ORIGINAL RESEARCH—INTERSEX AND GENDER IDENTITY DISORDERS

Specific Cerebral Activation due to Visual Erotic Stimuli in Male-to-Female Transsexuals Compared with Male and Female Controls: An fMRI Study

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ABSTRACT

Introduction. Transsexuals harbor the strong feeling of having been born to the wrong sex. There is a continuing controversial discussion of whether or not transsexualism has a biological representation. Differences between males and females in terms of functional imaging during erotic stimuli have been previously described, revealing gender-specific results.

Aim. Therefore, we postulated that male-to-female (MTF) transsexuals may show specific cerebral activation differing from their biological gender.

Main Outcome Measure. Cerebral activation patterns during viewing of erotic film excerpts in functional magnetic resonance imaging (fMRI).

Methods. Twelve male and 12 female heterosexual volunteers and 12 MTF transsexuals before any treatment viewed erotic film excerpts during fMRI. Additionally, subjective rating of sexual arousal was assessed. Statistics were performed using the Statistical Parametric Mapping software.

Results. Significantly enhanced activation for men compared with women was revealed in brain areas involved in erotic processing, i.e., the thalamus, the amygdala, and the orbitofrontal and insular cortex, whereas no specific activation for women was found. When comparing MTF transsexuals with male volunteers, activation patterns similar to female volunteers being compared with male volunteers were revealed. Sexual arousal was assessed using standard rating scales and did not differ significantly for the three groups.

Conclusions. We revealed a cerebral activation pattern in MTF transsexuals compared with male controls similar to female controls compared with male controls during viewing of erotic stimuli, indicating a tendency of female-like cerebral processing in transsexualism. **Gizewski ER, Krause E, Schlamann M, Happich F, Ladd ME, Forsting M, and Senf W. 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 2009;6:440–448.**

Key Words. fMRI; Transsexual; Emotional

Introduction

Transsexuals experience themselves as being of the opposite sex, despite having the biological characteristics of one sex [1]. This circumstance is an immense and dominating problem in the life of transsexuals. The technical possibility of surgical sex change has opened up a debate concerning the legitimacy and utility of carrying out such an intervention. Diagnostic, psychological, medical, and ethical arguments have been brought forth, both for and against. Regardless, surgical anatomical transformation has become an increasingly common practice, as the frequency of serious

gender identity disorders has steadily risen [2]. The increasing incidence is probably due to a better acceptance of transsexuals in the population, but influences of hormonal and environmental substances have also been discussed in the literature [3].

The origins of transsexualism are still unclear [1]. Certain prenatal factors seem to be associated with transsexualism, but it is still unclear to what extent cross-gender identity is due to the pre- and perinatal organizing effects of sex hormones on the brain [3–5]. Empirical evidence for a relationship between prenatal hormonal influences and certain aspects of gender-typical cognitive functions, e.g., in visuospatial tasks, has been demonstrated in pre- and postpubertal clinical samples. The results of various cognitive and emotional tests showed that gender differences were pronounced, and that the two transsexual groups (male-to-female [MTF] and female-to-male) occupied a position in between the two heterosexual gender groups (male and female), thus revealing a pattern of cognitive performance for the transsexuals departing from their biological sex [6]. A previous study has also demonstrated that 3 months of cross-sex hormone treatment clearly influenced cognitive functioning in transsexuals [7].

Swaab et al. found that genetic factors and prenatal hormone levels contributed to the determination of sexual orientation, such as heterosexuality, bisexuality, or homosexuality; postnatal social factors, on the other hand, did not [5]. Animal studies have revealed that prenatal exposure to the anticonvulsant drugs phenobarbital and phenytoin alters steroid hormone levels, which consequently leads to disturbed sexual differentiation, and there are first experiences regarding hormone influences in human groups [8].

First anatomic brain differences between transsexuals and nontranssexuals were described by Kruijver and Zhou [9,10]. Therefore, it seems evident that gender-specific cortical activation patterns could be of great scientific and clinical interest and might reveal further differences or similarities in transsexuals compared with male or female volunteers, as well as being a possible ancillary tool for clinical investigation, especially preceding gender-change surgery.

Gender differences with respect to erotic stimuli have been the subject of investigation for many years. Besides social factors that influence gender-specific behavior, genetic, and hormonal influences have also been discussed [11,12]. Cortical activation patterns of sexual arousal were first investigated by Stoleru et al. using H_2O positron emission tomography (PET) [13]. They utilized erotic film excerpts in male subjects, which revealed activations of the right orbitofrontal cortex and anterior cingulate cortex, and hypothalamus for the autonomic portion, as well as Brodmann areas 9 and 32 for the emotional aspect of the task. Another PET study found that sexual arousal was mainly associated with activation of bilateral, predominantly right, inferoposterior extrastriate cortices of the right inferolateral prefrontal cortex, and of the tegmentum in heterosexual men [14]. Redoute et al. described activations in the anterior cingulate gyrus, orbitofrontal cortex, in the striatum, and in the posterior hypothalamus [15]. The number of imaging studies has increased in recent years, and these methods have become an important tool in sexual research [16]. Gender differences for the neural correlates of sexual arousal have also been discussed in a few functional magnetic resonance imaging (fMRI) studies examining brain response to sexual stimulation in heterosexual males and females. These studies identified activated brain regions and revealed gender differences in brain response to sexual stimulation and arousal: men compared with women revealed a higher level of brain activation and a superior activation in the amygdala and hypothalamus, whereas women did not reveal any specific activation [17,18].

However, transsexual orientation has not been the focus of neural functional imaging studies to date. In this study, we used fMRI to explicitly examine the influence of transsexual orientation on brain response to visual sexual stimuli in MTF transsexuals. We postulated that MTF transsexuals before hormonal therapy may show specific cerebral activation, differing from their biological gender.

Materials and Methods

Subjects

Twelve male (mean age 29 years, range 22–53) and 12 female (mean age 29 years, range 17–55) healthy heterosexual volunteers as well as 12 MTF transsexuals (mean age 36 years, range 20–55) were studied. The MTF were non-autogynephilic. All subjects were right-handed. The female volunteers were scanned outside the menstrual phase. No subject revealed any brain tissue abnormality on structural MRI, and no subject had a history of neurological or psychiatric disease.

Only MTF subjects without any therapy were chosen for this study and were recruited from the outpatient Clinic of Psychosomatic Medicine (University Hospital Essen). MTF subjects were biological males living in a female gender role. None of the subjects had received any form of hormonal or surgical therapy at the time of this study. The volunteers did not have any abnormalities in blood hormone levels. Prior to inclusion, the individual transsexual orientation of each subject was assessed using the German Standards for the Treatment and Diagnostic Assessment of Transsexuals. These criteria are conformant with those described in the International Classification of Disease [19]. Diagnostic measures included case history focusing on gender identity, psychosexual development, and current life situation; physical examination including urological and endocrinological status; and clinical psychiatric evaluation. Ten of the transsexuals were heterosexual in respect to their biological gender, two were attracted to men.

Informed written consent was obtained prior to participation. The study was accepted by the local ethics committee.

Experimental Design

All MR images were acquired using a 1.5 Tesla scanner (Sonata, Siemens, Erlangen, Germany) with a standard head coil. A 3D FLASH (spoiled gradient echo) sequence (TR 10 ms, TE 4.5 ms, flip angle 30°, FOV 240 mm, matrix 512×512, slice thickness 1.5 mm) was acquired for individual co-registration of functional and structural images. Blood-oxygenation-level-dependent contrast fMRI images were acquired using an echo-planar technique (TR 3100 ms, TE 50 ms, flip angle 90°, FOV 240 mm, matrix 64×64) with 34 transverse slices with a thickness of 3 mm and 0.3 mm slice gap. Three "dummy" scans were eliminated prior to data analysis to account for T1 relaxation effects.

Each subject underwent one functional imaging session. The stimuli were presented in a block design and alternated with resting periods every 31 seconds. Each run was divided into seven epochs.

During stimulation, subjects were asked to lie relaxed inside the scanner and to try to focus on the presented stimuli. As sexually arousing stimuli, video film excerpts of heterosexual couples engaged in explicit sexual activity were used, whereas the sexually neutral stimuli were videos showing couples during routine nonsexual activity. This material had been evaluated in a previous study [18]. All stimuli were presented using a screen inside the scanner room and video projection from outside. A mirror was fixed to the head coil to place the screen in the subject's field of view.

At the end of scanning, the subject was asked to rate her or his level of sexual arousal on a visual analog scale ranging from 0 to 10 (with 0 = no sexual arousal and 10 = maximal sexual arousal compared with former experiences). The volunteers were asked to include both physical and psychological sexual arousal in their rating.

Data Analysis

For data analysis, Statistical Parametric Mapping (SPM) 99 software (Wellcome Department of Cognitive Neurology, London, UK) was used. Prior to statistical analysis, images were realigned utilizing sinc interpolation and normalized to the standard stereotactic space corresponding to the template from the Montreal Neurological Institute (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Bilinear interpolation was applied for normalization. The images were smoothed with an isotropic Gaussian kernel of 9 mm. A voxel-by-voxel comparison according to the general linear model was used to calculate differences in activation between the active and resting conditions. The model consisted of a boxcar function convolved with the hemodynamic response function (HRF) and the corresponding temporal derivative. High-pass filtering with a cutoff period of 118 seconds and low-pass filtering with the HRF were applied.

For group analysis, single-subject contrast images were entered into a random effects model. Significant signal changes for each contrast were assessed by means of a *t*-statistics test on a voxel-by-voxel basis [20]. The resulting set of voxel values for each contrast constituted an SPM of the *t*-statistic. The threshold was set to $P < 0.05$ (corrected for multiple comparisons).

For analysis of specific activation during each task, the resulting individual contrasts were carried over to the second level analysis and entered into a two-sample *t*-test. A random multiple regression analysis was performed using the subjective arousal as a covariate.

Thresholds for Two-Sample t-Test Analysis

The threshold of the *t*-statistic was additionally set to $P < 0.001$ uncorrected for multiple comparisons assuming a priori regions of interest (ROIs) as described in the following. For sexual arousal, acti-

vation of the following brain regions has been reported in men and women: thalamus; hypothalamus; anterior cingulate and orbitofrontal cortex; amygdala; hippocampal formation [13,21]. Sex differences have been revealed in the hypothalamus and thalamus, the amygdala, and the cingulate and orbitofrontal gyrus [17,18,22]. Gender differences in the perception of variant facial expressions exhibiting emotions have been revealed within the amygdala [23]. A Mann–Whitney *U*-test was used for group tests of the rated sexual arousal.

Results

Using erotic film excerpts as stimuli in contrast to emotionally neutral film excerpts, we reproduced the known activated areas in the occipitotemporal cortex, anterior cingulate cortex, medial prefrontal cortex, pre- and postcentral cortex, hypothalamus, thalamus, and partly bilateral amygdala in all three groups using a one-sample *t*-test for each group (male, female, and MTF; Figure 1A–C). Apart from these similarities, a two-sample *t*-test

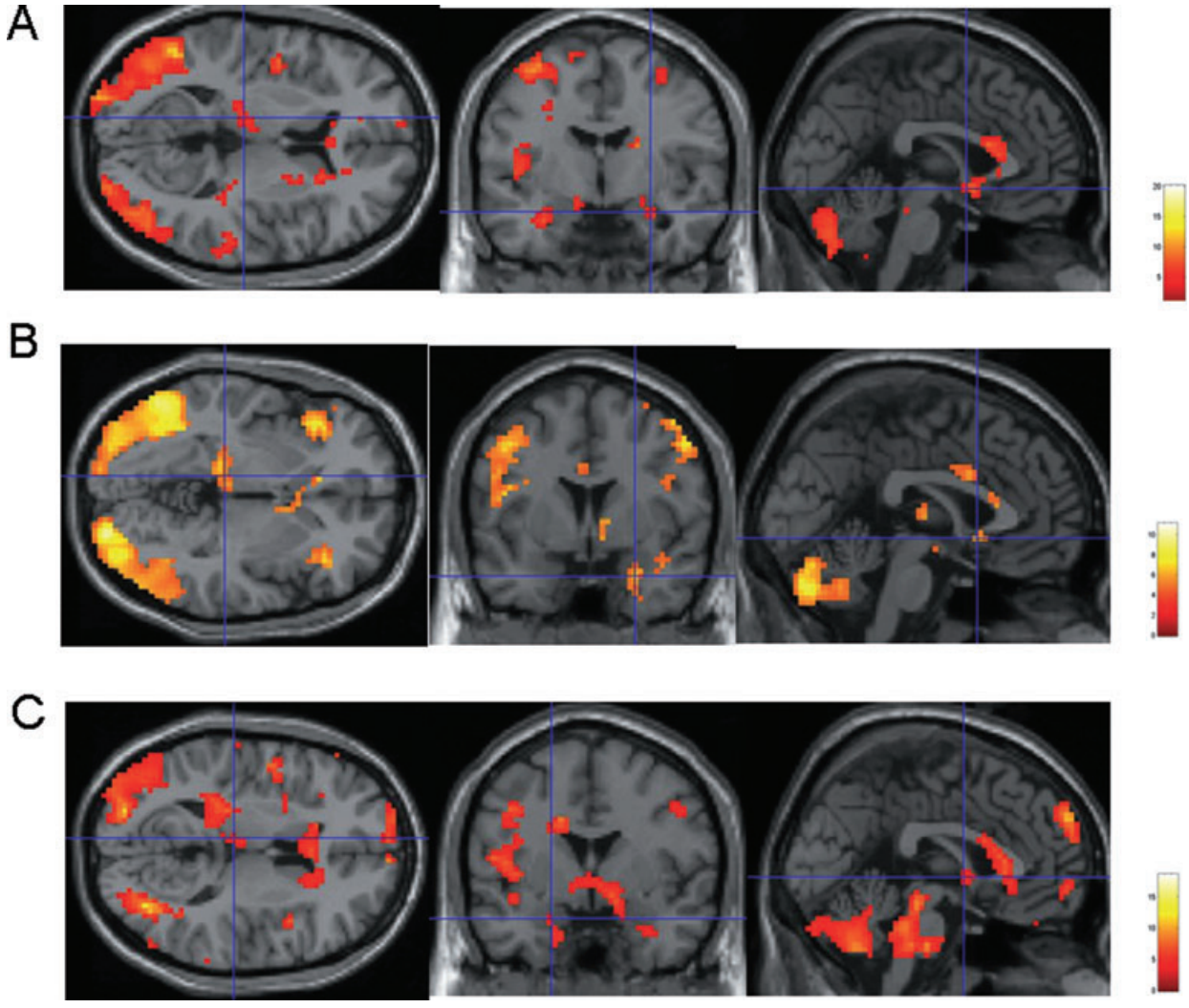

Figure 1 Specific cerebral activation patterns due to viewing of erotic film excerpts in contrast to emotionally neutral film excerpts. Statistical parametric maps of areas activated in each group analyzed using a one sample *t*-test and superimposed on three 3-D projections of a T1-weighted standard brain (uncorrected $P < 0.001$). (A) Activation in men was revealed in occipitotemporal cortex, anterior cingulate cortex, medial prefrontal cortex, pre- and postcentral cortex, thalamus, hypothalamus, and bilateral amygdala. (B) Activation in women was revealed in occipitotemporal cortex, anterior cingulate cortex, medial prefrontal cortex, pre- and postcentral cortex, thalamus, hypothalamus, and bilateral amygdala. (C) Activation in male-to-female transsexuals revealed activation of the same cortical areas as those of the male and female groups.

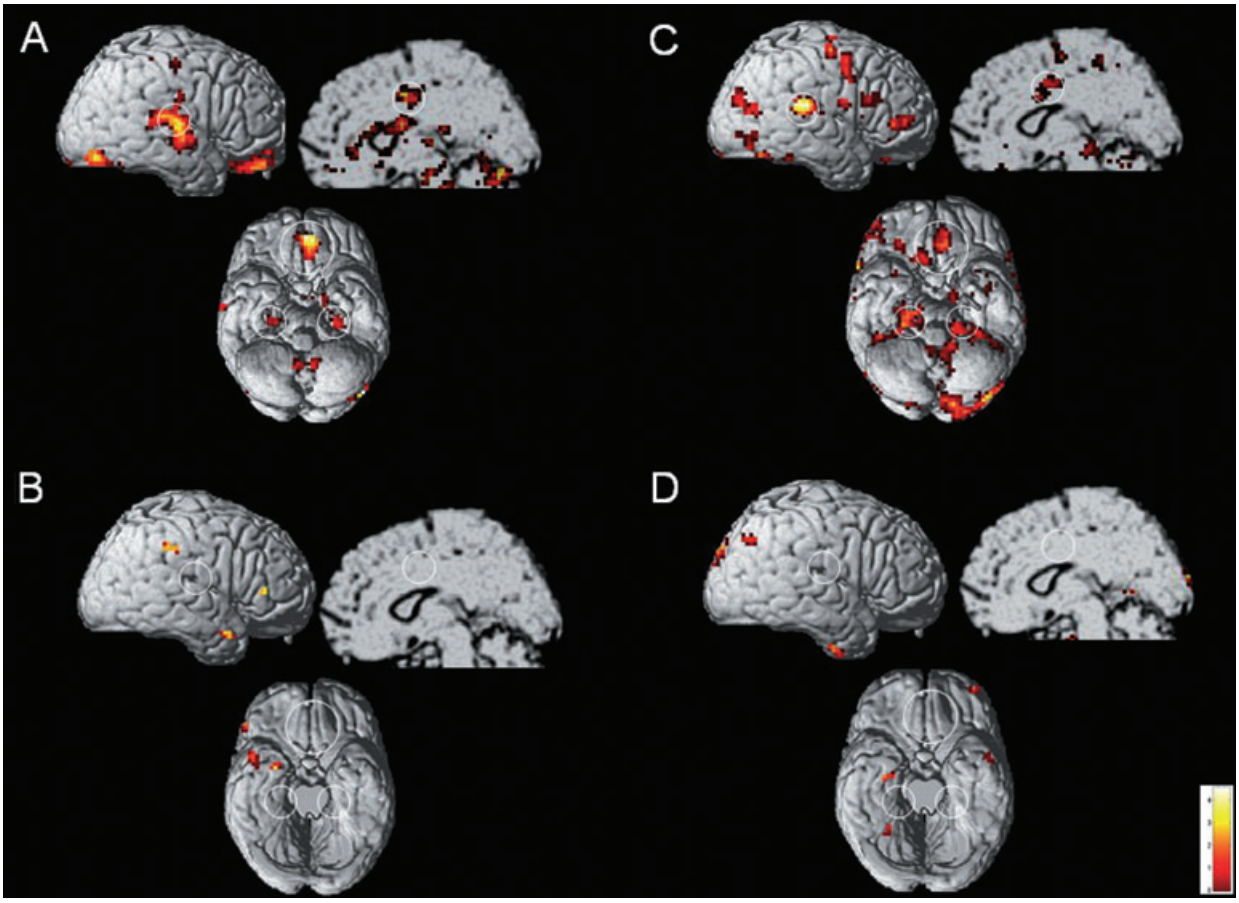

Figure 2 Specific cerebral activation patterns due to viewing erotic film excerpts. Statistical parametric maps of areas more prominently activated in each group analyzed using a two-sample *t*-test and superimposed on three 3-D projections of a T1-weighted standard brain (uncorrected $P < 0.001$, white circles indicate a priori regions of interest [ROI]). (A) Specific activation in men compared with women revealed greater activation of the thalamus, the amygdala, and the orbitofrontal and insular cortex. (B) Activation in women compared with men revealed no specific activation in the a priori ROIs. (C) Specific activation in men compared with male-to-female (MTF) transsexuals revealed activation of the same cortical areas than those shown in (A). (D) Activation in MTF transsexuals compared with men revealed no specific activation in the a priori ROIs.

revealed several differences in cerebral activation due to the stimulus.

A significantly enhanced activation for men compared with women was found in the left thalamus, the bilateral amygdala, and the orbitofrontal and insular cortex during erotic stimuli compared with nonerotic stimuli (Figure 2A). Women compared with men revealed an enhanced activation of the right medial and superior temporal cortex (Figure 2B); however, these activations were not significant (uncorrected $P < 0.001$), and the temporal cortex was not in a predefined ROI.

A significantly elevated activation for men compared with MTF was found in the left thalamus, the bilateral amygdala, and the orbitofrontal and insular cortex during viewing of the erotic stimuli (Figure 2C). This activation pattern was similar to that found in the male to female comparison. MTF revealed a higher activation in the medial temporal and inferior parietal cortex bilateral when compared with male volunteers (Figure 2D), which again was similar to that found in the female to male comparison, with the same restrictions in respect to significance.

No significant higher activation was found comparing MTF with female volunteers. Comparison of female with MTF volunteers also did not reveal any higher activation in the predefined ROIs. Using an uncorrected $P < 0.05$ over the whole brain also did not reveal any significant activation for either comparison. Comparing male with female contrasts and comparing male with MTF contrasts, no significant activations could be revealed. The comparison of the female with male,

Table 1 Gender-specific activated brain regions associated with the visual erotic stimuli

Comparison	Talairach coordinates (mm)	Region (cortex)	Side	*t* value
Male/female	–30; –9; –20	Amygdala	Left	3.9
	27; –21; –18	Amygdala	Right	2.3
	–3; –17; 9	Thalamus	Left	3.4
	–6; 48; –12	Orbitofrontal	Left	3.7
	12; 24; –18	Orbitofrontal	Right	2.0
	–42; –6; 6	Insular	Left	3.8
	45; –7; –1	Insular	Right	2.4
Male/MTF	–26; –3; –18	Amygdala	Left	3.9
	30; –18; –15	Amygdala	Right	3.1
	–6; –21; 6	Thalamus	Left	2.6
	–6; 42; –15	Orbitofrontal	Left	3.9
	12; 27; –21	Orbitofrontal	Right	1.8
	–42; –3; –12	Insular	Left	4.2
	51; –11; 11	Insular	Right	1.1

A summary of gender-specific activated areas as well as the voxel coordinates and *t* values (*z* score) are shown. The task-specific activations were analyzed for men, women, and male-to-female (MTF) transsexuals. Results from the multiple regression analysis using sexual arousal as a covariate are shown. Significance was $P < 0.001$ for uncorrected values at predefined regions of interest. Only statistically reliable areas are included. Talairach coordinates are given in the *x*, *y*, and *z* directions, respectively.

and MTF with male contrast also did not reveal any significant differences.

A summary of significant specific activated areas and t values is given in Table 1.

The sexual arousal rated by the subjects differed between the three groups, although the differences were not statistically significant (Figure 3). Medians of 4.35 ± 2.17 for MTF, 5.52 ± 1.89 for women, and 5.97 ± 1.98 for men were revealed. The individual ratings were entered as a covariate into the statistical model. The activated brain areas mentioned above were revealed using this analysis as there was no significant difference (Table 1).

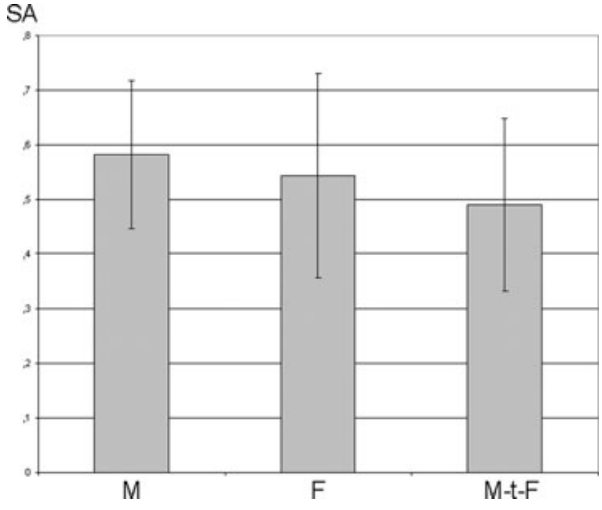

Figure 3 Sexual arousal (SA) of the three groups as revealed by a subjective rating scale from 0 to 10. These ratings were evaluated immediately after imaging. Results show slightly less arousal in female (F) and male-to-female (MTF) volunteers compared with male (M) volunteers, but these differences were not significant.

Discussion

Concerning the point of gender-specific cortical activation during erotic stimulation, our results are generally in line with former fMRI investigations [13,17,18,24]. Contradictory to the results of Karama et al., we could also reveal thalamic activation in female subjects, but nonetheless the male subjects of the control responded with superior strength in this area. The reason that we found thalamic activation in women may be related to the similar sexual arousal in both genders, which is at deviance to the former results [18]. This activation was also revealed in the MTF transsexual group, but again with a reduced strength compared with the male control group.

The more highly activated areas in men belong to the known areas involved in emotional and erotic processes such as the thalamus, the amygdala, and the orbitofrontal and insular cortex. Independent of the controversial discussions concerning gender differences during erotic stimuli, there is some supplementary evidence that fMRI is helpful in revealing differences between male and female brain activation patterns, particularly in limbic structures and herein the amygdala [17,18]. A further study using the stimulus material of film excerpts in a block design revealed superior activation in the group of male volunteers in the cingulate and orbitofrontal cortex [22]. The cingulate gyrus has been reported to be involved in sexual arousal but also in further, mostly emotional, stimuli, e.g., in the processing of painful but also joyful cues [15,25]. An overview of the cingulate areas involved in emotional processing is given by Vogt [25]. The medial part of the cingulate cortex revealed in the group comparisons in this study

seems to be related to a control function and positive emotional processing [25]. Connections have been described to the prefrontal cortex and also to the amygdala and orbitofrontal cortex [18]. Therefore, these areas are involved in attention and emotional processing. Amygdala and orbitofrontal cortex have been described to belong to a circuit that regulates the conscious perception of emotional content [13]. Our results revealed a nearly identical activation pattern in MTF and female volunteers compared with males of the control group, with increased activation in these areas in men of the control group. This indicates a similar cerebral processing of emotional content and sexual arousal in women and in MTF transsexuals, which is dissimilar to the male group. The only specific region for sexual stimulation that was activated in all three groups without any significant differences was the hypothalamus.

A shortcoming of this study is that only a subjective evaluation of sexual arousal in the participants was documented, but physiologic parameters are difficult to investigate within the MR scanner room, and the previous studies addressing gender differences that have been mentioned took the same decision to use subjective rating scales. For men, varying patterns of agreement between subjective estimates of sexual arousal and more objective psychophysiological measures have been reported [26]. For women, a correlation of subjective sexual arousal rating and physiological measurements could be detected in situations with large differences in genital arousal over the trials [27,28]. However, in situations with small differences the ratings were less correlated with the physiological measurement. Therefore, it has to be assumed that the issue with subjective ratings also exists for the MTF group and may influence the cerebral activation. Furthermore, the stimulus material could have had an influence on the cerebral activation patterns in MTF. We used erotic film excerpts with heterosexual couples. As the majority of MTF reported sexual interest in women film excerpts with female homosexual content might have had a higher impact for this group, even given the missing difference in subjective sexual arousal rating.

As mentioned above, the origins of transsexualism are still largely unclear but may be influenced by the prenatal sex steroid milieu [3]. Hormonal influence is also discussed for morphologic gender differences [29,30]. Morphologic characteristics were not assessed in our study, as the group was not large enough. It has been observed that psychotherapy is not helpful in altering a crystallized cross-gender identity, and that transsexuals do not show severe psychopathology [1]. But, as in the variation of gender identity expression in heterosexual men and women, social influences should nevertheless be taken into account in addition to a biological, e.g., hormonal, explanation. Baumeister, for example, found that the female sex drive is more malleable than the male drive in response to sociocultural and situational factors [31]. Therefore, the differing activation patterns in fMRI may be due to neurobiological differences, but these results cannot clarify the underlying mechanisms of the different cerebral activation patterns of MTF transsexuals, as cultural and educational influences are also possible.

Transsexual groups are often described as occupying a position in between the two gender groups, e.g., in aspects of gender-typical cognitive functioning [6]. Therefore, the expectation for the present study could have been to reveal a typical activation pattern for MTF transsexuals somewhere in between the activations of male and female volunteers. However, there are also findings indicating a female-like brain structure in MTF transsexuals and thus first evidence for biological expressions of MTF transsexuals; our results revealed a nearly identical activation pattern in MTF and female volunteers compared with men, supporting the finding of female anatomic structures in MTF transsexuals [9,10].

The functional cortical activation patterns presented in this study revealed a female-like cerebral activation pattern in MTF transsexuals when compared with male volunteers and vice versa during viewing of erotic stimuli in brain areas relevant for erotic and emotional processing. These results indicate that transsexualism has a correlate in brain activation patterns elicited by emotional stimuli, in this case those erotic in nature. Therefore, fMRI using this erotic stimulus form may become a further tool during the assessment and diagnosis of transsexual patients, and may contribute to the complex and difficult decision regarding surgical treatment. The goal would be to further objectify the evaluation process and ultimately avoid cases where patients suffer from postsurgical regret. A shortcoming of fMRI for clinical use, however, is its limited ability to do comparison analysis with single subjects. Furthermore, these results, together with anatomic differences described in other studies, support the biological theory of transsexualism [10]. However, fMRI studies cannot clarify the underlying mechanisms of

altered activation patterns. Genetic predispositions, social influences, or learning mechanisms during life development may play a role.

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Statement of Authorship

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