

## Effects of Cross-Sex Hormone Treatment on Cortical Thickness in Transsexual Individuals

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### ABSTRACT

**Introduction.** Untreated transsexuals have a brain cortical phenotype. Cross-sex hormone treatments are used to masculinize or feminize the bodies of female-to-male (FtMs) or male-to-female (MtFs) transsexuals, respectively.

**Aim.** A longitudinal design was conducted to investigate the effects of treatments on brain cortical thickness (CTh) of FtMs and MtFs.

**Methods.** This study investigated 15 female-to-male (FtMs) and 14 male-to-female (MtFs) transsexuals prior and during at least six months of cross-sex hormone therapy treatment. Brain MRI imaging was performed in a 3-Tesla TIM-TRIO Siemens scanner. T1-weighted images were analyzed with FreeSurfer software to obtain CTh as well as subcortical volumetric values.

**Main Outcome Measures.** Changes in brain CTh thickness and volumetry associated to changes in hormonal levels due to cross-sex hormone therapy.

**Results.** After testosterone treatment, FtMs showed increases of CTh bilaterally in the postcentral gyrus and unilaterally in the inferior parietal, lingual, pericalcarine, and supramarginal areas of the left hemisphere and the rostral middle frontal and the cuneus region of the right hemisphere. There was a significant positive correlation between the serum testosterone and free testosterone index changes and CTh changes in parieto-temporo-occipital regions. In contrast, MtFs, after estrogens and antiandrogens treatment, showed a general decrease in CTh and subcortical volumetric measures and an increase in the volume of the ventricles.

**Conclusions.** Testosterone therapy increases CTh in FtMs. Thickening in cortical regions is associated to changes in testosterone levels. Estrogens and antiandrogens therapy in MtFs is associated to a decrease in the CTh that consequently induces an enlargement of the ventricular system. **Zubiaurre-Elorza L, Junque C, Gómez-Gil E, and Guillamon A. Effects of cross-sex hormone treatment on cortical thickness in transsexual individuals. J Sex Med 2014;11:1248–1261.**

**Key Words.** Transsexuals; Cortical Thickness; MRI; Cross-Sex Hormone Therapy; Testosterone; Estrogens; Antiandrogens; Anabolic Steroids; Gender Dysphoria; Gender Identity Disorders; Sex Steroid Hormone Therapy

### Introduction

Transsexuals (female-to-male [FtMs] and male-to-female [MtFs]) are characterized by persistent cross-sex identification and uneasiness with their assigned sex. They consequently desire

and search out cross-sex hormonal treatment and surgical sex reassignment.

Recently, transsexual cerebral phenotypes have been described before cross-sex hormonal treatment [1–6]. Untreated FtMs had a similar cortical thickness (CTh) to control females and greater

CTh than males in the parietal and temporal cortices. With respect to subcortical structures, FtMs have a larger right putamen than females but do not differ from control males [6]. On the other hand, the CTh in untreated MtFs did not differ from that in female controls but was greater than in control males in the orbitofrontal, insular and medial occipital regions, a greater size in all these areas reflecting CTh feminization [6]. It was also reported that MtFs have greater CTh than control males [2]. Moreover, voxel-based studies of cortical volumetric measures run in the same direction [5]. Finally, most of the differences shown in untreated FtMs and MtFs are in the right hemisphere [3,6].

Sex steroid hormones have a wide and varied effect on body tissues. In the brain they are involved in sexual differentiation, development and behavior. In gray matter, androgen receptors (ARs) [7–9] as well as  $\alpha$  and  $\beta$ -estrogen receptors (ERs) [10–12] have been observed in primate and human cortices. In subcortical structures, ARs [13] and ERs have also been detected in humans [14,15]. In addition, ARs have been identified in axons, dendrites and glial cells in the rat cortex and amygdala [16] as well as in astrocytes and oligodendrocytes in the primate prefrontal cortex [8].

To the best of our knowledge only two published studies have focused on the effect of cross-sex treatments on the brain of transsexuals. Hulshoff Pol et al. [17] found that testosterone treatment increased total brain and hypothalamus volumes in FtMs while treatment with estrogens and antiandrogens decreased brain volumes of MtFs. Recently, Rametti et al. [18] reported that testosterone treatment increased fractional anisotropy (FA) values in the right superior longitudinal fasciculus and the right corticospinal tract of FtMs. These increments could be predicted from the free testosterone index before the hormonal treatment.

Cross-sex hormonal treatment with testosterone is directed toward body masculinization in FtMs whereas estrogens and antiandrogens are administered to produce a feminine body in MtFs [19,20]. Therefore, given that: (a) the gray matter contains AR and ER [7,9,11–14]; (b) testosterone treatment increases the volume of the hypothalamus in FtMs [17] and FA values of sexually dimorphic fascicles [18] while (c) estrogens + antiandrogens decreases brain volumes in MtFs [17]; the aim of the present study was to explore the effects of cross-sex hormonal treatment on the CTh of FtMs and MtFs. With the paucity of the available literature, only a

broad exploratory hypothesis could be advanced: we expected that hormonal treatments would modify CTh and the volumes of subcortical structures in our subjects. To address this possibility we performed a pre-post treatment study that independently compared the CTh of FtMs and MtFs before and after cross-sex hormonal treatment. This provides a unique opportunity to investigate the effects of cross-sex hormone treatment on the brain in humans.

## Methods

### Participants

Written informed consent was obtained from 15 FtMs and 14 MtFs patients treated at the Gender Identity Unit (GIU) at the Hospital Clínic of Barcelona (Spain). The current sample shows similar social and demographic characteristics previously described for Spanish transsexuals [21]. All participants were right-handed.

All transsexual subjects were diagnosed clinically according to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [22] and the tenth revision of the International Classification of Diseases [23]. Transsexualism diagnoses were based on several semi-structured interviews done independently by a psychiatrist and a psychologist [21]. The GIU ascribes to the standards of care guidelines of the World Professional Association for Transgender Health (WPATH) [24]. All subjects selected for this study evidenced early-onset gender nonconformity, were erotically attracted to females (FtMs) or males (MtFs), began cross-sex hormonal treatment, and were interested in sex reassignment. The inclusion criteria were: (1) no history of previous hormonal treatment before the first MRI scan and (2) to have been receiving cross-sex hormonal treatment for at least six months at the time of the second scan. Exclusion criteria for all participants were: (1) history of head trauma; (2) evidence of a neurological disorder or major medical condition; and (3) history of drug or alcohol abuse or dependence.

The first MRI scan was performed before beginning hormonal treatment and the second MRI was obtained after at least 6 months of hormonal treatment (Table 1). At the time of the second scan no subject had yet undergone mastectomy, hysterectomy, and/or phalloplasty (FtMs) and orchidectomy or vaginoplastia (MtFs). The work was conducted in accordance with the Declaration of Helsinki. Study approval was acquired

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