Androgen treatment effects on neurocognition in female-to-male transgender adolescents

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Introduction. It has been hypothesized that cognitive and memory-related brain function in transgender during cross-sex hormonal treatment might be activated towards that of the subjective gender. However, research on this topic has produced inconsistent results, and to the best of our knowledge no studies have investigated neurocognitive changes in androgen-treated female-to-male (FM) transgender adolescents.

Subjects and methods. A total of 15 FM transgender adolescents (14-17 years) underwent neuropsychological testing in order to examine the effects of androgen on visuo-spacial abilities, verbal memory language, processing speed and executive functions. We used a longitudinal design in which 10 participants were tested twice, before and after receiving 12 months of testosterone treatment. This group was also compared with 5 FM transgender adolescents off-androgen treatment.

Results. Participants tested before and after 12 months of androgen treatment improved significantly on processing speed in a visuo-spatial (Rey-Osterrieth complex figure test) and in a visuo-oral task (Stroop), their performance on a verbal memory task (TAVEC) and on interference (Stroop) and they exhibited lower impulsivity control (CARAS-R). On-androgen treatment adolescents exhibited worse cognitive impulsivity control than off-androgen treatment adolescents.

Conclusions. The results indicate that androgen has an influence on immediate verbal memory, cognitive interference, impulsivity control and processing speed.

Key words. Adolescent. Androgen treatment. Neurocognition. Neuropsychology. Transexual. Transgender.

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Introduction

Gender differences in cognitive functions have been widely documented [1,2]. However, most of the studies have been developed in cisgender (non-transgender) population. Results show males, including adolescents, tend to perform better than females on visuo-spatial tasks [3,4], while females generally perform better than males on verbal episodic memory tasks [5,6], and on some verbal tasks, such as verbal fluency [7,6]. Previous studies also shows that men exhibit a better performance in some inhibitory tasks (or Stroop effect) [8]. Nevertheless, it is important to note that differences between the sexes are smaller than differences within each sex. In other words, there is a considerable overlap in cognitive performance between men and women, and it is difficult to find sex differences in small populations [9]. Moreover, there is also evidence that gender differences in some cognitive domains may be attributed to differential practice and experience [10].

It has been suggested that these cognitive differences are related to sex hormonal mechanisms, because they tend to emerge convincingly during adolescence [3]. In this regard, it has been proposed that endogenous sex hormones, such as estrogen or androgen, affect cognitive functioning through both prenatal and perinatal organizational effects on brain structures, as well as through the postnatal activation effects that are thought to occur during puberty or in adulthood [11]. For example, some studies have failed to observe gender differences in cognitive functions in children in contrast to adolescents (for example in visuo-spatial tasks) [12] which suggests that postnatal factors, such as puberty with activation effects of sex hormones and experience, may also affect the sex-specific development in neurocognitive functioning. The evidence indicates that sex hormones are critical mod-

ulators of executive function [13] and puberty seems to be a sensitive period for brain organization [14]. It is a limited phase when developing neural connections are uniquely shaped by hormonal and experiential factors, with potentially lifelong consequences for cognitive function.

Transgender individuals experience a discordance between their personal sense of their gender (their gender identity) and the sex assigned to them at birth. As part of their sex reassignment, some of them are treated with cross-sex hormones. Gender-affirming health care in young adolescents going through puberty usually involves the administration of hormonal puberty blocking agents, namely gonadotropin-releasing hormone analogues. Female-to-male (FM) transgender older adolescents and adults typically receive supraphysiological doses of androgens to promote masculinization [15]. After three months of hormone treatment, sex hormone levels are in the range of non-transgender males [16]. The increased administration of gender-affirming hormone therapy in transgender individuals has raised concerns about its impact on cognitive function given the accumulating and long debated evidence concerning gender differentials in cognition [17]. And several studies have focused on the potential adverse health effects of the treatment. The conclusion of a recent meta-analysis showed an enhanced effect on visuo-spatial abilities following post-pubertal hormone therapy among transgender youth males [18]. Studies do not support an adverse impact of gender-affirming hormone therapy on cognitive performance in birth-assigned either male or female transgender individuals. It seems likely that testosterone is related to increases in visuo-spatial skills in adolescents [18,19]; however, due to heterogeneous findings, testosterone's effect on verbal abilities is less clear [20,21]. Recent research has examined the cognitive changes resulting from hormone therapy; however, the existing literature remains limited, and longitudinal studies with extended follow-up periods are recommended, particularly among younger individuals. The number of studies is so limited that the effects of treatment duration have not been analyzed.

The aim of this study was to examine effects of androgens on cognition in transgender adolescents. The hypotheses tested were that FM adolescents taking androgens for 12 months would show enhanced visuospatial skills, visual memory, interference and processing speed, worse verbal memory, verbal fluency and impulsivity compared to: a) before starting hormonal treatment; and b) FM adolescents off androgen treatment.

Subjects and methods

Study design and participants

A total of 15 FM transgender adolescents aged 14 to 17 years underwent neuropsychological testing in order to examine the effects of androgen therapy on cognition. Participants were recruited through the gender identity unit of the Hospital Clinic San Carlos of Madrid between 2020 and 2022, through prospective cohort sampling design. Inclusion criteria for participation in the study were transgender identity diagnosis and, for the longitudinal group, being on androgen treatment for 12 months. Exclusion criteria were any form of neurologic disorder and to not speak Spanish. No potential subject refused to participate. The standards of care guidelines of the transgender health [15] were adopted.

This study used a longitudinal design to examine the effects of testosterone treatment on 10 participants who were tested before and after receiving 12 months of treatment. Additionally, a cross-sectional design was used to compare five testosterone-naive adolescents to the same 10 participants who had been on testosterone treatment for at least 12 months. Control participants for the cross-sectional study were drawn from a separate, independent sample.

All participants were informed that the purpose of the study was to investigate the effects of hormone fluctuations on certain cognitive functions; none of them was aware of the specific nature of our hypotheses. Participants and their guardians provided written informed assent and parental consent and were not paid for taking part in the study. The study was approved by the ethics committee of the Hospital San Carlos of Madrid and was conducted in accordance with the Declaration of Helsinki.

Instruments

Measurement protocol was selected according to cognitive domains that previous literature has found different between males and females, adding executive functions as outcome. There were selected instruments with adequate psychometric properties for Spanish people. Cognitive functioning was assessed using well-validated neuropsychological measures.

Test on perception of differences (CARAS-R) [22]
It is used to study attentional skills as sustained and selective attention, and impulsivity. The main task of the test is to identify differences between similar

elements. We used it to analyze two measures of our interest: Effectiveness in attention (correct answers-errors) is based on the number of correct answers (A) and errors (E) made during the test. Impulsivity (impulsivity control index) is calculated by dividing the number of net correct answers by the number of answers given by the subject (A + E), and multiplying the index by 100, that eliminates the decimals. It has good psychometric characteristics, detailed in the Spanish manual (alpha = 0,91) and an adequate convergent and divergent validity.

Complutense verbal learning test (TAVEC) [23]
The TAVEC is a sensitive and a well-recognized measure of a person's ability to encode, combine, store and recover verbal information in different stages of immediate, short-term and delayed/long-term memory. Regarding the psychometric properties of the TAVEC, satisfactory results of reliability and validity have been reported, detailed in the Spanish manual (alpha = 80-86), and the factor analysis explains 66,7% of variance.

Rey-Osterrieth complex figure test (ROCF) [24]
A complex geometric form is presented to the subject, who is instructed to copy the figure on paper as accurately as possible. After a delay of 30 minutes the subject is requested to recall the figure and to draw it without a model (incidental visual short-term memory). Each element of the figure is scored in terms of accuracy and correct location for the copy and memory trials. Maximum score for each trial is 36. The reliability achieved in 8-18 years old Spanish subjects was of alpha = 0,82 for the copy and alpha = 0,78 for the memory. The factor analysis explains 43,6% of the total variance for the copy and 38,6% for memory [25].

Stroop color and word test (SCWT) [26]
It is used to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute, known as the Stroop effect. Subjects are required to read three different tables as fast as possible. Two of them represent the 'congruous condition' in which participants are required to read names of colors (henceforth referred to as color-words) printed in black ink (W) and name different color patches (C). Conversely, in the third table, named color-word (CW) condition, color-words are printed in an inconsistent color ink (for instance the word 'red' is printed in green ink). Thus, in this incongruent condition, participants are required to name the color of the ink instead of reading the word. Some authors have highlighted the influence of speed in the performance of these three conditions [27]. Stroop interference is the extent of delay in naming the color of an incongruent color word relative to naming the color of a congruent color word or of a neutral non-color word. The analyzes reflected adequate psychometric properties (test-retest, r = 0,84-0,91), detailed in the Spanish manual [26].

Controlled oral word association test (COWAT) [28]
Assesses phonemic verbal fluency by requesting an individual to orally produce words that begin with the letters F, A and S, and semantic category (for example., animals). Individuals are given one min to name as many words as possible beginning with one of the letters or categories. Test–retest reliability coefficients in youth were high to modest (r = 0,74) in a six-month interval and the coefficient alpha of r = 0,83 was acceptably high. Significant improvement in performance was observed across most COWAT indices, suggesting a practice effect [29].

Procedures

During an initial phone call, following up on an invitation to participate in the study, participants were evaluated on whether they were interested in participation. The neuropsychological assessment was carried out individually by two psychologists with experience in test administration and scoring. Each evaluator assessed the same subject pre-post. A third psychologist reviewed the evaluation booklets in order to improve reliability. The procedure typically lasted one hour. In the longitudinal design, patients were tested twice, before starting hormone treatment and 12 months after it began. We chose a 12-month post-test evaluation point in order to ensure a stable level of sex hormones and to limit learning effect. In the cross-sectional design, participants were only tested once.

Data analysis

Data were analyzed using the SPSS V.22 statistical software package and RStudio V2023.03.0+386. Raw scores were used for all the analyses of cognitive measures.

In order to determine whether the participants of the two studies (longitudinal and cross-sectional) were comparable, sociodemographic characteristics of the two groups were analyzed by Kruskal-Wallis test and chi square.

Table I. Socio-demographic characteristics of female-to-male transgender adolescents.

	Longitudinal study (n = 10)	Control group off treatment Cross-sectional study (n = 5)	p-value
Age (mean, SD)	15.5 (1.58)	15 (2.44)	0.327
Years of Education (mean, SD)	9.7 (2.35)	9.4 (2.07)	0.407

SD: standard deviation.

Table II. Performance on cognitive tests for female-to-male transgender adolescents tested when off and on androgen treatment (cross-sectional design).

	Off treatment (n = 5) (mean, SD)	On treatment (n = 10) (mean, SD)	p-value	Effect size (Cohen's d)
CARAS-R (A-E)	48.4 (6.2)	42.30(13.67)	0.622	
CARAS-R (ICI)	96.02 (3.9)	81.59 (20.03)	0.026	0.858
TAVEC (immediate memory)	51 (11.47)	56.70 (12.63)	0.394	
TAVEC (short-term memory)	10 (3.67)	11.3 (3.77)	0.536	
TAVEC (delayed memory)	13 (2.74)	12.80 (3.49)	0.95	
ROCF (copy)	35.8 (0.45)	34.7 (1.77)	0.342	
ROCF (time)	3.78 (1.69)	2.77 (1.42)	0.121	
ROCF (memory)	24 (4)	33.15 (18.14)	0.219	
Stroop (CW)	48.4 (8.64)	50.1 (17.53)	0.421	
Stroop (interference)	7.52 (8.13)	6.97 (12.43)	0.951	
Phonetic verbal fluency (COWAT)	8.25 (4.19)	12.78 (4.47)	0.103	
Semantic verbal fluency (COWAT)	16.75 (1.71)	19.89 (5.33)	0.394	

CARAS-R: test on perception of differences; Complutense verbal learning test; COWAT: Controlled Oral Word Association test; ROCF: Rey-Osterrieth complex figure test; Stroop: Stroop color and word test (SCWT); TAVEC: Complutense verbal learning test.

The cognitive measures in the longitudinal design were analyzed using the Wilcoxon test for dependent samples for each cognitive measure.

For the cross-sectional study it was used the Mann-Whitney U test for independent samples. Effect size was measured by Cohen's d [30]. In behavioral science research, d values of 0,2 are considered small; those of 0,5 moderate; and those of 0,8 or greater as large values [30]. The level of significance was set at $p < 0,05$.

Results

Age and years of education of the participants are shown in table I. There were no differences between groups.

When comparing individuals receiving androgen treatment with those not receiving androgen treatment alone, there were only significant differences in the impulsivity control index (CARAS-R) with a high effect size (Table II).

When comparing pre-post treatment, results showed a small increase in all the cognitive measures (Table III). Participants improved significantly on speed on a visuo-spatial task (ROCF, copy task) and on a reading task (color-word Stroop), on a verbal immediate memory test (TAVEC Stroop), and on an interference measure (Interference Stroop) and they worsened in impulsivity control (CARAS-R, impulsive indic of control) after 12 months of androgen treatment. Effect sizes were from medium to high for all measures except for impulsivity control where the Cohen's d value was small. There were no significant differences in verbal fluency tasks.

Discussion

Studies investigating cognitive changes in transgender adolescents receiving hormonal treatment are scarce [18]. A number of studies have provided support for the idea that cross-sex hormone treatment skews the cognitive performance of transgender youth and adults towards the pattern of the desired gender. Memory, processing speed and executive functioning has received relatively little attention in research on cognition in transgender individuals. To our knowledge, this is the first study about changes in processing speed (in visuo-verbal and visuo-spacial tasks), attention, immediate memory, and ability to inhibit cognitive interference in FM transgender adolescents receiving androgenic treatment.

Consistently with previous studies with youth [18], the present research provides some evidence for a differential sex effect of androgen treatment on visuospatial speed ability among FM adolescents, which seems biologically plausible. Participants in the longitudinal study, tested before and after 12 months of androgen treatment, improved their performance on processing speed on a visuo-spatial task with a large effect size. As regards visuo-spatial ability and visual memory, our findings of no improvement in this domain agree with

recent studies [31,32] but not with early research [21,33]. Although a significant post-treatment advantage in visuo-spatial memory was not verified, a tendency could be documented. A possible explanation about the lack of a clear improvement is that some FM people may have reached a ceiling in performance and therefore do not benefit from activating hormonal effects [31]. In fact, the majority of FM participants' punctuations in ROCF (copy and memory tasks) were in the high range of percentiles.

FM adolescents after testosterone treatment also obtained better scores on a verbal immediate memory test in accordance with previous research although not with transgender participants [34]. In fact, there are studies in which administration of 17b-estradiol showed improvements in verbal memory in women with Alzheimer's disease [35]. However, previous studies suggest that sex hormones do not globally improve memory, visuospatial or attention domains but selectively affect some specific processing [36,37].

FM participants after androgen treatment improved their processing speed in two tasks. Male superiority in reaction time and finger tapping tests has been previously demonstrated [38]. Moreover, FM adolescents improved their ability to inhibit cognitive interference, something consistent with previous results that men tend to be more resistant to interference [26] and in consonance with prior literature with transgender adults [3].

In contrast, the FM adolescents participating in this study worsened impulsivity control after androgen treatment and compared with FM adolescents off-androgen treatment. The ability to inhibit cognitive interference (that improves in on-treatment FM participants) is considered an indirect indicator of cognitive impulsivity and a dimension of executive function, whereas the impulsive indic of control of CARAS-R test could be interpreted as a measurement of motor impulsivity. Circulating levels of testosterone have been positively associated with behavioral impulsivity in nontrasgender men (but with a small size effect) [18]. Our results suggest that physicians prescribing testosterone should be aware that FM individuals could be at risk for motor impulsivity.

It is very important to note that the magnitude of these differences is moderate or small. Nevertheless, previous research has found that cognitive function in transgender individuals naive to gender-affirming treatment seems to be more congruent with their gender identity than their birth-assigned sex, and this characteristic could create a restricted potential for treatment change [39-41]. Otherwise, puberty is a sensitive period for brain organization and the evidence indicates that androgens are critical modulators of executive function [13] and behavior control [18].

Our study has some limitations. Sample size limited the statistical power to conduct sub-analyses, and the adjustment for other potential confounders, such as age, educational level, or general intelligence. However, the present study has a similar sample size to previous studies [18] and it is a group that is difficult to access due to its low incidence. The short follow-up period (12 months), although similar to previous studies [18], may have hampered the potential for a statistically significant difference in less plastic cognitive functions to be shown and the stability of cognitive changes. Moreover, without a control group in the longitudinal study, it's harder to be certain that the outcome was caused by the treatment and not by other variables.

Table III. Performance on cognitive tests for female-to-male transgender adolescents tested before and after 12 months of androgen treatment (longitudinal study).

	Before treatment (n = 10) (mean, SD)	After treatment (n = 10) (mean, SD)	p-value	Effect size (Cohen's d)
CARAS-R (A-E)	41.7 (14.3)	42.3 (13.67)	0.909	
CARAS-R (ICI)	85.67 (13.9)	81.59 (20.03)	0.05	0.23
TAVEC (immediate memory)	49.2 (13.3)	56.7 (12.63)	0.0009	0.57
TAVEC (delayed memory)	11.6 (4.03)	12.8 (3.49)	0.423	
TAVEC (short-term memory)	11.3 (3.77)	12.2 (3.48)	0.434	
ROCF (copy)	32.4 (2.8)	34.7 (1.77)	0.221	
ROCF (time)	4.24 (2.07)	2.73 (1.47)	0.018	0.84
ROCF (memory)	23.8 (5.36)	33.15 (18.14)	0.088	
Stroop (CW)	42 (15.7)	50.1 (17.5)	0.001	0.48
Stroop (interference)	1.5 (11.2)	6.97 (12.43)	0.001	0.46
Phonetic verbal fluency (COWAT)	10.9 (4.9)	12.78 (4.47)	0.46	
Semantic verbal fluency (COWAT)	18.2 (7.2)	19.89 (5.33)	0.652	

CARAS-R: test on perception of differences; COWAT: Controlled Oral Word Association test; ROCF: Rey-Osterrieth complex figure test; Stroop: Stroop color and word test (SCWT); TAVEC: Complutense verbal learning test.

The positive unidirectional learning effect in the longitudinal design may be interpreted as a test/retest or learning effect because of the absence of a control group for the longitudinal study. Larger-scale, longitudinal studies for more than 12 months are required to understand possible neurodevelopmental impacts of gender-affirming hormone therapy over time in male transgender adolescents. Changes in hormones can profoundly affect cognition, and exogenous hormone administration must further be studied to better inform patients about potential changes in cognitive functioning and behavior.

Conclusions

The present study, in consonance with previous studies in youth, provides some evidence for an effect of androgen treatment on cognition among FM transgender adolescents. Specifically, this research also provides some evidence for an impact of androgen treatment on improved processing speed and interference and worsened impulsivity control after androgen therapy making the cognitive discrepancy between the biological sex and the gender identity smaller.

Further research is needed to determine the psychological benefits of these long-term effects of hormone therapy on cognitive function, that could inform clinical decision-making regarding the use of hormone therapy in the transgender population.

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Efectos del tratamiento con andrógenos sobre la neurocognición en adolescentes transgénero de mujer a hombre

Introducción. Se ha planteado la hipótesis de que la neurocognición en personas transgénero durante el tratamiento hormonal cruzado podría aproximarse a la del género subjetivo. Sin embargo, la investigación sobre este tema ha producido resultados inconsistentes y, hasta donde sabemos, ningún estudio ha investigado los cambios neurocognitivos en adolescentes transgénero de mujer a hombre (FM) tratados con andrógenos.

Sujetos y métodos. Quince adolescentes transgénero FM (14-17 años) se sometieron a pruebas neuropsicológicas para examinar los efectos de los andrógenos en sus habilidades visuoespaciales, memoria verbal, velocidad de procesamiento y funciones ejecutivas. Utilizamos un diseño longitudinal en el que se evaluó a 10 participantes dos veces, antes y después de recibir, durante 12 meses, tratamiento con testosterona. Este grupo también se comparó con cinco adolescentes transgénero FM sin tratamiento con andrógenos.

Resultados. Los participantes evaluados antes y después de 12 meses de tratamiento con andrógenos mejoraron significativamente en velocidad de procesamiento en una tarea visuoespacial (prueba de la figura compleja de Rey-Osterrieth) y en una tarea visual (Stroop), en una tarea de memoria verbal (test de aprendizaje verbal España-Complutense) y en interferencia (Stroop), y exhibieron un menor control de la impulsividad (test de percepción de diferencias revisado). Los adolescentes que recibieron tratamiento con andrógenos mostraron un peor control de la impulsividad cognitiva que los adolescentes que no recibieron tratamiento con andrógenos.

Conclusiones. Los resultados indican que los andrógenos influyen en la memoria verbal, la interferencia cognitiva, el control de la impulsividad y la velocidad de procesamiento.

Palabras clave. Adolescente. Neurocognición. Neuropsicología. Transexual. Transgénero. Tratamiento con andrógenos.