Sylvian fissure morphology in Prader-Willi syndrome and early-onset morbid obesity

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Purpose: Prader-Willi syndrome is a well-defined genetic cause of childhood-onset obesity that can serve as a model for investigating early-onset childhood obesity. Individuals with Prader-Willi syndrome have speech and language impairments, suggesting possible involvement of the perisylvian region of the brain. Clinical observations suggest that many individuals with early-onset morbid obesity have similar speech/language deficits, indicating possible perisylvian involvement in these children as well. We hypothesized that similar perisylvian abnormalities may exist in both disorders. **Methods:** Participants included individuals with Prader-Willi syndrome ($n = 27$), their siblings ($n = 16$), individuals with early-onset morbid obesity ($n = 13$), and their siblings ($n = 10$). Quantitative and qualitative assessments of sylvian fissure conformation, insula closure, and planum temporale length were performed blind to hemisphere and diagnosis. **Results:** Quantitative measurements verified incomplete closure of the insula in individuals with Prader-Willi syndrome. Planar asymmetry showed its normal bias toward leftward asymmetry in all groups except those with Prader-Willi syndrome maternal uniparental disomy. Individuals with Prader-Willi syndrome and siblings had a normal distribution of sylvian fissure types in both hemispheres, while individuals with early-onset morbid obesity and their siblings had a high proportion of rare sylvian fissures in the right hemisphere. **Conclusions:** The contrast between the anatomic findings in individuals with Prader-Willi syndrome and early-onset morbid obesity suggests that the language problems displayed by children with these two conditions may be associated with different neurodevelopmental processes. ***Genet Med* 2007:9(8):536–543.**

Key Words: *Prader-Willi syndrome, early-onset obesity, sylvian fissure, speech, language*

Prader-Willi syndrome (PWS) is an imprinted condition with approximately 70% of the cases due to a de novo deletion in the paternally inherited chromosome 15 q11-q13 region (PWS-D), 25% from a maternal uniparental disomy (PWS-UPD) of chromosome 15, and the remaining 5% from either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (i.e., imprinting defects).[1–3] The loss of several paternally expressed genes in the PWS region is thought to contribute to the abnormalities in brain development in this syndrome. The *MKRN3*, *MAGEL2*, *NDN*, SNURF-SNRPN, and *sno-RNA* genes are expressed in the brain.[4–7] The loss of some of these genes may result in misrouting of long projection axons, resulting in abnormalities of cortical development in individuals with PWS.[6]

Many of the features of PWS suggest that brain abnormalities may play an important role in the clinical phenotype. Speech impediments and repetitive speech have drawn attention to areas of the brain involved in speech and language processing, such as the parietal lobe, insula, and Heschl's gyrus.[8] Individuals with PWS also have difficulties with receptive language and articulation, again suggesting possible abnormalities in the areas surrounding the sylvian fissure.[9] However, only a few small studies of brain structure in individuals with PWS have been published. One study, using magnetic resonance imaging (MRI), reported a lack of normal sylvian fissure asymmetry in four individuals with PWS.[10] A previous qualitative study from our group identified multiple brain abnormalities in individuals with PWS, including ventriculomegaly, sylvian fissure polymicrogyria, and incomplete sylvian fissure/insula closure.[11]

Although no abnormalities were seen in a comparison group of individuals with early-onset morbid obesity (EMO) of unknown etiology, we did note similarities between individuals with PWS and those with EMO on cognitive and achievement testing using the Woodcock-Johnson Tests of Cognitive Abilities and Achievement, Third Edition (WJ-III).[12] Individ-

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uals with EMO had a phonemic awareness cluster score and an incomplete words subtest score that were more similar to those of individuals with PWS than to normal-weight control siblings. However, individuals with EMO had better verbal comprehension and sound blending subtest scores than those with PWS.[12] Thus, we hypothesized that individuals with EMO may also have neurodevelopmental abnormalities in the areas surrounding the sylvian fissure as well, but that these abnormalities may differ from those seen in individuals with PWS.

Cognitive and achievement findings in individuals with PWS are somewhat variable.[13–15] One study found that although 58% of individuals with PWS had an IQ in the normal-borderline range (i.e., >70), all of them had learning disabilities and 75% had dyslexia.[16] In general, studies have found that individuals with PWS-UPD have better verbal ability and higher verbal IQ scores than those with PWS-D.[14,15] Some individuals with PWS-D have been shown to have strong visuospatial skills.[15] Therefore, we hypothesized that we would see abnormalities in the perisylvian region in individuals with PWS and possibly greater abnormalities in individuals with PWS-D than those with PWS-UPD.

The sylvian fissure forms when the frontal, parietal, and temporal opercula grow over the insular cortex.[16] Sylvian fissure morphology influences the size and shape of the temporal and parietal cortex and has been associated with differences in phonologic and auditory processing.[17,18] One component of the sylvian fissure, the planum temporale, may play a role in both visual and auditory language comprehension.[19] Previous studies have found that the planum temporale is larger in the left hemispheres of 68%–78% of individuals from a normal population.[18,20,21] The planum parietale, which is the posterior part of the sylvian fissure, tends to be larger in the right hemisphere than the left.[22,23] Although the clinical significance of these asymmetries is controversial,[24] a previous study found a lack of this asymmetry in four individuals with PWS, suggesting that some of the speech and language abnormalities in this syndrome may be associated with structural brain differences.[10]

Sylvian fissure morphology has been classified by a system developed by Steinmetz et al.[25] Long fissures (type 2/3), associated with multiple gyri in the operculum, are more common on the left, whereas short fissures (type 4), associated with missing gyri, are more common on the right.[25] Given the indications of sylvian fissure/insula abnormalities in PWS, we aimed to characterize fissure morphology within our sample of individuals with PWS and EMO and compare the prevalence of various fissure types with a previously recorded distribution in a normal population.[25]

The primary aims of the current study were to (1) establish whether quantitative measurements of insula closure verified our qualitative findings that individuals with PWS have incomplete insula closure[12]; (2) investigate whether the proportion of nontypical sylvian fissure types differ in PWS, EMO, and controls as would be predicted by the speech and language problems exhibited in individuals with PWS and EMO; and (3) determine whether individuals with PWS have diminished planar asymmetry, confirming findings from the small sample studied previously.[10]

METHODS

Subjects were recruited from the general pediatrics clinics, as well as from the pediatric genetics and endocrine clinics. The subjects were individuals with PWS ($n = 27$, age 3 months to 39 years; 16 males, 11 females), their siblings ($n = 16$, age 2 months to 43 years; five males, 11 females), and individuals with EMO ($n = 13$, age 4 to 16 years; four males, nine females), and their siblings ($n = 10$, age 4 to 24 years; five males, five females) participating in a study of the natural history of PWS and EMO. All subjects who were able to express hand preference were right-handed. This case-control study was approved by the University of Florida Institutional Review Board, and all participants and/or their guardians provided written informed consent.

All individuals with PWS were first characterized by DNA methylation analysis at the 5′ *SNURF-SNRPN* locus and by fluorescence in situ hybridization using the *SNURF-SNRPN* probe and a distal chromosome 15 control probe. If a subject was positive for PWS by DNA methylation analysis but had an intact 15q11-q13 region by fluorescence in situ hybridization, then DNA polymorphism analysis was used to distinguish maternal UPD 15 from an imprinting defect. Seventeen individuals with PWS had a paternal deletion of the chromosomal 15q11-q13 region, and six had maternal UPD 15. For this study, we did not distinguish size of deletion in those patients with paternal deletion of 15q11-q13.

Subjects with EMO were recruited based solely on a history of a body mass index >95% for age and gender before the age of 4 years and no recognized syndromal cause of obesity, as determined by a board-certified geneticist (D.J.D.). All participants in the EMO group had a normal chromosomal, *SNURF-SNRPN* fluorescence in situ hybridization, and DNA methylation analysis for PWS,[1] melanocortin 4 receptor mutation testing,[26] and fragile X DNA testing. Additionally, no subjects were found to be leptin deficient by commercial testing with radioimmunoassay (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA).

Cognitive testing

All subjects older than 3 years of age received the WJ-III cognitive standard battery and all subjects older than 6 years of age received the WJ-III standard achievement battery.[27] Individuals younger than 6 years of age were unable to complete the achievement portion of the test. In addition to the overall cognitive and achievement scores on the standardized cognitive and achievement tests, we evaluated 10 subtests of the cognitive portion (including verbal comprehension, visual-auditory learning, and visual matching among others), and 12 subtests of the achievement portion (including letter-word identification among others).

Scanning procedure

All subjects underwent head MRI scans in a 3-T Siemens Allegra scanner (Siemens, Munich, Germany). Three-dimensional anatomic images were obtained from 160 axial slices, with a matrix of 256 × 256, and a slice thickness of 0.9–1.3 mm.[11] Scans were processed using Functional MRI Brain Software Library[28] for brain extraction, rigid-body transformation, and alignment to standard Talairach space.

MRI measurements

At least two raters performed all measures, blind to the identity and diagnosis of the individuals. Quantitative measurements included identification of the lateral position for sylvian fissure/insula closure and total length of the planum temporale. To assess degree of insula closure, we paged through sagittal images beginning when the insular cortex was fully visible until reaching a lateral slice where the insular cortex was no longer visible and the sylvian fissure appeared tightly closed and recorded the lateral position from the midline in standard Talairach coordinates (Tal mm). Planum temporale length was measured by manually tracing the planum using boundaries defined by Heschl's sulcus anteriorly and the origin of the planum parietale posteriorly. Raters were blind to hemisphere of the brain being measured.

Sylvian fissure morphology was determined based on the relationship between the planum parietale, postcentral sulcus, and posterior parietal gyri, using types defined by Steinmetz et al.[25] Seven infants (i.e., younger than the age of 2 years) were excluded from assessment of sylvian fissure morphology due to lack of gray/white matter differentiation.

Statistical methods

This was a cross-sectional, nonrandomized study examining insula closure, length of planum temporale, and sylvian fissure types in five different test groups: EMO, PWS deletions (PWS-D), PWS-UPD, sibling controls of EMO patients, and sibling controls of all subjects with PWS (PWS-D and PWS-UPD siblings combined). For the quantitative variables total brain volume, total insula closure (bilateral), and total planum length (bilateral), a hierarchical testing method was employed. First, to control study-wide error in each variable tested, a five-way analysis of covariance contrasting the five groups, using age as a covariate was employed. If this was not statistically significant at $P < 0.05$, no subgroups were compared statistically. If significance was obtained at $P < 0.05$, the following two-sided group contrasts were made by analysis of covariance controlling for age: EMO versus EMO-control, PWS-D versus PWS-UPD, all PWS versus PWS-control, and all PWS versus EMO. In addition, for planum length, we looked at the left hemisphere minus the right hemisphere (Δ-planum), and compared this to a mean of zero first stratified for the five subject groups. If that was significant at $P < 0.05$ (two sided), we ran the pairwise comparison by matched *t* tests. Finally, the left and right consensus for sylvian fissure assessment were cross-tabulated over the five groups, yielding cross-tabulation tables. To control study-wide error, an exact conditional χ^2 test was run asking whether the distributions were the same over the five subject groups. Further contrasting was done in the same manner within subsets if and only if the *P* value for the five-group comparison was significant at <0.05.

To demonstrate that differences between groups were not due to differences in age, gender, or brain volume, multiple linear regression was performed including brain volume, planum temporale length, planum temporale asymmetry, and insula closure as dependent variables and age ($\log_{10}$-transformed), brain volume, gender, and group as independent variables (using Sigmastat 2.03, Jandel Corp., San Rafael, CA).

RESULTS

Cognitive testing

Similarities were noted between individuals with PWS and those with EMO on cognitive and achievement testing using the WJ-III. On the cognitive portion of the WJ-III, both individuals with PWS and EMO had significantly lower scores than their sibling controls in general intellectual ability (GIA), the phonemic awareness cluster, and the verbal ability cluster (Table 1). However, the individuals with EMO, as well as both sibling control groups, scored higher than the PWS group on some of the speech- and language-specific subtests of the WJ-III Cognitive test, including the visual auditory learning subtest and the visual matching subtest (Table 1). The EMO and PWS groups and the siblings of individuals with EMO all scored lower than the siblings of individuals with PWS on the incomplete words subtest (Table 1). Individuals with PWS-UPD either scored 1 SD lower or did not score significantly differently than individuals with PWS-D on the cognitive portion of the WJ-III.

On the achievement portion of the WJ-III, the siblings control groups scored higher on the oral language cluster than the individuals with EMO and PWS (Table 1). There was no difference between individuals with PWS-D and PWS-UPD for this cluster (Table 1). Furthermore, both control groups and the EMO group scored significantly higher on the letter-word identification subtest than the individuals with PWS (Table 1). Individuals with PWS-D scored >1 SD higher (Table 1) than individuals with PWS-UPD on this subtest ($P = 0.008$).

Sylvian fissure/insula closure

In all subjects (PWS- and EMO-siblings combined), the lateral extent of left or right insula closure was not significantly influenced by age ($r^2 = 0.01–0.07$, $P = 0.2–0.7$), brain volume ($r^2 = 0.01–0.08$, $P = 0.2–0.7$), or gender ($P = 0.6–0.8$). Individuals with PWS had more lateral closure of the insula bilaterally than either controls (combined PWS- and EMO-siblings) or individuals with EMO ($P < 0.05$) (Table 2, Fig. 1). This finding was significant in both PWS-D and PWS-UPD, and there were no significant differences between these two groups. No differences in insula closure were noted between individuals with EMO and the control group, suggesting that

Table 1
WJ-III speech and language testing

Variable	EMO sibs ($n = 7$)	PWS sibs ($n = 13$)	EMO (E) ($n = 13$)	PWS-D ($n = 13$)	PWS-UPD ($n = 7$)	ANOVA post hoc[a,b]
M/F	2/5	4/9	4/9	7/6	5/2	
Age, yr	12.3 (8.6)	15.4 (11.7)	9.6 (3.9)	17.9 (10.6)	23.1 (8.3)	
Age range, yr	4–27	2–43	4–16	3–39	8–34	
GIA	111 (16)	113 (11)	82 (18)	72 (24)	55 (13)	C > P ($P < 0.001$), C > E ($P < 0.01$), E > P ($P = 0.04$), D = UPD ($P = 0.28$)
Phonemic awareness	114 (10)	113 (10)	96 (19)	90 (13)	78 (12)	C > P ($P < 0.001$), C > E ($P < 0.001$), E = P ($P = 0.2$), D = UPD ($P = 0.5$)
Verbal ability	112 (17)	111 (16)	94 (17)	79 (17)	65 (12)	C > P ($P < 0.001$), C > E ($P = 0.001$), E > P ($P = 0.006$), D = UPD ($P = 0.6$)
Visual-auditory learning	97 (19)	112 (20)	89 (13)	74 (22)	41 (21)	C > P ($P < 0.001$), C > E ($P = 0.001$), E > P ($P = 0.01$), D > UPD ($P = 0.01$)
Visual matching	105 (15)	105 (15)	80 (24)	76 (18)	59 (12)	C > P ($P < 0.001$), C > E ($P < 0.001$), E = P ($P = 0.2$), D > UPD ($P = 0.04$)
Sound blending	117 (11)	111 (8)	99 (11)	88 (16)	75 (9)	C > P ($P < 0.001$), C > E ($P < 0.001$), E > P ($P < 0.05$), D = UPD ($P = 0.4$)
Incomplete words	106 (7)	113 (16)	103 (17)	96 (7)	91 (12)	C > P ($P < 0.05$), C > E ($P < 0.05$), E = P ($P = 0.4$), D = UPD ($p = 0.9$)
Oral language	110 (18)	113 (12)	100 (16)	80 (19)	73 (10)	C > P ($P < 0.001$), C > E ($P = 0.013$), E > P ($P = 0.001$), D = U ($P = 0.2$)
Letter-word identification	107 (10)	109 (15)	91 (14)	84 (24)	63 (15)	C > P ($P < 0.001$), C > E ($P = 0.007$), E = P ($P = 0.2$), D > UPD ($P = 0.04$)

Values in table represent mean scores on the Woodcock-Johnson Tests of Cognitive Abilities (WJ-III); SDs are in parentheses. Normal range for all aspects of testing is 85–115 for the general population. EMO, early-onset morbid obesity; GIA, general intellectual ability; PWS, Prader-Willi syndrome (PWS-D, PWS due to paternal deletion and PWS-UPD, PWS due to maternal disomy); sibs, sibling controls.
[a]Sibling control groups were combined (using the letter C) in post hoc analyses as the only difference between EMO sibs and PWS sibs was on incomplete words subtest. The remainder of the cognitive and achievement testing showed no significant differences between the two control groups. PWS groups are shown as P in post hoc analysis and EMO group as E.
[b]Values denoted with an equal sign demonstrate nonsignificance in post hoc analyses, whereas values with > denote $P < 0.05$ between the groups.

Table 2
Perisylvian findings

Variable	EMO sibs ($n = 10$)	PWS sibs ($n = 16$) (planum measured: $n = 13$)	EMO ($n = 13$)	PWS-D ($n = 20$) (planum measured: $n = 17$)	PWS-UPD ($n = 7$)
Insula closure (Tal mm)					
L	48.0 (2.2)	47.7 (1.6)	48.0 (1.8)	49.0 (1.7)	50.1 (2.8)
R	46.8 (2.0)	47.2 (2.6)	47.3 (2.3)	48.9 (2.4)	49.2 (1.5)
Planum (cm)					
L	3.14 (1.1)	2.94 (0.76)	3.24 (0.67)	2.63 (0.77)	2.51 (0.52)
R	2.25 (0.93)	2.27 (0.52)	2.37 (0.46)	2.04 (0.68)	2.40 (0.77)
Δ(L-R)	0.89 (0.97)	0.67 (0.86)	0.87 (0.82)	0.59 (0.83)	0.11 (0.93)

All values are expressed in standard Talairach coordinates. The rows indicating insula closure contain the Talairach value in millimeters at which the insular cortex was no longer visible and the SD for those measurements in parentheses. The rows indicating planum measurements contain the measurement value in centimeters for the total planum length with the SD for those measurements in parentheses. EMO, early-onset morbid obesity; PWS, Prader-Willi syndrome; PWS-D, PWS due to a de novo deletion in the paternally inherited chromosome 15 q11-q13 region; PWS-UPD, PWS due to maternal uniparental disomy.

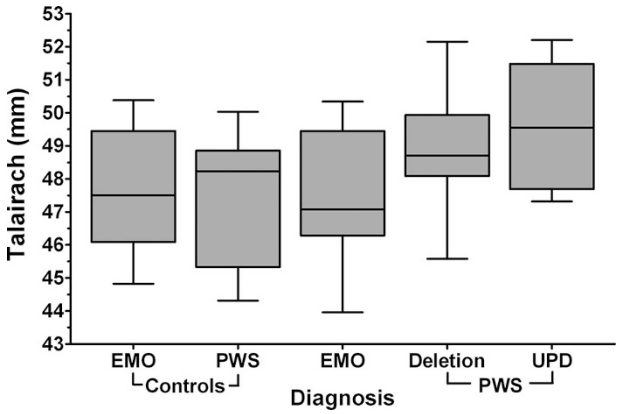

Fig. 1. Lateral closure of insula in individuals with Prader-Willi syndrome (PWS). Individuals with PWS have more lateral closure of the insula bilaterally compared with controls and individuals with early-onset morbid obesity (EMO). UPD, uniparental disomy.

this finding is specific to the genetic abnormality associated with PWS (Fig. 3).

Planum temporale

In all subjects (PWS- and EMO-siblings combined), neither the left nor right planum temporale length nor the Δ-planum length was significantly influenced by age ($r^2 = 0.01–0.11$, $P = 0.1–0.7$), brain volume ($r^2 = 0.01–0.06$, $P = 0.3–0.6$), or gender ($P = 0.1–0.9$). No significant differences were found in length of the planum temporale in either hemisphere between individuals with PWS, those with EMO, and normal weight controls, although there was a trend toward a smaller left planum temporale in the subjects with PWS ($P = 0.08$) (Table 2). In all groups except the PWS-UPD group ($n = 7$), the left planum temporale was significantly larger than the right ($P < 0.05$ for PWS deletion, EMO, and controls). In the small PWS-UPD group, there was no significant difference ($P = 0.76$) in the length of the planum temporale between the right and left hemispheres. This group difference was significant ($P < 0.001$).

Sylvian fissure

Individuals with PWS and their siblings had normal proportions of sylvian fissure types in the right and left hemispheres, relative to a reference population.[25] The majority of individuals with PWS had bilateral type 1 fissures with a minority having type 2 and 3 fissures in the left hemisphere and type 4 in the right hemisphere (Table 3). Families with EMO had normal sylvian fissure proportions in the left hemisphere, but tended to have a higher proportion of type 4 sylvian fissures in the right hemisphere ($P = 0.056$; Table 3, Fig. 2). Those EMO sibs with type 4 fissures had a mean GIA of 122 (normal range for general population, 85–115), whereas those who had nontype 4 fissures had a mean GIA of 110. Although this difference was not statistically significant ($P = 0.2$), it represents a difference of >1 SD between the groups and bears further investigation.

Table 3.
Sylvian fissure categories (proportion of hemispheres)

Type	EMO-sibs	PWS-sibs	EMO	PWS-D	PWS-UPD
1					
L	6	10	9	16	4
R	6	15	9	19	7
2/3					
L	5	6	4	4	3
R	0	0	0	0	0
4					
L	0	0	0	0	0
R	4	1	4	1	0

EMO, early-onset morbid obesity; PWS, Prader-Willi syndrome; PWS-D, PWS due to a de novo deletion in the paternally inherited chromosome 15 q11-q13 region; PWS-UPD, PWS due to maternal uniparental disomy. L, left; R, right.

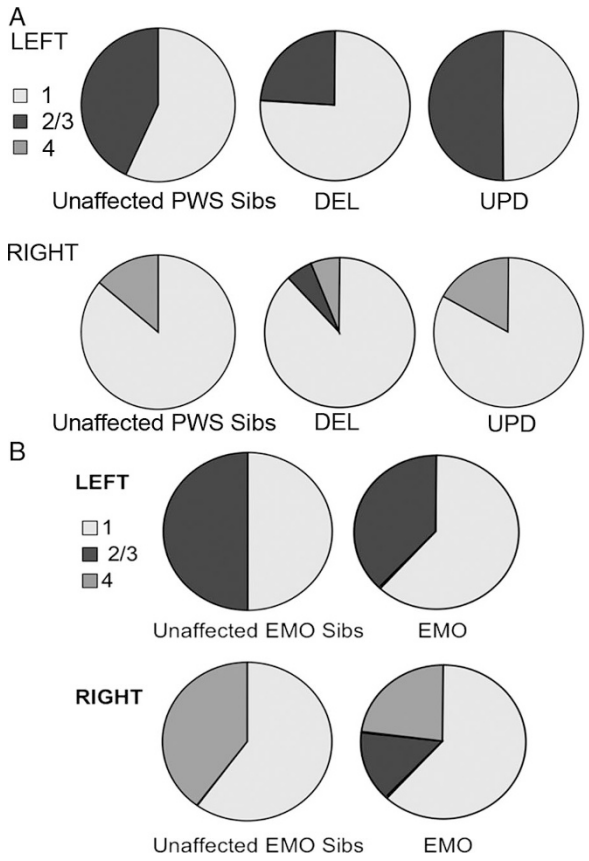

Fig. 2. Proportion of sylvian fissure types among groups. (A) Individuals with Prader-Willi syndrome (PWS) and their siblings have a normal distribution of sylvian fissure types. (B) Individuals with early-onset morbid obesity (EMO) and their siblings have a higher proportion of the rare type 4 fissure in the right hemisphere.

DISCUSSION

Individuals with PWS have abnormalities in the perisylvian region that may contribute to the high frequency of speech and language abnormalities in individuals with this condition. We

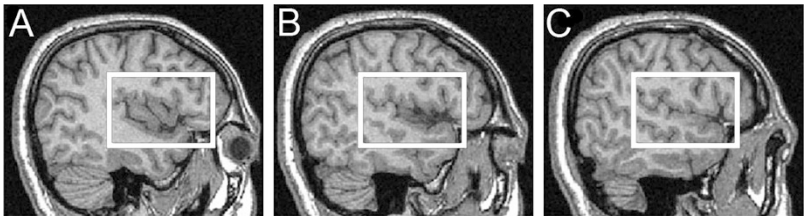

Fig. 3. Insula closure in Prader-Willi syndrome (PWS) versus controls. To measure insula closure, we paged through consecutive brain slices beginning at the outer edge of the insular cortex (A). (B) The insular cortex is still visible in an individual with PWS, as compared with a control sibling (C) in which the sylvian fissure is tightly closed.

noted similarities on cognitive and achievement testing between individuals with PWS and those with EMO of unknown etiology. We found that both individuals with PWS and those with EMO scored significantly lower on tests of overall cognitive ability, phonemic awareness, and oral language skills than their normal control siblings. However, the two groups had different morphologic findings in the perisylvian region.

The more lateral closure of the insula in PWS reflects a failure of development in the frontal, temporal, and parietal opercula. This failure is particularly notable in that it occurs in the context of normal brain size. This failure of cortical growth over the insula could be caused by the absence of paternally expressed genes in the PWS region related to cortical development.[4–7] Further support for an underlying genetic etiology of these structural brain abnormalities comes from the identification of these changes in individuals with PWS at all stages of development, from infancy through adulthood. In addition to the motor planning of speech, pain perception and autonomic control are functions associated with the insula. These functions are frequently abnormal in individuals with PWS.[7,29,30] The insula also houses the primary gustatory cortex, an area involved with integrating taste with appetite and food craving.[29,31] Although we currently do not understand the mechanisms responsible for differential insula closure, it is possible that differences in white matter connectivity between the insula and surrounding cortex may be involved. The lack of insula closure could play a role in the clinical phenotype of individuals with PWS. Further studies using functional MRI should be conducted to further examine the role of these brain regions in individuals with PWS and to correlate structural MRI findings with functional and clinical characteristics.

Leftward asymmetry of the planum temporale in right-handed individuals is associated with verbal and phonologic skill in children,[32,33] whereas a lack of leftward asymmetry has been noted in some individuals with oral language disorders.[34] In light of the prevalence of speech and language disorders in individuals with PWS,[9,35] as well as an indication of decreased asymmetry reported earlier,[10] we expected to find decreased asymmetry again. In contrast, the larger group of PWS-D had a normal pattern of planum temporale asymmetry. Only the small group of PWS-UPD had equal frequencies of left and right asymmetry. It is interesting to note that the individuals with PWS-UPD had scores >1 SD below the PWS-D in areas of cognition, processing, and letter-word identification, supporting previous evidence that poor phonology and poor reading comprehension is associated with small symmetrical plana.[34,36]

Structural variation of the sylvian fissure occurs in the normal population.[25] Most frequently seen in both hemispheres is the type 1 fissure in which the posterior ascending ramus (PAR) rises posterior to the postcentral sulcus. Rare variants in the left hemisphere include the type 2 fissure, which lacks a PAR, and the type 3 fissure in which there is interposition of an intermediate opercular sulcus anterior to the PAR. In the right hemisphere, the rare variant is the type 4 fissure, where the PAR enters the postcentral gyrus, directly posterior to the central sulcus.[25,37] Interestingly, although the individuals with PWS, as well as their siblings, had a normal distribution of sylvian fissure types compared with the original reference population,[25] the families of the individuals with EMO showed a trend toward a higher proportion of the rare type 4 fissure. The unusual truncation of the planum temporale seen in type 4 fissures results in a smaller temporal lobe, with a relative enlargement of the parietal lobe. This finding has been documented in some individuals who have poor "bottom-up" word and number processing compared with superior "top-down" functions requiring inferencing and visualization.[23,38] Although this fissure type is rare, it is much more commonly seen in the right hemisphere.[25,37] Individuals with type 4 fissures have been reported to be more successful with visuospatial than linguistic skills.[20,37]

In our study, both individuals with EMO and their siblings did more poorly than other controls on the incomplete words subtest of the WJ-III, a measure of bottom-up word processing. However, neither group showed superior levels of inferencing or visualization. In fact, the individuals with EMO had a lower GIA and performed more poorly than controls on the majority of the subtests of the WJ-III,[11] indicating overall cognitive dysfunction. By contrast, their siblings had a normal GIA, with average scores on the remainder of the subtests. Those EMO siblings with type 4 sylvian fissures performed superiorly on the cognitive testing compared with those with nontype 4 fissures. Although not statistically significant in this small sample, the observation that the EMO families appeared to have a higher percentage of the rare type 4 fissure warrants further investigation in a larger sample.

Although we did see abnormalities in the perisylvian region in both individuals with EMO and those with PWS, the findings differed between the two groups as well as between families of the groups. Individuals with PWS had abnormal closure

of the insula, but this group as a whole had a normal distribution of planar asymmetry (except the group with PWS-UPD) and a normal distribution of sylvian fissure types, whereas individuals with EMO and their siblings had a higher percentage of type 4 fissures than a reference population. Because the individuals with EMO whom we studied likely have a variety of different etiologies for becoming obese, the only commonality between the individuals with PWS and those with EMO is the development of obesity early in childhood. Therefore, we have hypothesized that becoming obese early in life may result in cognitive compromise,[12] which may contribute to difficulties with speech and language. The fact that the EMO families had a higher percentage of the rare type 4 fissure suggests an underlying genetic mechanism that is influencing brain development in those families. The individuals with EMO may have less ability to compensate for the structural brain anomalies than their siblings, due to other factors contributing to or arising from obesity. Therefore, the differences in cognitive phenotype between the children with EMO and PWS and their siblings may be due to metabolic perturbations caused by the accumulation of adipose tissue early in life.[12]

Future studies will need to correlate our findings with specific speech and language assessments in these individuals. Additionally, we plan to measure planum temporale length in a larger group of individuals with PWS-UPD and investigate the etiology of differences in insula closure between groups by assessing differences in frontal and temporal cortical volumes.

Our findings, when taken together, suggest that there is independence of various hemispheric development processes among the different groups. The limitations of this study include its cross-sectional nature and the lack of ability to perform the WJ-III on everyone who had an MRI scan (those individuals younger than 2 years of age cognitively or developmentally could not take the WJ-III). However, the anomalies we have seen in the perisylvian regions of the brain suggest that genetic mechanisms may be responsible for some of the speech and language abnormalities seen in PWS and may contribute to difficulties with oral language and phonemic awareness in families with EMO.

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