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Cerebellar growth and behavioural & neuropsychological outcome in preterm adolescents

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Adolescence is a time of social and cognitive development associated with changes in brain structure and function. These developmental changes may show an altered path in individuals born before 33 weeks' gestation (very preterm; VPT). The cerebellum is affected by VPT birth, but no studies have yet assessed the adolescent development of this structure, or whether developmental changes in cerebellar structure are associated with cognitive and behavioural outcome. We measured cerebellar volumes on structural magnetic resonance images in 65 adolescents who were born before 33 weeks' gestation (VPT) and 34 term-born adolescents (mean age VPT = 15.09, SD = 1.43/mean age term-born = 15.43, SD = 0.56) and again in adulthood (mean age VPT = 18.61, SD = 1.02/mean age term-born = 19.17, SD = 0.95). Participants also underwent neuropsychological tests; the Wechsler Abbreviated Scale of Intelligence and the Controlled Oral Word Association Test and completed the General Health Questionnaire-12. Repeated measures ANOVA showed a main effect of time-point ($F = 4.59$, df = 1, $P = 0.035$) and a time-point by group interaction ($F = 8.03$, df = 1, $P = 0.006$) on cerebellar growth. By adulthood, cerebellar volumes were 3.11% smaller in the preterm group than they had been in early adolescence ($P = 0.000$). Cerebellar volume did not change significantly in the control group ($P = 0.612$). There were significant negative correlations between change in cerebellar volume and GHQ-12 in the VPT group; total score ($r = -0.324$ $P = 0.028$) and several subscales; concentration ($r = -0.378$ $P = 0.010$), feeling useful ($r = -0.311$ $P = 0.035$), decision-making capability ($r = -0.348$ $P = 0.018$), overcoming difficulties ($r = -0.331$ $P = 0.025$), feeling confident ($r = -0.309$ $P = 0.037$) and feeling worthless ($r = -0.329$ $P = 0.026$). In the VPT group there were positive correlations between cerebellar volume and full-scale IQ (adolescence; $r = 0.471$, $P = 0.002$/adulthood; $r = 0.309$, $P = 0.047$), performance IQ (adolescence; $r = 0.434$, $P = 0.004$/adulthood; $r = 0.345$, $P = 0.025$) and verbal IQ (adolescence; $r = 0.401$, $P = 0.008$) which were not maintained after controlling for white matter volume. We have demonstrated a reduction in cerebellar volume between adolescence and young adulthood in VPT individuals, which is correlated with reduced self-reported wellbeing.

Keywords: neuroanatomy; brain development; psychiatry; MRI/fMRI; preterm birth

Abbreviations: GHQ-12 = 12-item General Health Questionnaire; VPT = very preterm

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Introduction

Premature birth predisposes an individual to brain injury during the prenatal, perinatal or neonatal periods. The cerebellum is one of the last brain structures to reach maturity with cellular development continuing for several months after birth. It is also susceptible to environmental insults such as birth anoxia and toxins such as lead (Wallace *et al.*, 2006). Individuals born preterm have been shown to have reduced cerebellar volume in adolescence (Allin *et al.*, 2001; Argyropoulou *et al.*, 2003; Messerschmidt *et al.*, 2005) and white and grey matter volume in selective cerebellar areas has been found to be positively associated with gestational age (Nosarti *et al.*, 2007). The cerebellum is a node in the distributed neural networks underlying

cognitive function (Diamond, 2000) and reduced cerebellar volume is associated with deficits in neuropsychological performance (Allin *et al.*, 2001).

Much converging evidence now supports the role of the cerebellum in non-motor functions. Functional connectivity studies using MRI show coherence of the thalamus, parietal and prefrontal cortices with the dentate nucleus (Allen *et al.*, 2005), indicating the presence of cerebellar-parietal and cerebellar-prefrontal functional connectivity. Animal studies of cerebellar anatomy reveal that multiple cerebral domains, with roles in cognition or affect, link to the lateral lobes of the cerebellum (Brodal, 1978; Glickstein *et al.*, 1985; Schmahmann and Pandya, 1991, 1993, 1995, 1997). Trans-synaptic tracers have successfully mapped connections to and from the cerebral and cerebellar cortex in non-human primates suggesting several closed feedback loops between the cerebrum and cerebellum (Kelly and Strick, 2003). In the human brain the major mossy fibre pathway connects the cerebral hemisphere with the contralateral cerebellum via the pons through which it is likely that the cerebellum receives an efferent copy of signals from the cortex (Voogd, 2003). Beck (1950) established that the human corticopontine system takes its origin from several areas, including parietal and prefrontal cortices in addition to sensorimotor cortex. Diffusion tensor-MRI of converging corticopontine fibres, have shown that the largest contribution comes from the prefrontal cortex (Ramnani *et al.*, 2006), which adds further weight to the hypothesis that the cerebellum is involved in processes other than motor co-ordination in humans.

Clinically significant neuropsychological and behavioural symptoms have been associated with cerebellar disorders; Schmahmann and Sherman's (1998) 'cerebellar cognitive affective syndrome' describes impaired executive functioning, spatial cognition and behavioural change resulting from acquired cerebellar lesions. Perceptual organization and working memory capacity has been related to cerebellar volume in healthy individuals (Posthuma *et al.*, 2003) and Ravizza *et al.* (2006) identified verbal working memory deficits in patients with cerebellar lesions. In very preterm adolescents, cognitive function is associated with total cerebellar volume (Allin *et al.*, 2001) and more specifically, with volume decrement of the lateral lobes (Allin *et al.*, 2005). Limperopoulos *et al.* (2007) found a greater risk of long-term pervasive neuro-developmental disabilities in preterm infants with isolated cerebellar haemorrhagic injury. Correlations between cerebellar volume and cognitive development were principally mediated by cerebral white matter injury in a preterm cohort described by Shah *et al.* (2006).

Like the prefrontal cortex the cerebellum reaches maturity late in human development (Diamond, 2000), but the trajectory of cerebellar development has been rather neglected in the literature in favour of studies of cerebral cortical development. Thus, normal cerebral cortical development is characterized by linear increases in white matter and non-linear changes in grey matter, with a pre-adolescent increase followed by a post-adolescent decrease (Giedd *et al.*, 1999; Gogtay *et al.*, 2004). However, relatively little is known about how the cerebellum develops over time and if this maturation differs in those born prematurely. One study of early cerebellar development found that smaller mean cerebellar volumes relating to preterm birth were associated with an increased rate of growth from 28 weeks post-conception to term compared to mean intracranial volumes suggesting rapid growth of the immature cerebellum during late gestation (Limperopoulos *et al.*, 2005*a*). However by term equivalent age the preterm born infants continued to have smaller mean cerebellar size compared to controls suggesting that early cerebellar development is impeded during the early weeks of premature life (Limperopoulos *et al.*, 2005*a*). Mackie *et al.* (2007) compared cerebellar development in adolescents with ADHD compared with controls. Groups differed in the trajectory of growth for the entire cerebellum with the worse outcome group exhibiting a progressive relative decrease in total volume, falling further away from the normal trajectory during adolescence. Cerebellar function and plasticity may play a role in other neuro-developmental disorders such as schizophrenia (Rapoport and Gogtay, 2008).

In this study, we have measured cerebellar volume longitudinally between adolescence and adulthood in a group of preterm individuals, and a term-born comparison group. We hypothesized that preterm birth would be associated with altered cerebellar development during adolescence, such as a delay in maturation or deviance from the observed maturation of controls. We further hypothesised that altered development would be associated with disrupted behavioural and neuropsychological outcome in adulthood.

Methods

Very preterm group (VPT)

VPT individuals were recruited from a cohort of individuals born before 33 weeks' gestation between 1982 and 1984, who were admitted to the neonatal unit of University College London Hospital (UCLH) within 5 days of birth and later discharged. From this population 302 survived and were recruited as part of a long-term follow-up study. The cohort was assessed at 1, 4, 8 and 15 years old using a battery of neuropsychological tests. These results have been published elsewhere (Costello *et al.*, 1988; Stewart *et al.*, 1989; Roth *et al.*, 1993; Stewart *et al.*, 1999). At 15 years, 111 of these individuals were assessed (the *adolescent* assessment). For the *young adult* assessment these individuals were re-contacted. Sixty-five (58.5%) were successfully assessed at both time-points. Preterm individuals who were not assessed did not differ significantly from those who were assessed in their gestational age ($P = 0.12$), Apgar scores at 1 min ($P = 0.86$) and 5 min ($P = 0.35$), gender ($P = 0.37$), social class ($P = 0.87$) or full-scale IQ at 14 years ($P = 0.311$). In this longitudinal study,

analysis was restricted to those individuals who were assessed at both time points.

A term-born comparison group of 71 individuals was recruited by advertisement in the local (South London) press for the *adolescent* assessments, to act as controls. These same individuals were invited back for the *young adult* assessments. Successful MRI scanning was carried out in 34 (48%) individuals at both time-points.

Magnetic resonance imaging

Three-dimensional T1-weighted inversion recovery prepared spoiled gradient echo recall (IR-SPGR) images were acquired on a GE Signa 1.5 Tesla MRI system (General Electric, Waukesha, WI, USA) at the Institute of Psychiatry, London, with contiguous 1.5 mm coronal slices, allowing reconstruction of the images in any plane. The volume of the cerebellum was determined by the Cavalieri method, using 'MEASURE' (Johns Hopkins University, Baltimore, USA) (Frangou *et al.*, 1997; Allin *et al.*, 2001). Ratings were performed blind to group membership and time point, by AM and AK. Inter-rater-reliability was high ($\alpha = 0.993$).

Whole brain volume at both time-points was also calculated using Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neurosciences, University College London, UK). Whole brain volumes at adolescent and adult assessments, and a measure of change in whole brain volume, were used as covariates in the subsequent analysis. In brief, each subject's SPGR MRI data were masked to exclude non-brain tissues, and each voxel classified as grey matter, white matter or cerebrospinal fluid by an automated segmentation algorithm. Total brain grey and white matter volumes were derived from the images in native space (i.e. without being subjected to any spatial transformation).

Neuropsychometry

In *young adulthood*, the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), which comprises four subtests: Vocabulary, Block design, Similarities and Matrix Reasoning, was administered. Measures of verbal, performance and full-scale IQ were derived. Two tests were used to assess verbal fluency. To measure phonemic or letter fluency, we administered the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976). In this task, participants are requested to overtly produce words beginning with a given letter: F, A and S, in 60 s. To assess category fluency, we administered the Animal Naming and Object Naming tests. In these tests, participants are required to say as many names of animals and objects as they can in 60 s for each category (Strauss and Spreen, 2006). Verbal fluency assesses the executive system that enables initiation of response, mental flexibility and the ability to use different strategies, such as clustering, where words are produced in subcategories, either phonemic or semantic. Verbal fluency tasks place demands on short-term memory of phonological information and simple word retrieval processes as well as on executive function (Abrahams *et al.*, 2000). Scores used in the analysis included the total number of words produced during the F, A and S trials for the COWAT. Category fluency was defined as the number of words produced on the Animal Naming and Object Naming tests combined.

Behavioural and psychological screen

The 12-item General Health Questionnaire (GHQ-12) was completed. Two domains have been identified from the GHQ-12 in a multiple centre trial; psychological distress and social dysfunction (Werneke *et al.*, 2000). We used the Likert scoring method which produces a wider and smoother score distribution (Goldberg *et al.*, 1998). None of the versions of the GHQ are recommended for use with children, although Goldberg and Williams (1988) note that several researchers appear to have used it successfully with adolescents.

Ethics

This study was approved by the Medical Ethical Committee of the Institute of Psychiatry, King's College London. At adolescence, written informed consent was obtained from a parent or guardian. All participants provided written informed consent in adulthood.

Statistical analysis

Analysis was performed using SPSS version 15.0 (SPSS, Chicago). Between group differences were examined using *t*-test or χ^2 tests. Longitudinal between group differences were assessed using repeated-measures ANOVA, with volume as dependent variable at two time-points. Significant effects were explored with *post hoc* paired-sample *t*-tests. Measures of change of cerebellar and white matter volume were derived [(*adult* volume) – (*adolescent* volume)]. Relationships between cerebellar volume and neuropsychological and behavioural data in adolescence and young adulthood were determined using Kendall partial correlations, controlling for socioeconomic status, which is known to influence neuropsychological performance, assessment age, white matter volume and/or change in white matter volume, which may be associated with cerebellar volume. We also controlled for full scale IQ when determining relationships between cerebellar volume and behavioural data.

Results

Study group characteristics

There was no significant difference in gender distribution between the VPT and term-born participants. Socioeconomic status did vary significantly between the groups ($\chi^2 = 8.53$, $P = 0.014$). Term-born subjects were significantly older at the time of first ($F = 3.98$, $P = 0.031$) and second scans ($F = 0.41$ $P = 0.011$). As expected, birth weight and gestation were different between the groups (Table 1).

Cerebellar development

Repeated measures ANOVA of cerebellar volume at two time points and VPT/term-born group as between-subject factor, showed a main effect of time-point ($F = 4.59$, df = 1, $P = 0.035$, partial $\eta^2 = 0.045$) and a time-point by group interaction ($F = 8.03$, df = 1, $P = 0.006$, partial $\eta^2 = 0.076$). There was no significant main effect of group ($F = 0.48$, df = 1, $P = 0.491$, partial $\eta^2 = 0.005$).

Further exploration of these relationships using paired *t*-tests revealed a significant effect of time on cerebellar volume in the preterm group. By adulthood cerebellar

Table 1 Demographic comparison between VPT subjects and term-born controls

	VPT subjects ($n = 65$)	Term-born subjects ($n = 34$)	Statistics
Females/males	30/35	14/20	$F = 0.98$, $P = 0.640$
Parental social class			
I–II	21	20	
III	37	9	
IV–V	7	5	$\chi^2 = 8.53$, $P = 0.014$
Mean age at first scan years(SD)	15.09 (0.84)	15.43 (0.56)	$F = 3.98$, $P = 0.031$
Mean age at second scan years(SD)	18.61 (1.02)	19.17 (0.95)	$F = 0.41$, $P = 0.011$
Birth weight in grams (SD)	1234.68 (396.43)	[$n = 29$] 3283.79 (414.74)	
Gestation at birth in weeks (SD)	28.63 (2.24)	[$n = 31$] 40.22 (1.43)	

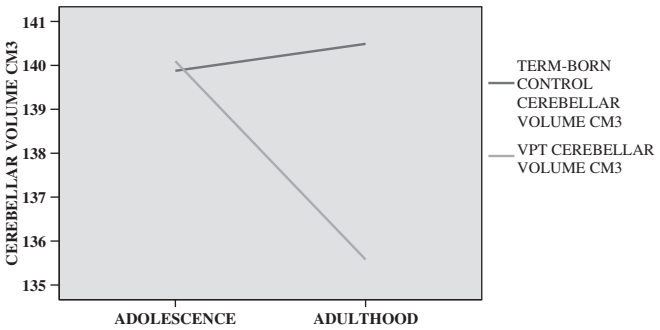

Fig. 1 Cerebellar growth. Cerebellar volume change between adolescene and adulthood in VPT and term-born controls.

volumes were 3.11% smaller in this group than they had been in early adolescence ($P = 0.000$). The cerebellar volume in the term group increased by 0.44% over this time, an increase that was not statistically significant ($P = 0.612$) (Fig. 1). Independent *t*-tests revealed no-significant difference of cerebellar volume between groups at either first or second scan ($P = 0.969$ and $P = 0.115$, respectively) (Table 2).

Grey matter development

Repeated measures ANOVA of grey matter volume at two time-points and VPT/term-born group as between-subject factor showed a main effect of time-point ($F = 88.14$, df = 1, $P = 0.000$, partial $\eta^2 = 0.479$) and group ($F = 10.33$, df = 1, $P = 0.002$, partial $\eta^2 = 0.097$), but no time-point by group interaction ($F = 0.06$, df = 1, $P = 0.809$, partial $\eta^2 = 0.001$). Further exploration of these relationships using paired *t*-tests revealed a significant change in grey matter volume in both groups and independent *t*-tests revealed significant differences of grey matter volume between groups at both ages (Table 2).

White matter development

Repeated measures ANOVA of white matter volume at two time points and VPT/term-born group as between-subject factor showed a main effect of time-point ($F = 23.70$, df = 1, $P = 0.000$, partial $\eta^2 = 0.198$) and group ($F = 6.26$, df = 1, $P = 0.014$, partial $\eta^2 = 0.061$), but no time-point by group interaction ($F = 0.05$, df = 1, $P = 0.822$, partial $\eta^2 = 0.001$). Further exploration of these relationships using paired *t*-tests revealed a significant change in white matter volume in both groups and independent *t*-tests revealed significant differences of white matter volume between groups at both ages (Table 2).

Cerebellar volume and cognitive function

Relationships between cerebellar volume and neuropsychological tests in both early adolescence and adulthood were assessed using Kendall partial correlations controlling for age at both assessments and socioeconomic status and then additionally controlling for white matter volume at each age. In the VPT group there were positive correlations between cerebellar volume and full-scale IQ, verbal IQ and performance IQ in early adolescence. However these did not persist after controlling for white matter volume. There were no such correlations in the term-born control group at this age (Table 3).

By adulthood cerebellar volume in the VPT group positively correlated with full-scale and performance IQ, but these did not persist after controlling for white matter volume. Again cerebellar volume was not correlated with IQ in the term-born control subject group (Table 4). Neither group showed correlation of cerebellar volume with semantic or phonological fluency in early adolescence or adulthood.

Relationships between cerebellar growth and behavioural and cognitive outcome in adulthood

The relationship between change in cerebellar volume and neuropsychological tests scores in adulthood were assessed using Kendall partial correlations controlling for age at each assessment, socioeconomic status, change in white matter volume and white matter volume in adulthood. There was a positive correlation between phonological verbal fluency and cerebellar change in the term-born control group, but not the VPT group. There were no significant correlations

Table 2 Cerebellar, grey and white matter development; paired and independent *t*-tests

	VPT subjects ($n = 65$)	Term-born controls ($n = 34$)	Independent *t*-test statistics
Cerebellar volume (cm^3) first scan (SD)	140.0952 (18.49)	139.8771 (12.06)	$t = 3.64$, $P = 0.969$
Cerebellar volume (cm^3) second scan (SD)	135.5800 (19.50)	140.4903 (11.17)	$t = 4.51$, $P = 0.115$
Paired *t*-test statistics	$t = 3.92$, $P = 0.000$	$t = -0.51$, $P = 0.612$	
Grey matter volume (cm^3) first scan (SD)	790.23 (92.02)	846.86 (92.53)	$t = 0.06$, $P = 0.005$
Grey matter volume (cm^3) second scan (SD)	746.12 (77.04)	804.97 (91.23)	$t = 0.94$, $P = 0.002$
Paired *t*-test statistics	$t = 7.48$, $P = 0.000$	$t = 7.14$, $P = 0.000$	
White matter volume (cm^3) first scan (SD)	412.48 (56.81)	441.91 (49.28)	$t = 0.844$, $P = 0.009$
White matter volume (cm^3) second scan (SD)	424.30 (57.90)	452.68 (54.34)	$t = 0.51$, $P = 0.019$
Paired *t*-test statistics	$t = -3.79$, $P = 0.000$	$t = -4.42$, $P = 0.000$	

Table 3 Kendall partial correlations between cerebellar volume at first scan and neuropsychological test scores in early adolescence in VPT and Term-born Control Groups

	VPT subjects		Term-born controls	
	Controlling for; age, SES	Controlling for; age, SES and white matter volume	Controlling for; age, SES	Controlling for; age, SES and white matter volume
Full Scale IQ	0.471 ($P = 0.002$)	0.202 ($P = 0.183$)	0.177 ($P = 0.559$)	0.266 ($P = 0.148$)
Verbal IQ	0.401 ($P = 0.008$)	0.187 ($P = 0.219$)	0.204 ($P = 0.287$)	0.252 ($P = 0.171$)
Performance IQ	0.434 ($P = 0.004$)	0.163 ($P = 0.286$)	0.106 ($P = 0.584$)	0.197 ($P = 0.289$)
FAS	0.163 ($P = 0.303$)	−0.054 ($P = 0.725$)	0.010 ($P = 0.960$)	0.098 ($P = 0.600$)
CAT	0.067 ($P = 0.674$)	−0.055 ($P = 0.721$)	0.047 ($P = 0.809$)	0.122 ($P = 0.514$)

Table 4 Kendall partial correlations between cerebellar volume at second scan and neuropsychological test scores in adulthood in VPT and term-born control groups

	VPT subjects		Term-born controls	
	Controls; age, SES	Controls; age, SES, white matter volume	Controls; age, SES	Controls; age, SES, white matter volume
Full Scale IQ	0.309 ($P = 0.047$)	0.083 ($P = 0.550$)	−0.133 ($P = 0.491$)	0.120 ($P = 0.535$)
Verbal IQ	0.180 ($P = 0.255$)	0.127 ($P = 0.361$)	0.095 ($P = 0.626$)	0.199 ($P = 0.300$)
Performance IQ	0.345 ($P = 0.025$)	−0.022 ($P = 0.877$)	0.020 ($P = 0.917$)	0.016 ($P = 0.935$)
FAS	0.175 ($P = 0.268$)	0.037 ($P = 0.791$)	0.398 ($P = 0.032$)	0.159 ($P = 0.409$)
CAT	0.043 ($P = 0.787$)	−0.031 ($P = 0.825$)	0.229 ($P = 0.231$)	0.146 ($P = 0.450$)

between cerebellar volume change and IQ in either group. There were no significant correlations between change in Full Scale IQ or change in verbal fluency with cerebellar volume change in either group (Table 5).

Kendal partial correlations were used to assess the relationship between the change in cerebellar volume and domains of mental well being as scored in the GHQ while controlling for age at each assessment, socioeconomic status and full scale IQ. We also controlled for change in white matter volume and white matter volume in adulthood which was significantly smaller the preterm individuals. There were significant negative correlations between change in cerebellar volume and GHQ-12 total score and several questions pertaining to concentration, feeling useful, decision-making capability, overcoming difficulties, feeling confident and feeling worthless in the VPT group, but not the term-born control group (negative correlations here indicated that cerebellar diminution was associated with worse behavioural and psychological outcome) (Table 5).

Discussion

In this study we demonstrated that cerebellar volume decreased by 3.11% during late adolescence in individuals born VPT. Over the same period, cerebellar volume remained stable in term-born controls. To our knowledge, a comparable growth pattern of the cerebellum has not been reported previously in preterm individuals. The significantly different developmental growth patterns between VPT individuals and controls were limited to the cerebellum. Grey and white matter volumes showed similar growth patterns in both VPT individuals and controls.

Table 5 Kendall partial correlations between change in cerebellar volume and neuropsychological test scores and General Health Questionnaire in adulthood in VPT and Term-born Control Groups

	VPT subjects	Term-born controls
Full Scale IQ	0.102 ($P = 0.520$)	−0.111 ($P = 0.566$)
Verbal IQ	−0.044 ($P = 0.789$)	−0.024 ($P = 0.906$)
Performance IQ	−0.059 ($P = 0.721$)	−0.219 ($P = 0.283$)
FAS	−0.133 ($P = 0.420$)	0.546 ($P = 0.004$)
CAT	0.036 ($P = 0.829$)	0.311 ($P = 0.122$)
Change in Full Scale IQ	0.191 ($P = 0.245$)	−0.039 ($P = 0.262$)
Change in FAS	−0.061 ($P = 0.714$)	0.249 ($P = 0.220$)
Change in CAT	0.23 ($P = 0.883$)	−0.039 ($P = 0.851$)
General Health Questionnaire		
Q1. Concentration	−0.378 ($P = 0.010$)	0.090 ($P = 0.661$)
Q2. Sleep	0.092 ($P = 0.543$)	−0.009 ($P = 0.964$)
Q3. Feeling Useful	−0.311 ($P = 0.035$)	−0.124 ($P = 0.545$)
Q4. Decision-making Capability	−0.348 ($P = 0.018$)	−0.114 ($P = 0.578$)
Q5. Strain	−0.130 ($P = 0.389$)	0.131 ($P = 0.523$)
Q6. Overcoming difficulties	−0.331 ($P = 0.025$)	0.052 ($P = 0.802$)
Q7. Enjoy normal activities	−0.236 ($P = 0.114$)	−0.161 ($P = 0.433$)
Q8. Face up to problems	−0.241 ($P = 0.107$)	0.094 ($P = 0.649$)
Q9. Unhappy/Depressed	−0.014 ($P = 0.925$)	0.271 ($P = 0.180$)
Q10. Confidence	−0.309 ($P = 0.037$)	0.266 ($P = 0.189$)
Q11. Worthlessness	−0.329 ($P = 0.026$)	0.058 ($P = 0.778$)
Q12. Happy	−0.046 ($P = 0.764$)	−0.070 ($P = 0.733$)
GHQ Total score	−0.324 ($P = 0.028$)	0.082 ($P = 0.690$)

In the cerebrum, growth trajectories of grey and white matter have been well characterised (Giedd *et al.*, 1999; Gogtay *et al.*, 2004; Sowell *et al.*, 2004) with regionally heterogeneous white matter growth (usually attributed to myelination) and a concomitant decrease in grey matter (usually attributed to pruning and stabilisation of synaptic connections). In this study, VPT and term-born controls have similar growth patterns of grey and white matter, which are consistent with observations described above. However, grey and white matter volumes were significantly smaller in the VPT group in adolescence and young adulthood.

There is a paucity of evidence on cerebellar development. Our results suggest that cerebellar volume remains stable in term-born adolescents, although it is possible that this apparent stability is masking differential changes in cerebellar grey and white matter with the net effect that cerebellar volume is unchanged. Unfortunately, the methods we have used to measure cerebellar volume cannot elucidate this.

In the VPT group, there is a clear diminution in overall cerebellar volume, although again we cannot be certain whether change in grey matter or white matter (or both) is responsible for this. One possibility is that the changes we have observed in cerebellar development in the VPT group are a reflection of changes elsewhere in the brain. Lesions of the cerebrum can cause a crossed cerebellar diaschisis, with consequent under activity and hypoplasia of the cerebellar hemisphere contralateral to the lesion (Limperopoulos *et al.*, 2005*b*). In this model, failure to strengthen appropriate white matter connections in frontal cortex might have knock-on effects on cerebellar size by depriving it of its expected inputs. However, in this adolescent sample, white matter volume is increasing over the same time period that the cerebellar volume is decreasing in preterm individuals. An alternate possibility is that this reduction in cerebellar volume represents a delay in maturation in the VPT group—for instance, cerebellar size decrease may be part of a maturational process that has already been completed in our term-born comparison group. Extrapolating Giedd's work on the cerebrum, the reduction in cerebellar size may reflect a post-peak reduction in grey matter volume. Another possibility is that excessive pruning of cerebellar synapses is occurring, with loss of grey matter volume, or that axons or myelin are being lost in the white matter of the cerebellum.

We also report, for the first time to our knowledge, a correlation between cerebellar development and psychiatric symptoms. The GHQ is used to detect caseness for possible psychiatric disorder in the general population or non-psychiatric clinical settings including general medical out-patients. The direction of the correlation indicates that high GHQ-12 scores, associated with increased risk of mental health problems, are correlated with a reduction in cerebellar volume during late adolescence. After controlling for white matter volume we conclude that abnormal cerebellar development in individuals born very preterm is associated with a diminution in their psychological wellbeing in adulthood, although we are not able to infer the direction of causality from this. It is possible that abnormal cerebellar development may be directly related to behavioural and psychological outcome, since cerebellar injury in children and adults is associated with impaired emotional regulation in response to stimuli (Schmahmann *et al.*, 1998). Limperopoulous *et al.* (2007) have demonstrated an association between cerebellar hemorrhagic injury (in preterm infants of ~30 months old) and dysfunction in non-motor domains including socialisation, communication and cognition that was not dependant on supra-tentorial injury. An alternative possibility is that cerebellar pathology is associated with neuropsychological deficits (Allin *et al.*, 2001), which then cause psychosocial difficulties. However, the association between cerebellar decrement and GHQ-12 that we report was present even after controlling for full scale IQ, which would argue against this.

A further finding of our study was a relationship between cerebellar size and neuropsychological tests in the VPT group. Cerebellar volume, although not significantly different between the groups, correlates positively with full scale, verbal and performance IQ in early adolescence in the VPT group but not the term-born group. It could suggest

that cognitive functioning of the cerebellum is more vulnerable to volume change in the VPT group. However, when white matter volume is controlled for, which is significantly smaller and potentially reflects white matter injury in the preterm group, these correlations were not maintained. This suggests that the relationship between cerebellar volume and neuropsychological functioning in the preterm group is mediated by white matter injury. This is consistent with the findings of Shah *et al.* (2006). Similar relationships with cognitive function were seen in adulthood in the VPT group. At this age, there was a correlation between cerebellar volume and full scale and performance IQ, but again these correlations were no longer present when white matter volume was controlled for.

Cerebellar volume change was positively correlated with verbal fluency in the term-born group which indicates that improved verbal fluency was associated with increased cerebellar size in adolescence. Longitudinal studies have shown that verbal fluency does indeed increase between adolescence and young adulthood (Allin, 2007*a*). There was no such positive correlation of verbal fluency with cerebellar volume change in the VPT group which could suggest a functional impairment of the cerebellum in this group.

There was no significant difference in mean cerebellar volume between VPT and term-born cohorts in our study at either time point which was surprising as studies of other preterm individuals have demonstrated a significantly smaller mean cerebellum size compared to term subjects (Allin *et al.*, 2001, 2005; Argyropoulou *et al.*, 2003; Limperopoulos *et al.*, 2005*b*; Messerschmidt *et al.*, 2005). It is possible that age differences between the study groups attenuated the differences, although we attempted to control for this where possible in the analysis. Another possibility is that there is a bias in our groups—for example, it is more likely that individuals who were successfully followed up at both time-points were those with less functional impairment. Additionally, there was considerable drop-out from the term group. These concerns are common to many long-term follow-up studies.

Although this was a relatively large follow-up study, assessments were only made at two time-points. Thus it is not possible for us to draw firm conclusions about growth trajectories in adolescence. Further follow-up studies will be useful in this regard. The VPT group was slightly, but statistically significantly, younger than the term-born control group at both assessment stages and the term-born group had higher socioeconomic status than the VPT group. This may have had confounding effects on neuropsychological tests and behavioural outcomes. We attempted to control statistically for these demographic differences when further analyses were carried out. Kendall partial correlations were used to elucidate relationships between data which cannot be interpreted as causal. Although multiple comparisons were used and we have not corrected for multiple testing, the comparisons between the pairs of groups were planned *a priori* to explore impact of very preterm birth. The pattern of correlations, being mainly confined to the VPT group, is unlikely to have arisen through chance alone.

Summary

We have demonstrated a reduction in cerebellar volume in very preterm born adolescents which is correlated with reduced mental wellbeing. This supports our hypothesis that preterm birth may be associated with altered cerebellar development during adolescence. The relationship between reduced cerebellar volume and mental wellbeing is independent of cerebral white matter volume. This adds to the literature which implicates the cerebellum in cognition and behaviour, in addition to its well-understood role in motor co-ordination.

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