Abnormal orbitofrontal development due to prematurity

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Abstract—*Objective:* To investigate the effects of prematurity on sulcal formation. *Methods:* We evaluated the depth and volume of the primary olfactory sulcus (developed at 16 weeks' gestation) and the secondary orbital sulci (which start to develop at 28 weeks' gestation) in a sample of 22 adolescents with history of very-preterm birth (VPTB). We compared this preterm sample with a sample of subjects born at term and matched by age, gender, and sociocultural status. The Anatomist/BrainVISA 3.0.1 package was used to identify and quantify the sulci. In addition, voxel-based morphometry (VBM) was used to analyze possible reductions of gray and white matter in the orbitofrontal area. *Results:* Compared with controls, we found a significant reduction in the secondary sulci depth but not in the primary sulcus in the VPTB. VBM analysis showed reduced gray-matter volume in VPTB in the orbital region. *Conclusions:* Premature birth affects cerebral gyrification, and this impairment is not reversible during childhood. Identification of the specific factors involved in abnormal brain maturation may lead to effective interventions.

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In full-term infants, the surface of the brain at birth resembles the adult brain because the sulci are well developed. In contrast, the preterm cortex appears lissencephalic at birth.[1] The data on sulci development patterns in fetuses come mainly from neuropathologic[2] and sonographic[3-5] studies. However, MRI has become an important source for identifying sulci and gyral abnormalities.[6-15]

Magnetic resonance (MR) studies demonstrated that brain maturation starts in the central area and proceeds toward the parieto-occipital cortex. The frontal cortex develops last.[15] The last areas to develop sulci are the frontobasal, frontolobar, and anterior parts of the temporal lobe.[16] In the human orbitofrontal cortex, the gestational age (GA) of sulci and gyrus maturation ranges from 16 to 44 weeks,[2] with mediolateral and posteroanterior development trends.

We hypothesized that prematurity would affect the sulci that were more immature at birth. Accordingly, we investigated structural abnormalities in orbitofrontal cortical folding in adolescents with history of very-preterm birth (VPTB) in two different sulcus types: a) the olfactory sulcus (primary sulcus), which appears early (≥16 gestational weeks); and b) the rest of the orbitofrontal sulci, including the medial, lateral, and transverse sulcus (secondary sulci).

Methods. *Subjects.* This study is part of a larger project on cognitive and cerebral abnormalities associated with prematurity. The preterm children are a subgroup of a cohort enrolled in previous MRI studies,[17-19] recruited at the Pediatric Service of the Hospital Clinic in Barcelona. Inclusion criteria for this study were current age between 12 and 17 years and GA less than 32 weeks for preterm and 37 weeks or more for controls. Exclusion criteria were history of focal traumatic brain injury, cerebral palsy or other neurologic diagnosis, motor or sensory impairments, and presence of global mental disabilities (IQ score < 70). Twenty-two adolescents with a GA less than 31 weeks participated. In the retrospective clinical files, five preterm subjects had history of intraventricular hemorrhage identified by ultrasonography. These five subjects had ventricular dilatation with posterior predominance. Five out of the 22 VPTB subjects had low weight for their GA. Preterm adolescents were matched by age, sex, and sociocultural status to 22 controls born at term. Controls had no brain abnormalities on the MRI and no history of neurologic or psychiatric diseases. We used the Wechsler intelligence scales to obtain a global measure of intellectual functioning. Either the Wechsler Adult Intelligence Scale III or the Wechsler Intelligence Scale for Children (Revised) was used, depending on the age of the subjects. Only two subjects had an IQ score below 85 (borderline range). All subjects followed normal schooling, although five VPTB subjects had received extra educational support in the past, and five were receiving extra educational support during the study period. Table 1 summarizes the main demographic and clinical characteristics of the groups.

The study was approved by the ethics committee of the University of Barcelona. All families gave written informed consent before participation.

Image acquisition. MR images of each subject were acquired in a GE Signa LX 1.5-T scanner (General Electric, Milwaukee, WI). A set of high-resolution inversion recovery T1-weighted im-

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Table 1 *Demographic and clinical characteristics of the sample*

	Very preterm birth group, mean ± SD	Control group, mean ± SD	*t* Statistic
Demographic data			
Age	14.8 ± 1.6	14.9 ± 1.5	t = −0.09
Gender, males/females	10/12	10/12	
Clinical data			
Gestational age, weeks	29.0 ± 1.6	39.8 ± 1.6	t = −21.81**
Weight at birth, g	1160.9 ± 297.5	3453.6 ± 398.0	t = −21.64**
IQ			
Verbal IQ	106.2 ± 17.8	115.3 ± 14.6	t = −1.84
Performance IQ	95.6 ± 12.3	105.7 ± 10.6	t = −2.90*
Full IQ	101.6 ± 14.8	112.2 ± 12.1	t = −2.60*
Early neurodevelopmental outcome			
Beginning of walking, mo.	13.1 ± 3.3	11.7 ± 2.0	t = 1.47
Beginning of speech, mo.	15.9 ± 5.5	17.5 ± 6.2	t = −0.72

* $p < 0.05$; ** $p < 0.001$.

ages was obtained with a fast spoiled gradient-recalled 3-day sequence (TR/TE = 12/5.2 ms; TI 300 1 nex; field of view = 24 cm; 256 × 256 matrix). The whole-brain data were acquired in an axial plane yielding contiguous 1.5-mm slices. The inversion recovery T1 sequence parameter has been reported to be the best image type for creating a representation of the cortical topography using Anatomist/BrainVisa 3.0.1.[20]

Sulci measurements. To identify and quantify the sulci, we used the Anatomist/BrainVISA 3.0.1 package (http://brainvisa.info/). This approach adapts the T1-weighted MR images in a structure that summarizes the main information about the cortical folding patterns. The program filters the huge amount of information in the gray levels to build a simplified graph formed by information nodes. Each node corresponds to elementary cortical folds, and the links correspond to the relative topographies of these folds.[20,21]

The sulci automatically detected by the program were inspected visually by two investigators (MG, PV) to correct misclassified sulci segments. To do so, they followed the patterns for the orbitofrontal sulci described by the Atlas of the Cerebral Sulci.[22] Figure 1 shows an example of sulci identification in two subjects. We obtained measures for each sulcus: the primary sulcus and the secondary sulci (including the medial, lateral, and transverse sulcus as a whole). The volume (mm^3) and the maximum depth of sulci (mm) were calculated (figure 2). The maximum depth of the primary and secondary sulci were calculated as the averages of each maximum depth in each sulcus segment. In figure 2B, the maximum depth for the primary sulcus was obtained through the two maximum depth values for each segment.

Voxel-based morphometry protocol. Because sulci characteristics are related to the adjacent gyri, a separate, complementary volumetric analysis was conducted using the voxel-based morphometry (VBM) approach to evaluate the possible gray- and white-matter volume reductions in the orbitofrontal gyri in the preterm group. Automatic image processing from both controls and VPTB subjects was performed using Statistical Parametric Mapping (SPM2) software, running in Matlab 6.5 (MathWorks, Natick, MA). Table 2 shows the VBM protocol.

Data analysis. Sulci. We performed two 2 × 2 × 2 repeated-measures analysis of variance (ANOVA) analyses (one for depth and one for volume) with hemispheric laterality and sulcus type as intrasubject factors and group as intersubject factor. The ANOVA for depth accounts for the differences between groups in the primary sulcus vs the secondary sulci, taking the hemispheric laterality into account. The ANOVA for volume accounts for the intrasulci differences between groups.

VBM. Two separate regions of interest (ROI) analyses were conducted to evaluate the possible volume reductions in the orbitofrontal gyral region in the preterm sample. We selected two ROIs contained in the WFU Pickatlas toolbox software for SPM, version 1.02 (Joseph Maldjian, Wake Forest University Baptist,

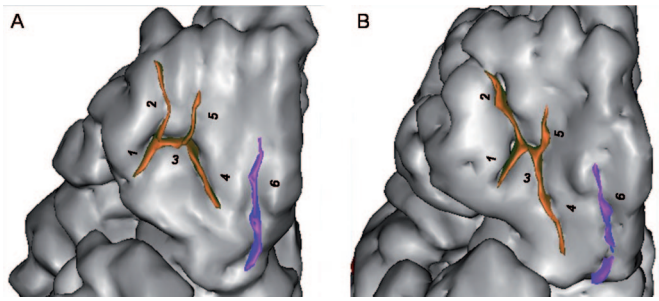

Figure 1. Examples of the orbitofrontal sulci identification by the Anatomist/BrainVisa 3.0.1 in the (A) control subject and (B) preterm subject. 1 = lateral orbital sulcus, caudal part; 2 = lateral orbital sulcus, rostral part; 3 = tranverse orbital sulcus; 4 = medial orbital sulcus, caudal part; 5 = medial orbital sulcus, rostral part; 6 = olfactory sulcus.

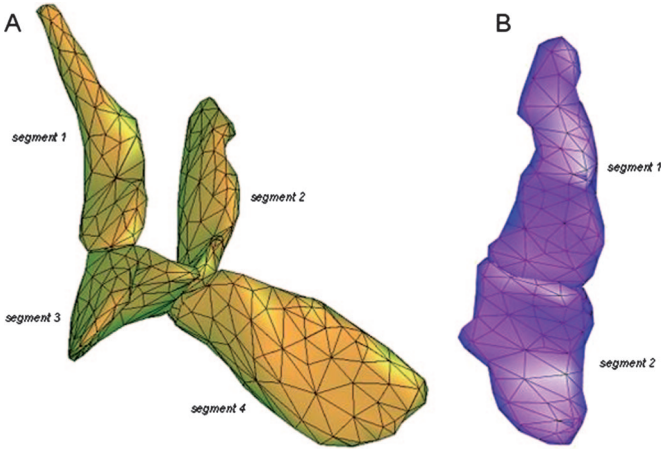

Figure 2. Lateral view of the orbitofrontal sulci. Filled faces and wireframe appearance for (A) secondary orbital sulci and (B) primary sulcus (olfactory sulcus).

Table 2 *Voxel-based morphometry protocol*

1. Reorientation of the original T1 images (n = 44), attending to the anteroposterior commissure orientation.
2. Segmentation of the original images.
3. Determination of the normalization parameters in the previous segmented gray-matter images using a standard gray-matter template from our laboratory, including a sample of adolescents (n = 127; 68 preterms and 59 controls; mean age = 14.3 ± 2.0 y). The template is adapted to the Montreal Neurological Institute–Statistical Parametric Mapping coordinates.
4. Application of the previous gray-matter normalization parameters to the original T1 images.
5. Segmentation of the original and normalized T1 images.
6. Application of the Jacobean's determinants → modulated images = volume
7. Smoothing of the modulated normalized gray-matter files: full width at half-maximum Gaussian kernel = 8 mm.

We repeated the same procedure for the white matter (we also had a standard white-matter template from the same large sample [n = 127]).

Medical Center, Department of Radiology, Winston-Salem, NC)[23]: a) the olfactory gyrus and b) the orbital gyrus. Both ROIs were based on normalized brains and adapted to the Montreal Neurologic Institute coordinates. We evaluated both gray- and white-matter differences between groups involved in each ROI as defined above, using the SPM2 Student's *t* test group comparison. The VBM protocol was applied separately to the gray- and white-matter images.

We used the convention that the ROI group comparison results should survive at the corrected false-discovery rate (FDR) *p* value ($p < 0.05$). Moreover, only clusters of more than 10 contiguous voxels were considered in the statistical model.

Results. *Neuroradiologic evaluation.* Visual inspection of the MRI images from the five subjects with intraventricular hemorrhage showed ventricular dilatation with posterior predominance. Seven other subjects also had ventricular dilation, but no subjects had active hydrocephalus or shunt. Corpus callosum reductions were clinically reported in five patients; in three of these patients, corpus callosum size was two standard deviations below the control group mean. There were no cases of corpus callosum agenesia. In two cases, T2-weighted MRI images showed mild white-matter abnormalities. In addition, the scores of hippocampal volumes in eight patients were two standard deviations below the group mean (procedures for measurements of these structures were described elsewhere).[19,24]

Sulci measurements. Descriptive data from sulcal measurements are detailed in table 3. The ANOVA for sulcal depth showed significant interactions between type of sulcus (primary vs secondary) and group ($F_{1,42} = 5.492$, $p = 0.024$) (figure 3). We observed significant reductions in the orbital sulci depth of the preterm group vs controls (bilateral preterm mean: 9.7 mm ± 1.0; bilateral control mean: 10.4 mm ± 0.8). Volumetric measures did not differ in the two groups ($F_{1,42} = 0.027$, $p = 0.871$).

VBM: ROI analyses. VBM showed a reduced gray-matter volume in the preterm group in the orbital ROI that mainly involved the medial gyral region (cluster size = 88 mm^3, local maxima Talairach coordinates = 4, 51, −19, FDR-corrected *p* value at voxel level = 0.026). We found no significant gray-matter volume differences between groups in the olfactory ROI. In the white-matter comparison, no differences were found between groups for any gyral region.

Table 3 *Measurements of the orbitofrontal sulci*

	Very preterm birth group, mean ± SD	Control group, mean ± SD
Left hemisphere		
Primary sulcus volume, mm^3	242.2 ± 53.0	246.8 ± 72.6
Primary sulcus depth, mm	11.0 ± 1.5	10.4 ± 1.1
Secondary sulci volume, mm^3	376.0 ± 117.5	420.0 ± 114.2
Secondary sulci depth, mm	9.8 ± 1.0	10.7 ± 1.0
Right hemisphere		
Primary sulcus volume, mm^3	232.5 ± 77.8	278.9 ± 98.2
Primary sulcus depth, mm	10.9 ± 1.9	10.8 ± 1.6
Secondary sulci volume, mm^3	389.0 ± 117.8	385.9 ± 113.3
Secondary sulci depth, mm	9.6 ± 1.2	10.1 ± 1.0

Discussion. Consistent with our hypothesis, we observed a significant reduction in secondary sulci depth in adolescents with history of VPTB vs a term sample. In contrast, the depths of the primary sulci were similar.

The dissociation between primary and secondary orbitofrontal sulci is consistent with the fetal stage of development of these sulci at birth. Whereas the primary olfactory sulci appear at 16 weeks' gestation and are prominent at 25 weeks, the secondary orbital sulci are not recognizable until 36 weeks.[2] All

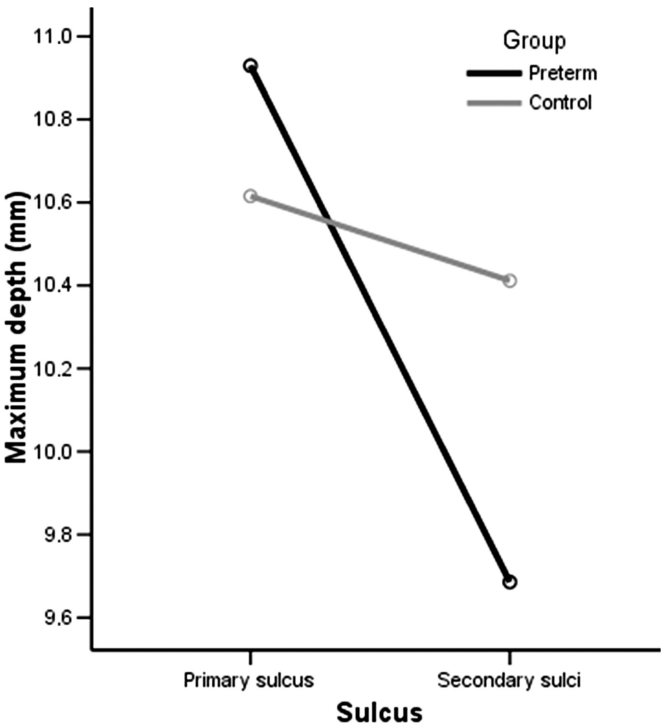

Figure 3. Interaction effect between the sulcus type and group in the depth sulci analysis.

subjects from our premature sample were born before week 32, at which point the development of the secondary orbital sulci has just started.

In research into the cerebral effects of prematurity, qualitative scales of gyration have normally been used to estimate the cerebral maturation of the fetuses or the premature newborn.[7] Scales of this kind have generally been useful for identification of cerebral maturation stage, detection of major neurologic abnormalities, and prediction of neurologic outcomes of preterm newborns, but they are unable to determine mild cerebral dysfunctions. Using a whole-cortex convolution index, a previous study found that preterm infants significantly differed from controls born at term.[1] These findings are to be expected, given the difference in the groups' GAs. A recent report introduced quantitative measures of cortical gyration, such as the ratio of gyral height to width from volumetric MRI studies in premature newborns.[25] From the analysis of four cerebral regions (superior frontal, superior occipital, precentral and postcentral gyri), the authors obtained a gyral ratio that was found to be correlated with GA. These studies, however, cannot determine the possible persistence of gyral abnormalities after postnatal brain maturation.

To our knowledge, there are no studies quantifying sulcal depth in adolescents with history of premature birth. Recently, a study tested whether possible abnormalities in the temporal lobe were associated with prematurity.[26] The authors used a gyrification index, which is a measure of the degree of cortical folding, providing an estimate of gyral width. Larger values in this gyrification index suggest a higher degree of cortical folding and smaller gyral width. They reported that children born prematurely had increased gyrification in the bilateral temporal lobe when they were examined at 8 years of age, but they did not explore the medial frontal lobe. These investigators demonstrated that increases of the temporal lobe gyrification were related to decreases in temporal gray-matter volume in the preterm sample. Sulcal depth has been previously investigated in patients with Williams's syndrome.[27,28] In these patients, in addition to bilateral reductions in sulcal depth in the intra/parietal/occipital sulcus, the authors observed a decrease in the depth of the left orbitofrontal region and a correlation between intra/parietal/occipital sulcal depth and gray-matter reduction in the same area.

In our study, we observed that sulcal depth reductions in the orbital sulci were accompanied by reduced gray-matter volume in the same area using VBM analysis. This finding suggests that sulcal abnormality may be caused by gray-matter reduction. The mechanisms of folding are not fully known. It is currently believed that the pattern of cortical folding depends in part on the size of the cortical area, which in turn is dependent on cell migration and cell volume (dendritic and synaptic volumes).[29] In a large cohort of 119 premature infants, a significant gray-matter volume reduction was observed compared with controls. The reduction was independent of evident brain injury such as intraventricular hemorrhage.[30] The authors of the investigation suggested that gray-matter damage may be due to impaired neuronal differentiation with a reduction in dendritic and axonal development or neuronal loss. In addition, periventricular white-matter lesions may also contribute to gray-matter reductions. The destruction of ascending and descending axons in white matter can result in damage of overlying cortical gray matter. The specific vulnerability of oligodendrocytes to the effects of ischemia and infection in the immature brain[31] could lead to a primary white-matter impairment and secondary gray-matter damage. One study clearly demonstrated that periventricular white-matter injury in the premature infant is followed by reduced cortical gray-matter volume at term.[32] In our study, only two subjects had mild white-matter lesions on clinical MRI visual inspection. This low frequency compared with other samples[33] may be attributable to our inclusion criteria, which excluded all subjects with sensory or motor impairments. However, our subjects probably had subtle white-matter damage, as has been observed in VBM studies.[34]

The secondary orbitofrontal sulci comprise the medial and lateral orbital sulci and the transverse sulcus.[14] Because these components have a high intersubject variability and are difficult to separate automatically, we took the secondary orbital sulci as a whole. Future MRI procedures for the separate analysis of each secondary orbital sulcus would be of interest because they mature at different rates. The medial and lateral orbital sulci can be initially distinguished around the 28th week of gestation, but the anterior and posterior parts of the orbital sulci are not identified until week 36.[2]

Several cortical gray-matter changes occur between childhood and adolescence, and the peak of the development of the frontal lobe is around age 12.[35,36] Because cortical maturation in the orbital area in our sample was completed, sulcal abnormality seems to be a definitive sequela of premature birth.

An important question is whether the adverse effects on brain development are caused by prematurity per se, by other concomitant negative factors (mainly complications in the early neonatal period), or both. Identification of the specific factors involved may lead to effective interventions. An increasing number of studies are demonstrating negative effects of prematurity on brain development in preterm infants with[32] and without brain lesions.[30] Increasingly sophisticated quantitative MR techniques such as the one used in this study are available for detecting subtle changes on brain structure, which might influence cognitive and behavioral development. Future studies are needed to show the link between these types of development.

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