Brain Morphology In Typically Developing Boys and Girls and Gender Variant Boys

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Objective

Recent advances in brain-imaging methods increasingly contribute to our understanding of the neuroanatomic characteristics that underlie differences between the sexes in humans, and between gender variant (GV) individuals and controls. The present study was carried out in order to determine sex differences in cortical morphology in prepubertal children and to compare the results with cortical morphology in GV boys.

Prior neuroimaging studies involving typically developing (TD) boys and girls along with older individuals have demonstrated sex dimorphisms in cortical mantle thickness.[1] To date, however, we are not aware of any published study that have examined differences in brain morphology between samples consisting solely of prepubertal boys and girls. **The first aim** of the present study was to demonstrate sex differences in the cortical surface morphology of prepubertal children using high-resolution anatomical magnetic-resonance (MR) imaging.

The study of sex differences in neuroanatomy should also help in clarifying the etiology of gender variation seen in "Gender Identity Disorder" (DSM-IV-TR) or "transsexualism" (ICD-10). Such GV individuals demonstrate strong and persistent cross-sex identification and behavior without evidence of a somatic intersex condition. A prior study in transsexual adults, as yet unreplicated, has identified differences from non-GV controls in cortical morphology.[2] No such studies have been conducted with GV children. **The second aim** of the present study was to compare cortical surface morphology of prepubertal GV boys to that of a subsample of TD boys from aim 1. Given the feminization of behavior and gender identity in GV boys, we hypothesized that aspects of their brain anatomy were also feminized.

Methods

Families with TD children were recruited from a list of names purchased from a telemarketing company. Families of GV children were recruited from the Tri-State area using flyers distributed at clinics and other locations. The protocol was approved by the IRB at New York State Psychiatric Institute (#5321R), and written informed consent was obtained from all families. TD children included 22 Tanner-1 boys and 11 Tanner-1 girls between 7 and 13 years of age. From among more than a dozen GV youth 7-20 years of age recruited for the study, we chose for analysis 3 Tanner-1 boys, ages 7-9 years, meeting diagnostic criteria for Gender Identity Disorder. From the group of TD boys, we selected 9 TD boys such that all of the boys, TD and GV, were white, between 7 and 10 years of age, Tanner-1, right-handed, fit, and medication-free. Each child's mental health status and gender presentation were evaluated using a number of validated instruments, including the Gender Identity Interview,[3] and the Child Behavior and Attitude Questionnaire.[4] Review of clinical data and consensus diagnoses were made by two doctoral level clinicians.

Methods cont.

Brain images were acquired from a high resolution MR scanner (GE Signa, Milwaukee, WI) using a sagittal 3D volume spoiled gradient echo sequence. Morphometric analyses were performed using ANALYZE 7.5 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Brain segmentation was semi-automated, and corrected by hand in 3 planes by operators unaware of left-right orientation of the image or clinical status of the participant.

For each child, we calculated the difference in center-to-surface distance from 100,000 voxel-sized points on the surface of his or her cortex in comparison to the distance measurements obtained from the corresponding points on a template brain. The previously validated method[5] first uses rigid-body similarity transformation to register brain images of participants with a template brain chosen via a rigorous method from among the control group. Global scaling and estimated parameters from the first transformation were used to register a participant's entire brain into the space created by the template brain, thereby eliminating the need to further adjust for differences in overall brain size between children. This method of controlling for global brain volume allows the surface protrusions and indentations to be interpreted as local volume increases and decreases, respectively. A second rigid co-registration created a "refined registration" suitable for detailed morphometrics. Each cortex was then warped to the corresponding anatomy of the template using a high-dimensional, non-rigid algorithm based on the techniques of fluid-flow dynamics. This method permitted point-to-point matching of images that essentially pins together homologous tissue in the template and participant cortices. Subsequently, high-dimensionally warped images were unwarped to the "refined registration." The unwarping process maintained pinpoint correspondence between the template and participant images, but allowed for measurements to occur while images were contorted as little as possible from the original structure of the tissue. Completion of the procedure resulted in a set of distance measurements at each cortical surface point ready for statistical modeling.

We twice performed the morphometric analysis described above, choosing separate template brains for each analysis. The first analysis compared 22 TD boys with 11 TD girls, all Tanner-1. The second preliminary analysis compared 3 GV boys to the 9 matched TD boys. For each analysis, we then used linear regression to compare between-group differences in signed Euclidean distance at each cortical surface point. Statistical models were designed to assess the main effect sex, while covarying for age. We used the False Discovery Rate (FDR) method set at 5% to correct p-values for multiple comparisons in the presence of intercorrelated measures of distance. Voxels with p-values of <0.05 were color-coded and displayed on the template brain.

Results

The results of surface morphometry revealed focal areas of sexually dimorphic brain volume in prepubertal children. The relative protrusion in the temporo-parietal cortex of girls was consistent with previous reports of increased thickness in females when compared to males in this cortical area.[1] Results also indicated that the volume enlargement in the temporo-parietal cortex in typically developing (TD) girls was mirrored in gender variant (GV) boys. Similarly, data demonstrated a frontal cortex indentation in both TD girls and GV boys when compared to TD boys.

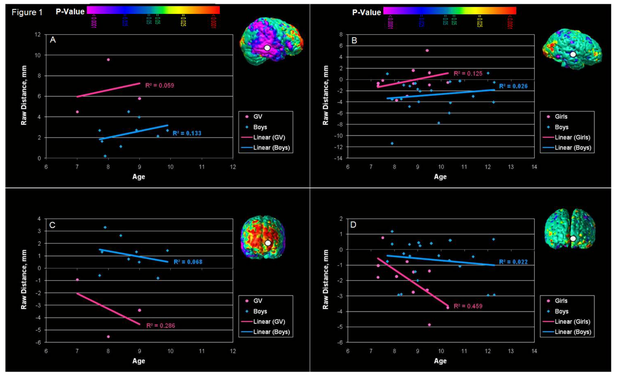


Figure 1 *Trends in cortical morphology comparisons at cortical surface points* Figure 1 highlights statistical differences in surface contour between GV and TD boys (1A and 1C) and between TD girls and boys (1B and 1D). The color bar provides the color-coding for p-values associated with the main effect of sex that have been mapped onto the template brain. Yellows and reds indicate protruding surfaces in TD boys, whereas blues and purples indicate protruding surfaces in GV boys and TD girls. As the methodology controlled for global brain volume, protrusions and indentations represent local volume increases and decreases, respectively. The scatter diagrams plot by age distance measurements for each child from a single cortical surface point. Scatter from GV boys and TD girls are shown in pink, and scatter from TD boys are shown in blue. Data shown in Parts A and C (detailed in Figure 3) are from a different analysis using a different template brain from the data in Parts B & D (detailed in Figure 2). Thus, the two morphometric analyses are not directly comparable. Note, however, that TD girls and GV boys vary in the same direction from TD boys at each cortical surface point that was probed.

Figure 2. *Cortical contour In TD males and females* We have undertaken analyses that have proved useful in understanding the morphology of normal sexual dimorphisms of the cortex in a group of males and females ranging in age from 6-63 yrs whose assessment and imaging data were obtained from our databank of healthy participants. In the subgroup analysis shown here, the healthy participants were 28 Tanner 1 children (19 boys vs 9 girls; age=9.8±1.4 vs 8.9±0.9 years; t=2.77, p=0.11) Data were entered into a general linear model with sex as the independent variable, and thickness as the dependent variable. The model controlled for age. The figure below depicts three views of the FDR-corrected p-map representing group differences in cortical thickness between the boys and girls. Multiple areas of the frontal, parietal and temporal cortices show increased thickness in girls compared to boys. Consistent with prior reports, there are few areas of elevated thickness in boys.

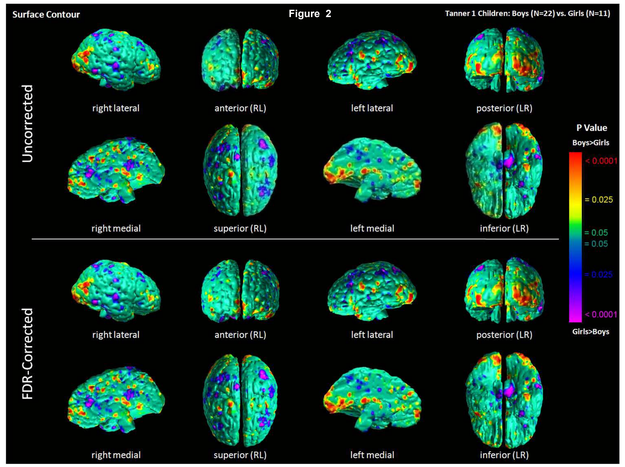
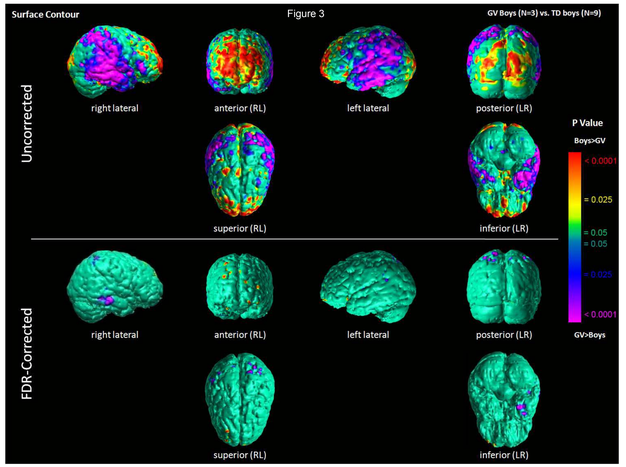


Figure 3. *Comparison Of Cortical Morphology Between TD And GV Boys* Three GV boys, and 10 TD boys whose data were obtained from our repository were selected to be Tanner stage 1, white, right-handed, comorbidity-free and medication-free. Comparison of surface deformation at each cortical point was performed by measuring the distance from the surface of the test brain to the homologous point on the designated template brain. The statistical comparison controlled for age. The map of corrected p-values has been displayed on the template brain. Note the uniform inward deformation of the frontal lobe and outward deformation of the parietal lobe in GV boys. Although the overall pattern of alteration is similar to that seen when comparing TD boys and girls, there exist important differences between maps of GV and TD boys and TD boys and girls which suggest that the developmental trajectory in GV boys is more complex than a straight-forward global feminization of the brain.



Conclusions:

These data demonstrate sex differences in cortical surface morphology in an analysis limited to prepubertal children. Our data indicate that differences in surface contour between GV boys and TD boys are in the same directions as differences between TD girls and boys. These preliminary but pioneering results support the idea of focal areas of feminization of brain development in prepubertal GV boys.

Abbreviations

GV: gender variant; FDR: False Discovery Rate; MR: magnetic resonance TD: typically developing

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