doi:10.1093/brain/awm282 *Brain* (2008), **131**, 205–217

Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome

Chiara Nosarti,[1] Elena Giouroukou,[1] Elaine Healy,[1] Larry Rifkin,[1] Muriel Walshe,[1] Abraham Reichenberg,[1] Xavier Chitnis,[2] Steven C. R. Williams[2] and Robin M. Murray[1]

[1]Department of Psychiatry, King's College London Institute of Psychiatry and [2]Centre for Neuroimaging Sciences, King's College London Institute of Psychiatry and South London and Maudsley NHS Trust, London, UK

Correspondence to: Dr Chiara Nosarti, Department of Psychiatry, PO Box 63, King's College London Institute of Psychiatry, 16 De Crespigny Park, Denmark Hill, London SE5 8AF, UK
E-mail: c.nosarti@iop.kcl.ac.uk

Very preterm (VPT) birth is associated with altered cortical development and long-term neurodevelopmental sequelae. We used voxel-based morphometry to investigate white (WM) and grey matter (GM) distribution in VPT adolescents and controls, and the association with gestational age and neonatal ultrasound findings in the VPT individuals. GM and WM volumes were additionally investigated in relation to adolescent neurodevelopmental outcome. Structural MRI data were acquired with a 1.5 Tesla machine in 218 VPT adolescents (<33 weeks, gestation) and 128 controls aged 14–15 years, and analysed using SPM2 software. VPT individuals compared to controls showed reduced GM in temporal, frontal, occipital cortices and cerebellum, including putamen, insula, cuneus, fusiform gyrus, thalamus and caudate nucleus, and increased GM predominantly in temporal and frontal lobes, including cingulate and fusiform gyri and cerebellum. WM loss was concentrated in the brainstem, internal capsule, temporal and frontal regions and the major fasciculi. WM excesses were observed in temporal, parietal and frontal regions. Investigation of the inter-relationships between brain regions and changes revealed that all selected areas where between-group increased and decreased WM and GM volumes differences were observed, were structurally associated, highlighting the influence that abnormalities in one brain area may exert over others. VPT individuals with evidence of periventricular haemorrhage and ventricular dilatation on neonatal ultrasound exhibited the greatest WM and GM alterations. VPT adolescents obtained lower scores than controls on measures of language and executive function and were more likely to show cognitive impairment compared to controls (27% versus 14%, respectively). Several areas where VPT individuals demonstrated decreased GM and WM volume were linearly associated with gestational age and mediated cognitive impairment. To summarize, our data demonstrates that VPT birth is associated with altered brain structure in adolescence. GM and WM alterations are associated with length of gestation and mediate adolescent neurodevelopmental impairment. Thus, anatomical brain changes may contribute to specific cognitive deficits associated with VPT birth and could be used in the identification of those individuals who may be at increased risk for cognitive impairment.

Keywords: preterm birth; magnetic resonance; neurocognition; neural plasticity

Abbreviations: GM = grey matter; LBW = low birth weight; VPT = very preterm; WM = white matter

Received August 15, 2007. Revised September 20, 2007. Accepted October 19, 2007. Advance Access publication December 3, 2007

Introduction

Individuals born very preterm (VPT) (e.g. <33 weeks of gestation) and low birth weight (LBW) (e.g. <2500 g) are at risk of disruption of the normal processes of cerebral development; the immature brain is vulnerable to haemorrhage and hypoxic-ischaemic damage, often resulting in ventricular dilatation, white matter damage, immature gyral development and enlarged subarachnoid space (Inder *et al.*, 2003). In addition to the immediate consequences, brain lesions associated with VPT and LBW birth may adversely affect subsequent cortical development by interfering with myelination (Sie *et al.*, 1997). Abnormalities of brain morphology persist in later life, especially in those individuals with evidence of periventricular haemorrhage and ventricular dilatation in the neonatal period (Nosarti *et al.* 2002, 2004). Thus, approximately half of VPT adolescents demonstrate brain abnormalities (Cooke and Abernethy 1999; Stewart *et al.* 1999), with smaller cortical

volumes and larger lateral ventricles compared to controls (Cooke and Abernethy 1999; Nosarti *et al.* 2002). Studies looking at specific structures [hippocampus, cerebellum, corpus callosum (CC), caudate nucleus] reported decreases in size in VPT individuals compared to controls, after adjusting for cerebral volumes (Peterson *et al.* 2000; Allin *et al.* 2001; Nosarti *et al.* 2002, 2004). These abnormalities may underlie the long-term cognitive and behavioural sequelae observed in VPT samples (Stewart *et al.* 1999; Rushe *et al.* 2001; Nosarti *et al.* 2004; Taylor *et al.* 2004a).

Voxel-based morphometry has been used to investigate the long-term effects of LBW birth on the adult brain (Allin *et al.*, 2004), showing distributed and spatially-complex regions of excesses and deficits in both grey matter (GM) and white matter (WM), as well as the effects of VPT birth on WM distribution in adolescence, showing periventricular injury and the involvement of the longitudinal fascicles (Gimenez *et al.* 2006a). These results suggest that localized lesions may affect the development of distant areas—an effect that has been defined 'secondary cortical dysplasia' (Hack and Taylor, 2000). These data also imply an alteration of WM connectivity, as do diffusion tension imaging (DTI) studies (Nagy *et al.*, 2003).

As part of a longitudinal study (Stewart *et al.*, 1999; Allin *et al.*, 2001; Rushe *et al.*, 2001; Nosarti *et al.*, 2002, 2004), we used a voxel-based automated method to investigate regional GM and WM distribution in what we believe to be the largest group of VPT adolescents to date followed-up with neonatal ultrasound, neurodevelopmental and neuroimaging data, as well as controls. We hypothesized that VPT individuals would show diffused WM and GM abnormalities, especially in the prefrontal and temporal cortices on the basis of cognitive deficits observed in VPT and LBW populations (Isaacs *et al.*, 2000; Rushe *et al.*, 2001; Taylor *et al.*, 2004*b*), and these alterations would be associated with neurodevelopmental outcome (Hack and Taylor, 2000). We further hypothesized that the extent of GM and WM changes would be proportionally associated with the length of gestation (Gimenez *et al.*, 2006*a*), and that those VPT individuals who had evidence of periventricular haemorrhage and/or ventricular dilatation on neonatal ultrasound would exhibit increased GM and WM abnormalities compared with VPT individuals with normal results.

Methods

Participants

Two cohorts of infants, born before 33 weeks of gestation and admitted consecutively to the Neonatal Unit of University College London Hospital (UCLH), were studied. The first series drew on all individuals born in 1979–82 ($n = 223$) who were enrolled for long-term follow-up (Stewart *et al.*, 1999; Nosarti *et al.*, 2002, 2004). At 14–15 years, 221 individuals were traced. Of those 205 living in the UK, 156 (76.1%) agreed to undergo assessment, including MRI ($n = 128$). The second cohort included a selected group of individuals born in 1983–84 ($n = 147$). This selection was necessitated by an expansion in capacity of UCLH in 1983 which prevented inclusion of the entire consecutive series due to limited research resources. The selection criteria were: all individuals born at 28 or less weeks of gestation ($n = 78$), as well as a random sample of one in four of those born from 29 to 33 weeks of gestation ($n = 69$). In adolescence, 113 (76.9%) of these individuals were assessed, 90 (61.2%) had an MRI. In both cohorts, VPT participants did not differ from non-participants in gestational age (GA), birth weight (BW), family socio-economic status (SES), neonatal ultrasonographic findings, nor in neurodevelopmental status when assessed at 1, 4 and 8 years of age. Analysis of all the neurodevelopmental scores described below revealed no statistically significant differences between the two cohorts and between those VPT individuals who had an MRI scan and those who did not.

A group of 47 infants delivered at term at UCLH in 1979–80 had been enrolled to act as controls. Inclusion criteria were full-term birth (38–42 weeks) and birth weight >2500 g. Forty-five individuals were living in the UK at 14–15 years, and 21 agreed to have MRI (Stewart *et al.* 1999). Additionally, 106 full-term individuals matched for year of birth and SES, recruited through advertisements in the press, were studied. Inclusion criteria were the same used for the UCLH controls; exclusion criteria included any history of neurological conditions including meningitis, head injury and cerebral infections. MRI data was obtained for a total of 218 VPT adolescents and 128 controls.

Ethical approval for the study was obtained from local ethical committees. Written informed consent was obtained from an accompanying parent and verbal consent was obtained from participants.

Neurodevelopmental outcome data

VPT participants and controls were assessed with neurodevelopmental scales assessing language [Schonnel Graded Reading Test and Schonnel Spelling Test (Schonnel and Schonnel, 1960)], executive function and in particular cognitive flexibility [phonemic fluency with the 'FAS' test (Benton and Hamsher, 1976), semantic fluency with the Animals and Objects Trials (Newcombe, 1969), conceptual tracking with the Trail Making Test (Trails B) (Reitan and Wolfson, 1985)]; verbal memory [Logical Memory subtest of the Rivermead Behavioural Memory Test (Wilson *et al.*, 1985)], non-verbal memory [Rey-Osterrieth Complex Figure Design (ROCFD) Recall] and visual-motor integration [Beery test (Beery, 2007), ROCFD Copy (Osterrith, 1944)]. Reading age was treated as a proxy for intelligence quotient (Stewart *et al.*, 1999). A subset of participants (116 cases and 35 controls) had a clinical structured neuromotor assessment. Neurodevelopmental data for the 1979–80 cohort was previously published (Stewart *et al.*, 1999; Rushe *et al.*, 2001).

MRI image acquisition and analysis

MRI was performed on two sites. For the 1979–82 cohort and controls a 1.5 Tesla GE Signa Horizon machine (General Electric Medical Systems, Milwaukee, WI, USA) was used at the Institute of Neurology, London. For the 1983–84 cohort and controls, a 1.5 Tesla GE N/Vi Signa System machine of the same make was used at the Maudsley Hospital, London. For all participants in the two

sites previously documented sequences were obtained (Nosarti *et al.*, 2002).

The three-dimensional MRI data sets were processed using optimized voxel-based morphometry (VBM) in Statistical Parametric Mapping SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/), running on Matlab 6.5 (MathWorks, Natick, USA). The full details of the processing protocol used in VBM are presented elsewhere (Good *et al.*, 2001).

A customized template of the whole brain was obtained with a standard VBM protocol (Ashburner and Friston, 2000) through normalization of the GRASS T1-weighted gradient-echo sequences for all study participants (preterm and controls, $n = 311$) to the T_1-weighted stereotactic template of SPM2 using a 12 parameter affine transformation, followed by smoothing with an 8 mm FWHM isotropic Gaussian kernel (in order to reduce the effects of individual variation in sulcal/gyral anatomy). All spatially normalized images were resliced with a voxel size of $1 \times 1 \times 1\,mm^3$ in order to reduce the partial volume problem and insure optimal tissue segmentation. Finally all smoothed normalized images were averaged. Starting estimates for the registration were assigned by specifying the position of the anterior commissure (Ashburner *et al.*, 1997). This method employs a Bayesian framework, whereby the construction of posterior probability maps (PPM) based on prior knowledge of the normal variability in brain size (Good *et al.*, 2001) allows inferences about regionally specific effects.

The normalized averaged whole brain images were segmented into grey matter, white matter and cerebrospinal fluid using a modified mixture model cluster algorithm which identifies voxels assigned to a particular tissue type combined with an *a priori* knowledge of the spatial distribution of the these tissue types in normal populations derived by probability maps. Segmentation includes a correction for intensity non-uniformity in order to account for image intensity variations due to differing positions of cranial structures in the MRI scanner (Ashburner and Friston, 2000). Finally, the segmented images were smoothed with an 8 mm FWHM isotropic Gaussian filter. Smoothing is used to improve the signal-to-noise ratio, as it reduces the influences of individual variations in gyral anatomy after spatial normalization and permits application of Gaussian random-field theory for corrected statistical inference (Friston *et al.*, 1995).

Separate stereotactic customized grey and white matter templates were created with an optimized VBM protocol (Good *et al.*, 2001), by averaging all the 311 smoothed normalized grey/white matter images from the standard VBM protocol described earlier using affine transformation with sinc interpolation algorithm. Images from the whole group were chosen in order to minimize any potential bias for spatial normalization. Customized priors were computed from these templates, which were used to improve the accuracy of the extraction of grey and white matter of each subject in the normalization process described in the text (Good *et al.*, 2001).

All original MRI images (in native space) were segmented into GM and WM using a SPM2 script. Non-brain voxels were removed from the segmented images. The extracted GM and WM images were spatially normalized onto the customized GM and WM templates using the optimum 12-parameter affine transformations. The spatially normalized images were segmented into GM and WM and subjected to a second extraction of normalized segmented GM and WM images. A brain extraction and cleaning procedure was applied and the cleaned GM and WM images were modulated, i.e. the spatially normalized GM and WM were multiplied by their relative volumes before and after spatial normalization, in order to adjust for the expansion and shrinkage of voxels that can occur during spatial normalization (Ashburner and Friston, 2000). Finally, the segmented images were smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel (Ashburner and Friston, 2000). All the described SPM2 steps were fully automated. The estimates of the adjusted group means were compared using a linear contrast (control versus preterm group—firstly including and secondly excluding the subjects with evidence of uncomplicated periventricular haemorrhage (PVH) and ventricular dilatation (DIL) on neonatal ultrasound, to calculate t values at each voxel. The resulting statistical parametric maps (SPM) from these contrasts (based on probability assignment to WM or GM) were transformed to the unit normal distribution SPM (Z). Group effects according to neonatal ultrasound classification in VPT individuals were compared: (i) normal (NM); (ii) PVH; (iii) PVH + DIL (Nosarti *et al.*, 2002). Firstly, analyses used gender and chronological age at time of assessment as covariates. Separate analyses were conducted for the two MRI acquisitions sites and showed virtually identical results (available upon request). Therefore, images from the two sites were combined, and acquisition site was added as a confounder (Schnack *et al.*, 2004). All analyses were adjusted for gender, chronological age at assessment and MRI acquisition site. Voxel level local maxima more than 8.0 mm apart with a P value corrected for family-wise error (FWE) of <0.05 are reported in Tables 2–4. Simple linear regression of gestational age (number of completed weeks) to WM and GM maps was performed at each voxel. From the location where significant group differences were obtained, GM and WM values were calculated for each cluster in each scan using SPM's volume of interest (VOI) data extraction tool. One-sample Kolmogorov–Smirnov tests were performed, which revealed a normal distribution of the data. In order to explore structural covariance in areas where significant group differences were observed, GM and WM values from selected areas were investigated with correlation analyses (Mechelli *et al.*, 2005). When investigating neurodevelopmental outcome data, we conducted two sets of analyses in order to: (i) demonstrate the quantitative contribution of anatomical brain alterations to severity of cognitive deficits and (ii) demonstrate the clinical significance of this association. First, linear regression models were constructed using the neurodevelopmental scores where VPT individuals showed significant differences from controls, global executive function and language scores, as dependent variables, and all regions of between group GM and WM differences and group membership (VPT or control) as predictors. Next, we classified all subjects in the study, VPT participants and controls as 'cognitively impaired' or 'cognitively normal'. Impairment was defined as performance of 1SD or more below the mean of the control group for both language and executive function scores. This criterion follows the commonly used definition of clinically significant impairment used in the neuropsychological literature (Lezak, 1995). GM and WM volume data were categorized into quartiles and then a test of linearity was performed treating the quartile assignments as linear. Binary logistic regression models were created using quartiles of extracted values for selected regions of GM and WM as predictors.

Table 1 Characteristics VPT individuals and controls

	Cases ($N = 207$)	Controls ($N = 104$)
Neonatal characteristics[a]		
Birth weight (g)	1276.0 ± 353.8 (552–2390)	3358.4 ± 394.3 (3200–4120)
Gestation at birth (weeks)	29.1 ± 2.2 (24–32)	40.1 ± 1.3 (38–41)
Males/females (number)	115/92	59/45
Anthropometric data at assessment		
Head circumference (cm)***	55.1 ± 1.9 (50.0–60.0)	56.1 ± 1.7 (52.0–61.2)
Height (cm)	164.7 ± 8.4 (145–184)	166.9 ± 7.4 (150–184)
Body Mass Index	20.5 ± 3.9 (12.8–35.0)	21.0 ± 4.0 (14.5–37.4)
Chronological age (years)***	15.2 ± 0.5 (13.9–16.7)	15.0 ± 0.7 (14.1–16.8)
Parental socio-economic status at assessment—Number, percent		
I–II	81 (39%)	48 (46%)
III	65 (31%)	24 (23%)
IV–V	49 (24%)	25 (24%)
Missing	12 (6%)	7 (7%)
Neonatal ultrasound results—Number, percent		
Normal	106 (51%)	n/a
Uncomplicated PVH	67 (32%)	n/a
PVH and ventricular dilatation	34 (17%)	n/a
Neurodevelomental outcome[b]		
Language		
Reading Age**	13.70 ± 2.5 (6–18)	14.7 ± 2.3 (5–17)
Spelling Age*	12.11 ± 1.9 (6–15)	12.8 ± 1.9 (5–15)
Global Language score**[c]	−0.79 ± 2.0 (−7.84–2.14)	
Executive function		
Phonological Fluency**	29.1 ± 8.6 (8–57)	32.7 ± 8.5 (12–53)
Semantic Fluency*	38.7 ± 11.2 (18–73)	42.2 ± 11.6 (21–77)
Trails B (time, s)*[d]	83.9 ± 29.1 (35–213)	73.2 ± 23.0 (32–136)
Global executive function score***[c]	−1.1 ± 2.4 (−8.0–6.7)	
Verbal memory		
Logical memory immediate recall	8.9 ± 4.0 (1–22)	8.9 ± 3.4 (1–18)
Logical memory delayed recall	7.6 ± 3.8 (0–19)	7.8 ± 3.2 (0–17)
Non-verbal memory		
Rey–Osterrieth Recall	18.00 ± 6.7 (2–31)	19.9 ± 6.0 (2–31)
Visual-motor integration		
Rey–Osterrieth copy	29.5 ± 4.5 (18–36)	30.3 ± 3.7 (19–36)
Beery total	20.3 ± 4.0 (0–24)	21.5 ± 3.0 (11–24)
Neuromotor assessment	1.4 ± 0.6 (1–4)	1.1 ± 0.4 (1–2)

Mean, SD and range are given, unless otherwise specified.
[a]For controls: birth weight ($n = 67$) and gestation ($n = 72$). [b]Adjusted for participant's chronological age at assessment and gender. [c]Global scores are calculated as the sum of domain-specific Z scores: for the VPT group these were calculated using means and SDs from the control group, which are omitted from the table as by default they are set at 0 and 1. [d]Longer response time refers to poorer performance. After Bonferroni's correction, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Before Bonferroni's correction: spelling age ($F = 9.6$, $P = 0.002$), reading age ($F = 11.8$, $P = 0.001$), phonological fluency ($F = 12.2$, $P = 0.001$), semantic fluency ($F = 9.8$, $P = 0.002$), Trails B ($F = 10.0$, $P = 0.002$).

Results

Thirty-five scans could not be analysed due to movement (3 VPT, 14 controls), signal artefact (6 VPT, 10 controls) or ventricular enlargement (2 VPT). Thus, a total of 207 VPT individuals and 104 controls were studied.

Table 1 displays their socio-demographic, perinatal, anthropometric and neurodevelopmental characteristics. VPT individuals and controls did not differ in gender distribution ($\chi^2 = 2.1$, $P = 0.45$), SES as measured by Her Majesty's Stationary Office Standard Occupational Classification criteria [Her Majesty's Stationary Office (HMSO) 1991] ($\chi^2 = 3.1$, $P = 0.38$), height ($F = 2.1$, $P = 0.15$), or body mass index (BMI) calculated as (weight/height^2) ($F = 1.2$, $P = 0.28$). However, the two groups differed in head circumference ($F = 17.1$, $P < 0.0001$), and chronological age at time of assessment ($F = 16.2$ $P < 0.0001$).

The VPT group showed worse performance than controls on global scores of language and executive function ($F = 12.4$, $P = 0.001$; $F = 21.49$, $P < 0.0001$, respectively). Global language and executive scores were positively associated with length of gestation in the VPT group ($r = 0.14$, $P = 0.04$; $r = 0.21$, $P = 0.002$, respectively).

Table 2 Mean differences in GM volume between VPT individuals and controls

GM—VPT < Controls					GM—VPT > Controls				
Cerebral region	Talairach coordinates			SPM[Z]	Cerebral region	Talairach coordinates			SPM[Z]
	x	*y*	*z*			*x*	*y*	*z*	
Middle temporal gyrus (BA 21)	48	2	−18	Inf.	Cingulate gyrus (BA 31)	8	−35	35	Inf.
Ext. to putamen	32	−8	−2	Inf.		−6	−30	35	Inf.
Ext. to precentral gyrus (BA 43) and insula (BA 13)	51	−16	11	7.22	Ext. to posterior cingulate gyrus (BA 24)	8	−11	38	7.34
Middle temporal gyrus (BA 21) Ext. to putamen	−47	−3	−17	Inf.	Middle temporal gyrus (BA 37)	57	−47	−8	Inf.
Ext. to precentral gyrus (BA 44) and insula (BA 13)	−45	2	6	Inf.	Middle temporal gyrus (BA 20)	−57	−44	−12	5.65
Ext. to precentral gyrus (BA 43)	−50	−8	12	Inf.	Medial frontal gyrus (BA 11)	6	62	−17	7.76
Inferior temporal gyrus (BA 20)	50	−11	−36	7.50	Ext. to anterior cingulate gyrus (BA 24)	6	38	5	7.47
Ext. to middle temporal gyrus (BA 38)	39	8	−39	5.00	Ext. to orbitofrontal gyrus (BA 11)	8	50	−17	6.69
Inferior temporal gyrus (BA 20)	−45	−8	−39	6.01	Middle frontal gyrus (BA 10)	38	59	−11	7.58
Superior occipital gyrus (BA 19)	32	−84	24	6.05	Ext. to middle frontal gyrus (BA 11)	38	38	−17	6.87
	−30	−83	23	5.87	and superior frontal gyrus (BA 10)	32	62	−3	6.67
Lingual gyrus (BA 18)	−18	−84	−12	6.05	Anterior cerebellum, culmen	−12	−44	−3	7.57
Fusiform gyrus (BA 20)	33	−38	−17	6.05		12	−45	−2	6.43
Fusiform gyrus (BA 36)	−47	−39	−23	5.22	Posterior cerebellum, semi-lunar lobule	14	−69	−38	5.84
Precuneus (BA 7)	15	−75	35	5.48		−30	−63	−38	5.31
Ext. to cuneus (BA 19)	5	−86	32	4.39	Posterior cerebellum, uvula	−9	−66	−30	5.17
Precuneus (BA 19)	−30	−78	35	5.32	Superior frontal gyrus (BA 10)	−21	63	2	7.37
Ext. to superior parietal lobule (BA 7)	−27	−72	48	4.94	Ext. to middle frontal gyrus (BA 10)	−36	59	2	7.28
Inferior frontal gyrus (BA 9)	47	8	26	5.15	Superior frontal gyrus (BA 10)	14	56	−8	4.36
Inferior frontal gyrus (BA 47)	−29	23	−23	4.76	Medial frontal gyrus (BA 11)	−8	53	−12	7.18
Inferior occipital gyrus (BA 18)	−38	−89	−12	4.78	Ext. to anterior cingulate gyrus (BA 32)	−9	42	3	6.91
Inferior parietal lobule (BA 40)	39	−53	5	4.68	and medial frontal gyrus (BA 11)	−8	63	−15	6.69
Precentral gyrus (BA 4)	65	−3	15	4.66	Lingual gyrus (BA 18)	−18	−84	−12	6.05
Posterior cerebellum, semi-lunar lobule	−27	−87	−38	4.58	Fusiform gyrus (BA 20)	33	−38	−17	6.05
Anterior cerebellum, culmen	15	−38	−20	4.43	Fusiform gyrus (BA 37)	−38	−47	−18	5.13
Superior temporal gyrus (BA 21)	−66	−20	−2	4.39	Precuneus (BA 19)	32	−75	36	5.75
Caudate nucleus	14	8	17	5.00	Superior occipital gyrus (BA 19)	−30	−83	23	5.97
Thalamus, medial dorsal nucleus	3	−17	3	5.57	Frontal subcallosal gyrus (BA 34)	8	0	−17	5.48
	−3	−20	8	5.21	Inferior parietal lobule (BA 40)	57	−29	32	5.43
Ext. to pulvinar	8	−24	5	5.02	Precentral gyrus (BA 4)	−38	−18	42	5.42
Cuneus (BA 19)	−12	−77	33	6.39		60	−6	21	5.01
					Parahippocampal gyrus (BA 27)	−21	−33	−3	5.34
						23	−32	−2	4.80
					Superior temporal gyrus (BA 13)	−45	−42	18	5.11
					Ext. to insula (BA 13)	−38	−35	21	5.03
					Thalamus, ventral posterior nucleus	15	−24	2	4.81
					Postcentral gyrus (BA 43)	65	−21	14	4.53
					Uncus (BA 28)	18	5	−30	4.45

x = left(−) vs. right(+); y = anterior(+) vs. posterior(−) and z = ventral(+) vs. dorsal(−). 0 is taken as being at the level of the anterior commissure.

Grey and white matter differences

VPT adolescents compared to controls showed extensive areas of decreased GM volume (e.g. the absolute amount of GM in different regions), bilaterally distributed, predominantly in the temporal lobe, extending medially to the basal ganglia (putamen), superiorly to inferior frontal gyrus and inferiorly to cuneus and precuneus. Subcortical GM nuclei such as the thalamus and the caudate also showed decreased volume. Larger GM volume was found bilaterally in frontal cortices, cerebellum, middle temporal, parahippocampal and fusiform gyri (Table 2, Fig. 1). When the PVH + DIL group was excluded, VPT individuals

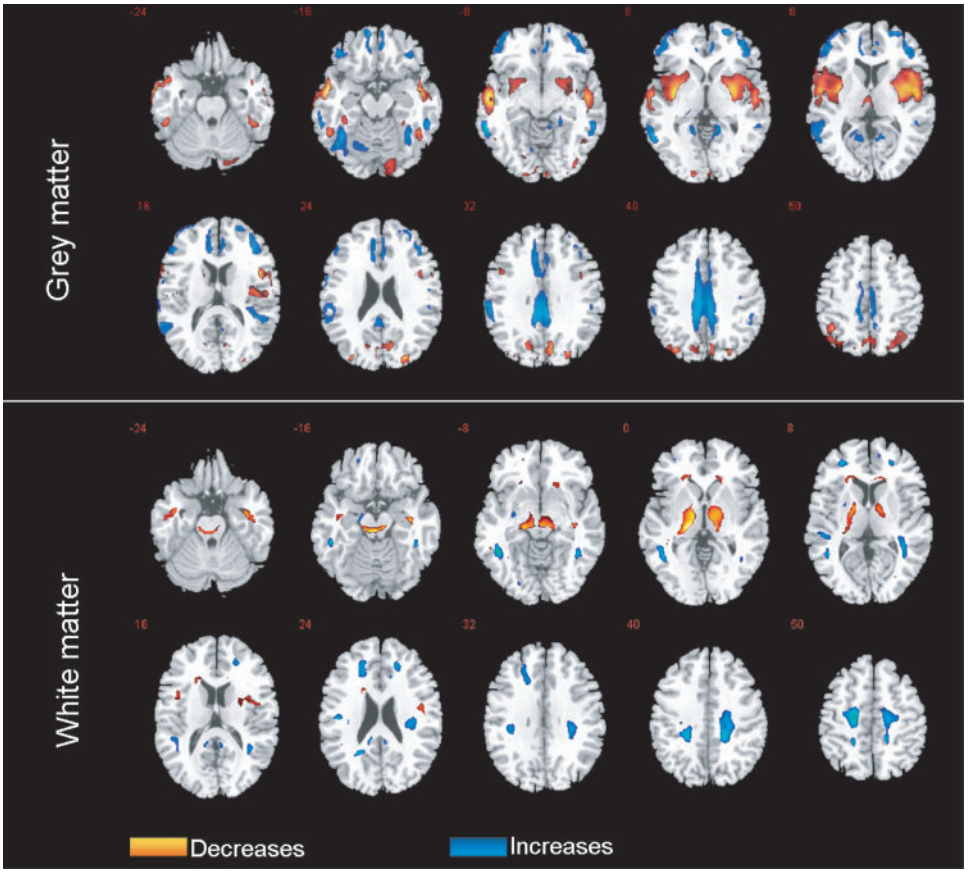

Fig. 1 Three-dimensional representation of regions of lower (orange) and higher (blue) probability in VPT individuals compared to controls (left = right).

showed smaller GM volume in brain regions almost identical in number and location to those observed in the analysis comparing all VPT individuals to controls (see supplementary appendix, Table 1A). However, when the PVH+DIL group was excluded, the only larger GM volumes observed in VPT individuals were in the right cingulate gyrus, right middle temporal gyrus and left parahippocampal gyrus.

Smaller WM volume in the VPT group was diffused, with peak in brainstem extending to internal capsule, and in temporal and frontal regions, including the anterior cingulate gyrus, insula, CC and occipito-temporal fasciculus. Larger WM volume was observed predominantly in fusiform gyrus, parietal, temporal and frontal regions (Table 3, Fig. 1). When the PVH + DIL group was excluded, VPT individuals showed a very similar number and location of clusters of smaller WM volume to those obtained in the analysis comparing all VPT individuals to controls (see supplementary appendix, Table 1A). When investigating larger WM volume excluding the PVH + DIL group, only the following regions remained statistically significant: fusiform gyri bilaterally, right parietal and frontal areas and posterior cingulate gyri bilaterally.

Figure 2 shows the distribution of WM values in the largest cluster of WM where VPT individuals displayed decreased volume compared to controls (e.g. brainstem), and of GM values in the largest cluster of GM where VPT individuals showed decrease volume compared to controls (e.g. middle temporal gyrus).

Structural associations for a sample of the four most significant clusters for each contrast (e.g. WM decreases, WM increases, GM decreases and GM increases) were explored with correlation analyses; when more than one cluster was centered in the same anatomical location, the adjacent most significant cluster was modelled. All selected regions of interest (same as those displayed in Table 6) were structurally positively associated and all associations had $P < 0.01$, after Bonferroni's correction. However, as both areas of increased and decreased WM and GM volume were entered in the analyses our results revealed both positive and negative associations. Regions were defined as been positively associated when increased/decreased values in one area were associated with increased/decreased values in another (e.g. GM decreases in middle temporal gyrus positively correlated with WM decreases in the brainstem), and negatively associated when increased values in one area were associated with decreased values in another (e.g. WM decreases in inferior temporal gyrus positively correlated with GM increases in cingulate gyrus).

Table 3 Mean differences in WM volume between VPT individuals and controls

WM—VPT < Controls					WM—VPT > Controls				
Cerebral region	Talairach coordinates			SPM[Z]	Cerebral region	Talairach coordinates			SPM[Z]
	x	*y*	*z*			*x*	*y*	*z*	
Brainstem/internal capsule	15	−24	−2	Inf.	Fusiform gyrus	48	−45	−14	Inf.
	0	−27	−15	7.31	Ext. to middle temporal gyrus	44	−50	5	5.64
	−14	−23	−5	6.36	Fusiform gyrus	36	−45	−11	4.63
Middle temporal gyrus	−41	−14	−15	6.46	Parietal lobe	18	−41	47	7.61
Ext. to fusiform gyrus	−48	−12	−26	5.96		48	−15	21	6.47
Inferior temporal gyrus	50	−11	−26	5.96	Posterior cingulate gyrus	8	−46	20	6.74
Ext. to middle temporal gyrus	38	−35	−3	5.01	Precentral gyrus	−18	−36	41	6.38
Occipito-frontal fasciculus	20	24	15	5.35	Middle frontal gyrus	29	48	11	6.28
Ext. to corpus callosum	15	30	8	5.14	Middle temporal gyrus	−45	−51	9	6.12
and anterior cingulate gyrus	18	29	−3	4.76	Parahippocampal gyrus	20	−12	−14	5.78
Insula	41	6	15	5.21	Superior temporal gyrus	−41	−51	12	5.74
Inferior frontal gyrus	−21	20	−11	4.71	Middle frontal gyrus	−29	47	9	5.65
Ext. to medial frontal gyrus	−18	27	−3	4.67	Ext. to superior frontal gyrus	−23	41	21	5.14
and corpus callosum	−9	29	6	4.59	Superior frontal gyrus	17	51	−14	5.49
					Medial frontal gyrus	18	38	26	5.27
					Lingual gyrus	21	−81	−8	4.79
					Lentiform nucleus	26	2	9	4.62
					Cingulate gyrus	−14	26	26	4.44

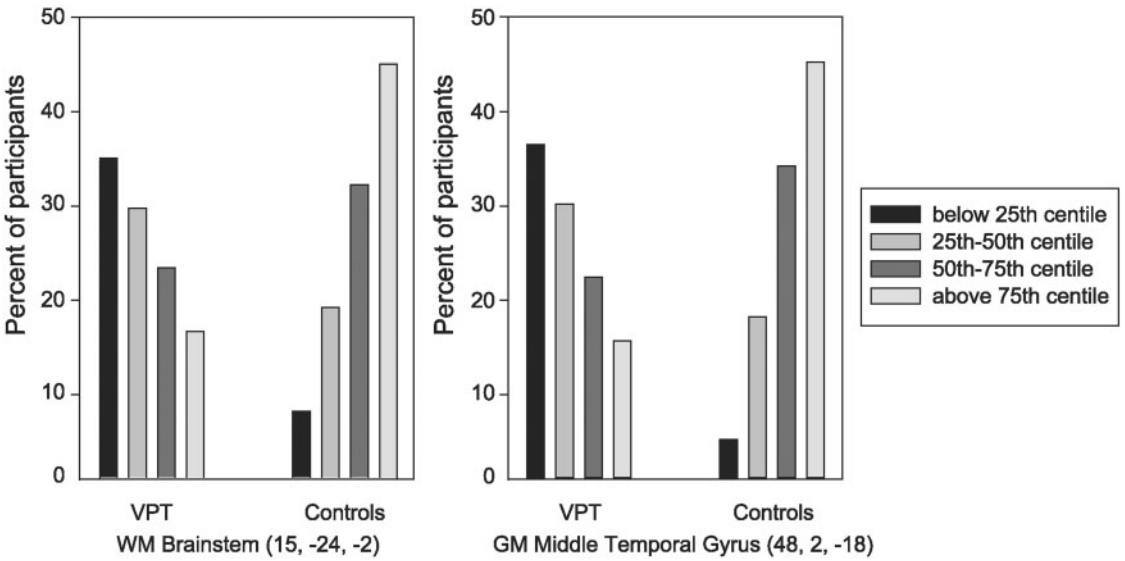

Fig. 2 Distribution of WM and GM values into quartiles in brain areas where VPT individuals showed decreased volume compared to controls.

Correlation with gestational age

Gestational age was positively correlated with GM volume bilaterally in a large area with peak in the sensorimotor cortex (BA 6), including portions of the inferior frontal and superior temporal gyri and insula; in the cerebellum, middle temporal and fusiform gyri and thalamus. WM volume proportionally increased with gestational age especially in the precentral and postcentral gyri bilaterally, and in the brain stem and major white matter tracts, such as the CC and the longitudinal fasciculus (Table 4).

Neonatal ultrasound and grey and white matter distribution in the adolescent brain

In VPT individuals, GM and WM distribution was compared according to neonatal ultrasound classification, i.e. NM versus PVH; NM versus PVH + DIL and PVH versus PVH + DIL (Table 5). No differences in GM and WM volume were observed between the NM and PVH groups. The PVH + DIL compared to the NM group showed smaller GM volume in thalamus and cerebellum bilaterally and larger volume in precuneus and medial

Table 4 Correlation between GM, WM and gestational age in VPT individuals

Gestational age and grey matter					Gestational age and white matter				
Cerebral region	Talairach coordinates			SPM(Z)	Cerebral region	Talairach coordinates			SPM(Z)
	x	*y*	*z*			*x*	*y*	*z*	
Sensorimotor cortex (BA 6)	56	−6	11	5.67	Postcentral gyrus	−53	−6	20	6.32
Ext. to superior temporal gyrus	56	−21	8	5.56	Postcentral gyrus	53	−6	23	6.04
Post-central gyrus (BA 43)	−63	−11	18	5.57	Ext. to longitudinal fasciculus	36	6	15	4.10
Ext. to pre-central gyrus (BA 6)	−50	−8	11	5.35	Ext. to precentral gyrus (BA 6)	45	−3	39	3.97
Cerebellum crus II Ext. to Cr I	−15	−90	−33	5.57	Brain stem, pons	5	−29	−23	5.29
Crus II ext. to VI	15	−89	−36	5.35	Ext. left brain stem, pons	−6	−27	−21	5.08
Crus I	−45	−54	−41	4.18	Anterior corpus callosum	−3	23	−2	5.08
Middle temporal gyrus (BA 21)	51	−6	−15	5.31	Ext. to anterior cingulate	−12	27	15	4.33
Superior temporal gyrus (BA 22)	69	−26	5	5.29	Middle temporal gyrus	53	−45	−8	4.94
Superior temporal gyrus (BA 38)	−26	21	−23	4.53	Fusiform gyrus	51	−15	−24	4.92
Medial frontal gyrus (BA 9)	44	12	36	4.47	Sub-callosal gyrus	−9	21	−11	4.80
	−44	11	29	4.47	Corpus callosum	11	30	8	4.64
Inferior frontal gyrus (BA 45)	62	11	20	5.28	Fusiform gyrus	53	−21	−24	4.58
Ext. to pre-central gyrus (BA 6)	63	5	12	5.16	Parahippocampal gyrus	35	−9	−15	4.50
Fusiform gyrus (BA 37)	47	−47	−17	5.02	Ext. to fusiform gyrus	42	−27	−17	4.00
	−47	−48	−17	4.37	Cerebellum, inf. semi-lunar lobule	17	−71	−38	4.44
Thalamus (pulvinar)	−8	−27	8	4.43	Middle frontal gyrus	−33	24	29	4.39
Thalamus (dorsomedial nucleus)	3	−17	8	4.43	Supramarginal gyrus	−50	−44	35	4.34
						50	−41	33	4.29
					Precuneus	−12	−57	44	4.23
					Fusiform gyrus	−42	−26	−18	4.20
					Ext. to parahippocampal gyrus	−36	−12	−17	4.17

Table 5 GM and WM differences according to neonatal ultrasound classification in VPT individuals

Grey matter						Ultrasound classification and white matter					
Ultrasound group	Cerebral region	Talairach coordinates			SPM(Z)	Ultrasound group	Cerebral region	Talairach coordinates			SPM(Z)
		x	*y*	*z*				*x*	*y*	*z*	
NM > PVH	Non-significant					NM > PVH	Non-significant				
NM < PVH	Non-significant					NM < PVH	Non-significant				
NM > PVH + DIL	Thalamus	8	−27	−3	5.48	NM > PVH + DIL	Middle temporal gyrus	39	−41	0	5.42
	Red nucleus	9	−26	−2	5.22		Ext. to inferior temporal	39	−50	−3	3.79
	Pulvinar, thalamus	−8	−27	8	4.47		Cerebellum crus I	17	−71	−38	5.17
	Cerebellum crus I	−42	−78	−29	4.41		Posterior cingulate gyrus	−15	−48	17	4.99
NM < PVH + DIL	Precuneus (BA 7)	−9	−59	36	5.01		Middle cingulate gyrus	−15	−2	32	4.97
	Medial frontal gyrus (BA 6)	11	5	50	4.20		Ext. to anterior CC	−12	6	29	4.71
PVH > PVH + DIL	Thalamus	−8	−27	−3	4.43		Posterior CC	15	−44	15	4.96
PVH < PVH + DIL	Non-significant						Cingulum	15	8	27	4.74
							Middle temporal gyrus	−35	−42	6	4.57
						NM < PVH + DIL	Middle occipital gyrus	−30	−80	−9	5.22
							Fusiform gyrus	42	−51	−12	4.51
							Ext. to occipital lobe	41	−63	−6	4.27
							Middle temporal gyrus	35	−72	24	4.45
							Cuneus	−8	−89	15	4.41
						PVH > PVH + DIL	Non-significant				
						PVH < PVH + DIL	Fusiform gyrus	41	−51	−12	4.39
							Parietal lobe	−29	−45	39	4.38

frontal gyrus. Smaller GM volume in thalamus was also observed in the PVH + DIL group compared to the PVH group. When investigating WM, the PVH + DIL compared to the NM group showed smaller volume in temporal gyri bilaterally, and in the left limbic lobe, the cerebellum and CC; additionally, it showed larger volume in the middle temporal and fusiform gyri of the right temporal lobe and in the occipital lobe bilaterally. Larger WM volume in the left parietal cortex and in the right fusiform gyrus was observed in the PVH + DIL compared to the PVH group.

Neurodevelopmental outcome and grey and white matter distribution in the adolescent brain

Linear regression demonstrated a strong relationship between group membership (VPT or control) and global language and executive (global language, $F = 18.9$; $P < 0.0001$; executive scores, $F = 11.8$; $P = 0.001$). To examine if GM and WM alterations laid on a causal pathway between gestation and neurodevelopmental outcome we performed linear regression analyses using global executive function and language scores as dependent variables and all regions of between group GM and WM differences (volume decreases and increases) and group (VPT or control) as predictors. Results revealed that structural alterations accounted for 29% of the variance of executive function ($F = 2.3$, $P < 0.0001$) and 28% of language scores ($F = 2.3$, $P < 0.0001$), while group membership was no longer statistically significant ($F = 3.21$, $P = 0.07$ and $F = 1.98$, $P = 0.16$, respectively).

Participants were further classified as 'cognitively impaired' on the basis of their average performance on both global executive function and language measures. 14% of the controls and 27% of VPT adolescents were classified as impaired ($\chi^2 = 6.11$, $P = 0.013$). Results of binary logistic regression models, using quartiles of extracted values for selected regions of GM and WM as predictors (i.e. the same areas used for exploration of inter-regional associations), revealed that all selected areas of GM and WM decreases in VPT participants compared to controls were predictive of cognitive outcome (Table 6). For example, every 25% decrease in quartiles of WM values in middle temporal gyrus was associated with a 60% increase in the risk of cognitive impairment. Only two brain areas where VPT participants were found to have increased volume compared to controls, WM in cingulate gyrus and GM in middle temporal gyrus, were predictive of cognitive outcome.

Table 6 Regional WM and GM volumes and cognitive impairment in all participants

Brain volume differences[a]	Cognitive impairment[b]		
Cerebral region, Talairach (x, y, z)	Odds-ratio	P	95% CI
WM, VPT < Controls			
Brainstem, (15, −24, −2)	1.47	0.002	1.15–1.89
Middle temporal gyrus (−41, −14, −15)	1.59	<0.0001	1.23–2.04
Inferior temporal gyrus (50, −11, −26)	1.59	<0.0001	1.22–2.04
Occipito-frontal fasciculus (15, 30, 8)	1.33	0.020	1.04–1.72
WM, VPT > Controls			
Fusiform gyrus (48, −45, −14)	1.06	0.61	0.83–1.35
Parietal lobe (18, −41, 47)	0.99	0.92	0.78–1.25
Posterior cingulate gyrus (8, −46, 20)	1.28	0.049	1.00–1.64
Precentral gyrus (−18, −36, 41)	1.05	0.70	0.83–1.33
GM, VPT < Controls			
Middle temporal gyrus (48, 2, −18)	1.52	0.001	1.18–1.96
Middle temporal gyrus (−47, −3, −17)	1.49	0.002	1.16–1.92
Inferior temporal gyrus (50, −11, −36)	1.41	0.007	1.10–1.82
Fusiform gyrus (33, −38, −17)	1.30	0.014	1.52–1.59
GM, VPT > Controls			
Cingulate gyrus (8, −35, 35)	1.01	0.98	0.76–1.32
Middle temporal gyrus (57, −47, −8)	1.59	0.004	1.16–2.17
Medial frontal gyrus (6, 62, −17)	1.10	0.45	0.86–1.39
Anterior cerebellum (−12, −44, −3)	1.20	0.14	0.94–1.54

[a]WM and GM values for a sample of the four most significant clusters for each contrast were used, recoded into quartiles; when more than one cluster was centred in the same anatomical location, the adjacent most significant cluster was modeled.
[b]Defined as SDs ≤ −1.0 below the control group mean, for both executive function and language measures.

Discussion

This study demonstrated that VPT birth is associated with widespread alterations in brain structure in adolescence. Not only were conspicuous localized patterns of lower GM and WM matter probability observed in VPT adolescents compared to controls, but higher probability was noted in regions adjacent to, and distant from, the areas with decreased probability. This pattern of GM and WM distribution is in line with pathological (Hargitai *et al.*, 2004) and neuroimaging data (Allin *et al.*, 2004) and is best interpreted within a 'neuroplastic' framework, which posits that developmental changes in any brain region may result in a cascade of alterations in many other regions (Hack and Taylor, 2000).

Concerning GM, VPT adolescents showed decreased volume in regions where volume reductions have been previously reported in VPT and LBW populations. These comprised the temporal lobe bilaterally (Peterson *et al.*, 2000; Reiss *et al.*, 2004) including putamen, insula, and precentral gyrus (Allin *et al.*, 2004), extending superiorly to inferior frontal gyrus and inferiorly to cuneus and precuneus; in the fusiform gyrus bilaterally, cerebellum (Peterson *et al.*, 2000; Allin *et al.*, 2001), thalamus

(Gimenez *et al.*, 2006*b*) and right caudate nucleus (Abernethy *et al.*, 2002). Some of these areas may be particularly susceptible to cerebral injury during the third trimester of gestation, and following hypoxic-ischaemic episodes associated with VPT birth. The nature of the GM and WM changes is difficult to interpret as the quantitative MRI provides a measure of *concentration* or *density* of a region of tissue (Good *et al.*, 2001), but gives no information about cell cytoarchitectural structure such as neuronal packing or cell morphometry. Thus, from these results, we can only speculate that GM loss may reflect compromised synaptogenesis, which in turn could result in increased tissue atrophy (Huttenlocher and Dabholkar, 1997), or that reductions in synaptic density may be accompanied by increased myelination, which could result in some brain regions changing from grey to white matter signal on MRI (Sowell *et al.*, 1999). If this hypothesis is true, decreased GM volume in VPT individuals may underlie disrupted myelination processes, consistent with studies reporting associations between WM injury and impaired GM development (Inder *et al.*, 2003, 2005).

Lower WM probability in VPT adolescents was diffused (Allin *et al.* 2004; Reiss *et al.*, 2004), and was observed in some brain regions which have previously been reported as altered in VPT and LBW samples. These included, mostly bilaterally, the brainstem (Hargitai *et al.*, 2004), internal capsule (Partridge *et al.*, 2004), subthalamic nuclei, the pons, temporal and frontal regions, including the anterior cingulate gyrus, insula, occipito-frontal fasciculus (Gimenez *et al.*, 2006*a*) and CC (Cooke and Abernethy, 1999; Peterson *et al.*, 2000; Nagy *et al.*, 2003; Nosarti *et al.*, 2004). Perinatal WM injury may be partly explained by the vulnerability of the developing structures to hypoxic-ischaemic damage and haemorrhage, possibly due to the intrinsic vulnerability of immature oligodendrocytes (Back *et al.*, 2001).

The current study suggests that developmental changes following VPT birth and early brain insult do not simply result in GM and WM tissue loss, but in complicated patterns of cortical and subcortical alterations (Allin *et al.*, 2004). Increased GM probability was observed bilaterally in the cingulate gyrus, temporal and frontal lobes, left cerebellum and right precuneus and fusiform gyrus. WM excesses were observed in fusiform gyrus, temporal, parietal, and frontal regions. In some instances, GM increases were observed adjacently to WM decreases (e.g. cingulate gyrus); and WM increases were observed adjacently to GM decreases (e.g. frontal lobe). Increased tissue probabilities in VPT adolescents compared to controls could be secondary to less efficient or delayed programmed cell death in selective developing cortices, or may reflect delayed processes of synaptic pruning. Although other groups have reported larger selective brain areas in VPT individuals compared to controls (Peterson *et al.*, 2000; Allin *et al.*, 2004), there is a marked paucity of previous reports of increased GM and WM matter volumes in VPT populations, due to the fact that the majority of studies so far have adopted a region of interest approach rather than computational morphometry, which identifies local changes in WM and GM concentration throughout the brain.

Investigation of the inter-relationships between brain regions and volumetric changes revealed that all selected areas where between-group increased and decreased WM and GM differences were observed, were structurally associated, highlighting the influence that abnormalities in one brain area may exert over others. These findings are in line with the results of other recent investigations with very preterm infants, which reported significant associations between WM injury and abnormalities in deep GM structure (Boardman *et al.*, 2006).

Comparison of WM and GM distribution within VPT adolescents according to neonatal ultrasound classification suggested that those individuals who experienced the greatest degree of perinatal insult, i.e. PVH + DIL, other then being vulnerable to developmental compromise (Vollmer *et al.*, 2006), exhibit the greatest extent of cortical and subcortical alteration. This is reflected by both WM and GM volume increases *and* decreases compared to VPT individuals with normal ultrasound results. Furthermore, when the PVH + DIL group was excluded from the VPT versus controls analyses, areas of increased tissue probability in VPT individuals dramatically decreased, whereas areas of decreased probability remained almost unaltered. This suggests that when VPT birth is accompanied by severe brain injury, extensive plastic processes occur in order to compensate for the effects of cell loss caused by the injury, demonstrating both specific deficits and adaptive developmental changes. It could be speculated that the extra cells and synapses produced by the developing brain, which are normally later 'pruned', may provide the mechanism underlying enhanced early plasticity, and maintain existing projections that would otherwise have been 'pruned', as has been demonstrated in animal models (Lindholm, 1994). Other explanations could include increased synaptic sprouting (Noppeney *et al.*, 2005), and precocious prefrontal maturation associated with stunted final capacity (Teicher and Ito, 1996). However, selective regions of WM in frontal, parietal and occipital cortices and GM in cingulate, temporal and parahippocampal gyri were also increased in VPT with normal neonatal ultrasound classifications. These results suggest the existence of widespread compensatory processes following 'uncomplicated' VPT birth, although these are not as extensive as those observed in preterm individuals with the most severe neonatal ultrasound ratings.

The current results suggest that there may be selective vulnerability associated with the stage of development of different brain regions. Non-linear dynamic changes are observed in normative samples between childhood and adolescence in both GM and WM. GM volume in the frontal lobes increases during preadolescence, followed by a

decline in teen age years with the prefrontal cortex not being fully mature until late adolescence. In temporal lobes, GM development is also non-linear; the peak being reached at about 16–17 years (Sowell *et al*., 2002; Barnea-Goraly *et al*., 2005). We report foci of GM deficit and GM increase in bilateral temporal and frontal lobes in the brains of VPT adolescents. Most of the temporal foci suggested decreased GM, whereas the predominant difference in frontal lobes was of GM excess. These findings are consistent with global maturation delay in the brain development of VPT adolescents. VPT individuals may follow an essentially normal trajectory of cortical development but in mid-adolescence, may not yet have 'caught up' with controls and show regional GM densities consistent with those of a younger age. However, the extensive brain anatomical differences observed in the current study suggest that brain development following VPT birth appears to be both different and delayed. It remains yet to be established whether the observed differences in the VPT sample will persist in adult life. The identification of GM and WM differences in 'late developing' cortices could potentially allow for interventions aimed at minimizing the impact of anatomical alterations to be devised, so as to preserve the functional attributes of these brain regions.

Several of the areas where VPT individuals demonstrated altered GM and WM concentration were linearly associated with gestational age. The most immature individuals had decreased GM bilaterally in the sensorimotor cortex, including portions of the inferior frontal and superior temporal gyri and insula; and decreased WM probability especially in pre- and post-central gyri bilaterally, the brainstem and major WM fasciculi (Partridge *et al*., 2004; Gimenez *et al*. 2006*a*). A direct association between immaturity and altered GM and WM probability could be understood in relation to the timing of formation of axonal projections and primary connections between neurons, i.e. the second half of gestation. Abnormalities in neuronal migration may result in cytoarchitectonic changes and subsequent abnormalities in axonal projections and WM tracts (Nagy *et al*., 2003; Barnea-Goraly *et al*., 2005), as well as in deep nuclear GM in VPT cohorts (Inder *et al*., 2005). Furthermore, during the period between premature birth and term, fibre organization and myelination of VPT infants may not 'keep up' with that taking place in the brains of term-born children who are still in the intrauterine environment (Counsell and Boardman, 2005).

VPT individuals obtained lower scores than controls on selective standard assessments tapping language and high-order cognitive functions. The identification of selective cognitive weaknesses associated with VPT birth that persist into adolescence may have important implications for academic as well as vocational training, by highlighting areas whose function could possibly be improved by means of explicit teaching of organizational strategies and other methods to enhance learning (Taylor *et al*., 2004*a*). Lower neurodevelopmental scores were associated with lower gestational age, replicating previous findings (Hack and Taylor, 2000). However, our results suggested that GM and WM concentration where between-group anatomical differences were observed, rather than group membership (e.g. VPT or control), were predictive of language and executive function scores. In other words, our results suggest that GM and WM values in brainstem, frontal, temporal and limbic regions mediate the relationship between VPT birth and adolescent 'cognitive impairment', and could be used as a clinical marker for the identification of those individuals at increased risk for cognitive impairment, at whom targeted interventions could be directed.

Strengths of our study include the fact that it is the largest published consecutive sample to date of VPT adolescents who have been extensively studied over time, and the analysis of *in vivo* MRI data with VBM, which is an unbiased automated quantification method. Methodological limitations of VBM include the difficulty in normalizing images with substantial distortion in their anatomy, which we attempted to address by using a customized template (Good *et al*., 2001); the heterogeneity of the population used to generate the *a priori* customized brain templates, and the nature of the statistical inferences used in SPM, which assume normally distributed data. There is evidence however that this latter limitation is confined to non-balanced study designs (Salmond *et al*., 2002). Additional limitations of the current study include the reliance on neonatal cranial ultrasound to assess earlier cerebral abnormalities, given clear evidence demonstrating that ultrasound is much less sensitive to diffused WM abnormalities than MRI (Volpe, 2003) and is therefore likely to under-represent children with earlier cerebral abnormalities. Other limitations comprise the age difference between the studied groups, although age was used as a confounder in the analyses: controls were recruited by year of birth (1979–84); therefore the age difference between the groups was explained by the fact that controls were tested a few months before the VPT participants. A further issue on the use of a full-term birth volunteers, although matched by year of birth and SES, relates to other potential differences that are either unknown or difficult to take into account.

To summarize, VPT birth is associated with alterations of GM and WM volume. In several brain areas (e.g. frontal and temporal cortices) these alterations are linearly associated with length of gestation and mediate adolescent neurodevelopmental outcome. This suggests that alternative or delayed patterns of brain development following VPT birth may be at least partly responsible for subsequent cognitive impairment.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgements

We are grateful to Dr M.P. Allin, Dr T. Rushe and Dr S.J. Frearson for providing neurodevelopmental outcome data and to Dr P. Dazzan for scientific advice. Finally we thank all participants and their parents for their loyalty and cooperation. The Sir Jules Thorne Foundation (UK) and the Stanley Medical Research Institute (US) funded the study.

References

Abernethy LJ, Palaniappan M, Cooke RW. Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight. Arch Dis Child 2002; 87: 279–83.

Allin M, Henderson M, Suckling J, et al. Effects of very low birthweight on brain structure in adulthood. Dev Med Child Neurol 2004; 46: 46–53.

Allin M, Matsumoto H, Santhouse AM, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very preterm. Brain 2001; 124: 60–6.

Ashburner J, Friston KJ. Voxel-based morphometry – the methods. NeuroImage 2000; 11: 805–21.

Ashburner J, Neelin P, Collins DL, Evans A, Friston K. Incorporating prior knowledge into image registration. NeuroImage 1997; 6: 344–52.

Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci 2001; 21: 1302–12.

Barnea-Goraly N, Menon V, Eckert M, et al. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cereb Cortex 2005; 15: 1848–54.

Beery KE. Developmental test of visual-motor integration. Cleveland: Modern Curriculum Press; 2007.

Benton AL, Hamsher Kd. Multilingual Aphasia Examination. Iowa City: University of Iowa; 1976.

Boardman JP, Counsell SJ, Rueckert D, et al. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. NeuroImage 2006; 32: 70–8.

Cooke RW, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. Arch Dis Child Fetal Neonatal Ed 1999; 81 (F): 116–21.

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: 403–10.

Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ. Spatial registration and normalisation of images. Hum. Brain Mapp. 1995; 2: 165–89.

Gimenez 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 2006a; 32: 1485–98.

Gimenez M, Junque C, Narberhaus A, Botet F, Bargallo N, Mercader JM. Correlations of thalamic reductions with verbal fluency impairment in those born prematurely. Neuroreport 2006b; 17: 463–6.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 2001; 14: 21–36.

Hack M, Taylor HG. Perinatal brain injury in preterm infants and later neurobehavioral function. JAMA 2000; 284: 1973–4.

Hargitai B, Szabo V, Cziniel M, et al. Human brain of preterm infants after hypoxic-ischaemic injuries: no evidence of a substantial role for apoptosis by using a fine-tuned ultrasound-guided neuropathological analysis. Brain Dev 2004; 26: 30–6.

Her Majesty's Stationary Office (HMSO). Office of Population Censuses and Surveys, Standard Occupational Classification. London: HMSO; 1991.

Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997; 387: 167–78.

Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005; 115: 286–94.

Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. J Pediatr 2003; 143: 171–9.

Isaacs EB, Lucas A, Chong WK, et al. Hippocampal volume and everyday memory in children of very low birth weight. Pediatr Res 2000; 47: 713–20.

Lezak M. Neuropsychological Assessment. 3rd edn., New York, NY: Oxford University Press; 1995.

Lindholm D. Role of neurotrophins in preventing glutamate induced neuronal cell death. J Neurol 1994; 242: S16–8.

Mechelli A, Friston KJ, Frackowiak RS, Price CJ. Structural covariance in the human cortex. J Neurosci 2005; 25: 8303–10.

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: 672–9.

Newcombe F. Missile Wounds of the Brain. London: Oxford University Press; 1969.

Noppeney U, Friston KJ, Ashburner J, Frackowiak R, Price CJ. Early visual deprivation induces structural plasticity in gray and white matter. Curr Biol 2005; 15: R488–90.

Nosarti C, Al Asady MH, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. Brain 2002; 125: 1616–23.

Nosarti C, Rushe TM, Woodruff PW, Stewart AL, Rifkin L, Murray RM. Corpus callosum size and very preterm birth: relationship to neuropsychological outcome. Brain 2004; 127: 2080–9.

Osterrith PA. Le test de copie d'une figure complexe. Archives de Psychologie 1944; 30: 206–356.

Partridge SC, Mukherjee P, Henry RG, et al. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. NeuroImage 2004; 22: 1302–14.

Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA 2000; 284: 1939–47.

Reiss AL, Kesler SR, Vohr B, et al. Sex differences in cerebral volumes of 8-year-olds born preterm. J Pediatr 2004; 145: 242–9.

Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery. Tucson, AZ: Neuropsychology Press; 1985.

Rushe TM, Rifkin L, Stewart AL, et al. Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. Dev Med Child Neurol 2001; 43: 226–33.

Salmond CH, Ashburner J, Vargha-Khadem F, Connelly A, Gadian DG, Friston KJ. Distributional assumptions in voxel-based morphometry. NeuroImage 2002; 17: 1027–30.

Schnack HG, van Haren NE, Hulshoff Pol HE, et al. Reliability of brain volumes from multicenter MRI acquisition: a calibration study. Hum Brain Mapp 2004; 22: 312–20.

Schonnel FJ, Schonnel FE. Diagnostic and attainment testing. London: Oliver and Boyd; 1960.

Sie LT, van der Knaap MS, van Wezel-Meijler G, Valk J. MRI assessment of myelination of motor and sensory pathways in the brain of preterm and term-born infants. Neuropediatrics 1997; 28: 97–105.

Sowell ER, Trauner DA, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev Med Child Neurol 2002; 44: 4–16.

Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW. Localizing age-related changes in brain structure between childhood and

adolescence using statistical parametric mapping. NeuroImage 1999; 9: 587–97.

Stewart AL, Rifkin L, Amess PN, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 1999; 353: 1653–7.

Taylor HG, Minich N, Bangert B, Filipek PA, Hack M. Long-term neuropsychological outcomes of very low birth weight: associations with early risks for periventricular brain insults. J Int Neuropsychol Soc 2004a; 10: 987–1004.

Taylor HG, Minich NM, Klein N, Hack M. Longitudinal outcomes of very low birth weight: Neuropsychological findings. J Int Neuropsychol Soc 2004b; 10: 149–63.

Teicher MH, Ito Y. Neurophysiological mechanisms of stress response in children. In: Pfefter CR, editor. Severe stress and mental disturbance in children. Washington DC: American Psychiatric Association Press; 1996. p. 59–84.

Vollmer B, Roth S, Riley K, et al. Neurodevelopmental outcome of preterm infants with ventricular dilatation with and without associated haemorrhage. Dev Med Child Neurol 2006; 48: 348–52.

Volpe JJ. Cerebral white matter injury of the premature infant - more common than you think. Pediatrics 2003; 112: 176–80.

Wilson BA, Cockburn JM, Baddeley AD. The rivermead behavioural memory test. Hampshire: Thames Valley Test Co.; 1985.