocabulary ($p = .169$), but on all tasks expected to show sex differences. Men with hypospadias outperformed female controls on spatial direction: ($p = .003$), mental rotation ($p = .004$), whereas they performed at a lower level on tasks assessing episodic memory ($p = .005$), word fluency ($p < .001$), emotion recognition ($p = .012$), and typing ($p = .021$) (Table 2).

Additional analyses contrasting men with distal and proximal hypospadias revealed Cohen's d effect size differences in the medium to large range (see Table 3). The small group of men with proximal hypospadias performed at a lower level on all tasks, except on the test of emotion recognition. The differences between men with distal and proximal hypospadias reached significance only for the test of episodic

memory, F (1,74) = 4.85, $p = .031$ and word fluency, F (1,69) = 4.50, $p = .038$ where men with distal hypospadias showed superior performance (Table 3).

The results on the cognitive profile score showed significant differences between groups F (3, 191) = 23.60, $p < .001$. There were significant difference between men and women ($p < .001$) but not between men with and without hypospadias ($p = .763$) or between men with distal or proximal hypospadias ($p = .766$) please see Fig. 1.

3.3. Self-reported childhood gender role behavior

Toy and activity preferences were significantly different between the groups (male controls, female controls, men with hypospadias) on questions regarding feminine preferences, χ^2 (2, N = 241) = 109.29, $p < .001$ masculine preferences, χ^2 (2, N = 244) = 43.82, $p < .001$, neutral preferences, χ^2 (2, N = 244) = 13.61, $p = .001$. Post hoc analyses revealed significant differences between male and female controls on questions regarding feminine preferences, where female controls recalled more feminine preferences than male controls, ($p < .001$), whereas men recalled more masculine preferences than women ($p < .001$). There were also differences regarding neutral preferences, where female controls recalled playing with neutral toys more than male controls ($p = .001$). There were no differences between men with hypospadias and male controls (Table 4a).

3.4. Girlish/boyish

On the retrospective global self-assessment questions, answers differed significantly between groups on girlishness, χ^2 (2, N = 240) = 141.99, $p < .001$, and boyishness, χ^2 (2, N = 238) = 330.00, $p < .001$. In the post hoc analyses, male controls and men with hypospadias differed significantly from female controls ($p < .001$), but men with hypospadias did not differ from male controls (Table 4a).
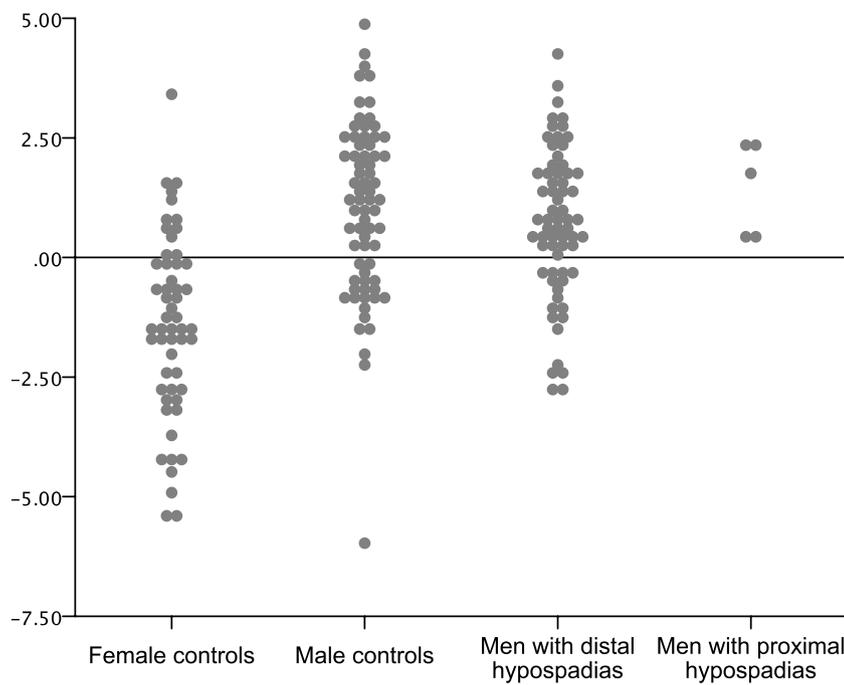
Table 3
Mean performance, standard deviation (SD), p-values and effect size Cohens d for men with proximal vs distal hypospadias. The expected directions of sex differences are N = neutral, M = male superior, F = female superior.

Expected direction of sex difference on cognitive tasks		Men w distal hypospadias n = 73		Men w proximal hypospadias n = 10			
		Mean (SD)	Min/max	Mean (SD)	Min/max	p	d
N	Vocabulary	22.3 (4.5)	(6–29)	18.7 (7.6)	(7–27)	n.s.	0.58
M	Spatial direction	19.3 (3.9)	(2–24)	17.3 (4.5)	(10−23)	n.s.	0.47
M	Mental rotation	12.3 (5.2)	(0−20)	10.4 (4.7)	(6–18)	n.s.	0.38
F	Episodic memory	29.1 (3.5)	(22–39)	25.8 (3.3)	(23−32)	0.03	1.00
F	Word fluency[a]	45.3 (12.6)	(10–80)	37.8 (14.0)	(13–48)	0.04	0.56
N	Typing	21.6 (7.0)	(9–40)	19.5 (4.6)	(14–27)	n.s.	0.35
F	Emotion recognition	26.3 (4.4)	(13–35)	26.3 (1.5)	(25–29)	n.s.	0.00

[a] indicates that typing was included as a covariate in an ANCOVA when calculating the p-value.

Fig. 1. Distribution of cognitive profile score. The profile score represents the difference between mean composite score for tests where men typically outperform women (mental rotation, spatial direction) subtracted from mean composite score for tests where women typically outperform men (episodic memory, verbal fluency). A score above 0 indicates that the individual is performing relatively better on spatial tasks (mental rotation, spatial direction) than on memory/verbal tasks (episodic memory, verbal fluency) and the other way around for scores below 0. As can be seen, most but not all male controls and men with distal and proximal hypospadias have a spatial advantage, whereas most but not all women have a memory/verbal advantage.

3.5. Sex of friends

The groups differed on all three questions regarding sex of friends during childhood, χ^2 (2, $N = 228$) = 128.27, $p < .001$, adolescence, χ^2 (2, $N = 227$) = 112.94, $p < .0005$, and in adulthood, χ^2 (2, $N = 228$) = 108.92, $p < .001$. Post hoc analyses showed that male and female controls differed significantly on all three questions ($p < .001$), whereas men with hypospadias also differed from the female control group ($p < .001$), but not from male controls on any of the questions (Table 4a).

3.6. Contrasts of groups based on severity of hypospadias

There were no significant differences between men with proximal hypospadias ($n = 10$) and distal hypospadias ($n = 73$) on any of the survey questions (Table 4b).

4. Discussion

In this study, we compared performance on cognitive tasks and retrospectively self-reported childhood gender role behavior, for men with hypospadias and controls from the general population. The main finding was that there were no significant differences between men with and without hypospadias on any of the measures used. The cognitive performance of men with hypospadias was similar to that of the

male control group and different from that of the female control group. Self-reported recalled childhood gender role behavior was similar in men with and without hypospadias. This is consistent with earlier findings in men with hypospadias concerning play behavior in boys (Sandberg et al., 1995) and gender role behavior in adulthood (Örtqvist et al., 2016).

The pathophysiology of the majority of the men in the presented cohort was not known, which is typical for this patient group. It is plausible that the background is heterogeneous. Besides dysfunction in androgen action, disturbances of male genital development can occur due to mutations in single genes or be the result of problems on the level of gene transcription but they can also be related to issues with general growth. There is an association between hypospadias and low birth weight, and some studies point to placental dysfunction as a critical background factor in many cases. Environmental factors also contribute (van der Zanden et al., 2012) to the background of hypospadias. Therefore, not detecting a difference may be due to the fact that the causative mechanisms were other than androgen-related and/or mixed. It is also possible that a hormonal change at a certain time point during development may be large enough to disturb the genital development, but not large enough to have an effect on brain development and cognition. In order to determine effects of androgens in hypospadias, studies would have to focus on individuals with a known molecular diagnosis and include information on treatment in the beginning of life, for instance DHT or other treatments affecting the hormonal situation.

Table 4a
Medians, range and *p* values for differences in self rated gender role behavior between female controls (FC), male controls (MC) and males with hypospadias (HS men).

	Female controls (FC)		Male controls (MC)		Men with hypospadias		FC vs MC	MC vs hypospadias
	Median	Range	Median	Range	Median	Range	*p*	*p*
Toys/activities (F)	13.3	13.3	6.7	12.0	6.7	12.0	0.00	n.s.
Toys/activities (M)	13.0	10.0	16.0	10.0	16.0	12.0	0.00	n.s.
Toys/activities (N)	15.0	12.0	14.0	12.0	14.0	12.0	0.00	n.s.
Friends in childhood	2.0	3.0	4.0	3.0	4.0	3.0	0.00	n.s.
Friends during adolescence	2.0	3.0	4.0	3.0	2.0	3.0	0.00	n.s.
Friends as an adult	2.0	3.0	4.0	3.0	3.5	3.0	0.00	n.s.
I was girlish	3.0	4.0	1.0	2.0	1.0	3.0	0.00	n.s.
I was boyish	3.0	4.0	4.0	2.0	4.0	2.0	0.00	n.s.

Table 4b
Medians, range and *p*-values for men with proximal vs distal hypospadias.

	Men w distal hypospadias *n* = 73		Men w proximal hypospadias *n* = 10		
	Median	Range	Median	Range	*p*
Toys/activities (F)	6.7	12.0	6.7	4.0	n.s.
Toys/activities (M)	16.0	12.0	16.0	10.0	n.s.
Toys/activities (N)	14.0	12.0	13.0	5.0	n.s.
Friends in childhood	4.0	3.0	4.0	1.0	n.s.
Friends during adolescence	4.0	3.0	4.0	2.0	n.s.
Friends as an adult	4.0	3.0	3.0	2.0	n.s.
I was girlish	1.0	3.0	1.0	1.0	n.s.
I was boyish	4.0	2.0	4.0	2.0	n.s.

On comparing the men with hypospadias of different severity, men with proximal hypospadias underperformed relative to men with distal hypospadias on the cognitive tasks except on the emotion recognition task. The effect sizes were of medium to large magnitudes, although the differences did not reach statistical significance, presumably due to the small number of participants. The range in performance within the group was comparable to that in the group of men with hypospadias, which suggests high variability in the group. Neither age nor the level of education differed significantly between the three groups (male controls, female controls, men with hypospadias); see Table 1. Relative to the control groups, the men with hypospadias less often had higher education although this did not reach significance, in contrast to the male control group (*p* = .11) or the female control group (*p* = .36).

In previous research, men with proximal hypospadias have reported a higher rate of avoidance of close relationships, weaker self-confidence, and lower educational achievements compared to male controls (Örtqvist et al., 2016). In a register-based study, performed by our group, patients with hypospadias were more likely to be diagnosed with intellectual disability (OR 3.2; 95% CI 2.8–3.8) compared with the controls (Butwicka et al., 2015).

Our finding of slightly lower cognitive performance in men with proximal hypospadias may indicate that this group is more vulnerable, not only because of hypospadias and subsequent treatments, but also due to other forms of comorbidity, temporarily or permanently affecting cognitive functions. The results on gender role behavior questions did not differ from those of males with distal hypospadias or those of the male controls.

The results in our study are of clinical importance for families with affected children, individuals with hypospadias and physicians giving information to the parents of children born with hypospadias. It is of value to know that the condition generally is not associated with affected gender role development or negative effects on cognitive abilities. The lower performance of men with proximal hypospadias may be an indication of comorbidity affecting cognitive development, at least in some cases.

4.1. Strengths and limitations

This is, to the best of our knowledge, the first study investigating cognitive abilities in men with hypospadias. It was conducted in a cohort where the patients were recruited from hospital records and compared with age-matched controls from the general population. It is an obvious limitation that the etiology of the hypospadias was not known, which is often the case due to the complex background.

Another limitation is the relatively low overall participation rate. All patients with mid-severity hypospadias declined participation in the cognitive assessments for unknown reasons. The proportion of distal and proximal hypospadias in the groups participating or not participating was approximately the same as in the larger psychosocial study (Örtqvist et al., 2016).

A potential source of bias is the difference in the administration of tests. Patients with hypospadias were more often invited to participate in the web-based assessments at the clinic, whereas controls typically answered questions and participated in the web-based assessments from home. We believe that the online administration generally increased the probability of participation overall in the cohort; however, it could also have increased the risk for self-selection of participants differently, particularly between male and female controls.

The use of retrospective questions introduces a potential bias in remembering. The childhood gender role behavior questions required the participants to remember back over 20 years, making an overall judgment of their own toy preferences and play style. There is therefore a risk of their being influenced by a bias connected to stereotypical expectations regarding sex-typed behavior (Lenton et al., 2001). Further studies with direct observation of play behavior would be needed to validate our results.

5. Conclusion

Men with hypospadias do not perform differently on cognitive tasks and report similar retrospective gender role behavior to that of men without hypospadias. Severe hypospadias can be associated with generally lower performance on cognitive tests, but as our findings were based on a small sample size, these questions should be explored and confirmed in larger samples. In addition, to study hormonal effects, further studies are warranted in boys and men with proximal hypospadias with defined deficiencies in hormone synthesis or action.

References

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42, 241–251.

Berenbaum, S.A., 1999. Effects of early androgens on sex-typed activities and interests in adolescents with congenital adrenal hyperplasia. Horm. Behav. 35, 102–110. https://doi.org/10.1006/hbeh.1998.1503.

Berenbaum, S.A., Bryk, K.L.K., Beltz, A.M., 2012. Early androgen effects on spatial and mechanical abilities: evidence from congenital adrenal hyperplasia. Behav. Neurosci. 126, 86–96. https://doi.org/10.1037/a0026652.

Bouty, A., Ayers, K.L., Pask, A., Heloury, Y., Sinclair, A.H., 2016. The genetic and environmental factors underlying hypospadias. Sex. Dev. 9, 239–259. https://doi.org/10.1159/000441988.

Butwicka, A., Lichtenstein, P., Landen, M., Nordenvall, A.S., Nordenstrom, A., Nordenskjold, A., Frisen, L., 2015. Hypospadias and increased risk for neurodevelopmental disorders. J. Child Psychol. Psychiatry Allied Discip. 56, 155–161.

Collaer, M.L., Nelson, J.D., 2002. Large visuospatial sex difference in line judgment: possible role of attentional factors. Brain Cogn. 49, 1–12. https://doi.org/10.1006/brcg.2001.1321.

Collaer, M.L., Reimers, S., Manning, J.T., 2007. Visuospatial performance on an internet line judgment task and potential hormonal markers: sex, sexual orientation, and 2D:4D. Arch. Sex. Behav. 36, 177–192. https://doi.org/10.1007/s10508-006-9152-1.

Dekhtyar, S., Weber, D., Helgertz, J., Herlitz, A., 2018. Sex differences in academic strengths contribute to gender segregation in education and occupation: a longitudinal examination of 167,776 individuals. Intelligence 67, 84–92. https://doi.org/10.1016/j.intell.2017.11.007.

Engberg, H., Butwicka, A., Nordenström, A., 2015. Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: a total population study. Psychoneuroendocrinology 60, 195–205. https://doi.org/10.1016/j.psyneuen.2015.06.017.

Frisén, L., Nordenström, A., Falhammar, H., 2009. Gender role behavior, sexuality, and psychosocial adaptation in women with congenital adrenal hyperplasia due to CYP21A2 deficiency. J. Clin. Endocrinol. Metab. 94, 3432–3439. https://doi.org/10.1210/jc.2009-0636.

Herlitz, A., Nilsson, L.G., Bäckman, L., 1997. Gender differences in episodic memory. Mem. Cogn. 25, 801–811.

Herlitz, A., Rehman, J., 2008. Sex differences in episodic memory. Curr. Dir. Psychol. Sci. 17, 52–56. https://doi.org/10.1111/j.1467-8721.2008.00547.x.

Hines, M., Ahmed, S.F., Hughes, I.A., 2003. Psychological outcomes and gender-related

development in complete androgen insensitivity syndrome. Arch. Sex. Behav. 32, 93–101. https://doi.org/10.1023/A:1022492106974.

Hines, M., Constantinescu, M., Spencer, D., 2015. Early androgen exposure and human gender development. Biol. Sex Differ. 6, 3. https://doi.org/10.1186/s13293-015-0022-1.

Hughes, I.A., Houk, C., Ahmed, S.F., Lee, P.A., 2006. Consensus statement on management of intersex disorders 2. J. Pediatr. Urol. 2, 148–162. https://doi.org/10.1016/j.jpurol.2006.03.004.

Hyde, J.S., 2005. The gender similarities hypothesis. Am. Psychol. 60, 581–592. https://doi.org/10.1037/0003-066X.60.6.581.

Kalfa, N., Philibert, P., Werner, R., Audran, F., Bashamboo, A., Lehors, H., Haddad, M., Guys, J.M., Reynaud, R., Alessandrini, P., Wagner, K., Kurzenne, J.Y., Bastiani, F., Bréaud, J., Valla, J.S., Lacombe, G.M., Orsini, M., Daures, J.-P., Hiort, O., Paris, F., McElreavey, K., Sultan, C., 2013. Minor hypospadias: the "tip of the iceberg" of the partial androgen insensitivity syndrome. PLoS One 8, e61824–e61826. https://doi.org/10.1371/journal.pone.0061824.

Lenton, A.P., Blair, I.V., Hastie, R., 2001. Illusions of gender: stereotypes evoke false memories. J. Exp. Soc. Psychol. 37, 3–14. https://doi.org/10.1006/jesp.2000.1426.

Miller, D.I., Halpern, D.F., 2014. The new science of cognitive sex differences. Trends Cogn. Sci. 18, 37–45. https://doi.org/10.1016/j.tics.2013.10.011.

Nordenström, A., Servin, A., Bohlin, G., 2002. Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by CYP21 genotype in girls with congenital adrenal hyperplasia. J. Clin. Endocrinol. Metab. 87, 5119–5124. https://doi.org/10.1210/jc.2001-011531.

Nordenvall, A.S., Frisén, L., Nordenström, A., 2014. Population Based Nationwide Study of Hypospadias in Sweden, 1973 to 2009: Incidence and Risk Factors. vol. 191. pp. 783–789. https://doi.org/10.1016/j.juro.2013.09.058.

Örtqvist, L., Andersson, M., Strandqvist, A., 2016. Psychosocial outcome in adult men born with hypospadias. J. Pediatr. Urol. 13 (1). https://doi.org/10.1016/j.jpurol.2016.08.008. 79.e1-79.e7.

Örtqvist, L., Fossum, M., Andersson, M., Nordenström, A., Frisén, L., Holmdahl, G., Nordenskjöld, A., 2015. Long-term followup of men born with hypospadias: urological and cosmetic results. J. Urol. 193, 975–982. https://doi.org/10.1016/j.juro.2014.09.103.

Örtqvist, L., Fossum, M., Andersson, M., Nordenström, A., Frisén, L., Holmdahl, G., Nordenskjöld, A., 2017. Sexuality and fertility in men with hypospadias; improved outcome. Andrology 5, 286–293. https://doi.org/10.1111/andr.12309.

Pasterski, V., Acerini, C.L., Dunger, D.B., Ong, K.K., Hughes, I.A., Thankamony, A., Hines, M., 2015. Postnatal penile growth concurrent with mini-puberty predicts later sextyped play behavior: evidence for neurobehavioral effects of the postnatal androgen surge in typically developing boys. Horm. Behav. 69, 98–105. https://doi.org/10.1016/j.yhbeh.2015.01.002.

Pasterski, V.L., Geffner, M.E., Brain, C., Hindmarsh, P., Brook, C., Hines, M., 2005. Prenatal hormones and postnatal socialization by parents as determinants of male-typical toy play in girls with congenital adrenal hyperplasia. Child Dev. 76, 264–278. https://doi.org/10.1111/j.1467-8624.2005.00843.x.

Russell, D.W., Wilson, J.D., 1994. Steroid 5alpha-reductase: two genes/two enzymes. Annu. Rev. Biochem. 63, 25–61. https://doi.org/10.1146/annurev.bi.63.070194.000325.

Sandberg, D.E., Meyer Bahlburg, H.F.L., Yager, T.J., Hensle, T.W., Levitt, S.B., Kogan, S.J., Reda, E.F., 1995. Gender development in boys born with hypospadias. Psychoneuroendocrinology 20, 693–709. https://doi.org/10.1016/0306-4530(95)00025-9.

Sandberg, D.E., Meyer-Bahlburg, H.F., Aranoff, G.S., Sconzo, J.M., Hensle, T.W., 1989. Boys with hypospadias: a survey of behavioral difficulties. J. Pediatr. Psychol. 14, 491–514.

Schönbucher, V.B., Landolt, M.A., Gobet, R., Weber, D.M., 2008. Health-related quality of life and psychological adjustment of children and adolescents with hypospadias. J. Pediatr. 152, 865–872. https://doi.org/10.1016/j.jpeds.2007.11.036.

Sharpe, R.M., 2006. Pathways of endocrine disruption during male sexual differentiation and masculinisation. Best Pract. Res. Clin. Endocrinol. Metab. 20, 91–110. https://doi.org/10.1016/j.beem.2005.09.005.

Speiser, P.W., 2015. Congenital Adrenal Hyperplasia. F1000Research. https://doi.org/10.12688/f1000research.6543.1.

Springer, A., Van Den Heijkant, M., Baumann, M., 2016. Worldwide prevalence of hypospadias. J. Pediatr. Urol. 12, 152.e1–152.e7. https://doi.org/10.1016/j.jpurol.2015.12.002.

Strandqvist, A., Herlitz, A., Nordenskjöld, A., Örtqvist, L., Frisén, L., Hirschberg, A.L., Nordenström, A., 2018. Cognitive abilities in women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Psychoneuroendocrinology 1 (8). https://doi.org/10.1016/j.psyneuen.2018.05.003.

van der Zanden, L., van Rooij, A., Human reproduction, I, 2012. Aetiology of Hypospadias: a Systematic Review of Genes and Environment. academic.oup.com vol. 18. pp. 260–283. https://doi.org/10.1093/humupd/dms002.

Vandenberg, S.G., Kuse, A.R., 1978. Mental rotations, a group test of three-dimensional spatial visualization. Percept. Mot. Skills 47, 599–604. https://doi.org/10.2466/pms.1978.47.2.599.

Welsh, M., Saunders, P., Fisken, M., Scott, H., Hutchison, G., Smith, L., Sharpe, R., 2008. Identification in rats of a programming window for reproductive tract masculinization, disruption of which leads to hypospadias and cryptorchidism. J. Clin. Invest. 118, 1479–1490. https://doi.org/10.1172/JCI34241.