Brain structure may determine gender identity - a VBM study on transsexualism

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Purpose

Transsexualism is characterized by a long-standing and strong distressful feeling of being a member of another gender, and feeling of incongruity with the assigned gender-roles causing significant impairment in the individual's social and professional life (1). It is a heterogeneous condition both in its manifestation and etiology. There are cases with well identifiable genetic or somatic changes that may lie behind this condition, and there are individuals who do not show such disturbances and yet experience a strong incongruence between their biological gender and gender identity. The latter condition is referred as Gender Identity Disorder or GID (1).

Transsexuality is considered to be the result of the fact that during fetal life the differentiation of sexual organs is on a different timescale than the sexual differentiation of the brain. Thus, hormonal disturbances that may affect the sexual differentiation of the brain may lead to a mismatch between biological gender and gender identity (2).

In this study we aimed to investigate the structural correlates of gender identity. To this end we compared regional voxelwise grey matter concentration of transsexual patients and healthy controls.

Images for this section:

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Fig. 1: Purpose
Methods and Materials

Subjects:

Seventeen patients of the Transgender Special Outpatient Service of the Psychiatry and Psychotherapy Department of Semmelweis University (Budapest, Hungary) with the DSM-IV-based diagnosis of GID (10 male-to-female [MTF], age: 28.5±7.69; 7 female-to-male [FTM], age: 24.8±6.45) and 17 healthy age-matched controls (7 males, age: 27.1±5.54; 10 females, age: 23.9±3.42) were involved in our study.

Imaging:

MR imaging of all participants were performed at the MR Research Center of Semmelweis University (Budapest, Hungary) on a 3 Tesla Philips Achieva whole-body clinical MRI scanner (Philips, Best, The Netherlands) equipped with an 8-channel SENSE head-coil. A single whole-brain T1-weighted three dimensional spoiled gradient echo (T1W 3D TFE) volume was collected from each participant.

The vendor-provided imaging sequence was tuned to provide the best possible separation between white and gray matter. The following imaging parameters were used: TR = 9.7 ms; TE = 4.6 ms; flip angle = 8°; FOV of 240 mm × 240 mm; voxel size of 1.0 × 1.0 × 1.0 mm; 180 contiguous sagittal slices.

Data processing

The collected images were analyzed using voxel based morphometry (VBM) in order to compare regional gray matter concentration between our subject groups (3). Data processing and analysis were performed within the SPM8 software framework (http://www.fil.ion.ucl.ac.uk/spm/) using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/). We applied the default preprocessing steps with the default processing parameters of the VBM8 toolbox. The processing pipeline consisted of the following steps:

1. segmentation of the different tissue classes (gray matter, white matter, cerebrospinal fluid)
2. linear (i.e. affine) and nonlinear (i.e., Dartel) registration of the subjects brains to the MNI template (4)
3. modulation of the gray matter tissue segments by the nonlinear normalization parameters to account for individual brain size differences
4. evaluation of the whole data set for outliers by checking sample homogeneity using covariances between image pairs
5. smoothing of the realigned and normalized gray matter segments with an 8 mm FWHM Gaussian kernel
6. statistical analysis
The segmentation procedure was refined by accounting for partial volume effects (5), by applying adaptive maximum a posteriori estimations (6), and by applying denoising using a hidden Markov random field model (7), and also by using a spatially adaptive non-local means filter (8).

Visualization and atlasing of significant clusters was performed using the xjView toolbox (http://www.alivelearn.net/xjview).

Statistical analysis:

Voxel-wise image intensities (representing local gray matter concentrations) of the smoothed warped gray matter compartments were compared using a 2x2 ANCOVA model specified in SPM8, with Biological Gender, and Illness (i.e. the presence of GID) as main effects and age as a covariate of no interest. Upon whole brain model estimation F contrasts were calculated to access the sites of main effects and interactions (Illness, Biological gender and Illness x Biological gender), furthermore T contrasts were calculated for the within Biological gender comparisons (FTM transsexuals vs. control females and MTF transsexuals vs. control males). Statistical maps were considered significant at the level of p<0.001 uncorrected with a cluster size threshold of 50 voxels.

Region of interest (ROI) analyses were performed on significant clusters of the Biological gender, Illness, and Illness x Biological gender interaction contrasts and on those of the within Biological gender comparisons, as well. To this end gray matter concentration values corresponding to the clusters were extracted from the individual brains, then averaged within subject and processed further. In case of clusters of the Illness x Biological gender contrast a 2x2 ANOVA was performed, followed by all possible groupwise comparisons of the control females, control males, FTM transsexuals and MTF transsexuals, using unpaired two-sample Student's tests between the groups. For the other contrasts unpaired two-sample Student's tests between groups were performed.

Results

Effect of Illness:

The whole brain analysis showed 2 significant cerebellar clusters bilaterally for the Illness effect (ROIs Ill#1 and Ill#2; see Table 1 on page 8 and Fig. 2 on page 9). Results of the ROI-analyses showed that grey matter concentration was higher in healthy controls than in GID patients in both ROIs (see Table 1 on page 8).
**Fig. 2**: Clusters with significant Illness effect. In these clusters the regional grey matter concentration is higher in controls than in transsexual patients. See Table 1 for details.

**References**: MR Research Center, Semmelweis University - Budapest/HU

**Effect of Biological Gender**: 

The whole brain statistical parametric maps of the Biological Gender main effect, accounting for gender differences but not for GID status was found to be significant in 2 clusters (see Table 2 on page 9) involving parts of the splenium of the corpus callosum, the bilateral posterior cingulate cortices, and the precuneus (ROI Gen#1), and parts of left mesial temporal lobe, and the cerebellum (ROI Gen#2).

**Illness x Biological Gender interactions**: 

Significant Illness x Biological Gender interactions were found in 2 clusters (see Table 3 on page 10 and Fig. 3 on page 10 top panel), involving the left pre- and postcentral gyri (ROI IxG#1) and parts of the right occipital lobe including the fusiform gyrus (ROI IxG#2).
Fig. 3: Clusters with significant Illness x Biological Gender interaction. In these ROIs the regional grey matter concentration of GID patients is more similar to the controls of similar gender identity, compared to that of controls of same biological gender. Top panel: cluster localization, bottom panel: local regional grey matter concentrations in the ROIs shown above, horizontal lines above the bars represent significant differences on between subgroup comparisons. See Table 4 for details.

References: MR Research Center, Semmelweis University - Budapest/HU

The ROI based analyses showed that transsexual patients had significantly different grey matter concentration in these significant clusters compared to that of controls sharing their biological gender and showed similar cortical structure to that of controls sharing their gender identity (Fig. 3 on page 10, bottom panel).

Specifically, the 304 voxel sized cluster affecting the left pre- and postcentral gyri (including the somatosensory cortex and the primer motor cortex) $[F(1,30) = 25.08, p < 0.001]$ had lower regional grey matter concentration in MTF transsexual patients and female controls compared to FTM transsexual patients and male controls. The opposite direction could be observed in a 123 voxel sized cluster in the right occipital lobe involving the middle and inferior occipital, the fusiform, and the lingual gyri $[F(1,30) = 21.17, p < 0.001]$ where regional grey matter concentration proved to be higher in MTF transgender patients and female controls compared with FTM transgender patients and male controls.
In both cases there were significant within Illness category differences, as well (see Fig. 3 on page 10 and the legend for details).

**Within Biological Gender comparisons:**

Comparing regional grey matter concentration between female controls and FTM transsexuals yielded 2 significant clusters, while comparing regional grey matter structure between male controls and MTF transsexuals yielded 5 significant clusters (see Fig. 4 on page 11 and Table 4 on page 12). Two of these clusters showed overlap with the clusters of Illness x Biological gender interaction, and two other showed overlap with the cluster of the Illness main effect to a variable degree. However, there were no overlaps between the within biological gender statistical parametric maps, and the clusters of the Biological gender main effect (see Table 4 on page 12 for details).
Fig. 4: Significant differences in regional cortical structure between patients and controls sharing the same biological gender. Red clusters: patients have higher local grey matter concentration than controls; blue clusters: controls have higher local grey matter concentration than patients.

References: MR Research Center, Semmelweis University - Budapest/HU

Images for this section:
Table 1: Significant effect of GID on regional grey matter concentration. a: in MNI space in mm-s relative to the origin; b: based on the atlases provided with xjView (see methods).

<table>
<thead>
<tr>
<th>ROI name</th>
<th>Cluster peak [x,y,z]^a</th>
<th>Localization^b</th>
<th>Number of voxels</th>
<th>ROI statistics</th>
<th>ROI p</th>
</tr>
</thead>
<tbody>
<tr>
<td>III#1</td>
<td>-25.5, -70.5, -24</td>
<td>Left Cerebellum Anterior and Posterior Lobe, Declive, Dentate</td>
<td>229</td>
<td>t(33)=4.376</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III#2</td>
<td>13.5, -49.5, -25.5</td>
<td>Right Cerebellum Anterior Lobe, Culmen, Dentate</td>
<td>76</td>
<td>t(33)=4.567</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fig. 2: Clusters with significant Illness effect. In these clusters the regional grey matter concentration is higher in controls than in transsexual patients. See Table 1 for details.
Table 2: Regions of interest with significant Gender effect. a: in MNI space in mm-s relative to the origin; b: based on the atlases provided with xjView (see methods).

<table>
<thead>
<tr>
<th>ROI name</th>
<th>Cluster peak [x,y,z]a</th>
<th>Localizationb</th>
<th>Number of voxels</th>
<th>ROI statistics</th>
<th>ROI p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen#1</td>
<td>1.5, -40.5, 12</td>
<td>Corpus Callosum, Right and Left Posterior Cingulate and Precuneus</td>
<td>239</td>
<td>t(33)= 4.925</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gen#2</td>
<td>-15, -33, -10.5</td>
<td>Left Parahippocampal Gyrus, Left Cerebellum Anterior Lobe, Left Culmen</td>
<td>51</td>
<td>t(33)=4.68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fig. 3: Clusters with significant Illness x Biological Gender interaction. In these ROIs the regional grey matter concentration of GID patients is more similar to the controls of similar gender identity, compared to that of controls of same biological gender. Top panel: cluster localization, bottom panel: local regional grey matter concentrations in the ROIs shown above, horizontal lines above the bars represent significant differences on between subgroup comparisons. See Table 4 for details.
Table 3: Regions of interest with significant Illness x Biological Gender interaction. a: in MNI space in mm-s relative to the origin; b: based on the atlases provided with xjView (see methods).

<table>
<thead>
<tr>
<th>ROI name</th>
<th>Cluster peak [x,y,z]</th>
<th>Localization</th>
<th>Number of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>IxG#1</td>
<td>-34.5, -27.66</td>
<td>Left Precentral and Postcentral Gyri</td>
<td>304</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right Occipital Lobe, Right Middle and Inferior Occipital Gyri, Right Fusiform Gyrus, Right Lingual Gyrus</td>
<td></td>
</tr>
<tr>
<td>IxG #2</td>
<td>34.5, -72, -10.5</td>
<td></td>
<td>123</td>
</tr>
</tbody>
</table>

Female-to-male patients vs. healthy controls

<table>
<thead>
<tr>
<th>#1 (x = 15, y = -91.5, z = 40.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2 (x = 34.5, y = -73.5, z = -9)</td>
</tr>
</tbody>
</table>

Male-to-female patients vs. healthy controls

<table>
<thead>
<tr>
<th>#1 (x = 31.5, y = -63, z = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#3 (x = -16.5, y = -60, z = -31.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#2 (x = -36, y = -30, z = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#4 (x = -15, y = -33, z = 61.5)</td>
</tr>
</tbody>
</table>

| #5 (x = 16.5, y = -46.5, z = -30) |
**Fig. 4:** Significant differences in regional cortical structure between patients and controls sharing the same biological gender. Red clusters: patients have higher local grey matter concentration than controls; blue clusters: controls have higher local grey matter concentration than patients.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Cluster peak ([x,y,z])^a</th>
<th>Localization^b</th>
<th>Number of voxels</th>
<th>Overlapping ROIs with main effect and/or interaction</th>
<th>ROI statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTM &lt; control females</td>
<td>15, -91.5, 40.5</td>
<td>Right Cuneus, Right Precuneus</td>
<td>111</td>
<td>-</td>
<td>(t(16)=5.67)</td>
</tr>
<tr>
<td></td>
<td>34.5, -73.5, -9</td>
<td>Right Inferior and Middle Occipital Gyri, Right Fusiform and Lingual Gyri</td>
<td>74</td>
<td>IxG#2</td>
<td>(t(16)=3.43)</td>
</tr>
<tr>
<td>MTF &gt; control males</td>
<td>31.5, -63, 27</td>
<td>Right Middle Temporal Gyrus, Right Parietal and Temporal Lobe</td>
<td>69</td>
<td>-</td>
<td>(t(15)=5.09)</td>
</tr>
<tr>
<td></td>
<td>-36, -30, 66</td>
<td>Left Precentral and Postcentral Gyri</td>
<td>398</td>
<td>IxG#1</td>
<td>(t(15)=4.97)</td>
</tr>
<tr>
<td></td>
<td>-16.5, -60, -31.5</td>
<td>Left Cerebellum Anterior and Posterior lobes, Dentate, Declive, Culmen</td>
<td>168</td>
<td>III#1</td>
<td>(t(15)=3.41)</td>
</tr>
<tr>
<td></td>
<td>-15, -33, 61.5</td>
<td>Left Parietal Lobe, Left Precentral and Postcentral gyri</td>
<td>89</td>
<td>-</td>
<td>(t(15)=3.85)</td>
</tr>
<tr>
<td></td>
<td>16.5, -46.5, -30</td>
<td>Right Cerebellum Anterior lobe, Dentate, Culmen</td>
<td>56</td>
<td>III#2</td>
<td>(t(15)=3.55)</td>
</tr>
</tbody>
</table>

**Table 4:** Significant differences in regional cortical structure between patients and controls sharing the same biological gender. a: in MNI space in mm-s relative to the origin; b: based on the atlases provided with xjView (see methods).
Conclusion

In conclusion, our findings support the notion that structural differences exist between patients with GID and control subjects from the same biological gender.

We found that transsexual subjects showed similar cortical structure to that of controls with the same gender identity and not to those from the same biological gender in brain areas, including the left pre- and postcentral gyri (including the somatosensory cortex and the primer motor cortex) and the right fusiform, lingual, middle and inferior occipital, and inferior temporal gyri. Additionally, we also found areas in the cerebellum that showed significant structural difference between transsexual patients and controls, independent from their biological gender.

There is only small number of studies in the field of structural imaging of transgender subjects (9, 10, 11) and although the applied methods are different, sample sizes are modest and results are therefore yet inconclusive in details, significant structural differences were already found between transgender patients and controls repeatedly and in some cases, in overlapping brain areas. These initial results, including the results of our study, need to be further replicated and refined in future studies on larger samples, as well as followed by functional imaging studies that might clarify how these structural differences impact the process of the disturbed evolution of gender identity and/or how disturbed gender identity affect brain structure and functions.

Images for this section:

In conclusion, our findings support the notion that structural differences exist between patients with GID and control subjects from the same biological gender.

Fig. 5: Conclusion
References


Personal Information