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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 males than females. 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) independent neuroanatomical mechanisms underlying ASD.

Method—MRI data were acquired from Autism Brain Imaging Data Exchange (ABIDE). A two (diagnosis) by two (sex) design was used. Subjects whose ages were between 6 to 20 years were included for analysis, with matched full scale IQ between groups for each data set. The resulting effective numbers of subject were: 36 females with ASD, 54 TD females, 182 males with ASD, and 172 TD males. Twenty independent gray matter (GM) and 20 white matter (WM) volume sources were estimated using source-based morphometry (SBM).

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 significant larger volume in ASD than TD individuals, and in males than in females. This diagnosis effect was age sensitive, and was only present in participants between 8 to 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; sex; female; brain volume; temporal lobe; extreme male brain theory

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Introduction

Autism spectrum disorder (ASD) is more prevalent in males than females (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 volumes (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 (VBM) (5; 6) and cortical thickness (7; 8). However, due to the unbalanced number of females and males with ASD and 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 and white matter regions, such as the inferior parietal lobe and rolandic operculum (10), showed a sex $\times$ diagnosis interaction, implying sex dependent neuroanatomical mechanisms underlying ASD.

One limitation of the previous studies is that they only investigated 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 adult (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 multi-sites, which enables us to analyze a large number of female subjects. A recent study has used the ABIDE data to 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 to 20 years old. Another potential problem of Schaer et al. (2015) is that they included subjects with full scale IQ (intelligence quotient) as low as 61. To study high functioning ASD, we discarded subjects whose full scale IQ was less than 70 (9), and matched full scales 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 females, 182 males with ASD, and 172 TD males.

After the structural MRI images were segmented into gray matter (GM) and white matter (WM) images, independent component analysis (ICA) was applied to identify independent sources of regional brain anatomical variances (20–22). Such source-based analysis was chosen because cortical structures of certain brain regions tend to co-vary (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 multiple comparison correction problem is less severe than in voxel-wise analysis. The first question we asked was whether there were sex dependent or independent neuroanatomical mechanisms underlying ASD in the current sample. A two (diagnosis) by two (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 only present or 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. Secondly, we tested whether the resulting independent sources favor 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 males and females with ASD fell toward the TD male or female direction.

Materials and Methods

Subjects and inclusion criteria

Structural MRI data were derived from the Autism Brain Imaging Data Exchange (ABIDE) project (18). A dataset was included for analysis if it included more than or equal to 3 females with ASD and 3 TD females. Secondly, 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. Thirdly, full scale IQ was available. Individuals with full scale IQ score less than 70 were discarded. For each remaining dataset, two (diagnosis) by two (sex) analysis of variance (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 analysis. For the remaining datasets, 2 by 2 ANOVA didn't 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, NYU 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 females with ASD, 54 TD females, 182 males with ASD, and 172 TD males (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 SPM. Total tissue volumes of GM (TGV), WM (TWV), and CSF were calculated for each dataset from the segmented images. The total intracranial volume (TIV) was calculated by summing the volumes of GM, WM, and CSF. 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 FWHM (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/>). 20 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 that 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) (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 reflect GMV and WMV. 8 mm FWHM spatial smoothing was applied at the same time.

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 4D 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. 20 components were extracted for both modalities (denoted as GMIC1 through GMIC20 and WMIC 1 through WMIC20). For each resulting component, a map representing spatial distributions of the independent source and a subject-wise source load representing regional volumes for each subject were obtained. A total of 40 (GM and WM) sources and associated source loads were obtained for statistical analysis.

Statistical analysis

Firstly, a two (diagnosis) by two (sex) ANOVA was performed on the three total volume measures: TGV, TWV, and TIV. Age, age², IQ, and five dummy variables representing site effects were added as covariates. Secondly, the same analysis was performed on the forty independent sources. The effects of interest are the diagnosis by sex interaction, and two main effects of diagnosis and sex. Therefore, there were a total of 120 (40 × 3) comparisons. False discovery rate (FDR) correction was used to accounting for multiple comparisons.

For any independent sources that showed significant diagnosis by sex interaction or diagnosis main effect, we further performed post-hoc group-wise comparisons by using two sample t-test using the source load adjusted for age, IQ and site effects. Specifically, we tested whether there were sex differences in TD individuals, and tested whether the source load in males and females with ASD fell toward the TD male or female direction.

For any independent sources that showed significant diagnosis by sex interaction or diagnosis main effect, we further examined the effect of age on the source load. The effect of IQ and sites were first removed from the source load using a linear regression model. To ensure enough samples at each age range, especially for the female ASD group, we grouped

the sample using a two-year increment. Five age groups were constructed: 8 – 10, 10 – 12, 12 – 14, 14 – 16, and 16 – 18 years old (Table S4 in Supplement). Two (diagnosis) by two (sex) ANOVA was performed for each age group.

There were more males subjects than females in the current analysis. We included all possible subjects, because more subjects could give more accurate parameter estimates for statistical analysis. There was a conjecture, however, that different numbers of subjects in different groups might generate biased results. To rule out this possibility, we calculated effect size (Cohen's d) between ASD and TD individuals for males and females, separately. This post hoc analysis verified that whether the effects observed in males and females were comparable or not. Cohen's d with pooled standard deviation was calculated between ASD and TD individuals for males and females separately. In addition, we also performed the same two (diagnosis) by two (sex) ANOVA using a balanced sample. Thirty-six subjects were included in each group. Subjects from the TD females, males with ASD, and TD males were chosen by matching age with each of the 36 female subjects with ASD. Since the results were in general consistent with those using the whole sample, the results are reported in the supplementary materials.

Results

The effect of IQ

Even though full scale IQ was matched for each single dataset, when merging data of all the six datasets, there was a significant effect of diagnosis on full scale IQ after controlling for age, age², and site effects ($F(1,433) = 4.861$, $p = 0.028$). No effect of sex ($F(1, 433) = 0.346$, $p = 0.557$) and sex by diagnosis interaction ($F(1,433) = 0.165$, $p = 0.685$) was observed. Therefore, full scale IQ was added in the subsequent analysis as a covariate.

Total tissue volumes

Total gray matter volume, total white matter volume, and total intracranial volume of the four groups of individuals are shown in Figure 1. For all three measures, no significant sex by diagnosis interactions were observed (Diagnosis by sex interaction: TGV, $F(1,432) = 1.342$; $p = 0.242$; TWV, $F(1,342) = 0.218$; $p = 0.641$; TIV, $F(1,432) = 0.505$; $p = 0.478$). The male individuals showed significantly larger volumes in all three measures (Main effect of sex: TGV, $F(1,432) = 49.154$; $p < 0.001$; TWV, $F(1,432) = 61.544$; $p < 0.001$; TIV, $F(1,432) = 56.518$; $p < 0.001$). Differences between individuals with ASD and TD individuals were not significant (Main effect of diagnosis: TGV, $F(1,432) = 3.618$; $p = 0.058$; TWV, $F(1,432) = 0.020$; $p = 0.886$; TIV, $F(1,432) = 3.023$; $p = 0.083$).

Source-based morphometry

The results of the two (diagnosis) $\times$ two (sex) ANOVA of all twenty GM independent sources and twenty WM sources are listed in Table 2, and the corresponding GM and WM IC maps are reported in Figures S1, S2, and S3, respectively (see Supplement). No significant diagnosis by sex interactions were observed in any sources at $p < 0.05$ of FDR correction, or even without correction.

One GM source (GMIC 18) showed significant effects of diagnosis ($F(1,432) = 22.196$; $p < 0.001$) and sex ($F(1,432) = 18.673$; $p < 0.001$). This GM source mainly covered the bilateral inferior and middle temporal sulcus (Figure 2A and supplementary Figures S1 and S2). The source load was higher in individuals with ASD compared with TD individuals, and was higher in males than in females (Figure 1B). The effect size between ASD and TD individuals in females (Cohen's $d = 0.64$) was slightly larger in number than in males (Cohen's $d = 0.52$), even though the diagnosis by sex interaction was not significant.

To test the extreme male brain hypothesis on this bilateral temporal source, a series of two sample t-test were performed between groups. Firstly, within TD individuals, males had larger source load than females ($t = 3.56$, $p < 0.001$). Secondly, for males, individuals with ASD had larger source load than TD individuals ($t = 4.87$, $p < 0.001$). Thirdly, females with ASD had larger source load than TD females ($t = 3.010$, $p = 0.003$). And lastly, there was no difference of source load in females with ASD and TD males ($t = 0.21$, $p = 0.84$), although the mean source load of females with ASD was slightly larger than those of TD males.

The effects of diagnosis and sex on gray matter volume of the bilateral temporal sources were further analyzed in five age groups: 8 – 10, 10 – 12, 12 – 14, 14 – 16, and 16 – 18 years old (Figure 2C and Table 3). Significant diagnosis effects were only present in the age periods of 8 – 10, 10 – 12, and 12 – 14 years. A significant effect of sex was only observed in the age periods of 8 – 10 and 10 – 12 years. And at the age period of 12 – 14 years old, there was a significant diagnosis by sex interaction.

In addition to the bilateral temporal source, eleven other GM sources also showed significant effects of sex at $p < 0.05$ of FDR correction (Table 2). All of these GM sources showed higher source load in males than in females. Fifteen WM sources (Table 2) revealed significant effects of sex. Fourteen of these WM sources showed higher source load in male than in female individuals. In contrast, one WM source (WMIC 11) that mainly covered right sensorimotor WM and left occipital WM showed higher source load in females than in males (Figure 4H).

Discussion

By aggregating MRI data from a large online data sharing initiative, the current analysis examined sex modulations of brain volumetric differences in individuals with ASD and TD individuals. Among all identified independent GM and WM sources, only one component, consisting of the bilateral temporal lobe, showed significantly higher volumes in individuals with ASD compared with TD individuals, and higher volumes in males than in females. No diagnosis by sex interaction was observed. Additional analyses suggested different developmental progressions of the bilateral temporal lobe source in the four groups of subjects, and significant diagnosis effects were only observed before 14 years of age.

The increased volume in bilateral temporal regions in individuals with ASD are consistent with a previous study of cortical thickness using the same ABIDE data but only with male subjects (29). GM volume increases in similar brain regions have also been reported in previous studies using voxel-based morphometry (VBM) (9; 30) and cortical thickness

methods (7; 8). It is noteworthy that all these previous studies except Lai et al. (2013) only recruited male subjects for analysis. The present study indicated that this GM source not only showed higher volumes in males with ASD than TD males, but also showed the same pattern in female subjects, i.e. no diagnosis by sex interaction was evident. This suggests that this neuroanatomical pathology presents similarly in both male and female individuals with ASD.

In contrast to the current findings that no independent GM or WM sources showed significant diagnosis by sex interaction, three studies have found diagnosis by sex interactions in structural measures in different brain regions (9; 10; 19). Specifically, Beacher et al. (2012) found a GM cluster in the inferior parietal lobe and rolandic operculum, which was spatially overlapped with the current GM source GMIC20. Lai et al. (2013) found two WMV clusters in the splenium of corpus callosum and internal capsule, which were spatially overlapped with the current WM sources WMIC14 and WMIC2, respectively. All of these three sources had significant effects of sex, but not significant diagnosis by sex interactions or diagnosis effects. These discrepancies may mainly due to the differences of ages in the different samples. For example, the diagnosis by sex interaction in the splenium of corpus callosum observed by Lai et al. (9) was driven by significant smaller WM volumes in females with autism than other three groups. It is possible that white matter reductions in females with ASD only take place in adulthood. Therefore, age could be a sensible factor influencing the observation of diagnosis by sex interactions. In addition, Schaer et al. (2015) utilized a novel gray matter measure of gyrification on the ABIDE data, and found a diagnosis by sex interaction in the ventromedial prefrontal cortex. These results suggest that sex dependent morphological differences may be present in ASD, but in complex representations.

In addition to the diagnosis related effects, 12 GM sources and 15 WM sources showed significant effect of sex. This included the bilateral temporal source that showed both significant main effects of diagnosis and sex. Specifically, after controlling total gray matter volumes, males had larger bilateral temporal volumes than females, which is consistent with previous studies in normal subjects (31; 32). It should be noted that Schaer et al. (2015) showed a reversed effect in similar temporal regions, i.e. higher local cortical volumes in females. This may due to that they have controlled total cortical volumes, but not total gray matter volumes. Their results without controlling for total cortical volumes had similar pattern as the current results.

Out of 40 independent GM/WM sources tested in the current analysis, 39 sources did not show any sex dependent or independent diagnosis effects. This suggests local but not global neuroanatomical mechanisms underlying ASD. The only GM source showed both main effects of diagnosis and sex. And interestingly, the source volumes of individuals with ASD fell in line with the hypothesis of the extreme male brain theory (26; 33). This theory hypothesizes that the same biological factors that influence the expression of sexual dimorphism also influence the pathology of ASD, resulting in “masculinization” of ASD individuals. In line with this hypothesis, the males with ASD demonstrated larger regional volumes in the bilateral temporal sources than TD males, conveying an extreme level of male characteristics. Females with ASD also showed larger regional volumes in the bilateral

temporal source than TD females, and showed similar level of volumes compared with TD males, which also could result from “masculinization” of the brain in females with ASD.

The interpretation of the sex dimorphism of brain structures usually links to sex hormonal or X chromosome effects (9). However, unlike the regions observed in the previous study (9), the bilateral temporal regions are among the regions in the brain that have developmentally low levels of sex steroid receptors (34). Therefore, sex hormone levels are not likely the factor causing the observed diagnosis and sex effects. On the other hand, female patients with Turner syndrome, who have only one copy of the X chromosome, showed higher GM volumes and cortical thickness in the superior and middle temporal lobe regions than typical females who have two copies of X chromosomes (35–37). This is in line with the current results of increased temporal lobe volumes in TD males who also have one copy of X chromosome compared with TD females who have two copies of the X chromosome. These two lines of studies convergently suggest that some genes in the X chromosome may affect regional volumes in the bilateral temporal lobe. This is consistent with the theory suggesting an association between X chromosome linked genes and ASD, which may result in sex differences of prevalence of the disorder (38). Specifically, some X chromosome linked genes may express as protective mechanisms, rendering females less likely to suffer ASD.

Along the age span of the current sample, we further examined whether the observed diagnosis and sex effects in the bilateral temporal source were present throughout the age range. We observed that significantly higher GM in individuals with ASD was only present before age of 14 years, and significantly higher GM in males than females was only present before 12 years. These results suggest different neurodevelopmental trajectories in the four groups of subjects. In line with the notion of early brain overgrowth in ASD (14), the higher volumes in the bilateral temporal lobe may result from early overgrowth in individuals with ASD. As data from infancy through age 6 are not available in the ABIDE dataset, this hypothesis cannot be tested from the current data. These results also suggest that diagnosis effects may become weaker or even negligible when individuals become older, therefore highlighting the importance of taking into account age as a key factor when examining brain mechanisms underlining ASD (15–17; 39). We note that because the number of female subjects is limited for each age group, it is not possible to match sites for each age group. Therefore, the age effects might be confounded by site effects. However, we have adjusted site effects from all the subjects, therefore site effects for each age group would also be minimized. Further studies are definitely needed to include large sample for each age group or using longitudinal design to confirm the age effects findings in the current analysis.

The current analysis took advantage of the wave of data sharing to gather a large sample of female subjects with ASD. This enables us to have a larger sample of females with ASD compared with previous studies of sex differences. The female/male ratio of ASD individuals is about 1:5, which is close to the overall sex ratio of the disease (1; 2). Compared with studies that are predesigned to investigate sex differences, which generally adopt a sex-balanced sample size, the current comparisons represent the real distribution of male and female individuals with ASD. A pitfall of this design is that the observed differences between ASD and TD individuals may be dominated by the effect of male subjects. It is, however, not the case for the bilateral temporal source because post-hoc

calculation of effects between ASD and TD individuals for males and females showed similar patterns. The Cohen's d for males and females were 0.52 and 0.64, respectively, indicating that the diagnosis effect is even larger for females than males on this bilateral temporal source. In addition, we performed the same 2 by 2 ANOVA analysis for all the 40 independent sources using a balanced sample (36 subjects in each group), and the results were in general the same as what using the whole sample (supplementary materials).

Taken together, the current results demonstrate a neuroanatomical focus where the extreme male brain theory of autism manifests. Future efforts to collect data from larger numbers of females with ASD at the same site will be necessary to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Total gray matter volume (TGV), total white matter volume (TWV), and total intracranial volume (TIV) for the four groups of subjects. For all three measures, only the main effects of sex were significant, i.e. the male individuals had larger TGV, TWV, and TIV than female individuals. Error bars represent standard deviation. * indicates statistical differences at $p < 0.05$. ASD, autism spectrum disorder; TD, typically developed.

Figure 2.

A) The independent gray matter source that showed significant effects of diagnosis and sex. Source maps were thresholded at $z > 2.3$. B) Mean source loads of this independent source in the four groups of subjects. Error bars represent standard deviation. * indicates statistical differences at $p < 0.05$. C) Age effects on the source loads in the four groups of subjects. ASD, autism spectrum disorder; TD, typically developing. *, †, and ‡ indicate significant diagnosis effect, sex effect, and diagnosis by sex interaction at $p < 0.05$, respectively.

Sample sizes, ages, and full scale intelligence quotients (IQ) of included subjects in the current analysis.

Table 1

		n	Age				IQ			
			ASD		TD		ASD		TD	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
PITT	Female	4	12.6	1.0	14.4	1.3	111.5	12.3	111.0	16.5
	Male	15	14.8	2.7	14.8	2.9	106.9	11.9	107.4	7.2
UM_1	Female	8	13.2	3.1	14.6	2.9	109.5	18.5	104.0	10.5
	Male	43	12.7	2.3	13.4	3.2	102.5	17.6	107.8	9.3
YALE	Female	8	12.9	3.0	13.5	2.6	95.1	13.7	110.9	17.4
	Male	18	12.6	3.2	12.3	2.8	99.2	20.1	102.6	17.2
NYU	Female	6	12.4	2.5	11.9	2.8	106.5	24.8	113.8	15.1
	Male	55	11.4	3.1	13.0	3.4	107.7	16.5	112.2	13.8
STANFORD	Female	4	10.0	1.6	9.0	1.0	102.8	6.6	116.0	24.7
	Male	16	9.9	1.6	10.2	1.7	115.0	19.0	111.1	13.1
UCLA_1	Female	6	12.5	3.4	12.8	1.1	104.7	16.6	105.5	11.1
	Male	35	13.2	2.5	13.3	2.2	102.4	12.7	104.7	10.7
Total	Female	36	12.4	2.7	12.9	2.9	104.5	16.8	109.9	14.9
	Male	182	12.3	2.9	12.9	3.1	105.2	16.7	108.5	12.8

Table 2

Statistical results of two (diagnosis) $\times$ two (sex) ANOVA (analysis of variance) of twenty gray matter and twenty white matter sources. For each analysis, age, age², full scale IQ (intelligence quotient), and five variables representing site effects were added as covariance.

	Gray matter sources				White matter sources			
	Diagnosis	Sex	Diagnosis $\times$ sex		Diagnosis	Sex	Diagnosis $\times$ sex	
	F(1, 432)	p	F(1, 432)	p	F(1, 432)	p	F(1, 432)	p
IC1	0.952	0.330	17.650	<0.001*	1.389	0.239	1.747	0.187
IC2	0.861	0.354	11.794	0.001*	0.005	0.942	0.418	0.518
IC3	1.159	0.282	38.295	<0.001*	3.158	0.076	0.074	0.786
IC4	0.284	0.594	1.388	0.239	1.090	0.297	1.105	0.294
IC5	0.967	0.326	2.873	0.091	0.713	0.399	1.331	0.249
IC6	0.719	0.397	0.099	0.753	0.353	0.553	0.119	0.731
IC7	0.245	0.621	8.356	0.004*	0.167	0.683	0.856	0.355
IC8	0.658	0.418	6.033	0.014	0.207	0.649	2.167	0.142
IC9	1.008	0.316	20.423	<0.001*	0.091	0.763	2.379	0.124
IC10	0.899	0.343	0.270	0.604	1.826	0.177	3.185	0.075
IC11	1.129	0.289	9.653	0.002*	0.060	0.806	0.440	0.507
IC12	2.592	0.108	37.729	<0.001*	1.091	0.297	1.930	0.165
IC13	2.187	0.140	10.053	0.002*	0.062	0.803	0.538	0.464
IC14	0.548	0.460	5.349	0.021	0.008	0.930	0.548	0.460
IC15	0.575	0.449	10.911	0.001*	3.147	0.077	0.669	0.414
IC16	0.017	0.896	6.711	0.010	0.300	0.584	0.577	0.448
IC17	0.240	0.625	4.078	0.044	1.418	0.234	0.116	0.733
IC18	22.196	<0.001*	18.673	<0.001*	0.036	0.850	1.463	0.227
IC19	0.059	0.808	7.144	0.008*	1.240	0.266	1.891	0.170
IC20	0.346	0.557	33.888	<0.001*	0.845	0.359	0.146	0.703

* statistically significant at $p < 0.05$ after FDR (false discovery rate) correction for totally 120 effects.

Statistical results of two (diagnosis) by two (sex) analysis of variance (ANOVA) on the bilateral temporal lobe independent source at different age ranges. Full scale IQ (intelligence quotient) and five variables representing site effects were removed using linear regression before ANOVA.

Table 3

	8 – 10 years		10 – 12 years		12 – 14 years		14 – 16 years		16 – 18 years	
	F	p	F	p	F	p	F	p	F	p
Diagnosis	7.616	0.007 *	4.562	0.035 *	11.327	0.001 *	2.041	0.157	0.409	0.525
Sex	5.405	0.023 *	4.319	0.040 *	3.350	0.070	1.437	0.234	2.388	0.129
Diagnosis × sex	2.495	0.118	0.007	0.931	4.460	0.037 *	1.131	0.291	0.465	0.498

* statistically significant at $p < 0.05$.