Significance of Planum Temporale and Planum Parietale Morphologic Features in Neurofibromatosis Type 1

Rebecca L. Billingsley, PhD; Gregory W. Schrimsher, PhD; Edward F. Jackson, PhD; John M. Slopis, MD; Bartlett D. Moore III, PhD

Background: Neurofibromatosis type 1 (NF-1) is associated with learning disabilities and cognitive impairment in childhood and adolescence. Individuals with NF-1 have a propensity for brain hyperintensities on T2-weighted magnetic resonance images, macrocephaly, and optic gliomas. Few clear relationships between these central nervous system abnormalities and cognitive function, however, have been found in this population.

Objectives: To determine whether planum temporale (PT) and planum parietale (PP) morphologic features are associated with learning disabilities in NF-1.

Patients and Methods: We measured and compared the surface area, gray matter volume, and asymmetry of the PT and PP on T1-weighted MRIs from 24 children and adolescents with NF-1 and an equal number of controls. Relationships between these measurements and cognitive and academic achievement scores were examined.

Results: The left PT in boys with NF-1 was significantly smaller in both surface area and gray matter volume compared with girls with NF-1 and controls. Boys with NF-1 also showed greater symmetry between the left and right hemispheres in this region compared with girls with NF-1 and controls, who showed a pattern of left greater than right asymmetry of the PT. Intelligence-based discrepancy scores of reading and math achievement, which are commonly used to define learning disabilities, were significantly related to PT asymmetry in the NF-1 group as a whole. Less leftward asymmetry of the PT was associated with poorer reading and math achievement in relation to intellectual test scores.

Conclusions: The high susceptibility of individuals with NF-1 to develop reading and other learning disabilities seems to be related to the development of the sylvian fissure. These results provide further support for the hypothesized association between sylvian fissure morphologic features and learning disabilities.

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PARTICIPANTS AND METHODS

PARTICIPANTS

Twenty-four individuals diagnosed as having NF-1 and 24 controls were included (Table 1). Participants were not preselected based on reading ability but were a subsample of individuals who received an MRI as part of a larger study of cognitive impairment in NF-1. One control was a sibling of a participant with NF-1 who had no family history of the disorder; the control showed no NF-1 characteristics. The patient and control groups did not differ significantly in age or education level. The Institutional Review Board (University of Texas, M. D. Anderson Cancer Center) approved all procedures. Informed consent was obtained from participants’ parents, and assent was obtained from the participants themselves.

Eleven participants with NF-1 had hyperintensities visible on T2-weighted and FLAIR MRI images. No participant had a hyperintensity in the lateral temporal or parietal lobe (regions of interest for the brain tracings). One participant with NF-1 had an optic glioma that was untreated and presumed to be nonprogressive. No control had evidence of abnormalities on MRI.

MRI PROCEDURE

All participants underwent scanning with a 1.5-T EchoSpeed scanner (GE Medical Systems, Milwaukee, Wis). Sagittal T1-weighted MRI images were obtained from contiguous sections (2.0-3.0 mm) covering the entire brain using a 3-dimensional fast spoiled gradient recalled echo sequence (echo time, 4.2 milliseconds; repetition time, 13 milliseconds; flip angle, 25°; 256×192 matrix; 60 sections; field of view [FOV], 220-240 mm; 1 excitation). This protocol was chosen because it is short enough (<3 minutes) that children as young as 6 years can tolerate the procedure with minimal motion.

BRAIN MEASUREMENTS

To ensure that comparable regions were examined in each brain, particularly given the tendency of individuals with NF-1 toward macrocephaly, proportional grid method was used. We divided each hemisphere into 4 equal units and measured sections between 2.25 and 3.25 units from midline, determined as the midsagittal section containing the anterior and posterior commissures, mammillary bodies, and infundibulum. The anterior border of the PT was defined as the most anterior Heschl’s sulcus (including cases in which more than 1 Heschl’s gyrus was evident). The posterior termination of the PT and the starting point of the PP were determined as the bifurcation into a posterior ascending and descending ramus. When the posterior ascending ramus originated before the termination of the sylvian fissure, the portion of the fissure posterior to the posterior ascending ramus was included in the PT measurement. Termination of the PP was defined as the dorsal tip of the posterior ascending ramus. In cases where the sylvian fissure merged with occipital and parietal sulci, termination of the measurements was at the merging point.

Surface contours were manually traced with a computer mouse and ImageJ software (National Institutes of Health, Bethesda, Md). The sum of the contour lengths in each hemisphere was multiplied by the slice thickness and pixel size for surface area estimates. Gray matter area in each slice was subsequently traced, and volume estimates were obtained by multiplying the sum of the areas by slice thickness and square pixel size.

Given the potential variability in estimating the anterior and posterior points of the PT and PP, interrater class correlations were calculated for the tracers (R.L.B. and G.W.S.). These individuals were blinded to the identity of the participants’ scans. In the 2 hemispheres, interrater class correlations were each 0.90. Examples of PT and PP tracings are presented in Figure 1.

COGNITIVE AND ACADEMIC TESTS

Each participant underwent comprehensive neuropsychological testing in 5 different domains: reading, math, spelling, phonologic processing, and visual-spatial processing. The reading domain consisted of Letter-Word Identification and Passage Comprehension. The math domain consisted of Calculation and Applied Problems. The spelling domain consisted of the Spelling subtest from the Wide Range Achievement Test. Phonologic processing tests included the Test of Auditory Analysis Skills and Word Attack. The visuospatial processing domain consisted of the Judgment of Line Orientation and Recognition Discrimination tests. Scores for Letter-Word Identification, Passage Comprehension, and Word Attack were not available for one patient. In addition to examining mean scores, we examined group differences in discrepancy scores between full-scale IQ and academic achievement in reading, math, and spelling. Discrepancy scores are commonly used to define LDs.

REGRESSION METHOD

Linear regression analyses were conducted to determine whether PT and PP asymmetry, surface area, or volume measurements were predictive of performance on each of the tests. We assessed whether brain measurements accounted for significant variance in performance above what was accounted for by the group and sex factors. Group was entered first in each regression analysis, followed by sex and asymmetry quotient, surface area, or volume measurement.

recent evidence suggests that both verbal and nonverbal deficits are common. To date, however, no definitive relationship between central nervous system anomalies and reading or other LDs has been demonstrated in patients with NF-1. Reading disability in the general population has been found to be associated with several cortical abnormalities. Studies of individuals with dyslexia have shown macroscopic hemispheric symmetry of the planum temporale (PT). An absence of the usual left greater than right asymmetry that is typically found in healthy individuals is a well-documented finding in postmortem studies of dyslexia. Early MRI studies also tended to show left-right symmetry of the PT or rightward asymmetry in reading-impaired populations, with notable exceptions. The superior extension of the sylvian fissure, the planum parietale (PP), has also been associated with read-
ing disability. Robichon and colleagues have suggested that phonologic impairment in dyslexia may be associated with greater PP asymmetry. In addition, PP morphologic features have been hypothesized to be associated with visuospatial function. Although neuroimaging and lesion evidence suggests that this region supports visuospatial processing, few direct correlations between visuospatial function and PP morphologic features have been reported.

One reason for inconsistency in studies that have examined associations between sylvian fissure symmetry and reading disability may be heterogeneity in the genotypes of the samples studied. Some investigators have attempted to associate specific phenotypic expression of reading disability (eg, dyslexic patients with vs without phonologic impairments) with neuroanatomic variants. Others have performed genetic linkage analysis to identify genomic regions that contribute to LDs. Our approach was to examine the brains of children who met diagnostic criteria for NF-1 to assess the hypothesized morphometric-functional relationships of the sylvian fissure in a population specifically at risk for LDs.

We measured the surface area and gray matter volume of the PT and PP in children and adolescents with NF-1 and matched controls. Given the incidence of reading disabilities and other LDs in NF-1, we hypothesized that patients would show less hemispheric asymmetry of the PT and PP, as has been observed for individuals with dyslexia in the general population. We hypothesized that less PT asymmetry would be associated with poorer performance on reading and phonologic processing tests. We expected that PT surface area and gray matter volume would be larger in the patient group, because previous investigations have shown greater total gray and white matter volume in NF-1. Finally, given the tendency of individuals with NF-1 to have visuospatial processing deficits and the possible association of PP morphologic features with visuospatial skills, we hypothesized that morphometric differences in this region would be related to performance on tasks that require visuospatial analysis.

## RESULTS

### BRAIN MEASUREMENTS

**Surface Area and Volume**

Table 2 gives the surface area and gray matter volume of the PT and PP. A 2 (group) × 2 (sex) analysis of variance revealed a main effect of group ($F_{1,43}=10.49, P=.002$) and a group-by-sex interaction ($F_{1,43}=7.04, P=.01$) for surface area of the left PT. Post hoc tests showed that this area was smaller for boys with NF-1 compared with controls. A main
The effect of group and a group-by-sex interaction were also found for gray matter volume of the left PT (F1,44 = 8.23, P = .006, and F1,44 = 5.99, P = .02, for the main effect and interaction, respectively), which was smaller for boys with NF-1. No significant group differences were observed in the right PT or the PP of either hemisphere.

**Asymmetry**

Hemispheric asymmetry ratios were calculated for the PT and PP separately as \((R-L)/(0.5(R+L))\). Controls showed greater leftward PT asymmetry than the NF-1 group in surface area (F1,44 = 12.24, P = .001) and gray matter volume (F1,44 = 7.26, P = .01). Group-by-sex interactions, however, modified these differences (F1,44 = 14.89, P < .001, and F1,44 = 12.38, P = .001, for surface area and volume, respectively). Boys with NF-1 tended to show less asymmetry than girls with NF-1 and controls. The PT asymmetry scores are presented in Figure 2. No group differences were found for PP asymmetry.

**READING AND COGNITIVE PERFORMANCE**

**Test Scores**

Neuropsychological and academic scores are listed in Table 3. Two (group) × 2 (sex) analyses of variance showed that the NF-1 group performed marginally worse than controls on Recognition Discrimination (F1,44 = 3.56, P = .07) and Applied Problems (F1,44 = 3.26, P = .08). Main effects of sex were observed for the Test of Auditory Analysis Skills (F1,44 = 14.89, P < .001, and F1,44 = 12.38, P = .001, for surface area and volume, respectively). Boys with NF-1 tended to show less asymmetry than girls with NF-1 and controls. The PT asymmetry scores are presented in Figure 2. No group differences were found for PP asymmetry.

**Discrepancy Scores**

A main effect of sex was found for the IQ-based discrepancy score for *letter-word identification* (F1,44 = 11.91, P = .001). Girls in both groups tended to perform above IQ expectations on this test. A group-by-sex interaction was found for the IQ-based discrepancy score for Applied Problems (F1,44 = 4.96, P = .03). Girls with NF-1 performed above IQ expectations on this test, whereas boys tended to perform below expectations (mean±SD difference scores, 3.3±13.7 for boys and −9.7±10.3 for girls); male and female control participants tended to perform above their full-scale IQ test scores (mean±SD difference scores, −8.4±11.0 for boys and −5.6±13.9 for girls).

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**Table 2. Mean (SE) Brain Measurements by Group and Sex**

<table>
<thead>
<tr>
<th></th>
<th>NF-1 Male</th>
<th>NF-1 Female</th>
<th>Control Male</th>
<th>Control Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface area, mm²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left PT</td>
<td>598.1 (39.6)†</td>
<td>687.1 (45.4)</td>
<td>862.1 (53.8)</td>
<td>713.3 (38.8)</td>
</tr>
<tr>
<td>Right PT</td>
<td>585.6 (37.3)</td>
<td>541.2 (30.9)</td>
<td>528.0 (46.5)</td>
<td>578.4 (30.1)</td>
</tr>
<tr>
<td>Left PP</td>
<td>138.6 (33.9)</td>
<td>130.5 (24.2)</td>
<td>170.4 (51.0)</td>
<td>108.6 (23.7)</td>
</tr>
<tr>
<td>Right PP</td>
<td>147.5 (25.0)</td>
<td>143.8 (24.9)</td>
<td>147.5 (25.0)</td>
<td>93.3 (21.2)</td>
</tr>
<tr>
<td><strong>Gray matter volume, mm³</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left PT</td>
<td>2290.3 (133.6)†</td>
<td>2619.7 (187.5)</td>
<td>3208.7 (221.7)</td>
<td>2692.4 (132.3)</td>
</tr>
<tr>
<td>Right PT</td>
<td>2262.7 (103.4)</td>
<td>1990.0 (87.3)</td>
<td>2196.6 (216.4)</td>
<td>2221.6 (151.9)</td>
</tr>
<tr>
<td>Left PP</td>
<td>541.0 (127.6)</td>
<td>543.6 (93.1)</td>
<td>660.9 (162.5)</td>
<td>415.5 (86.0)</td>
</tr>
<tr>
<td>Right PP</td>
<td>590.9 (93.2)</td>
<td>619.4 (90.4)</td>
<td>944.2 (175.5)</td>
<td>402.6 (86.3)</td>
</tr>
<tr>
<td><strong>Asymmetry coefficient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT area</td>
<td>−0.02 (0.06)†</td>
<td>−0.2 (0.06)</td>
<td>−0.5 (0.08)</td>
<td>−0.2 (0.06)</td>
</tr>
<tr>
<td>PT volume</td>
<td>−0.01 (0.05)†</td>
<td>−0.2 (0.07)</td>
<td>−0.4 (0.08)</td>
<td>−0.2 (0.06)</td>
</tr>
<tr>
<td>PP area</td>
<td>0.3 (0.3)</td>
<td>0.09 (0.26)</td>
<td>0.6 (0.3)</td>
<td>−0.03 (0.4)</td>
</tr>
<tr>
<td>PP volume</td>
<td>0.3 (0.3)</td>
<td>0.16 (0.25)</td>
<td>0.5 (0.2)</td>
<td>0.07 (0.4)</td>
</tr>
</tbody>
</table>

*NF-1 indicates neurofibromatosis type I; PT, planum temporale; and PP, planum parietale.
† P < .05 for group-by-sex interactions.
‡ P < .01 for group-by-sex interactions.

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**Figure 2. Planum temporale (PT) volume asymmetry score by group and sex. The hemispheric asymmetry score was calculated as \((R-L)/(0.5(R+L))\).**
Planum temporale surface area asymmetry accounted for a marginal increase in predicted variance \( R^2 = 0.06 \) in Letter-Word Identification discrepancy scores \( (F_{1,43} = 3.44, P = .07) \). Significant correlations were found between PT surface area asymmetry scores and Letter-Word Identification discrepancy scores for the NF-1 but not the control group \( (r_{23} = 0.43, P = .04, \text{and } r_{24} = 0.04, P = .85, \text{for NF-1 and controls, respectively}) \). Direct group comparisons of the slopes of the regression lines, however, were not significant.

Planum temporale gray matter volume asymmetry accounted for a significant increase in the predicted variance \( R^2 = 0.09 \) of discrepancy scores for Passage Comprehension \( (F_{1,43} = 4.87, P = .03) \). Correlations between PT volume asymmetry and Passage Comprehension discrepancy scores were significant for the NF-1 group but not for controls \( (r_{23} = 0.46, P = .03, \text{and } r_{24} = 0.17, P = .42, \text{for NF-1 and controls, respectively}) \); a direct group comparison of the slopes of the regression lines, however, was not significant \( (\text{Figure 3}) \). Surface area and volume of the right PP also accounted for a significant increase in the predicted variance \( R^2 = 0.08 \) for both surface area and volume of Passage Comprehension discrepancy scores \( (F_{1,43} = 4.39, P = .04, \text{and } F_{1,43} = 4.07, P = .05, \text{for surface area and volume, respectively}) \). Negative correlations between these measures, however, failed to reach significance.

Planum temporale surface area and volume asymmetry accounted for a significant increase in the predicted variance \( R^2 = 0.11 \) and \( 0.08 \) for area and volume, respectively of discrepancy scores for Applied Problems \( (F_{1,43} = 6.11, P = .02, \text{and } F_{1,43} = 4.16, P = .05, \text{respectively}) \). Correlations between PT surface area and volume asymmetry and the Applied Problems discrepancy score were significant only in the NF-1 group \( (\text{surface area: } r_{23} = 0.47, P = .02; \text{volume: } r_{24} = 0.45, P = .03) \) \( (\text{Figure 4}) \). Direct group comparisons of the slopes of the regression lines did not reach significance.

**COMMENT**

We expected to find larger surface area and gray matter volume measurements of the PT and PP in our sample because we previously demonstrated greater total gray matter volume in children with NF-1.\(^2\) However, we found that both the surface area and volume of the left PT were smaller in boys with NF-1 compared with controls. Boys with NF-1 also had less left-right PT asymmetry, similar to what has been reported for reading-impaired individuals in the general population.\(^3\) Although previous NF-1 studies have measured total brain volume by hemisphere,\(^2,3\) our results suggest that macrocephaly is not a uniform characteristic across cortical regions.

Comparisons of PT and PP asymmetry in nonreading-disabled populations have revealed a greater

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**Table 3. Mean (SE) Cognitive Domain Standard Scores by Group and Sex**

<table>
<thead>
<tr>
<th>Domain and Test</th>
<th>NF-1 Male</th>
<th>Female</th>
<th>Control Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading (WJ-R)</td>
<td>97.5 (6.3)</td>
<td>105.5 (4.2)</td>
<td>101.5 (3.9)</td>
<td>116.9 (4.5)</td>
</tr>
<tr>
<td>Letter-Word Identification</td>
<td>102.5 (7.4)</td>
<td>107.3 (4.5)</td>
<td>108.5 (4.3)</td>
<td>113.5 (4.7)</td>
</tr>
<tr>
<td>Passage Comprehension</td>
<td>95.3 (7.1)</td>
<td>100.5 (4.9)</td>
<td>100.8 (4.4)</td>
<td>107.2 (3.0)</td>
</tr>
<tr>
<td>Math (WJ-R)</td>
<td>97.0 (5.0)</td>
<td>97.1 (2.9)</td>
<td>97.8 (3.6)</td>
<td>106.9 (4.4)</td>
</tr>
<tr>
<td>Calculation</td>
<td>97.8 (7.2)</td>
<td>101.8 (4.0)</td>
<td>99.8 (4.6)</td>
<td>111.1 (4.0)</td>
</tr>
<tr>
<td>Applied Problems</td>
<td>95.2 (6.5)</td>
<td>103.6 (2.8)</td>
<td>92.2 (4.9)</td>
<td>107.4 (3.3)</td>
</tr>
<tr>
<td>Spelling (WRAT-III)</td>
<td>77.4 (8.2)</td>
<td>75.1 (5.4)</td>
<td>88.2 (5.3)</td>
<td>84.4 (7.2)</td>
</tr>
<tr>
<td>Phonologic processing</td>
<td>83.0 (7.0)</td>
<td>95.5 (4.8)</td>
<td>101.4 (4.7)</td>
<td>98.4 (5.8)</td>
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<td>JLO</td>
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<td>TAAS</td>
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<td>Visuospatial processing</td>
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<tr>
<td>Reading (WJ-R)</td>
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</tr>
</tbody>
</table>

\( ^{a} \text{NF-1 indicates neurofibromatosis type I; WJ-R, Woodcock Johnson Tests of Achievement, Revised; WRAT-III, Wide Range Achievement Test, 3rd ed; TAAS, Test of Auditory Analysis Skills; JLO, Judgment of Line Orientation; and RD, Recognition Discrimination.} \)

\( ^{\dagger} P < .05 \text{ for sex differences (combined group effect).} \)

\( ^{\ddagger} P < .005 \text{ for sex differences (combined group effect).} \)
tendency toward leftward asymmetry of the PT and rightward asymmetry of the PP.\textsuperscript{35,43} One report of PT asymmetry in children without reading disabilities found greater leftward asymmetry in girls, suggesting that sex may be a significant factor in the development of hemispheric asymmetry.\textsuperscript{35} Sex differences in PT asymmetry, however, have not been uniformly observed.\textsuperscript{44} Although our results showed that boys with NF-1 tended to have less PT asymmetry than girls with NF-1, we failed to find differences between boys and girls in our control group.

Overall, the neuropsychological profile of the participants with NF-1 in this study differed in several ways from that described by Cutting et al.\textsuperscript{13} Although the NF-1 group included herein tended to perform worse on a visuospatial analysis test,\textsuperscript{45} as has been reported in many investigations,\textsuperscript{5,6,11,45} as a group they did not differ from controls in reading or phonologic processing. Nonetheless, we found that in the NF-1 group, IQ-based discrepancy scores for reading comprehension and applied arithmetic were significantly related to PT asymmetry. Less asymmetry in the PT was associated with poorer performance relative to full-scale IQ in the NF-1 group. These relationships suggest that the susceptibility of individuals with NF-1 to develop LDs is associated with greater symmetry of the left and right PT.

Larsen and colleagues\textsuperscript{28} were the first to suggest that PT symmetry is associated with phonologic processing deficits in dyslexia. We did not find asymmetry scores to predict phonologic processing skills, but our ability to detect a relationship between these variables may have been restricted by the fact that few participants in this sample had a phonologic deficit. Leonard et al.\textsuperscript{19} suggested that phonologic dyslexia is associated with cumulative anatomic risk factors, including the number of perisylvian abnormalities. None of their participants with a phonologic deficit, however, showed rightward asymmetry or a symmetrical PT. The potential relationship of PT asymmetry and phonologic skills in the NF-1 population awaits further investigation, particularly of individuals who show greater phonologic deficits than those studied herein.

Previous investigations\textsuperscript{3,4,8} of NF-1 have failed to identify neuroanatomic abnormalities, including hyperintensities on MRI, that are consistently correlated with the visuospatial deficits commonly observed in this population. Investigators studying correlates of sylvian fissure morphologic features and LDs,\textsuperscript{6,8,11} have therefore limited our power to detect some morphometric-functional relationships. Nonetheless, the relationships observed suggest that the high susceptibility of individuals with NF-1 for reading and math disabilities is related to sylvian fissure development. Previous studies have demonstrated a relation between other neuroanatomic and neurocognitive features of NF-1. These include macrocephaly\textsuperscript{2} and the presence,\textsuperscript{3} number,\textsuperscript{6} or location\textsuperscript{8} of hyperintensities. This study provides additional evidence of brain-behavior relationships in children and adolescents with NF-1, specifically sylvian fissure morphologic features and LDs.

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Author contributions: Study concept and design (Drs Billingsley and Moore); acquisition of data (Drs Billingsley, Schrimsher, and Moore); analysis and interpretation of data (Drs Billingsley, Schrimsher, Jackson, Slopis, and Moore); drafting of the manuscript (Drs Billingsley and Moore); critical revision of the manuscript for important intellectual content (Drs Billingsley, Schrimsher, Jackson, Slopis, and Moore); statistical expertise (Drs Billingsley and Schrimsher); obtaining funding (Dr Moore); administrative, technical, and material support (Dr Jackson); study supervision (Dr Moore).

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