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Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis

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ABSTRACT

Background: Previous studies have examined whether steroid hormone treatment in transgender individuals may affect cognitive function; yet, their limited power does not allow firm conclusions to be drawn. We leveraged data from to-date literature aiming to explore the effect of gender-affirming hormone administration on cognitive function in transgender individuals.

Methods: A search strategy of MEDLINE was developed (through June 1, 2019) using the key terms transgender, hormone therapy and cognitive function. Eligible were (i) cohort studies examining the longitudinal effect of hormone therapy on cognition, and (ii) cross-sectional studies comparing the cognitive function between treated and non-treated individuals. Standardized mean differences (Hedges' *g*) were pooled using random-effects models. Study quality was evaluated using the Newcastle-Ottawa Scale.

Outcomes: Ten studies (seven cohort and three cross-sectional) were eligible representing 234 birth-assigned males (aM) and 150 birth-assigned females (aF). The synthesis of cohort studies (n = 5) for visuospatial ability following hormone treatment showed a statistically significant enhancement among aF (g = 0.55, 95% confidence intervals [CI]: 0.29, 0.82) and an improvement with a trend towards statistical significance among aM (g = 0.28, 95%CI: -0.01, 0.58). By contrast, no adverse effects of hormone administration were shown. No heterogeneity was evident in most meta-analyses.

Interpretation: Current evidence does not support an adverse impact of hormone therapy on cognitive function, whereas a statistically significant enhancing effect on visuospatial ability was shown in aF. New longitudinal studies with longer follow-up should explore the long-term effects of hormone therapy, especially the effects on younger individuals, where there is greater scarcity of data.

1. INTRODUCTION

Transgender individuals (shortened as *trans*) experience a discordance between their personal sense of their gender (their gender identity) and the sex assigned to them at birth. Transgender is an umbrella term including not only people whose gender identity differs from their sex assigned at birth (*trans* men and *trans* women), but also people who are not exclusively masculine or feminine (non-binary or genderqueer, bigender, pangender, genderfluid or agender) (Drescher et al., 2012; Winter et al., 2016). Natal sex, either male or female, is typically designated according to the appearance of a newborn's genitalia (Nguyen et al., 2018). For the purposes of the present study, we use the terms *natal* sex and *sex assigned at birth* interchangeably to refer to this same concept. In 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) established the term gender dysphoria (GD), which refers to the discomfort or distress caused in an individual by the incongruence between their gender identity and their birth-assigned sex (Beek et al., 2016; Kraus, 2015). Nonetheless, it should be noted that GD diagnosis has been argued and upcoming efforts propose the removal of gender incongruence from the list of mental and behavioral disorders in DSM in an effort to avert the potential stigma and associated challenges transgender people may face (Reed et al., 2016; Winter et al., 2016). In the latest version of the International Classification of Diseases (ICD-11), the diagnosis of gender incongruence is included in a separate chapter on conditions related to sexual health (Drescher et al., 2012; Reed et al., 2016).

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Crude estimates of the prevalence of transgender people rely on indirect methods and they are gauged by the number of individuals pursuing hormonal treatment or other surgical options. The reported overall incidence of transgender people is estimated to 4.6 per 100.000 individuals; 2.6 for *trans* men and 6.8 for *trans* women (Arcelus et al., 2015; Collin et al., 2016). There is an upward trend in the incidence of transgender people mainly due to the increased number of transgender individuals, who pursue gender-affirming health care over the past decade (Dhejne et al., 2014; Wiepjes et al., 2018). Concurrently, there has been a dramatic increase in younger transgender individuals seeking medical care over the last years, among whom birth-assigned females (aF) are overrepresented (Littman, 2018; Skordis et., 2018). Gender-affirming health care in young adolescents going through puberty usually involves the administration of hormonal puberty blocking agents, namely gonadotropin-releasing hormone analogues. Older adolescents and adults typically seek masculinizing or feminizing steroid hormones, gender reassignment surgery or several other healthcare services (Winter et al., 2016). Assigned female transgender people typically take testosterone, while assigned males (aM) typically take estradiol with or without androgen blockers (Drescher et al., 2012; Nguyen et al., 2018).

The increased administration of gender-affirming hormone therapy in transgender individuals has raised concerns about potential adverse health effects of the treatment (Mehringer and Dowshen, 2019; Shadid et al., 2019). Several studies have focused on the potential impact of gender-affirming therapy on cognitive function given the accumulating and long debated evidence concerning gender differentials in cognition (Nguyen et al., 2018; Nota et al., 2017). Previous research has shown that aF perform better than aM on verbal tests, perceptual speed, memory for object location and fine motor skills, while aM outperform aF on certain mathematical tasks, such as approximate arithmetic, visuospatial ability, targeted motor skills and map reading (Slabbekoorn et al., 1999; Van Goozen et al., 1994). Current evidence supports that gender differences in math performance are small, particularly in developed countries (O'Dea et al., 2018). However, despite the small sex differences (O'Dea et al., 2018), there are certain cognitive domains including approximate arithmetic, visuospatial ability and mental rotation where aM consistently outperform aF (Breda and Napp, 2019; Palmiero et al., 2016). It is plausible that the larger parietal cortex in aM, especially in the right hemisphere and the physiological effects of sex hormones on brain function may account for these differentials (Wei et al., 2016). Indeed, some aspects of cognitive function may be shaped during sensitive periods of brain development, thus leading to permanent sex differences (Breda and Napp, 2019; Wei et al., 2016). It is thus biologically plausible that cognitive performance during gender-affirming hormone treatment might change towards that of the experienced gender. Previous studies have examined whether hormone treatment in aF and aM transgender individuals may affect cognitive function, whereas neuroimaging studies have also shown changes in brain structure in transgender individuals under hormonal treatment (Hahn et al., 2015). However, the limited statistical power of existing literature due to small sample sizes and the investigation of specific cognitive domains do not allow a broader and more global assessment of cognitive function.

Acknowledging the inherent limitations of existing literature, in the present systematic review and meta-analysis, we leveraged data from published studies, and by increasing statistical power, we set out to explore the effect of gender-affirming hormone administration on cognitive function in transgender individuals.

2. Methods

The present systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) (Supplementary Table 1) based on a predefined protocol.

2.1. Search strategy and eligibility criteria

Two independent reviewers (T.V., N.D.) performed an in-depth search of the Medline database from its inception up to June 1, 2019 using combinations of the following MeSH terms: "transgender", "gender dysphoria", "hormone therapy" and "cognitive function"; the complete search strategy is available in the Supplementary Methods. We set no limitations on language and publication year. Articles were initially selected based on title and abstract; the full-texts were thereafter obtained and reviewed. Pairs of reviewers performed the selection of studies independently and blindly to each other. Reference lists of the eligible studies and identified relevant reviews were subsequently hand searched for potentially additional eligible studies ("snowball procedure"). Eligible studies were evaluated for overlap by contacting the authors (Van Goozen et al., 1994, 1995; Van Goozen et al., 2002). We contacted the corresponding authors of eligible studies in case of missing data in the published articles, inquiries regarding the eligibility of the study or ambiguous cases of potential population overlap between studies.

Eligible studies included cohort and cross-sectional studies that assessed the relationship between gender-affirming hormone therapy and cognitive function in transgender individuals. Acknowledging the controversies in the diagnosis of GD, we primarily searched for studies on transgender individuals who explicitly met the diagnostic criteria of a GD diagnosis. The most comprehensive definition of GD was selected, preferably the assessment of GD by psychiatrists based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). However, to avoid publication bias studies using alternative diagnostic criteria or not specifying the diagnostic method, as well as studies on transgender people not clearly meeting the criteria of GD were also considered eligible. To this end, we avoided the term GD for the purposes of the present study to prevent a potential misclassification bias, but we used only the term transgender individuals who received gender-affirming hormone treatment irrespectively of meeting or not the criteria of a GD diagnosis. We included cohort studies assessing any cognitive domain among aF or aM transgender individuals in at least two different serial assessments (pre- and post-treatment), as well as cross-sectional studies comparing aF or aM transgender individuals who were under gender-affirming treatment versus those who did not receive any treatment. The measurement of cognitive function was estimated using validated standardized tests, which examined one or more domains of cognition.

2.2. Data extraction and quality assessment

General information (year, author, journal, region of origin and study period), study characteristics (design, duration of follow-up, description of participants), cohort size, mean age, age range, as well as characteristics of the hormonal treatment (type of intervention, onset of treatment, average dosage, average period exposed to treatment, administration route) were abstracted in a pre-piloted spreadsheet. Furthermore, the different cognitive tests were abstracted and categorized based on the properties of the test in the main cognitive domains, namely attention, computation, motor coordination, verbal memory, verbal reasoning, verbal working memory, visual working memory, total working memory and visuospatial ability. The final classification of the tests by cognitive domain, reviewed by two clinical neuropsychologists (T.H. and J.I.) and a senior psychiatrist (F.P.) is available in Supplementary Table 2. Regarding the results of the studies, we extracted the mean values and standard deviations of scores achieved at each test before and after the intervention for cohort studies, as well as the scores achieved by treated and non-treated individuals in cross-sectional studies.

Two independent reviewers conducted the data abstraction and quality assessment of the eligible studies (N.D., I.S.). The quality of each study was evaluated using the Newcastle-Ottawa Quality Assessment

Scale (NOS) (Wells et al., 2011). In the ´´Selection´´ section of the NOS scale, studies including individuals diagnosed with GD according to DSM-IV and seeking a gender affirming hormone treatment would be considered truly representative of the exposed cohort/sample, whereas studies on transgender people not clearly meeting the criteria of GD were also considered representative of the community and were allotted a star. Furthermore, the ''Selection of the non-exposed cohort'' category was not evaluated given that the eligible cohort studies performed a comparison between pre- and post-treatment of each study participant (absence of non-exposed group); for the same reason all cohort studies were awarded with two stars in the ''Comparability'' section. Regarding the ''Outcome'' section, studies assessing cognitive performance via a validated cognitive test were allotted a star. Additionally, the duration of follow-up cut-off for granting a star was defined at 6 months, whereas the minimum follow-up adequacy was set at 80%. By definition, the cross sectional studies received no stars in the categories: ''Long enough follow-up'' and ''Follow-up adequacy of cohorts''. In case of a study with both a longitudinal and a cross-sectional analysis, we presented the evaluation of its longitudinal section.

2.3. Statistical analysis

We calculated standardized mean differences (SMD) and 95% confidence intervals (CI) between scores in pre- and post-treatment cognitive assessments in cohort studies, as well as between scores in treated and non-treated individuals in cross-sectional studies using the Cohen's *d* formulae (Durlak, 2009). Due to small sample sizes, we then applied the Hedges' *g* correction (Lakens, 2013). The effect estimates for each cognitive domain examined in at least two studies were, thereafter, separately pooled for aF and aM individuals using random-effects models (DerSimonian and Laird, 2015) to incorporate any apparent heterogeneity in study design and analytic approach between studies (Tufanaru et al., 2015). Separate meta-analyses were run for cohort and cross-sectional studies. The statistical significance was set at $p < 0.05$. Heterogeneity was assessed with the I^2 estimation and the Cochran Q statistic (significance level was set at $p < 0.10$) (Cohen et al., 2015). The impact of potential effect modifiers, namely country, publication year, average follow-up period and mean age on the associations of interest was estimated through meta-regression. The examination of publication bias was not possible due to the limited number of study arms in each meta-analysis.

Analyses were performed using the STATA Software (v13.0, Stata Corporation, College Station, TX, USA).

3. Results

3.1. Search results

The initial database search yielded 151 results (Fig. 1). Five additional articles were derived from the "snowball" procedure. At the title and abstract screening level, 141 records were considered irrelevant, while the remaining 15 articles were forwarded for full-text evaluation. Among them, four articles were excluded due to assessment of cortical lateralization (Beking et al., 2019; Cohen-Kettenis et al., 1998; Wisniewski et al., 2005) and cortical activation by fMRI (Carrillo et al., 2010) and not cognitive function. Another study was excluded due to insufficient data for the quantitative synthesis (Van Goozen et al., 1995). Following the exclusion of these five studies due to the aforementioned reasons (Supplementary Table 3), 10 studies were deemed eligible for this systematic review (Burke et al., 2016a; Friedman, 2000; Gomez-Gil et al., 2009; Haraldsen et al., 2005; Miles et al., 2006; Miles et al., 1998; Schoning et al., 2010; Slabbekoorn et al., 1999; Van Goozen et al., 1994; Van Goozen et al., 2002). There was no overlap between the study populations, as also confirmed after contacting the corresponding authors (Van Goozen et al., 1994, 1995; Van Goozen et al., 2002).

3.2. Characteristics of included studies

The descriptive characteristics of the eligible studies are summarized in Table 1. Briefly, eight studies were conducted in Europe (Burke et al., 2016a; Gomez-Gil et al., 2009; Miles et al., 2006; Miles et al., 1998; Schoning et al., 2010; Slabbekoorn et al., 1999; Van Goozen et al., 1994; Van Goozen et al., 2002), one in the USA (Friedman, 2000) and one in both Europe and the USA (Haraldsen et al., 2005). Six studies were cohort (Burke et al., 2016a; Haraldsen et al., 2005; Miles et al., 2006; Slabbekoorn et al., 1999; Van Goozen et al., 1994; Van Goozen et al., 2002) and three cross-sectional (Friedman, 2000; Miles et al., 1998; Schoning et al., 2010), whereas one study presented both a longitudinal and a cross-sectional analysis (Gomez-Gil et al., 2009). Overall, there were 91 aM and 131 aF transgender individuals in the cohort studies and 143 aM and 19 aF transgender individuals in cross-sectional studies. The gender-affirming hormone treatment mainly consisted of androgen for aF individuals and estrogen usually combined with antiandrogen for aM; however, the dosages and frequencies of hormonal administration showed a large variability among the eligible studies. In addition, the majority of eligible studies lacked information on history of treatment prior to the gender-affirming hormone protocol including the type, dosage and frequency of medications administered. Though variable across studies, the mean age at first cognitive assessment was 36.0 years for aM and 25.6 years for aF individuals. For cohort studies, the follow-up period ranged between 2 and 12 months. The specific cognitive tests are described in detail in Supplementary Table 2. In brief, visuospatial ability (6 cohort and 2 cross-sectional studies) and verbal memory (5 cohort and 3 cross-sectional studies) were the most commonly assessed cognitive domains across studies, followed by visual memory (5 cohort and 1 cross-sectional studies) and verbal reasoning (4 cohort and 2 cross-sectional studies).

3.3. Quality of studies

High quality was recorded for the majority of the included studies with only two cross-sectional studies losing over two NOS points due to short follow-up (< 6 months), inadequate follow-up (< 80%) and non-comparability on other risk factors. However, all studies ascertained the exposures and outcomes of interest using validated measures, whereas the follow-up was adequate (> 80%) in all cohort studies (Supplementary Table 4).

3.4. Synthesis of results

The pooled analysis of cohort studies showed a significant medium-sized enhancement in visuospatial ability following gender-affirming hormone treatment for 3-12 months in aF transgender (N = 117) individuals (g = 0.55, 95% CI: 0.29, 0.82; n = 5 study arms (Burke et al., 2016a; Haraldsen et al., 2005; Slabbekoorn et al., 1999; Van Goozen et al., 1994; Van Goozen et al., 2002); Fig. 2) without significant between-study heterogeneity (I^2 = 0.0%, *p* for heterogeneity = 0.856). No statistically significant changes were found in the remaining cognitive domains (verbal memory, verbal reasoning, verbal working memory, computation, motor coordination) between pre-treatment and post-treatment performance (Fig. 2); of note, the pooled analysis in aF individuals was not feasible for cross-sectional studies due to insufficient data.

Pooling data from cohort studies on aM transgender individuals (N = 91) showed an enhancement, albeit with a trend towards statistical significance, in visuospatial ability following gender affirming hormone treatment (g = 0.28, 95% CI: -0.01, 0.58; n = 5 study arms (Haraldsen et al., 2005; Miles et al., 2006; Slabbekoorn et al., 1999; Van Goozen et al., 2002); I^2 = 0.0%, *p* for heterogeneity = 0.561; Fig. 3). The pooled analysis of cross-sectional studies showed higher performance in verbal working memory among gender-affirming hormone treated (N = 50) compared to non-treated (N = 61) aM individuals (g = 0.52,

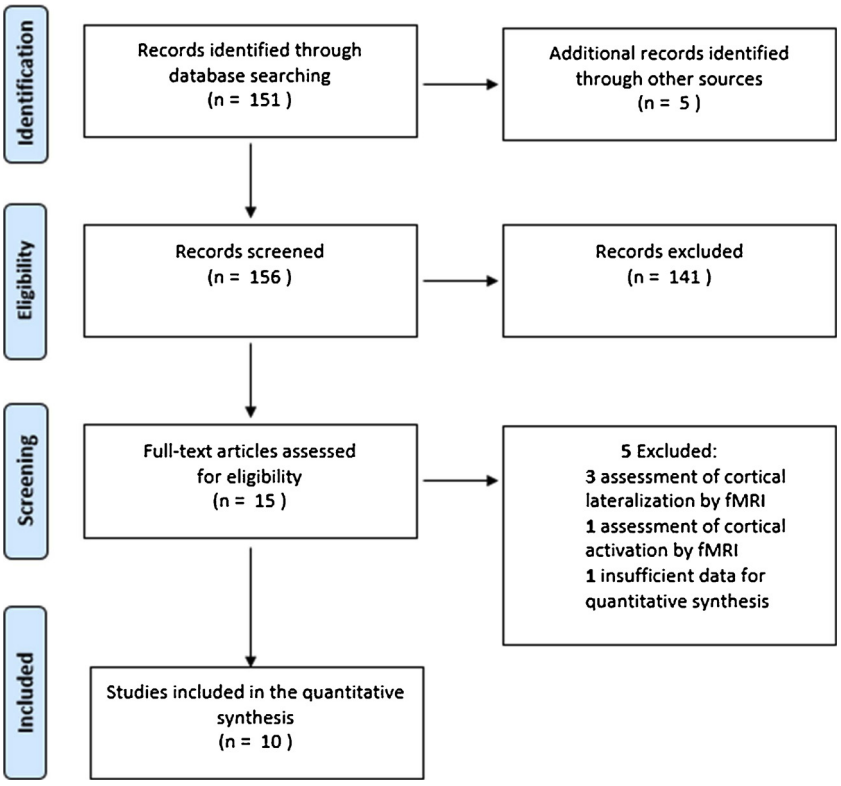

Fig. 1. Flowchart of the successive steps of the systematic review process.

95% CI: 0.13, 0.90; n = 2 study arms (Friedman, 2000; Miles et al., 1998); I^2 = 0.0%, *p* for heterogeneity = 0.671; Supplementary Fig. 1).

Meta-regression analyses did not show any significant modifying effect of the major confounding factors, namely publication year, average follow-up period, country of origin and mean age, on the observed associations (*p* = 0.225-0.972; Supplementary Table 5).

4. Discussion

4.1. Principal findings

This comprehensive systematic review and meta-analysis summarizes evidence from 10 studies that examined the relationship between gender-affirming steroid hormonal therapy and cognitive function in transgender young adults. All but one studies focused on young adults (age range 16.0-42.0 years) examining the effect of post-pubertal gender-affirming hormonal treatment on different cognitive domains. Identified studies used mainly longitudinal, but also cross-sectional design and focused mostly on visuospatial ability and verbal memory. The results showed a statistically significant enhancement in visuospatial ability in aF following gender-affirming hormone treatment. The pooling of cross-sectional studies showed an improved performance in verbal working memory among treated compared to non-treated aM individuals. Importantly, the synthesis of to-date published literature did not support an adverse effect of gender-affirming hormone administration on any cognitive domain. Despite the variability in exposure and outcome assessment, no between-study heterogeneity was evident in most meta-analyses; in addition, meta-regression analyses showed no significant effect of potential confounders on the associations of interest.

4.2. Previous literature-Interpretation of results

A persistent finding among studies of gender differentials in cognitive performance is that aM seem to outperform aF on tests of visuospatial skills, whereas aF surpass aM on tests of verbal abilities (Breda and Napp, 2019; Kimura, 1996; Maccoby and Jacklin, 1974; Palmiero et al., 2016; Wei et al., 2016); these differences seem to be mainly attributed to circulating hormonal changes (Ali et al., 2018; Beking et al., 2018; Burke et al., 2016b; Nguyen, 2018; Silverman et al., 1999). Consistently with the results of these studies, the present meta-analysis suggests that an androgenic hormonal environment may have a beneficial effect on visuospatial ability. Similar results were found in studies on aF with congenital adrenal hyperplasia showing enhanced spatial ability (Berenbaum, 2001), as well as in studies supporting that human spatial ability may be beneficially affected by prenatal androgens (Beking et al., 2018; Nguyen et al., 2017). In particular, second trimester testosterone levels seem to predict spatial ability positively in aF and negatively in aM at age seven (Grimshaw et al., 1995). Moreover, according to a twin study, aF with a aM co-twin exhibited superior spatial ability, possibly due to the *in utero* exposure to the androgens produced by their co-twin (Cole-Harding et al., 1988). On the contrary, aF with Turner syndrome, who in general have lower androgen levels usually demonstrate cognitive deficits in spatial ability (Nijhuis-van der Sanden et al., 2003). Likewise, the complete androgen insensitivity syndrome (CAIS) characterizes individuals with a 46XY karyotype, undescended testes, normal to high levels of testosterone and a birth-assigned female phenotype due to lack of functional androgen receptors (Imperato-McGinley et al., 1982). Studies have shown that individuals with CAIS perform worse on spatial tasks compared to both their aM and non-CAIS aF counterparts (Imperato-McGinley et al., 1991). Whether androgens have activation effects that enhance spatial ability in aM and aF with functional androgen receptors cannot be oversimplified and remains less conclusive (Pintzka et al., 2016; Puts et al., 2010; Spritzer et al., 2011). Indeed, there seems to be different and more complex mechanisms that underlie the potential enhancing effect of androgens on spatial ability in aF with functional androgen receptors. However, there is some evidence that high testosterone levels improve specific tasks of spatial ability including mental rotation ability, route-learning and performance of a block design task (Pintzka et al., 2016;

Table 1
Descriptive characteristics of eligible studies

Author, Year	Country	Study design	Sex	Type of treatment	Study population, N (Exposed to treatment)	Age at first cognitive assessment (mean ± SD)	Follow-up (months)	Cognitive domains assessed
Van Goozen, 1995	The Netherlands	cohort	aF	IM 250 mg/2 weeks or PO 2 x 40 mg/day androgen	22	25.7 (range 18-49)	3	VM, VR, VSA
Miles, 1998	United Kingdom	cross-sectional	aM	4.47 mg/day estrogens or (2.5 mg estrogens and 5 mg progesterone) or (5 mg estrogens and 100 mg anti-androgen)	59 (29)	34.8 ± 10.2	NR	VM, VR, VWM, WM, VSA
Slabbekoorn, 1999	The Netherlands	cohort	aM	PO 2 x 50 μg/day estrogen and PO 2 x 50 mg/day anti-androgen	20	29.1 ± 8.0	12	A, MC, VM, VR, VSA
			aF	IM 250 mg/2 weeks androgen	25	26.0 ± 7.7	10	A, MC, VM, VR, VSA
Friedman, 2000	USA	cross-sectional	aM	Estrogen (routine dosage as part of the process of changing gender)	62 (31)	42.5 ± 8.6	NR	VWM, WM
Van Goozen, 2002	The Netherlands	cohort	aM	PO 2 x 0.05 mg/day or 0.10 mg/day estrogen and PO 2 x 50 mg/day anti-androgen	22	31.4 ± 10.8	3.5	MC, VSA
			aF	IM 2 x 250 mg/2weeks or 100 mg/2weeks or PO 200 mg/day androgen	19	26.2 ± 7.5	3.5	MC, VSA
Haraldsen, 2005	Norway	cohort	aM	PO 50 μg/day estrogen	12	26.7 ± 5.9	12	C, VM, VR, VWM, VSA
			aF	IM 180 mg/3weeks androgen	21	26.7 ± 5.9		C, VM, VR, VWM, VSA
	USA		aM	PO 100 μg/day estrogen	10	35.2 ± 10		C, VM, VR, VWM, VSA
			aF	IM 180 mg/3weeks androgen	9	35.2 ± 10		C, VM, VR, VWM, VSA
Miles, 2006	United Kingdom	cohort	aM	10-100 mg estrogen or (50-100 mg estrogen and 50-100 mg anti-androgen)	27	37.1 ± 8.7	3 - 12	VM, VWM, ViWM, WM, VSA
Gómez-Gil, 2009	Spain	cohort	aF	IM (100-200 mg/ 2-4 weeks) or TD (5–10 g/day) androgen	14	27.4 ± 9.3	6	VWM, ViWM
		cross-sectional	aF	IM (100-200 mg/ 2-4 weeks) or TD (5-10 g/ day) androgen	19 (10)	27.7 ± 5.44	NR	VWM, ViWM
Schöning, 2010	Germany	cross-sectional	aM	PO estrogen or PO estrogen and anti-androgen for 0.5-2 years (mean duration: 1.14 years)	22 (11)	36.2 ± 9.8	NR	VR, VSA
Burke, 2016	The Netherlands	cohort	aF	250 mg/ml/2 weeks or 12 weeks testosterone ester mixture	21	16.0 ± 0.8	NR	VSA

Abbreviations: aF, assigned female; aM, assigned male; SD, standard deviation; PO, per os; IM, intramuscular depot; TD, transdermal; NR, not reported; A, Attention; MC, motor coordination; C, Computation; VM, Verbal memory; VR, Verbal reasoning; WM, Working memory; VWM, Verbal working memory; ViWM, Visual working memory; VSA, visuospatial ability

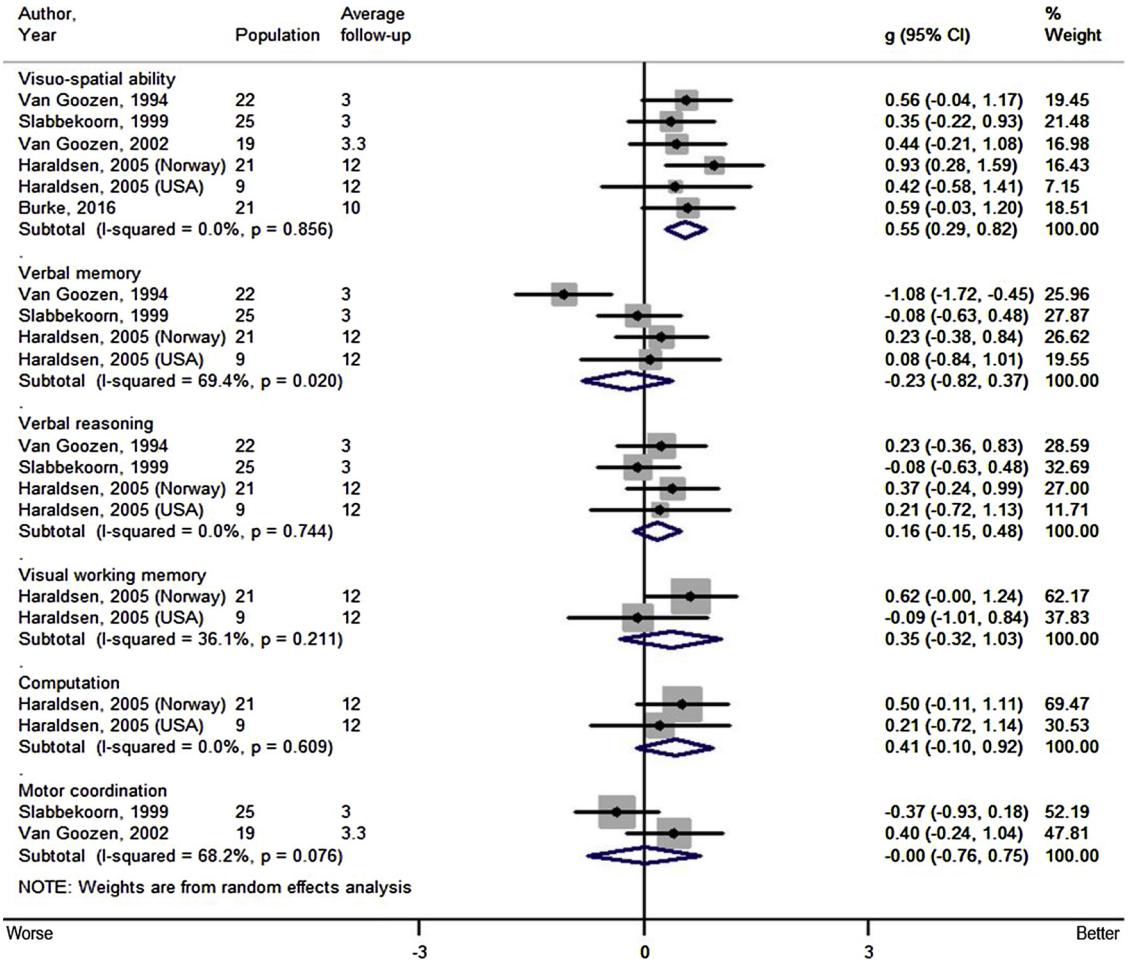

Fig. 2. Effect of gender affirming hormone treatment on cognitive performance in assigned female (aF) transgender individuals among cohort studies*. The data markers correspond to pooled-effect standardized mean differences between pre-treatment and post-treatment performance in the examined cognitive domains, while 95% confidence intervals (CI) are indicated by error bars. Negative values indicate association of gender affirming hormone treatment with deteriorated cognitive performance, whereas positive values with enhanced cognitive performance.
*The *p*-values refer to the Cochran Q statistic (significance level was set at $p < 0.10$)

Puts et al., 2008).

In the same context and consistently with recent studies, the present meta-analysis provides some evidence for a sex differential effect of hormone treatment on cognition confined mainly to visuospatial ability among aF (Jäncke, 2018), which seems biologically plausible. Indeed, cognitive function in transgender individuals naive to gender-affirming treatment seems to be more congruent with their gender identity than their birth-assigned sex, creating, thus, a restricted potential for change (Nawata et al., 2010; Rametti et al., 2011; Simon et al., 2013; Zhou et al., 1995). Taking also into account neurogenesis, the most plastic regions of human brain are the subventricular (SVZ) and the subgranular zone (SGZ) of the hippocampus (Bacigaluppi et al., 2020; Kolb et al., 2017). Recent research has shown a strong correlation between cells in the hippocampal formation and spatial ability (Hartley et al., 2014; Laube et al., 2020), which may at least partially explain why this cognitive domain may be more prone to alteration. Of note is the trend towards statistically significant enhancement in visuospatial ability among aM transgender individuals following gender-affirming hormone treatment. Oestrogens are not currently considered to have a major role in the masculinization of the human brain, but data are scarce (Swaab, 2004). There are indications from lower mammals that estrogenic receptors are involved in the masculinization of neural circuits in brain areas important for sexual behaviour (Kudwa et al., 2006; McCarthy, 2008), as well as that oestrogens may upregulate the expression of androgen receptors (McAbee and Doncarlos, 1999). A recent study on transgender individuals supports the involvement of estrogen receptors together with the androgen receptor in gender development (Fernandez et al., 2018). Moreover, in human prostate cells, 17β-estradiol, but not diethylstilbestrol was found to be a natural ligand for androgen receptor and may play an essential role for the development of the male reproductive system (Yeh et al., 1998). Given the complex physiological effects of steroid hormones on brain function and the scarcity of research on the effects of prenatal or pubertal testosterone and oestrogen levels in aM individuals, the present results, especially regarding the weak and non-statistically significant enhancement in visuospatial ability among aM following hormonal treatment need to be replicated in future studies to allow firm conclusions to be drawn. Moreover, other factors, such as a possible positive effect of experiencing less gender incongruence along with gender-affirming treatment on the performance on cognitive tests cannot also be excluded (van de Grift et al., 2016v; Wiepjes et al., 2018), but this still cannot explain why such an effect is only seen in visuospatial ability and no other domains.

Regarding other cognitive domains beyond visuospatial ability, the absence of verbal cognitive enhancements besides verbal working memory among aM transgender individuals following hormonal treatment might be due to the absence of circulating progesterone, which differentiates them from their cisgender aF counterparts (Maki and Henderson, 2012; Nguyen et al., 2018; Sherwin and Grigorova, 2011; Shumaker et al., 2003). Indeed, exogenous progesterone seems to be

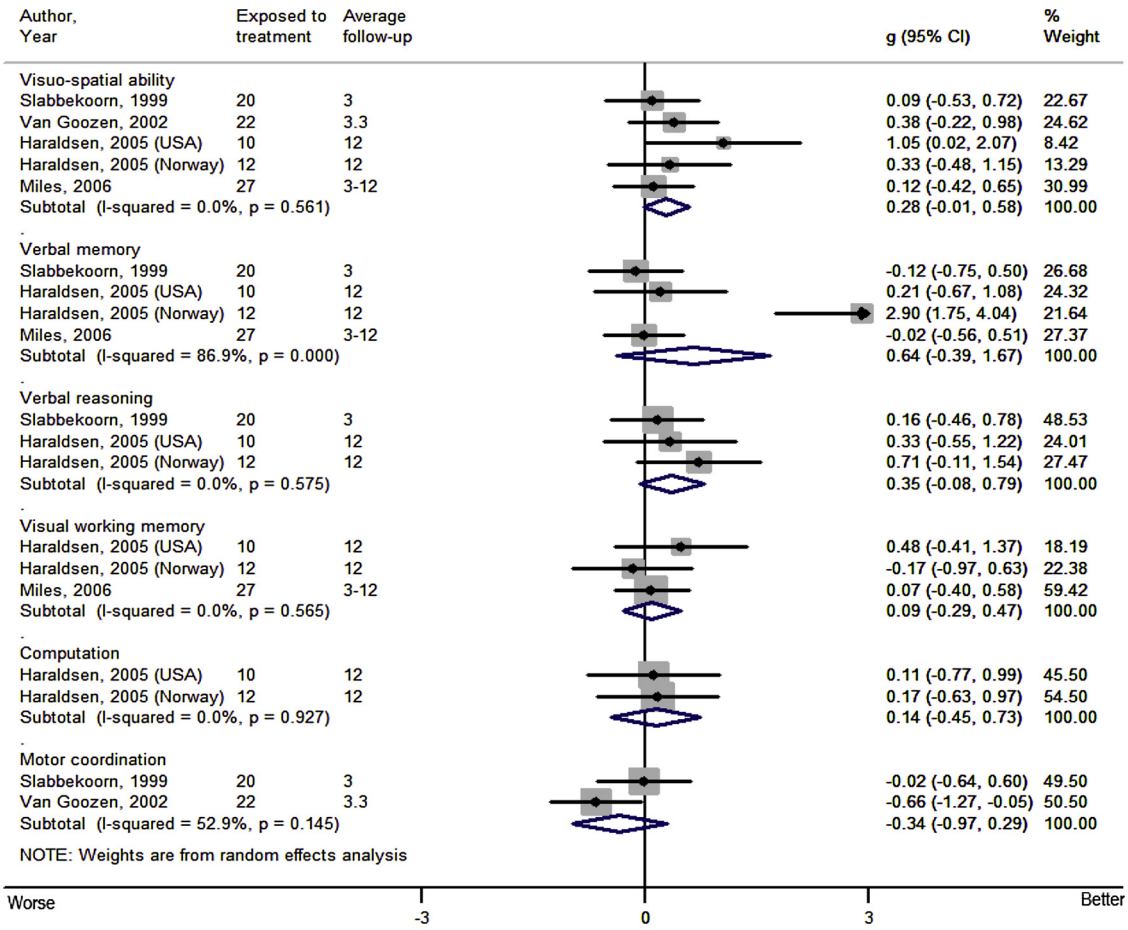

Fig. 3. Effect of gender affirming hormone treatment on cognitive performance in assigned male (aM) transgender individuals among cohort studies*. The data markers correspond to pooled-effect standardized mean differences between pre-treatment and post-treatment performance in the examined cognitive domains, while 95% confidence intervals (CI) are indicated by error bars. Negative values indicate association of gender affirming hormone treatment with deteriorated cognitive performance, whereas positive values with enhanced cognitive performance.
*The *p*-values refer to the Cochran Q statistic (significance level was set at $p < 0.10$)

associated with improved neuropsychological measures in verbal memory compared to placebo (Berent-Spillson et al., 2015; Sherwin and Grigorova, 2011). In addition, recent studies suggest that sex hormones do not globally modulate verbal memory or forgetting, but selectively affect cue-specific processing (Kerschbaum et al., 2017; Resnick et al., 2006); specifically, there is some evidence that progesterone may enhance the inhibitory mechanism in item-context binding in forget-cued young aF individuals (Kerschbaum et al., 2017).

To this end, although the results of the present meta-analysis confirm current evidence that gender-affirming hormone treatment enhances specific cognitive domains in transgender individuals congruently with their gender identity (Nguyen et al., 2018), these stipulations merit cautious interpretation. Future studies are needed to address the inherent limitations of to-date literature, including the cross-sectional design, the limited follow-up times and the lack of adjustment for other potential confounders, such as prior hormonal treatment modalities. Indeed, the short follow-up period (maximum of 12 months) may have hampered the potential for a statistically significant difference in less plastic cognitive functions to be shown. In particular, the potential adverse long-term effects of estrogenic depletion on specific executive areas of cognition, such as memory and attention should be targets of future longitudinal studies with longer follow-up given that transgender individuals are usually under long-term gender-affirming hormone administration (Shanmugan and Epperson, 2014; Shanmugan et al., 2017).

4.3. Strengths and limitations

A major strength of this first meta-analytic attempt lies in its sound methodologic approach according to current guidelines. Following an independent dual screening of the existing literature and rigorous communication with the authors of potentially eligible articles, the study participants contributing information in main analyses were more than 200 aM and 150 aF, with no significant heterogeneity noticed among included studies. Moreover, separate meta-analyses by study design were undertaken, as well as meta-regression analyses, which showed no significant impact of the main potential effect modifiers including publication year, average follow-up period, country of origin and mean age on the associations of interest. However, it must be noted that only one study included adolescents while most individuals included in the present meta-analysis were at the mid-20 s to 30 s. We can thus not generalize our findings in the younger group of transgender people who are increasingly seeking gender-affirming treatment during the last decade.

Our findings should be interpreted in view of inherent limitations involving the small number of published studies, which limited the statistical power to conduct sub-analyses and the variable study periods, though meta-regression did not show any significant effect of publication year on the observed associations. Likewise, despite the absence of significant between-study heterogeneity, our results may have been hampered by differential exposure and outcome ascertainment bias due to the heterogeneous gender-affirming treatment

modalities (different regiments, dosages and frequencies of steroid hormonal treatment; sex reassignment surgery) and the diverse cognitive assessment tests implemented by each study. In addition, the majority of included studies lacked information on potential confounding factors, such as history of previous treatment modalities prior to the gender-affirming hormone protocol including the type, dosage and frequency of medications administered. Though the majority of eligible studies were of cohort design and high quality, the cross-sectionally derived summary effect estimates should be interpreted with caution given the potential for inverse causality. Moreover, although meta-regression did not show a significant modifying effect of the diverse between-study follow-up periods on the observed associations, the short follow-up in all studies remains an issue of concern, which may have not allowed a statistically significant change in cognitive function to be shown, beyond visuospatial ability. Furthermore, the assessment of publication bias was not feasible due to the small number of study arms. Of note, the majority of studies were conducted in Europe pointing to the need for more ethnically diverse populations in future studies to allow generalizable conclusions to be made. Lastly, gender non-binary or gender non-conforming individuals who do not identify as transgender were absent from to-date published literature; future research should target these populations to assess how hormones to develop more masculine or feminine sexual secondary characteristics might also affect their cognitive performance.

4.4. Conclusions

The present meta-analysis suggests a potentially enhancing effect of gender-affirming hormone treatment on cognitive function in transgender young adult individuals congruently with their gender identity than birth-assigned sex. Specifically, the existing body of research provides epidemiologic evidence that supports the enhancing role of post-pubertal steroid hormonal administration in visuospatial ability in aF individuals. Given the inherent limitations and methodological obstacles of current literature derived from the older studied populations and short follow-up, as well as the interference of many potential confounders, these results are by no means definite, but they do warrant further investigation on an international basis. Longitudinal properly designed and culturally diverse studies with larger and homogeneous samples, longer follow-up periods and control for all intermediate covariates including history of prior treatments are needed to allow firm conclusions to be drawn. To this end, the present results, if confirmed in future research, could have a significant clinical impact for health care professionals and health policy planners. Finally, further gender-affirming research should focus on the effects on younger transgender individuals, as well as on the full spectrum of diversity in gender identity and gender expression beyond the binary to allow assessment of the potential health-related issues along the entire gender spectrum.

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Declarations of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.104721.

References

Ali, S.A., Begum, T., Reza, F., 2018. Hormonal Influences on Cognitive Function. Malays J Med Sci 25, 31–41.
Arcelus, J., et al., 2015. Systematic review and meta-analysis of prevalence studies in transsexualism. Eur. Psychiatry 30, 807–815.
Bacigaluppi, M., Sferruzza, G., Butti, E., Ottoboni, L., Martino, G., 2020. Endogenous neural precursor cells in health and disease. Brain Res 1730, 146619.
Beek, T.F., Cohen-Kettenis, P.T., Kreukels, B.P., 2016. Gender incongruence/gender dysphoria and its classification history. Int Rev Psychiatry 28, 5–12.
Beking, T., Burke, S.M., Geuze, R.H., Staphorsius, A.S., Bakker, J., Groothuis, A.G.G., Kreukels, B.P.C., 2019. Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. Psychoneuroendocrinology 111, 104461.
Beking, T., Geuze, R.H., van Faassen, M., Kema, I.P., Kreukels, B.P.C., Groothuis, T.G.G., 2018. Prenatal and pubertal testosterone affect brain lateralization. Psychoneuroendocrinology 88, 78–91.
Berenbaum, S.A., 2001. Cognitive function in congenital adrenal hyperplasia. Endocrinol Metab Clin North Am 30, 173–192.
Berent-Spillson, A., Briceno, E., Pinsky, A., Simmen, A., Persad, C.C., Zubieta, J.K., Smith, Y.R., 2015. Distinct cognitive effects of estrogen and progesterone in menopausal women. Psychoneuroendocrinology 59, 25–36.
Breda, T., Napp, C., 2019. Girls' comparative advantage in reading can largely explain the gender gap in math-related fields. Proc Natl Acad Sci U S A 116, 15435–15440.
Burke, S., Kreukels, B., Cohen-Kettenis, P., Veltman, D., Klink, D., Bakker, J., 2016a. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. Journal of psychiatry & neuroscience: JPN 41, 395–404.
Burke, S.M., Kreukels, B.P., Cohen-Kettenis, P.T., Veltman, D.J., Klink, D.T., Bakker, J., 2016b. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. J Psychiatry Neurosci 41, 395–404.
Carrillo, B., Gomez-Gil, E., Rametti, G., Junque, C., Gomez, A., Karadi, K., Segovia, S., Guillamon, A., 2010. Cortical activation during mental rotation in male-to-female and female-to-male transsexuals under hormonal treatment. Psychoneuroendocrinology 35, 1213–1222.
Cohen-Kettenis, P.T., van Goozen, S.H., Doorn, C.D., Gooren, L.J., 1998. Cognitive ability and cerebral lateralisation in transsexuals. Psychoneuroendocrinology 23, 631–641.
Cohen, J.F., Chalumeau, M., Cohen, R., Korevaar, D.A., Khoshnood, B., Bossuyt, P.M., 2015. Cochran's Q test was useful to assess heterogeneity in likelihood ratios in studies of diagnostic accuracy. J Clin Epidemiol 68, 299–306.
Cole-Harding, S., M.A, Wilson, J.R., 1988. Spatial ability in members of opposite-sex twin pairs. Behavior Genetics 710.
Collin, Lindsay, et al., 2016. Prevalence of Transgender Depends on the "Case" Definition: A Systematic Review. Journal of sexual medicine 13, 613–626.
DerSimonian, R., Laird, N., 2015. Meta-analysis in clinical trials revisited. Contemp Clin Trials 45, 139–145.
Dhejne, C., Oberg, K., Arver, S., Landen, M., 2014. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch. Sexual Behav. 43, 1535–1545.
Drescher, J., Cohen-Kettenis, P., Winter, S., 2012. Minding the body: situating gender identity diagnoses in the ICD-11. Int Rev Psychiatry 24, 568–577.
Durlak, J.A., 2009. How to select, calculate, and interpret effect sizes. J Pediatr Psychol 34, 917–928.
Fernandez, R., Guillamon, A., Cortes-Cortes, J., Gomez-Gil, E., Jacome, A., Esteva, I., Almaraz, M., Mora, M., Aranda, G., Pasaro, E., 2018. Molecular basis of Gender Dysphoria: androgen and estrogen receptor interaction. Psychoneuroendocrinology 98, 161–167.
Friedman, G., 2000. The effects of estrogen on short-term memory in genetic men. Journal of the American Medical Directors Association 1, 4–7.
Gomez-Gil, E., Canizares, S., Torres, A., de la torre, F., Halperin, I., Salamero, M., 2009. Androgen treatment effects on memory in female-to-male transsexuals. Psychoneuroendocrinology 34, 110–117.
Grimshaw, G.M., Sitarenios, G., Finegan, J.A., 1995. Mental rotation at 7 years: relations with prenatal testosterone levels and spatial play experiences. Brain Cogn 29, 85–100.
Hahn, A., Kranz, G.S., Kublbock, M., Kaufmann, U., Ganger, S., Hummer, A., Seiger, R., Spies, M., Winkler, D., Kasper, S., Windischberger, C., Swaab, D.F., Lanzenberger, R., 2015. Structural Connectivity Networks of Transgender People. Cerebral cortex (New York, N.Y. : 1991) 25, 3527–3534.
Haraldsen, I., Egeland, T., Haug, E., Finset, A., Opjordsmoen, S., 2005. Cross-sex hormone treatment does not change sex-sensitive cognitive performance in gender identity

disorder patients. Psychiatry research 137, 161–174.
Hartley, T., Lever, C., Burgess, N., O'Keefe, J., 2014. Space in the brain: how the hippocampal formation supports spatial cognition. Philos Trans R Soc Lond B Biol Sci 369, 20120510.
Imperato-McGinley, J., Pichardo, M., Gautier, T., Voyer, D., Bryden, M.P., 1991. Cognitive abilities in androgeninsensitive subjects: comparison with control males and females from the same kindred. Clin Endocrinol (Oxf) 34, 341–347.
Imperato-McGinley, J., Peterson, R.E., Gautier, T., Cooper, G., Danner, R., Arthur, A., et al., 1982. Hormonal evaluation of a large kindred with complete androgen insensitivity: evidence for secondary 5 alpha-reductase deficiency. J Clin Endocrinol Metab 54, 931–941.
Jäncke, L., 2018. Sex/gender differences in cognition, neurophysiology, and neuroanatomy. F1000Res 7.
Kerschbaum, H.H., Hofbauer, I., Gfollner, A., Ebner, B., Bresgen, N., Bauml, K.T., 2017. Sex, age, and sex hormones affect recall of words in a directed forgetting paradigm. J Neurosci Res 95, 251–259.
Kimura, D., 1996. Sex, sexual orientation and sex hormones influence human cognitive function. Curr. Opin. Neurobiol 6, 259–263.
Kolb, B., Harker, A., Gibb, R., 2017. Principles of plasticity in the developing brain. Dev Med Child Neurol 59, 1218–1223.
Kraus, C., 2015. Classifying Intersex in DSM-5: Critical Reflections on Gender Dysphoria. Arch Sex Behav 44, 1147–1163.
Kudwa, A.E., Michopoulos, V., Gatewood, J.D., Rissman, E.F., 2006. Roles of estrogen receptors alpha and beta in differentiation of mouse sexual behavior. Neuroscience 138, 921–928.
Lakens, D., 2013. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 4, 863.
Laube, C., van den Bos, W., Fandakova, Y., 2020. The relationship between pubertal hormones and brain plasticity: Implications for cognitive training in adolescence. Dev Cogn Neurosci 42, 100753.
Littman, L., 2018. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One 13, e0202330.
Maccoby, E., Jacklin, C., 1974. The psychology of sex differences. Stanford University Press, Stanford, CA.
Maki, P.M., Henderson, V.W., 2012. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. Climacteric 15, 256–262.
McAbee, M.D., Doncarlos, L.L., 1999. Estrogen, but not androgens, regulates androgen receptor messenger ribonucleic acid expression in the developing male rat forebrain. Endocrinology 140, 3674–3681.
McCarthy, M.M., 2008. Estradiol and the developing brain. Physiol Rev 88, 91–124.
Mehringer, J.E., Dowshen, N.L., 2019. Sexual and reproductive health considerations among transgender and gender-expansive youth. Curr Probl Pediatr Adolesc Health Care, 100684.
Miles, C., Green, R., Hines, M., 2006. Estrogen treatment effects on cognition, memory and mood in male-to-female transsexuals. Hormones and behavior 50, 708–717.
Miles, C., Green, R., Sanders, G., Hines, M., 1998. Estrogen and memory in a transsexual population. Hormones and behavior 34, 199–208.
Nawata, H., Ogomori, K., Tanaka, M., Nishimura, R., Urashima, H., Yano, R., Takano, K., Kuwabara, Y., 2010. Regional cerebral blood flow changes in female to male gender identity disorder. Psychiatry Clin Neurosci 64, 157–161.
Nguyen, H.B., Chavez, A.M., Lipner, E., Hantsoo, L., Kornfield, S.L., Davies, R.D., Epperson, C.N., 2018. Gender-Affirming Hormone Use in Transgender Individuals: Impact on Behavioral Health and Cognition. Curr Psychiatry Rep 20, 110.
Nguyen, T.V., 2018. Developmental effects of androgens in the human brain. J Neuroendocrinol 30.
Nguyen, T.V., Lew, J., Albaugh, M.D., Botteron, K.N., Hudziak, J.J., Fonov, V.S., Collins, D.L., Ducharme, S., McCracken, J.T., 2017. Sex-specific associations of testosterone with prefrontal-hippocampal development and executive function. Psychoneuroendocrinology 76, 206–217.
Nijhuis-van der Sanden, M.W., Eling, P.A., Otten, B.J., 2003. A review of neuropsychological and motor studies in Turner Syndrome. Neurosci Biobehav Rev 27, 329–338.
Nota, N.M., Kreukels, B.P.C., den Heijer, M., Veltman, D.J., Cohen-Kettenis, P.T., Burke, S.M., Bakker, J., 2017. Brain functional connectivity patterns in children and adolescents with gender dysphoria: Sex-atypical or not? Psychoneuroendocrinology 86, 187–195.
O'Dea, R.E., Lagisz, M., Jennions, M.D., Nakagawa, S., 2018. Gender differences in individual variation in academic grades fail to fit expected patterns for STEM. Nat Commun 9, 3777.
Palmiero, M., Nori, R., Rogolino, C., D'Amico, S., Piccardi, L., 2016. Sex differences in visuospatial and navigational working memory: the role of mood induced by background music. Exp Brain Res 234, 2381–2389.
Pintzka, C.W., Evensmoen, H.R., Lehn, H., Haberg, A.K., 2016. Changes in spatial cognition and brain activity after a single dose of testosterone in healthy women. Behav Brain Res 298, 78–90.
Puts, D.A., Cardenas, R.A., Bailey, D.H., Burriss, R.P., Jordan, C.L., Breedlove, S.M., 2010. Salivary testosterone does not predict mental rotation performance in men or women. Horm Behav 58, 282–289.
Puts, D.A., McDaniel, M.A., Jordan, C.L., Breedlove, S.M., 2008. Spatial ability and prenatal androgens: meta-analyses of congenital adrenal hyperplasia and digit ratio (2D:4D) studies. Arch Sex Behav 37, 100–111.
Rametti, G., Carrillo, B., Gomez-Gil, E., Junque, C., Segovia, S., Gomez, A., Guillamon, A., 2011. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. J Psychiatr Res 45, 199–204.
Reed, G.M., Drescher, J., Krueger, R.B., Atalla, E., Cochran, S.D., First, M.B., Cohen-Kettenis, P.T., Arango-de Montis, I., Parish, S.J., Cottler, S., Briken, P., Saxena, S., 2016. Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations. World Psychiatry 15, 205–221.
Resnick, S.M., Maki, P.M., Rapp, S.R., Espeland, M.A., Brunner, R., Coker, L.H., Granek, I.A., Hogan, P., Ockene, J.K., Shumaker, S.A., Women's Health Initiative Study of Cognitive Aging, I., 2006. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab 91, 1802–1810.
Schoning, S., Engelien, A., Bauer, C., Kugel, H., Kersting, A., Roestel, C., et al., 2010. Neuroimaging differences in spatial cognition between men and male-to-female transsexuals before and during hormone therapy. Journal of sexual medicine 7, 1858–1867.
Shadid, S., Abosi-Appeadu, K., De Maertelaere, A.S., Defreyne, J., Veldeman, L., Holst, J.J., Lapauw, B., Vilsboll, T., T'Sjoen, G., 2019. Effects of Gender-Affirming Hormone Therapy on Insulin Sensitivity and Incretin Responses in Transgender People. Diabetes Care.
Shanmugan, S., Epperson, C.N., 2014. Estrogen and the prefrontal cortex: towards a new understanding of estrogen's effects on executive functions in the menopause transition. Hum Brain Mapp 35, 847–865.
Shanmugan, S., Loughead, J., Nanga, R.P., Elliott, M., Hariharan, H., Appleby, D., Kim, D., Ruparel, K., Reddy, R., Brown, T.E., Epperson, C.N., 2017. Lisdexamfetamine Effects on Executive Activation and Neurochemistry in Menopausal Women with Executive Function Difficulties. Neuropsychopharmacology 42, 437–445.
Sherwin, B.B., Grigorova, M., 2011. Differential effects of estrogen and micronized progesterone or medroxyprogesterone acetate on cognition in postmenopausal women. Fertil Steril 96, 399–403.
Shumaker, S.A., Legault, C., Rapp, S.R., Thal, L., Wallace, R.B., Ockene, J.K., Hendrix, S.L., Jones 3rd, B.N., Assaf, A.R., Jackson, R.D., Kotchen, J.M., Wassertheil-Smoller, S., Wactawski-Wende, J., Investigators, W., 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289, 2651–2662.
Silverman, I., Kastuk, D., Choi, J., Phillips, K., 1999. Testosterone levels and spatial ability in men. Psychoneuroendocrinology 24, 813–822.
Simon, L., Kozák, L.R., Simon, V., Czobor, P., Unoka, Z., Szabó, Á., Csukly, G., 2013. Regional grey matter structure differences between transsexuals and healthy controls–a voxel based morphometry study. PLoS One 8, e83947.
Skordis, N., Butler, G., de Vries, M.C., Main, K., Hannema, S.E., 2018. ESPE and PES International Survey of Centers and Clinicians Delivering Specialist Care for Children and Adolescents with Gender Dysphoria. Horm Res Paediatr 90, 326–331.
Slabbekoorn, D., van Goozen, S., Megens, J., Gooren, L., Cohen-Kettenis, P., 1999. Activating effects of cross-sex hormones on cognitive functioning: a study of short-term and long-term hormone effects in transsexuals. Psychoneuroendocrinology 24, 423–447.
Spritzer, M.D., Daviau, E.D., Coneeny, M.K., Engelman, S.M., Prince, W.T., Rodriguez-Wisdom, K.N., 2011. Effects of testosterone on spatial learning and memory in adult male rats. Horm Behav 59, 484–496.
Stroup, D., Berlin, J., Morton, S., Olkin, I., Williamson, G., Rennie, D., et al., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283, 2008–2012.
Swaab, D.F., 2004. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. Gynecol Endocrinol 19, 301–312.
Tufanaru, C., Munn, Z., Stephenson, M., Aromataris, E., 2015. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc 13, 196–207.
van de Grift, T.C., Kreukels, B.P., Elfering, L., Ozer, M., Bouman, M.B., Buncamper, M.E., Smit, J.M., Mullender, M.G., 2016v. Body Image in Transmen: Multidimensional Measurement and the Effects of Mastectomy. J Sex Med 13, 1778–1786.
Van Goozen, S., Cohen-Kettenis, P., Gooren, L., Frijda, N., Van de Poll, N., 1994. Activating effects of androgens on cognitive performance: causal evidence in a group of female-to-male transsexuals. Neuropsychologia 32, 1153–1157.
Van Goozen, S., Cohen-Kettenis, P., Gooren, L., Frijda, N., Van de Poll, N., 1995. Gender differences in behaviour: activating effects of cross-sex hormones. Psychoneuroendocrinology 20, 343–363.
Van Goozen, S., Slabbekoorn, D., Gooren, L., Sanders, G., Cohen-Kettenis, P., 2002. Organizing and activating effects of sex hormones in homosexual transsexuals. Behavioral neuroscience 116, 982–988.
Wei, W., Chen, C., Zhou, X., 2016. Spatial Ability Explains the Male Advantage in Approximate Arithmetic. Front Psychol 7, 306.
Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2011. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
Wiepjes, C.M., Nota, N.M., de Blok, C.J.M., Klaver, M., de Vries, A.L.C., Wensing-Kruger, S.A., de Jongh, R.T., Bouman, M.B., Steensma, T.D., Cohen-Kettenis, P., Gooren, L.J.G., Kreukels, B.P.C., den Heijer, M., 2018. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 15, 582–590.
Winter, S., Diamond, M., Green, J., Karasic, D., Reed, T., Whittle, S., Wylie, K., 2016. Transgender people: health at the margins of society. Lancet 388, 390–400.
Wisniewski, A.B., Prendeville, M.T., Dobs, A.S., 2005. Handedness, functional cerebral hemispheric lateralization, and cognition in male-to-female transsexuals receiving cross-sex hormone treatment. Archives of sexual behavior 34, 167–172.
Yeh, S., Miyamoto, H., Shima, H., Chang, C., 1998. From estrogen to androgen receptor: a new pathway for sex hormones in prostate. Proc Natl Acad Sci U S A 95, 5527–5532.
Zhou, J.N., Hofman, M.A., Gooren, L.J., Swaab, D.F., 1995. A sex difference in the human brain and its relation to transsexuality. Nature 378, 68–70.