A Structural Magnetic Resonance Imaging Study in Transgender Persons on Cross-Sex Hormone Therapy

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Key Words

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Abstract

Background: To date, research findings are inconsistent about whether the neuroanatomy in transgender persons resembles that of their natal sex or their gender identity. Moreover, few studies have examined the effects of long-term cross-sex hormonal treatment on neuroanatomy in this cohort. The purpose of the present study was to examine neuroanatomical differences in transgender persons after prolonged cross-sex hormone therapy. **Methods:** Eighteen transgender men (female-to-male), 17 transgender women (male-to-female), 30 nontransgender men (natal men), and 27 nontransgender women (natal women) completed a high-resolution structural magnetic resonance imaging scan at 3 T. Eligibility criteria for transgender persons were gender-affirming surgery and at least 2 years of cross-sex hormone therapy. Exclusion criteria for nontransgender persons were presence of psychiatric or neurological disorders. **Results:** The mean neuroanatomical volume for the amygdala, putamen, and corpus callosum differed between transgender women and natal women but not between trans-

gender women and natal men. Differences between transgender men and natal men were found in several brain structures, including the medial temporal lobe structures and cerebellum. Differences between transgender men and natal women were found in the medial temporal lobe, nucleus accumbens, and 3rd ventricle. Sexual dimorphism between nontransgender men and women included larger cerebellar volumes and a smaller anterior corpus callosum in natal men than in natal women. The results remained stable after correcting for additional factors including age, total intracranial volume, anxiety, and depressive symptoms. **Conclusions:** Neuroanatomical differences were region specific between transgender persons and their natal sex as well as their gender identity, raising the possibility of a localized influence of sex hormones on neuroanatomy.

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Introduction

Sexual dimorphism is widespread in the brain. Such dimorphism suggests, for example, that cerebellar, putamen, amygdala, and hippocampal volumes are larger in men than in women, whereas women have larger thalamic nuclei, lateral frontal gyri, and insular cortices than

men [1]. However, the relationship between brain structure and gender identity is less clear. Presently, findings are inconsistent about whether the neuroanatomy of transgender persons resembles that of their natal sex or their gender identity (for a recent review, see [2]). One central question that remains to be determined is whether cross-sex hormone treatment ‘reverses’ neuroanatomical sexual dimorphism, resulting in neuroanatomical features characteristic of gender identity rather than natal sex. Currently, however, studies on the neuroanatomical changes in transgender persons after prolonged cross-sex hormone treatment are too few in number to examine the putative effects of hormone therapy on neuroanatomy.

A post-mortem study in a small sample of hormonally treated transgender women (TW; male-to-female) found that the bed nucleus of the stria terminalis was similar in size to that typically found in nontransgender females, an effect that might have been partly driven by cross-sex hormone exposure [3]. More recent studies evaluated the effects of testosterone treatment in transgender men (TM; female-to-male) and estrogen and antiandrogen treatment in TW [4–6]. Although one of these studies found cortical thickness was more characteristic of participants’ gender identity than their natal sex in TM receiving androgens and TW receiving antiandrogens and estrogens [4], the findings contradict a study with an opposite pattern of cortical thickness in nontreated TW in the same areas [7]. Likewise, although one study reported a decrease in hypothalamus volume in TW with no changes in TM after treatment [5], another cross-sex hormone study [6] documented increases in TM in this region. Moreover, findings in transgender persons before they received hormone treatment are also difficult to interpret. Such studies have documented either a larger [8] or a smaller [9] putamen volume in TW than in natal men, and some studies [10] could not find differences in other sexually dimorphic structures such as the corpus callosum [11]. Thus, current findings are inconsistent, and more complementary and confirmatory evidence is needed.

Despite the small number of structural magnetic resonance imaging (MRI) studies in transgender persons, parallel neuroimaging work in endocrine conditions of gonadal hormone perturbations might aid in predicting which brain regions are sensitive to sex steroid fluctuations [12–15]. The commonly found larger amygdala and hippocampal volumes in males than in females are reduced in androgen deficiency [15]. Likewise, both androgen deficiency in Klinefelter syndrome patients and antiandrogen treatment in TW appear to reduce cortical thickness in the temporal cortex and to increase ventricle size [4, 5, 14]. Fi-

nally, similar to striatal changes in transgender persons [8, 9], boys with early androgen excess have a larger putamen volume and an enlarged medial temporal lobe (MTL) relative to unaffected controls [16]. Taken together, these converging lines of evidence indicate sensitivity to sex hormone fluctuations in several regions including the MTL, the striatum, and the ventricles. However, data regarding specific associations of these structures with hormonal treatment in transgender persons are scarce.

This study examined whether the neuroanatomy in transgender persons receiving cross-sex hormone therapy resembled that of their natal sex or their gender identity in regions sensitive to gonadal hormone fluctuations. Additionally, global brain changes including total and subcortical grey matter volume (GMV), cerebellum, and corpus callosum size were examined. To this end, we used a comprehensive morphometric analysis, analyzing not only volume but also cortical thickness and surface area. Based on the limited evidence available [4, 6–9, 16], we hypothesized patterns consistent with gender identity rather than natal sex in transgender persons.

Subjects and Methods

Participants

Eighteen TM (mean age = 37.22 years, SD = 8.29), 17 TW (mean age = 41.47 years, SD = 6.86), 27 nontransgender women (NTW; mean age = 32.63 years, SD = 10.02), and 30 nontransgender men (NTM; mean age = 31.50 years, SD = 8.52) participated in the study. Originally, another 7 participants were recruited but had to be excluded due to missing values on the anxiety and depression questionnaires. All transgender participants had undergone gender-affirming surgery and had been receiving cross-sex hormone therapy for at least 2 years. Thus, the final sample consisted of 92 participants in total (table 1). The sample differed significantly in age [$F(3, 88) = 5.82, p = 0.001$] as well as depression [$F(3, 88) = 6.32, p = 0.001$] and trait anxiety [$F(3, 88) = 4.14, p = 0.009$]. Age, depression, and trait anxiety were consequently used as covariates of no interest in all subsequent analyses. Transgender persons were recruited through flyers and through the Department of Endocrinology of Ghent University Hospital and scanned on a 3-tesla Siemens Trio (Siemens, Erlangen, Germany) MRI Scanner on site. Comparison participants were recruited through word of mouth and flyers. Exclusion criteria were present neurological or psychiatric disorders or usage of psychotropic medication. The study was approved by the Medical Ethical Committee of Ghent University Hospital. All participants signed an informed consent prior to the study.

Screening Questionnaires

Previous studies have acknowledged the presence of mood and anxiety problems in transgender persons [17]. To be able to covary for potential differences in depression or anxiety, all participants completed the Beck Depression Inventory (BDI [18]) and the Spielberger State/Trait Anxiety Inventory (STAI [19]).

Fig. 1. Means and 95% CIs of the volumetric analyses for the four groups are shown. Horizontal lines indicate significant differences ($p_{\text{corrected}} < 0.05$) between groups after correction for multiple comparisons.

Table 1. Demographic information for each of the four groups

	NTM (n = 30)	NTW (n = 27)	TM (n = 18)	TW (n = 17)	Effect (Bonferroni corrected)
Age, years	31.50±8.52	32.63±10.02	37.22±8.29	41.47±6.86	NTM, NTW < TW
BDI	2.73±3.57	3.89±4.96	5.17±5.62	10.76±11.02	TW > NTM, NTW
STAI Trait	41.23±8.83	43.63±8.72	47.72±3.44	47.59±5.23	TW, TM > NTM
Testosterone ^a , ng/dl	418.58±214.49	27.36±10.31	854.63±658.36	14.76±5.26	
Androstenedione ^a , ng/dl	67.79±33.28	81.98±36.94	105.33±50.62	54.65±18.92	
LH ^a , mU/ml	5.71±2.40	13.04±13.97	4.74±7.44	26.78±16.12	
E1 ^a , pg/ml	36.89±31.25	79.78±64.67	60.24±21.91	230.77±441.19	
E2 ^a , pg/ml	24.83±21.40	91.37±98.11	37.01±16.42	105.86±129.12	
Cortisol ^a , µg/dl	9.96±4.15	7.94±3.38	7.89±3.37	8.56±3.45	

Values are means ± SD. LH = Luteinizing hormone; E1 = estrone; E2 = estradiol. ^a For hormonal analyses, only a subset of hormones was available in comparisons (n = 16 for NTM and n = 18 for NTW), while 3 assays could not be analyzed in the transgender group (n = 16 for TM and n = 16 for TW).

MRI Acquisition

A high-resolution T1-weighted MP-RAGE anatomical image was acquired (duration = 5:14 min) in ascending order with a FOV = 256 mm², slice thickness 1 × 1 × 1 mm, TR = 2,250 ms, TE = 2.52 ms, and flip angle = 9°.

MRI Processing and Analysis

The original images were first visually inspected for artifacts and abnormal clinical findings that would lead to exclusion. Data were analyzed with freesurfer (release 4.3.0; Martinos Center for Biomedical Imaging, Charlestown, Mass., USA; <http://surfer.nmr.mgh.harvard.edu> [20, 21]) using an automated procedure. Briefly,

images were registered to a common stereotaxic space using affine transforms, normalized with respect to intensity, and skull stripped. Quality control was performed on a semi-automated basis checking for outliers and visual inspection after each processing step.

Structural neuroanatomy was characterized at three levels: (1) GMV of subcortical brain structures, (2) cortical thickness, and (3) surface area size. Based on prior structural MRI findings [4, 7, 9, 22], and to reduce the chance of false-positive findings, this study focused specifically on a priori regions of interest, namely the MTL (amygdala, hippocampus, parahippocampus, and fusiform gyrus) and the striatum (caudate nucleus, putamen, and nucleus accumbens). In addition, major global volumetric effects (i.e. cortical and

Table 2. Results of morphometric analyses for each of the groups in the MTL

MTL	NTM (n = 30)	NTW (n = 27)	TM (n = 18)	TW (n = 17)	Effect (Bonferroni corrected)
L. amygdala volume	1,653.41 (1,585–1,721)	1,517.15 (1,447–1,587)	1,629.17 (1,549–1,709)	1,702.23 (1,612–1,793)	TW > NTW
R. amygdala volume	1,619.64 (1,556–1,683)	1,500.08 (1,434–1,566)	1,549.82 (1,475–1,625)	1,648.32 (1,564–1,733)	n.s.
L. HP volume	4,227.24 (4,058–4,396)	4,185.45 (4,011–4,360)	4,352.58 (4,154–4,551)	4,439.60 (4,215–4,664)	–
R. HP volume	4,272.34 (4,100–4,444)	4,275.46 (4,098–4,453)	4,395.08 (4,193–4,597)	4,491.71 (4,263–4,720)	–
L. PH volume	2,288.18 (2,170–2,406)	2,401.79 (2,280–2,523)	2,553.02 (2,414–2,692)	2,389.11 (2,232–2,546)	–
R. PH volume	2,314.14 (2,181–2,447)	2,186.24 (2,049–2,323)	2,258.36 (2,101–2,415)	2,212.57 (2,036–2,390)	–
L. PH thickness	2.70 (2.58–2.82)	2.93 (2.80–3.05)	3.03 (2.88–3.17)	2.88 (2.72–3.04)	n.s.
R. PH thickness	2.76 (2.64–2.88)	2.94 (2.81–3.06)	2.97 (2.83–3.11)	2.84 (2.68–3.00)	–
L. PH area	731.00 (699–763)	687.39 (654–721)	707.43 (669–746)	697.62 (654–741)	–
R. PH area	738.76 (701–776)	655.95 (617–694)	668.33 (624–712)	681.26 (631–731)	n.s.
L. FF volume	10,557.87 (10,029–11,087)	9,863.12 (9,318–10,408)	9,988.88 (9,367–10,611)	10,382.27 (9,679–11,086)	–
R. FF volume	10,544.10 (10,106–10,982)	10,220.28 (9,769–10,672)	9,543.13 (9,028–10,058)	10,307.10 (9,724–10,889)	NTM, NTW > TM
L. FF thickness	2.78 (2.73–2.83)	2.82 (2.76–2.87)	2.84 (2.78–2.90)	2.74 (2.67–2.81)	–
R. FF thickness	2.80 (2.75–2.85)	2.83 (2.78–2.88)	2.85 (2.79–2.91)	2.83 (2.77–2.90)	–
L. FF area	3,296.69 (3,162–3,431)	3,061.25 (2,923–3,200)	3,112.89 (2,955–3,271)	3,271.21 (3,093–3,450)	–
R. FF area	3,360.81 (3,240–3,482)	3,190.07 (3,065–3,315)	2,983.85 (2,842–3,126)	3,225.74 (3,065–3,387)	NTM, NTW > TM

Results are mean values with 95% CIs in parentheses underneath. For volume, values are mm³, for area they are mm², and for thickness they are mm. L. = Left; R. = right; HP = hippocampus; PH = parahippocampus; FF = fusiform; n.s. = not significant after follow-up; – = no significant main effects of group.

subcortical total GMV), cerebellum size, ventricle (3rd, 4th, and 5th) size, and corpus callosum volume (anterior/middle/posterior) were investigated. Data were analyzed using SPSS v.21 ($\alpha = 0.05$, two tailed). Multivariate analysis of variance (MANOVA) was used with group as the between-subjects factor (TM, TW, NTM, and NTW) and the following covariates of no interest: age, total intracranial volume, total depressive symptoms (BDI), and total trait anxiety symptoms (STAI Trait). Of note, given that total intracranial volume was covaried for, all differences in size have to be interpreted as being relative rather than absolute. To correct for multiple comparison testing, follow-up tests of significant effects were corrected using a step-down Bonferroni (Holm) procedure ($p_{\text{corrected}} < 0.05$, two tailed). To provide a more comprehensive picture of the results than normally given by p values, upper and lower limits of the 95% CI are also presented in tables 2–4 [23].

Results

Medial Temporal Lobe

In the MTL, a main effect of group was found for the left [$F(3, 84) = 3.68$, $p = 0.02$] and right [$F(3, 84) = 2.81$, $p = 0.045$] amygdala. After correction, follow-up tests indicated a larger left amygdala volume for TW than for NTW ($p_{\text{corrected}} = 0.018$). Follow-up tests in the right amygdala did not survive statistical correction. A main effect in the right fusiform gyrus volume [$F(3, 84) = 2.76$, $p = 0.047$] revealed a significantly smaller volume in TM than in both NTW ($p_{\text{corrected}} = 0.048$) and NTM ($p_{\text{corrected}} = 0.053$) (fig. 1; table 2). In addition, the right fusiform

Table 3. Results of morphometric analyses of the striatum for each of the groups

Striatum	NTM (n = 30)	NTW (n = 27)	TM (n = 18)	TW (n = 17)	Effect (Bonferroni corrected)
L. caudate volume	3,698.01 (3,533–3,863)	3,643.14 (3,473–3,813)	3,718.87 (3,525–3,913)	3,751.87 (3,532–3,971)	–
R. caudate volume	3,736.21 (3,567–3,905)	3,757.99 (3,584–3,932)	3,777.79 (3,579–3,977)	3,792.14 (3,567–4,017)	–
L. putamen volume	5,650.38 (5,415–5,886)	5,341.97 (5,099–5,585)	5,662.87 (5,386–5,940)	5,875.99 (5,562–6,190)	–
R. putamen volume	5,331.76 (5,135–5,528)	5,048.15 (4,846–5,251)	5,277.10 (5,046–5,508)	5,640.87 (5,379–5,902)	TW > NTW
L. accumbens volume	504.07 (463–545)	448.58 (406–491)	501.78 (453–550)	500.71 (446–556)	–
R. accumbens volume	591.05 (554–628)	540.20 (503–578)	614.77 (572–658)	592.78 (544–641)	TM > NTW

Results are mean values with 95% CIs in parentheses underneath. Volumetric values are mm³. L. = Left; R. = right; – = no significant main effect.

area was significantly different between the groups [$F(3, 83) = 4.74$, $p = 0.004$]. Here, NTM and NTW had a larger surface area than TM ($p_{\text{corrected}} = 0.042$ and $p_{\text{corrected}} = 0.06$, respectively). A main effect of group in the right parahippocampal area [$F(3, 84) = 3.08$, $p = 0.03$] did not result in significant effects after correction.

Striatum

In the striatum, a significant effect of group was found in the right putamen volume [$F(3, 84) = 3.63$, $p = 0.02$] indicating a larger volume for TW than for NTW ($p_{\text{corrected}} = 0.042$). No other effect survived correction. Follow-up tests for a main effect in the right accumbens [$F(3, 84) = 2.68$, $p = 0.05$] indicated a larger volume in TM than in NTW ($p_{\text{corrected}} = 0.024$) (fig. 1; table 3).

Global Effects

Global analyses revealed significant group differences in the left [$F(3, 84) = 5.34$, $p = 0.002$] and right [$F(3, 84) = 5.67$, $p = 0.001$] cerebellum. Specifically, in the left cerebellum, corrected follow-up tests indicated a larger relative left cerebellar volume in NTM than in NTW ($p_{\text{corrected}} = 0.006$) and TM ($p_{\text{corrected}} = 0.02$). The same effect was present for the right cerebellum, showing a larger volume in NTM than in NTW ($p_{\text{corrected}} = 0.006$) and TM ($p_{\text{corrected}} = 0.006$) (table 4). A group effect in the anterior corpus callosum [$F(3, 83) = 4.70$, $p = 0.004$] indicated that this region was larger in NTW than in NTM ($p_{\text{corrected}} = 0.045$) and TW ($p_{\text{corrected}} < 0.001$). A similar effect in the posterior corpus callosum [$F(3, 83) = 3.40$,

$p = 0.02$] (fig. 1) revealed a larger volume for NTW and TM than for TW ($p_{\text{corrected}} = 0.01$ for both comparisons). A different pattern was observed for the 3rd ventricle [$F(3, 84) = 3.99$, $p = 0.01$]. It was smaller in TM than in TW ($p_{\text{corrected}} = 0.035$) and NTW ($p_{\text{corrected}} = 0.03$) (table 4).

In summary, neuroanatomical differences between TW and NTW were found in the left amygdala, right putamen, and anterior/posterior corpus callosum. No differences were found in any measure between TW and NTM. Differences between TM and NTM were detected in fusiform gyrus volume and surface area and the cerebellum. TM differed from NTW in right accumbens and fusiform gyrus volume/surface area and 3rd ventricle size. TM differed from TW in the posterior corpus callosum. Sexually dimorphic effects indicated larger cerebellar volumes in natal men relative to natal women but a larger anterior corpus callosum for natal women.

Discussion

The present study examined differences in neuroanatomy between cross-sex hormone-treated TM and TW. Based on prior work in transgender persons [4, 6, 8, 9] and in patients who had endocrine conditions with gonadal hormone perturbations [12, 15, 16], group differences were expected in the MTL, striatum, and ventricles. Three main findings pertinent to the study hypotheses

Table 4. Results of global volumetric analyses for each of the groups

Global volumes	NTM (n = 30)	NTW (n = 27)	TM (n = 18)	TW (n = 17)	Effect (Bonferroni corrected)
Total GMV	656,994 (644,039–669,949)	641,529 (628,182–654,877)	643,721 (628,485–658,957)	665,766 (648,538–682,994)	–
Cortical GMV	484,854.03 (473,591–496,116)	479,198.85 (467,594–490,803)	482,071.37 (468,825–495,317)	493,958.59 (478,981–508,936)	–
Subcortical GMV	59,079.25 (57,755–60,403)	57,080.06 (55,716–58,444)	58,313.06 (56,756–59,870)	60,250.41 (58,489–62,011)	–
L. cerebellum	56,052.88 (54,420–57,685)	52,027.63 (50,345–53,710)	51,048.09 (49,127–52,968)	54,561.48 (52,390–56,732)	NTM > NTW, TM
R. cerebellum	57,689.51 (55,981–59,398)	53,644.94 (51,885–55,405)	52,697.74 (50,689–54,707)	57,421.48 (55,150–59,693)	NTM > NTW, TM
3rd ventricle	993.77 (863–1,123)	1,003.31 (869–1,137)	800.99 (648–953)	1,190 (1,017–1,363)	TM < TW, NTW
4th ventricle	1,828.36 (1,593–2,064)	2,025.95 (1,783–2,269)	1,574.04 (1,301–1,856)	1,987.43 (1,674–2,301)	–
5th ventricle	6.06 (2–10)	8.59 (4–13)	6.75 (2–11)	4.00 (–1 to 9)	–
CC – anterior	857.83 (807–908)	955.54 (903–1007)	910.33 (851–970)	788.13 (721–855)	NTW > NTM, TW
CC – central	454.25 (419–489)	493.69 (457–530)	476.63 (435–518)	426.58 (380–473)	–
CC – posterior	966.64 (910–1,023)	1,019.95 (962–1,078)	987.21 (921–1,054)	858.74 (784–934)	NTW, TM > TW

Results are mean values with 95% CIs in parentheses underneath. Values are mm³. L. = Left; R. = right; CC = corpus callosum; – = no significant main effect.

were found: (1) consistent with their natal sex, TW did not differ from NTM and showed differences relative to NTW in the corpus callosum, putamen, and amygdala; (2) consistent with their gender identity, TM differed from NTW in the 3rd ventricle and the nucleus accumbens, and (3) TM differed from both natal men and natal women in fusiform volume.

Much of the brain is sexually dimorphic, especially the MTL, given (1) larger amygdala and hippocampus volume in men than in women [1], (2) high sex steroid receptor density in the MTL [24], and (3) volumetric alterations of these structures in endocrine conditions of gonadal hormone perturbations [12]. To date, findings in transgender persons are highly inconsistent. Whereas some [9] have documented altered hippocampal volumes in TW before hormone treatment, others [4] could not replicate this effect. Associations in the present study indicated that amygdala volume in TW was consistent with their natal sex rather than their gender identity. However, one surprising finding was that volume and area size in the fusiform gyrus were smaller in TM than in both NTM and NTW, a finding that has not been reported previ-

ously. By comparison, no group differences were present in the hippocampus. Thus, although some differences might exist before treatment [9], the present findings and those of others [4] indicate that the amygdala and hippocampus volumes do not reverse to mirror gender identity after hormone treatment.

Based on prior work in endocrine conditions [16] and transgender persons [4], we had also hypothesized significant group differences in the striatum. Prior work has noted volumetric differences in the dorsal striatum (putamen) in transgender persons [8, 9] and endocrine disorders of androgen excess [16] albeit with mixed results to date. Whereas Savic and Arver [9] reported a reduced putamen volume in TW relative to NTM and NTW, the opposite finding, namely a larger putamen in TW relative to NTM was found by Luders et al. [8]. The present finding of a larger putamen volume in TW relative to NTW is thus largely consistent with that latter study. Given that the participants in the study by Luders et al. [8] were TW who had not received hormone treatment and our participants were already receiving hormones for more than 2 years, the current data suggest that the

putamen effect is stable and does also not change with cross-sex hormone therapy. Instead, it might indicate preexisting group differences. One interesting, previously not reported association concerned the ventral striatum, i.e. the nucleus accumbens. Here, TM showed an effect consistent with their gender identity rather than their natal sex.

Finally, the present study also revealed associations between gender identity and global volumetric effects. Previous studies have documented larger ventricles in TW [4] but reductions in TM after cross-sex hormone therapy [5]. Consistent with the latter investigation [5], TM in the present study also had significantly smaller 3rd ventricles with no differences in the 4th or 5th ventricles relative to both TW and NTW. In agreement with the suggestion by Hulshoff Pol et al. [5], such a ventricular change might be due to a volumetric change in the structures surrounding the 3rd ventricle. Although further consistent with a sexually dimorphic pattern [11], the larger corpus callosum in TM and NTW than in TW and NTM would indicate no change in this structure with cross-sex hormone treatment. Supplementing this finding, prior work to date has failed to identify differences in pre-hormone-treated transgender persons in this structure [10]. Therefore, although 3rd ventricle size may be sensitive to hormonal treatment in TM, the corpus callosum does not appear to be responsive, indicating regional sensitivity to hormone therapy.

The precise clinical relevance of neuroanatomical changes after hormone therapy remains to be determined. However, characterizing the different changes associated with cross-sex hormone treatment is important. For example, ventricular enlargement has not only been associated with grey matter reduction due to ageing [25] but has also been identified as a putative marker for progression of Alzheimer's disease [26] or a risk factor for psychopathology [27]. Hulshoff Pol et al. [5] observed a final 3rd ventricle size in transgender women on hormonal therapy that was larger after treatment than the ventricle size observed in both natal men and women. Although the mechanisms and clinical implications of such effects are unknown, they deserve further study given reports of physiological risk with hormonal treatment [28] and prevalence of psychopathology [17] in transgender persons. Much more complementary information on the physiological and neurological changes with hormonal treatment is therefore needed.

Some limitations of the present study require discussion. First, the relatively small sample size of the patients needs to be acknowledged. However, the sample size of

the present study was within the range of prior work (e.g. [4, 8, 10, 22]). The second limitation concerns the fact that although all participants had received gender-affirming surgery and had already been taking cross-sex hormone therapy for a minimum of 2 years, MRI scans from before the genital surgery were lacking. Thus, we cannot make any statements regarding the causality of treatment and merely report associations. However, we nonetheless believe these data worthwhile to be reported for the following reasons. First, with the exception of 4 prior studies, 3 in vivo [4–6] and 1 post mortem [3], the majority of earlier morphometric work has examined structural brain differences in transgender persons who had not received hormone treatment. Moreover, these prior studies were characterized by a relatively small sample size requiring independent replication. Second, our study included both TM and TW, whereas a few prior studies only included TW [3, 7–9] or TM [6], thus enabling a more comprehensive comparison. Third, in the present study, subthreshold mood and anxiety symptoms were taken into consideration. This has not been examined in prior work, although it may have played an important role in previous findings. Although it could be criticized that such differences in mood and anxiety only occurred in our sample, we believe this to be unlikely given convincing documentation of depressive and anxious symptoms in transgender persons [17]. This would suggest that our sample is representative of transgender persons living in their gender identity. Fourth and finally, direct sex differences between natal men and natal women were few and limited to the cerebellum and the corpus callosum. However, due to the large variability among the population, large-scale studies (e.g. [1, 11]) are needed to make definitive statements. Therefore, the findings should be considered relative to the transgender groups rather than displaying a lack of normal sexual dimorphism.

Broadly speaking, the findings of the present study are largely consistent with prior work [4–6] in that they suggest some plasticity of the brain even during adulthood with cross-sex hormone treatment. However, they also appear to indicate regionally specific changes, such that some, but not all, investigated structures transition towards gender identity. Future studies are needed to replicate these findings and examine in a next step whether these neuroanatomical differences are associated with functional or cognitive changes of the subserving brain regions.

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Disclosure Statement

The authors have nothing to disclose.

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