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Similarly Expanded Bilateral Temporal Lobe Volumes in Female and Male Children With Autism Spectrum Disorder

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ABSTRACT

BACKGROUND: Autism spectrum disorder (ASD) is more prevalent in male than female individuals. Very few studies have examined sex modulations of brain anatomical differences between individuals with ASD and typically developing (TD) individuals, especially in children. The current study aimed to identify sex-dependent and/or sex-independent neuroanatomical mechanisms underlying ASD.

METHODS: Magnetic resonance imaging data were acquired from the Autism Brain Imaging Data Exchange. A 2 (diagnosis) × 2 (sex) design was used. Subjects whose ages were between 6 and 20 years were included for analysis, with matched full-scale IQ between groups for each dataset. The resulting effective numbers of subjects were 36 female subjects with ASD, 54 TD female subjects, 182 male subjects with ASD, and 172 TD male subjects. Twenty independent gray matter (GM) and 20 white matter (WM) volume sources were estimated using source-based morphometry.

RESULTS: Among all the independent GM and WM sources, none of them showed a significant diagnosis by sex interaction. One GM source of the bilateral inferior and middle temporal lobe showed a significantly larger volume in ASD than TD individuals and in male than in female subjects. This diagnosis effect was age sensitive and was present only in participants between 8 and 14 years of age.

CONCLUSIONS: Only sex-independent, large-scale neuroanatomical alterations could be observed in children with ASD. The directionality of bilateral temporal GM alterations was in line with the prediction of the extreme male brain hypothesis, supporting the view that similar neurobiological mechanisms may drive sexual dimorphism and the onset of ASD.

Keywords: Autism, Brain volume, Extreme male brain theory, Female, Sex, Temporal lobe

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Autism spectrum disorder (ASD) is more prevalent in male than in female individuals (1,2). Understanding sex differences of neuroanatomical mechanisms underlying ASD can therefore further our knowledge of the etiology and diagnosis of this prevalent neurodevelopmental disorder (3). In addition to conventional global measures of head circumference and total brain volume (4), current advances of neuroimaging analysis methods have enabled researchers to study brain regional morphometric differences between individuals with ASD and typically developing (TD) individuals using both voxel-based morphometry (5,6) and cortical thickness (7,8). However, due to the unbalanced number of female and male individuals with ASD and the limited number of subjects in a neuroimaging study, the numbers of female subjects examined has been very small or female subjects have been excluded from research. Two studies have investigated the influence of biological sex on neuroanatomical differences between individuals with ASD and TD individuals (9,10). Several gray matter (GM) and white matter (WM) regions, such as the inferior parietal lobe and rolandic operculum (10), showed a sex × diagnosis interaction, implying sex-dependent neuroanatomical mechanisms underlying ASD.

One limitation of the previous studies is that they investigated only adult subjects. However, ASD is a developmental disorder, and studies have suggested that brain anatomical alterations take place as early as the first year of life (11). The developmental patterns of brain anatomy differ between patients with ASD and TD individuals (4,12,13), resulting in a theory of overgrowth of the brain in ASD in early life and arrested growth later on (14). In line with this view, meta-analyses of neuroimaging studies convergently suggested that brain anatomical, functional, and connectivity differences between ASD and TD individuals can be consistently detected in childhood but not in adults (15–17). Therefore, it is critical to study earlier ages when studying sex modulation of neuroanatomy in ASD.

The Autism Brain Imaging Data Exchange (ABIDE) (18) provides an opportunity to aggregate neuroimaging data from multiple sites, which enables us to analyze a large number of female subjects. A recent study has used the ABIDE data to

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study sex differences in cortical volume, thickness, and gyrification in ASD (19). However, this study included a sample with a large age range (8.1 to 46 years old). Most datasets from ABIDE have an age range younger than 20 years, and some datasets have samples mainly older than 20 years. Because aging is a critical factor in the analysis, we restricted our analysis with the age range between 6 and 20 years old. Another potential problem of Schaer *et al.* (19) is that they included subjects with full-scale IQ as low as 61. To study high-functioning ASD, we discarded subjects whose full-scale IQ was less than 70 (9) and matched full-scale IQ between groups for each dataset. Therefore, more homogeneous samples of subjects were used in the current analysis: 36 female subjects with ASD, 54 TD female subjects, 182 male subjects with ASD, and 172 TD male subjects.

After the structural magnetic resonance imaging (MRI) images were segmented into GM and WM images, independent component analysis (ICA) was applied to identify independent sources of regional brain anatomical variances (20–22). Such a source-based analysis was chosen because cortical structures of certain brain regions tend to covary (23), and the identified sources form meaningful networks that have been indicated in aging (24) and patients with schizophrenia (25). In addition, the source-based approach reduces the number of comparisons so that the multiple comparison correction problem is less severe than in voxel-wise analysis. The first question we asked was whether there were sex-dependent or sex-independent neuroanatomical mechanisms underlying ASD in the current sample. A 2 (diagnosis) × 2 (sex) analysis of variance (ANOVA) was performed on each independent GM and WM source after accounting for full-scale IQ, age, and site effects. A significant diagnosis by sex interaction would indicate a sex-dependent neuroanatomical mechanism, i.e., anatomical differences between ASD and TD individuals were present in only one sex group or were more severe in one sex group than the other. Alternatively, if the diagnosis by sex interaction was not significant but the main effect of diagnosis was significant, it would indicate a sex-independent neuroanatomical mechanism, i.e., the same anatomical structure may be altered in individuals with ASD and TD individuals similarly in both sexes. Second, we tested whether the resulting independent sources favored the prediction of the extreme male brain hypothesis (9,26). Specifically, we tested whether the independent sources that showed diagnosis by sex interactions or main diagnosis effects also showed sex differences in TD individuals and asked whether the volumes in male and female subjects with ASD fell toward the TD male or female direction.

METHODS AND MATERIALS

Subjects and Inclusion Criteria

Structural MRI data were derived from the ABIDE project (18). A dataset was included for analysis if it included three or more female subjects with ASD and three TD female subjects. Second, because most of the datasets covered the age range below 20 years, we only included datasets that had samples younger than 20 years of age. Third, full-scale IQ was available. Individuals with a full-scale IQ score less than 70 were discarded. For each remaining dataset, 2 (diagnosis) × 2 (sex) ANOVA was used to test whether the IQ scores had significant diagnosis effect and diagnosis by sex interaction. Significant effect of diagnosis on IQ was found in one dataset (Kennedy Krieger Institute); therefore, this dataset was discarded from the analysis. For the remaining datasets, 2 × 2 ANOVA did not show significant main effects or interactions. As a result, six datasets were included in the current analysis: University of Pittsburgh School of Medicine, University of Michigan sample 1, Yale Child Study Center, New York University Langone Medical Center, Stanford University, and University of California Los Angeles sample 1. Finally, an ICA-based quality control process was applied to the MRI images as described below. The effective sample sizes of the four groups were: 36 female subjects with ASD, 54 TD female subjects, 182 male subjects with ASD, and 172 TD male subjects (details in Table 1).

Data Processing and Quality Control

MRI image segmentation was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The MRI image of each subject was segmented using the segment routine in SPM12. Total tissue volumes of GM (TGV), WM (TWV), and cerebrospinal fluid were calculated for each dataset from the segmented images. The total intracranial volume (TIV) was calculated by summing the volumes of GM, WM, and cerebrospinal fluid. Resulting images were visually inspected to check segmentation quality. In addition, all the segmented gray matter volume (GMV) images were smoothed using an 8-mm full width at half maximum Gaussian kernel and submitted to quality control group ICA (27) using the GIFT software v3.0a (http://mialab.mrn.org/software/). Twenty components were extracted. Outliers of the subject series associated with each of the components were visually checked. Such outliers are usually due to signal dropout in the component regions, so these subjects were discarded from further analysis. These quality control ICA analyses were repeated for several rounds until no outliers could be identified from the subject time series. Six subjects' data were discarded after quality control.

After the quality control, the remaining GMV images were analyzed using DARTEL (a fast diffeomorphic registration algorithm) in SPM12 (28). A sample-specific template was generated. The segmented images for each subject were normalized to the sample-specific template utilizing Jacobian modulation, so that the resulting images reflected GMV and WM volume (WMV). Spatial smoothing was applied at the same time using a Gaussian kernel of 8 mm full width at half maximum.

Source-Based Morphometry Analysis

After DARTEL procedures, source-based morphometry analysis (spatial ICA) was performed on the resulting GMV images and WMV images separately, again using GIFT v3.0a. The series of 444 GMV or WMV images were concatenated as a four-dimensional dataset. The mean of each image was removed, so that the resulting independent component load for each subject reflected relative GM or WM volume after controlling total GM or WM volume. Twenty components were extracted for both modalities (denoted as gray matter independent component 1 [GMIC1] through GMIC20 and white