Perinatal cortical growth and childhood neurocognitive abilities

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ABSTRACT

Objective: This observational cohort study addressed the hypothesis that after preterm delivery brain growth between 24 and 44 weeks postmenstrual age (PMA) is related to global neurocognitive ability in later childhood.

Methods: Growth rates for cerebral volume and cortical surface area were estimated in 82 infants without focal brain lesions born before 30 weeks PMA by using 217 magnetic resonance images obtained between 24 and 44 weeks PMA. Abilities were assessed at 2 years using the Griffiths Mental Development Scale and at 6 years using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), the Developmental Neuropsychological Assessment (NEPSY), and the Movement Assessment Battery for Children (MABC). Analysis was by generalized least-squares regression.

Results: Mean test scores approximated population averages. Cortical growth was directly related to the Griffiths Developmental Quotient (DQ), the WPPSI-R full-scale IQ, and a NEPSY summary score but not the MABC score and in exploration of subtests to attention, planning, memory, language, and numeric and conceptual abilities but not motor skills. The mean (95% confidence interval) estimated reduction in cortical surface area at term corrected age associated with a 1 SD fall in test score was as follows: DQ 7.0 (5.8–8.5); IQ 6.0 (4.9–7.3); and NEPSY 9.1 (7.5–11.0) % $\cdot$ SD⁻¹. Total brain volume growth was not correlated with any test score.

Conclusions: The rate of cerebral cortical growth between 24 and 44 weeks PMA predicts global ability in later childhood, particularly complex cognitive functions but not motor functions. *Neurology*® 2011;77:1510–1517

GLOSSARY

CI = confidence interval; **DQ** = Developmental Quotient; **MABC** = Movement Assessment Battery for Children; **NEPSY** = Developmental Neuropsychological Assessment; **PMA** = postmenstrual age; **WPPSI-R** = Wechsler Preschool and Primary Scale of Intelligence-Revised.

During late fetal life, brain growth is rapid, particularly in the cerebral cortex. In infants born preterm, the reduced growth of the cortical surface area relative to total brain volume correlates with lower postmenstrual age (PMA) at birth and a lower Griffiths Developmental Quotient (DQ) at 2 years of age.¹ Preterm birth also leads to local changes in brain volume² and perhaps to a reduction in total brain volume, although this is controversial.^{3,4}

These data raised the hypothesis that brain growth in the perinatal period, particularly of the cerebral cortex, predicts later neurocognitive function in infants born preterm. To address this, we examined childhood abilities in a cohort of infants in whom growth of the cortical surface area and cerebral volume between 24 and 44 weeks PMA had been measured.

METHODS Subjects. A previously reported, unselected, sequential cohort of infants born before 30 weeks PMA underwent serial MRI from soon after delivery until around term equivalent age.¹ Between January 1997 and November 2000, 162 infants were born at less than 30 weeks gestational age at the Hammersmith Hospital, London, and 119 underwent serial MRI with 106 survivors

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Supplemental data at
www.neurology.org

Supplemental Data

From the Centre for the Developing Brain (R.R., S.J.C., O.K., L.D., N.K., J.H., J.M.A., F.C., A.D.E.), Imperial College; MRC Clinical Sciences Centre (S.J.C., O.K., L.D., N.K., J.H., J.M.A., F.C., A.D.E.), Hammersmith Hospital; and Division of Neonatology (O.K., L.D., N.K., F.C., A.D.E.), Imperial College Healthcare NHS Trust, London, UK.

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Table 1 Neurocognitive assessment scores and Cronbach α

	Griffiths DQ	WPPSI-R	NEPSY	MABC
No. of infants assessed	62	71	63	70
Mean	97.11	101.72	103.91	12.81
SD	18.06	19.55	13.62	7.63
Median	95	103	103	11.75
Minimum	59	54	69.7	1.5
Maximum	154	145	135	33
Cronbach α	0.83	0.72	0.73	0.79

Abbreviations: DQ = Developmental Quotient; MABC = Movement Assessment Battery for Children; NEPSY = Developmental Neuropsychological Assessment; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised.

entering a follow-up program with scheduled assessments at 2 and 6 years of age. More detailed information is provided in tables e-1 and e-2 on the *Neurology*[®] Web site at www.neurology.org and in a previous publication.¹

Standard protocol approvals, registrations, and patient consents. Ethical approval was given by the Hammersmith Hospital Research Ethics Committee, and written parental consent was obtained in each case.

Magnetic resonance image acquisition. A dedicated 1.0-T MRI system (Oxford Magnet Technology/Marconi Medical) sited within the neonatal intensive care unit, with full intensive care capacity, allowed imaging of infants from 23 weeks PMA. Safety and physiologic data have been published previously.⁵ Serial transverse T2-weighted fast-spin echo images (repetition time = 3,500 msec, effective echo time = 208 msec, echo train length = 16, matrix = 192 $\times$ 256, field of view = 20 cm, slice thickness = 4 mm) were collected from immediately after delivery until term corrected age.

Cortical surface area and cerebral volume measurements. Magnetic resonance images were analyzed using a semi-automatic technique.⁶ In brief, the boundary of the cortex was extracted semi-interactively using a combination of thresholding, manual tracing, and a contour-following algorithm. Total cerebral volume was calculated as the total number of voxels in each brain slice less voxels representing the ventricles and cerebellum multiplied by the planar dimensions of the voxels and the thickness of the brain slices. The surface area of the cortex was calculated from the total length of the measured cortex contour in each slice, defined as the number of voxel edges it contained, multiplied by the voxel dimension in plane and by the slice thickness, summed over all slices. Test-retest error was 2% for cerebral volume and 1% for cortical surface area.

Neurodevelopmental assessment. We used 4 neurocognitive tests to estimate global ability, with subscales that allowed exploratory analysis of specific functions.

At about 2 years of age corrected for prematurity, we offered assessment using the Griffiths Mental Developmental Scales,⁷ which provide an overall DQ with standardized Locomotor, Personal and Social, Hearing and Language, Eye-Hand Coordination, and Performance subscales. These data were reported previously in relation to allometric scaling but not cerebral surface area or volume.¹

At about 6 years we offered the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), and the Movement Assessment Battery for Children (MABC).^{8,9} The

WPPSI-R assesses IQ and provides Verbal and Performance subscales. The MABC yields a total motor impairment score based on 8 tasks: we used age band 1 (4–6 years). Approximately 6 months later we offered the Developmental Neuropsychological Assessment (NEPSY),¹⁰ which has Attention-Executive, Language, Learning and Memory, Sensorimotor, and Visuospatial domains that are normally interpreted separately. However, to provide a test of global ability analogous to the other batteries, we made a summary score by averaging the 5 domain scores for each child. All tests provide results standardized for age.

Statistical analysis. For analyses, we used STATA 11.1 (StataCorp, College Station, TX). We calculated the Cronbach α to check that the assessment batteries were consistent estimators of the latent variable global ability.

We modeled the relation of the change in cerebral volume or cortical surface area over time to neurocognitive variables as the interaction term (variable $\times$ PMA at the time of imaging) using cross-sectional time series analysis by generalized least-square regression for random effects with cortical surface area or total brain volume as dependent variables. The main effects were antenatal growth, coded as the SD (z) score of birthweight; postnatal somatic growth, defined as the z score of the weight at imaging; gender; and social class, captured as the Carstairs Index of Social Deprivation. The interactions were age at scan with test result, birthweight, gender, and weight at time of scan and test result with social class.

Our previous analysis showed that brain growth was directly related to PMA at delivery, suggesting that effects of prematurity on neurocognitive function would be mediated by variation in brain growth. We thus predicted multicollinearity with PMA at birth and excluded it from the model.

To test the validity of each model we examined histograms of subject-specific and idiosyncratic errors as well as residual vs predictor and time plots. Initially we used untransformed brain size data, but although histograms of residuals approximated normality, there was heteroscedasticity in the residual vs time plots so we log-transformed the data, which produced normal and homoscedastic residuals. The Hausman test was used to check the correct specification of the random-effects model. For each significant primary analysis, we tested the stability of the model using perturbation analysis, adding random values to each independent variable and reestimating the model 500 times. To check the assumption that PMA at birth would introduce multicollinearity, we added PMA to the model and again used perturbation analysis. To assess sampling bias, the subgroup of infants seen at both 2 and 6 years was examined separately.

The partial regression coefficient for the variable $\times$ age at scan interaction estimates the relation between that variable and brain growth. To provide a more intuitive measure of the effect magnitude, for significantly related outcomes we calculated for each infant the percentage difference in brain size at 40 weeks PMA attributable to a 1 SD change in test score and present the mean and 95% confidence intervals (CI) for the cohort.

To explore neurocognitive abilities in more detail, we examined the strength of the association between brain growth and domains and subscales from the Griffiths DQ, WPPSI-R, and NEPSY.

The family-wise error rate was controlled in primary and exploratory analyses using the Bonferroni correction. However, because this method is conservative, we also explored the results after control of the false discovery rate using the method of Benjamini and Hochberg.¹¹

Figure Relations between cortical surface area and postmenstrual age at scan with data divided into groups greater or less than mean values for the Griffiths Developmental Quotient (DQ; A), Movement Assessment Battery for Children (MABC; B), Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; C), and Developmental Neuropsychological Assessment (NEPSY; D) summary scores

Simple regression lines are provided to guide the eye but do not represent effect sizes detected by the full statistical models.

RESULTS Subjects. Eighty-two children returned for assessment; other families could not be traced or declined the invitation. Sixty-two children returned at age 2, 71 at age 6, and 51 at both ages. These children were representative of the population as shown by the demographic, clinical, and imaging details given in tables e-1 and e-2.

From these subjects, 217 magnetic resonance images were analyzed. None showed evidence of cystic periventricular leukomalacia, hemorrhagic parenchymal infarction, or porencephalic cysts. One infant was imaged 8 times, 3 infants 7 times, 1 infant 6 times, 6 infants 5 times, 6 infants 4 times, 21 infants 3 times, 21 infants twice, and 23 infants once.

Neurocognitive tests. The Griffiths DQ was assessed in all infants who returned at 2 years of age. At a median of 6.1 (range 5.9–6.5) years, the WPPSI-R full-score IQ was measured in 71 children and the MABC in 70 children. At median 6.6 (range 6.3–6.9) years, 63 children took the NEPSY. Group means for primary outcomes are given in table 1 and for domains and subscales in table e-3, together with values for the Cronbach α . The overall α was 0.82 for primary and 0.91 for exploratory outcomes.

The figure shows the relation of cortical surface area and PMA for each primary outcome. For illustration only and not representing true effect sizes,

Table 2 Growth of cortical surface area and neurocognitive assessments^a

	Griffiths DQ	WPPSI-R	NEPSY	MABC
Overall R^2	0.93	0.92	0.93	0.92
Primary outcomes				
Interaction of Griffiths DQ with age at scan				
Slope	0.0004			
p	0.0069 ^a			
Interaction of WPPSI-R with age at scan				
Slope		0.0003		
p		0.0050 ^a		
Interaction of NEPSY with age at scan				
Slope			0.0005	
p			0.0013 ^a	
Interaction of MABC with age at scan				
Slope				-0.0005
p				0.143
Other variables				
Interaction of Griffiths DQ with social class				
Slope	0.0003			
p	0.191			
Interaction of WPPSI-R with social class				
Slope		3.9×10^{-5}		
p		0.843		
Interaction of NEPSY with social class				
Slope			0.0001	
p			0.816	
Interaction of MABC with social class				
Slope				-0.0001
p				0.878
Interaction of z score weight at scan with age at scan				
Slope	0.0068	0.0047	0.0072	0.0052
p	0.017	0.092	0.004	0.069
Interaction of z score birth weight with age at scan				
Slope	-0.0056	-0.0030	-0.0057	-0.0030
p	0.071	0.300	0.023	0.333
Interaction of gender with age at scan				
Slope	0.0128	0.0072	0.0059	0.0095
p	0.006	0.105	0.149	0.046
Age at scan				
Slope	0.0619	0.0768	0.0603	0.1127
p	0.001	<0.00001	0.002	<0.00001

—Continued

data divided at the mean test score and regression lines are provided to guide the eye.

Primary analysis. The statistical models fitted well with overall R^2 values of 0.92–0.93 for cortical surface area and 0.83–0.87 for cerebral volume. Control of the family-wise error rate to the 5% level required $p < 0.0125$, and control of the false discovery rate required $p < 0.0375$ for analyses of surface area and 0.0125 for cerebral volume.

Controlling for the family-wise error rate, there was a highly significant positive relation between the rate of growth of the cortical surface area and the Griffiths DQ (0.044% surface area, DQ point⁻¹ · week⁻¹), the WPPSI-R full-score IQ (0.032% surface area, IQ point⁻¹ · week⁻¹), and the NEPSY summary score (0.052% surface area, summary score point⁻¹ · week⁻¹). There was no relation between cortical growth and MABC score. Analysis of potential confounders showed no association of cognitive ability with social class, and the association of cortical growth with gender, somatic growth, and birth-weight was inconsistent across analyses. These results are given in table 2.

The mean (95% CI) reduction in surface area at 40 weeks PMA attributable to a 1 SD change in test score was biologically relevant: Griffiths DQ 7.0 (5.8–8.5)% · SD⁻¹; WPPSI-R IQ, 6.0 (4.9–7.3)% · SD⁻¹; and NEPSY summary score, 9.1 (7.5–11.0)% · SD⁻¹.

There was no relation between any primary outcome and the growth in cerebral volume before or after control of the family-wise error rate. These data are given in table 3.

Exploratory analyses. After control of the family-wise error rate, cortical growth was related to the WPPSI-R Verbal subscore, the NEPSY Attention-Executive function domain, and the Griffiths Hearing and Language subscore. Total brain volume growth was not related to any subscore or domain.

Control of the false discovery rate caused no change in the primary outcomes or results for brain volume growth, although it appeared that the NEPSY Visuospatial and Learning domains and Griffiths Personal and Social subscale might also be significantly related to cortical growth (table 4).

Model testing. The Hausman test showed no evidence of misspecification. Perturbation analysis produced unaltered Griffiths DQ, WPPSI-R IQ, and NEPSY summary scores, showing that the model was stable. When PMA at birth was added into the model, cortical surface area remained related to Griffiths DQ ($p = 0.015$), WPPSI-R IQ ($p = 0.045$), and NEPSY summary scores ($p = 0.032$), although these values do not survive correction of family-wise

Table 2 Continued

	Griffiths DQ	WPPSI-R	NEPSY	MABC
z Score of weight at scan				
Slope	-0.1727	-0.1171	-0.1901	-0.1373
p	0.078	0.219	0.029	0.160
z Score of birth weight				
Slope	0.1860	0.1189	0.1940	0.1182
p	0.078	0.236	0.027	0.258
Gender^c				
Slope	-0.3206	-0.1460	-0.1086	-0.2082
p	0.035 ^b	0.320	0.427	0.182
Social class (Carstairs Index)				
Slope	-0.0300	-0.0016	-0.0048	0.0020
p	0.216	0.940	0.891	0.820
Griffiths DQ				
Slope	-0.0130			
p	0.014 ^b			
WPPSI-R				
Slope		-0.0098		
p		0.008 ^a		
NEPSY				
Slope			-0.0141	
p			0.009 ^a	
MABC				
Slope				0.0142
p				0.175
Constant				
Slope	3.4356	2.9904	3.3136	1.8832
p	<0.00001	<0.00001	<0.00001	<0.00001

Abbreviations: DQ = Developmental Quotient; MABC = Movement Assessment Battery for Children; NEPSY = Developmental Neuropsychological Assessment; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised.

^a p Values are uncorrected: primary outcomes were significant after control of the family-wise error rate ($p < 0.0125$) and the false discovery rate.

^b Significant after control of the false discovery rate ($p < 0.0375$).

^c Female/male ratio = 0:1.

error rate, but perturbation analysis showed increased SEs and marked instability in the coefficients for birthweight, weight at scan, and gender, consistent with the predicted multicollinearity.

Analysis of the subgroup of infants studied at both 2 and 6 years of age largely replicated the primary analysis. Cortical growth was significantly related to the Griffiths DQ ($p = 0.007$) and NEPSY summary score ($p = 0.007$) but not the MABC, whereas the WPPSI-R full-score IQ was significant at $p = 0.014$, which survived control of the false discovery rate but not family-wise error rate. Cerebral volume was not related to any outcome.

DISCUSSION In this study of infants born preterm, the rate of growth of the cortical surface area between

24 and 44 weeks PMA was directly related to neuro-cognitive ability at 2 and 6 years of age. The difference in cortical growth associated with changes in global ability was large, consistent, and specific: 1 SD difference in the Griffiths, WPPSI-R, and NEPSY scores was associated with a 5%–11% difference in surface area, and no relation was seen between cortical growth and motor abilities either in the primary outcomes or in test subscores or between total brain volume and any functional assessment.

These conclusions depend on the accuracy of the measures of surface area and volume growth, the correct specification and fitting of the statistical models, and the precision and consistency of the neuropsychological tests. We address these in turn.

The measurement of surface area using the semi-interactive approach is conceptually simple, avoids some technical problems inherent in measurements of cortical volumes and thickness, and captures the massive increase in brain size during this period. The approach has limitations: partial volume effects associated with the finite resolution of images necessarily make the precise definition of the cortical surface uncertain at the level of an individual voxel, and the 4-mm slice thickness adds errors to the data, but these are common to all the images analyzed. More advanced approaches for cortical segmentation and surface reconstruction are now available¹² but are not suitable for these images captured a decade ago, and comparison has shown that our simple approach achieves similar quantitative results.¹³

Using the generalized least-squares method for cross-sectional longitudinal data produced robust results that allowed for different numbers and timing of repeated MRI scans within individuals. The model was well-specified and stable, and fits of log-transformed data were good. Control of the family-wise error provides confidence that all positive results are accurate although allowing the possibility of type 2 error, but controlling the less conservative false discovery rate produced no difference in interpretation because there was no change in the primary outcomes, only a small increase in the number of subscales and domains related to cortical growth.

The Griffiths, WPPSI-R, and NEPSY all interrogate cognitive and psychological abilities and include some subscores or domains affected by locomotor function, whereas the MABC focuses on detecting movement impairment. High values for Cronbach α showed that the tests provided consistent estimates of global ability. However, the test results were not uniform. Cortical growth was strongly related to global ability as assessed by the Griffiths, WPPSI-R, and NEPSY, but not to the MABC test of motor function. Exploratory studies were consistent with this

Table 3 Growth of brain volume and neurocognitive assessments

	Griffiths DQ	WPPSI-R	NEPSY	MABC
Overall R^2	0.827	0.858	0.873	0.855
Primary outcomes				
Interaction of Griffiths DQ with age at scan				
Slope	0.0001			
p	0.435			
Interaction of WPPSI-R and age at scan				
Slope		0.0002		
p		0.053		
Interaction of NEPSY and age at scan				
Slope			0.0002	
p			0.267	
Interaction of MABC with age at scan				
Slope				−0.0002
p				0.648
Other variables				
Interaction of Griffiths DQ and social class				
Slope	2.9×10^{-6}			
p	0.993			
Interaction of WPPSI-R and social class				
Slope		−0.0002		
p		0.366		
Interaction of NEPSY and social class				
Slope			−0.0003	
p			0.335	
Interaction of MABC with social class				
Slope				−0.0002
p				0.679
Interaction of z score weight at scan with age at scan				
Slope	0.0019	0.0018	0.0032	0.0025
p	0.518	0.530	0.248	0.456
Interaction of z score birth weight with age at scan				
Slope	−0.0017	−0.0016	−0.0031	−0.0034
p	0.591	0.615	0.267	0.342
Interaction of gender with age at scan				
Slope	0.0001	−0.0020	−0.0014	0.0011
p	0.989	0.675	0.753	0.836
Age at scan				
Slope	0.0864	0.0641	0.0681	0.0710
p	<0.00001	<0.00001	0.002	0.001

—Continued

result, with Griffiths, subscales, and NEPSY domains testing locomotor function showing no significant association with cortical growth and the WPPSI-R performance subscore, which contains items relying on motor function, also failing to reach statistical significance. Instead, cortical growth seemed to be particularly related to attention and executive function, planning, learning, memory, language, numeric, conceptual, and social abilities, which may reflect the integration of widespread cortical regions in these tasks. Further local analysis of brain growth may clarify this, and methods for local cortical growth analysis are being developed with focal structural differences associated with specific abilities such as arithmetic,¹⁴ working memory,¹⁵ and verbal abilities,¹⁶ as well as regional changes in brain volume associated with neurocognitive impairment having been described.

The results have been influenced by the absence of infants with focal lesions known to be associated with motor deficits, and it is also possible that rapid growth of frontal relative to motor cortex during the study period might obscure relations to motor skills. Excluding the cerebellum from brain measurements might also be relevant, although the cerebellum is involved in neurocognitive function as well as motor control. Nevertheless, these data show a strong relation between cortical growth and cognitive abilities. There was no evidence that social class influenced the association between test score and brain growth.

This study cannot ascertain whether the relation between cortical growth and neurocognitive function reflect the (epi)genetic control of brain development or the environmental effects of preterm birth. These are some reasons to suggest that it reflects normal development: mean test scores in the group approximated to the population-standardized means, and no infants had focal brain lesions; therefore, the relation was observed in a group of relatively normal children. Indeed, different neuroanatomical correlates of neurologic impairment in preterm infants have been detected. For example, we found in a separate but similar cohort that local white matter microstructural changes were specifically related to cognitive impairment^{17,18} and have suggested that specific abnormalities in cerebral white matter, thalamic nuclei, and basal ganglia may underlie neurodevelopmental impairment in children born preterm.²

However, the infants in this study were a large and representative subset of the original sequential cohort in which reduced cortical growth relative to brain volume was predicted in a dose-dependent fashion by earlier preterm birth.¹ A previous analysis of this cohort showed that reduced cortical growth was predicted by adverse clinical events around the

Table 3 Continued

	Griffiths DQ	WPPSI-R	NEPSY	MABC
z Score of weight at scan				
Slope	−0.0368	−0.0367	−0.0693	−0.0476
p	0.714	0.715	0.471	0.682
z Score of birthweight				
Slope	0.0903	0.0871	0.1267	0.1325
p	0.403	0.413	0.193	0.288
Gender^a				
Slope	0.1213	0.1776	0.1509	0.1055
p	0.452	0.255	0.317	0.555
Social class (Carstairs Index)				
Slope	−0.0007	0.0141	0.0269	−0.0053
p	0.934	0.480	0.439	0.874
Griffiths DQ				
Slope	−0.0020			
p	0.753			
WPPSI-R				
Slope		−0.0060		
p		0.129		
NEPSY				
Slope			−0.0037	
p			0.537	
MABC				
Slope				0.0014
p				0.894
Constant				
Slope	2.0799	2.6015	2.3792	2.2201
p	<0.00001	<0.00001	0.001	0.002

Abbreviations: DQ = Developmental Quotient; MABC = Movement Assessment Battery for Children; NEPSY = Developmental Neuropsychological Assessment; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised.

p Values are uncorrected: no primary outcomes were significant after control of the family-wise error and false discovery rates ($p < 0.0125$).

^a Female/male ratio = 0:1.

time of birth and chronic ill health during the between birth and term corrected age, notably the development of chronic lung disease.¹⁹ This finding suggests that the adverse effects of premature extra-uterine life may reduce both cortical growth and neurocognitive function.

Two attractive interpretations of these data are available: first, genetic and environment influences that determine global ability are both mediated at least in part through effects on cortical growth between 25 and 44 weeks PMA; and, second, childhood cognitive abilities, particularly complex functions requiring executive function, attention, and planning, are directly related to the growth of the cerebral cortex during this period. These conclusions could be tested by suitably designed and powered studies.

Table 4 Exploratory analysis

Test subscale or domain	p Values ^a	
	Cortical surface area	Cerebral volume
Griffiths Hearing and Language	0.0001 ^b	0.0636
NEPSY Attention-Executive	0.0002 ^b	0.0337
WPPSI-R Verbal	0.0006 ^b	0.0267
NEPSY Visuospatial	0.0048 ^c	0.36
Griffiths Personal and Social	0.0065 ^c	0.4136
NEPSY Memory	0.0157 ^c	0.7742
WPPSI-R Performance	0.0525	0.1466
Griffiths Eye-Hand Coordination	0.0975	0.7412
NEPSY Language	0.1348	0.5529
Griffiths Performance	0.1498	0.8467
Griffiths Locomotor	0.3313	0.4665
NEPSY Sensorimotor	0.3541	0.3678

Abbreviations: MABC = Movement Assessment Battery for Children; NEPSY = Developmental Neuropsychological Assessment; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised.

^a Uncorrected p values for testing the relation of cortical surface area and cerebral volume vs with subscores and domains.

^b p Values significant at $p < 0.05$ after control of the family-wise error (which requires $p < 0.004$).

^c p Values significant at $p < 0.05$ after controlling for the false discovery rate (which requires $p < 0.025$ for surface area and $p < 0.042$ for volume).

AUTHOR CONTRIBUTIONS

R. Rathbone: drafting/revising the manuscript and acquisition of data. Dr. Counsell: drafting/revising the manuscript and acquisition of data. Dr. Kapellou: drafting/revising the manuscript, analysis or interpretation of data, and acquisition of data. Dr. Dyet: drafting/revising the manuscript and acquisition of data. Dr. Kennea: drafting/revising the manuscript, study concept or design, acquisition of data, and patient recruitment and imaging. Dr. Hajnal: drafting/revising the manuscript and acquisition of data. J. Allsop: analysis or interpretation of data and acquisition of data. Dr. Cowan: drafting/revising the manuscript, study concept or design, acquisition of data, and study supervision. Dr. Edwards: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, and obtaining funding.

COINVESTIGATOR

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DISCLOSURE

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REFERENCES

1. Kapellou O, Counsell SJ, Kennea N, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;3:e265.
2. Boardman JP, Craven C, Valappil S, et al. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. *Neuroimage* 2010;52:409–414.
3. Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics* 2005;115:286–294.
4. Ajayi-Obe M, Saeed N, Rutherford M, Cowan FM, Edwards AD. Reduced development of the cerebral cortex in extremely preterm infants. *Lancet* 2000;356:1162–1163.
5. Battin M, Maalouf E, Counsell S, et al. Physiological stability of preterm infants during magnetic resonance imaging. *Early Hum Dev* 1998;52:101–110.
6. Saeed N, Hajnal JV, Oatridge A. Automated brain segmentation from single slice, multislice, or whole-volume MR scans using prior knowledge. *J Comput Assist Tomogr* 1997;21:192–201.
7. Huntley M. The Griffiths Mental Developmental Scales: From Birth to 2 Years. London: Test Agency Ltd.; 1996.
8. Henderson SE, Sugden D. Movement Assessment Battery for Children. London: The Psychological Corporation; 1992.
9. Weschler D. Wechsler Preschool and Primary Scale of Intelligence-Revised. London: The Psychological Corporation; 1989.
10. Korkman M, Kirk U, Kemp S. A Developmental Neuropsychological Assessment. London: The Psychological Corporation; 1998.
11. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995;57:289–300.
12. Xue H, Srinivasan L, Jiang S, et al. Automatic segmentation and reconstruction of the cortex from neonatal MRI. *Neuroimage* 2007;38:461–477.
13. Srinivasan, L. Advanced neuroimaging techniques to study the development of the cerebral cortex, subplate and thalamus in preterm infants at 3 Tesla. London: Imperial College, 2010. PhD thesis.
14. Isaacs EB, Edmonds CJ, Lucas A, Gadian DG. Calculation difficulties in children of very low birthweight: a neural correlate. *Brain* 2001;124:1701–1707.
15. Beauchamp MH, Thompson DK, Howard K, et al. Preterm infant hippocampal volumes correlate with later working memory deficits. *Brain* 2008;131:2986–2994.
16. Lawrence EJ, McGuire PK, Allin M, et al. The very preterm brain in young adulthood: the neural correlates of verbal paired associate learning. *J Pediatr* 2010;156:889–895.
17. Counsell SJ, Edwards AD, Chew AT, et al. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. *Brain* 2008;131:3201–3208.
18. Krishnan ML, Dyet LE, Boardman JP, et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. *Pediatrics* 2007;120:e604–e609.
19. Kaukola T, Kapellou O, Laroche S, et al. Severity of perinatal illness and cerebral cortical growth in preterm infants. *Acta Paediatr* 2009;98:990–995.

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