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Activating effects of cross-sex hormones on cognitive functioning: a study of short-term and long-term hormone effects in transsexuals

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Abstract

In an earlier study we demonstrated that 3 months of cross-sex hormone treatment clearly influenced cognitive functioning in transsexuals. The aims of the present study were to examine: (a) whether we could replicate these findings in a new group of transsexuals; (b) whether a similar pattern of change could be found for novel tasks, i.e. tasks, not used in the previous study, that measured closely related cognitive abilities; (c) whether the cognitive changes following cross-sex hormone treatment had stabilized after 3 months or continued to develop over a period of 1 year; and finally, (d) whether the effects were quickly reversible when the hormone treatment was temporarily stopped. Again a pronounced effect of androgen treatment was found on spatial ability in female-to-male transsexuals (FMs) over a period of one and a half years. As expected, untreated male-to-female transsexuals (MFs) had higher scores on visuo-spatial tasks than untreated FMs; after 3 months of cross-sex hormone treatment, the group difference had disappeared, while after about 10 months of hormone treatment, the sex difference was reversed. These effects did not disappear after termination of cross-sex hormone therapy for a period of 5 weeks, but continued to change slightly in the same direction. Earlier findings of an opposite effect of cross-sex hormones on

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verbal fluency (i.e. MFs improved and FMs deteriorated after 3 months of cross-sex hormone treatment) were not replicated in this study, nor did we find an hormonal influence on other cognitive functions. This study shows that testosterone had an enhancing, and not quickly reversible effect, on spatial ability performance, but no deteriorating effect on verbal fluency in adult women (FMs). In contrast, anti-androgen treatment in combination with estrogen therapy had no declining effect on spatial ability, nor an enhancing effect on verbal fluency in adult men (MFs).

Keywords: Sex differences; Sex hormones; Activating effects; Spatial ability; Verbal fluency; Transsexuals

1. Introduction

Sex differences in cognitive functioning may be noticed as early as in preschool children (Maccoby and Jacklin, 1987). However, it is not until after puberty, when sex hormone levels are rising, that cognitive sex differences become more prominent (Maccoby and Jacklin, 1987; Alyman and Peters, 1993; Saucier and Kimura, 1998). Two meta-analyses revealed that sex differences in mathematical problem solving (Hyde et al., 1990) and different forms of spatial ability (Voyer et al., 1995), both favoring men, emerged convincingly during adolescence. Although adult men and women do not differ in general intelligence level (Halpern, 1992), they can be distinguished on different aspects of verbal and performance intelligence (Nyborg, 1984). Men usually outperform women on mathematical problem solving (e.g. Benbow and Benbow, 1984; Feingold, 1988; Gouchie and Kimura, 1991; Geary, 1996), visuo-spatial ability (Linn and Petersen, 1985; Gladue et al., 1990; Mann et al., 1990; Gouchie and Kimura, 1991; Gladue and Bailey, 1995; Collins and Kimura, 1997), map reading (Galea and Kimura, 1993; Gladue and Bailey, 1995) and targeted motor skills (Watson and Kimura, 1989; Kimura and Watson, 1991; Hall and Kimura, 1995). By contrast, compared to men, women generally excel in verbal fluency (Feingold, 1988; Hyde and Linn, 1988; Mann et al., 1990; Halpern, 1992), memory for object location (Eals and Silverman, 1994; James and Kimura, 1996), fine motor skills (Hall and Kimura, 1995) and perceptual speed tasks (Feingold, 1988; Mann et al., 1990). The function that has been shown to differ most clearly between sexes, is the visuo-spatial ability test of three-dimensional figures (effect sizes sometimes as high as 0.94 are reported; Vandenberg and Kuse, 1978; McGee, 1979; Linn and Petersen, 1985; Halpern, 1992). Nevertheless it is important to note that differences between the sexes are smaller than differences within each sex. In other words, males and females show a considerable overlap in their cognitive abilities. Due to this large variation within each sex, discrimination of sex differences in small populations is difficult.

In view of these sex differences in cognitive functioning, hormonal mechanisms have been inferred. Hormonal explanations for sex differences in cognitive functioning have focused both on prenatal organizing effects of sex hormones on the brain and postnatal activating effects, for instance during puberty, or as a result of menstrual cycle fluctuations. We will discuss the findings of some of these studies in the next two sections.

1.1. Organizational hormone effects

Organizing effects are the prenatal and perinatal influences of sex hormones on the brain structure. These effects are assumed to be permanent and irreversible. Animal studies have shown that both androgens and estrogens (their aromatization products) play an important role in neural development and neural circuit formation in sensitive periods of the perinatal developing brain (Döhler et al., 1984; Matsumoto, 1989; Williams and Meck, 1991). Early exposure to estradiol seems to cause long-term organizational effects on visuo-spatial ability in both male and female rats (Williams and Meck, 1991). It still has to be determined how exactly these sex steroids affect brain differentiation.

Evidence of an organizational effect of sex hormones on cognitive functioning in humans comes from studies testing subjects who have been exposed to diethylstilbestrol (DES) or children with congenital androgen hyperplasia (CAH). DES is a non-steroidal estrogen with five times the biopotency of estradiol when taken orally (Reinisch and Sanders, 1984) and appears to have an androgenizing effect on the brain. DES-exposed women had a more masculine pattern of lateralization, that is they showed an enhanced right ear advantage on a dichotic listening task compared to their control sisters (Hines and Shipley, 1984). However, no differences were found between these groups in lateralization index, or in verbal or visuo-spatial ability. Paradoxically, Reinisch and Sanders (1992) showed that DES-exposed males had *reduced* hemispheric laterality and a lowered spatial ability compared to their unexposed brothers. These findings, along with outcomes based on research with laboratory animals, provide support that DES and perhaps other sex hormones (Witelson, 1991) affect females and males differently (Reinisch and Sanders, 1992).

CAH, due to an enzymatic disorder in cortisol synthesis, leads to increased levels of adrenal androgens in both girls and boys (Reinisch et al., 1979). This syndrome results in various degrees of masculinization of the female genitalia in women and a precocious puberty in men. For example, Helleday et al. (1994) observed a more masculine cognitive pattern for both spatial and verbal tasks in CAH women compared to a matched group of control women.

1.2. Activational hormone effects

Numerous studies on sex differences suggest that the performance on certain cognitive tests may be influenced by variations in circulating estrogen and testosterone blood levels. These are the so-called activational effects of sex hormones, acting on brain patterns organized by sex hormones prenatally. These activating effects are phasic and thought to occur at puberty and in adulthood.

Research on correlations between sex hormone levels, obtained either from blood or saliva samples, and performance on cognitive tasks in adults may indicate whether circulating hormone levels are associated with cognitive performance. In women, some positive relationships between free testosterone and different spatial ability tests have been found (Shute et al., 1983; McKeever, 1987); it seems that the relationship in men is more similar to that of an inverted U-shape curve (Shute et al., 1983; Gouchie and Kimura, 1991; Moffat and Hampson, 1996).

To study the activational effects of sex hormones on cognitive functioning in humans more directly, two types of studies have commonly been conducted. Firstly, in women, the cognitive effects of fluctuating hormone levels during the menstrual cycle have been investigated. Women did better on a speeded motor coordination test during the midluteal phase, when levels of estrogen and progesterone are high (Hampson and Kimura, 1988) and showed an enhanced verbal articulation during the preovulatory phase, when only levels of estrogens are ascended (Hampson, 1990). Both studies demonstrated that during these phases, women did worse on spatial ability tests than during menses, when these hormone levels are relatively low. Similar results were found after examining changes in two or three-dimensional mental rotations (Silverman and Phillips, 1993 and Ho et al., 1986 respectively). Performances on these tests were better during the menstrual phase.

Secondly, hormone levels have been manipulated directly in humans through hormone administration. For example, Gordon et al. (1986) tested healthy young men before and 1 week after an injection of luteinizing hormone releasing hormone (LHRH) and compared these findings with placebo-injected men. It was found that the LHRH-injected group improved more on verbal ability tasks, while the placebo-injected group improved more on some spatial ability tasks. It was concluded that LHRH administration, resulting in higher levels of gonadotropins (LH and FSH), stimulated verbal ability and prevented learning effects on some spatial ability tasks. The same experiment was repeated with testosterone injections by Gordon et al. (1986) in a different group of healthy young men. This time, no relation was found for testosterone fluctuations and cognitive functioning. Two possible explanations were offered for this result. Firstly, it was suggested that testosterone levels measured at the time of testing were not related to the amount of exposure to androgens prenatally. Secondly, the increase of the testosterone level in blood might have been faster than its effect on cognitive functioning (Gordon et al., 1986).

Additionally, patient groups that receive hormone treatment for medical reasons are suitable for investigating the effects of varying hormone levels on cognitive function. In this respect hypogonadotropic hypogonadal men, surgically menopausal women and transsexual patients have been good samples. In the patient group of idiopathic hypogonadotropic hypogonadal men, low testosterone levels were found to be associated with an impaired spatial ability in comparison to control men and men with acquired hypogonadism (Hier and Crowley, 1982). Three months of androgen-replacement therapy did not improve the spatial ability of idiopathic hypogonadotropic hypogonadal men. It was suggested that these findings indicate a permanent organizing effect of androgens on the brain before or at puberty in boys, an effect which the hypogonadotropic hypogonadal men had missed. However, it might also be the case that this finding was due to the small sample size (six subjects) or to an unknown genetic influence contributing to a permanent impairment of spatial ability. Another patient group consists of women with lowered estrogen levels because of surgical removal of the ovaries or because of treatment with a gonadotropin-releasing hormone agonist, leading to a strong reduction in ovarian hormone production. Remarkably, the female patients who received estrogen replacement therapy remained constant in immediate and delayed verbal memory, while placebo-treated subjects decreased pre- to post-operatively (Sherwin, 1988; Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996).

Finally, studies have focused on transsexual patients receiving high doses of opposite-sex hormones in the course of the sex reassignment procedure. Transsexuality is defined as an incongruence between the biological sex and the experienced and self-declared gender identity (Gooren, 1984). Anti-androgens in combination with estrogens are administered to male-to-female transsexuals (MFs), while female-to-male transsexuals (FMs) receive androgen therapy. Earlier studies established that untreated MFs do not differ in sex-hormone levels from other biological men (Spijkstra et al., 1988), and that FMs do not differ in this respect from other biological women (Spinder et al., 1989). After 3 months of hormone treatment, sex hormone levels of transsexuals are in the range of those of the opposite sex (Meyer et al., 1986). In earlier studies, we showed that the cross-sex hormone treatment had clear effects on cognitive functioning in transsexuals (Van Goozen et al., 1994, 1995). Under the influence of testosterone administration, FMs increased in visuo-spatial ability and decreased in verbal fluency. By contrast, after 3 months of androgen depletion and estrogen administration, MFs scored higher on verbal fluency, whereas their visuo-spatial ability was deteriorated.

The aim of the present study was to examine: (a) whether we could confirm these findings in a new group of transsexuals; (b) whether a similar pattern of change could be found for novel tasks, i.e. tasks, not used in the previous studies that measured closely related cognitive abilities; (c) whether the cognitive changes had stabilized after 3 months of hormone therapy or continued to develop over a period of 1 year; and (d) whether the observed effects were quickly reversible when the hormone treatment was temporarily stopped. In order to prevent thrombosis, transsexuals were advised to stop their hormone treatment about 4 weeks before sex reassignment surgery until 1 week after surgery, enabling us to measure hormone ablation effects after 5 weeks.

2. Method

2.1. Sample

Our sample included 20 male-to-female transsexuals (MFs) and 25 female-to-male transsexuals (FMs), all diagnosed as such by the psychologists and psychiatrists of the Free University Hospital genderteam in Amsterdam. They were all eligible for sex reassignment and participated voluntarily in our research. All procedures were carried out with the adequate understanding and written consent of the subjects. The study was approved by the institutional ethical review board. The mean age of MFs in the whole sample was 29.1 years (SD = 8.0; range 19–45 years) and that of FMs was 26.0 years (SD = 7.7; range 16–44 years), while the mean ages were, respectively 27.4 and 25.4 years in the subsample, which was used for analyzing long-term and deprivation effects of cross-sex hormones. In both samples, the mean ages did not differ statistically ($F[1,43]=1.34$, ns; and ($F[1,28]=0.79$, ns, respectively). Hormone treatment for MFs consisted of anti-androgens (cyproterone acetate (Androcur): 50 mg/twice a day, PO) and estrogens (ethinyl-oestradiol (Lynoral): 50 μg/twice a day, PO). To all FMs IM testosterone-esters (Sustanon: 250 mg) were administered intramuscularly once every 2 weeks.

2.2. Instruments

Seven tests were selected since they earlier had established sex differences; a verbal reasoning task was included as a neutral task (Woordmatrijzen: Luteijn and Van der Ploeg, 1983). Male favoring tasks were two-dimensional rotated figures (Ekstrom et al., 1976), three-dimensional rotated figures (Vandenberg and Kuse, 1978) and hidden figures (Ekstrom et al., 1976). Female favoring tasks were verbal fluency-words and verbal fluency-sentences (adapted from Gordon et al., 1986), fine motor movement (developed in our own department; adapted from Tiffin, 1968), and a perceptual speed task (test D2: Brickenkamp, 1981).

2.2.1. Verbal reasoning (VR); Luteijn and Van der Ploeg, 1983 as an indication of general intelligence

The subject had to identify the relationship common to two word-pairs. The relationship then had to be applied to a third word on the basis of which the respondent had to choose its pair from a list of five possibilities. This test contained 20 items, scores were based on correct answers. There was no time limit.

2.2.2. Rotated figures two-dimensional (RF-2D; Ekstrom et al., 1976) to measure spatial ability

The original test, containing 30 items, was divided in half, in order to have more versions for four test sessions. By comparing five alternatives with the example figure given, the subject had to decide which alternatives are identical by rotating them in a two-dimensional way. The subject had to identify the right answers by circling the letter above each figure. After practicing four example items and receiving feedback about the correct answers, the subject had 3 min to finish the task (15 items). A total score was calculated by counting the points for all correct answers. The maximum score for the total test was 75.

2.2.3. Rotated figures three-dimensional (RF-3D; Vandenberg and Kuse, 1978) to measure spatial ability

The original test, consisting of 20 items, was divided in two subtests of ten items each. While the correct answers were identical to the criterion figure but shown in a rotated position, the incorrect answers or 'distractors' were either mirror-images of the criterion or rotations of other criteria. In both subtests the degrees of rotation of the correct answers and the amount of mirror-images among the incorrect answers were equally distributed. The subtests were administered for 3 min alternately on each of the four occasions. The maximum score per item was two points, this was given only when both answers were correct; the total score per subtest was 20.

2.2.4. Hidden figures (HF; Ekstrom et al., 1976)

One model figure was shown at the top of the paper. After practicing, the subject had to cross out as quickly as possible all the figures in which the model was hidden and fill out a zero when the model was not applicable. The subject was allowed 3 min to solve 200 items. The total score of the correct answers had a maximum of 200 points.

2.2.5. Verbal fluency-words (VF-W; adapted from Gordon et al., 1986)

Two different versions with each two sections were used: section (a) word fluency without restriction, writing down in 2 min as many words as possible starting with the letter 'S' (version I) or 'L' (version II); section (b) word fluency with restriction, writing down in 2 min as many words as possible, using at least four letters per word, starting with the letter 'B' (version I) or 'D' (version II). Both versions were matched upon words with equally distributed frequencies in the Dutch language that start with this particular letter. The total score was the total amount of words generated in both subversions. Gordon and Lee (1986) administered a similar verbal fluency test to their subjects and reported a significant sex difference.

2.2.6. Verbal fluency sentences (FV-S; adapted from Gordon et al., 1986)

The subjects were instructed to make as many sentences as possible using the letters 'V E L' (version I) or 'W A B' (version II) as starting letters of the words newly used in every sentence within 5 min. Again, both versions were matched upon equally distributed frequencies of words starting with the particular letters. A score for the total amount of generated sentences was calculated.

2.2.7. Fine motor movement (FMM; adapted from Tiffin, 1968): a dexterity task, measuring fine motor behavior and complex finger movements

Without practicing, the subject had to place as many pins as possible in small holes on a board, first with the preferred hand, then with the unpreferred hand and finally with both hands concurrently. Every subpart of the test took 1 min.

2.2.8. Test D2 (TD2; Brickenkamp, 1981) testing perceptual speed

In 14 lines containing p's and d's, the subject had to cross out all the d's with two dashes either on top, underneath or one dash on both sides as quickly and accurately as possible. Every 20 s, the subject was instructed to start a new line. A total score was obtained by subtracting the errors from the total of items crossed out on every line.

2.3. Procedure

The design of the study is shown in Table 1. A test battery containing eight different cognitive tests was applied twice to all transsexuals: once just before the onset of hormone therapy (t1) and once after 3 months of hormone treatment (t2). A subgroup of transsexuals (24 FMs, 18 MFs) was retested after 10 and 12 months of hormone treatment respectively (t3), to establish long-term hormonal effects. Of this subgroup, 16 FMs and 14 MFs were tested again after 12 and 18 months, respectively (t4), shortly after the sex reassignment surgery (SRS, including gonadectomy), when they had been off hormones for 5 weeks, to test whether the effects were quickly reversible. To this end, five tests (VR, RF-2D, RF-3D, VF-W, VF-S) were used. This subgroup of patients was selected because they had undergone surgery; no other systematic selection criteria were used. The two parallel test versions were alternately administered on the four test sessions, but not counterbalanced within the two groups of transsexuals. To minimize the hormone level variability within FMs, they were all tested on day six after their last androgen injection at t2 and t3.

2.4. Statistics

In order to compare tests with different outcome scores (including different versions) and to add more power to the analyses, four composites were calculated from the mean of the standardized z-scores of the tests (using a similar method as reported in Gouchie and Kimura (1991)). The composite for short-term effects

Table 1
Design of the study

	t1: baseline	t2: short-term	t3: long-term	t4: withdrawal after 5 weeks
MFs[a]	Pretreatment ($n = 20$)	After 3 months ($n = 20$)	After 12 months ($n = 18$)	Post surgery after 18 months ($n = 14$)
FMs[b]	Pretreatment ($n = 25$)	After 3 months ($n = 25$)	After 10 months ($n = 24$)	Post surgery after 12 months ($n = 16$)
Tests administered	VR, HF, FMM, TD2[c]	VR, HF, FMM, TD2	VR	VR
	Version I: RF-2D, RF-3D[d] VF-W, VF-S[e]	Version II: RF-2D, RF-3D VF-W, VF-S	Version I: RF-2D, RF-3D VF-W, VF-S	Version II: RF-2D, RF-3D VF-W, VF-S

[a] MFs, male-to-female transsexuals.
[b] FMs, female-to-male transsexuals.
[c] VR, verbal reasoning test; HF, hidden figures test; FMM, fine motor movement; TD2, perceptual speed test.
[d] RF-2D, rotated figures test-2D; RF-3D, rotated figures test-3D.
[e] VF-W, verbal fluency test-words; VF-S, verbal fluency test-sentences.

(using t1 and t2 in a group of 25 FMs and 20 MFs) of male favouring tasks was named male composite (based on RF-2D, RF-3D and HF) and the composite for short-term effects of female favouring tasks was named female composite (based on VF-W, VF-S, FMM and TD2). In the subsample of transsexuals, two composites were generated for short-term and the long-term measurements and hormone ablation effects (using t1 through t4 in a group of 16 FMs and 14 MFs): Spatial ability composite (based on RF-2D and RF-3D) for the male favouring tasks and verbal ability composite for the female favouring tasks (based on VF-W and VF-S). All composites were analyzed by separate repeated measures ANOVAs ($\alpha = 0.05$). Whenever a significant main effect of time or an interaction between time and group was found, paired comparison analyses were carried out to supply more information about the time of testing at which sex differences occurred and how the cognitive performances of each group changed over time.

To analyze hormonal effects in different task conditions, separate repeated measures ANOVAs were calculated for the non-standardized scores of all cognitive tests used in that particular condition. Short-term hormonal effects were analyzed by comparing t1 and t2 (in a group of 25 FMs and 20 MFs); the long-term hormonal effects were analyzed by comparing t1 and t3 (in a group of 24 FMs and 18 MFs), at which times version I of all tests was applied. The effect of hormone deprivation on cognition made use of the comparison between t1 through t4 (in a group of 16 FMs and 14 MFs), including both version I and version II. Polynomial contrast analyses revealed whether a linear, quadratic or cubic Time effect was significant.

Because sex differences on a finger movement task are more pronounced when using both hands concurrently than separately, only the concurrent task was used for the female composite. Finally, all analyses were done with 'time' as a within-subjects variable and 'group' as a between-subjects variable.

3. Results

3.1. Hormone levels

Although we did not take blood samples from this particular group of transsexuals, we do have some reference data of measured hormone levels in transsexuals (Giltay et al., 1998). In a group of 17 FMs and 17 MFs, plasma testosterone levels in FMs were 1.6 ± 0.6 nmol/l before testosterone administration and rose to 29.6 ± 11.2 nmol/l under androgen administration. Plasma estradiol levels did not change significantly following testosterone administration: 164 ± 60 pmol/l was measured before and 132 ± 36 pmol/l (ns) after 4 months of androgen administration. Plasma hormone levels were not measured after 5 weeks of hormone ablation, following ovariectomy. However, in view of the well-known profile of plasma testosterone levels following parenteral administration they must have been close to zero. After ovariectomy plasma estradiol is largely derived from aromatization from testosterone, therefore plasma estradiol levels must have been close to zero as well.

In the same study, the plasma testosterone levels of MFs fell from 23 ± 6.5 nmol/l before administration of cyproterone acetate (CA) and ethinyl-estradiol (EE) to 1.0 ± 0.0 nmol/l (these levels were lower than normally found in women which show values up to 2.5 nmol/l). Since the synthetic EE was used which is not measured in the laboratory determination of 17β-estradiol, we were unable to provide plasma estrogen levels. However, based on the strong rise of plasma levels of sex hormone binding globulin (SHBG), which is a very sensitive marker of estrogenic action, the biological action of the given dose of EE must have been strong. For comparison: the administered daily dose of EE is three times the daily dose of a modern contraceptive pill. The plasma half-lives of both EE and CA are so short that at the time of postoperative testing their plasma levels must have been close to zero too.

3.2. Sex differences before hormone treatment

For the whole sample, one tailed *t*-tests showed a trend for a sex difference before hormone treatment (t1) on 3D-spatial ability ($t(1,43) = 1.22$, $p < .1$), with MFs scoring higher. A significant sex difference was found on the Purdue Pegboard task ($t(1,43) = 2.77$, $p < .01$) and a trend for verbal fluency-words ($t(1,43) = 1.31$, $p < .1$), resulting in a sex difference on the female composite ($t(1,43) = 2.19$, $p < .05$) on the account of FMs.

3.3. Data analyses of short-term hormonal effects (t1 and t2)

The data revealed no significant main effect of group over a 3 months period on VR, as an indicator of general intelligence, nor was there a main time effect or an time $\times$ group interaction effect on VR (Table 2).

3.3.1. Short-term effects on male favoring tasks

Fig. 1A shows the mean *z*-scores of the male composite for short-time hormonal effects. While no main effects of time or group were found for this composite, there was a marginally significant interaction between time and group ($F[1,43] = 2.85$, $p < .10$).

This small interaction effect on all male favoring tests together could mainly be attributed to a significant interaction effect, which was found for spatial ability-3D (RF-3D; $F[1,43] = 4.35$, $p = .043$). Although Fig. 1A shows that the sex difference in spatial ability on the account of MFs has reversed into a sex difference on the account of FMs, additional paired comparison tests show that this effect is mainly due to an increase of the performance in 3D-spatial ability in FMs and not to a decrease of performance in MFs (Table 2). According to paired comparison tests, untreated MFs performed better than untreated FMs on RF-3D ($t(1,43) = 1.75$, $p < .05$), while no sex difference was observed after 3 months of hormone treatment ($t(1,43) = 1.20$, ns). Furthermore, after 3 months of hormone treatment FMs improved their performance on RF-3D ($t(1,43) = 3.83$, $p < .001$), whereas the performance of MFs remained stable over time ($t(1,43) = 0.88$, ns). This finding

Table 2
Short-term effects (3 months) of cross-sex hormones on cognitive functioning in transsexuals, using MANOVAs with time (t1 vs. t2) as within-subjects factor and group as between-subjects factor

Instrument	t[a]	MF ($n=20$)	sd	FM ($n=25$)	sd	Time $F[1,43]$	Group $F[1,43]$	Time × group $F[1,43]$
Verbal reasoning	1	12.7	3.3	13.4	2.3	0.18	0.26	0.33
	2	13.2	3.0	13.2	2.9			
Rotated figures-2D	1	48.4	15.1	48.0	12.4	11.8***	0.07	0.12
	2	43.6	13.1	42.2	7.3			
Rotated figures-3D	1	7.4	5.5	5.8	2.8	11.1**	0.04	4.35*
	2	8.2	5.2	9.2	4.3			
Hidden figures	1	87.6	24.3	90.4	20.6	31.1***	0.49	0.59
	2	99.3	26.2	105.8	23.8			
Verbal fluency-W	1	33.8	13.6	37.6	7.3	3.28~	2.71~	0.53
	2	30.7	11.2	36.3	9.8			
Verbal fluency-S	1	5.9	4.0	6.8	2.4	0.004	1.17	0.004
	2	5.9	3.4	6.8	2.3			
Fine mot. Movement	1	20.5	7.0	26.2	6.7	2.23	7.59**	1.69
	2	20.4	6.1	24.0	4.9			
Test-D2	1	366.8	67.2	391.1	91.7	24.9***	2.03	2.12
	2	395.8	106.9	443.9	85.4			

[a] t1, before hormone treatment; t2, after 3 months of hormone treatment.
~ $p<.1$.
* $p<.05$.
** $p<.01$.
*** $p<.001$.

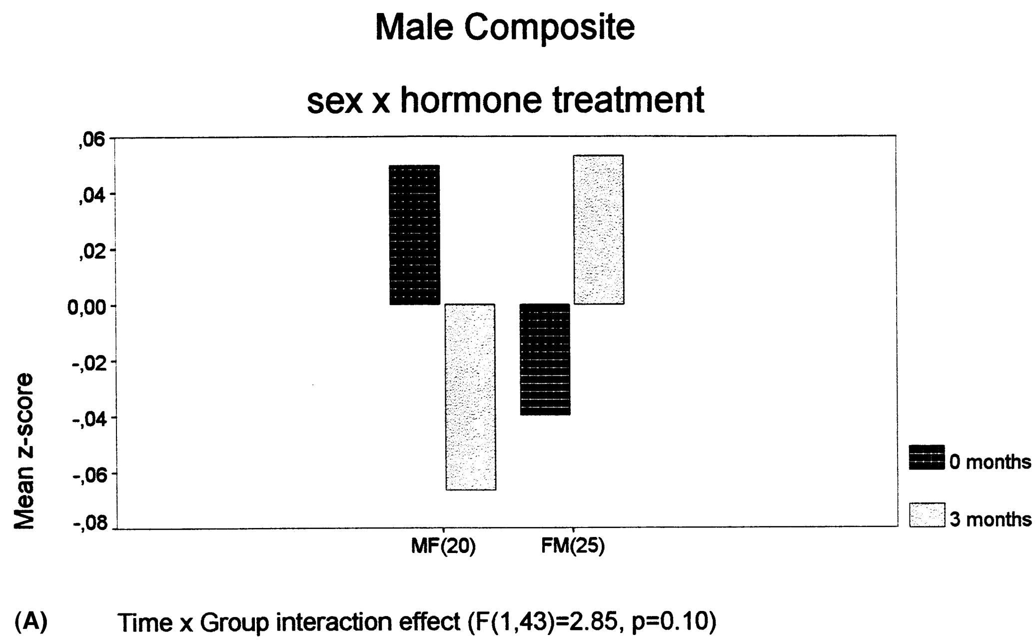
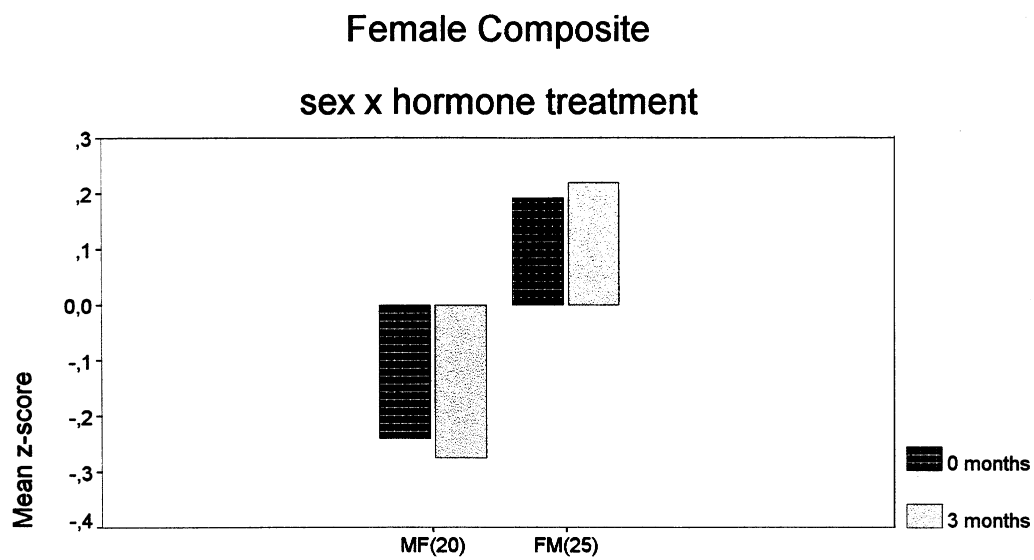


Fig. 1. Composites of the mean z-scores before and after 3 months of hormone treatment: (A) male composite (based on RF-2D, RF-3D, and HF) and (B) female composite (based on FMM, VF-W, VF-S and TD2).



(B) * Main effect of Group (F(1,43)=6.15, p=0.017)

Fig. 1. (*Continued*)

also explains the time effect observed for RF-3D (Table 2), which is solely accountable to the FMs. A significant main effect of time was also present for spatial ability-2D (RF-2D) and for the speed of form recognition (HF). The performance on RF-2D decreased for both FMs and MFs, whereas the performance on HF increased in both transsexual groups (Table 2). Since two different versions were used for RF-2D, the time effect might indicate that version II was more difficult than version I. None of the male favoring tasks showed a group effect over a period of 3 months.

3.3.2. Short-term effects of female favoring tasks

Fig. 1B shows the mean z-scores of the female composite for short-time hormonal effects. Scores on the female composite revealed no main effect of time, a significant main effect of group ($F[1,43]=6.15$, $p=.017$), but no interaction of time × group.

Although FMs had higher scores on all female favoring tasks, both before and after 3 months of hormone treatment, a significant group difference was only found for the fine motor movement task (FMM; $F[1,43]=7.59$, $p=.009$), while a trend was observed for verbal fluency-words (VF-W; $F[1,43]=2.71$, $p=.107$).

After 3 months of hormone therapy, a significant main effect of Time was found for the perceptual speed task (TD2), possibly attributable to a learning effect and a small one for verbal fluency-words (VF-W), but not for FMM or verbal fluency-sentences (VF-S; Table 2). On none of these four tests significant interaction effects between time and group were found.

3.4. Data analyses of long-term hormonal effects (t1 and t3)

After about 12 months of hormone therapy, a small time effect was found for VR ($F[1,40]=3.78$, $p<.1$), probably due to a practice effect (data not shown).

3.4.1. Long-term effects of male favoring tasks

No group effect was observed for spatial ability (RF-2D and RF-3D) in a group of 24 FMs and 18 MFs. Although no significant interaction between time and group occurred for RF-2D, the observation was in the right direction ($F[1,40]=2.27$, $p=.14$) and this interaction effect was significant for RF-3D ($F[1,40]=6.35$, $p=.016$). Paired comparison tests revealed that FMs improved on RF-3D ($t(1,40)=2.69$, $p<.01$), while MFs remained stable over a period of 12 months ($t(1,40)=0.97$, ns). This finding is in concordance with the finding of the short-term hormonal effect on RF-3D. Although FMs performed better on RF-3D at both t2 and t3 compared to t1, there was no significant increase of performance between t2 and t3 ($t(2,80)=0.87$, ns), i.e. the short-term hormonal effect at t2 had stabilized on the long term (t3). Both groups of transsexuals together also demonstrated a trend for a main time effect for RF-2D ($F[1,40]=2.89$, $p=.097$), but not for RF-3D.

3.4.2. Long-term hormonal effects of female favoring tasks

As for verbal fluency, in a group of 24 FMs and 18 MFs an overall small group effect was present for VF-W only ($F[1,40] = 2.78$, $p < .1$), with FMs showing a slightly better performance than MFs on both t1 and t3, but not for VF-S ($F[1,40] = 1.36$, ns).

3.5. Hormone-ablation effects (t1 through t4, Table 3)

A trend for a main time effect was found for VR ($F[3,84] = 2.34$, $p < .1$), which might be ascribed to a minor practice effect.

3.5.1. Hormone-ablation effects of male favoring tasks

Fig. 2A shows the mean z-scores of the spatial ability composite for long-term hormonal effects over a period of 12 to 18 months, over four test sessions for 16 FMs and 14 MFs. While no main effect of time or group was found for the spatial ability composite, there was a highly significant interaction between time and group ($F[3,84] = 3.98$, $p < .02$). One way paired comparison tests revealed that MFs performed slightly better than FMs on spatial ability tasks at t1, i.e. before hormone treatment ($t(3,84) = 1.57$, $p < .1$), no group difference was present at t2 ($t(3,84) = 0.15$, ns), whereas the group difference had reversed at t3 ($t(3,84) = 2.25$, $p < .05$). After 5 weeks of hormone ablation (t4) this reversed group difference became more significant ($t(3,84) = 3.65$, $p < .001$).

Next, separate repeated measures ANOVAs with polynomial contrast tests over the two spatial ability tests over four test sessions were executed. Although the multivariate repeated measures analyses for RF-2D showed a significant time effect ($F[3,84] = 8.15$, $p < .001$), univariate tests revealed that the significancy was due to a cubic time effect (data not shown) and not to a linear or the predicted quadratic time effect. The finding of a cubic time effect strengthens the idea that version II of the RF-2D test was more difficult than version I. Therefore a separate ANOVA was executed on the data collected at t2 and t4, i.e. when version II had been applied. No time or group effects were found, but a significant interaction between time and group became apparent ($F[1,28] = 6.65$, $p = .015$). As for the paired comparison analyses, no group differences were found on t1 ($t(3,84) = 0.26$, ns) and t2 ($t(3,84) = 0.45$, ns), a small group difference was observed at t3 ($t(3,84) = 1.30$, $p < .1$), which was significant during hormone ablation ($t(3,84) = 2.23$, $p < .025$). These results are comparable to those of spatial ability-3D.

As for RF-3D, there was not only a significant linear time effect ($F[3,84] = 3.62$, $p = .016$), but also an interaction between time and group over all four test session ($F[3,28] = 3.53$, $p = .018$), which is shown in Fig. 3. Apparently, MFs excelled in spatial ability-3D before treatment ($t(3,84) = 1.84$, $p < .05$), no group difference was observed after 3 months of hormone treatment ($t(3,84) = 0.67$, ns), FMs performed better than MFs after 10–12 months of hormone treatment ($t(3,84) = 1.81$, $p < .05$), as they did after 5 weeks of hormone ablation ($t(3,84) = 2.40$, $p < .001$).

Paired comparison analyses revealed that the performance on RF-3D of MFs remained stable during hormone ablation (t3–t4; $t(3,84) = 0.71$, ns), like during

Table 3
Repeated measures ANOVAs with time (t1, t2, t3 and t4) as a within-subjects factor and group as between-subjects factor. The *F*-values of the averaged univariate tests of significance are presented, involving time as a within-subject effect

Instrument	t[a]	MF ($n=14$)	sd	FM ($n=16$)	sd	Time $F[3,84]$	Group $F[1,28]$	Time × group $F[3,84]$
Verbal reasoning	1	12.4	3.0	13.6	2.4	2.34~	2.28	0.14
Reasoning	2	13.0	2.9	14.0	2.1			
	3	13.3	3.2	14.4	2.0			
	4	13.1	2.9	14.6	1.7			
Rotated figures 2-D	1	49.4	12.7	48.7	11.5	8.15***	0.26	1.65
	2	44.1	13.1	42.9	7.1			
	3	49.2	16.0	52.5	10.1			
	4	41.4	11.3	47.0	6.8			
Rotated figures 3-D	1	7.7	6.2	5.7	3.8	3.62*	0.35	3.53*
	2	8.1	5.4	8.8	5.0			
	3	7.1	3.7	9.1	5.2			
	4	7.9	4.3	10.5	4.9			
Verbal fluency-W	1	29.9	8.1	40.0	6.3	0.93	12.1**	0.06
	2	28.9	11.3	38.8	9.0			
	3	30.5	9.2	41.3	11.0			
	4	30.9	10.0	40.6	8.6			
Verbal fluency-S	1	4.6	3.4	7.8	2.1	2.15~	8.35**	2.15
	2	5.1	3.5	7.6	2.1			
	3	4.7	2.6	7.4	3.1			
	4	6.0	2.8	8.0	2.6			

[a] t1, before hormone treatment; t2, after 3 months hormone treatment; t3, after 10–12 months hormone treatment; t4, after 5 weeks of hormone ablation (12–18 months after the onset of hormone therapy).
~ $p<0.1$.
* $p<.05$.
** $p<.01$.
*** $p<.001$.

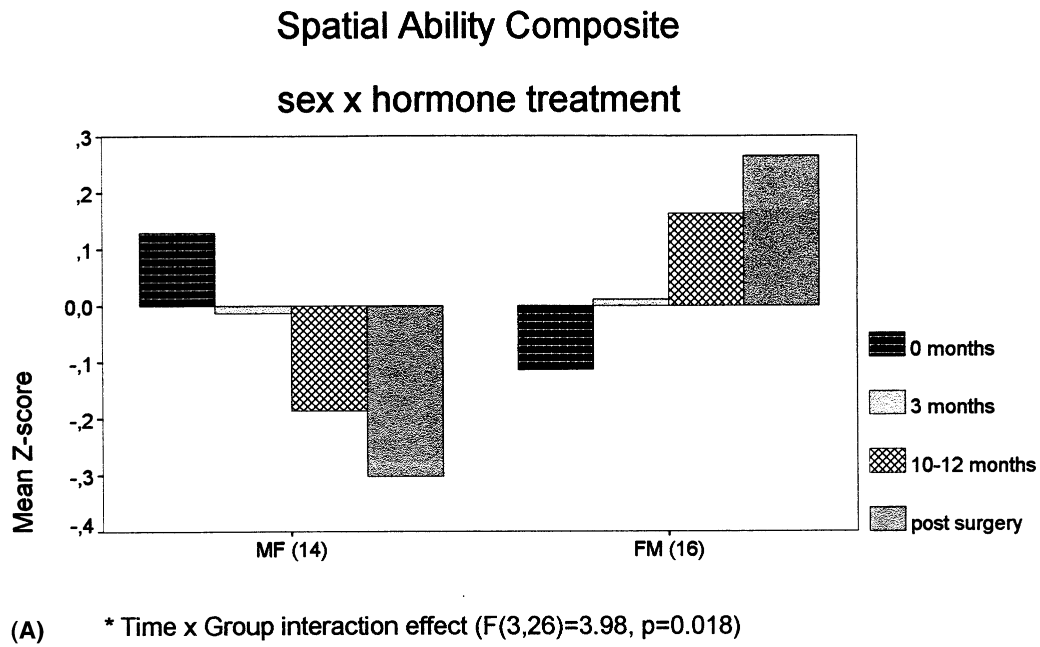
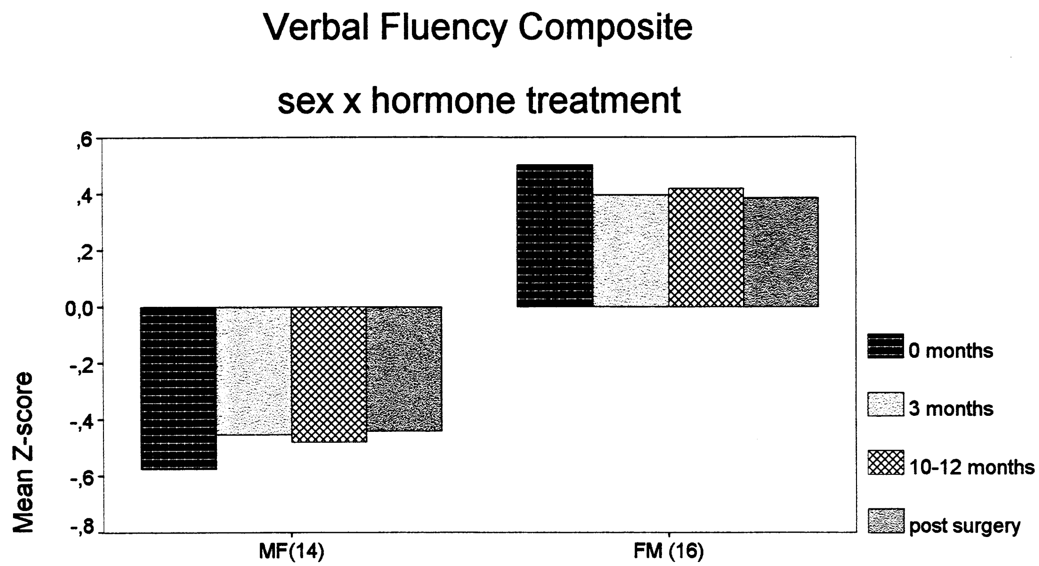


Fig. 2. Composites of the mean z-scores before hormone treatment, after 3 months hormone treatment, after 10–12 months hormone treatment and during 4–5 weeks hormone ablation: (A) spatial ability composite (based on RF-2D and RF-3D) and (B) verbal ability composite (based on VF-W and VF-S).



(B) * Main effect of Group (F(1,28)=12.16, p=0.002)

Fig. 2. (*Continued*)

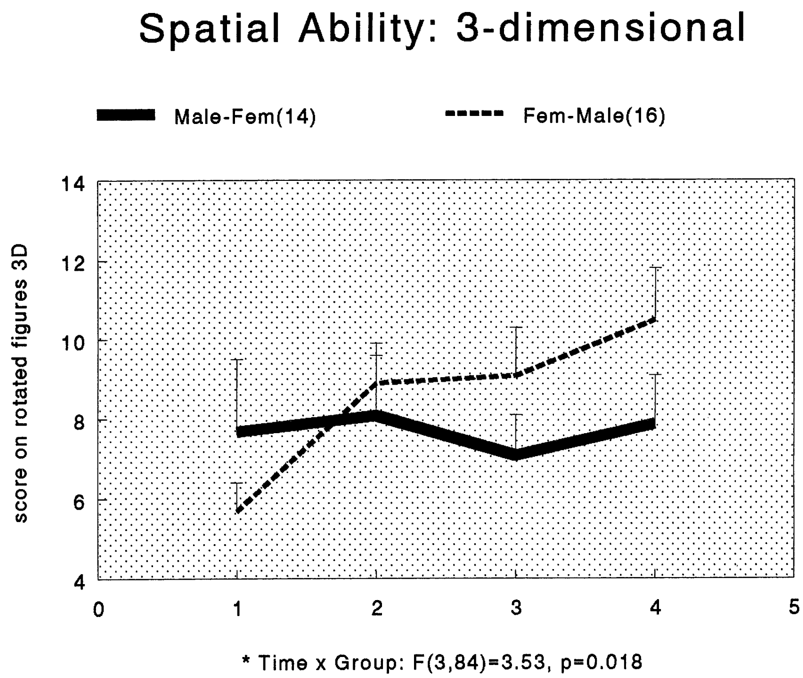


Fig. 3. Long-term effects (12–18 months) of cross-sex hormones on three-dimensional rotated figures in transsexuals, using repeated measures ANOVAs with time as within-subjects factor and group as between-subjects factor. (1) Before hormone treatment; (2) after 3 months of hormone treatment; (3) after 10–12 months of hormone treatment; and (4) after 5 weeks hormone ablation (post surgery).

short-term (t1–t2) and long-term hormone treatment (t2–t3), compared to pretreatment (Sections 3.3.1 and 3.4.1). By contrast, the performance of FMs increased slightly (t3–t4; $t(3,84) = 1.31$, $p < .1$) during hormone ablation, compared to a stable performance level during the period of 3 months (t1–t2) until 10 months of hormone treatment (t2–t3). As indicated before, the largest increase of spatial ability-3D in FMs took place within 3 months after the start of androgen treatment (Sections 3.3.1 and 3.4.1).

Thus, both RF-2D (to a lesser extent) and RF-3D (to a greater extent) contributed to the findings of the spatial ability composite.

3.5.2. Hormone-ablation effects of female favoring tasks

Fig. 2B shows the mean z-scores of the verbal fluency composite for long-term hormonal effects over a period of 12 to 18 months, over four test sessions for 16 FMs and 14 MFs. FMs performed better than FMs on the verbal fluency composite ($F[1,28] = 12.16$; $p < .01$), but no main time effect or interaction between time and group was found.

In the subgroup FMs performed significantly better than MFs on both verbal ability tests at t1 through t4 (VF-W: $F[1,28] = 12.1$, $p < .01$; VF-S: $F[1,28] = 8.35$, $p < .01$; Table 3).

4. Discussion

In the present study the effects of cross-sex hormone manipulations on cognitive functioning were studied in male-to-female transsexuals (MFs) and female-to-male transsexuals (FMs). The study shows that testosterone manipulations have a clear, and not quickly reversible, effect on spatial ability in adult women. Besides inducing rapid overt changes in the physical appearance of FMs, androgen therapy apparently also favors the capacity of these biological women to develop spatial abilities that eventually may outscore those of biological males (untreated MFs). Furthermore, in this study, we found some evidence for reciprocal effects on spatial ability in biological males treated with a combination of anti-androgens and estrogens. Their hormone treatment seems to prevent a learning effect as observed in other biological males (Slabbekoorn et al., 1998 unpublished data). However, while during treatment the hormone blood levels of MFs resembled those of biological women (Meyer et al., 1986), their spatial ability performance did not decline accordingly when compared to pretreatment levels. It seems that effects of perinatal and possibly also pubertal hormone influences of testosterone on spatial ability in biological males are not simply overruled by activating effects of estrogens in combination with androgen blocking in adult life. However, this particular cross-sex hormone treatment seems to prevent a learning effect as shown previously by Van Goozen et al. (1995). Vice versa, the activating effect of testosterone on spatial ability in adult women seems to overcome more easily the earlier organizing and activating effects of estrogens. Manipulations of sex hormone levels appeared to be unrelated to verbal fluency, form recognition, fine motor movement or perceptual speed in both groups of FMs and MFs. In this study we found less pronounced sex differences in untreated transsexuals as compared to non-patients. This could be due to an organizational hormone effect in transsexuals (Cohen-Kettenis et al., 1998).

In the next section, the four aims of the study will be considered in turn.

(a) *Replication of short-term cross-sex hormonal effects*

The findings of our earlier study were only partially replicated. A hormonal influence on two-dimensional visuo-spatial ability, such as found in previous studies (Van Goozen et al., 1994, 1995) could not be demonstrated in the present study. In fact, both groups of transsexuals showed a performance decline over the first 3 months of hormone treatment. This finding may be explained by the fact that different test versions were used: the current study used half the length of the original test used in the two previous studies. However, a clear hormonal effect was found on a more difficult spatial ability task, namely the three-dimensional rotated figures task. In biological women (FMs) after testosterone administration three-dimensional visuo-spatial ability was enhanced, while in biological men (MFs) after deprivation of testosterone this particular visuo-spatial ability did not change. It is possible that the learning effects in MFs were overruled by the deteriorating hormone effects on spatial ability of anti-androgens and estrogens. Additional support for this interpretation comes from control data of normal women and men in our earlier study. A learning effect was found in both groups for the two-dimensional visuo-spatial ability task after 3 months (Van Goozen et al., 1995). Unpublished data (Slabbekoorn et al., 1998) also showed that similar learning effects are evident for the three-dimensional visuo-spatial ability task.

Earlier findings of a hormonal influence on verbal fluency (i.e. MFs receiving estrogens improved and FMs receiving androgens deteriorated after 3 months (Van Goozen et al., 1995) were not replicated in this study, nor did we observe a sex difference. While a different version of verbal fluency-words test was used in the previous study, in the present study the same task of verbal fluency-sentences was administered. It is unclear why we were unable to replicate the findings of the earlier study. With respect to potential confounding factors such as hand preference (e.g. McCormick et al., 1990), sexual orientation (e.g. Halpern and Cass, 1994), age, and general intelligence, the transsexual groups were comparable in both studies. These findings implicate that verbal ability, as measured by verbal fluency, varies not only across different samples, but perhaps also as a result of individual differences in susceptibility to the effects of cross-sex hormones. Concerning the control test of verbal reasoning, we again showed that hormone treatment does not seem to influence this indicator of general intelligence.

(b) *Short-term cross-sex hormone effects on the novel cognitive tasks*

No sex differences were found for the hidden figure test and the perceptual speed task, either before or after 3 months of hormone treatment. Both FMs and MFs showed a considerable learning effect on these tasks. Although, compared to untreated MFs, untreated FMs excelled in fine motor movement, this group difference remained stable over time. The marginally enhancing effect of testosterone therapy in FMs on the three male favoring tasks (i.e. the male composite; Fig. 1A) could clearly be ascribed to the three-dimensional rotated figures test. The sex difference that we found on the female composite (Fig. 1B) with FMs performing better, was primarily caused by the fine motor movement task and did not change over time.

(c) *Long-term cross-sex hormone effects*

No additional effects of long-term hormone intake were observed in both transsexual groups. That is, FMs had not further increased their spatial ability performance after 10 months hormone treatment, whereas MFs again remained stable over this longer period of time. Although the performance levels did not change significantly after the short-term effects, the group differences did shift slightly over time. Untreated MFs (biological males) performed better than untreated FMs (biological females) on three-dimensional visuo-spatial ability; after 3 months of hormone treatment the group difference had disappeared and after 10–12 months of hormone treatment, albeit slightly, the sex difference had reversed. A small sex difference for verbal fluency-words favouring FMs was observed before the onset of hormone treatment, which remained stable over 10–12 months of hormone treatment.

(d) *Hormone-ablation effects*

In a subgroup of transsexuals, in which possible hormone ablation effects were measured, similar effects of short-term and long-term hormonal effects were registered regarding spatial ability. After 5 weeks of hormone ablation, FMs still outscored MFs after a small increase in the first group on this task. It might be that only after a longer period of hormone ablation a reversal of improved the visuo-spatial ability would be found. This slight increase could also be caused by differences in the test versions used or by the relatively short time-interval between the two measurements to overcome any practice effects. In this subgroup of transsexuals FMs outperformed MFs on verbal fluency not only before hormone treatment, but also during hormone therapy and after a period of 5 weeks of hormone ablation.

The fact that different versions of the cognitive tasks were used, which were administered without a randomized counterbalancing, makes the interpretation of the result somewhat difficult. However, only on the two-dimensional rotated figures test, we have some evidence that version II was slightly more difficult than version I. On this particular task, no sex differences were observed on either the more easy version before treatment or the more difficult version after 3 months of hormone treatment. This result could be in line with findings from Collins and Kimura (1997), who demonstrated that the large sex difference usually found on a three-dimensional rotated figures task was comparable with a sex difference on a two-dimensional rotated figures task that was hard, but not with one that was easy. If this is correct, it explains why we found no sex difference on the easy task, while the hormone treatment might have prevented a sex difference to occur on the difficult task. When analysing the easier version of RF-2D over a period of 10 months (t1 and t3), performance of FMs increased slightly more than that of MFs, while the performance of FMs increased significantly more than that of MFs on the hard version of RF-2D when comparing t2–t4. Of course, this reasoning is only speculative and it is impossible to draw a conclusion about the point in time of hormone treatment when the FMs started to become differentiated from the MFs regarding their performance on the more difficult version of RF-2D.

In sum, we observed that suppression of testosterone combined with estrogen administration over a 12 month period failed to reduce spatial ability performance in MFs when compared to pretreatment levels. However, in FMs testosterone administration clearly favored their spatial ability. Taken together, these observations suggest that both organizing and activating effects of testosterone play an important role in spatial ability. Compared to the seasonal hormonal effects on cognitive performance (Kimura and Toussaint, 1991) as well as the diurnal testosterone effects in men (Moffat and Hampson, 1996), it is remarkable that our study only found relatively small cognitive effects despite the very strong hormonal manipulations. However, both studies employed a between-subjects design in which men with lower testosterone levels were found to perform better on spatial ability. Such studies do not allow to draw any conclusion about within-subjects variability of testosterone and it's relationship to variations in spatial ability. It seems worthwhile to study in future whether untreated MFs with lower levels of testosterone perform better on spatial ability than untreated MFs with higher levels of testosterone and how this ability changes during the hormone treatment. Additionally, it would be interesting to compare spatial ability performance in FMs at the peak and the lowest point of their testosterone levels within their 2 weeks cycle of hormone treatment.

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