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Subcortical gray matter changes in transgender subjects after long-term cross-sex hormone administration

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ABSTRACT

Sex-steroid hormones are primarily involved in sexual differentiation and development and are thought to underlie processes related to cognition and emotion. However, divergent results have been reported concerning the effects of hormone administration on brain structure including side effects like brain atrophy and dementia. Cross-sex hormone therapy in transgender subjects offers a unique model for studying the effects of sex hormones on the living human brain. In this study, 25 Female-to-Male (FtM) and 14 Male-to-Female (MtF) subjects underwent MRI examinations at baseline and after a period of at least 4-months of continuous cross-sex hormone administration. While MtFs received estradiol and anti-androgens, FtM subjects underwent high-dose testosterone treatment. The longitudinal processing stream of the FreeSurfer software suite was used for the automated assessment and delineation of brain volumes to assess the structural changes over the treatment period of cross-sex hormone administration. Most prominent results were found for MtFs receiving estradiol and anti-androgens in the form of significant decreases in the hippocampal region. Further analysis revealed that these decreases were reflected by increases in the ventricles. Additionally, changes in progesterone levels correlated with changes in gray matter structures in MtF subjects. In line with prior studies, our results indicate hormonal influences on subcortical structures related to memory and emotional processing. Additionally, this study adds valuable knowledge that progesterone may play an important role in this process.

1. Introduction

Sex-steroid hormones are involved in sexual differentiation, development and behaviour (Zubiaurre-Elorza et al., 2014) and play a pivotal role in the development and function of the central nervous system (Paus et al., 2010; Peper et al., 2009). They exert varied effects on the brain and the body and are thought to alter several processes related to cognition and emotion (Höfer et al., 2013; Toffoletto et al., 2014). For example, higher levels of progesterone and estradiol during pregnancy have been associated with a worsening of mood and an impairment of memory performance (Buckwalter et al., 1999; van Wingen et al., 2008). Studies also revealed an impact on emotional processing, as indicated by alterations in amygdala activation due to changing hormonal levels during the menstrual cycle (Derntl et al., 2008). These results were also substantiated by the fact that cognitive changes have been associated with hormonal contraceptive use. Specifically, performance changes on verbal memory, verbal fluency and on the mental rotation task in woman using oral contraceptives have been observed (Griksiene and Ruksenas, 2011).

Gonadal hormones either act as neuroactive steroids by modulating ligand-gated ion channels and G-protein coupled receptors or by binding to nuclear androgen (Beyenburg et al., 2000; Finley and Kritzer, 1999; Puy et al., 1995) and estrogen receptors (González et al., 2007; Montague et al., 2008; Osterlund et al., 2000a), directly influencing gene expression (Brinton et al., 2008; Rupprecht and Holsboer, 1999). These receptors have been detected in gray matter (GM) cortical areas as well as in subcortical

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structures (Fernández-Guasti et al., 2000; Finley and Kritzer, 1999; Kruijver et al., 2002; Osterlund et al., 2000b; Puy et al., 1995).

Animal studies already indicated influences of sex-steroid exposure on brain morphology. In this regard, hippocampal synaptic plasticity and neurogenesis in rodents after testosterone and estrogen administration has been observed (Galea et al., 2006; Gould et al., 1990; MacLusky et al., 2006).

In addition, sex hormones influence neural development during puberty and in the adult human brain. For example, increasing levels of circulating testosterone during puberty in boys indicate a contribution to sex differences in the amygdala and hippocampus region during adolescence (Neufang et al., 2009). It was further shown that circulating sex hormones were related to GM structures in several areas of the brain, indicating an influence of steroid hormones on brain morphology in the human brain (Witte et al., 2010).

Treatment studies involving humans are scarce, due to ethical and methodological reasons. However, a unique model to study the influence of long-term high-dose sex-steroid hormone treatment onto the living human brain can be achieved by the investigation of Female-to-Male (FtM) and Male-to-Female (MtF) transgender people. These subjects are characterized by strong and persistent cross-gender identification, experience an incongruency between their biological sex and their gender identity, finally seeking hormonal treatment and in some cases sex reassignment surgery (Bao and Swaab, 2011).

First evidence for a putative influence of cross-sex hormone treatment on brain structures in transgender subjects was observed in post-mortem studies. It was shown that the bed nucleus of the stria terminalis of the hypothalamus was of female size in MtFs and of male size in one observed FtM subject, which may have been attributable to cross-sex hormone administration (Kruijver et al., 2000; Zhou et al., 1995). So far, only two studies have investigated the influence of long-term high-dose cross-sex hormone treatment on gray matter brain morphology in FtM and MtF transgender individuals in vivo. Pol et al. showed that testosterone in FtM subjects increased total brain volume and the hypothalamus, whereby estrogens and anti-androgens in MtF subjects led to decreases in brain volume and to an increase in the ventricles. Authors concluded that testosterone led to masculinization, whereby estradiol and anti-androgens to feminization of the brain (Pol et al., 2006). However, sample size was rather small, with only 8 MtF and 6 FtM transgender participants and a limited number of brain structures have been evaluated. Detailed results were delivered by a more recent study, where it was shown that testosterone therapy increases cortical thickness in FtM subjects (Zubiaurre-Elorza et al., 2014). The thickening in cortical regions was associated with changes in testosterone levels. On the other hand, estrogens and anti-androgen therapy in MtFs was associated with a decrease in cortical thickness. But also subcortical structures were affected in the form of GM increases in the thalamus after testosterone administration and decreases in the thalamus as well as in the pallidum due to estradiol and anti-androgen treatment. Interestingly, also an enlargement of the ventricles was observed in the MtF cohort.

Taken together, studies on the influence of sex hormones in transgender individuals are scarce and limited by small sample sizes. Moreover, only uncorrected results have been reported so far in the literature. Here, we used the longitudinal processing stream implemented in FreeSurfer to increase statistical power by reducing the confounding effect of between-subject variability. Based on prior observations, we expected GM decreases due to estradiol and anti-androgen treatment and testosterone induced increases in gray matter structures, while for ventricular structures the opposite effect is expected.

2. Methods

2.1. Subjects

29 FtM and 21 MtF transgender participants underwent MRI assessment after the screening phase. However, 4 FtM (mean age ± SD = 28.5 ± 7.2) and 7 MtF (32.8 ± 10.0) subjects had to be excluded due to early study termination after the first measurement or movement artefacts during scanning. Hence, structural brain changes of 25 FtM (27.1 ± 6.0) and 14 MtF (26.9 ± 6.1) transgender participants were finally analysed in this longitudinal study. The second measurement was carried out at least after 4 months of continuous cross-sex hormone administration while FtM subjects had slightly larger intervals between the scans (days ± SD = 180 ± 130) than the MtF population (169 ± 38). Furthermore, 14 female (mean age ± SD = 24.9 ± 4.9) and 12 male subjects (28.0 ± 5.9) were included as control participants and were also measured at two time points (days ± SD = FC: 95 ± 34.2; MC: 85 ± 40.5).

Structural data from a subsample of subjects have been published in two previous cross-sectional studies (Hahn et al., 2015; Kranz et al., 2014). Participants were recruited from the Transgender outpatient unit of the Department of Obstetrics and Gynecology, Medical University of Vienna. All subjects were naïve to steroid hormone treatment and transgender participants reported onset of gender dysphoria before or at puberty. Subjects underwent standard medical examinations including electrocardiogram, routine laboratory tests and the Structural Clinical Interview for DSM-IV Disorders. Exclusion criteria included (1) intake of psychotropic medication and hormones (prior to baseline measurement), (2) past or current substance abuse, (3) pregnancy, (4) history of psychiatric, neurological, or medical disorders and (5) MRI contraindications.

The diagnosis of gender identity disorder was assessed according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) by an experienced psychiatrist at the screening visit. It is stated as a strong and persistent (>6 months) cross-gender identification and discomfort with the current sex, causing clinically significant distress or impairment in social, occupational or other areas of functioning. All participants provided written informed consent after detailed explanation of the study protocol. This study was approved by the Ethics Committee of the Medical University of Vienna and procedures were performed according to the Declaration of Helsinki.

2.2. Study design and treatment protocol

The study was designed as a longitudinal monocentric study. All transgender participants underwent a baseline MRI scan before start of hormone treatment and were measured again after 4 months of high-dose cross sex hormone administration. Control subjects were also measured at a second time point within 4 months but without receiving any hormonal treatment.

Hormone treatment followed protocols routinely implemented at the Department of Obstetrics and Gynecology, Unit for Gender Identity Disorder, at the Medical University of Vienna. While FtM subjects underwent testosterone treatment, MTFs received estradiol and anti-androgen medication. Specifically, FtM subjects received either 1000 mg testosterone undecanoate every 12 weeks (Nebido 250 mg/ml, 4 ml vial, intramuscular) or 50 mg testosterone daily (Testogel 50 mg/5 mg bag, transdermal). If menstruation still persisted, additionally either 10–15 mg lynestrenol (Orgametril 5 mg, oral) or in some cases 75 μg desogestrel (Cerazette 75 μg, oral) daily were administered.

MtF participants were treated with daily 50 mg cyproterone acetate (Androcur 50 mg tablet, oral). Additionally, 4 mg/day