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Gender transition affects neural correlates of empathy: A resting state functional connectivity study with ultra high-field 7T MR imaging

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ABSTRACT

Sex-steroid hormones have repeatedly been shown to influence empathy, which is in turn reflected in resting state functional connectivity (rsFC). Cross-sex hormone treatment in transgender individuals provides the opportunity to examine changes to rsFC over gender transition. We aimed to investigate whether sex-steroid hormones influence rsFC patterns related to unique aspects of empathy, namely emotion recognition and description as well as emotional contagion. RsFC data was acquired with 7 Tesla magnetic resonance imaging in 24 male-to-female (MtF) and 33 female-to-male (FtM) transgender individuals before treatment, in addition to 33 male- and 44 female controls. Of the transgender participants, 15 MtF and 20 FtM were additionally assessed after 4 weeks and 4 months of treatment. Empathy scores were acquired at the same time-points. MtF differed at baseline from all other groups and assimilated over the course of gender transition in a rsFC network around the supramarginal gyrus, a region central to interpersonal emotion processing. While changes to sex-steroid hormones did not correlate with rsFC in this network, a sex hormone independent association between empathy scores and rsFC was found. Our results underline that 1) MtF transgender persons demonstrate unique rsFC patterns in a network related to empathy and 2) changes within this network over gender transition are likely related to changes in emotion recognition, -description, and -contagion, and are sex-steroid hormone independent.

Introduction

Numerous studies have demonstrated sex differences in the functional organization of the brain. Functional magnetic resonance imaging (fMRI) has allowed for elucidation of sex differences in functional connectivity, for example during utilization of working memory (Hill et al., 2014) and affective regulation (Moriguchi et al., 2014). In addition, sex differences have also consistently been shown in functional connectivity during the resting state (Zuo et al., 2010; Casanova et al., 2012; Wu et al., 2013; Hjelmervik et al., 2014; Scheinost et al., 2015). Individual studies are underlined by a large, multicenter investigation by Biswal et al., which assessed resting state functional connectivity (rsFC) in over 1400 healthy controls and demonstrated a decisive influence of sex, particularly in medial brain regions (Biswal et al., 2010). In transgender individuals, cortical thickness (Manzouri et al., 2015; Luders et al., 2012), gray matter volume (Simon et al., 2013), white matter microstructure (Kranz et al., 2014) as well as structural connectivity (Hahn et al., 2015), and rsFC (Lin et al., 2014) have been shown to differ from controls groups. However, changes to rsFC over the course of gender transition induced by cross-sex hormone treatment have yet to be investigated.

One may assume that the sexual dimorphism in rsFC demonstrated in cis-sexual individuals, i.e. persons that demonstrate concordant gender identity and biological sex, may be related to differences in sex-steroid hormones, as these obviously differ between the sexes. However, research on this topic is limited. A recent study reported an influence of sex-steroid hormones by showing rsFC changes related to the menstrual cycle and oral contraceptive use in the default mode and executive control networks (Petersen et al., 2014). An investigation of 32 scans across the menstrual cycle of a single female subject also demonstrated an influence of sex-steroid hormones on rsFC between the dorsolateral prefrontal cortex, sensorimotor regions, and hippocampal regions, to the rest of the brain (Arelin et al., 2015). Furthermore, it has been suggested that estrogen may modulate rsFC between the amygdala and other brain regions (Engman et al., 2016). In contrast, Hjelmervik et al. found no influence of sex-steroid hormones and

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argue that observed rsFC differences between males and females are likely to be fundamentally sex rather than hormone related (Hjelmervik et al., 2014). Thus, further studies investigating possible modulation of rsFC by sex-steroid hormones are warranted.

On the other hand, numerous studies have demonstrated that predisposition for empathic function is reflected in rsFC patterns. RsFC within the default mode network assessed before exposure to visual stimuli depicting painful experiences was shown to correlate with the extent of subjects' empathic response (Otti et al., 2010). Another investigation showed increased rsFC in regions often associated with empathic response, more specifically the medial prefrontal cortex and lateral paralimbic regions, in persons exhibiting personality traits with predilection to empathic concern (Adelstein et al., 2011). Similarly, tendency for empathizing, rather than systemizing, was associated with higher rsFC between the medial prefrontal cortex, dorsal anterior cingulate cortex, precuneus, and superior temporal regions (Takeuchi et al., 2014). Accordingly, patients with high functioning autism, which is associated with deficits in empathic processing, also show altered rsFC (Mueller et al., 2013).

Interestingly, behavioral and neural markers of empathy show sex differences (Takeuchi et al., 2014; Baron-Cohen and Wheelwright, 2004) and are influenced by sex hormones (Witte et al., 2010). Estradiol and testosterone have been shown to influence empathic behavior (Bos et al., 2012) and structural changes within regions associated with empathy (Morelli et al., 2014) were influenced by sex-steroid hormone levels (Witte et al., 2010). In fact, it has been suggested that autism, which is related to deficits in empathy, may be associated with excessive brain masculinization (Baron-Cohen et al., 2014).

Therefore, extensive research demonstrates that empathy's neuronal correlates entail specific rsFC patterns. Although behavioral studies on empathy show decisive sex and hormone effects, the extent to which sex-steroid hormones modulate the association between empathy and rsFC is not fully understood.

This novel study employs cross-sex hormone treatment in transgender persons as a model to investigate the relationship between sex-steroid hormones, empathy, and rsFC. In order to differentially assess unique aspects of empathic processing we used the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001) and Emotional Contagion Scale (ECS) (Doherty, 1997). The BVAQ assesses proneness to alexithymia, which is characterized by deficits in emotion recognition and description (Vorst and Bermond, 2001; Lane et al., 2015), while the ECS assesses emotional contagion (Doherty, 1997), or proneness for transfer of emotion (Bird and Viding, 2014). Emotion recognition and attribution as well as emotional contagion can be understood as components of empathic function (Bird and Viding, 2014).

For rsFC we utilized network based statistics (NBS), which exhibits multiple benefits in comparison to other methods for assessment of functional connectivity. Most importantly, it overcomes seed selection bias and is therefore explorative rather than hypothesis driven (Cole et al., 2010). This study aims to utilize this model to investigate 1) putative unique rsFC patterns in transgender individuals, 2) their changes over gender transition, and 3) to which extent empathy's rsFC correlates are mediated by sex-steroid hormones and hereby reflect behavioral data.

Materials and methods

Subjects

24 male-to-female (MtF, mean age ± SD = 30.25 ± 8.07), 33 female-to-male (FtM, 26.79 ± 6.36), 33 male controls (MC, 27.48 ± 6.78), and 44 female controls (FC, 26.16 ± 6.07) were included in this study. Transgender participants were recruited from the Department of Gynecology and Obstetrics, Unit for Gender Identity Disorder, at the Medical University of Vienna, while controls were recruited via advertisement in the community. All transgender subjects fulfilled the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000) diagnoses of gender identity disorder. Gender identity disorder is characterized by a strong incongruence between a person's experienced or expressed gender and their assigned gender, which persists over more than 6 months and causes clinically significant distress and impairment in daily life (American Psychiatric Association, 2000). All transgender participants were free of current psychiatric comorbidities, which were assessed using the Structured Clinical Interview for DSM-IV Disorders (SCID), though some subjects showed a history of previous depressive symptoms (9 FtM, 3 MtF) and substance abuse (5 FtM, 1 MtF). 3 FtM, 3 FtM, and 1 MtF showed a previous history of eating disorders, anxiety symptoms, and obsessive–compulsive symptoms, respectively. The relatively high rate of psychiatric symptoms is to be expected considering the risk for psychiatric comorbidities in transgender persons (Terada et al., 2012). In control subjects, the SCID was used to exclude all current or past psychiatric disorders. At screening, all participants underwent standard medical examination including a physical examination, routine laboratory testing and electrocardiography as well as a thorough medical history in order to exclude severe internal or neurological illnesses. Urine pregnancy testing was performed in females to exclude pregnancy and breastfeeding females were excluded from the study. Drug-urine tests were performed to exclude current substance abuse. Transgender subjects with current substance abuse and controls with any history of substance abuse were excluded. Additional exclusion criteria included all contraindications for magnetic resonance imaging (MRI) measurement including implants, pacemakers, and claustrophobia. All subjects provided written informed consent and received financial reimbursement for participation. This study was approved by the Ethics Committee of the Medical University of Vienna and was performed according to the Declaration of Helsinki.

Cross-sex hormone treatment

All transgender participants were seeking cross-sex hormone treatment, to which they were naïve at the screening visit. Medical care related to cross-sex hormone treatment was provided by, and followed protocols routinely implemented at, the Department of Obstetrics and Gynecology, Unit for Gender Identity Disorder, Medical University of Vienna. In Austria, the recommendations for gender transition are based on the Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th Version, set forth by The World Professional Association for Transgender Health, Atlanta, Georgia, 2011. For FtM, cross-sex hormone treatment consisted of 1000 mg testosterone undecanoate administered every 8–12 weeks (Nebido 250 mg/mL 4 mL vial, intramuscular; Bayer, Vienna, Austria, 17 subjects) or 50 mg testosterone daily (Testogel 50 mg/5 g bag, transdermal; Bayer, Vienna, Austria, 3 subjects). One case received 10–15 mg lynestrenol daily (Orgametril 5 mg tablet, oral; Organon, Oss, The Netherlands) to support cessation of menstruation in addition to testosterone treatment. In MtF, 25 to 50 mg cyproterone acetate daily (Androcur 50 mg tablet, oral; Bayer, Vienna, Austria, 8 subjects) or 4.12 mg triptorelin acetate every 4–6 weeks (Decapeptyl 172 mg powder for suspension for injection, subcutaneous or intramuscular; Ferring Arzneimittel, Vienna, Austria, 5 subjects) was given, while two MtF did not receive antiandrogen or GnRH analog treatment. MtF were also prescribed either 75–100 μg estradiol daily (via a transdermal therapeutic system applied twice a week; Estradot, Novartis, Vienna, Austria or Estramon, Hexal, Vienna, Austria, 2 subjects) or 4 mg estradiol hemihydrate daily (Estrofem 2 mg tablet, oral; Novo Nordisk, Vienna, Austria, 6 subjects). Seven MtF subjects received 0.75 to 1.5 mg estradiol hemihydrate daily (Estrogel 0.75 mg/pump, transdermal; Meda, Vienna, Austria). Five MtF additionally received 2.5 mg finasterid every 1–2 days (5 mg tablet, oral; Ratiopharm, Vienna, Austria) in