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Brain development in Turner syndrome: a magnetic resonance imaging study

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Abstract

Turner syndrome (TS) results from the absence of an X chromosome in females. This genetic condition is associated with specific cognitive deficits and variations in brain volumes. The goal of this study was to use high-resolution magnetic resonance imaging (MRI) to determine morphological variations in TS and to investigate the effects of parental origin of the X chromosome on brain development in TS. MRI brain scans were acquired from 26 girls with TS and 26 age- and gender-matched controls. Seventeen of the TS subjects had a maternally inherited X chromosome (Xm), and nine of the subjects had a paternally inherited X chromosome (Xp). Rater-blind morphometric analyses were conducted to compare tissue volume differences between girls with TS and controls. Three-way analyses were used to compare subgroups and controls. Subjects with TS demonstrated bilateral decreases in parietal gray and occipital white matter accompanied by increased cerebellar gray matter. Subjects with Xm showed decreased occipital white matter and increased cerebellar gray matter compared to controls. No differences were found in comparisons between subjects with Xp and controls or between subjects with Xm and Xp. Results suggest that X monosomy affects posterior cerebral and cerebellar anatomy in TS. While differences between comparisons of Xm and Xp to controls might suggest an imprinting effect, no significant differences were found when the two subgroups were directly compared to each other. Further investigation into the possible role of genomic imprinting is therefore warranted.

Keywords

Turner Syndrome; MRI; Genomic imprinting; Parietal lobe; Cerebellum

1. Introduction

Turner syndrome (TS), a genetic disorder, affecting 1 out of 2000 live female births (Lippe, 1991), arises from partial or complete X monosomy. Physical features of TS include short stature, low-set ears, webbing of the neck, gonadal dysgenesis, and a reduction of estrogen production and development of puberty. While the physical effects of X monosomy are well known, far less is understood about how it affects brain development. Although there is wide variation within the overall population of individuals with TS, neuropsychological studies are generally consistent in demonstrating specific deficits in visual-spatial skills and visual memory (Pennington et al., 1985; McCauley et al., 1987; Murphy et al., 1994) as well as in attention and executive function (McCauley et al., 1987; Murphy et al., 1994). These impairments also may be accompanied by greater risk for difficulties in school adjustment, social relations and facial affect recognition (Downey et al., 1989; McCauley et al., 1987).

The difficulties in specific cognitive domains, learning and social functioning often experienced by girls with TS suggest that the loss of a particular subset of X chromosome genes might directly or indirectly contribute to alterations in brain development and functioning. Neuroimaging techniques have allowed researchers to begin to investigate brain structure and function in TS. Functional imaging studies using positron emission tomography (PET) have found abnormal patterns of activation and metabolism in the parietal and occipital regions (Clark et al., 1990; Murphy et al., 1997) and in the temporal cortex and insula (Murphy et al., 1997) in subjects with TS compared to controls. A recent functional magnetic resonance imaging (MRI) study of working memory reported decreased activation bilaterally in the dorsolateral prefrontal cortex, supramarginal gyrus and caudate of TS subjects (Haberecht et al., 2001). Anatomic imaging studies using MRI have reported decreased volumes in brain tissue in the parietal and occipital regions (Murphy et al., 1993; Reiss et al., 1995) as well as in the hippocampus, lenticular nucleus, and thalamus (Murphy et al., 1993).

One variable not yet examined in neuroimaging studies, and which might contribute to variability within the TS population, is the potential role of parental origin of the single X chromosome in girls with TS, a phenomenon known as genomic imprinting. In a study of 80 subjects with TS (Skuse et al., 1997), it was reported that individuals with TS who retained the paternal X chromosome (Xp) had better psychosocial functioning than individuals who inherited the X chromosome from their mothers (Xm). In particular, subjects with Xp showed better social adjustment, verbal skills and executive functioning than girls with Xm. Although the precise molecular mechanisms underlying imprinting are still under investigation, it is likely that this epigenetic phenomenon involves the reversible addition of methyl groups to either the maternal or paternal copy of a gene during gametogenesis. The addition of the methyl group prevents the expression of the gene from that chromosome and is non-random such that either the maternal copy of the gene or the paternal copy is always inactivated. If there were a gene on the X chromosome that exhibited the imprinting effect such that the gene on the maternal chromosome were always inactivated, then females with Turner syndrome who inherited a single X chromosome from their father would still be able to express that gene. Females who inherited a single X chromosome from the mother, on the other hand, would be deficient in that gene. Increased social and learning difficulties among girls with Xm compared to girls with Xp could therefore potentially be explained by a putative imprinted locus on the X chromosome that is not expressed from the maternally derived X chromosome. Indeed, it has already been established that genomic imprinting contributes to phenotypic variation in several genetic disorders that are associated with significant cognitive and behavioral dysfunction, including Prader-Willi syndrome, Beckwith-Wiedemann syndrome and Angelman syndrome (Nicholls, 2000).

The overarching goal of the study described here was to continue our laboratory's investigation into the effects of X monosomy on brain development utilizing new image-analysis techniques for more precisely characterizing neuroanatomical variation. On the basis of previous volumetric imaging studies, we hypothesized that regional differences in the volume of the parietal and occipital lobes would distinguish persons with TS from healthy controls. We also sought to determine whether the parental origin of the single X chromosome in females with monosomic karyotypes might be an epigenetic factor that contributes to morphological differences in TS. We hypothesized that the parental origin of the X chromosome in TS would have a specific impact on neurodevelopment. Based on the findings of poorer social and cognitive functioning in girls with the Xm genotype (Skuse et al., 1997), we expected to find neuroanatomical alterations in the parietal region to be more evident in females from the Xm population than the Xp population.

2. Methods

2.1. Subjects

The study group consisted of 26 children and adolescents with TS (mean age=13.2±4.3) and 26 age-matched normal control females (mean age=13.4±4.0). Subjects with TS were recruited through the National Turner Syndrome Foundation, the Human Growth Foundation, local and regional TS support groups, local physicians and the Stanford Psychiatry Neuroimaging Laboratory website. Because the presence of a second 46, XX cell-line might lessen the effects of the monosomic state of the X chromosome, only subjects with monosomic 45, X karyotypes (non-mosaic) were included in this study. Individuals included in the comparison group were recruited through newspaper advertisements and parental networks. All control subjects had no history of neurological or psychiatric disorder.

Subjects and controls under the age of 17 received the Wechsler Intelligence Scale for Children, third edition (WISC-III, Wechsler, 1991). Subjects and controls 17 years and older received the Wechsler Adult Intelligence Scale, third edition (WAIS-III, Wechsler, 1997). The mean FSIQ for subjects with TS was 98.9±16.1. The mean FSIQ for controls was 113.2±16.3. FSIQ data were not available for one subject with TS. Subjects with TS had a mean PIQ of 90.3±13.1 and a VIQ of 105.2±19.3. Controls had a mean PIQ of 110.5±16.0 and a VIQ of 115±14.3. ANOVAs indicated that subjects with TS had a reduced total IQ ($F=9.9$, d.f.=1, 51; $P=0.003$) and PIQ ($F=21.0$, d.f.=1, 44; $P=0.000$) compared to controls. The VIQ difference between the groups approached significance ($F=3.7$, d.f.=1, 44; $P=0.06$). There was no significant difference between IQ scores for the Xm (mean=98.5±19.1) and Xp (mean=99.6±7.5) groups (Mann-Whitney $U=65.5$, $P=0.89$). VIQ and PIQ scores were not available for three subjects with TS and five controls.

Seven subjects with TS and two controls were included in a previous volumetric study from our laboratory (Reiss et al., 1995).

2.2. Procedures

2.2.1. Genetic analysis—Genetic testing was done on blood samples from the patients and both parents if available. Of the 26 subjects, 19 had both parents' samples. Five subjects had samples available from the mother. One patient had samples from the mother and a brother. One patient had samples from the mother and two sisters. Most patients with the respective parents had testing at the androgen receptor (Xq11.2–Xq12), HPRT (Xq26.1–Xq26.1), DXS6809 (pter–Xqter) and DXS9895 (X chromosome). In the case of three families where only samples from the patient and mother were available, the patient had an allele consistent with inheritance from the mother at each of the four sites listed above.

Therefore, the following markers were used in patients where the first four markers were not informative: DXS6799 (Xpter–Xqter), DXS8378 (Xpter–Xqter), DXS9898 (X chromosome), DXS101 (Xq22–Xq22), DXS733 (Xq24–Xq26), and DXS1120 (Xq22.2–Xq22.3). The markers DXS731 (Xq27–Xq28), DXS1125 (Xq11.2–Xq13), DXS1190 (Xpter–Xqter) and DXS1123 (Xq27–Xq27/Xq28–Xq28) were also used.

When both maternal and paternal blood was available and the X was paternal in origin, the majority showed discordance with the maternal alleles in the first four markers. Thus, it is unlikely that the X chromosome could have had maternal alleles at all of the original sites and the seven additional sites yet still have been paternally inherited. It is also unlikely that a second X chromosome (i.e. from deletion) was missed since there was no evidence of a non-45, X genotype seen on karyotype.

Seventeen subjects had a single X chromosome inherited from their mother (mean age=12.7±3.7) while 9 subjects inherited their single X chromosome from their father (mean age=14.2±5.2).

2.2.2. Neuroimaging—MR data were acquired on 1.5 Tesla G.E. Signa scanners (General Electric Medical Systems, Milwaukee, WI, USA) at Stanford University and at Johns Hopkins University School of Medicine. Coronal 3D volumetric spoiled gradient echo (SPGR) series were acquired with the following parameters: TR=35–45, TE=6, flip angle=45°, number of excitations=1, FOV=20–24, slice thickness=1.5 mm, and matrix=256×192 for 124 contiguous slices.

2.2.3. Imaging processing and measurement—Image data were imported into the program *BrainImage* for semi-automated image-processing analyses and quantification as described and validated in previous reports (Subramaniam, 1997; Reiss et al., 1998; Kates et al., 1999). MRI data were imported into *BrainImage* and corrected for image non-uniformity between slices. Non-brain tissue was then removed using a semi-automated process. The remaining brain tissue was segmented into gray matter, white matter, and CSF using a fuzzy tissue segmentation algorithm. To specify regional differences, each brain was divided into lobes with a semiautomated stereotactic-based parcellation method (Talairach, 1988; Kates et al., 1999). The brain was divided into cerebral lobes, subcortical nuclei, cerebellum, and lateral ventricles based on the rater's identification of three anchor points: the anterior commissure, the posterior commissure, and a midsagittal point above the axis created by the first two points. Raters who conducted morphometric analyses were blind to the diagnosis of each subject. Interrater reliability obtained by interclass correlation exceeded 0.90.

2.2.4. Statistical analysis—Data were first examined for normality and equality of variance to confirm the assumptions of the parametric statistics used. One-way analyses of variance (ANOVAs) were performed on total brain tissue, total brain gray matter, and total brain white matter. A multivariate analysis of variance (MANOVA) was used to determine whether the subjects with TS and control subjects had unique patterns in gray tissue composition. The dependent variables included frontal, parietal, temporal, occipital, cerebellar and subcortical gray matter. Similarly, a MANOVA was used to determine whether subjects with TS showed differences in white matter tissue composition when compared to control subjects with frontal, parietal, temporal, occipital, and cerebellar white matter as the dependent variables. Follow-up ANOVAs were used to specify regional differences in gray matter and white matter when the overall MANOVA model was significant. For those regions that reached significance, ANOVAs were performed to investigate whether regional tissue differences were specific to one hemisphere. The significance level for the MANOVAs and ANOVAs was set at $P<0.05$.

Post-hoc analyses using Scheffé's test explored the possibility of genomic imprinting on those regions in which subjects with TS were found to be significantly different. Scheffé's tests allowed direct comparisons to be made between the origin groups (Xm, Xp and controls).

3. Results

As shown in Table 1, there were no significant differences between subjects with TS and controls for total cerebral volume ($F=1.1$, d.f.=1, 50, $P=0.235$), total cerebral gray matter ($F=0.5$, d.f.=1, 50, $P=0.482$) or total cerebral white matter ($F=1.3$, d.f.=1, 50, $P=0.265$). We therefore did not adjust further analyses for intracranial volume. To investigate the hypothesis that there are distinct patterns in gray matter composition between subjects with TS and control subjects, a MANOVA was performed with the gray matter volumes of the frontal, temporal, parietal, and occipital lobes, cerebellum, and subcortical region entered as dependent variables. A Wilk's lambda value of 0.661 ($F=3.9$, d.f.=6, 45, $P=0.004$) indicated a unique pattern of cerebral morphology in gray matter that distinguishes subjects with TS from controls.

Follow-up ANOVAs were performed to investigate possible regional differences in gray matter between the subjects with TS and controls. The subjects with TS showed a significant decrease in parietal gray matter ($F=5.4$, d.f.=1, 50, $P=0.024$). The results also indicated significantly larger cerebellar gray matter volumes ($F=7.6$, d.f.=1, 50, $P=0.008$) in subjects with TS compared to control subjects. ANOVAs were utilized to determine whether regional differences in gray matter might be specific to one hemisphere. The decrease in parietal gray matter in individuals with TS was found to be significant in both the right ($F=4.1$, d.f.=1, 50, $P=0.048$) and left ($F=6.3$, d.f.=1, 50, $P=0.015$) hemispheres. The increase in the cerebellar gray matter in females with TS also was found to be significant in both the right ($F=7.4$, d.f.=1, 50, $P=0.009$) and left ($F=6.4$, d.f.=1, 50, $P=0.015$) hemispheres. No differences in gray matter were found in the frontal, temporal, occipital, or subcortical gray matter.

Similar statistical analyses were used to compare white matter tissue volumes between TS subjects and controls. A MANOVA was computed with the white matter of the four cerebral lobes and the cerebellum as dependent variables. A Wilk's Lambda value of 0.716 ($F=3.7$, d.f.=5, 46, $P=0.007$) suggested differences in regional white matter distribution between the two groups. Follow-up ANOVAs indicated that the TS group had significantly reduced white matter volumes in the occipital lobe ($F=9.1$, d.f.=1, 50, $P=0.004$). No other regions showed significant differences in white matter. This decrease in occipital white matter was significant in both the right ($F=10.6$, d.f.=1, 50, $P=0.002$) and left ($F=5.3$, d.f.=1, 50, $P=0.026$) hemispheres.

To determine whether the regional differences in TS might be influenced by parental origin, post-hoc analyses with Scheffé's test were utilized for three-way comparisons. Because the differences in parietal gray matter, cerebellar gray matter, and occipital white matter were found to be bilateral, the dependent variables that were used included both right and left hemisphere contributions. Table 2 presents the volumes of these regions for each subgroup. Females with Xm showed significantly larger cerebellar gray matter volumes ($P=0.0195$), and decreased occipital white matter when compared to controls ($P=0.083$). There were no significant differences found between subjects with Xp and controls or between Xm and Xp. All of the above effects for diagnosis and origin remained significant even after covarying for age.

A regression analysis was performed to determine the relationship between visual-spatial functioning (PIQ) and parietal lobe gray volume after removing the effects of total cerebral gray volume. No significant relationship was found.

4. Discussion

Our study provides evidence of morphological alterations in the parietal, occipital and cerebellar regions in females with TS, irrespective of age. While previous volumetric studies have consistently reported aberrant neuroanatomy in the parietal-occipital regions in TS, findings across studies have been variable. Murphy et al. (1993) measured the brains of 18 subjects with TS (mean age=30±7 years) and showed that the TS females had significantly smaller volumes of the cerebral hemispheric and parietal-occipital brain matter, the hippocampus, and the lenticular and thalamic nuclei. In contrast to our results, they found no differences in cerebellar volumes. However, nine out of the 18 females with TS in Murphy's study had a mosaic karyotype which might have diminished actual differences between the two populations, while we excluded any mosaic subjects. The discrepancies in our results also might be related to differences in image acquisition and processing. Murphy et al. utilized images with a larger slice thickness (5 mm vs. 1.5 mm), which tends to decrease image resolution. Furthermore, Murphy et al. measured combined tissue (gray+white) volumes, thereby obscuring possible tissue- and region-specific neuroanatomical differences. While Murphy et al. reported decreased volumes in the hippocampus, our parcellation method, which included the hippocampus as part of the temporal lobe and subcortical nuclei measurements, might not have been sensitive enough to detect differences in this structure.

Reiss et al. (1995) collected and analyzed MRI data from a younger population of 30 females with TS (mean age=10.5±3.41) that included three girls with a mosaic karyotype and 27 girls with a monosomic karyotype. The principal finding of that study, reduced gray matter volumes in the right and left parietal regions, is replicated in the present study. However, the reduced occipital white matter volume in the TS group observed in the present study is not consistent with results from the earlier study, where no significant between-group white matter volume differences were observed. This discrepancy may be attributable to differences in scan acquisition parameters, tissue segmentation procedures or, in particular, the methods chosen for cerebral parcellation. Specifically, Reiss et al. used 5-mm-thick slices that were acquired with a 2-D spin density/double echo pulse sequence, a categorical/discrete tissue segmentation algorithm, and planar divisions of the cerebrum that were not based on standard cerebral lobe boundaries. In contrast, the present study used 1.5-mm-thick slices acquired with a T1-weighted 3-D acquisition, a fuzzy tissue segmentation algorithm, and a parcellation method based on a standardized stereotaxic grid. The regions described by Reiss et al. that are most comparable to the definition of occipital lobe used in the present study included segments from the parietal and posterior temporal lobes, thus potentially masking lobe-specific white matter differences between groups. Cerebellar morphology was not measured in Reiss et al., and thus between-study results could not be compared for this structure.

The most consistent finding across volumetric studies on TS, also reported in the present study, is an absolute or proportional reduction in parietal lobe tissue. The parietal lobe has been implicated in functional tasks including mental rotation (Harris et al., 2000) and judgment of line orientation (Ng et al., 2000). While many studies have proposed that the right parietal lobe is specialized for visuospatial processing, other studies have concluded that the left parietal lobe also is involved in visuospatial cognition (Mehta et al., 1987; Ng et al., 2000). The decrease in parietal lobe gray matter in both the left and right hemispheres therefore is consistent with the broad impairment in visuospatial skills frequently reported in

girls with TS (McCauley et al., 1987; Murphy et al., 1994). While TS subjects demonstrated significantly lower PIQ scores than controls, no relationship between PIQ and parietal lobe volume was noted in this study. This could reflect the fact that PIQ data was missing for several subjects, reducing the power of this analysis.

The decrease in parietal volumes in the subjects with TS might also account for the impairment in executive functioning and attention that has been reported in females with TS. Several neuroimaging studies have suggested that the parietal lobe as well as the frontal lobe plays a significant role in tasks such as working memory (Diwadkar et al., 2000; Jansma et al., 2000) and spatial attention (Rosen et al., 1999). Furthermore, a recent functional imaging study of working memory in females with TS found decreased activation bilaterally in the supramarginal gyrus as well as in the dorsolateral prefrontal cortex (Haberecht et al., 2001). Thus, decreased volumes of the parietal lobe in females with TS might account for difficulties in working memory and attention as well as in visuospatial functioning.

The decrease in white matter observed in the occipital lobe also might be related to visuospatial deficits that have been reported in females with TS. While visuospatial processing is typically associated with the parietal lobe, visuospatial functioning also might depend on intact connectivity between the primary visual areas of the occipital lobe and the parietal lobe. For example, a topographical study of macaques revealed retinotopically organized inputs from visual areas V1, V2, V3, V4 and MT to the parietal-occipital region, which in turn sends a large number of projections to the parietal lobe (Colby et al., 1988). Consequently, a decrease in occipital white matter might offer another neuroanatomical explanation for the deficits in visuospatial functioning observed in TS.

The increase in cerebellar gray matter in females with TS was unexpected. Except for a study showing that the midsagittal area of the cerebellar vermis was smaller in a girl with TS compared to her monozygotic twin sister who did not have X monosomy (Reiss et al., 1993), this region had not been implicated as aberrant in any other neuroimaging studies of TS. Recently, evidence from patients with cerebellar lesions has suggested that the cerebellum plays a role in a wide range of cognitive abilities and behavioral symptoms. Impaired visual-spatial processing and impaired executive functioning, most notably in planning and abstract reasoning, are among the cognitive impairments known to occur in patients with cerebellar lesions (Schmahmann and Sherman, 1998; Levisohn et al., 2000). While researchers are still investigating the nature of cerebro-cerebellar circuitry, the increased size of the cerebellum in TS and its association with the behavioral and cognitive profile of girls with X monosomy may help elucidate the functional role of the cerebellum in higher order processing.

Evidence for genomic imprinting in TS was first reported by Skuse et al. (1997), who found that girls with TS who had a maternally derived X chromosome showed greater impairment in social-cognitive skills, verbal skills, and executive function when compared to girls with TS with a paternally derived X-chromosome. However, our preliminary analyses comparing the neuroanatomy of subjects with Xm and Xp with controls provide only mildly suggestive evidence that genomic imprinting is related to neurodevelopment in TS. Females with Xm showed significantly less white matter in the occipital lobe and more gray matter in the cerebellum compared to controls, with effect sizes approaching or exceeding 1.0. Differences between the females with Xp and controls were not significant for these same measures. While statistical comparisons of each of the TS subgroups with the control group might suggest a genomic imprinting effect, these results must be taken with caution. No statistically significant differences were observed when the two TS groups were directly compared with one another. There were also no differences in IQ scores between the Xm and Xp groups. Thus, our results are tenuous at best.

It is possible that differences between the Xm and Xp groups or between Xp subjects and controls might not have been able to reach statistical significance because of small group size and resulting lack of statistical power. Because there was a slight difference in the average age of females with Xm and females with Xp, the differences in the comparisons of each parental origin group to controls might reflect normal changes in brain development that occur during late childhood and adolescence (Jernigan et al., 1991; Sowell et al., 1999, 2002). However, there were no significant differences in age between the Xp and Xm groups or between the TS and control groups. Additionally, there was no significant age by origin interaction for any of the variables of interest.

In summary, this high-resolution brain-imaging study confirms previous findings of anomalous patterns of cortical development in parietal and occipital regions and provides new findings indicating aberrant cerebellar morphology in TS. The findings of this study also suggest that further investigation of the putative effects of genomic imprinting on brain development may be warranted in TS. Furthermore, while the Talairach coordinate system used to generate regional measurements is sensitive to differences on the lobar level (Kaplan et al., 1997; Kates et al., 1999), this method is not sensitive to differences that may occur in the smaller sub-lobar structures of the brain. Future studies with larger TS subgroups are clearly warranted and should further focus on (1) analyzing the integrity of white matter tracts in TS using techniques such as diffusion tensor imaging (Peled et al., 1998) and (2) subdividing the parietal lobe and cerebellum to examine what particular substructures within these regions might be associated with the neurocognitive profile of girls with TS. Additionally, the difference in the morphological profile between the TS Xm and Xp groups warrants further investigation.

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Table 1

Mean tissue volumes in cubic centimeters for subjects with TS and controls

	45X (N=26) Mean±S.D. (cm ³)	Controls (N=26) Mean±S.D. (cm ³)	ANOVA*	
			F	P-value
Total brain volume	1217.3±93.5	1247.4±87.3	1.448	0.235
Total gray	749.4±64.2	761.4±57.0	0.502	0.482
Frontal	233.8±21.4	237.8±21.7	0.455	0.503
Parietal	151.5±15.6	161.1±14.3	5.386	0.024*
Right	76.4±8.3	80.9±7.5	4.124	0.048*
Left	75.0±7.7	80.2±7.0	6.342	0.015*
Temporal	143.4±10.9	147.7±11.0	1.944	0.169
Occipital	64.0±11.5	69.1±9.0	3.162	0.081
Subcortical nuclei	43.9±5.8	44.5±3.7	0.172	0.680
Cerebellum	95.4±14.9	84.7±13.3	7.556	0.008*
Right	47.9±7.6	42.5±6.6	7.401	0.009*
Left	47.6±7.9	42.2±7.4	6.408	0.015*
Total white matter	467.8±65.4	486.1±50.4	1.270	0.265
Frontal	153.0±24.4	153.7±18.8	0.014	0.906
Parietal	110.3±14.2	115.3±12.9	1.787	0.187
Temporal	62.0±9.9	61.5±8.4	0.031	0.860
Occipital	44.9±8.0	51.6±8.1	9.099	0.004*
Right	21.1±3.9	25.0±4.6	10.597	0.002*
Left	23.8±4.9	26.7±4.2	5.253	0.026*
Cerebellar white matter	36.4±16.7	39.8±13.1	0.646	0.425

* Significant at $P < 0.05$.

Table 2

Mean tissue volumes in cubic centimeters for subjects with Xm, subjects with Xp, and controls (CON)

Structure	Controls (n=26) Mean±S.D. (cm ³)	Xm (n=17) Mean±S.D. (cm ³)	Xp (n=9) Mean±S.D. (cm ³)	Scheffé's test		
				Xm vs. CON	Xm vs. CON	Xm vs. Xp
Parietal gray	161.1±14.3	152.9±14.0	148.7±18.8	0.2279	0.1161	0.8000
Cerebellar gray	84.7±13.3	97.5±14.1	91.5±16.6	0.0195*	0.4653	0.5845
Occipital white	51.6±8.15	43.5±6.8	47.5±9.7	0.0083*	0.4234	0.4796

* Significant at $P<0.05$.