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Anomalous sylvian fissure morphology in Williams syndrome

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The unusual sensitivity and attraction to auditory stimuli in people with Williams syndrome (WS) has been hypothesized to be the consequence of atypical development of brain regions surrounding the Sylvian fissure. Planum temporale surface area, which is determined in part by Sylvian fissure patterning, was examined in 42 WS and 40 control participants to determine if anomalous Sylvian fissure morphology is present in WS. WS participants had significantly reduced leftward asymmetry of the planum temporale compared to control participants, due to a significant expansion in the size of the right planum temporale. The increased right planum temporale size was largely due to WS participants (24%) who had a right hemisphere Sylvian fissure that coursed horizontally and failed to ascend into the parietal lobe. This sulcal pattern is unusual in the right hemisphere and is more commonly found in the left hemisphere of typically developing individuals. There were no control participants with this type of right hemisphere Sylvian fissure pattern. The right hemisphere Sylvian fissure sulcal patterns were also related to a measure of cortical complexity and the amount of right hemisphere occipital lobe volume, suggesting that intrinsic genetic influences leading to anomalous visual system development in WS have widespread influences on cortical morphology that are similar in manner to extrinsic embryonic visual system lesions.

Introduction

People with Williams syndrome (WS) demonstrate a remarkable profile of neurobiological, cognitive, and behavioral impairments that result from a hemideletion of approximately 28 genes on chromosome 7 (Bayes et al., 2003; Korenberg et al., 2000). The most profound WS impairments fall in the visual spatial domain and include problems with visual constructive, visual motor, visual spatial working memory, selective attention, and saccadic eye movement tasks (Atkinson et al., 1997; Bellugi et al., 2000; Farran et al., 2003; Frangiskakis et al., 1996; Scerif et al., 2004; van der Geest et al., 2004). These problems representing visual space are hypothesized to stem from impaired visual dorsal stream development (Atkinson et al., 1997). The results of neuroimaging and postmortem studies strongly support this hypothesis and demonstrate anomalous function and structure of occipital and posterior parietal cortex (Eckert et al., 2005; Galaburda and Bellugi, 2000; Meyer-Lindenberg et al., 2004; Reiss et al., 2004). Anomalous development of the WS visual system is likely due to hemizygosity for genes such as GTF2I and LIMK1, which have been associated with the visual spatial impairment and general cognitive impairment observed in WS (Botta et al., 1999; Gagliardi et al., 2003; Hirota et al., 2003; Korenberg et al., 2000). Reasons for unusual WS auditory system function are less clear.

People with WS demonstrate a hypersensitivity to high frequency sounds (Levitin et al., 2005), strong attraction to particular sounds and music (Levitin et al., 2004), use of vocal prosody (Reilly et al., 1990), and a relative strength in auditory rote memory (Udwin and Yule, 1991; Wang and Bellugi, 1994). Atypical primary auditory cortex cytoarchitecture (Holinger et al., 2005) and increased volume of the superior temporal gyrus has been observed in people with WS and could account for the increased sensitivity and attractions to sound in people with WS (Reiss et al., 2004), but it is not clear whether these behavioral and anatomical findings are a consequence of anomalous visual system development or have a unique genetic etiology.

The posterior superior temporal gyrus, auditory association cortex, includes the planum temporale. The planum temporale exhibits a prominent leftward hemispheric asymmetry in most people

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(Geschwind and Levitsky, 1968; Steinmetz et al., 1991). There is, however, considerable individual variability in planum morphology that appears to have functional significance. The degree of planum temporale asymmetry, often due to variation in right planum size (Galaburda et al., 1987), has been related to verbal ability (Eckert et al., 2001; Rumsey et al., 1997), handedness (Steinmetz et al., 1991), and perfect pitch in professional musicians (Keenan et al., 2001).

The size of the planum temporale is due, in part, to qualitative features of the Sylvian fissure. Witelson and Kigar classified the Sylvian fissure as having three patterns. Most Sylvian fissures demonstrate a horizontal bank behind Heschl's gyrus and a vertical bank that extends into the parietal lobe (H and V-Type). Some exhibit only a vertical bank (V-Type). And some exhibit only a horizontal bank (H-Type). The type of Sylvian fissure and size of the planum temporale may be related to the volume of surrounding brain regions (Binder et al., 1996). Parietal and occipital lobe volumes are reduced in WS and thus could influence qualitative features of the Sylvian fissure and the planum temporale measurement.

Two planum temporale findings have been reported in WS. A structural MRI study of WS found that three of the four WS individuals had prominent leftward planum temporale asymmetry that was equivalent in degree to musicians with perfect pitch (Hickok et al., 1995). Hickok et al. study hypothesized that the leftward planar asymmetry might be related to preserved musical and linguistic abilities. In contrast planum temporale symmetry was observed in two of four postmortem WS brains (Galaburda and Bellugi, 2000). The present study was designed to determine whether (1) WS and control participants exhibit differences in planum morphology, (2) whether these differences could be explained by group differences in Sylvian fissure patterning, and (3) whether anomalous Sylvian fissure patterning was related to anatomical variability in the visual system.

Experimental procedures

Participants

The WS participants were recruited and evaluated at the Salk Institute as part of a program project designed to examine associations across measures of WS behavior, neurophysiology, neuroanatomy and molecular genetics. Participants were excluded from the study if they exhibited confounding medical or neurological histories, such as epilepsy. A WS diagnosis was made based on clinical features and fluorescence in situ hybridization (FISH) indicating a deletion that included the elastin gene on chromosome band 7q11.2 (Korenberg et al., 2000).

Healthy control participants were recruited at both the Salk Institute and Stanford University. These participants had no history of major psychiatric, neurological or cognitive impairment. The institutional review boards of both universities approved the procedures. All participants and, if appropriate, their parents or guardians, provided written informed consent for the study.

Forty-two WS participants and 40 healthy control participants were compared in this study. The WS sample was composed of 23 females and 19 males (mean age=29.2±9.0 years). The control sample was composed of 24 females and 16 males (27.5±7.4 years). These groups were studied previously and the WS group exhibited less gray matter volume in the occipital lobe and equivalent superior temporal gyrus volume compared to the control group (Reiss et al., 2004).

MRI protocol

Brain images for each participant were acquired using a GE-Signa 1.5 T scanner (General Electric, Milwaukee, Wisconsin) at the University of California, San Diego (UCSD) Medical Center Magnetic Resonance Imaging Institute (WS=25, controls=17), Scripps Clinic, San Diego (WS=17, controls=21), or at Stanford University (controls=2). The distribution of images from each imaging center was not statistically different between the WS and control groups ($\chi^2_{(2,82)}=3.90$, ns). Sagittal brain images were acquired at each site with the same 3D volumetric radio frequency spoiled gradient echo (SPGR) pulse sequence using the following scan parameters: TR=24 ms, TE=5 ms, flip angle=45°, NEX=2, matrix size=256×192, field of view=24 cm, slice thickness=1.2 mm, 124 contiguous slices. Image pre-processing and data collection were performed at the Stanford Psychiatry Neuroimaging Laboratory by raters blinded to participant group membership. We previously showed that data collected from images acquired at multiple sites are compatible when the same magnetic field strength, pulse sequence and image processing methods are used (Patwardhan et al., 2001).

Neuroanatomical measures

Quantitative planum measures

The Sylvian fissure is bounded by horizontal and vertical planes of cortical tissue. The planum temporale is defined by the horizontal bank, which extends from Heschl's sulcus to the origin of the vertical bank or posterior ascending ramus. The surface area of the planum temporale was measured between 46 and 56 mm lateral to the midline in sagittal sections using a custom Matlab program (Mathworks, Natick, MA). Asymmetry of the planum is most dramatic in this lateral region of the planum temporale (Best and Demb, 1999). These coordinates were also chosen in order to replicate the methods of previous MRI studies showing cognitive associations with planum temporale measures (Eckert et al., 2001; Leonard et al., 1996). BrainVisa (Cointepas et al., 2001), a software tool that automatically identifies and labels sulci (Riviere et al., 2002), was used to provide an external index of reliability for the planum measurement technique. There was a significant correlation between the BrainVisa measurement of the entire medial to lateral extent of the planum temporale and the manual planum measurement ($r=0.93$, $p<0.001$). Two raters manually measured the planum and met to discuss the appropriate measurement when there were inconsistent planum measurements between raters for a particular planum. Intraclass correlation for the manual measurement demonstrated an intrarater reliability of alpha=0.97 and an interrater reliability of alpha=0.92. An alternative method of measuring the planum is to include the ascending branch of the Sylvian fissure, or the planum parietale (Westbury et al., 1999). We chose to exclude the planum parietale in the planum measurement in order to compare our results with the 2 previous planum studies on WS that reported different findings using the same measurement used in this study (Galaburda and Bellugi, 2000; Hickok et al., 1995).

Qualitative measures

Qualitative measures of Sylvian fissure and superior temporal gyrus morphology were collected because qualitative variation in these regions influence the planum temporale quantitative measures. The Sylvian fissure was classified according to the presence of a horizontal branch (H-Type), a vertical branch (V-Type), or both horizontal and vertical branches (H and V-Type) (Witelson and Kigar, 1992). Fig. 1 presents examples of these Sylvian fissure types. Two raters characterized qualitative features of the Sylvian fissure and temporal lobe. The raters met to discuss the appropriate classification when there were inconsistent classifications between raters for a particular sulcal feature. Intraclass correlation for the Sylvian fissure classification demonstrated an intrarater reliability of alpha = 0.98 and an interrater reliability of alpha = 0.87.

A surprising number of sulcal disruptions of the posterior superior temporal gyrus were observed. Fig. 2 shows that a disrupted superior temporal gyrus appeared in the sagittal plane of section when the superior temporal sulcus merged with the Sylvian fissure. Each participant was classified as to whether they had a sulcal connection between the Sylvian fissure and superior temporal sulcus specifically within the planum temporale. Intrarater and interrater reliability was 100%.

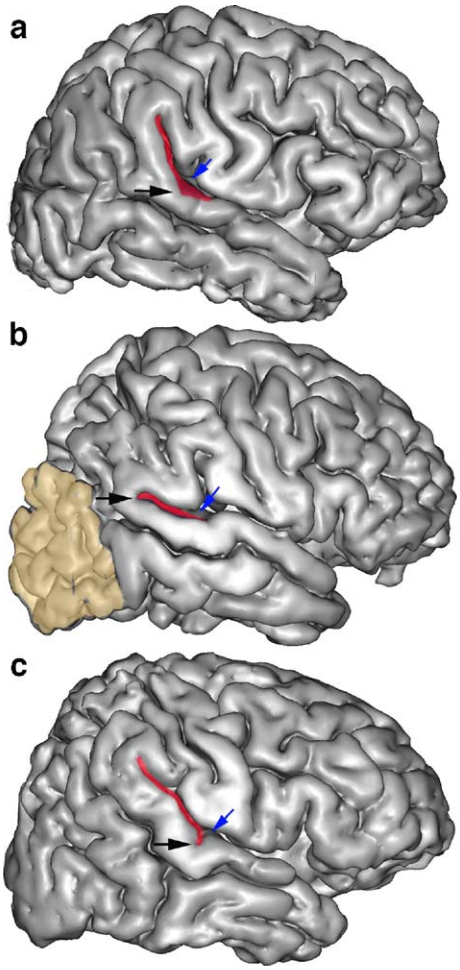

Fig. 1. Examples of the three Sylvian fissure types from three WS brain renderings: (a) Horizontal and vertical branches of the Sylvian fissure are present (H and V-Type); (b) only the horizontal branch of the Sylvian fissure is present (H-Type); (c) only the vertical branch of the Sylvian fissure is present (V-Type). The blue arrow indicates the location of Heschl's gyrus. The black arrow indicates the termination of the horizontal branch of the Sylvian fissure. The shaded region in b. highlights the reduced occipital lobe finding in the H-Type WS cases.

Cortical complexity

A measure of fractal dimension, or cortical complexity, was used to determine if cortical complexity was related to the Sylvian fissure patterns observed in the WS participants. This measure of cortical complexity accounts for the full 3D surface geometry, produces a measure that is independent of brain size and orientation, and does not depend on the direction of image acquisition. Cortical complexity was computed using an algorithm developed for mapping the complexity of deep sulcal surfaces in the cortex (Thompson et al., 1996). Points on the cortical surfaces around and between sulci were drawn on each individual's brain surface. The cortical pattern matching algorithm used these sulcal landmarks as anchors to reparameterize the cortex so that corresponding sulci and cortical regions occur at the same parameter space locations. A surface mesh was deformed onto the cortex of each participant using their individual sulcal landmarks as anatomical constraints. Quadtree meshes were then used to represent the spatial frequency of the cortical surface (geometric detail). This information can be used to measure the cortical surface area. The rate of increase in surface area with increasing spatial frequency was estimated by a least squares linear model of the estimated surface area versus frequency, on a log–log plot. The cortical complexity, or fractal dimension, was computed as $\mathrm{Dim}_F = 2 + \{d(A\{M(N)\})/d \ln N\}$, where $A\{M(N)\}$ represents the surface area of the cortical mesh $M(N)$. For a flat surface the log–log plot slope is zero with a dimension of 2. Values above 2 indicate increasing surface detail and greater gyral complexity. This method has been used to show increased cortical complexity in this sample of WS and control participants (Thompson et al., 2005). The left and right hemisphere cortical complexity measurement ranged from 2.2325 to 2.2845 (mean = 2.2532; standard deviation = 0.0105) in the WS adults, and ranged from 2.2285 to 2.2722 (mean = 2.4740; standard deviation = 0.0098) in the control adults. Please note the small standard deviation for this measurement. Please see Thompson et al. (2005) for additional details.

Regional brain volumes

BrainImage v5.x (Reiss, 2003) was used to remove non-brain tissues from the images, correct equipment related image artifacts, normalize image position, and parcellate the cerebral cortex into lobe and subcortical regions based on a stereotaxic atlas template (Talairach and Tournoux, 1988). This validated procedure (Kates et al., 1999; Reiss et al., 1998) was used to collect occipital lobe gray and white matter volume. Reiss et al. (2004) reported significantly reduced occipital lobe volume in this sample of WS compared to control participants, after adjusting for total brain volume differences between the groups.

Handedness

Handedness was determined by writing hand. There was no difference in the frequency of left or right hand writers between the groups ($\chi^2_{(2,78)} = 0.01$, ns). Thirty-seven of the 42 WS participants wrote with their right hand compared to 32 of the 36 control participants with handedness data. Writing hand data were missing for 4 control participants.

Results

The planum temporale

Descriptive statistics and group comparison results for the planum surface area measures are presented in Table 1. The WS

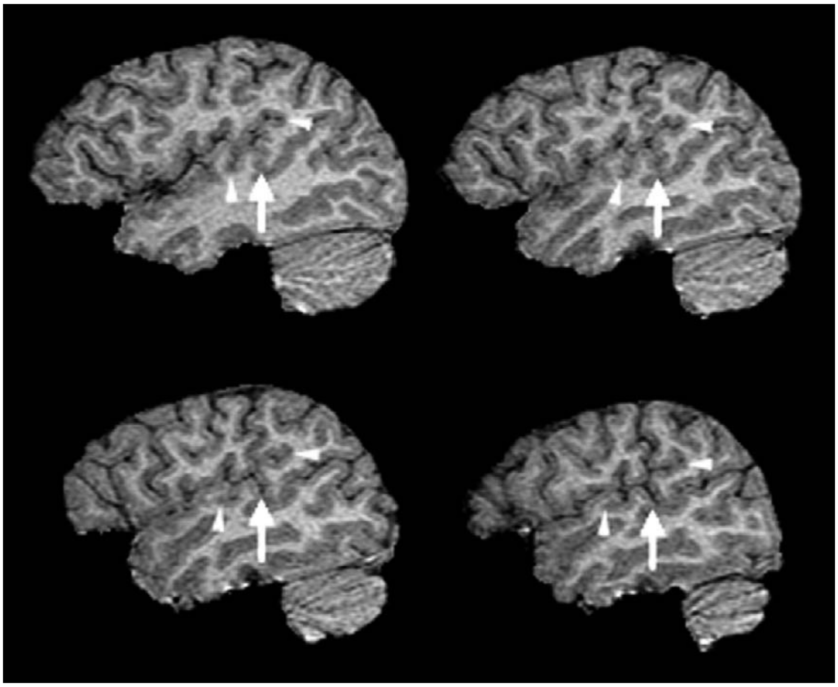

Fig. 2. The left hemisphere superior temporal sulcus merged with the left hemisphere Sylvian fissure in a significant number of WS brains. The arrow indicates where the superior temporal sulcus merges with the Sylvian fissure in a WS participant. The arrowheads identify the anterior and posterior boundaries of the planum temporale.

participants had significantly reduced leftward planum temporale asymmetry compared to control participants ($F_{(1,82)}=4.60, p<0.05$). Table 1 shows WS participants had a significantly larger right planum temporale, but not left planum temporale, compared to control participants before and after adjusting the planum measures for cerebral tissue volume.

Sulcal morphology

A high frequency of unusual sulcal/gyral features was observed during collection of the quantitative planum temporale data. In particular, a subset of WS participants exhibited atypical sulcal/gyral morphology in the superior temporal gyrus. Five WS participants (14%) and none of the controls had a left planum temporale that was disrupted by a sulcal connection between the Sylvian fissure and superior temporal sulcus ($\chi^2_{(1,82)}=5.07$, $p<0.05$). One WS participant and none of the controls had this type of morphology in the right hemisphere. Fig. 2 presents an example of a disrupted planum temporale.

There was also an unusual distribution of Witelson Sylvian fissure Types among WS participants. Ten of the WS participants (24%) exhibited a right hemisphere Sylvian fissure that did not ascend, but remained horizontal (H-Type). There were no controls who exhibited this type of morphology in the right hemisphere ($\chi^2_{(2,82)}=13.67$, $p<0.001$). There was no difference between WS and control groups for left hemisphere Sylvian fissure morphology ($\chi^2_{(2,82)}=1.70$, ns).

Sulcal morphology: relation to planum and cortical measures

The right hemisphere Witelson classification was included in an ANOVA with diagnosis to determine if qualitative features of sulcal morphology could explain the right planum finding. This analysis demonstrated that group differences in right planum size were largely due to WS participants with an H-Type Sylvian fissure (Model $F_{(4,82)}=10.87, p<0.000001$; Group $F_{(1,82)}=0.03$, ns; Witelson classification $F_{(2,82)}=7.69, p<0.001$).

We then examined measures of cortical complexity and regional brain volume to determine if the Sylvian fissure findings were locally specific or were related to anatomical features shown to be anomalous in the WS brain (Reiss et al., 2004; Thompson et al., 2005). Within the WS participants, left hemisphere cortical complexity was greatest among WS participants with a right hemisphere H-Type Sylvian fissure (means: H-Type=2.261±0.009; V, H and V Types=2.250±0.009; $F_{(1,41)}=11.70, p<0.001$) and they

Table 1
Planum temporale surface area (cm^2) group comparison results

Variable	Control mean (SD)	WS mean (SD)	Group difference	Group difference adjusted for cerebral volume
Left PT	2.68 (1.08)	2.57 (0.78)	ns	ns
Right PT	1.63 (1.04)	2.21 (0.85)	**	***
PT asymmetry	0.55 (0.77)	0.20 (0.68)	*	*

*$p<0.05$, **$p<0.01$, ***$p<0.001$.

were less likely to have rightward complexity asymmetry compared to other WS participants (means: H-Type = 0.002 ± 0.006; V, H and V Types = −0.002 ± 0.005; $F_{(1,41)} = 4.22$, $p < 0.05$). In addition, WS participants with a right hemisphere H-Type Sylvian fissure had smaller right occipital lobe volumes ($F_{(1,41)} = 4.\ 95$, $p < 0.05$) than WS participants with an H and V-Type Sylvian fissure. An H-Type Sylvian fissure does not appear to be simply related to a small occipital lobe, however. Nine control participants with left hemisphere H-Type Sylvian fissures did not have significantly smaller left occipital lobes than controls with H and V-Type Sylvian fissures ($F_{(1,37)} = 1.43$, ns).

Discussion

People with WS have uniquely shaped brains that are reduced in volume and have altered sulcal morphology compared to typically developing individuals. The results of this study indicate a greater degree of atypical Sylvian fissure patterning in people with WS. Further, this atypical patterning appeared to be associated with the difference in planum temporale size between the WS and control groups. Specifically, 24% of the WS participants had a right hemisphere Sylvian fissure that did not ascend into the parietal lobe. These WS participants also exhibited decreased right hemisphere occipital lobe volume compared to the rest of the WS participants, suggesting that Sylvian fissure and planum temporale development can be influenced by atypical development of brain regions principally involved in the WS visual spatial impairment.

The first study examining planum temporale morphology in WS demonstrated greater leftward planum temporale asymmetry in 3 of 4 WS participants (Hickok et al., 1995). The authors noted that the degree of planum temporale asymmetry was equivalent to the extreme leftward asymmetry observed in musicians with perfect pitch and suggested that this structural asymmetry could be the basis for the musicality and linguistic skills of people with WS (Keenan et al., 2001). WS participants with extreme leftward planum temporale asymmetry were also observed in the current study. However, many more WS participants had reversed asymmetry or symmetrical plana, a finding consistent with a postmortem study of 2 of 4 WS brains (Galaburda and Bellugi, 2000). Our MRI study of 42 WS participants demonstrates that variation in sulcal patterning in a large sample of subjects is critical to assessing the degree of planum temporale asymmetry in WS.

The WS participants with an H-Type Sylvian fissure in this study contributed to the overall group findings of significantly larger right planum temporale and reduced planar asymmetry in WS compared to control participants. The high frequency of right hemisphere H-Type Sylvian fissures (24%) is notable given the absence of a right hemisphere H-Type Sylvian fissure in 40 control participants in this study and the low frequency of this feature reported in 25 cadaver brains (4%) (Ono et al., 1990). This is not the first report of atypical morphology of a major sulcus in people with WS. There are two reports of the central sulcus failing to reach the interhemispheric fissure in WS brains (Galaburda et al., 2001; Jackowski and Schulz, 2005). Regional decreases in brain volume, as well as altered connectivity among cortical regions may account for these sulcal morphology findings.

The Sylvian fissure may be particularly susceptible to the effects of reduced occipital and parietal lobe volume because the ascending branch of the Sylvian fissure typically terminates in the supramarginal gyrus of the parietal lobe. The normal expansion of the right hemisphere occipital and parietal lobes may force the Sylvian fissure to turn upwards into parietal cortex during development (Binder et al., 1996). In support of this premise, WS participants with the H-Type Sylvian fissure had reduced right hemisphere occipital lobe volume. This association between sulcal morphology and regional brain volume may be specific to WS, however, as the controls with left hemisphere H-Type Sylvian fissures did not have significantly smaller left hemisphere occipital lobes compared to the other controls with Sylvian fissures with horizontal and vertical banks.

A related explanation for the sulcal findings is that variation in the pattern of fiber projections should influence the morphology of the Sylvian fissure according to the tension-based theory of morphogenesis (Van Essen, 1997). The macaque striate cortex (Ungerleider and Mishkin, 1979) and rhesus monkey parietal lobe (Seltzer and Pandya, 1984) project to neurons surrounding the superior temporal sulcus. The unusual Sylvian fissure patterning and the left hemisphere superior temporal sulcus interruptions observed in this study may reflect anomalous connectivity between temporal lobe and occipital and/or parietal lobe regions.

Studies of macaques with early retinal lesions may help explain the findings from this study and other neuroanatomical observations of WS brains. Early-enucleated macaques (bilateral retina lesions before embryonic day 77) demonstrate (a) dramatic reduction in the visual thalamus and striate cortex size, (b) increased occipital lobe convolutions, (c) a surprising increase in the amount of extrastriate cortex, and (d) disruption and fusion of major sulci (Dehay et al., 1996; Rakic, 1988). These findings appear to parallel the findings in WS. Compared to controls, people with WS demonstrate (a) decreased subcortical and posterior cortical regions (Meyer-Lindenberg et al., 2004; Reiss et al., 2004; Thompson et al., 2005), (b) increased in gyrification compared to controls (Schmitt et al., 2002), (c) increased gray matter in the right hemisphere inferior parietal lobule and posterior temporal lobe (Thompson et al., 2005), and (d) the sulcal disruptions and atypical Sylvian fissure patterning observed in this study. The parallel between the early-enucleated macaque and WS findings suggest that developmental impairment of visual systems in WS leads to widespread effects on brain development.

The unusually high frequency of right hemisphere H-Type Sylvian fissures in the WS sample raises interesting questions about why this sulcal feature would develop in a subset of people with WS. There is behavioral variability among people with WS (Bellugi et al., 2000) that probably reflects, in part, variation in genetic background as well as the degree of gene expression on the intact chromosome 7. A similar explanation may account for the varied development of cortical regions surrounding the Sylvian fissure in this subset of people with WS. Understanding the anatomical constraints that produce the H-Type Sylvian fissure may guide the search for genetic factors that influence Sylvian fissure development. For example, unique patterns of white matter fiber projections may be associated with the H-Type Sylvian fissure. The origin and termination of these fibers might indicate whether genes associated with visual–spatial function (Hirota et al., 2003) contribute to the unusual sulcal patterning in a subset of people with WS.

Finally, the findings from this study suggest that atypical visual system development can produce anatomical anomalies outside of the visual system. The findings also raise the question as to whether early visual system impairments can also produce altered function outside of the visual system or whether the hypersensitivity to high frequency sounds (Levitin et al., 2005), strong attraction to particular sounds and music (Levitin et al., 2004), excess use of vocal prosody

(Reilly et al., 1990), and a relative strength in auditory rote memory (Udwin and Yule, 1991; Wang and Bellugi, 1994) stem from unique, syndrome-specific developmental mechanisms.

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