IV. Neuroanatomy of Williams Syndrome: A High-Resolution MRI Study

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Abstract

Williams syndrome (WMS), a genetic condition resulting from a contiguous deletion on the long arm of chromosome 7, is associated with a relatively consistent profile of neurocognitive and neurobehavioral features. The distinctiveness and regularity of the profile of learning and behavioral characteristics in this genetic condition suggests that underlying neurobiological correlates may be identifiable. In this initial study, we report findings derived from a high-resolution neuroimaging study of 14 young adult subjects with WMS and an individually matched normal control group. Compared to controls, subjects with WMS were noted to have decreased overall brain and cerebral volumes, relative preservation of cerebellar and superior temporal gyrus (STG) volumes, and disproportionate volume reduction of the brainstem. Analyses also suggested that the pattern of cerebral lobe proportions in WMS may be altered compared to normal controls with a greater ratio of frontal to posterior (parietal+occipital) tissue. Assessment of tissue composition indicated that, relative to controls, individuals with WMS have relative preservation of cerebral gray matter volume and disproportionate reduction in cerebral white matter volume. However, within the cerebral gray matter tissue compartment, the right occipital lobe was noted to have excess volume loss. Combined with our growing knowledge of the function of genes in the commonly deleted region for WMS, more detailed information regarding the structure and function of the WMS brain will provide a unique opportunity for elucidating meaningful correlations amongst genetic, neurobiological, and neurobehavioral factors in humans.

INTRODUCTION

The study of discrete genetic causes of cognitive and behavioral dysfunction in humans presents a unique opportunity to expand our knowledge of associations among specific genetic factors, brain development and function, and neurobehavioral outcome. Of the many genetic conditions that provide a model for furthering our knowledge in this regard, few are as intriguing or enigmatic as Williams syndrome (WMS). This condition, originally named to represent a syndromic constellation of developmental, physical, cognitive, and behavioral features, is now known to be caused by a contiguous deletion on the long arm of chromosome 7 (band 7q11.23) (Ewart et al., 1993; Korenberg et al., 1996; Korenberg, Chen, Lai, et al., 1997a; Korenberg, Chen, Mirchell, & Sun, 1997b; Korenberg et al., this volume; Lowery et al., 1995).

Despite the presence of a number of physical features and medical problems that are of potential clinical significance in persons with WMS, such as failure to thrive, infantile hypercalcemia, and cardiac or vascular malformations (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988), sequelae of central nervous system dysfunction predominate as the most impeding in an affected individual's daily functioning. In particular, individuals with WMS usually function within the mild to moderate mentally retarded range of intelligence. However, cognitive function is typically uneven with the characteristic profile including relative strengths in particular components of expressive language, musical abilities and face processing, and relative weakness in nonverbal functions such as spatial cognition and visual-motor abilities (Bellugi, Bihrlle, Jernigan, Trauner, & Doherty, 1990; Bellugi, Wang, & Jernigan, 1993; Bellugi, Lichtenberger, Mills,
Galaburda, & Korenberg, 1999a; Bellugi, Mills, Jernigan, Hickok, & Galaburda, 1999b; Bellugi et al., this volume; Hickok, Bellugi, & Jones, 1995a; Lenhoff, Wang, Greenberg, & Bellugi, 1997).

The presence of a predictable neurobehavioral phenotype, coupled with the availability of increasingly sophisticated technology for assessing brain structure and function, led to preliminary brain imaging studies in individuals with WMS. Although these studies often employed comparison subjects with another specific genetic condition, Down syndrome, as well as normal controls, the current discussion focuses on the latter comparison, as it is most applicable to the data provided in the present study. Initial findings from these preliminary imaging studies suggested that the brains of individuals with WMS were reduced in volume overall compared to normal controls (Jernigan & Bellugi, 1990; Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993). However, brain volume reductions in WMS, like cognitive abilities, appeared uneven on a regional basis with relative preservation of temporal-limbic and cerebellar volumes (Jernigan et al., 1993), and superior temporal auditory cortex (Hickok et al., 1995b). A recent preliminary report also suggested that gray matter might be preferentially preserved in WMS (Harris-Collazo, Archibald, Lai, Bellugi, & Jernigan, 1997).

However, previous imaging studies investigating brain structure in WMS have limitations. First, these studies typically employed small group sizes. Second, much of the volumetric-anatomical data on subjects with WMS and controls were established with image acquisitions characterized by relatively low resolution (e.g., 5-mm brain slices with 2.5-mm gaps in-between slices) (Jernigan & Bellugi, 1990; Jernigan et al., 1993) as compared to current imaging techniques that permit 1–2-mm resolution on a routine basis. Third, previous studies emphasized comparisons between WMS and Down syndrome. This made it difficult to determine whether group differences should be attributed to abnormal brain morphology in the WMS group, the Down syndrome group, or both. Accordingly, the need for further studies to investigate brain structure and function in this important genetic condition is great, and promises to reveal information of significance to a broader understanding of gene–brain–behavior associations in humans.

The data presented here represents our laboratory’s first 6 months of collaborative work on elucidating the neuroanatomical basis of the cognitive and behavioral features associated with WMS. Data from previous imaging and postmortem studies reporting on small numbers of subjects with WMS, provided a focal point from which initial questions and hypotheses could be generated. Specifically, in this initial imaging study of WMS, we sought preliminary answers to the following questions:

1. Is decreased brain volume a consistent feature of WMS?
2. Is there relative sparing of the frontal lobe and cerebellum, and disproportionate reduction of parietal and occipital regions, during brain development in WMS?
3. Is white matter disproportionately affected and gray matter preferentially preserved during brain development in WMS?
4. Are relative strengths in specific language and music abilities in subjects with WMS reflected in preserved development of the superior temporal gyrus (STG), a region known to be of importance to both of these cognitive domains?

In this study, we report on preliminary information derived from a comparison of 14 young adult subjects with WMS to a normal control group individually matched for gender and age.

RESULTS

Overall Brain and Tissue Volumes in WMS

As shown in the Table 1 and Figure 1, total brain volume was decreased 13%, on average, in subjects with WMS compared to controls ($F = 14.4, p < .001$). However, this reduction in volume did not extend across the brain in a proportional manner. Specifically, while cerebral volume showed a 13% decrease in subjects with WMS ($F = 14.9, p < .001$), cerebellar volume was decreased to a lesser extent (7%). Moreover, the cerebellar volume difference between the two groups was not significant ($F = 3.7, p < .10$). When a variable reflecting the ratio of cerebellar volume to cerebral volume was created, WMS subjects were noted to have significantly higher ratios compared to controls ($z = 2.4, p < .02$) (Figure 2). In contrast to the cerebellar findings, brainstem tissue volumes were significantly reduced (20%) in individuals with WMS compared to controls ($F = 27.5; p < .0001$). This reduction in brainstem tissue volume was proportionally greater ($F = 8.8, p < .007$) than that observed for reduction in overall brain tissue volume in the WMS group.

Analysis of cerebral tissue components revealed significant differences in relative gray and white matter tissue composition between the groups. Using total cerebral volume and age as covariates in an analysis of covariance (ANCOVA), subjects with WMS were shown to have relative “sparing” of their cerebral gray matter volume compared to controls ($F = 5.3, p = .05$), and disproportionate reduction in cerebral white matter volume ($F = 4.3, p = .05$). CSF volume was reduced in a manner proportional to overall cerebral volume in the WMS group. Using a similar ANCOVA with total cerebellar volume and age as covariates, the pattern of gray matter sparing or disproportionate white matter reduction was not observed in the cerebellum of individuals with WMS. Similarly, neither subcortical gray matter volume nor lateral ventricular volume was observed to be reduced...
or increased in a disproportionate manner compared to the respective overall cerebral tissue volume.

### Brain Asymmetry in WMS

Repeated measures analysis of variance (ANOVA) revealed a significant group by side difference for occipital-lobe tissue \((F = 5.0, p < .04\) for the group \(\times\) side interaction term). Specifically, as opposed to control subjects who showed relative symmetry in occipital-lobe tissue volumes for the right and left sides (62.5 and 61.8 cm\(^3\), respectively), the WMS group showed leftward predominance for this region (47.3 and 50.2 cm\(^3\), respectively). This finding appeared to be secondary to a left>right shift in gray matter of the occipital lobe in the WMS group \((F = 4.6, p < .05)\) as opposed to white matter \((F = 2.5, p = .13)\). No other variable assessed suggested group differences in asymmetry including hemispheric and individual lobe gray and

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The table shows comparative brain volumes in 14 subjects with WMS as compared to a group of age- and gender-matched normal controls. All volumes are in cubic centimeters (cm\(^3\)). The last column shows the ratio (provided as a percentage) of the average WMS volume to the average control subject volume. Nonproportional differences between the two groups are illustrated by the 12 percent reduction in frontal-lobe tissue volume as compared to a nearly 22 percent reduction for occipital-lobe tissue volume in subjects with WMS. Cerebellar volume is reduced only 7 percent in subjects with WMS relative to normal controls.
white matter volumes, subcortical gray volumes, and ventricular volumes. These findings indicate that the brains of individuals with WMS show abnormal patterns of asymmetry in the occipital lobe, primarily due to an abnormal leftward predominance of gray matter.

Cerebral Lobe Proportions in WMS

Multivariate analysis of covariance (MANCOVA) was initially utilized to determine whether individuals with WMS demonstrate an atypical pattern of cerebral morphology. This analysis used group as the main effect (i.e., WMS vs. Controls), total cerebral tissue as a covariate, and the combined right and left tissue volumes of each the four lobes of the brain as the dependent variables (i.e., frontal-lobe tissue, parietal-lobe tissue, temporal-lobe tissue, and occipital-lobe tissue). The F-value for the main effect of group was not significant (Wilks’ lambda $F = 0.92$, $p < 0.50$) indicating that individuals with WMS did not possess a unique pattern of cerebral tissue morphology in comparison to the control group. However, to further explore this issue, a variable was constructed that consisted of the ratio of frontal-lobe tissue volume to the combined tissue volumes of the parietal and occipital lobes. Nonparametric analysis using this variable indicated that the WMS group showed larger ratios compared to controls ($z = 2.2$, $p < .03$) suggesting that cerebral lobe brain proportions may be aberrant in WMS.

Given the disproportionate effect of WMS on gray and white matter volumes, MANCOVAs were also utilized to investigate patterns of tissue-specific brain development. For example, analysis of gray matter morphology used total cerebral gray matter and age as covariates, and the combined right and left gray matter volumes of each the four lobes of the brain as dependent variables. The white matter analysis was identical with the exception of using white matter volumes as the covariate and dependent variables. A statistical trend was observed for the gray matter lobe MANCOVA (Wilks’ lambda $F = 2.27$, $p < .10$), thus suggesting that the pattern of gray matter cerebral morphology in WMS was distinct from that observed in controls; the MANCOVA for cerebral white matter was not significant (Wilks’ lambda $F = 0.73$, $p < 0.60$).

Further exploratory analyses were conducted for possible group differences in gray matter lobe volumes because of the statistical trend observed in the gray matter MANCOVA and because differences in patterns of asymmetry for occipital-lobe gray matter were previously noted between subjects with WMS and controls. Specifically, these analyses included (1) evaluation of individual ANCOVA components comprising the gray matter lobe MANCOVA described in the preceding paragraph, and (2) assessment of individual right- and left-occipital-lobe gray matter volumes using total cerebral gray matter and age as covariates. These analyses indicated that parietal-lobe gray matter volume tended to be disproportionately increased in subjects with WMS ($F = 5.6$, $p < .03$) while occipital-lobe gray matter volume was disproportionately reduced ($F = 4.9$, $p < .04$) compared to controls. Analysis of separate right and left occipital gray matter volumes indicated that disproportionate volume loss in this region was

Figure 1. Brain Volume in WMS and Normal Controls. Average brain volumes in subjects with WMS were decreased 13 percent compared to controls. All values are in cubic centimeters (cm$^3$).

Figure 2. Ratio of Cerebellum to Cerebrum Volumes in WMS and Normal Controls. The greater ratio observed in subjects with WMS compared to control subjects represents a relative preservation of cerebellar volume in comparison to cerebral volume.
predominately on the right side \((F = 10.4, p < .004)\) as opposed to the left \((F = 1.8, p < .20)\).

### Superior Temporal Gyrus

ANCOVA was used to assess the relative volume of the STG, and its gray and white matter components. These analyses used group as the main effect, age and total cerebral tissue, gray or white matter volume respectively, as covariates, and STG tissue volumes (total tissue, gray matter, and white matter, respectively) as dependent variables. The analyses revealed that, after statistically adjusting for overall cerebral gray matter volume, gray matter STG volumes in subjects with WMS were proportionally larger compared to controls \((F = 4.7, p = .05)\). In fact, the unadjusted mean gray matter volume \((± SD)\) for the WMS group \((22.6 ± 1.7 \text{ cm}^3)\) was slightly larger than that observed for the normal control group \((22.0 ± 2.4 \text{ cm}^3)\). This between-group difference is reflected in Figure 3, that shows the STG gray/cerebral gray ratios in the two groups.

### Age-Associated Effects

ANOVA was utilized to investigate potential group differences in brain morphology associated with age. In these analyses, a group by age interaction term was the primary effect of interest. Dependent variables of interest included cerebral and cerebellar total tissue, gray, white, and CSF volumes, and lateral ventricular CSF and subcortical gray matter volumes. The interaction term was significant only for ventricular CSF volume \((F = 12.8, p = .002)\). Specifically, analysis of age-related changes by group showed that the trajectory of CSF volume in WMS was increasing with age \((r = 0.68, p < .008)\) compared to a nonsignificant trend for ventricular CSF volume to decrease with age in the control group \((r = -0.51, p < .10)\). A statistical trend also was observed for total cerebral CSF volume \((F = 4.1, p = .06)\). Individual group-age-by-volume analysis showed a pattern similar to that observed for ventricular CSF volume. The WMS group demonstrated increasing cerebral CSF volume with age \((r = 0.61, p < .02)\), while the control group showed no apparent correlation between these variables \((r = .05, p = .85)\).

### DISCUSSION

It is clear that precise characterization of anomalous brain development in WMS will eventually require longitudinal comparison of large numbers of young individuals with this condition to persons with both nonspecific as well as other specific causes of developmental disability, in addition to typically developing age- and developmental-age matched controls. Nevertheless, the findings presented here provide preliminary direction for future studies.

In this study, subjects with WMS were found to have smaller brain volumes than controls, with relative preservation of cerebellar volume (see Figure 4). An additional finding was the occurrence of disproportionate reduction in brainstem tissue volume in subjects with WMS. The results pertaining to cerebral and cerebellar volumes replicate findings from a previous study that assessed brain morphology in nine subjects with WMS (one subject overlapping with the present study), compared to six subjects with Down syndrome and 21 normal controls (Jernigan et al., 1993).

The presence of unusual patterns of brain morphology in the posterior fossa of individuals with WMS is of potential significance to recent reports describing genes present in the commonly deleted region on chromosome 7q. In particular, FZD3, a human homologue of the Drosophila gene “frizzled,” is thought to be involved in early development of the mammalian central nervous system, particularly the midbrain, pons and cerebellum (Wang et al., 1997). This apparent convergence of findings from imaging and molecular genetic studies of WMS suggests that future research should focus on the association of FZD3 and this brain region as a potential contributor to the neurobehavioral phenotype occurring in individuals with WMS.

Qualitative postmortem examination of gross neuroanatomy from persons with WMS has suggested that a pattern of frontal sparing and disproportionate posterior (parietal-occipital) reductions in cerebral volume may characterize the condition (see Figure 4) (Bellugi et al., 1999b; Galaburda & Bellugi, this volume; Gal-
The initial statistical analyses used in the present study provided only partial quantitative support for this hypothesis. While the MANCOVA for cerebral-lobe tissue failed to demonstrate a morphological pattern that differentiated subjects with WMS from controls, a variable representing the ratio of frontal-lobe volume to parietal + occipital-lobe volumes suggested the possibility of abnormal cerebral proportions in WMS. Further, occipital-lobe gray matter volume, particularly on the right, was noted to be decreased in the WMS group compared to controls while parietal-lobe gray matter volume was noted to be increased. These results are generally consistent with earlier imaging studies reporting reductions in brain volumes across cerebral regions in subjects with WMS (Jernigan et al., 1993); these subjects also were described as having relative “sparing” of frontal regions when compared to subjects with Down syndrome.

Relative preservation of gray matter and disproportionate reduction in white matter in subjects with WMS compared to normal controls is a particularly intriguing finding of the present study. This finding could result from alteration of any of a number of progressive or regressive events occurring during normal central nervous system development. These include cellular proliferation, migration and programmed death, growth and refinement of the neuropil, and myelination. A previous study, examining gray–white proportions in subjects with WMS, failed to detect differences from normal subjects (Jernigan et al., 1993). However, scan acquisition parameters for this prior study differed significantly from those utilized in the present study. In particular, image slice thickness in the earlier study was five times larger than the 1.5-mm slices utilized here. Increased slice thickness (and accordingly, voxel size) is associated with greater volume averaging artifacts occurring in image voxels that contain nonhomogenous tissues, thus potentially resulting in loss of image resolution and accuracy of tissue segmentation. The hypothesis that increased slice thickness, and thus, greater volume averaging, may explain the discrepancy in findings of this earlier study is supported by a more recent report from this same group. Specifically, using higher resolution scans that decreased artifact resulting from volume averaging, Harris-Collazo et al. (1997) reported that gray matter proportions appeared increased in a group of seven young adult subjects with WMS when plotted on a scattergram showing the proportion of gray matter as a function of age in normal controls.

If confirmed as a consistent feature of this genetic condition, the finding of abnormal proportions of gray
and white matter may also help guide the investigation of the function of other proteins resulting from genes deleted in persons with WMS. For example, the protein kinase resulting from the gene LIMK1, located in the commonly deleted WMS region, has been hypothesized to play a role in intracellular signaling, and synapse formation and maintenance in the central nervous system (Wang, Frenzel, Wen, & Falls, 1998). Similarly, syntaxin, the protein product of another gene deleted in WMS (STX1A), is thought to be involved in exocytosis of neurotransmitters from neurons (Nakayama et al., 1998). More detailed information regarding the role of these and other genes in the WMS critical region in human brain structure and function will provide a unique opportunity for elucidating meaningful correlations amongst genetic, neurobiological, and neurobehavioral factors in this genetic condition.

One brain area found to be preserved in size in subjects with WMS in this study, as well as in past imaging investigations of this condition (Hickok et al., 1995a; Hickok et al., 1995b), is the superior temporal region. This region of the brain is thought to be important in the perception and processing of music (Liegeois-Chauvel, Peretz, Babai, Laguitton, & Chauvel, 1998; Zatorre, Evans, & Meyer, 1994), as well as its well-known function in auditory and language processing (Demontet et al., 1992; Price et al., 1992; Schlosser et al., 1998). It is of potential interest that the gray matter volume of this region appears most preserved in individuals with WMS, given their relative cognitive strengths in both of these domains of cognitive processing and function. However, it would be premature to directly relate relatively larger gray matter volume of the superior temporal region in WMS to the cognitive profile exhibited by persons with this condition. As opposed to “endowing” persons with WMS with language and musical abilities, larger superior temporal gray matter volume in WMS might, alternatively, be secondary to consistently greater use of these cognitive skills over time resulting in larger cortical representation (Pantev et al., 1998) and corresponding increased neuropil (Sirevaag, Black, Shaftron, & Greenough, 1988). Longitudinal structural and functional imaging studies of young children with WMS are likely to help resolve this question.

Finally, in contrast to controls, age-related increases in total cerebral and, more specifically, lateral ventricular CSF, were noted in subjects with WMS. Positive correlations between CSF volume and age in subjects with WMS were not accompanied by significant negative correlations between age and tissue in this study. However, as CSF volume is significantly smaller than either gray or white matter volumes, relatively small, nonsignificant reduction in tissue volume over time could theoretically result in a proportionally larger, complementary change in CSF volume that is statistically significant. Longitudinal imaging studies of a large cohort of subjects with WMS will be essential in helping to resolve the question of whether abnormal age associated changes in neuroanatomy exist in WMS. If confirmed, clinical correlates of these age-related changes will be of great importance. For example, while WMS is clearly not a typical neurodegenerative disorder, recent studies suggest that some behavioral problems may intensify as some affected individuals enter adulthood (Gosch & Pankau, 1997).

Conclusion

This report represents the first in a series of investigations of the structure and function of the brain in individuals with WMS. Planned future studies will focus on limbic, mesial temporal, and subcortical regions, subregions of the cerebellum that have been reported to be particularly spared from volume reduction in this disorder (Wang, Hesselink, Jernigan, Doherty, & Bellugi, 1992), and the integrity and morphology of major white matter tracts, particularly the corpus callosum. Shape-based analyses of the cerebral lobes and their relation to the posterior fossa also are underway to more fully elucidate possible patterns of altered brain morphological development in individuals with WMS. Eventual correlation of neurocognitive and structural imaging findings with results obtained from functional imaging studies will be particularly important in elucidating the topography of neuroanatomical function and dysfunction underlying cognition and behavior in individuals affected with this enigmatic genetic condition.

METHODS

Subjects

Fourteen individuals with WMS, (nine men and five women; mean age: 28.7 ± 8.9, range 19 to 44 years), and 14 normal controls matched individually for gender and age (mean age: 29.0 ± 9.0 years; range 20 to 48 years) were studied. All subjects gave informed consent in writing prior to participation and were physically healthy. Subjects with WMS were tested as part of a large program project examining the associations among behavior, neurophysiology, neuroanatomy, and molecular genetics (see papers, this volume). All subjects with WMS were diagnosed clinically by a medical geneticist or other physician familiar with the characteristic features of WMS prior to inclusion into the current study (Jones, 1990; Morris et al., 1988). Subjects were excluded from the study if they had a history of concurrent medical conditions not typically associated with WMS, particularly those with confounding medical or neurological consequences. All clinical diagnoses were confirmed by trained researchers using the Williams Syndrome Diagnostic Scoresheet, a screening measure developed by the medical advisory board of the Williams Syndrome Association (1994). In addition, the diagnosis of WMS was genetically confirmed in all of the subjects.
using the fluorescent in situ hybridization (FISH) test for a deletion of one copy of the elastin gene on chromosome 7, as part of the molecular genetic studies (Korenberg et al., this volume).

**Imaging**

Magnetic resonance images of each subject’s brain were acquired with a GE-Signa 1.5 T scanner (General Electric, Milwaukee, WI). Sagittal images were acquired with a 3-D volumetric radio frequency spoiled gradient echo (SPGR) using the following scan parameters: TR = 24, TE = 5, flip angle = 45, NEX = 2, matrix size = 256 × 192, field of view = 24, slice thickness = 1.2 mm, 124 slices. Twenty-six of the 28 scans were acquired at the University of California, San Diego (UCSD) Medical Center Magnetic Resonance Imaging Institute. Two control scans were acquired at Stanford University using an identical pulse sequence and scanner. The SPGR image data were imported into the program BrainImage (Reiss, 1999) for semiautomated image processing analysis and quantification. These procedures have been described and validated elsewhere (Kaplan et al., 1997; Kates et al., 1999; Reiss et al., 1998; Subramaniam, Hennessey, Rubin, Beach, & Reiss, 1997). Data resulting from this semiautomated image-processing pipeline is in the form of left and right gray matter, white matter, and cerebrospinal (CSF) fluid volumes for each of the cerebral lobes, a subcortical region including the basal ganglia and thalamus, the cerebellum, brainstem, and the lateral ventricles. An exception to the semiautomated parcellation scheme typically utilized in our laboratory was employed due to the fact that subjects with WMS have been noted to have possible shape differences in the posterior-inferior part of their brain. Therefore, to increase accuracy of the brain parcellation component of our image-processing pipeline, manual delineation of the cerebellum and brainstem was utilized using modifications of a previously established protocol (Aylward & Reiss, 1991). After measuring and masking out posterior fossa tissue, the remainder of the brain tissue (i.e., cerebrum) was subdivided into the respective cerebral lobes and subcortical regions with a Talairach-based automated parcellation procedure as previously described (Andreasen et al., 1996; Kaplan et al., 1997).

Manual delineation of the STG was also used to supplement the semiautomated procedure. The STG was measured in the rostral-caudal direction from images in the coronal plane that were derived from the original image dataset. This coronal dataset was oriented parallel to the plane defined by the anterior and posterior commissures. The boundaries of the STG were defined laterally by the cortical surface and medially by a line connecting the deepest extension of the superior temporal sulcus (STS) to the furthest extent of the inferior ramus of the sylvian fissure. The most anterior slice of the STG measured coincided with the halfway point between the head of the putamen and the anterior commissure. This designation ensured the operational exclusion of medial-temporal gyral tissue, which merges with the STG at the temporal pole. The most posterior slice of the STG measured coincided with the first slice where the crus of the fornix was clearly identified laterally from the pulvinar. Interrater reliability for measurement of the volume of this region as measured by the intraclass correlation coefficient was 0.96.

**Data Analyses**

Data were first examined for normality to conform to the assumptions of the parametric statistics employed. Uni- and multi-variate analyses of variance and co-variance were performed to analyze group differences in overall and regional brain volumes. In general, because the processes of myelination and remodeling of the neuropil progress well into young adulthood, age was used as a standard covariate in all analyses in which either gray or white matter volumes were determined. Investigation of brain asymmetry utilized repeated measures ANOVA, which took diagnostic category as a between-subject factor and side (left vs. right) as a within-subject factor. The interaction effect (group × side) was used to determine group differences in asymmetry. Nonparametric statistical tests (Mann–Whitney U test) were used in all cases in which a ratio variable was assessed for group differences (e.g., cerebellar:cerebral ratio). A two-sided p value of .05 was chosen as the significant threshold except for analyses in which there was an a priori hypothesis in which case a one-sided test was utilized.

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