PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Decreased Regional Brain Volume and Cognitive Impairment in Preterm Children at Low Risk

Sara Soria-Pastor, Nelly Padilla, Leire Zubiaurre-Elorza, Naroa Ibarretxe-Bilbao, Francesc Botet, Carme Costas-Moragas, Carles Falcon, Nuria Bargallo, Josep Maria Mercader and Carme Junqué

Pediatrics 2009;124;e1161-e1170
DOI: 10.1542/peds.2009-0244

Decreased Regional Brain Volume and Cognitive Impairment in Preterm Children at Low Risk

AUTHORS: Sara Soria-Pastor, MSc,[a,b] Nelly Padilla, MD, PhD,[b,c,d] Leire Zubiaurre-Elorza, MSc,[a,b] Naroa Ibarretxe-Bilbao, MSc,[a,b] Francesc Botet, MD, PhD,[b,e] Carme Costas-Moragas, PhD,[f] Carles Falcon, PhD,[b,g] Nuria Bargallo, PhD,[h] Josep Maria Mercader, MD, PhD,[b,h] and Carme Junqué, PhD[a,b]

[a]Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, University of Barcelona, Barcelona, Spain; [b]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [c]Centre for Biomedical Research on Rare Diseases, Instituto de Salud Carlos III, Barcelona, Spain; [d]Department of Maternal-Fetal Medicine, [e]Pediatrics Section, Department of Obstetrics and Gynaecology, Paediatrics, Radiology and Medical Physics, and [h]Neuroradiology Section, Radiology Department, Centre de Diagnòstic per la Imatge, Hospital Clínic, Barcelona, Spain; [f]Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona, Barcelona, Spain; and [g]CIBER BBN, Barcelona, Spain

KEY WORDS
children, MRI, neurocognition, preterm, voxel-based morphometry

ABBREVIATIONS
GA—gestational age
WM—white matter
GM—gray matter
VBM—voxel-based morphometry
WISC-IV—Wechsler Intelligence Scale for Children, Fourth Edition
CBCL—Child Behavior Checklist
DARTEL—Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra

www.pediatrics.org/cgi/doi/10.1542/peds.2009-0244

doi:10.1542/peds.2009-0244

Accepted for publication Jul 9, 2009

Address correspondence to Carme Junqué, PhD, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Psychiatry and Clinical Psychobiology, Casanova, 143, 08036 Barcelona, Spain. E-mail: cjunque@ub.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

WHAT'S KNOWN ON THIS SUBJECT: Although there is extensive knowledge about the neurodevelopmental and cognitive outcome of preterm children at high risk, little research has been conducted on preterm children with a low risk for neurologic deficits.

WHAT THIS STUDY ADDS: We investigated brain volume characteristics and related these changes to cognitive outcome in preterm children at low risk for neurologic deficits. Preterm children were mainly characterized by cortical GM damage with associated but less manifest WM impairment.

abstract

OBJECTIVE: To investigate whether preterm children with low risk for neurodevelopmental deficits show long-term changes in gray matter (GM) and white matter (WM) volumes compared with term children and to relate these changes to cognitive outcome.

METHODS: MRI was used to evaluate 20 preterm children who were determined to be at low risk for neurodevelopmental deficits and were born between 30 and 34 weeks' gestational age without major neonatal morbidity or cerebral pathology in the neonatal period and 22 matched, term control subjects. Volumetric images were analyzed by means of voxel-based morphometry to identify regional cerebral alterations. Children also underwent cognitive and behavioral/emotional assessments.

RESULTS: Preterm children showed global and regional GM volume reductions in several brain areas, including temporal and parietal lobes and concomitant WM volume reductions in the same areas, although only the left temporal regions achieved statistical significance. Global intellectual performance in the preterm group was significantly decreased compared with control subjects. Neither behavioral nor emotional problems were found in the preterm group. In the whole sample, we found a positive correlation between GM volume bilaterally in the middle temporal and in the postcentral gyri with IQ. Positive correlations were observed between GM and gestational age at birth in parietal and temporal cerebral regions and with WM in parietal regions.

CONCLUSION: Preterm birth has an important impact on the neurodevelopmental and cognitive outcome of children at 9 years of age, being a risk factor for decreased regional cortical GM and WM even in preterm children with low risk for neurodevelopmental deficits. *Pediatrics* 2009;124:e1161–e1170

Preterm birth is frequently associated with an increased risk for neurodevelopmental difficulties[1] and for cognitive, behavioral, and emotional problems during childhood.[2,3] Among preterm children, neurodevelopmental outcome has been related with gestational age (GA)[2,4,5]—the worst outcomes being recorded in those born most preterm—and the type of the intracranial lesion,[6,7] highlighting the developmental vulnerability of the immature brain.

MRI has been widely used to detect brain damage subsequent to preterm birth.[8] Although in preterm infants the most common cerebral injury is periventricular white matter (WM) damage,[9,10] preterm birth is also associated with smaller volumes of cortical[11,12] and subcortical gray matter (GM).[13,14] Furthermore, MRI has shown that regional brain volumes are affected by preterm birth, particularly GM volumes, which correlate with poorer cognitive outcome.[15–18] The application of quantitative MRI techniques, such as voxel-based morphometry (VBM), to preterm samples offers the possibility of objectively measuring brain development and provides an accurate correlate for neurodevelopmental outcome.[19]

Although the neurodevelopmental and cognitive outcome of preterm samples at high risk is widely known, little research has been conducted on preterm children with a low risk for neurologic deficit or developmental difficulties, such as those born between 30 and 34 weeks of GA, with uncomplicated perinatal histories, normal cranial ultrasound scans, and no obvious neurodevelopmental deficits.[8,20] There is a lack of MRI studies that are based on preterm samples at low risk, and only the infancy period has been studied.[21,22] Few studies have examined the long-term neurodevelopmental outcome of preterm children at low risk,[23,24] and regarding neuropsychological abnormalities, subtle deficits have been identified early in childhood in seemingly normal ex-preterm infants.[20] To our knowledge, no research has yet studied the brain volume characteristics of a preterm sample at low risk in childhood by using an MRI approach or has sought to relate these measures to cognitive performance.

METHODS

The study was approved by the ethics committee of the University of Barcelona. Informed parental consent was obtained for each infant.

Subjects

The preterm group was selected from the preterm population born at the Hospital Clinic (Barcelona, Spain) between 1996 and 1998. The inclusion criteria for the preterm group were a current age between 8 and 10 years and fulfill the following criteria to be considered a preterm child with a low risk for neurodevelopmental deficits: (1) history of preterm birth with GA between 30 and 34 weeks; (2) birth weight $<$ 2500 g; (3) Apgar score at 5 minutes of $>$7; (4) absence of major neonatal morbidity (severe respiratory distress syndrome, mechanical support, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia); and (5) absence of cerebral pathology, such as intraventricular hemorrhage, ventriculomegaly, or WM injury assessed by cranial ultrasound in the neonatal period. Neonatal data of preterm children from the archives of the neonatology service of the hospital clinic were recorded retrospectively. The GA was calculated according to the mother's last menstrual period. Exclusion criteria for the whole sample were history of focal traumatic brain injury, cerebral palsy or neurologic impairment (including seizure and motor disorders), cerebral lesions visually detected by the current MRI, and the presence of global mental disabilities (full IQ $\leq$ 80).

After analysis of the database from the neonatology service, 76 preterm children met these criteria. From these children, updated addresses or telephone numbers were not available for 36. Nineteen children were not enrolled in the study because their parents declined to participate; therefore, the initial sample comprised 44 children: 21 preterm children and 23 control subjects. Because of the abnormalities in the MRI findings described in the section MRI Data, 2 children were excluded. Finally, our study sample included 20 preterm children with a low risk for neurodevelopmental deficits and 22 term children who had no history of perinatal problems, matched by age, gender, and sociocultural status, who were mainly friends and classmates of the preterm children. All of the children followed normal schooling, and information about requiring extra educational provision was registered. Parental education was collected according to the highest education of the parents: low, intermediate, or high.[25]

Cognitive and Behavioral Assessment

Children underwent a cognitive assessment by using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV).[26] The WISC-IV comprises 4 indices: Verbal comprehension; perceptual reasoning; working memory; and processing speed. Taken together, these give a full-scale IQ score. The Child Behavior Checklist (CBCL)[27] was used as a dimensional assessment of children's behavioral and emotional symptoms on the basis of the opinion of their parents.

MRI Data

MRI was performed by using a TIM TRIO 3T scanner (Siemens, Erlangen, Germany). A set of high-resolution, 3-dimensional,

T1-weighted images were acquired with a MPRAGE sequence in sagittal orientation (repetition time/echo time: 2300/2.98 milliseconds; inversion time: 900 milliseconds; 256 × 256 matrix; 1-mm isotropic voxel). T2-weighted images in axial orientation (repetition time/echo time: 5533/88 milliseconds; 122 × 122 matrix; flip angle: 90°; slice thickness: 2 mm; gap: 0.6 mm) were acquired. No sedation was necessary, and no children were excluded because of suboptimal images.

MRI scans were reviewed by a neuroradiologist (Dr Bargallo) who was blind to group membership. A control subject with a venous vascular malformation and a preterm child with a giant arachnoid cyst were excluded. Conventional T2-weighted images showed no evidence of WM injury in the preterm sample.

TABLE 1 Characteristics of the Sample: Neonatal and Demographic Data

Characteristic	Preterm ($N = 20$)	Term ($N = 22$)	Statistic (P)
Neonatal data			
Gender, male/female	11/9	14/8	0.32 (.569)[a]
GA, mean ± SD, wk	32.5 ± 1.4	39.5 ± 1.0	−18.80 (<.001)[b]
Birth weight, mean ± SD, g	1754 ± 452	3392 ± 357	−13.10 (<.001)[b]
Length, mean ± SD, cm	42.9 ± 4.1	50.7 ± 2.1	−7.74 (<.001)[b]
Head circumference, mean ± SD, cm[c]	30.0 ± 2.3	35.2 ± 1.1	−8.66 (<.001)[b]
Demographic data			
Age at scan, mean ± SD, y	9.3 ± 0.7	9.3 ± 0.6	0.14 (.892)[b]
Right-handed, *n* (%)	18 (90)	22 (100)	2.31 (.129)[a]
Extra education assistance, *n* (%)	1 (5)	1 (5)	0.01 (.945)[a]
Parental education, *n* (%)			
High	12 (60)	15 (68)	0.33 (.564)[a]
Intermediate	4 (20)	4 (18)	0.22 (.881)[a]
Low	4 (20)	3 (14)	0.14 (.705)[a]

[a] χ^2 statistic.
[b] t statistic.
[c] $N = 20$ for preterm group and 18 for control group.

Image Analysis

The image processing was done by using SPM5 software (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm), running in Matlab 7.0 (MathWorks, Natick, MA). We segmented the original whole-brain files and obtained the native volumes of GM, WM, and cerebrospinal fluid for each child. A specific value in mm^3 was obtained for each tissue. Intracranial volume was calculated as the sum of the 3 values.

For the VBM group analysis, the GM and WM segments were further normalized to the population templates generated from all of the images in each group by using an implementation of a Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) algorithm.[28] A separate "modulation" step[29] was used to ensure that the overall amount of each tissue class was not altered by the spatial normalization procedure. Modulation was performed by multiplying the warped tissue probability maps by the Jacobian determinant of the warp on a voxel-by-voxel basis, thereby allowing voxel intensities in the segmented GM or WM map, together with the size of the voxels, to reflect regional volume and preserve total GM or WM volume from before the warp. Modulated images were smoothed by using an 8-mm full-width at half-maximum Gaussian kernel. Affine transformation of the DARTEL template to Montreal Neurological Institute space was applied.

Statistical Analyses

Group comparisons were conducted by using Student's t test for normally distributed quantitative variables; when the variables did not fulfill the requirements for normality 2 nonparametric approaches were used: χ^2 test of independence with categorical variables and 2-tailed Mann-Whitney U test for quantitative ones. Pearson correlations were used to evaluate associations in neonatal, cognitive, and MRI data. All statistical analyses were conducted by using SPSS 14.0. (SPSS Inc, Chicago, IL). Bonferroni's correction for multiple comparisons was not applied because of the exploratory nature of the study and the low sample size.[30,31] Effect-size analyses were conducted.[32]

For VBM-DARTEL analyses, t test group comparisons were performed to evaluate the volume changes between groups, and "simple regression" (correlation) analyses were performed in the whole group to test for a possible relationship between whole-brain GM volume and both cognitive data and GA. Whole sample correlations between cerebral regions with GM reductions in preterm children and IQ were performed. We analyzed these regions of interest (middle temporal gyrus and postcentral gyrus) contained in the Pickatlas 2.4.[33] For statistical purposes, we used a threshold corrected at the false discovering rate level ($P < .05$), and only clusters larger than 20 voxels were considered.

RESULTS

Subjects

Neonatal and demographic results are detailed in Table 1. In the preterm children, antenatal steroids were administered to 80% of newborns, the mean umbilical arterial pH was 7.29 ± 0.03, and the mean of length of stay in the NICU was 7.94 ± 11.97 days. Three of the 20 preterm children were small for GA.

Cognitive Performance

Although global intellectual performance was within normal limits in the preterm group, it was significantly de-

creased compared with control subjects (Table 2). For the whole sample, there were positive correlations between WISC-IV full-scale IQ and neonatal data (GA: $r = 0.46$, $P = .002$; birth weight: $r = 0.55$, $P = .001$; length: $r = 0.49$, $P = .001$; head circumference: $r = 0.43$, $P = .007$). The CBCL results showed no significant differences between groups (Table 3).

Global Brain Volume Data

The preterm group showed reduced global GM volume compared with control subjects (Table 4). In the whole sample, there were significant positive correlations between neonatal data and global brain volumes (Table 5). Regarding the preterm children, there was a significant positive relationship between birth weight and GM volume ($r = 0.46$, $P = .042$), whereas the correlation of birth weight with WM showed a trend toward significance ($r = 0.43$, $P = .056$). There was also a positive correlation between the length and GM ($r = 0.47$, $P = .036$) and WM ($r = 0.47$, $P = .036$) volumes.

VBM-DARTEL Analyses

In the "term group > preterm group" comparison, preterm children had significantly reduced GM volumes in several brain regions than term children. Decreased GM volumes were found bilaterally in the temporal lobe and in the left parietal lobe. Mean differences in WM volume between groups demonstrated WM decreases in the temporal and parietal regions that were concomitant with GM loss, although only left temporal regions achieved statistical significance (Table 6, Fig 1).

In the whole sample, we observed positive correlations between GA at birth and GM and WM volumes (Table 7, Fig 2). Moreover, the temporal and parietal regions with GM reductions in preterm children (middle temporal gyrus and postcentral parietal gyrus) showed positive correlations with IQ at the voxel false discovering rate–corrected level ($P > .03$; Fig 3).

TABLE 2 Cognitive Performance: Intelligence Global Indices and Their Corresponding Subtests

Cognitive Measures WISC-IV	Preterm, Mean ± SD	Term, Mean ± SD	*t* (*P*)	Effect Size, Cohen's *d*[a]
Verbal comprehension index	107.3 ± 15.2	123.7 ± 19.0	−3.09 (.004)	0.2
Similarities	18.4 ± 6.2	24.5 ± 9.0	−2.55 (.015)	0.2
Vocabulary	33.0 ± 6.3	40.4 ± 8.2	−3.25 (.002)	0.3
Comprehension	19.7 ± 5.4	25.2 ± 7.6	−2.67 (.011)	0.2
Perceptual reasoning index	101.1 ± 13.6	115.6 ± 16.6	−3.08 (.004)	0.2
Block design	29.0 ± 9.8	37.7 ± 10.3	−2.82 (.007)	0.2
Picture concepts	15.5 ± 3.3	18.5 ± 2.9	−3.18 (.003)	0.2
Matrix reasoning	18.1 ± 6.1	22.0 ± 5.3	−2.20 (.033)	0.2
Working memory index	107.6 ± 15.2	108.5 ± 16.2	−0.19 (.854)	
Digit span	14.4 ± 2.6	15.2 ± 2.4	−1.07 (.291)	0.1
Letter-number sequencing	16.3 ± 3.3	16.6 ± 3.2	−0.34 (.736)	
Arithmetic	18.3 ± 3.6	20.8 ± 3.9	−2.14 (.039)	0.2
Processing speed index	107.3 ± 14.5	114.5 ± 8.8	−1.98 (.055)	0.1
Digit symbol	44.3 ± 7.6	44.6 ± 6.6	−0.18 (.861)	
Symbol search	21.4 ± 4.8	26.8 ± 3.9	−4.02 (<.001)	0.3
Animals	63.0 ± 16.9	82.1 ± 20.9	−3.25 (<.001)	0.3
Full-scale IQ	105.8 ± 13.8	121.9 ± 15.3	−3.57 (.001)	0.3

[a] 0.2 is indicative of a small, 0.5 a medium, and 0.8 a large effect size.

TABLE 3 CBCL Scores Between Preterm and Term Children

CBCL Problem Scales	Preterm, Mean ± SD ($n = 20$)	Term, Mean ± SD ($n = 21$)	Statistic (*P*)
Withdrawn	2.35 ± 1.50	2.00 ± 1.60	0.727 (.471)[a]
Somatic complaints[b]	1.80 ± 2.20	1.10 ± 2.00	162.0 (.186)
Anxious/depressed	4.60 ± 3.50	4.67 ± 2.90	−0.067 (.947)[a]
Social problems	1.75 ± 1.90	2.62 ± 2.50	−1.258 (.216)[a]
Thought problems[b]	0.50 ± 0.80	0.67 ± 1.00	190.0 (.553)
Attention problems	4.75 ± 3.60	4.24 ± 3.60	0.455 (.652)[a]
Delinquent behavior	1.40 ± 1.20	1.19 ± 1.20	0.570 (.572)[a]
Aggressive behavior	7.95 ± 5.40	8.14 ± 4.90	−0.120 (.905)[a]
Total problems	25.40 ± 14.70	24.62 ± 14.60	0.171 (.865)[a]
Internalizing problems	8.95 ± 6.10	7.76 ± 4.70	0.698 (.489)[a]
Externalizing problems	9.35 ± 6.00	9.33 ± 5.60	−0.009 (.993)[a]

[a] *t* statistic.
[b] *U* statistic.

TABLE 4 Global Brain Volume Data

Volumetric Data	Preterm, Mean ± SD, cm^3	Term, Mean ± SD, cm^3	*t* (*P*)
Cerebrospinal fluid	400.306 ± 60.767	401.895 ± 55.896	−0.06 (.953)
GM	821.684 ± 84.920	874.683 ± 70.431	−2.21 (.033)
WM	419.228 ± 53.829	439.585 ± 46.897	−1.31 (.198)
Total intracranial volume	1641.220 ± 172.625	1718.568 ± 145.409	−1.58 (.123)

DISCUSSION

Our study used a VBM technique to investigate the regional distribution of GM and WM volume reductions and their relationship with cognitive outcome in a sample of preterm children with low risk for neurodevelopmental deficits. We demonstrated that preterm children at low risk are characterized by the presence of regional cortical GM volume reductions unilaterally in the parietal lobe and bilaterally in the temporal lobe, which correlated strongly with IQ. Preterm children also showed WM volume reductions that were concomitant with

TABLE 5 Brain Volume Correlations With Neonatal Data for the Whole Sample ($N = 42$)

Neonatal Data	Global Brain Volume, r (P)[a]		
	GM	WM	Total Intracranial
GA	0.33 (.035)	0.18 (NS)	0.22 (NS)
Birth weight	0.45 (.003)	0.37 (.016)	0.40 (.008)
Length	0.45 (.003)	0.39 (.011)	0.40 (.009)
Head circumference[b]	0.45 (.004)	0.40 (.012)	0.45 (.005)

NS indicates not significant.
[a] 0.1 is indicative of a small, 0.3 a medium, and 0.5 a large effect size.
[b] $N = 38$.

TABLE 6 Decreased Areas of GM and WM Volume in Preterm Children Compared With Control Subjects

Anatomic Region (BA)	Cluster, mm³	Cluster Level (P Corrected)	Local Maxima MNI Coordinates[a]			t
			x	y	z	
GM results						
Parietal lobe						
Postcentral gyrus (3) L	51 371	<.001	−53	−21	39	6.35
Temporal lobe						
Middle temporal gyrus (21) L	15 690	<.001	−54	−15	−8	6.18
Middle temporal gyrus (21) R	49 875	<.001	60	−7	−11	5.60
WM results						
Parietal lobe						
Postcentral gyrus (3) L	1174	NS	−51	−21	23	4.90
Temporal lobe						
Middle temporal gyrus (21) L	128	.018	−54	−2	−23	5.45
Middle temporal gyrus (21) R	2041	NS	54	9	−41	5.06
	1181	NS	56	−15	−17	3.91

BA indicates Brodmann area; MNI, Montreal Neurological Institute; L, left hemisphere; R, right hemisphere; NS, not significant.
[a] x increases from left (−) to right (+), y increases from posterior (−) to anterior (+), and z increases from inferior (−) to superior (+).

the GM loss in the parietal and temporal regions.

In contrast to previous studies of preterm children at high risk, which demonstrated decreases in total cerebral volumes,[11,15,34,35] our preterm children had only reduced total GM volume. MRI studies reported abnormalities in several WM brain areas, including all lobes, associative tracts, and the corpus callosum, in preterm children and adolescents.[36–38] Contrary to these findings, the absence of major WM impairment in our preterm children could be attributable, in part, to the strict inclusion/exclusion criteria applied. Our preterm children showed a decreased GM volume in temporal and parietal regions, in accordance with volume reductions previously reported.[11,16,38] In contrast to previous studies,[16,38] we did not observe any region of increased GM volume in our preterm children; however, it is necessary to consider differences between these studies related to the inclusion of infants of different GA, the presence of significant neonatal morbidity, different ages of evaluation, and the use of different MRI techniques. There is controversy as to the origin of brain GM volume reductions linked with prematurity.[8] Although there is evidence that GM reductions are a secondary effect of WM damage,[9] other studies have noted that even without signs of WM injury, prematurity is associated with decreased cortical GM volumes, which are correlated with adverse neurodevelopmental outcome.[12] GM maturation in the intrauterine environment is genetically controlled and well protected, but, in preterm birth, it is exposed to several environmental factors that may influence normal development.[15,39] A recent study[40] reported that preterm birth continues to perturb the trajectory of cerebral development during late childhood. The mean GA of our study sample was 33 weeks, and it is in the last trimester when GM seems to be more vulnerable,[41] because this period is characterized by a dramatic growth in gyri, sulci, synapses, and dendritic arborization.[42] Hence, after preterm birth, the normal increase in cortical surface area and complexity might be impeded even in the absence of major WM destruction.[43] Our findings provide support for these assumptions and suggest that preterm birth itself might be a determining cause of altered GM.

Our results add new data to the divergent findings on preterm infants at low risk, with some authors having concluded that preterm infants at 40 weeks had similar brain tissue volumes compared with term infants,[21] whereas others have demonstrated a moderately decreased WM volume suggestive of an alteration in the course of myelination.[22] Our study demonstrated that both WM and especially GM volume abnormalities were mainly localized in the temporal lobe, particularly in the middle temporal gyrus. Volume reductions in the middle temporal gyrus were previously reported in preterm children.[38] Cortical GM reaches a peak maximal volume in the temporal lobe at ~16 years.[44] Late development of these regions might make these structures more vulnerable to the influence of environmental factors during childhood; therefore, we speculate that specific areas of lower GM volume found in our preterm children could be related to primary cortical neuronal damage because preterm labor occurs at a critical time

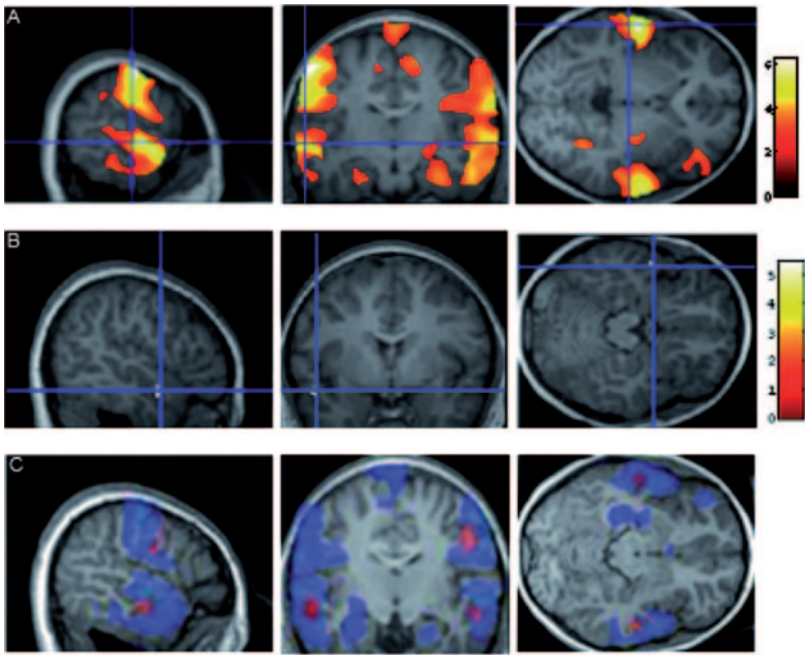

FIGURE 1
Statistical parametric maps illustrating GM (A) and WM (B) volume decreases between groups at false discovering rate–corrected *P* value. C, GM (blue) false discovering rate–corrected results and WM (red) results at an uncorrected voxel $P < .001$. Differences are mapped on a T1 standard control brain. The color bar represents the *t* scores. Display orientation: neurologic convention (A and B) and radiologic convention (C).

TABLE 7 Whole-Sample Correlations Between Cerebral Tissues and GA

Anatomic Region (BA)	Cluster, mm^3	Cluster Level (*P* Corrected)	Local Maxima MNI Coordinates[a]			*r*
			x	y	z	
GM correlations						
Parietal lobe						
Postcentral gyrus (1, 2, 3) L	73 713	<.001	−59	−20	45	0.72
Temporal lobe						
Middle temporal gyrus (21) L	20 749	.001	−59	−15	−11	0.71
Middle temporal gyrus (21) R	56 230	<.001	50	5	−27	0.65
WM correlations						
Parietal lobe						
Postcentral gyrus (1, 2, 3) L	870	.002	−51	−20	27	0.61

BA indicates Brodmann area; MNI, Montreal Neurological Institute; L, left hemisphere; R, right hemisphere.
[a] x increases from left (−) to right (+), y increases from posterior (−) to anterior (+), and z increases from inferior (−) to superior (+).

in which brain architecture has yet to develop fully.

The abnormal brain structure findings noted on our study children indicate that, even in preterm children at low risk, insults to the brain that occur at critical periods of development disrupt maturation. Kinney et al[42] postulated that the combined GM and WM damage in late preterm children could be attributable to hypoxia-ischemia, infection, and/or as-yet-undefined factors in a vulnerable period in the development of oligodendrocytes and neurons and that the combined lesions in the susceptible WM and GM sites reflect interactions between oxidative, nitrative, glutamate, and cytokine toxicity. Nevertheless, conventional MRI is not very sensitive to subtle changes in WM.[8,45] By using a noncorrected threshold, we saw WM changes underlying GM changes; our results may indicate the limitations of VBM analysis of T1-weighted images for detecting such WM decreases. Other techniques, such as diffusion tensor imaging, have proved useful for detecting microscopic WM changes in preterm neonates and children[46–50]; therefore, additional analyses by using the diffusion tensor imaging approach are necessary to clarify the integrity of WM in preterm children at low risk.

In agreement with Nosarti et al,[38] our correlation results showed that GM and WM changes were linearly associated with length of gestation. Authors have noted a GA-related gradient in IQ for those born before 33 weeks.[51] A meta-analysis study[2] concluded that preterm children are more likely to have low cognitive performance and that their immaturity at birth is directly proportional to their mean cognitive scores. These results are corroborated by our findings, given that we found a linear relationship between IQ and both birth weight and GA from 30 to 40 weeks.

Our preterm children achieved intelligence scores within the normal range, and this is consistent with the fact that adverse cognitive sequelae are a more frequent outcome among extremely preterm children.[52] In agreement with previous reports, our preterm children obtained lower scores on scales related to verbal and nonverbal material and time-dependent tasks compared with control subjects.[11,53] In contrast, a follow-up study of preterm infants at low risk reported no differences in general, verbal, and performance quotients at 7 years.[54] Although a greater need for extra educational provision has been reported in school-ages very preterm populations,[55–58] we have not found this tendency.

Correlations between intelligence and brain volume have been reported in preterm studies.[59,60] Peterson et al[15]

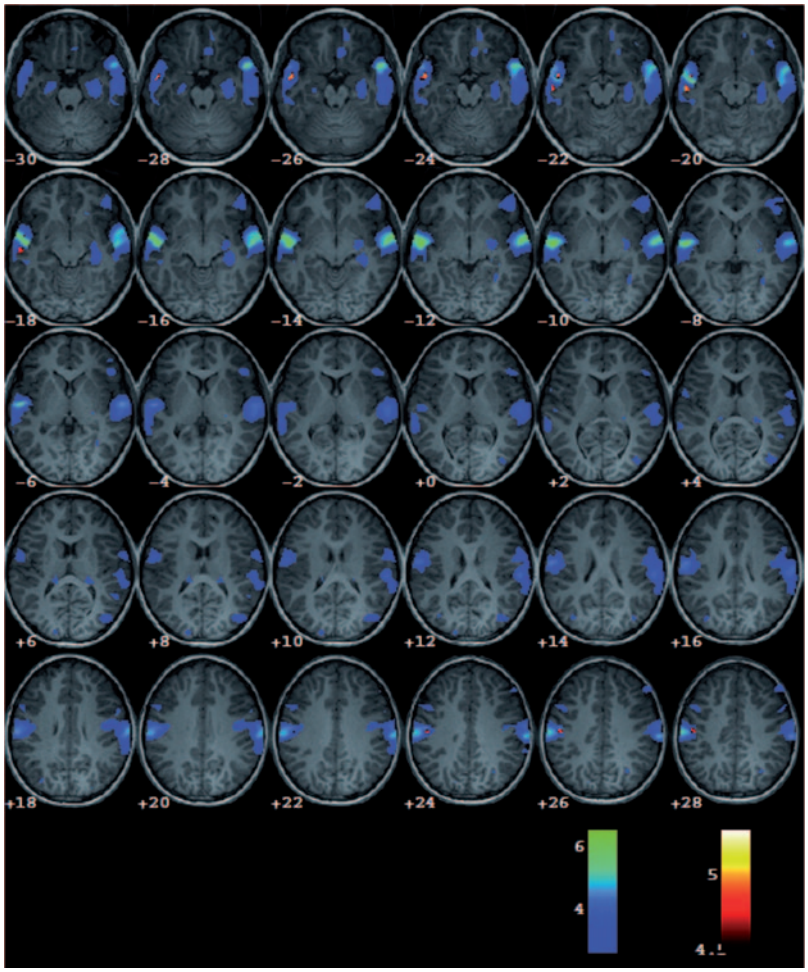

FIGURE 2

Axial slices showing the correlation between GA at birth and GM (right color bar) and WM (left color bar) volume decreases; the lower the GA, the lower the GM and WM integrity. Images are representative slices at a 2-slice interval. Left is left in accordance with neurologic convention. Results are superimposed on a T1 standard control brain.

noted that volume reductions in the temporal and sensorimotor language regions correlated with intelligence scores in preterm children, and Martinussen et al[61] demonstrated a thinner cortex involving these regions in very low birth weight adolescents. Indeed, we also found positive correlations between volume reductions in GM involving the middle temporal and the postcentral parietal gyri and IQ. Although we did not find brain regions associated with cognitive outcome in our preterm group, Isaacs et al[17] reported that preterm children are at risk for declining intelligence scores over time even when they have not sustained obvious neurologic damage. Because the number of children in the preterm group was small and this reduced the power of our analysis, the lack of any relationship between full cognitive scores and GM volumes may reflect insufficient power of our study rather than the absence of a true association.

Environmental factors, especially parental education, are the best predictors of later intelligence in preterm infants.[25] Moreover, the risk for impaired cognitive development increases with decreasing socioeconomic status.[62] The parental education of our sample was very high; hence, the good outcome obtained might be attributed in part to these favorable socioeconomic characteristics.[25,63] Our findings based on CBCL data demonstrated that our preterm children showed neither emotional nor behavior problems. In agreement with our results, Fredrizzi et al[54] reported no behavior problems in preterm children at low risk, whereas Schothorst et al[64] concluded a higher prevalence of social problems.

Our study has 2 main limitations. First, the relatively small sample may have meant that statistical differences could not be observed in some comparisons, and this prevents us from generalizing our findings to a wider and more heterogeneous population of preterm children at low risk. Second, the implicit in the VBM procedures; although the algorithms in SPM are considered robust, this software was not initially designed to evaluate structural abnormalities, and so imperfect registration may lead to inaccuracy.[65] However, the DARTEL method offers definite improvements for VBM studies in terms of localization, and it also increased sensitivity, which should decrease the impact of our sample size.[28] It will therefore be important to continue to follow this cohort of preterm children at low risk to study to what extent the decreased brain volumes that we found will compromise their neuropsychological and behavioral outcome in adolescent and adult life.

CONCLUSIONS

This MRI study demonstrates that preterm children at low risk are mainly characterized by cortical GM damage, which correlates with IQ performance. Preterm birth itself has a significant impact on GM and WM volume, the temporal lobe being the most affected region. Although preterm children at low risk show a cognitive outcome within the normal range, it remains significantly lower than that of term control subjects. No differences between the groups were found regarding behavioral or emotional problems. Additional

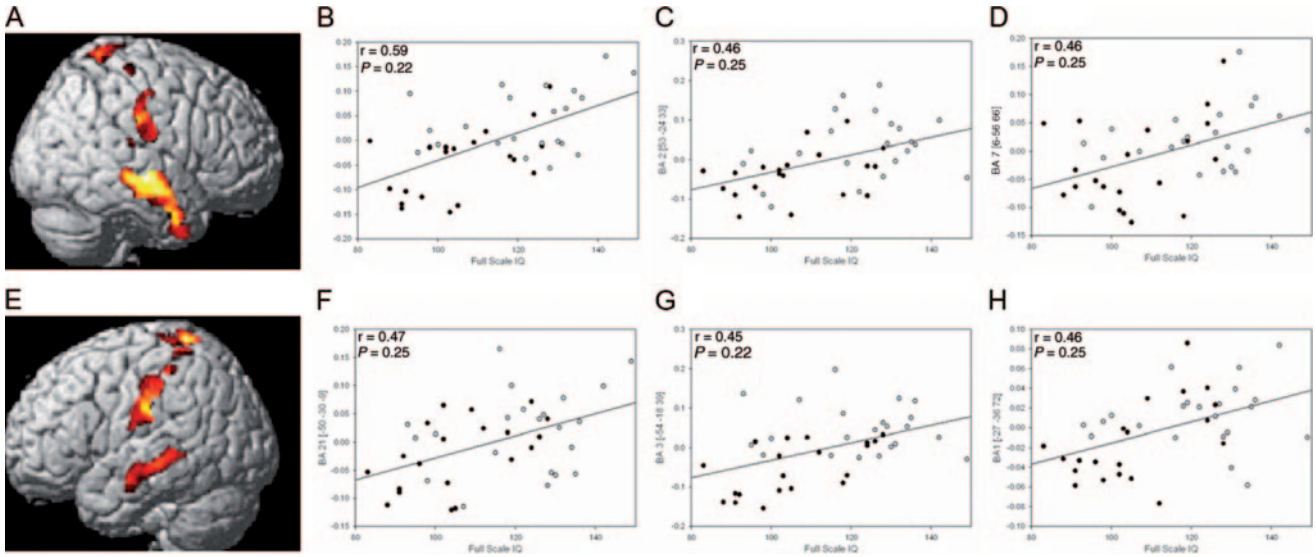

FIGURE 3

Correlations between GM volume involving the middle temporal (BA 21) and the postcentral parietal gyri (BA 1, 2, 3, and 7) and WISC-IV full-scale IQ in the whole sample. Statistical parametric maps are displayed on a lateral brain view in neurologic convention (A to D: right side; E to H: left side). Plots-points indicate real data (●, preterm; ○, term); the line indicates data adjusted to the theoretical model.

research is required to determine the effects of low-risk preterm birth on brain morphology and on subsequent cognitive and behavioral correlates.

ACKNOWLEDGMENTS

This study was supported by grants from the Ministerio de Ciencia y Tecnología (SAF2005-007340) and the Generalitat de Catalunya (2005 SGR 00855). Ms Soria-Pastor and Ms Ibarretxe-Bilbao hold a fellowship from the Ministerio de Educación y Ciencia (AP2005-0047 and AP2005-019, respectively). Dr Padilla is the recipient of an Early-Stage Fellowship from the European Commission (Marie Curie, FETAL-MED-019707-2).

We thank the families and children for participation in the study. We also thank Silvia Juanes Márquez for valuable statistical support.

REFERENCES

1. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr*. 2005;26(6):427–440
2. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA*. 2002;288(6):728–737
3. Reijneveld SA, de Kleine MJ, van Baar AL, et al. Behavioural and emotional problems in very preterm and very low birthweight infants at age 5 years. *Arch Dis Child Fetal Neonatal Ed*. 2006;91(6):F423–F428
4. Hack M, Taylor HG. Perinatal brain injury in preterm infants and later neurobehavioral function. *JAMA*. 2000;284(15):1973–1974
5. Larroque B, Breart G, Kaminski M, et al. Survival of very preterm infants: Epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(2):F139–F144
6. Sie LT, van der Knaap MS, Oosting J, de Vries LS, Lafeber HN, Valk J. MR patterns of hypoxic-ischemic brain damage after prenatal, perinatal or postnatal asphyxia. *Neuropediatrics*. 2000;31(3):128–136
7. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BG, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. *Pediatrics*. 2003;112(5):1108–1114
8. Hart AR, Whitby EW, Griffiths PD, Smith MF. Magnetic resonance imaging and developmental outcome following preterm birth: Review of current evidence. *Dev Med Child Neurol*. 2008;50(9):655–663
9. Volpe JJ. Cerebral white matter injury of the premature infant: more common than you think. *Pediatrics*. 2003;112(1 pt 1):176–180
10. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(2):F153–F161
11. Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA*. 2000;284(15):1939–1947
12. Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics*. 2005;115(2):286–294
13. Boardman JP, Counsell SJ, Rueckert D, et al. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. *Neuroimage*. 2006;32(1):70–78
14. Srinivasan L, Dutta R, Counsell SJ, et al. Quantification of deep gray matter in preterm infants at term-equivalent age using manual volumetry of 3-tesla magnetic resonance images. *Pediatrics*. 2007;119(4):759–765
15. Peterson BS, Anderson AW, Ehrenkranz R, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pediatrics*. 2003;111(5 pt 1):939–948
16. Kesler SR, Ment LR, Vohr B, et al. Volumetric

analysis of regional cerebral development in preterm children. *Pediatr Neurol.* 2004; 31(5):318–325

17. Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Morley R, Gadian DG. Brain morphometry and IQ measurements in preterm children. *Brain.* 2004;127(pt 12):2595–2607
18. Kesler SR, Reiss AL, Vohr B, et al. Brain volume reductions within multiple cognitive systems in male preterm children at age twelve. *J Pediatr.* 2008;152(4):513–520, 520.e1
19. Counsell SJ, Boardman JP. Differential brain growth in the infant born preterm: current knowledge and future developments from brain imaging. *Semin Fetal Neonatal Med.* 2005;10(5):403–410
20. Caravale B, Tozzi C, Albino G, Vicari S. Cognitive development in low risk preterm infants at 3–4 years of life. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(6):F474–F479
21. Zacharia A, Zimine S, Lovblad KO, et al. Early assessment of brain maturation by MR imaging segmentation in neonates and premature infants. *AJNR Am J Neuroradiol.* 2006;27(5):972–977
22. Mewes AU, Huppi PS, Als H, et al. Regional brain development in serial magnetic resonance imaging of low-risk preterm infants. *Pediatrics.* 2006;118(1):23–33
23. Pietz J, Peter J, Graf R, et al. Physical growth and neurodevelopmental outcome of nonhandicapped low-risk children born preterm. *Early Hum Dev.* 2004;79(2):131–143
24. Elgen I, Johansson KA, Markestad T, Sommerfelt K. A non-handicapped cohort of low-birthweight children: growth and general health status at 11 years of age. *Acta Paediatr.* 2005;94(9):1203–1207
25. Weisglas-Kuperus N, Hille EE, Duivenvoorden HH, et al. Intelligence of very preterm or very low birth weight infants in young adulthood. *Arch Dis Child Fetal Neonatal Ed.* 2009; 94(3):F196–F200
26. Wechsler D. *Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)* [in Spanish]. Madrid, Spain: TEA Ediciones; 2007
27. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth & Families; 2001
28. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage.* 2007; 38(1):95–113
29. Ashburner J, Friston KJ. Voxel-based morphometry: the methods. *Neuroimage.* 2000;11(6 pt 1):805–821
30. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology.* 1990; 1(1):43–46
31. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ.* 1998;316(7139): 1236–1238
32. Hojat M, Xu G. A visitor's guide to effect sizes: statistical significance versus practical (clinical) importance of research findings. *Adv Health Sci Educ Theory Pract.* 2004; 9(3):241–249
33. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage.* 2003;19(3):1233–1239
34. Isaacs EB, Lucas A, Chong WK, et al. Hippocampal volume and everyday memory in children of very low birth weight. *Pediatr Res.* 2000;47(6):713–720
35. Reiss AL, Kesler SR, Vohr B, et al. Sex differences in cerebral volumes of 8-year-olds born preterm. *J Pediatr.* 2004;145(2): 242–249
36. Giménez M, Junque C, Narberhaus A, Bargallo N, Botet F, Mercader JM. White matter volume and concentration reductions in adolescents with history of very preterm birth: a voxel-based morphometry study. *Neuroimage.* 2006;32(4):1485–1498
37. Allin M, Nosarti C, Narberhaus A, et al. Growth of the corpus callosum in adolescents born preterm. *Arch Pediatr Adolesc Med.* 2007;161(12):1183–1189
38. Nosarti C, Giouroukou E, Healy E, et al. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain.* 2008;131(pt 1): 205–217
39. Tzarouchi LC, Astrakas LG, Xydis V, et al. Age-related related grey matter changes in preterm infants: an MRI study. *Neuroimage.* 2009;47(4):1148–1153
40. Ment LR, Kesler S, Vohr B, et al. Longitudinal brain volume changes in preterm and term control subjects during late childhood and adolescence. *Pediatrics.* 2009;123(2): 503–511
41. Krägeloh-Mann I. Imaging of early brain injury and cortical plasticity. *Exp Neurol.* 2004; 190(suppl 1):S84–S90
42. Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Semin Perinatol.* 2006;30(2):81–88
43. Ajayi-Obe M, Saeed N, Cowan FM, Rutherford MA, Edwards AD. Reduced development of cerebral cortex in extremely preterm infants. *Lancet.* 2000;356(9236):1162–1163
44. Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neurosci Biobehav Rev.* 2006;30(6):718–729
45. Vangberg TR, Skranes J, Dale AM, Martinussen M, Brubakk AM, Haraldseth O. Changes in white matter diffusion anisotropy in adolescents born prematurely. *Neuroimage.* 2006;32(4):1538–1548
46. Hüppi PS, Murphy B, Maier SE, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics.* 2001; 107(3):455–460
47. Miller SP, Vigneron DB, Henry RG, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. *J Magn Reson Imaging.* 2002;16(6):621–632
48. Nagy Z, Westerberg H, Skare S, et al. Preterm children have disturbances of white matter at 11 years of age as shown by diffusion tensor imaging. *Pediatr Res.* 2003; 54(5):672–679
49. Counsell SJ, Shen Y, Boardman JP, et al. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics.* 2006; 117(2):376–386
50. Giménez M, Miranda MJ, Born AP, Nagy Z, Rostrup E, Jernigan TL. Accelerated cerebral white matter development in preterm infants: a voxel-based morphometry study with diffusion tensor MR imaging. *Neuroimage.* 2008;41(3):728–734
51. Johnson S. Cognitive and behavioural outcomes following very preterm birth. *Semin Fetal Neonatal Med.* 2007;12(5): 363–373
52. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med.* 2005;352(1):9–19
53. Aylward GP. Cognitive and neuropsychological outcomes: more than IQ scores. *Ment Retard Dev Disabil Res Rev.* 2002;8(4): 234–240
54. Fedrizzi E, Zuccarino ML, Vizziello P. Clinical problems in neurodevelopmental diagnosis: a 7-year neurological and psychological follow-up study of low risk preterm infants. *Ital J Neurol Sci.* 1986;suppl 5:117–126
55. Hille ET, den Ouden AL, Bauer L, van den Oudenrijn C, Brand R, Verloove-Vanhorick SP. School performance at nine years of age in very premature and very low birth weight infants: perinatal risk factors and predictors at five years of age. Collaborative Project on Preterm and Small for Gestational Age (POPS) Infants in the Netherlands. *J Pediatr.* 1994;125(3):426–434

56. Botting N, Powls A, Cooke RW, Marlow N. Cognitive and educational outcome of very-low-birthweight children in early adolescence. *Dev Med Child Neurol.* 1998;40(10):652–660
57. Horwood LJ, Mogridge N, Darlow BA. Cognitive, educational, and behavioural outcomes at 7 to 8 years in a national very low birthweight cohort. *Arch Dis Child Fetal Neonatal Ed.* 1998;79(1):F12–F20
58. O'Brien F, Roth S, Stewart A, Rifkin L, Rushe T, Wyatt J. The neurodevelopmental progress of infants less than 33 weeks into adolescence. *Arch Dis Child.* 2004;89(3):207–211
59. Allin M, Matsumoto H, Santhouse AM, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. *Brain.* 2001;124(pt 1):60–66
60. Soria-Pastor S, Gimenez M, Narberhaus A, et al. Patterns of cerebral white matter damage and cognitive impairment in adolescents born very preterm. *Int J Dev Neurosci.* 2008;26(7):647–654
61. Martinussen M, Fischl B, Larsson HB, et al. Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. *Brain.* 2005;128(pt 11):2588–2596
62. Sommerfelt K, Ellertsen B, Markestad T. Parental factors in cognitive outcome of non-handicapped low birthweight infants. *Arch Dis Child Fetal Neonatal Ed.* 1995;73(3):F135–F142
63. Saigal S, Stoskopf B, Streiner D, Paneth N, Pinelli J, Boyle M. Growth trajectories of extremely low birth weight infants from birth to young adulthood: a longitudinal, population-based study. *Pediatr Res.* 2006;60(6):751–758
64. Schothorst PF, van Engeland H. Long-term behavioral sequelae of prematurity. *J Am Acad Child Adolesc Psychiatry.* 1996;35(2):175–183
65. Bookstein FL. "Voxel-based morphometry" should not be used with imperfectly registered images. *Neuroimage.* 2001;14(6):1454–1462

Decreased Regional Brain Volume and Cognitive Impairment in Preterm Children at Low Risk

Sara Soria-Pastor, Nelly Padilla, Leire Zubiaurre-Elorza, Naroa Ibarretxe-Bilbao, Francesc Botet, Carme Costas-Moragas, Carles Falcon, Nuria Bargallo, Josep Maria Mercader and Carme Junqué

Pediatrics 2009;124;e1161-e1170
DOI: 10.1542/peds.2009-0244