Neuroscience and Biobehavioral Reviews 59 (2015) 251–266

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

The transsexual brain – A review of findings on the neural basis of transsexualism

Elke Stefanie Smith[a,*], Jessica Junger[a,b], Birgit Derntl[a,b,c], Ute Habel[a,b]

[a] Department of Psychiatry, Psychotherapy and Psychosomatics, Medical School, RWTH Aachen University, Germany
[b] JARA-Translational Brain Medicine, Jülich, Germany
[c] Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany

ARTICLE INFO

Article history:
Received 15 March 2015
Received in revised form
18 September 2015
Accepted 20 September 2015
Available online 30 September 2015

Keywords:
Transsexualism
Gender identity disorder
Gender dysphoria
Brain
MRI

ABSTRACT

Transsexualism describes the condition when a person's psychological gender differs from his or her biological sex and is commonly thought to arise from a discrepant cerebral and genital sexual differentiation. This review intends to give an extensive overview of structural and functional neurobiological correlates of transsexualism and their course under cross-sex hormonal treatment. Research in this field enables insight into the stability or variability of gender differences and their relation to hormonal status. For a number of sexually dimorphic brain structures or processes, signs of *feminisation* or *masculinisation* are observable in transsexual individuals, which, during hormonal treatment, partly seem to further adjust to characteristics of the desired sex. Still, it appears the data are quite inhomogeneous, mostly not replicated and in many cases available for male-to-female transsexuals only. As the prevalence of homosexuality is markedly higher among transsexuals than among the general population, disentangling correlates of sexual orientation and gender identity is a major problem. To resolve such deficiencies, the implementation of specific research standards is proposed.

Contents

* Corresponding author at: Department of Psychiatry, Psychotherapy, and Psychosomatics, University Hospital RWTH Aachen, Pauwelsstr. 30, 52074 Aachen, Germany.
E-mail address: esmith@ukaachen.de (E.S. Smith).

http://dx.doi.org/10.1016/j.neubiorev.2015.09.008
0149-7634/

1. Introduction

1.1. Description of the phenomenon

The term *transsexualism* describes the condition when a person identifies with a *gender* that differs from the at birth assigned *sex*. Although the terms gender and sex are often used interchangeably in common speech, their distinction in the context of research is meaningful. Sex refers to the biological and physiological properties of a person, whereas the term gender refers to one's psychological identification as a male or female and the assigned social role and lays emphasis on social and cultural imprinting processes. As a result of this incongruence of psychological gender and biological sex, transsexuals often try to resemble the preferred sex, for example by binding of breasts in the case of a female-to-male transsexual or permanent hair removal in the case of a male-to-female transsexual. Many transsexuals undergo *hormone replacement therapy* (HRT) and *sex-reassignment surgery* (SRS). Given the strong cross-gender identification in combination with the strict binary gender system of most cultures and general low social acceptance, many transsexual individuals suffer from severe psychological distress (Auer et al., 2013; Heylens et al., 2014). The rate of psychiatric disorders appears to be higher in these individuals compared to the general population, with affective and anxiety disorders being the most frequent (Bockting et al., 2013; Hepp et al., 2005; Heylens et al., 2014). Even so, transsexualism is not necessarily associated with psychiatric problems and it is assumed that these mainly occur as a result of experienced psychosocial distress (Hoshiai et al., 2010). Only recently, data from Finnish adolescents cast doubt on this assumption, as the onset of gender dysphoria was frequently preceded by severe psychopathology (Kaltiala-Heino et al., 2015). Considering this observation, the issue needs further investigation.

Transsexual individuals who suffer from their condition can be diagnosed with *gender dysphoria* (GD) or *gender identity disorder* (GID). In the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (World Health Organization, 2014) transsexualism is subsumed under the category of *gender identity disorders* (along with dual-role transvestism, gender identity disorder of childhood, other and unspecified gender identity disorders) and coded as F64.0. According to the ICD-10, transsexualism is characterised as:

> A desire to live and be accepted as a member of the opposite sex, usually accompanied by a sense of discomfort with, or inappropriateness of, one's anatomic sex, and a wish to have surgery and hormonal treatment to make one's body as congruent as possible with one's preferred sex. (World Health Organization, 2014)

For diagnosis of GD according to the latest edition of the *Diagnostic and Statistical Manual of Mental Diseases 5* (American Psychiatric Association, 2013a), the following two core criteria have to be fulfilled: strong incongruence between one's assigned and experienced gender that i.e. manifests itself in the desire to be of the other gender and to be treated as such, as well as clinically significant distress or impairment in functioning. Although there is still an ongoing debate whether there should be a clinical diagnosis of gender dysphoria, the diagnosis of GD or GID remains essential for the approval of medical treatment (hormone therapy and sex-reassignment surgery) (Coleman et al., 2012). Up to now, there is very little reliable epidemiological data on the prevalence of transsexualism or GD. The DSM-5 reports a prevalence of GD from 0.005% to 0.014% for natal males and a prevalence from 0.002% to 0.003% for natal females. Exact prevalence rates are not available, and they differ across countries, depending on depending on whether society and the authorities accept or impose sanctions on gender-nonconformity (Mitchell and Howarth, 2009). Also, numbers are likely to be underestimations, as in many cases only transsexual individuals asking for SRS are registered (Coleman et al., 2012). Numbers for the sex ratio of transsexualism also vary considerably across countries and timespan. A study conducted in Sweden reported a change from a 1:1 sex ratio in the late 1960s to 2:1 in favour of male-to-female (MtF) transsexuals in the 1990s (Olsson and Möller, 2003). For Germany, the sex ratio remained stable at 2:1 from 1970 to 1994 favouring males but changed to 1.2:1 in the late 1990s (Garrels et al., 2000). Many studies report a male predominance, i.e. a higher prevalence of MtF compared to female-to-male (FtM) transsexualism (Cohen-Kettenis and Gooren, 1999), whereas a recent study registered an inversion of the sex-ratio (favouring natal females) in adolescents presenting with gender dysphoria in specialised clinics (Aitken et al., 2015).

1.2. From gender identity disorder to gender dysphoria

In the course of the development of the 5th edition of the DSM in 2013 (American Psychiatric Association, 2013a), the previously used diagnosis of gender identity disorder was replaced by gender dysphoria. GID was previously subsumed under the category of *sexual and gender identity disorders*, together with sexual dysfunctions and paraphilias. GD now constitutes a new chapter, as it is neither a sexual dysfunction nor a paraphilia. The replacement of "disorder" through "dysphoria" lays emphasis on strong discomfort with the assigned gender and associated psychological strain rather than derangement per se. Besides, the additional specification of sexual orientation was removed in the DSM-5 (American Psychiatric Association, 2013b). Some authors consider sexual orientation as an essential or defining characteristic of transsexualism and propose a distinction of hetero- and homosexual (male-to-female) transsexualism (Blanchard, 1985; Freund et al., 1982). Certainly, transsexual individuals can be hetero-, bi- or homosexual, with sexual orientation defined according to their natal sex, and some evidence suggests differences between hetero- and homosexual transsexuals regarding prevalence and age of onset amongst other characteristics (Blanchard et al., 1987; Chivers and Bailey, 2000; Schagen et al., 2012). The removal of sexual orientation is nevertheless reasonable, for transsexualism bears on gender identity and not sexual orientation and there are substantiated doubts about the validity of such a classification (Moser, 2010). In research, the assessment of sexual orientation in transsexual individuals remains important to prevent mingling of two distinct phenomena. Note that for gender dysphoric individuals, the definition of sexual orientation based on their gender identity rather than natal sex probably better reflects their personal identification as hetero- or homosexual. However, for reasons of simplification, sexual orientation is used with reference to a person's natal sex throughout the review, as this is the definition commonly used.

1.3. Aetiology of transsexualism

Transsexualism can occur in the context of a physical intersex condition (Khandelwal et al., 2010; Meyer-Bahlburg et al., 2006), that is the ambiguity of the genital and gonadal apparatus and/or the chromosomes. Yet it is not clear, whether the co-occurrence is accidental or causally determined. Note that this article does not consider transsexualism with a concurrent congenital intersex condition. The DSM-IV states that GID shall not be diagnosed in these cases, the DSM-5 now requires the rater to specify if the diagnosis of GD is accompanied by a disorder of sex development (American Psychiatric Association, 2000, 2013a). If so, both diagnoses are coded. Research has put its focus on biological models of transsexualism. There are no overt biological anomalies, such as sex chromosome aberrations, that are associated with transsexualism (Hengstschläger et al., 2003). Yet, there are studies suggesting

that the development of transsexualism is related to biological mechanisms, such as genetic factors and prenatal exposure to sex hormones, rather than environmental factors like parenting practices. During pregnancy, the foetal brain develops into a male brain under the influence of the androgen testosterone, and into a female brain in the absence of this hormone. The sexual differentiation of the brain however, occurs much later in development than that of the genitals. These two processes could be influenced independently, which is postulated to result in transsexualism if they develop in opposing directions (Bao and Swaab, 2011). Thus, transsexualism is believed to result from a discrepancy between sexual brain and genital differentiation caused by genetic or hormonal deviations.

Twin-studies with transsexual children are sparse, as prevalence rates are very low. They also leave the problem of disentangling shared environmental and genetic factors. Although evidence for genetic influences on transsexuality is limited, the available data points out a possible hereditary component of transsexualism. A study with 995 transsexual individuals from Gómez-Gil et al. (2010) suggests that also non-twin siblings have a higher risk of being transsexual than the general population. The risk seems to be higher for brothers than sisters and for siblings of MtF transsexuals than FtM transsexuals. A rather recent review from Heylens et al. (2012) on GID in twins based on case report literature is also indicative of genetic factors contributing to the development of GID (higher concordance for GID in mono- than in dizygotic twins). It is estimated that the genetic vs. the nonshared environmental component accounts for up to 62% of the variance (Coolidge et al., 2002). A genetically determined aberrant hormonal status could result from an anomalous prenatal exposure to sex hormones, i.e. caused by an altered sensitivity or function of sex hormone receptors or synthesis of sex steroids. A rough indicator for prenatal testosterone exposure is the *digit ratio*, or *2D:4D ratio*, which describes the ratio of index finger and ring finger length. This measure correlates with prenatal androgen exposure, with lower 2D:4D ratio indicating higher prenatal androgen exposure. The 2D:4D ratio is a sexually dimorphic measure: relative to the length of the ring finger, a long index finger is considered a "more feminine" hand, a short index finger a "more masculine" hand (Zheng and Cohn, 2011). The digit ratio also has been studied in transsexuals, yielding a higher digit ratio in MtF transsexuals than in control males, similar to control females. By contrast, the digit ratio of FtM transsexuals was found to be in the range of control females (Kraemer et al., 2009; Schneider et al., 2006). The findings support the assumption of prenatal testosterone exposure as etiological factor of transsexualism, at least for MtF transsexualism. Data from girls with congenital adrenal hyperplasia (CAH), a metabolic disease characterised by a deficient production of sex steroids, indicate that prenatal androgenisation is indeed related to masculinisation of the child's later behaviour. Even so, no association with later gender confusion or dysphoria was found (Meyer-Bahlburg et al., 2004). Hence, gender identity does not seem to be absolutely determined by prenatal androgen exposure.

There are only very few studies on the relationship between transsexualism and genes involved in the synthesis of sex steroids and their results are rather mixed. Two studies suggest a link between polymorphisms of the CYP17 gene and transsexualism. CYP17 is associated with increased serum and plasma levels of estradiol, progesterone and testosterone. Bentz et al. (2008) could demonstrate that the loss of a female-specific allele distribution pattern of the CYP17 gene, specifically CYP17 T-34C, is associated with FtM but not MtF transsexualism. Data from Fernández et al. (2015) suggest an association with the A2 allele frequencies of the CYP17 MspA1 polymorphism, as the allele frequencies seem to be sex-dependent in the transsexual, but not in the general population, with higher frequencies in FtM compared to MtF transsexuals. Besides, cytosine-adenine repeat numbers in the oestrogen *receptor β* (ERβ) have been found to be higher, and androgen receptor (AR) repeat lengths longer in MtF transsexuals compared to control males (Hare et al., 2009; Henningsson et al., 2005).

Note that the association between repeat lengths for the oestrogen β receptor found by Henningsson et al. (2005) was not confirmed by Hare et al. (2009). However, in both studies no multiple testing correction was applied. Analysing sex-hormone related genes (i.a. ERβ, AR, and CYP19) in a large sample of MtF and FtM transsexuals and applying multiple testing correction, two studies suggest refuting the assumption that genetic variations of these sex-hormone related genes represent an enhanced susceptibility for transsexualism (Fernández et al., 2014; Ujike et al., 2009). Still, other polymorphisms not yet analysed in this context could be related to the development of transsexualism. The exact causal factors of transsexualism remain unresolved, but the condition very likely results from an interaction of multiple contributing factors. The available data suggests that transsexualism can be ascribed to biological factors, with psychosocial factors possibly mediating its genesis (Veale et al., 2009).

2. Brain morphometry

There is widespread evidence for differences between the sexes in brain morphometry. Differences exist both in total brain volume, as well as in several sex-dimorphic structures. It is a well-established finding, that the absolute brain volume is larger in men than in women (Lüders et al., 2002; Ruigrok et al., 2014), even after correcting for body size (Rushton and Ankney, 2009). Woman, however, have a higher proportion of grey matter, men a higher proportion of white matter (Cosgrove et al., 2007; Lüders et al., 2002). This raises the question whether the transsexuals' psychological identification with the other gender is reflected in their brains' anatomy and/or function. And indeed, both postmortem anatomical analyses and in vivo neuroimaging studies have pointed out structural differences between transsexual and control subjects in several areas of the brain, especially in those that are sexually dimorphic (Garcia-Falgueras and Swaab, 2008; Kruijver et al., 2000; Rametti et al., 2011a,b). This raises the question, whether the overall brain weight or volume and the anatomy of specific structures of transsexual individuals is closer to the natal or preferred sex, or rather intermediate. There are no direct studies comparing total brain weight of transsexual and control subjects, but the brain weight of transsexuals seems to lie somewhere in between that of males and females (Garcia-Falgueras and Swaab, 2008; Zhou et al., 1995). Several studies have compared morphometric characteristics of transsexual and control subjects in terms of grey and white matter patterns, which are presented in the following sections. Although the absolute number of studies assessing morphometric characteristics is not very high, they make up the largest part of studies in this field of investigation.

2.1. White matter

The probably earliest study on anatomical differences between transsexuals and control males and females was conducted by Emory et al. (1991) and focused on the *corpus callosum*, a structure of white matter interconnecting both hemispheres. The *corpus callosum*, or rather specific subparts of this structure are thought to be sexually dimorphic in size and shape, but findings are very contradictory (Ardekani et al., 2013; Bishop and Wahlsten, 1997; Davatzikos and Resnick, 1998). Emory et al. (1991) found no significant differences in shape between the sexes or between the transsexuals of either sex and control males and females. Contradicting these findings, a study from Yokota et al. (2005)

could discriminate between males and females with an accuracy of approximately 74% when comparing the shape of the *corpus callosum* at the midsagittal plane. Using this measure, the value of FtM and MtF transsexuals was closer to their gender identity than to their natal sex. The authors suggest the application of this measure as an objective criterion for the diagnosis of GID. In view of the fact that their results are not applicable at an individual level and haven't been replicated, the proposition seems preposterous.

Apart from these studies on callossal size and shape, there are other studies analysing cerebral white matter morphometry in transsexual individuals. Rametti et al. (2011a,b, 2012) used *diffusion tensor imaging* (DTI) to evaluate *fractional anisotropy* (FA) of white matter fibre tracts in transsexuals and control males and females. Both MtF transsexuals and FtM transsexuals were examined, all of whom stated homosexual orientation and early-onset gender nonconformity. The white matter microstructure pattern of MtF transsexuals differed from both male and female controls in nearly all fascicles that showed sex differences (*superior longitudinal fasciculus*, *inferior fronto-occipital fasciculus*, *cingulum*, *forceps minor* and *corticospinal tract*) and was intermediate between both groups. Hence, the authors assume that some white matter fibre tracts do not complete the masculinisation process during brain development of MtF transsexuals. In FtM transsexuals, the white matter microstructure pattern was closer to that of males, thus individuals sharing their gender identity, than to that of females. Just as the male control subjects, FtM transsexuals showed higher FA-values than female control subjects in several regions of the brain, including the *superior longitudinal fasciculus*, the *forceps minor*, and the *corticospinal tract* amongst others. These fibre tracts are thought to be *masculinised* or incompletely *feminised*, meaning within the average range of males or females. There is one caveat to the research of Rametti et al. (2011a,b), however. Unlike the transsexual individuals, the control subjects were heterosexually oriented. It is thus not clear to what extent the differences between the two groups reflect differences in sexual orientation rather than sexual identity. Apart from these two DTI studies, there's one other, recently published study investigating white matter microstructure in transsexuals and controls: Kranz et al. (2014a,b) employed diffusion weighted magnetic resonance imaging (DW-MRI) in a sample of hormonally untreated MtF and FtM transsexuals with early-onset gender dysphoria and controls to determine the influence of biological sex, gender identity as well as sexual orientation on several diffusivity parameters. The mean diffusivity (MD, a measure of the total diffusivity within a voxel) was observed to be highest for female controls, followed by FtM transsexuals, then MtF transsexuals, and lowest for male controls. For MD values, the transsexuals seem to take up an intermediate position between the sexes. No group differences were found in FA maps. Sexual orientation had no significant effect on the diffusivity parameters. Their results are conflicting with those from Rametti et al. (2011a,b) who reported FA-values only and found FA-values to be greater in male vs. female controls, FA-values of FtM transsexuals to be closer to males, and those of MtF transsexuals to fall halfway between male and female controls. As the results from both research groups differ substantially, no reliable conclusion can be made so far. Still, both studies indicate a deviation of white matter microstructure patterns in transsexuals from the biological sex towards values of the desired sex.

2.2. Grey matter

Two brain structures that have consistently been reported to be sexually dimorphic and altered in transsexual individuals include the *central subdivision of the bed nucleus of the stria terminalis* (BSTc) and the third interstitial nucleus of the anterior hypothalamus (INAH3). Both the BSTc and the INAH3 were found to be larger in men than in women and contain more somatostatin neurons (Byne et al., 2000; Swaab, 2007). The *bed nucleus of the stria terminalis* (BNST) is thought to be involved in the control of autonomic, neuroendocrine and behavioural responses and closely connected to the amygdala, hippocampus and medial prefrontal cortex (Crestani et al., 2013). The INAH3 is one of four cell groups of the preoptic-anterior hypothalamic area, which is involved in sexual and maternal behaviour and the secretion of gonadotropin (Allen et al., 1989). In transsexualism, these two structures seem to have developed in a sex-atypical way, with size and neuron number closer to the desired than to the natal sex. In MtF transsexuals, size and neuron number of the BSTc and INAH3 resemble that of control females (Garcia-Falgueras and Swaab, 2008; Kruijver et al., 2000; Zhou et al., 1995). This sex reversal also seems to occur in FtM transsexuals, but up to now, data is only available for two individuals (Garcia-Falgueras and Swaab, 2008; Kruijver et al., 2000; Zhou et al., 1995). According to the authors, the observed pattern appears to be independent from changes in sex hormone levels and sexual orientation, but it is actually not possible to definitely state whether the differences reflect initial differences between transsexuals and non-transsexuals or result from hormonal treatment, for the investigated individuals had been treated with cross-sex hormones. If the former was the case, the altered number of neurons and size of the BSTc and INAH3 could serve as a marker for atypical sexual differentiation of the brain in transsexualism. The exact role of the BSTc and INAH3 in transsexualism still needs to be delineated.

Regarding grey matter proportions in hormonally untreated transsexuals, three other studies are available. Luders et al. (2009) reported the overall pattern of grey matter in MtF transsexuals to resemble that of control males, thus subjects sharing their biological sex. They observed one exception, where grey matter volume appeared to be feminised: the putamen. Findings concerning the putamen are discussed in detail subsequently. Savic and Arver (2011) found no support for the feminisation of grey matter patterns in heterosexual MtF transsexuals. Applying *voxel-based morphometry* (VBM), the encountered differences between male and female control subjects (e.g. elevated hippocampus volume in women) were not reproducible when contrasting MtF transsexuals and males. Instead, when compared to both male and female controls, the MtF transsexuals had increased grey matter volumes in the right *temporo-parietal junction* (TPJ), right inferior frontal and insular cortex, and decreased grey matter volumes in the putamen and thalamus.

A recent study by Simon et al. (2013) analysed grey matter volumes in both MtF and FtM transsexuals and control males and females. A group effect was found in the cerebellum (anterior lobe, left posterior lobe, declive, dentate, culmen) left angular gyrus and left inferior parietal lobule, with both the MtF and FtM transsexual individuals having reduced grey matter volumes compared to controls. The study could identify a number of regions in which grey matter volumes of the transsexual individuals resembled those of control subjects having the same gender identity. In the right middle and inferior occipital gyri, fusiform and lingual gyri and right inferior temporal gyrus, grey matter volumes were higher in individuals having a female gender identity. In the left pre- and postcentral gyri, left posterior cingulate, calcarine gyrus and precuneus, grey matter volumes were higher in individuals having a male gender identity. Still, the majority of structural differences between transsexual and control subjects were dependent on biological sex rather than gender identity. Again, due to differences in the transsexuals' and control subjects' sexual orientation, a comparison of the three studies is only possible to a limited extent. Luders et al. (2009) did not assess the participants' sexual orientation, Savic and Arver (2011) contrasted heterosexual transsexuals against heterosexual control subjects, and Simon et al. (2013)

contrasted homosexual transsexuals against controls (no indication of sexual orientation).

The findings on putamen volume are quite inconsistent, as are those on the cerebellum. Luders et al. (2009) and Zubiaurre-Elorza et al. (2013) found the (right) putamen of MtF transsexuals to be feminised and that of FtM transsexuals to be masculinised, meaning they had a putamen volume within the average range of control females and males, respectively. The study by Savic and Arver (2011) yielded contrary results, with the volume of the putamen being smaller in MtF transsexuals than in men and women. Apart from Zubiaurre-Elorza et al. (2013), the findings on putamen volume in transsexuals are actually inconsistent with results from studies on sexual dimorphism in control subjects. A number of studies suggest that men have a higher bilateral putamen volume or grey matter density in the putamen (Abedelahi et al., 2013; Rijpkema et al., 2012; Ruigrok et al., 2014). Luders et al. (2009) found that females had a higher putamen volume than males, whereas Savic and Arver (2011) found no difference in putamen volume between both control groups applying structural volumetry. Further research is needed to clarify this issue. Concerning the cerebellum, both Simon et al. (2013) and Savic and Arver (2011) report structural differences between transsexuals and controls in the cerebellum. The findings are inconsistent, though: Savic and Arver (2011) found the MtF transsexuals to have a larger grey matter volume in the cerebellum than control women, Simon et al. (2013) found MtF (and FtM) transsexuals to have reduced grey matter volumes compared to controls. The reason for the discrepant findings is unknown, but in both cases, differences could stem from not having sufficiently controlled for the participants' sexual orientation. Support for this assumption comes from a study from Ponseti et al. (2007), who observed that homosexual women have less grey matter in the ventral cerebellum than heterosexual women. Unfortunately, no such data is available for homosexual men. The research on cerebellar sex differences is also quite inconsistent. Many studies report larger cerebellar hemispheres in men compared to women (Chung et al., 2005; Raz et al., 2001), but when correcting for overall brain size, there are studies reporting no sex difference (Nopoulos et al., 2000; Szabo et al., 2003), or even higher cerebellar grey matter volumes in females (Hutchinson et al., 2003). The cerebellum is critically involved in functions such as the coordination of movement, maintenance of balance and motor learning (Byrne, n.d.). But although the structure is mainly considered a structure for motor control, it also significantly contributes to non-motor functions. Damage to the cerebellum not only frequently results in motor dysfunctions, but also in cognitive and affective abnormalities, depending on the area affected (Schmahmann and Sherman, 1998). By all means, a direct link between grey matter volume changes and aspects of transsexualism cannot be established so far.

2.3. Cortical thickness

Sex differences are also observable in cortical thickness, independent of differences in brain and body size. Increased cortical thickness in females compared to males was registered in the frontal and parietal lobe (including the superior and inferior frontal gyrus amongst others), occipital and the temporal lobe (parts of the superior temporal gyrus and the left temporal pole) (Im et al., 2006; Sowell et al., 2007). For males, no significant increases in local cortical thickness have been detected when compared to females (Im et al., 2006; Luders et al., 2006). Given the existence of differences in cortical thickness between males and females, one could expect signs of feminisation/masculinisation when investigating transsexuals. So far, there are two studies comparing the thickness of the cerebral cortex between (untreated) transsexuals and control subjects. Zubiaurre-Elorza et al. (2013) measured cortical thickness in both MtF and FtM transsexuals. Cortical thickness in MtF transsexuals showed signs of feminisation, with it being thicker than in control males in orbitofrontal, insular and medial occipital regions. In FtM transsexuals, there were no signs of masculinisation. Similar to control females, the FtM transsexual individuals had a greater cortical thickness in parietal and temporal cortices. A study by Luders et al. (2012) supports the view of feminised cortical thickness in MtF transsexuals. They found thicker cortices in regions of the left hemisphere, including orbitofrontal cortex, middle frontal gyrus and orbitofrontal gyrus amongst others, and right hemisphere, including the parietal cortex, superior temporal sulcus, inferior temporal gyrus, fusiform and lingual gyrus. There were no cortical regions in which control males showed significantly increased thickness compared to MtF transsexuals. It seems that in MtF transsexuals, cortical thickness resembles that of individuals sharing their gender identity. Again, the two studies differ with regard to the participants' sexual orientation, with Luders et al. (2012) having a mixed transsexual sample and Zubiaurre-Elorza et al. (2013) exclusively homosexual transsexuals.

An overview of brain morphometric findings in transsexuals and their relation to values of control subjects sharing their biological sex vs. gender identity is given in Table 1. In summary, the brains of MtF and FtM transsexuals do not seem to be entirely feminised or masculinised. Instead, some of the typically sexually dimorphic structures seem to be feminised/incompletely masculinised or masculinised/incompletely feminised. Unfortunately, the studies on structural characteristics of the transsexual subjects' brains also yielded conflicting results, which are in many cases difficult to interpret and compare due to potential confounds of hormone replacement therapy and sexual orientation. Hence, it is not possible to define a neuroanatomical marker for transsexualism. The literature available suggests that there are certain neuroanatomical differences between transsexuals and same-sex controls, but these are, however, only detectable at the group level. Besides, being a psychiatric diagnosis, gender dysphoria or GID bears on symptomatology, not (neuro)anatomy.

3. Electrophysiological, molecular and metabolic neuroimaging findings

3.1. EEG studies

Several electroencephalography (EEG) studies have been conducted in transsexuals, all pointing more or less towards altered EEG patterns in transsexuals. A couple of early studies from the mid- and late 1960s report atypical EEG patterns in transsexual individuals (Blumer, 1969; Wålinder, 1965). The validity of these studies is questionable, however, as the observed patterns could have been related to hypertension and epilepsy (Blumer, 1969) or no clear distinction was made between transsexualism and transvestism (Wålinder, 1965). Hoenig and Kenna (1979) observed atypical (bilateral) temporal EEG patters in almost half of the examined transsexual group, whereby the FtM transsexuals were affected more frequently than the MtF transsexuals, and marginal EEG anomalies in a further 24%, which were rather equally distributed among both groups. Interestingly, the age at which the gender nonconforming behaviour became apparent to the family is significantly lower in those who showed atypical EEG patterns. Unfortunately, several transsexuals had additional personality disorders and suffered from epileptiform seizures, which could have influenced the results.

Analysing EEG patterns by means of quantitative frequency analysis, Grasser et al. (1989) found an atypical temporo-parietal EEG pattern in about one-fifth of the transsexual sample, consisting of both MtF and FtM transsexuals. A more recent study

Table 1
Overview of brain morphometric findings in transsexuals.

	Methods	Measure/structure	Sample	Brain morphometry		
				≙Biol. sex	Intermed.	≙Gend. Id.
Emory et al. (1991)	MRI	Corpus callosum	10 MtFs[a]		–[b]	
			10 FtMs[a]		–[b]	
Garcia-Falgueras and Swaab (2008)	Histology	Hypothalamic nucleus (INAH3)	11 MtFs[a]			×
			1 FtMs			×
Kranz et al. (2014a,b)	DW-MRI	White matter tracts	21 MtFs		×	
			23 FtMs		×	
Kruijver et al. (2000)	Histology	Stria terminalis (BSTc)	7 MtFs[a]			×
			1FtMs[a]			×
Luders et al. (2009)	MRI	Grey matter volume	24 MtFs	×		
		Putamen				×
Luders et al. (2012)	MRI	Cortical thickness (lateral and medial)	24 MtFs			×
Rametti et al. (2011a)	DT-MRI	White matter tracts	18 FtMs			×
Rametti et al. (2011b)	DT-MRI	White matter tracts	18 MtFs		×	
Savic and Arver (2011)	MRI (VBM and SV)	Total brain volume	24 MtFs	×		
		Grey matter volume		×		
		Hemispheric volume asymmetry		×		
Simon et al. (2013)	MRI (VBM)	Grey matter volume	10 MtFs			×
			7 FtMs	×		
Yokota et al. (2005)	MRI	Corpus callosum shape	22 MtFs			×
			28 FtMs			×
Zhou et al. (1995)	Histology	Stria terminalis (BSTc)	6 MtFs[a]			×
Zubiaurre-Elorza et al. (2013)	MRI	Cortical thickness	18 MtFs			×
			24 FtMs	×		

Note: The respective control groups are not listed. ≙ = "corresponds to"; Biol. sex = biological sex; BSTc = central subdivision of the bed nucleus of the stria terminalis; DT-MRI = diffusion tensor MRI; DW-MRI = diffusion weighted. MRI; FtMs = female-to-male transsexuals; Gend. Id. = gender identity; Intermed. = intermediate; INAH3 = third interstitial nucleus of the anterior hypothalamus; MtFs = Male-to female transsexuals; SV = structural volumetry; VBM = voxel-based morphometry.

[a] Mostly receiving hormone replacement therapy.

[b] No significant differences between the sexes or between transsexuals of either sex and controls.

compared EEG patterns of MtF transsexuals to those of male and female controls by means of discriminant function analysis, finding that the EEG pattern of the MtF transsexuals were similar to those of the female controls, with increased sources in the fast frequencies (beta and gamma bands) in the right hemisphere, mainly from orbital frontal and temporal regions (Flor-Henry, 2010). What is particularly conspicuous is that the latter three studies report anomalies in temporal areas. Notwithstanding these findings, the literature available does not permit a clear conclusion whether the occurrence of the reported EEG anomalies is actually related to transsexualism, or other factors such as comorbidities or treatment status.

3.2. PET and SPECT studies

Using positron emission tomography (PET), Kranz et al. (2014a,b) investigated the serotonin transporter (SERT) distribution in a group of MtF transsexuals and male and female controls. SERT is a protein of the cell membrane which transports serotonin from the synaptic cleft back to the presynaptic neuron, thereby terminating its effect. In nearly all brain regions, the analysis of SERT binding showed left and rightward asymmetries independent of the participants' sex. In all three groups, the asymmetries were very similar. In the midcingulate cortex however, a gender-dimorphic organisation of SERT was registered, with a rightward asymmetry in male controls, but not in female controls and MtF transsexuals. The absence of SERT asymmetry in this region is presumed to reflect an incomplete masculinisation (or feminisation) in MtF transsexuals. The midcingulate cortex, particularly its anterior part, is implicated in motor control and movement generation (Hoffstaedter et al., 2014). Besides, the midcingulate cortex has been identified as an area linking negative emotional signals and motor signals (Pereira et al., 2010), and cognitive control (Shackman et al., 2011). A study from Huster et al. (2011) strongly suggests, that the differences in SERT asymmetry between males and females are related to sex differences in cognitive control. Correlating behavioural and electrophysiological measures (event-related potentials) to morphological measures in a combined EEG/MRI study, sex differences in cognitive control were shown to be associated with the morphology of the midcingulate cortex. This calls for follow-up studies directly assessing cognitive control and its relation to the midcingulate cortex in transsexuals.

Spontaneous metabolic processes in transsexuals were also studied using single-photon emission computed tomography (SPECT). The analysis of regional cerebral blood flow (rCBF) in a group of FtM transsexuals and female controls revealed that the transsexuals' rCBF was significantly decreased in the left anterior cingulate cortex, and increased in the right insula (Nawata et al., 2010). The anterior cingulate and insular cortex are functionally tightly linked (Craig, 2009) and both associated with sexual arousal induced by visual sexual stimulation (Arnow et al., 2002; Redouté et al., 2000). Besides, the insula is proposed as integral centre for bodily self-awareness (Craig, 2009; Karnath et al., 2005), which might provide an explanation for the observed functional association between insular rCBF and transsexualism, as transsexuals feel their bodily state does not match their gender identity. Unfortunately, there was no male control group, so the patterns cannot be evaluated with regards to their resemblance to persons of the desired sex. As there are only very few studies examining spontaneous metabolic processes in transsexuals, further studies would be desirable. An overview of the presented EEG, PET and SPECT studies and their relation to findings from control subjects sharing their biological sex vs. gender identity is given in Table 2. The studies from Blumer (1969) and Wålinder (1965) were omitted because of the indicated methodical concerns.

Table 2
Overview of neuroimaging studies assessing spontaneous electrical and metabolic processes in transsexuals.

	Imaging technique	Sample	Observed pattern		
			≙Biol. sex	Intermed.	≙Gend. Id.
Flor-Henry (2010)	EEG	14 MtFs			×
Grasser et al. (1989)	EEG	22 MtFs		–[a,b]	
		11 FtMs		–[a,b]	
Hoenig and Kenna (1979)	EEG	35 MtFs		–[a]	
		11 FtMs		–[a]	
Kranz et al. (2014a,b)	PET	14 MtFs			×[c]
Nawata et al. (2010)	SPECT	11 FtMs		–[d]	

Note: The respective control groups are not listed. All transsexuals were hormonally untreated. ≙ = "corresponds to"; Biol. sex = biological sex; EEG = electroencephalography; FtMs = female-to-male transsexuals; Gend. Id. = gender identity; Intermed. = intermediate; MtFs = male-to-female transsexuals; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

[a] Observed pattern is atypical and resembles neither that of males nor females.
[b] Pooled analysis (transsexuals vs. controls).
[c] Midcingulate cortex.
[d] No male control group.

4. Findings from task-based functional neuroimaging studies

Meanwhile, there are also several functional neuroimaging studies comparing brain activation patterns of transsexuals and controls during task performance. Berglund et al. (2008) measured cerebral activation patterns of (nonhomosexual) MtF transsexual individuals with positron emission tomography (PET) while smelling odorous steroids (AND, 4,16-androstadien-3-one, a metabolite of testosterone and EST, estra-1,3,5(10),16-tetraen-3-ol, a derivate of estradiol). These socially relevant chemosignals can be found in human secretions of males or females (Gower and Ruparelia, 1993; Thysen et al., 1968) and differentially activate hypothalamic networks in males and females (Savic et al., 2001). The response-patterns of the MtF transsexuals were found to lie somewhere in between that of male and female controls, but with mainly female characteristics. When smelling AND, the MtF transsexuals recruited the same regions as (heterosexual) control women, whereas activation patterns of MtF transsexuals and men differed significantly. The authors relate the sex-atypical neurophysiological response patterns in hypothalamic networks to the supposedly female size and neuron number of the BSTc in MtF transsexual individuals (Kruijver et al., 2000; Zhou et al., 1995) (see paragraph "Brain morphometry"). In the rat, the BSTc has been shown to mediate pheromone signalling, in humans the BSTc and the anterior hypothalamus are reciprocally connected (Eiden et al., 1985).

A very similar study was conducted by Burke et al. (2014), but with gender dysphoric pre-pubertal children and adolescents. It thereby takes up an exceptional position, as there is hardly any neuroimaging data from underage gender dysphoric individuals. The sex difference in hypothalamic response to AND was already observable in pre-pubertal control children. The response of adolescent gender dysphoric boys and girls was sex-atypical, meaning very similar to controls of the desired sex. By contrast, the response of pre-pubertal gender dysphoric girls neither differed from that of boys nor girls, and that of pre-pubertal gender dysphoric boys was sex-typical, i.e. similar to control boys. This strongly points to puberty as developmental step during which sex differences in the response to AND emerge. The authors tried to assess the participants' sexual orientation, but the data are fragmentary though, for the participants were mostly too young to reliably report their sexual orientation (mean age of children = 9.8, mean age of adolescents = 15.9). There's a considerable rate of reported homosexual feelings among the GD sample, which might represent a confounding factor. Still, the found response pattern in the adolescent GD sample coincides with that found by Berglund et al. (2008), in spite of differences in sexual orientation. Besides, both samples were free from hormonal treatment, so the results are likely to reflect initial differences between transsexuals and non-transsexuals and might arise as a consequence of divergent differentiation of neural pathways.

Another interesting fMRI study in transsexuals comes from Gizewski et al. (2009), who measured cerebral activation patterns in MtF transsexuals while viewing erotic film scenes. Erotic stimuli have been repeatedly shown to produce gender-specific cerebral activation patterns in males and females. Contrasting men and women yielded increased activation in men in the thalamus, amygdala, orbitofrontal and insular cortex, regions that have frequently been reported to show enhanced activity while processing visual erotic stimuli (Hamann et al., 2004; Karama et al., 2002; Stoléru et al., 2012). No specific activation pattern was found for women. The comparison of cerebral activation between the MtF transsexuals and control males yielded similar patterns as such a comparison between control females and males, indicating that MtF transsexuals might process visual erotic stimuli in a way similar to control females. There's one caveat, however: when processing erotic stimuli, sexual orientation is of course of special relevance. While the control subjects were exclusively heterosexual, the transsexual group was mixed (but mainly heterosexual). Further studies are needed to clarify how functional activation patterns during visual erotic stimulation are influenced by sexual orientation vs. identity.

A recent study comes from Junger et al. (2014), who analysed neural activation patterns during voice gender perception in hormonally treated and untreated MtF transsexuals. As there were no differences between hormonally treated and untreated individuals, the study is not reported in the section "Hormonal influences on brain structure and function". The voice is, besides other characteristics, used to infer a person's gender. The study turns to account an important effect of voice gender perception: Voices of the other sex are better recognised (this is labelled the *opposite-sex effect*). The study participants were asked to identify a speaker's gender and were presented with unambiguous male and female voice stimuli, as well as gender ambiguous voice stimuli (voice stimuli, which were morphed towards the other sex). The neural activation patterns of the MtF transsexuals differed from both the male and female controls: When processing male vs. female voices, the MtF transsexuals showed weaker activation than men in the right hemispheric area triangularis, insula, cuneus, bilateral lingual gyrus, calcarine gyrus and in the left parahippocampus; and weaker activation than women in the medial prefrontal cortex, rostral anterior cingulate cortex, right superior temporal gyrus, precentral gyrus, cuneus, left precuneus, cerebellum and thalamus. When morphing the original voices into gender ambiguous stimuli, men showed increased activation in prefrontal areas compared to both women and MtF transsexuals. When processing male vs. female voices, the

Table 3
Overview of task-based functional neuroimaging studies in transsexuals.

	Methods	Stimuli/task	Sample	Brain activation pattern		
				≙ Biol. sex	Intermed.	≙ Gend. Id.
Berglund et al. (2008)	PET	Odourous steroids (AND and EST)	12 MtFs			×
Burke et al. (2014)	fMRI	Odourous steroid (AND)	19 pb MtFs	×		
			17 pb FtMs		×	
			17 ad MtFs			×
			21 ad FtMs			×
Gizewski et al. (2009)	fMRI	Erotic film sequences	12 MtFs			×
Junger et al. (2014)	fMRI	Voice gender perception:	32 MtFs			
		Male vs. female voices			–[a]	
		Voice gender morphing[b]				×

Note: The respective control groups are not listed. All transsexuals were hormonally untreated. ≙ = "corresponds to"; AND = 4,16-androstadien-3-one; ad = adolescent; Biol. sex = biological sex; EST = estra-1,3,5(10),16-tetraen-3-ol; Gend. Id. = gender identity; Intermed. = intermediate; MtFs = male-to female transsexuals; pb = pre-pubertal.

[a] Activation pattern differs from both males and females.

[b] Original male/female voices, morphed in semitone steps towards the other sex.

activation pattern of the MtF transsexuals differ from both men and women. In the gender-ambiguous range though, the activation pattern was not different from that of the female controls. The behavioural and neurobiological results are interpreted as an indicator for the transsexuals' lack of identification with their biological sex. An overview of task-based functional neuroimaging studies in transsexuals and their relation to findings from control subjects sharing their biological sex vs. gender identity is given in Table 3. Summarising the low number of studies available, it seems premature to draw definite conclusions, but the reported data suggests that in specific functional domains, the transsexual subjects' processing is closer to subjects of the desired sex. Unfortunately, no data is available for FtM transsexuals so far. The inclusion of FtM transsexuals in future fMRI studies is desirable, and it might be worthwhile investigating brain activation patterns for other functional domains.

5. Structural and functional connectivity

To gain insight into the (transsexual) brain, not only knowledge about structural and functional properties of brain regions should be acquired, but also how these are structurally and functionally interconnected. Structural connectivity is constituted by anatomical connections such as synapses and fibre tracts and is frequently assessed through diffusion MRI. To our knowledge, there is only one study on white matter connectivity in transsexual individuals, which has been recently published by Hahn et al. (2014). Structural connectivity was assessed on the basis of diffusion weighted images (DWIs) in (hormonally untreated) MtF and also FtM transsexuals. Compared to same-sex controls, the MtF transsexuals exhibited an increased *inter*hemispheric lobar connectivity between subcortical/limbic and cortical regions, and the FtM transsexuals a decreased *intra*hemispheric lobar connectivity between subcortical/limbic and cortical regions. Sex differences in structural connectivity have been validated in a large sample of males and females by Ingalhalikar et al. (2014): Males have a greater *intra*hemispheric connectivity than women, and women a greater *inter*hemispheric connectivity than men. The observed increase in interhemispheric connectivity could thus reflect feminisation of structural connectivity. The decrease in intrahemispheric connectivity in FtM transsexuals remains unaccounted for, however.

Beyond being structurally connected, brain regions can also be functionally connected, whereby *functional connectivity* is defined as the temporal correlation between neurophysiological events of anatomically distant brain regions (Friston et al., 1993). Functional connectivity is commonly assessed using *resting-state* fMRI (rsfMRI), which in opposition to *task-based* fMRI, measures spontaneous brain activity during rest, when the subject is not performing an explicit task (Raichle, 2009). This approach has evolved in the last few years and is thought to measure the brain's intrinsic functional organisation or connectivity. Even under conditions of rest, it is possible to detect the emergence of spatially remote but functionally linked networks (Damoiseaux et al., 2006; Fox et al., 2005; van den Heuvel and Hulshoff Pol, 2010). Most of these resting-state networks parallel known functional networks during active processing (Smith et al., 2009). The most consistently observed networks across different studies are a visual network, a sensory/motor-network, and the *default mode network* (DMN) amongst others (Moussa et al., 2012). In several psychiatric disorders, functional connectivity of the brain seems to be altered, e.g. in depression and autism (Greicius et al., 2007; Müller et al., 2011). Thus, the assessment of functional connectivity is of clinical relevance and provides additional information for diagnosis. The brain's intrinsic activity also varies with age, sexual orientation and presumably also gender and sex hormone concentrations (Chen et al., 2013; Damoiseaux et al., 2008; Filippi et al., 2013; Hu et al., 2013; Petersen et al., 2014; Savic and Lindström, 2008; Tian et al., 2011). As transsexuals exhibit sex-atypical anatomy in several brain regions (see paragraph "Brain morphometry"), knowing whether resting-state patterns of transsexuals resemble those of subjects with the same biological sex or rather those with the same gender identity is potentially meaningful. A future goal would be the creation of a *connectivity profile* of transsexual individuals and arranging it along the male/female-axis. As far as is known, there are two rsfMRI-studies with transsexuals, one by Santarnecchi et al. (2012) and one by Lin et al. (2014). Santarnecchi et al. (2012) analysed resting-state brain connectivity in one untreated FtM transsexual individual and a male and female control group using both seed- and atlas-based analysis. The results suggest that the connectivity profile of FtM transsexuals is closer to subjects having the same biological sex rather than gender identity. The interpretation should be made with caution, as only data from one homosexual transsexual was assessed, whereas both control groups were heterosexual. It remains unclear to what extent the results reflect the participant's sexual orientation, rather than transsexual identity. Differences in functional connectivity between homo- and heterosexual individuals have been demonstrated recently (Hu et al., 2013). Besides, the transsexual participant suffered from *polycystic ovary syndrome*, which frequently causes heightened levels of androgen. It cannot be ruled out that this syndrome alters functional connectivity patterns.

Lin et al. (2014) recently examined functional connectivity patterns in a Taiwanese sample of 10 untreated MtF and 13 FtM transsexuals using graph-based network analysis. The study was

Table 4
Overview of studies assessing functional and structural connectivity in transsexuals.

	Imaging technique	Analysis method	Sample	Connectivity profile		
				≙Biol. sex	Intermed.	≙Gend. Id.
Hahn et al. (2014)	DW-MRI	Graph-based network analysis	21 MtFs 23 FtMs		–[a]	×
Lin et al. (2014)	fMRI	Graph-based network analysis	11 MtFs 12 FtMs		–[b] –[b]	
Santarnecchi et al. (2012)	fMRI	Seed- and atlas-based analysis	1 FtMs	×		

Note: The respective control groups are not listed. All transsexuals were hormonally untreated. ≙ = "corresponds to"; Biol. sex = biological sex; DW-MRI = diffusion weighted MRI; FtMs = female-to-male transsexuals; Gend. Id. = gender identity; Intermed. = intermediate; MtFs = male-to-female transsexuals.

[a] Functional connectivity pattern resembles neither that of males nor females.

[b] Pooled analysis (transsexuals vs. controls).

part of a larger behavioural study using visual sexual stimuli to assess sexual arousal and identification with the gender of the depicted actors (Ku et al., 2013). The focus specifically lay on regions belonging to the body representation network, i.e. the primary somatosensory cortex (postcentral gyrus, postCG), superior parietal lobule (SPL) and insular cortex (IC). The authors expected the transsexuals' persistent negative experience of and emotions about their own body to manifest themselves in changes in the aforementioned body representation network, with transsexuals showing a higher *degree centrality* of the resting-state functional connectivity network. Degree centrality is a simple measure of centrality, defined as the number of a node's links to and from other nodes. The analyses revealed an increased degree centrality in transsexual compared to control subjects bilaterally in the postCG and SPL. The SPL is engaged in sensorimotor integration and updating of information about the body's condition, so the results could reflect a heightened attention to the as incongruent perceived body. Qualitative differences were also observable in terms of a different connectivity pattern between the two groups. In the transsexuals, the body representation network was more extensively connected to sensorimotor areas: the postCG was additionally connected to nodes in the temporal lobe, and the SPL to nodes in the occipital lobe, sensory area and SMA. So far, there are no other rsfMRI-studies investigating functional connectivity in transsexual individuals and the findings on gender differences in resting-state-networks are still rather heterogeneous. An overview of findings on functional connectivity in transsexuals and their relation to connectivity patterns of subjects sharing their biological sex vs. gender identity is given in Table 4, along with findings on structural connectivity.

6. Hormonal influences on brain structure and function

6.1. Brain morphometry

As many transsexuals eventually decide for hormone therapy and sex reassignment surgery, the question arises in what way this acts upon the brain's structure and function. During prenatal development, during puberty and even in young adulthood, sex hormones exert an organisational influence on the brain's morphology (Genazzani et al., 2007; Neufang et al., 2009; Witte et al., 2010). Neufang et al. (2009) for example could demonstrate a relationship between the levels of gonadal steroid hormones and sexually dimorphic increases/decreases of grey matter volumes in the amygdala and hippocampus in subjects of 8–15 years age. But also later in life, when the brain has fully developed, sex steroids can exert an influence on the brain, as in the case of cross-sex hormonal treatment. Hulshoff Pol et al. (2006) studied the effects of cross-sex hormone administration in a group of MtF and FtM transsexuals. MRI-scannings were conducted prior to and after 4 months of hormonal treatment and compared to a group of male and female control subjects. Treatment with antiandrogens and oestrogens led to a reduction of total brain volume in the MtF transsexuals, and testosterone administration led to an increase of total brain and hypothalamus volume in the FtM transsexuals. The absence of specific effects for white and grey matter volume suggests changes in nerve cells as well as fibre tracts. As there were no differences in brain volume between the transsexual and same-sex control subjects prior to hormonal treatment, it is reasonable to conclude that the shift in brain volume towards the proportions of the desired sex was actually hormonally induced. The effects of cross-sex hormonal treatment (for at least 6 months) on cortical and subcortical grey matter volume and cortical thickness have been recently analysed by Zubiaurre-Elorza et al. (2014), who published corresponding data for untreated transsexuals in 2013 (Zubiaurre-Elorza et al., 2013) (see paragraph "Brain morphometry"). Changes in cortical thickness are known to be associated with testosterone levels in males and females. The relationship is complex however, not fully understood and varies with age and gender (Nguyen et al., 2013). For FtM transsexuals, an increase of cortical and subcortical (specifically right thalamus) grey matter volume was observable after testosterone treatment. For MtF transsexuals, cortical and subcortical (specifically right thalamus, right pallidum) grey matter volume decreased after treatment with oestrogen and anti-androgen. Concomitant, an increase in the entire ventricular system was measured, probably attributable to the reduction of grey matter (no changes in white matter volume were seen). In the FtM transsexual sample, increases in cortical thickness after hormonal treatment were visible in the postCG (bilateral), in the inferior parietal, lingual, pericalcarine and supramarginal regions of the left hemisphere and right hemispheric in the cuneus and rostral middle frontal areas. For MtF transsexuals cortical thickness decreased after hormonal treatment in several regions, including bilateral superior frontal, left cingulate and right fusiform areas, the right insula and precuneus. These findings are basically in accordance with those from Hulshoff Pol et al. (2006). The latter are less specific however, what might be attributable to having measured a very small sample of transsexuals. The exact mechanisms through which cross-sex hormones act upon grey matter and cortical thickness are not fully understood. The authors assume that the thinning or thickening of the cortex is be attributable to anabolic and anticatabolic effects of testosterone or the absence of such effects in case of oestrogen and anti-androgen administration. Only recently, a study linked the loss of brain matter to an alteration in serum levels of brain-derived neurotrophic factor (BDNF). BDNF is a protein promoting the growth of new neurons and synapses (neurogenesis). Reduced serum BDNF levels have been associated with a reduction of hippocampal volume (Rizos et al., 2011) and were now found in MtF transsexuals after cross-sex hormonal treatment (Fuss et al., 2015), which could explain the observed decrease in brain matter in hormonally treated MtF transsexuals. Relating the changes to the transsexuals' state before hormonal treatment is of special interest. If compared to the pattern of untreated participants from Zubiaurre-Elorza et al. (2013), several aspects attract attention. Before hormonal treatment, (right-hemispherical) subcortical

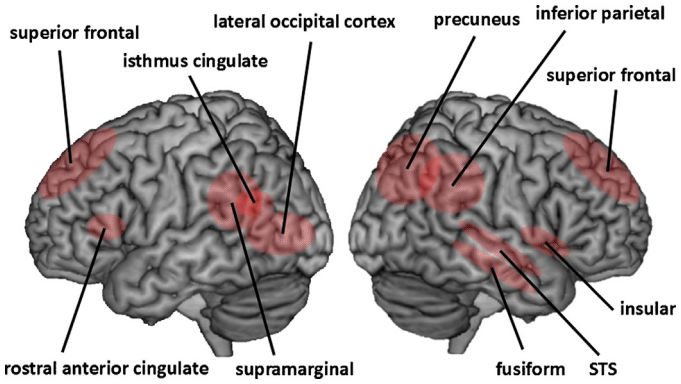

Fig. 1. Locations of significant hormone-induced structural changes in male-to-female transsexuals. Left- and right-hemispherical areas of decreased cortical thickness, as reported in Zubiaurre-Elorza et al. (2014). Furthermore, a general decrease in brain volume was reported in Hulshoff Pol et al. (2006). STS: superior temporal sulcus.

grey matter volume is partly feminised or masculinised in both MtF and FtM transsexuals. This deviation seems to consolidate under hormonal treatment (mainly affecting right-hemispherical structures). The cortical thickness of MtF transsexuals also shows signs of feminisation before hormonal treatment (in orbitofrontal, insular and medial occipital regions). Some of the already feminised structures were observed to further change towards female proportions (e.g. the right insula), but many regions that were altered after hormonal treatment were not observed to be feminised beforehand, however (e.g. the left isthmus of cingulate gyrus). Rametti et al. (2012) analysed white matter patterns using diffusion tensor imaging in a group of hormonally treated FtM transsexuals before and after at least 7 months of treatment. The study constitutes a follow-up study of the authors' preceding work (2011a; 2011b), which is discussed in the paragraph "Brain morphometry". The transsexual participants were scanned prior to and after at least seven months of hormone therapy. Interestingly, the transsexuals showed an increase in fractional anisotropy-values in the right superior longitudinal fasciculus and corticospinal tract – fibre tracts, in which they exhibited a rather male-like pattern before hormonal treatment (FA-values of control males > females). The superior longitudinal fasciculus is a bunch of fibres running from the frontal to the posterior part of the cerebrum. It integrates input from areas engaged in spatial attention and spatial working memory (Makris et al., 2005). The findings of an increased FA-value in the right superior longitudinal fasciculus might relate to the fact that experimental testing of these functions reveals performance differences between males and females (favouring males) (Halpern et al., 2007; Silverman et al., 2007). The corticospinal tract (also called pyramidal tract) is a motor neuron pathway originating in/arising from the primary motor cortex, premotor cortex, supplementary motor and somatosensory areas (Hall, 2011). The tract is engaged in the innervation of muscles and its FA-values appear to be sexually dimorphic (Rametti et al., 2011a,b). The findings may be related to the stimulating effect that testosterone has on the neoformation of myelin. In patients with chronic myelin damage for example, androgen treatment can successfully reverse myelin damage (Hussain et al., 2013). The exact mechanism responsible for the increase of FA-values in the two fibre tracts still needs to be resolved, but the outcome clearly reveals the plasticity of the brain's structural properties: Hormonal treatment affects white matter and structural brain connectivity and adjusts it towards characteristics of the desired sex. The locations of significant hormone-induced structural changes in FtM and MtF transsexuals reported in the presented studies are depicted in Figs. 1 and 2.

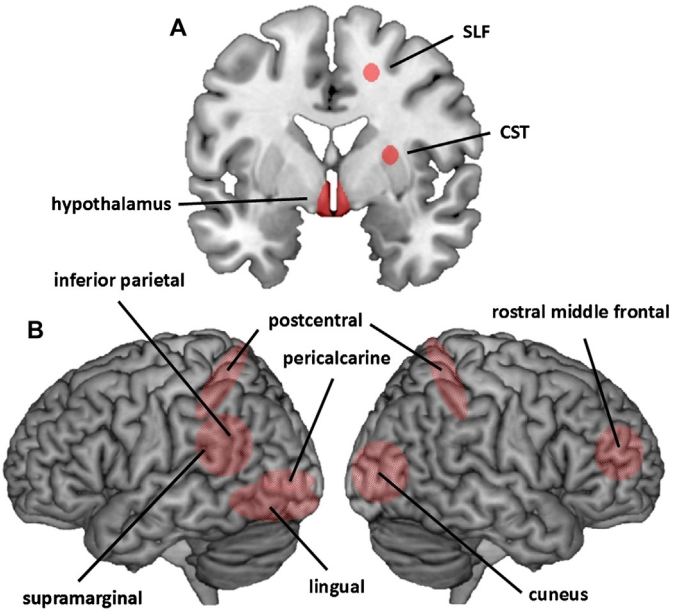

Fig. 2. Locations of significant hormone-induced structural changes in female-to-male transsexuals. (A) Clusters showing significantly increased fractional anisotropy values, as reported in Rametti et al. (2012), belonging to the CST and SLF; increased hypothalamus volume, as reported in Hulshoff Pol et al. (2006). (B) Left- and right-hemispherical areas of increased cortical thickness, as reported in Zubiaurre-Elorza et al. (2014). Furthermore, a general increase in brain volume was reported in Hulshoff Pol et al. (2006). CST = corticospinal tract; SLF = superior longitudinal fasciculus.

6.2. Functional connectivity

There is evidence that sex hormones not only alter the brain's anatomy, but also its activity during rest and performance. Several studies point out an influence of sex hormones on resting-state functional connectivity (Maki and Resnick, 2001). From research in animals it is known that steroid hormones act upon the myelination of fibres, which forms the basis of white matter connectivity. Ovarian hormones, such as estradiol and progesterone, in turn, can enhance functional connectivity between cortical and subcortical areas. Androgens such as testosterone can decrease functional connectivity between cortical and subcortical areas and increase functional connectivity between subcortical areas (Peper et al., 2011). It thus seems a plausible assumption, that hormonal treatment alters resting-state functional connectivity patterns, but as far as is known, there are no studies reporting a pre-post comparison of functional connectivity in transsexual subjects before and during hormonal treatment.

6.3. Task-related activity

The performance in specific tasks is mediated through hormone levels – this is especially true for tasks that reveal gender differences (Van Goozen et al., 1995). In control subjects, several cognitive abilities are thought to be modulated by hormone levels, including visuo-spatial abilities (Hampson, 1995). When testing for spatial abilities males most often outperform females. Although this performance difference is not found in all studies, it has been replicated numerous times and appears to be a relatively stable phenomenon (Halpern et al., 2007; Silverman et al., 2007). These gender differences in spatial ability are discussed to be of an adaptive character, but the available data suggests they rather might be concomitant effects of hormone levels (Clint et al., 2012). Results from several studies suggest that the male advantage in mental rotation tasks is mediated or even conditioned by higher levels of testosterone.

As an example, hypogonadal males receiving testosterone substitution therapy show improved performance and enhanced cerebral glucose metabolism compared to baseline (prior to hormonal treatment) during a mental rotation task (Zitzmann et al., 2001). In women, Hausmann et al. (2000) could for example demonstrate a modulation of spatial abilities through testosterone and estradiol during the menstrual cycle, with higher scores in a spatial ability test during the menstrual phase, when oestrogen levels are low. Testosterone seems to have a positive, estradiol a negative influence on spatial abilities.

There are several behavioural studies examining the influence of cross-sex hormonal treatment in transsexual individuals on the performance in various cognitive tasks, such as mental rotation and visual memory tasks. While spatial abilities have been mentioned before in the context of morphometric conspicuities in the superior longitudinal fasciculus, a fibre tract integrating input from areas processing spatial information, we now discuss spatial abilities in transsexuals under cross-sex hormonal treatment. Taken together, the results indicate that cross-sex hormonal treatment causes a shift in performance towards levels of subjects sharing the desired sex. Slabbekoorn et al. (1999) observed the reversal of the typical sex difference in a visuo-spatial task after hormone administration in FtM and MtF transsexuals. The activational effect of sex hormones was also confirmed by Van Goozen et al. (1995): cross-sex hormone administration led to an increase in spatial ability performance in FtM transsexuals and to an improvement in verbal fluency performance in MtF transsexuals. Gómez-Gil et al. (2010) observed an improvement in a visual memory task when comparing the performance of FtM transsexuals before and after (6–84 months of) androgen treatment. This activating effect of androgens corresponds to the observation, that tests of visual memory generally favour males. On the other hand, the treatment with oestrogen in MtF transsexuals has been observed to improve verbal memory abilities (Miles et al., 1998). Despite several lines of evidence supporting the assumption that, in the case of mental rotation, the transsexuals' performance adjusts towards the performance of people sharing the desired sex, there is also evidence challenging this view. The data from van Goozen et al. (2002) on homosexual transsexuals suggests the effect could be a *ceiling effect*, as the transsexuals also had performance scores similar to subjects of the desired sex pre-treatment. Besides, Wisniewski et al. (2005) found no evidence of a female-like pattern in cognitive performance of hormonally treated MtF transsexuals. Haraldsen et al. (2005) conducted the testing of several cognitive abilities (after 3 and 12 months of hormonal treatment), including rotation, arithmetic and verbal abilities, controlled the data for multiple factors, such as age, education, natal sex and endocrinological differences and found no performance difference between controls and hormonally treated GID patients. The influence of cross-sex hormone administration on brain activity during task performance has so far been tested using mental rotation and language paradigms, and visual sexual stimuli. Oh et al. (2012) assessed functional brain activation patterns during the processing of visual erotic stimuli in a group of homosexual MtF transsexuals, who had undergone sex reassignment surgery and hormone therapy (24–180 months). Viewing male vs. female nude pictures activated areas such as the amygdala, anterior cingulate gyrus, hippocampus, putamen, head and body of caudate nucleus, thalamus, insula, cerebellum and midbrain. Viewing female nude pictures induced brain activation in the hypothalamus and septal area only. As all participants were homosexual, the observed activation patterns are thought to reflect their sexual orientation towards males. The study exhibits several methodical constraints, however. The sample size is very small ($n = 9$), and with no direct comparison to a male or female control group and no pre-post treatment comparison, the results are difficult to interpret and the influence of treatment is not quantifiable. As far as is known, there are three studies analysing spatial abilities in transsexuals under cross-sex hormonal treatment. Carrillo et al. (2010) compared activation patterns of MtF and FtM transsexuals receiving hormonal treatment (116 and 60 months, respectively) and control subjects during a 3D mental rotation task. In the FtM transsexual sample, no specific activation pattern was observable. This absence of differences between the FtM transsexuals and MtF transsexuals as well as control subjects is rather surprising and could indicate an intermediate position of FtM transsexuals. The MtF transsexuals by contrast, displayed a distinctive pattern of activation during task performance: compared to males, they showed lower activation in the superior parietal lobe, compared to females stronger activation in orbital and right dorsolateral prefrontal regions and lower activation in the left postCG. The activation in several regions, including the superior parietal lobe (bilateral) and the posterior temporal lobe was negatively correlated with the number of months of hormonal treatment. Unfortunately, Carrillo et al. (2010) made no comparison of activation patterns between hormonally treated and untreated transsexuals. It is thus not possible to determine which of these differences were existent a priori. However, such a comparison was realised by Sommer et al. (2008) and Schöning et al. (2010), whose participants underwent fMRI-scanning prior to and during cross-sex hormonal treatment (3 and at least 6 months, respectively). The sample investigated by Schöning et al. (2010) comprised MtF transsexuals and male control subjects only. The contrast between both MtF transsexual groups yielded stronger activation in the middle frontal and fusiform gyrus in the untreated transsexual group. The stronger activation of temporo-occipital regions in both transsexual groups compared to control males suggests a priori differences between transsexual and control subjects, which remain stable during hormonal treatment. The differences between MtF transsexuals and males found by Schöning et al. (2010) and Carrillo et al. (2010) were not congruent, though. It is conceivable that some of the observed differences reflect a priori group differences, whereas others develop in consequence of hormonal treatment. The inclusion of control subjects is thus essential to disentangle these effects. Sommer et al. (2008) additionally assessed lateralisation of cerebral activation patterns of FtM and MtF transsexuals during a language task prior to and after approximately three months of hormonal treatment. Activation patterns were not contrasted against a control group of males and females, however. Lingual and spatial representations have an asymmetrical cerebral organisation – language contingent activation is mainly left, spatial contingent activation mainly right hemispherical. Data from several studies suggest lateralisation is affected by sex-steroid levels (Wisniewski, 1998) and, although not definitely solved (and challenged through recent findings), cerebral lateralisation is thought to be more pronounced in males than in females (Nielsen et al., 2013; Tomasi and Volkow, 2012). Interestingly, behavioural results revealed no significant effects for biological sex or status of treatment. Cerebral activation increased during the language task after treatment, but remained stable compared to baseline during mental rotation. There was a trend towards stronger activation in participants with higher testosterone levels (natal males and treated FtM transsexuals), but the effect failed to reach significance. Functional lateralisation remains stable and seems to be unaffected despite profound changes of the hormonal milieu. There are several other studies inferring cerebral lateralisation in transsexuals through behavioural measures yielding mixed results (Wisniewski et al., 2005). Further fMRI studies might help answering the question, whether transsexuals exhibit gender atypical cerebral lateralisation. All three of the above presented studies on mental rotation again evoke the issue of sexual orientation when investigating transsexualism. Sommer et al. (2008) made no specification of the participants' sexual orientation, Carrillo et al. (2010) contrasted homosexual transsexuals and Schöning et al. (2010) hetero- and

homosexual transsexuals against heterosexual control subjects. As the number of studies on the effects of cross-sex hormonal treatment on functional brain activation patterns is still very small and restricted to two paradigms, no definite conclusions can be drawn yet. The replication and continuation of research in this field using a broader range of paradigms would be desirable. Under the influence of cross-sex hormonal treatment, the brain's structure and function seems to adjust towards characteristics or performance of subjects sharing the desired sex in several brain areas or ability domains. The presented findings are an indicator of the brain's plasticity, although their interpretation is constrained. The mechanisms through which cross-sex hormone administration acts upon the brain's structure and function are not fully understood yet. There is a great variability in duration of hormonal treatment across the studies presented (3–180 months), whereby particularly long-term treatment effects on brain structure and function are underexplored. At this point, two main question emerge, that may point the way ahead for further studies: To what extent are these changes stable or reversible, e.g. in case of a patient's withdrawal from hormonal treatment and are these changes in turn associated with specific behavioural changes?

7. Discussion and research perspectives

The available data from structural and functional neuroimaging-studies promote the view of transsexualism as a condition that has biological underpinnings. The research in this field is ongoing at least since the early 1990s – yet, the phenomenon is far from being studied sufficiently. Many of the results are inconsistent or still need to be replicated and the sample sizes are often extremely small. Findings from studies with transsexual individuals are typically interpreted in relation to males or females. The brains of transsexual individuals do not seem to be entirely feminised or masculinised – instead, research points towards a selective feminisation or masculinisation of brain structures or processes that are sexually dimorphic in control subjects. Regarding brain morphometry, signs of masculinisation/feminisation are observable in cortical thickness and in several white matter fibre tracts and grey matter structures, including the BSTc and INAH3. Resting-state functional connectivity in transsexualism is only sparsely studied and the available studies exhibit several methological constraints. It is currently not possible to construct a connectivity profile of transsexual individuals based on the available data. Data on event-related fMRI in (untreated) transsexuals is available from three studies, measuring cerebral activation patterns of MtF transsexuals while smelling odorous steroids, viewing erotic film scenes, and discriminating male and female voices. Data for FtM transsexuals is not available. In either case, the observed activation patterns resembled those of the female rather than male control subjects. The replication of these findings and investigation of FtM transsexuals is still outstanding. Besides, for the future, the testing by means of other paradigms would be desirable to determine whether this response pattern also applies to other functional domains. For instance, these could be paradigms testing mathematical or empathic abilities, or stress reactions, which have been shown to elicit subtle, but significant sex differences (Christov-Moore et al., 2014; Kudielka and Kirschbaum, 2005; Zhu, 2007).

As many transsexuals wish for cross-sex hormonal treatment, the question arises which of the observed structural and functional differences remain stable, change or reverse after hormonal treatment and which differences develop not until several months of hormone therapy. In FtM transsexuals, an increase of cortical and subcortical grey matter volume after testosterone treatment, and in MtF transsexuals a decrease of cortical and subcortical grey matter volume after oestrogen and anti-androgen administration has been observed. The brain's structure and function seems to adjust towards characteristics or performance of subjects sharing the desired sex in several brain areas or ability domains. But due to the limited number of studies, the aforementioned question regarding the stability of the observed structural and functional differences in the course of hormonal treatment cannot be answered yet. Hormone-induced behavioural changes have been observed in the performance of cognitive tasks such as mental rotation and visual memory tasks: The performance typically adjusts to levels of subjects sharing the desired sex, resulting i.e. in a reversal of the typical sex difference in visuo-spatial tasks in hormonally treated FtM an MtF transsexuals. On a neurobiological level, these changes have only been studied sparsely and were restricted to mental rotation and language processing paradigms. The mechanisms through which cross-sex hormone administration acts upon the brain's structure and function are not fully understood.

Based on the current state of research on transsexualism, this review also aims to point out issues in need of improvement and providing several suggestions for future research projects. Quite a number of studies give no information about the participants' sexual orientation. The large variability of sexual orientation in transsexual compared to control subjects is an inherent characteristic of transsexualism, but mixing hetero- and homosexual subjects could affect results, as the two concepts represent confounding factors. Many studies compare homosexual transsexuals with heterosexual controls, which could increase group differences. A comparison of exclusively heterosexual transsexuals and controls or homosexual transsexuals and controls is thus recommended. The *Blanchard's typology of transsexualism* (Blanchard, 1985, 1989) suggests the distinction of transsexuals according to their sexual orientation. Although this approach is highly controversial as it could erroneously suggest an erotic background of the phenomenon, the assessment of sexual orientation is crucial to avoid confounding two distinct phenomena. As Hare et al. (2009) noted, the sexuality of their sample was only known in less than 50% of participants, as they either did not want to provide this kind of information or their sexual orientation was "fluid" and difficult to classify. The consistent use of standardised instruments for assessment of sexual orientation across studies would be beneficial to obtain a higher degree of comparability of the samples.

As described in the DSM-5 (American Psychiatric Association, 2013a), the development of transsexualism broadly falls into the categories of early and late onset. The two groups differ in several characteristics, e.g. ratio of affected males vs. females and homo- vs. heterosexuality (Nieder et al., 2011). Another research focus would thus not only be a neurobiological comparison of transsexual vs. non-transsexual individuals but also a comparison of early vs. late onset transsexualism. Some studies provide information about the age of onset of the participants, but direct comparisons are still outstanding. The two subgroups might differ with respect to causal factors, brain anatomy or functional activation patterns. A review from Lawrence (2010) compares typologies of transsexualism based on sexual orientation to those based on age of onset. There is considerable overlap between the two approaches, meaning that they generate very similar groups. Even so, a classification based on sexual orientation seems to be more precise in predicting treatment outcomes and comorbid psychopathology. The issue thus remains a subject for debate

Another issue is the comparability of FtM and MtF transsexualism. Are we investigating the same phenomenon in males and females or rather analogous outcomes in both sexes caused by different mechanisms? As the latter possibility cannot be ruled out, groups of MtF and FtM transsexuals should be analysed separately. Transsexualism may not be a heterogeneous phenomenon with regards to aetiological factors, and perhaps we are not even looking at the same phenomenon within the same sex. Between the sexes,

as well as within the same sex, transsexuals exhibit highly diverse symptom profiles, and comorbid disorders (Auer et al., 2013; Hepp et al., 2005; Landén et al., 1989). Transsexualism in natal females however, is far less studied. Most studies examine MtF transsexuals only, or only a small group of FtM transsexuals. Maybe future studies could address this problem.

As the research on transsexualism is predominantly carried out on adults it is unclear whether the observed findings have developed early or later in development or before the onset of overt gender dysphoric symptoms. It would be important to also collect structural and functional data from children and adolescents with gender dysphoric symptoms to determine when neural differences between transsexual and non-transsexual individuals emerge. Considering the current state of research in the field of transsexualism or GD, the implementation of standards for its research as the assessment of sexual orientation and the appropriate choice of control group is of central importance. For a more thorough investigation and characterisation of the phenomenon, a multidimensional approach considering factors such as age of onset, sexual orientation, psychiatric comorbidity and maybe others, is required. The research on transsexualism provides an opportunity for deeper insight into gender specific brain mechanisms, the stability or variability of gender differences and their relationship with hormonal status. The reported findings call for a paradigm shift in terms of a maceration of rigid gender categories and a more nuanced gender model. Viewing gender as a binary or dichotomous category has to be reconsidered, and locating transsexuals exactly in-between males and females is certainly constitutes an oversimplification. This could also find expression in the development of paradigms or stimulus sets comprising broader gender categories, or gender ambiguous or incongruous stimuli (e.g. female stimuli with male features). Hopefully, the appreciation of gender diversity in (neurobiological) research contributes to a better social acceptance of transsexual individuals.

Acknowledgement

This work was supported by the German Research Foundation (DFG: HA 3202/7-3).

References

Abedelahi, A., Hasanzadeh, H., Hadizadeh, H., Joghataie, M.T., 2013. Morphometric and volumetric study of caudate and putamen nuclei in normal individuals by MRI: effect of normal aging, gender and hemispheric differences. Pol. J. Radiol. 78 (3), 7–14, http://dx.doi.org/10.12659/PJR.889364.

Aitken, M., Steensma, T.D., Blanchard, R., VanderLaan, D.P., Wood, H., Fuentes, A., Zucker, K.J., 2015. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. J. Sex. Med. 12 (3), 756–763, http://dx.doi.org/10.1111/jsm.12817.

Allen, L.S., Hines, M., Shryne, J.E., Gorski, R.A., 1989. Two sexually dimorphic cell groups in the human brain. J. Neurosci. 9 (2), 497–506.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text rev. Author, Washington, DC.

American Psychiatric Association, 2013a. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Author, Washington, DC.

American Psychiatric Association, 2013b. Gender dysphoria fact sheet, Retrieved from: http:// www. dsm5. org/ Documents/ Gender%20Dysphoria%20Fact%20Sheet. pdf.

Ardekani, B.A., Figarsky, K., Sidtis, J.J., 2013. Sexual dimorphism in the human corpus callosum: an MRI study using the OASIS brain database. Cereb. Cortex 23 (10), 2514–2520, http://dx.doi.org/10.1093/cercor/bhs253.

Arnow, B., Desmond, A.J., Banner, E.L., Glover, L.G., Solomon, H., Polan, A.M., Atlas, L.S.W., 2002. Brain activation and sexual arousal in healthy, heterosexual males. Brain 125, 1014–1023.

Auer, M.K., Höhne, N., Bazarra-Castro, M., Pfister, H., Fuss, J., Stalla, G.K., Ising, M., 2013. Psychopathological profiles in transsexuals and the challenge of their special status among the sexes. PLOS ONE 8 (10), e78469, http://dx.doi.org/10.1371/journal.pone.0078469.

Bao, A.M., Swaab, D.F., 2011. Sexual differentiation of the human bra relation to gender identity sexual orientation neuropsychiatric disorders. Front. Neuroendocrinol. 32 (2), 214–226, http://dx.doi.org/10.1016/j.yfrne.2011.02.007.

Bentz, E.K., Hefler, L.A., Kaufmann, U., Huber, J.C., Kolbus, A., Tempfer, C.B., 2008. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. Fertil. Steril. 90 (1), 56–59, http://dx.doi.org/10.1016/j.fertnstert.2007.05.056.

Berglund, H., Lindström, P., Dhejne-Helmy, C., Savic, I., 2008. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cereb. Cortex 18 (8), 1900–1908, http://dx.doi.org/10.1093/cercor/bhm216.

Bishop, K.M., Wahlsten, D., 1997. Sex differences in the human corpus callosum: myth or reality? Neurosci. Biobehav. Rev. 21 (5), 581–601.

Blanchard, R., 1985. Typology of male-to-female transsexualism. Arch. Sex. Behav. 14 (3), 247–261.

Blanchard, R., 1989. The concept of autogynephilia and the typology of male gender dysphoria. J. Nerv. Ment. Dis. 177 (10), 616–623.

Blanchard, R., Clemmensen, L.H., Steiner, B.W., 1987. Heterosexual and homosexual gender dysphoria. Arch. Sex. Behav. 16 (2), 139–152.

Blumer, D., 1969. Transsexualism, sexual dysfunction and temporal lobe disorder. In: Green, R., Money, J. (Eds.), Transsexualism and Sex Reassignment. John Hopkins Press, Baltimore.

Bockting, W.O., Miner, M.H., Swinburne Romine, R.E., Hamilton, A., Coleman, E., 2013. Stigma, mental health, and resilience in an online sample of the US transgender population. Am. J. Public Health 103 (5), 943–951, http://dx.doi.org/10.2105/AJPH.2013.301241.

Byrne, J.H., n.d. Neuroscience Online. Retrieved from http://neuroscience.uth.tmc.edu.

Burke, S.M., Cohen-Kettenis, P.T., Veltman, D.J., Klink, D.T., Bakker, J., 2014. Hypothalamic response to the chemo-signal androstadienone in gender dysphoric children and adolescents. Front. Endocrinol. (Lausanne) 5, 60, http://dx.doi.org/10.3389/fendo.2014.00060.

Byne, W., Lasco, M.S., Kemether, E., Shinwari, A., Edgar, M.A., Morgello, S., Tobet, S., 2000. The interstitial nuclei of the human anterior hypothalamus: an investigation of sexual variation in volume and cell size, number and density. Brain Res. 856 (1–2), 254–258.

Carrillo, B., Gómez-Gil, E., Rametti, G., Junque, C., Gomez, A., Karadi, K., Guillamon, A., 2010. Cortical activation during mental rotation in male-to-female and female-to-male transsexuals under hormonal treatment. Psychoneuroendocrinology 35 (8), 1213–1222, http://dx.doi.org/10.1016/j.psyneuen.2010.02.010.

Chen, S.H., Wu, A., Lua, C.-Y., Mikyakoshi, R.-P., Nakai, M.T., 2013. Age-related changes in resting-state and task-activated functional MRI networks. In: Paper presented at the 7th International Symposium on Medical Information and Communication Technology (ISMICT), Tokyo, Japan.

Chivers, M.L., Bailey, J.M., 2000. Sexual orientation of female-to-male transsexuals: a comparison of homosexual and nonhomosexual types. Arch. Sex. Behav. 29 (3), 259–278.

Christov-Moore, L., Simpson, E.A., Coudé, G., Grigaityte, K., Iacoboni, M., Ferrari, P.F., 2014. Empathy: gender effects in brain and behavior. Neurosci. Biobehav. Rev. 46 (4), 604–627, http://dx.doi.org/10.1016/j.neubiorev.2014.09.001.

Chung, S.C., Lee, B.Y., Tack, G.R., Lee, S.Y., Eom, J.S., Sohn, J.H., 2005. Effects of age, gender, and weight on the cerebellar volume of Korean people. Brain Res. 1042 (2), 233–235, http://dx.doi.org/10.1016/j.brainres.2005.02.033.

Clint, E.K., Sober, E., Garland, T., Rhodes, J.S., 2012. Male superiority in spatial navigation: adaptation or side effect? Q. Rev. Biol. 87 (4), 289–313.

Cohen-Kettenis, P.T., Gooren, L.J., 1999. Transsexualism: a review of etiology, diagnosis and treatment. J. Psychosom. Res. 46 (4), 315–333.

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., Zucker, K., 2012. Standards of care for the health of transsexual, transgender, and gender-nonconforming people. Int. J. Transgend. 13 (4), 165–232.

Coolidge, F.L., Thede, L.L., Young, S.E., 2002. The heritability of gender identity disorder in a child and adolescent twin sample. Behav. Genet. 32 (4), 251–257.

Cosgrove, K.P., Mazure, C.M., Staley, J.K., 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol. Psychiatry 62 (8), 847–855, http://dx.doi.org/10.1016/j.biopsych.2007.03.001.

Craig, A.D., 2009. How do you feel – now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10 (1), 59–70, http://dx.doi.org/10.1038/nrn2555.

Crestani, C.C., Alves, F.H., Gomes, F.V., Resstel, L.B., Correa, F.M., Herman, J.P., 2013. Mechanisms in the bed nucleus of the stria terminalis involved in control of autonomic and neuroendocrine functions: a review. Curr. Neuropharmacol. 11 (2), 141–159, http://dx.doi.org/10.2174/1570159X11311020002.

Damoiseaux, J.S., Beckmann, C.F., Arigita, E.J., Barkhof, F., Scheltens, P., Stam, C.J., Rombouts, S.A., 2008. Reduced resting-state brain activity in the "default network" in normal aging. Cereb. Cortex 18 (8), 1856–1864, http://dx.doi.org/10.1093/cercor/bhm207.

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. U. S. A. 103 (37), 13848–13853, http://dx.doi.org/10.1073/pnas.0601417103.

Davatzikos, C., Resnick, S.M., 1998. Sex differences in anatomic measures of interhemispheric connectivity: correlations with cognition in women but not men. Cereb. Cortex 8 (7), 635–640.

Eiden, L.E., Hökfelt, T., Brownstein, M.J., Palkovits, M., 1985. Vasoactive intestinal polypeptide afferents to the bed nucleus of the stria terminalis in the rat: an immunohistochemical and biochemical study. Neuroscience 15 (4), 999–1013.

Emory, L.E., Williams, D.H., Cole, C.M., Amparo, E.G., Meyer, W.J., 1991. Anatomic variation of the corpus callosum in persons with gender dysphoria. Arch. Sex. Behav. 20 (4), 409–417.
Fernández, R., Esteva, I., Gómez-Gil, E., Rumbo, T., Almaraz, M.C., Roda, E., Haro-Mora, J.J., Guillamón, A., Pásaro, E., 2014. Association study of ERβ, AR, and CYP19A1 genes and MtF transsexualism. J. Sex. Med. 11 (12), 2986–2994, http://dx.doi.org/10.1111/jsm.12673.
Fernández, R., Cortés-Cortés, J., Esteva, I., Gómez-Gil, E., Almaraz, M.C., Lema, E., Rumbo, T., Haro-Mora, J.J., Roda, E., Guillamón, A., Pásaro, E., 2015. The CYP17 MspA1 polymorphism and the gender dysphoria. J. Sex. Med. 12 (6), 1329–1333, http://dx.doi.org/10.1111/jsm.12895.
Filippi, M., Valsasina, P., Misci, P., Falini, A., Comi, G., Rocca, M.A., 2013. The organization of intrinsic brain activity differs between genders: a resting-state fMRI study in a large cohort of young healthy subjects. Hum. Brain Mapp. 34 (6), 1330–1343, http://dx.doi.org/10.1002/hbm.21514.
Flor-Henry, P., 2010. EEG analysis of male to female transsexuals: discriminant function and source analysis. Clin. EEG Neurosci. 41 (4), 219–222.
Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102 (27), 9673–9678, http://dx.doi.org/10.1073/pnas.0504136102.
Freund, K., Steiner, B.W., Chan, S., 1982. Two types of cross-gender identity. Arch. Sex. Behav. 11 (1), 49–63.
Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. Blood Flow Metab. 13 (1), 5–14, http://dx.doi.org/10.1038/jcbfm.1993.4.
Fuss, J., Hellweg, R., Van Caenegem, E., Briken, P., Stalla, G.K., T'Sjoen, G., Auer, M.K., 2015. Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). Eur. Neuropsychopharmacol. 25 (1), 95–99, http://dx.doi.org/10.1016/j.euroneuro.2014.11.019.
Garcia-Falgueras, A., Swaab, D.F., 2008. A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity. Brain 131 (Pt 12), 3132–3146, http://dx.doi.org/10.1093/brain/awn276.
Garrels, L., Kockott, G., Michael, N., Preuss, W., Renter, K., Schmidt, G., Windgassen, K., 2000. Sex ratio of transsexuals in Germany: the development over three decades. Acta Psychiatr. Scand. 102 (6), 445–448.
Genazzani, A.R., Pluchino, N., Luisi, S., Luisi, M., 2007. Estrogen, cognition and female ageing. Hum. Reprod. Update 13 (2), 175–187, http://dx.doi.org/10.1093/humupd/dml042.
Gizewski, E.R., Krause, E., Schlamann, M., Happich, F., Ladd, M.E., Forsting, M., Senf, W., 2009. Specific cerebral activation due to visual erotic stimuli in male-to-female transsexuals compared with male and female controls: an fMRI study. J. Sex. Med. 6 (2), 440–448, http://dx.doi.org/10.1111/j.1743-6109.2008.00981.x.
Gower, D.B., Ruparelia, B.A., 1993. Olfaction in humans with special reference to odorous 16-androstenes: their occurrence, perception and possible social, psychological and sexual impact. J. Endocrinol. 137 (2), 167–187.
Grasser, T., Keidel, M., Kockott, G., 1989. [Frequency analytic EEG study on the topic of temporal function disorders in transsexuality]. EEG EMG Z. Elektroenzephalogr. Elektromyogr. Verwandte Geb. 20 (2), 117–120.
Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol. Psychiatry 62 (5), 429–437, http://dx.doi.org/10.1016/j.biopsych.2006.09.020.
Gómez-Gil, E., Esteva, I., Almaraz, M.C., Pasaro, E., Segovia, S., Guillamon, A., 2010. Familiality of gender identity disorder in non-twin siblings. Arch. Sex. Behav. 39 (2), 546–552, http://dx.doi.org/10.1007/s10508-009-9524-4.
Hahn, A., Kranz, G.S., Küblböck, M., Kaufmann, U., Ganger, S., Hummer, A., Lanzenberger, R., 2014. Structural connectivity networks of transgender people. Cereb. Cortex, http://dx.doi.org/10.1093/cercor/bhu194.
Hall, J.E., 2011. Guyton and Hall Textbook of Medical Physiology, 12th ed. Philadelphia, Saunders.
Halpern, D.F., Benbow, C.P., Geary, D.C., Gur, R.C., Hyde, J.S., Gernsbacher, M.A., 2007. The science of sex differences in science and mathematics. Psychol. Sci. Public Interest 8 (1), 1–51.
Hamann, S., Herman, R.A., Nolan, C.L., Wallen, K., 2004. Men and women differ in amygdala response to visual sexual stimuli. Nat. Neurosci. 7 (4), 411–416, http://dx.doi.org/10.1038/nn1208.
Hampson, E., 1995. Spatial cognition in humans: possible modulation by androgens and estrogens. J. Psychiatry Neurosci. 20 (5), 397–404.
Haraldsen, I.R., 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 Res. 137 (3), 161–174, http://dx.doi.org/10.1016/j.psychres.2005.05.014.
Hare, L., Bernard, P., Sánchez, F.J., Baird, P.N., Vilain, E., Kennedy, T., Harley, V.R., 2009. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. Biol. Psychiatry 65 (1), 93–96, http://dx.doi.org/10.1016/j.biopsych.2008.08.033.
Hausmann, M., Slabbekoorn, D., Van Goozen, S.H., Cohen-Kettenis, P.T., Güntürkün, O., 2000. Sex hormones affect spatial abilities during the menstrual cycle. Behav. Neurosci. 114 (6), 1245–1250.
Hengstschläger, M., van Trotsenburg, M., Repa, C., Marton, E., Huber, J.C., Bernaschek, G., 2003. Sex chromosome aberrations and transsexualism. Fertil. Steril. 79 (3), 639–640.
Henningsson, S., Westberg, L., Nilsson, S., Lundström, B., Ekselius, L., Bodlund, O., Landén, M., 2005. Sex steroid-related genes and male-to-female transsexualism. Psychoneuroendocrinology 30 (7), 657–664, http://dx.doi.org/10.1016/j.psyneuen.2005.02.006.
Hepp, U., Kraemer, B., Schnyder, U., Miller, N., Delsignore, A., 2005. Psychiatric comorbidity in gender identity disorder. J. Psychosom. Res. 58 (3), 259–261, http://dx.doi.org/10.1016/j.jpsychores.2004.08.010.
Heylens, G., De Cuypere, G., Zucker, K.J., Schelfaut, C., Elaut, E., Vanden Bossche, H., T'Sjoen, G., 2012. Gender identity disorder in twins: a review of the case report literature. J. Sex. Med. 9 (3), 751–757, http://dx.doi.org/10.1111/j.1743-6109.2011.02567.x.
Heylens, G., Elaut, E., Kreukels, B.P., Paap, M.C., Cerwenka, S., Richter-Appelt, H., De Cuypere, G., 2014. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. Br. J. Psychiatry 204 (2), 151–156, http://dx.doi.org/10.1192/bjp.bp.112.121954.
Hoenig, J., Kenna, J.C., 1979. EEG abnormalities and transsexualism. Br. J. Psychiatry 134, 293–300.
Hoffstaedter, F., Grefkes, C., Caspers, S., Roski, C., Palomero-Gallagher, N., Laird, A.R., Eickhoff, S.B., 2014. The role of anterior midcingulate cortex in cognitive motor control: evidence from functional connectivity analyses. Hum. Brain Mapp. 35 (6), 2741–2753, http://dx.doi.org/10.1002/hbm.22363.
Hoshiai, M., Matsumoto, Y., Sato, T., Ohnishi, M., Okabe, N., Kishimoto, Y., Kuroda, S., 2010. Psychiatric comorbidity among patients with gender identity disorder. Psychiatry Clin. Neurosci. 64 (5), 514–519, http://dx.doi.org/10.1111/j.1440-1819.2010.02118.x.
Hu, S., Xu, D., Peterson, B.S., Peterson, B., Wang, Q., He, X., Xu, Y., 2013. Association of cerebral networks in resting state with sexual preference of homosexual men: a study of regional homogeneity and functional connectivity. PLOS ONE 8 (3), e59426, http://dx.doi.org/10.1371/journal.pone.0059426.
Hulshoff Pol, H.E., Cohen-Kettenis, P.T., Van Haren, N.E., Peper, M.J., Brans, S.R.G., Cahn, H., Kahn, W.R.S., 2006. Changing your sex changes your brain: influences of testosterone and estrogen on adult human brain structure. Eur. J. Endocrinol. 155, S107–S114.
Hussain, R., Ghoumari, A.M., Bielecki, B., Steibel, J., Boehm, N., Liere, P., Ghandour, M.S., 2013. The neural androgen receptor: a therapeutic target for myelin repair in chronic demyelination. Brain 136 (Pt 1), 132–146, http://dx.doi.org/10.1093/brain/aws284.
Huster, R.J., Westerhausen, R., Herrmann, C.S., 2011. Sex differences in cognitive control are associated with midcingulate and callosal morphology. Brain Struct. Funct. 215 (3–4), 225–235, http://dx.doi.org/10.1007/s00429-010-0289-2.
Hutchinson, S., Lee, L.H., Gaab, N., Schlaug, G., 2003. Cerebellar volume of musicians. Cereb. Cortex 13 (9), 943–949.
Im, K., Lee, J.M., Lee, J., Shin, Y.W., Kim, I.Y., Kwon, J.S., Kim, S.I., 2006. Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. Neuroimage 31 (1), 31–38, http://dx.doi.org/10.1016/j.neuroimage.2005.11.042.
Ingalhalikar, M., Smith, A., Parker, D., Satterthwaite, T.D., Elliott, M.A., Ruparel, K., Verma, R., 2014. Sex differences in the structural connectome of the human brain. Proc. Natl. Acad. Sci. U. S. A. 111 (2), 823–828, http://dx.doi.org/10.1073/pnas.1316909110.
Junger, J., Habel, U., Bröhr, S., Neulen, J., Neuschaefer-Rube, C., Birkholz, P., Pauly, K., 2014. More than just two sexes: the neural correlates of voice gender perception in gender dysphoria. PLOS ONE 9 (11), e111672, http://dx.doi.org/10.1371/journal.pone.0111672.
Kaltiala-Heino, R., Sumia, M., Työläjärvi, M., Lindberg, N., 2015. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. Child Adolesc. Psychiatry Ment. Health 9, 9, http://dx.doi.org/10.1186/s13034-015-0042-y.
Karama, S., Lecours, A.R., Leroux, J.M., Bourgouin, P., Beaudoin, G., Joubert, S., Beauregard, M., 2002. Areas of brain activation in males and females during viewing of erotic film excerpts. Hum. Brain Mapp. 16 (1), 1–13.
Karnath, H.O., Baier, B., Nägele, T., 2005. Awareness of the functioning of one's own limbs mediated by the insular cortex? J. Neurosci. 25 (31), 7134–7138, http://dx.doi.org/10.1523/JNEUROSCI.1590-05.2005.
Khandelwal, A., Agarwal, A., Jiloha, R.C., 2010. A 47 XXY female with gender identity disorder. Arch. Sex. Behav. 39 (5), 1021–1023, http://dx.doi.org/10.1007/s10508-010-9628-x.
Kraemer, B., Noll, T., Delsignore, A., Milos, G., Schnyder, U., Hepp, U., 2009. Finger length ratio (2D:4D) in adults with gender identity disorder. Arch. Sex. Behav. 38 (3), 359–363, http://dx.doi.org/10.1007/s10508-007-9262-4.
Kranz, G.S., Hahn, A., Baldinger, P., Haeusler, D., Philippe, C., Kaufmann, U., Lanzenberger, R., 2014a. Cerebral serotonin transporter asymmetry in females, males and male-to-female transsexuals measured by PET in vivo. Brain Struct. Funct. 219 (1), 171–183, http://dx.doi.org/10.1007/s00429-012-0492-4.
Kranz, G.S., Hahn, A., Kaufmann, U., Küblböck, M., Hummer, A., Ganger, S., Lanzenberger, R., 2014b. White matter microstructure in transsexuals and controls investigated by diffusion tensor imaging. J. Neurosci. 34 (46), 15466–15475, http://dx.doi.org/10.1523/JNEUROSCI.2488-14.2014.
Kruijver, F.P., Zhou, J.N., Pool, C.W., Hofman, M.A., Gooren, L.J., Swaab, D.F., 2000. Male-to-female transsexuals have female neuron numbers in a limbic nucleus. J. Clin. Endocrinol. Metab. 85 (5), 2034–2041, http://dx.doi.org/10.1210/jcem.85.5.6564.
Ku, H.L., Lin, C.S., Chao, H.T., Tu, P.C., Li, C.T., Cheng, C.M., Hsieh, J.C., 2013. Brain signature characterizing the body–brain–mind axis of transsexuals. PLOS ONE 8 (7), e70808, http://dx.doi.org/10.1371/journal.pone.0070808.

Kudielka, B.M., Kirschbaum, C., 2005. Sex differences in HPA axis responses to stress: a review. Biol. Psychol. 69 (1), 113–132, http://dx.doi.org/10.1016/j.biopsycho.2004.11.009.
Landén, M., Wålinder, J., Lundström, B., 1998. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. Acta Psychiatr. Scand. 97 (3), 189–194.
Lawrence, A.A., 2010. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. Arch. Sex. Behav. 39 (2), 514–545, http://dx.doi.org/10.1007/s10508-009-9594-3.
Lin, C.S., Ku, H.L., Chao, H.T., Tu, P.C., Li, C.T., Cheng, C.M., Hsieh, J.C., 2014. Neural network of body representation differs between transsexuals and cissexuals. PLOS ONE 9 (1), e85914, http://dx.doi.org/10.1371/journal.pone.0085914.
Luders, E., Narr, K.L., Thompson, P.M., Rex, D.E., Woods, R.P., Deluca, H., Toga, A.W., 2006. Gender effects on cortical thickness and the influence of scaling. Hum. Brain Mapp. 27 (4), 314–324, http://dx.doi.org/10.1002/hbm.20187.
Luders, E., Sánchez, F.J., Gaser, C., Toga, A.W., Narr, K.L., Hamilton, L.S., Vilain, E., 2009. Regional gray matter variation in male-to-female transsexualism. Neuroimage 46 (4), 904–907, http://dx.doi.org/10.1016/j.neuroimage.2009.03.048.
Luders, E., Sánchez, F.J., Tosun, D., Shattuck, D.W., Gaser, C., Vilain, E., Toga, A.W., 2012. Increased cortical thickness in male-to-female transsexualism. J. Behav. Brain Sci. 2 (3), 357–362, http://dx.doi.org/10.4236/jbbs.2012.23040.
Lüders, E., Steinmetz, H., Jäncke, L., 2002. Brain size and grey matter volume in the healthy human brain. Neuroreport 13 (17), 2371–2374, http://dx.doi.org/10.1097/01.wnr.0000049603.85580.da.
Maki, P.M., Resnick, S.M., 2001. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. Neuroimage 14 (4), 789–801, http://dx.doi.org/10.1006/nimg.2001.0887.
Makris, N., Kennedy, D.N., McInerney, S., Sorensen, A.G., Wang, R., Caviness, V.S., Pandya, D.N., 2005. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb. Cortex 15 (6), 854–869, http://dx.doi.org/10.1093/cercor/bhh186.
Meyer-Bahlburg, H.F., Dolezal, C., Baker, S.W., Carlson, A.D., Obeid, J.S., New, M.I., 2004. Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. Arch. Sex. Behav. 33 (2), 97–104.
Meyer-Bahlburg, H.F., Dolezal, C., Baker, S.W., Ehrhardt, A.A., New, M.I., 2006. Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. Arch. Sex. Behav. 35 (6), 667–684, http://dx.doi.org/10.1007/s10508-006-9068-9.
Miles, C., Green, R., Sanders, G., Hines, M., 1998. Estrogen and memory in a transsexual population. Horm. Behav. 34 (2), 199–208, http://dx.doi.org/10.1006/hbeh.1998.1478.
Mitchell, M., Howarth, C., 2009. Trans Research Review. Equality and Human Rights Commission, Manchester.
Moser, C., 2010. Blanchard's autogynephilia theory: a critique. J. Homosex. 57 (6), 790–809, http://dx.doi.org/10.1080/00918369.2010.486241.
Moussa, M.N., Steen, M.R., Laurienti, P.J., Hayasaka, S., 2012. Consistency of network modules in resting-state FMRI connectome data. PLOS ONE 7 (8), e44428, http://dx.doi.org/10.1371/journal.pone.0044428.
Müller, R.A., Shih, P., Keehn, B., Deyoe, J.R., Leyden, K.M., Shukla, D.K., 2011. Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. Cereb. Cortex 21 (10), 2233–2243, http://dx.doi.org/10.1093/cercor/bhq296.
Nawata, H., Ogomori, K., Tanaka, M., Nishimura, R., Urashima, H., Yano, R., Kuwabara, Y., 2010. Regional cerebral blood flow changes in female to male gender identity disorder. Psychiatry Clin. Neurosci. 64 (2), 157–161, http://dx.doi.org/10.1111/j.1440-1819.2009.02059.x.
Neufang, S., Specht, K., Hausmann, M., Güntürkün, O., Herpertz-Dahlmann, B., Fink, G.R., Konrad, K., 2009. Sex differences and the impact of steroid hormones on the developing human brain. Cereb. Cortex 19 (2), 464–473, http://dx.doi.org/10.1093/cercor/bhn100.
Nguyen, T.V., McCracken, J., Ducharme, S., Botteron, K.N., Mahabir, M., Johnson, W., Group, B.D.C., 2013. Testosterone-related cortical maturation across childhood and adolescence. Cereb. Cortex 23 (6), 1424–1432, http://dx.doi.org/10.1093/cercor/bhs125.
Nieder, T.O., Herff, M., Cerwenka, S., Preuss, W.F., Cohen-Kettenis, P.T., De Cuypere, G., Richter-Appelt, H., 2011. Age of onset and sexual orientation in transsexual males and females. J. Sex. Med. 8 (3), 783–791, http://dx.doi.org/10.1111/j.1743-6109.2010.02142.x.
Nielsen, J.A., Zielinski, B.A., Ferguson, M.A., Lainhart, J.E., Anderson, J.S., 2013. An evaluation of the left-brain vs. right-brain hypothesis with resting state functional connectivity magnetic resonance imaging. PLOS ONE 8 (8), e71275, http://dx.doi.org/10.1371/journal.pone.0071275.
Nopoulos, P., Flaum, M., O'Leary, D., Andreasen, N.C., 2000. Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. Psychiatry Res. 98 (1), 1–13.
Oh, S.K., Kim, G.W., Yang, J.C., Kim, S.K., Kang, H.K., Jeong, G.W., 2012. Brain activation in response to visually evoked sexual arousal in male-to-female transsexuals: 3.0 tesla functional magnetic resonance imaging. Korean J. Radiol. 13 (3), 257–264, http://dx.doi.org/10.3348/kjr.2012.13.3.257.
Olsson, S.E., Möller, A.R., 2003. On the incidence and sex ratio of transsexualism in Sweden, 1972–2002. Arch. Sex. Behav. 32 (4), 381–386.
Peper, J.S., van den Heuvel, M.P., Mandl, R.C., Hulshoff Pol, H.E., van Honk, J., 2011. Sex steroids and connectivity in the human brain: a review of neuroimaging studies. Psychoneuroendocrinology 36 (8), 1101–1113, http://dx.doi.org/10.1016/j.psyneuen.2011.05.004.
Pereira, M.G., de Oliveira, L., Erthal, F.S., Joffily, M., Mocaiber, I.F., Volchan, E., Pessoa, L., 2010. Emotion affects action: midcingulate cortex as a pivotal node of interaction between negative emotion and motor signals. Cogn. Affect. Behav. Neurosci. 10 (1), 94–106, http://dx.doi.org/10.3758/CABN.10.1.94.
Petersen, N., Kilpatrick, L.A., Goharzad, A., Cahill, L., 2014. Oral contraceptive pill use and menstrual cycle phase are associated with altered resting state functional connectivity. Neuroimage 90, 24–32, http://dx.doi.org/10.1016/j.neuroimage.2013.12.016.
Ponseti, J., Siebner, H.R., Klöppel, S., Wolff, S., Granert, O., Jansen, O., Bosinski, H.A., 2007. Homosexual women have less grey matter in perirhinal cortex than heterosexual women. PLoS ONE 2 (8), e762, http://dx.doi.org/10.1371/journal.pone.0000762.
Raichle, M.E., 2009. A paradigm shift in functional brain imaging. J. Neurosci. 29 (41), 12729–12734, http://dx.doi.org/10.1523/JNEUROSCI.4366-09.2009.
Rametti, G., Carrillo, B., Gómez-Gil, E., Junque, C., Segovia, S., Gomez, Á., Guillamon, A., 2011a. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. J. Psychiatr. Res. 45 (2), 199–204, http://dx.doi.org/10.1016/j.jpsychires.2010.05.006.
Rametti, G., Carrillo, B., Gómez-Gil, E., Junque, C., Zubiarre-Elorza, L., Segovia, S., Guillamon, A., 2011b. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. J. Psychiatr. Res. 45 (7), 949–954, http://dx.doi.org/10.1016/j.jpsychires.2010.11.007.
Rametti, G., Carrillo, B., Gómez-Gil, E., Junque, C., Zubiaurre-Elorza, L., Segovia, S., Guillamon, A., 2012. Effects of androgenization on the white matter microstructure of female-to-male transsexuals. A diffusion tensor imaging study. Psychoneuroendocrinology 37 (8), 1261–1269, http://dx.doi.org/10.1016/j.psyneuen.2011.12.019.
Raz, N., Gunning-Dixon, F., Head, D., Williamson, A., Acker, J.D., 2001. Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. Am. J. Neuroradiol. 22 (6), 1161–1167.
Redouté, J., Stoléru, S., Grégoire, M.C., Costes, N., Cinotti, L., Lavenne, F., Pujol, J.F., 2000. Brain processing of visual sexual stimuli in human males. Hum. Brain Mapp. 11 (3), 162–177.
Rijpkema, M., Everaerd, D., van der Pol, C., Franke, B., Tendolkar, I., Fernández, G., 2012. Normal sexual dimorphism in the human basal ganglia. Hum. Brain Mapp. 33 (5), 1246–1252, http://dx.doi.org/10.1002/hbm.21283.
Rizos, E.N., Papathanasiou, M., Michalopoulou, P.G., Mazioti, A., Douzenis, A., Kastania, A., Lykouras, L., 2011. Association of serum BDNF levels with hippocampal volumes in first psychotic episode drug-naive schizophrenic patients. Schizophr. Res. 129 (2–3), 201–204, http://dx.doi.org/10.1016/j.schres.2011.03.011.
Ruigrok, A.N., Salimi-Khorshidi, G., Lai, M.C., Baron-Cohen, S., Lombardo, M.V., Tait, R.J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev. 39, 34–50, http://dx.doi.org/10.1016/j.neubiorev.2013.12.004.
Rushton, J.P., Ankney, C.D., 2009. Whole brain size and general mental ability: a review. Int J. Neurosci. 119 (5), 691–731, http://dx.doi.org/10.1080/00207450802325843.
Santarnecchi, E., Vatti, G., Déttore, D., Rossi, A., 2012. Intrinsic cerebral connectivity analysis in an untreated female-to-male transsexual subject: a first attempt using resting-state fMRI. Neuroendocrinology 96 (3), 188–193, http://dx.doi.org/10.1159/000342001.
Savic, I., Arver, S., 2011. Sex dimorphism of the brain in male-to-female transsexuals. Cereb. Cortex 21 (11), 2525–2533, http://dx.doi.org/10.1093/cercor/bhr032.
Savic, I., Berglund, H., Gulyas, B., Roland, P., 2001. Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. Neuron 31 (4), 661–668.
Savic, I., Lindström, P., 2008. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. Proc. Natl. Acad. Sci. U. S. A. 105 (27), 9403–9408, http://dx.doi.org/10.1073/pnas.0801566105.
Schagen, S.E., Delemarre-van de Waal, H.A., Blanchard, R., Cohen-Kettenis, P.T., 2012. Sibling sex ratio and birth order in early-onset gender dysphoric adolescents. Arch. Sex. Behav. 41 (3), 541–549, http://dx.doi.org/10.1007/s10508-011-9777-6.
Schmahmann, J.D., Sherman, J.C., 1998. The cerebellar cognitive affective syndrome. Brain 121 (Pt. 4), 561–579.
Schneider, H.J., Pickel, J., Stalla, G.K., 2006. Typical female 2nd–4th finger length (2D:4D) ratios in male-to-female transsexuals-possible implications for prenatal androgen exposure. Psychoneuroendocrinology 31 (2), 265–269, http://dx.doi.org/10.1016/j.psyneuen.2005.07.005.
Schöning, S., Engelien, A., Bauer, C., Kugel, H., Kersting, A., Roestel, C., Konrad, C., 2010. Neuroimaging differences in spatial cognition between men and male-to-female transsexuals before and during hormone therapy. J. Sex. Med. 7 (5), 1858–1867, http://dx.doi.org/10.1111/j.1743-6109.2009.01484.x.
Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12 (3), 154–167, http://dx.doi.org/10.1038/nrn2994.
Silverman, I., Choi, J., Peters, M., 2007. The hunter–gatherer theory of sex differences in spatial abilities: data from 40 countries. Arch. Sex. Behav. 36 (2), 261–268, http://dx.doi.org/10.1007/s10508-006-9168-6.

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 (12), e83947, http://dx.doi.org/10.1371/journal.pone.0083947.

Slabbekoorn, D., van Goozen, S.H., Megens, J., Gooren, L.J., Cohen-Kettenis, P.T., 1999. Activating effects of cross-sex hormones on cognitive functioning: a study of short-term and long-term hormone effects in transsexuals. Psychoneuroendocrinology 24 (4), 423–447.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106 (31), 13040–13045, http://dx.doi.org/10.1073/pnas.0905267106.

Sommer, I.E., Cohen-Kettenis, P.T., van Raalten, T., Vd Veer, A.J., Ramsey, L.E., Gooren, L.J., Ramsey, N.F., 2008. Effects of cross-sex hormones on cerebral activation during language and mental rotation: an fMRI study in transsexuals. Eur. Neuropsychopharmacol. 18 (3), 215–221, http://dx.doi.org/10.1016/j.euroneuro.2007.10.002.

Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., Toga, A.W., 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb. Cortex 17 (7), 1550–1560, http://dx.doi.org/10.1093/cercor/bhl066.

Stoléru, S., Fonteille, V., Cornélis, C., Joyal, C., Moulier, V., 2012. Functional neuroimaging studies of sexual arousal and orgasm in healthy men and women: a review and meta-analysis. Neurosci. Biobehav. Rev. 36 (6), 1481–1509, http://dx.doi.org/10.1016/j.neubiorev.2012.03.006.

Swaab, D.F., 2007. Sexual differentiation of the brain and behavior. Best Pract. Res. Clin. Endocrinol. Metab. 21 (3), 431–444, http://dx.doi.org/10.1016/j.beem.2007.04.003.

Szabó, C.A., Lancaster, J.L., Xiong, J., Cook, C., Fox, P., 2003. MR imaging volumetry of subcortical structures and cerebellar hemispheres in normal persons. Am. J. Neuroradiol. 24 (4), 644–647.

Thysen, B., Elliott, W.H., Katzman, P.A., 1968. Identification of estra-1,3,5(10),16-tetraen-3-ol (estratetraenol) from the urine of pregnant women (1). Steroids 11 (1), 73–87.

Tian, L., Wang, J., Yan, C., He, Y., 2011. Hemisphere- and gender-related differences in small-world brain networks: a resting-state functional MRI study. Neuroimage 54 (1), 191–202, http://dx.doi.org/10.1016/j.neuroimage.2010.07.066.

Tomasi, D., Volkow, N.D., 2012. Laterality patterns of brain functional connectivity: gender effects. Cereb. Cortex 22 (6), 1455–1462, http://dx.doi.org/10.1093/cercor/bhr230.

Ujike, H., Otani, K., Nakatsuka, M., Ishii, K., Sasaki, A., Oishi, T., Sato, T., Okahisa, Y., Matsumoto, Y., Namba, Y., Kimata, Y., Kuroda, S., 2009. Association study of gender identity disorder and sex hormone-related genes. Prog. Neuropsychopharmacol. Biol. Psychiatry 33 (7), 1241–1244, http://dx.doi.org/10.1016/j.pnpbp.2009.07.008.

van den Heuvel, M.P., Hulshoff Pol, H.E., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur. Neuropsychopharmacol. 20 (8), 519–534, http://dx.doi.org/10.1016/j.euroneuro.2010.03.008.

Van Goozen, S.H., Cohen-Kettenis, P.T., Gooren, L.J., Frijda, N.H., Van de Poll, N.E., 1995. Gender differences in behaviour: activating effects of cross-sex hormones. Psychoneuroendocrinology 20 (4), 343–363.

van Goozen, S.H., Slabbekoorn, D., Gooren, L.J., Sanders, G., Cohen-Kettenis, P.T., 2002. Organizing and activating effects of sex hormones in homosexual transsexuals. Behav. Neurosci. 116 (6), 982–988.

Veale, J., Clarke, F.D., Lomax, E.T.C., 2009. Biological and psychosocial correlates of adult gender-variant identities: a review. Pers. Individ. Differ. 48 (4), 357–366.

Wisniewski, A.B., 1998. Sexually-dimorphic patterns of cortical asymmetry, and the role for sex steroid hormones in determining cortical patterns of lateralization. Psychoneuroendocrinology 23 (5), 519–547.

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. Arch. Sex. Behav. 34 (2), 167–172, http://dx.doi.org/10.1007/s10508-005-1794-x.

Witte, A.V., Savli, M., Holik, A., Kasper, S., Lanzenberger, R., 2010. Regional sex differences in grey matter volume are associated with sex hormones in the young adult human brain. Neuroimage 49 (2), 1205–1212, http://dx.doi.org/10.1016/j.neuroimage.2009.09.046.

World Health Organization, 2014. International Statistical Classification of Diseases and Related Health Problems, 10th ed, Retrieved from: http://apps.who.int/classifications/icd10/browse/2014/en.

Wålinder, J., 1965. Transvestism, definition and evidence in favor of occasional derivation from cerebral dysfunction. Int. J. Neuropsychiatry 1 (6), 567–573.

Yokota, Y., Kawamura, Y., Kameya, Y., 2005. Callosal shapes at the midsagittal plane: MRI differences of normal males, normal females, and GID. Conf. Proc. IEEE Eng. Med. Biol. Soc. 3, 3055–3058, http://dx.doi.org/10.1109/IEMBS.2005.1617119.

Zheng, Z., Cohn, M.J., 2011. Developmental basis of sexually dimorphic digit ratios. Proc. Natl. Acad. Sci. U. S. A. 108 (39), 16289–16294, http://dx.doi.org/10.1073/pnas.1108312108.

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 (6552), 68–70, http://dx.doi.org/10.1038/378068a0.

Zhu, Z., 2007. Gender differences in mathematical problem solving patterns: a review of literature. Int. Educ. J. 8 (2), 187–203.

Zitzmann, M., Weckesser, M., Schober, O., Nieschlag, E., 2001. Changes in cerebral glucose metabolism and visuospatial capability in hypogonadal males under testosterone substitution therapy. Exp. Clin. Endocrinol. Diabetes 109 (5), 302–304, http://dx.doi.org/10.1055/s-2001-16351.

Zubiaurre-Elorza, L., Junque, C., Gómez-Gil, E., Guillamon, A., 2014. Effects of cross-sex hormone treatment on cortical thickness in transsexual individuals. J. Sex. Med. 11 (5), 1248–1261, http://dx.doi.org/10.1111/jsm.12491.

Zubiaurre-Elorza, L., Junque, C., Gómez-Gil, E., Segovia, S., Carrillo, B., Rametti, G., Guillamon, A., 2013. Cortical thickness in untreated transsexuals. Cereb. Cortex 23 (12), 2855–2862, http://dx.doi.org/10.1093/cercor/bhs267.