

Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term

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Summary

Individuals born before 33 weeks' gestation are at risk of brain lesions, which have the potential to disrupt subsequent neurodevelopment. As a result they manifest an increased incidence of neuromotor signs and cognitive deficits, which can still be detected in adolescence. The cerebellum is known to be involved in both the co-ordination of movement and in cognitive processes. We therefore set out to establish whether cognitive and motor impairments in adolescents born very pre-term are associated with abnormalities of the cerebellum as revealed by volumetric analysis of brain MRI scans. The volume of the whole cerebellum was determined manually using a PC-based Cavalieri procedure in 67 adolescents born very pre-term and 50 age-matched, full-term born controls. Cognitive and neurological assessments were

performed at 1, 4, 8 and 14–15 years of age as part of the long-term follow-up of the pre-term subjects. The pre-term-born subjects had significantly reduced cerebellar volume compared with term-born controls ($P < 0.001$). This difference was still present after controlling for potential confounders. There was no association between cerebellar volume and motor neurological signs. However, there were significant associations between cerebellar volume and several cognitive test scores, in particular the Wechsler Intelligence Scale for Children—Revised, the Kaufman Assessment Battery for Children and the Schonell reading age. This provides further evidence implicating the cerebellum in cognition and suggests that cerebellar abnormalities may underlie some of the cognitive deficits found in individuals born very pre-term.

Keywords: cerebellum; cognition; MRI; neurodevelopment; pre-term

Abbreviations: K-ABC = Kaufman Assessment Battery for Children; WISC-R = Wechsler Intelligence Scale for Children—Revised

Introduction

The morphological and functional development of the human brain involves a complex temporally and spatially ordered sequence of events. This process of neurodevelopment starts soon after conception and continues into the second decade of life (Brown and Minns, 1999). Individuals who are born very pre-term are prey to several potential adverse factors acting in the prenatal, perinatal and neonatal periods, including hypoxia, ischaemia, sepsis and under-nutrition, all of which may adversely affect brain development (Hoon, 1995; Rosenbloom and Sullivan, 1996). The survivors of very pre-term birth show an excess of neurological and cognitive impairments, reflecting the influence of early damage on their subsequent neurodevelopment. Once they reach school age they are more likely to be considered

'clumsy' than their term-born classmates (Powls *et al.*, 1995; Goyen *et al.*, 1998; Luoma *et al.*, 1998) and tend to do less well academically (Hadders-Algra *et al.*, 1988; Hall *et al.*, 1995; Botting *et al.*, 1998; Msall *et al.*, 1998; Snider, 1998).

In addition to cognitive impairments, such individuals manifest a constellation of neurological signs, including dysdiadochokinesis, poor co-ordination of fine movements and impaired motor sequencing (Hadders-Algra *et al.*, 1988; Marlow *et al.*, 1989; Hall *et al.*, 1995), which has been termed 'developmental co-ordination disorder' by some authors (Dunn, 1986; Huh *et al.*, 1998; Polatajko, 1999). Such motor signs are traditionally associated with dysfunction of the cerebellum, a brain structure known to be particularly vulnerable around the time of birth (Jacobson, 1991). There

have, however, been few studies of the cerebellum in pre-term-born subjects. We therefore set out to test the hypothesis that the cerebellum is damaged by very pre-term birth, by using MRI techniques to measure the volume of the cerebellum in a group of adolescents born prior to 33 weeks of gestation. We also hypothesized that reduced cerebellar volume would be associated with impaired cognitive and motor function in this group; no relationship has hitherto been established between cerebellar pathology *in vivo* and functional outcome for pre-term individuals.

Methods

Study population

The study group consisted of 109 individuals born before 33 weeks' gestation and admitted to University College Hospital London Neonatal Unit within 5 days of birth between 1979 and 1980. Four subsequently died within 24 months, and the remaining 105 were enrolled for a long-term follow-up programme. Assessments of neurological and cognitive development were performed at 1 and 4 years of corrected age and at 8 years of age. At 14–15 years of age, 103 individuals were traced but 11 were living abroad at that time. Of the 92 living in the UK, 76 (83%) agreed to attend for assessment. MRI brain scanning was successfully carried out on all but four of those attending for follow-up.

The cohort members unavailable for study did not differ significantly from those who attended in birthweight, gestational age at birth, sex ratio, mode of delivery, condition at birth, requirement for mechanical ventilation or neonatal cranial ultrasound findings. These details have been described elsewhere (Stewart *et al.*, 1999).

Forty-seven infants who were delivered at term (38–42 weeks) at University College Hospital in 1979–1980 were enrolled as age-matched controls for assessments made on the cohort at 4 years. Those 45 who were living in the UK were traced at age 14–15 years and asked to take part in the study. Of these, seven refused because of the MRI scan and 16 did not reply. Twenty-two agreed to take part, although one refused MRI on the day (Stewart *et al.*, 1999). A further 26 age-matched controls were recruited by advertisement in the local (South London) and national press.

MRIs

The scans were performed on a 1.5 T GE Signa machine at the Institute of Neurology, London. Three-dimensional T₁-weighted spoiled gradient echo recall sequences were acquired. These sequences consist of 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, supported by the 'MEASURE' software package (Johns Hopkins University, Baltimore, Md., USA). The Cavalieri method is derived from histopathological

stereology (Frangou *et al.*, 1997). It involves overlaying a grid of points on the reconstructed image slices. Those points falling within the region of interest are marked. The computer then counts the number of marked grid points and converts this number to a volume.

Three raters analysed the images (M.A., A.M.S., H.M.). Inter-rater reliability testing was carried out prior to the study. Five scans were independently rated by the three researchers and reliability (alpha) coefficients were calculated: between M.A. and A.M.S., $\alpha = 0.977$; between M.A. and H.M., $\alpha = 0.998$.

Neurological and cognitive assessments

Variables were chosen from cognitive and motor domains to test specific *a priori* hypotheses about the data. Cognitive tests were chosen with reference to Schmahmann and Sherman (1998). They included the Wechsler Intelligence Scale for Children—Revised (WISC-R) (Wechsler, 1974) and the Kaufman Assessment Battery for Children (K-ABC) (1983), both administered at age 8 years. Further cognitive measures were administered at age 14–15 years and comprised: trail-making tests A and B (Army Individual Test Battery, 1944); digit span; Schonnel reading age and spelling age (Schonnel and Schonnel, 1960); Rey complex figure copy and delayed recall (Rey, 1941); verbal fluency; and the Boston naming test. Neurological measures were chosen to reflect the known 'classical' motor functions of the cerebellum (Adams *et al.*, 1997). They comprised upper limb co-ordination, presence of eye movement abnormalities and clinical neurological examination at ages 1 and 14–15 years.

Statistical analysis

Statistical analysis was performed using SPSS 8.0.1 (SPSS, Ill., USA). Group differences were analysed using Student's *t*-test. Demographic details were examined by *t*-test or χ^2 analyses as appropriate. Analyses of covariance (ANCOVA) were used to control for the effects of whole brain volume, sex and social class on the cerebellar volume. Linear regression analyses were used to determine variables associated with cerebellar volume, as described above.

Ethics

Approval was obtained from the Joint University College London/University College Hospital Committee on the Ethics of Human Research, and the Joint Medical Ethical Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery. Informed, written consent was obtained from an accompanying parent or guardian and verbal consent obtained from the subjects and controls themselves.

Table 1 Demographic and clinical characteristics of cases and controls

	Cases (n = 67)	Controls (n = 50)
Parental social class		
I–II	29 (43.3%)	29 (58.0%)
III	19 (28.4%)	8 (16.0%)
IV–VI	19 (28.4%)	13 (26.0%)
Females/males	35/32	19/31*
Mean age at scan in years (SD)	14.9 (0.43)	14.9 (0.64)
Neurological examination at 14–15 years		
Normal	23 (34.8%)	39 (79.6%)
Mild abnormality	25 (37.9%)	4 (8.2%)
Definite abnormality	18 (27.3%)	6 (12.2%)†
Upper limb co-ordination at 14–15 years		
Normal	40 (72.7%)	28 (96.6%)
Mild abnormality	13 (23.6%)	1 (3.4%)
Definite abnormality	2 (3.6%)	0 (0%)‡
Eye movements at 14–15 years		
Normal	45 (81.8%)	27 (93.1%)
Mild abnormality	7 (12.7%)	0 (0%)
Definite abnormality	3 (5.5%)	2 (6.9%)§

* $\chi^2(1,1) = 1.808$; $P = 0.191$. † $\chi^2(1,2) = 23.33$; $P < 0.001$.
‡ $\chi^2(1,2) = 7.03$; $P < 0.05$. § $\chi^2(1,2) = 4.04$; $P = 0.133$.

Results

Characteristics of the study population

Seventy-six cases and 50 controls were studied at a mean age of 14.9 years (see Table 1). The distribution of social class (according to the Registrar General's classification) was similar between cases and controls. There was a gender asymmetry between cases and controls, but this was not statistically significant ($P = 0.191$). Details of the neonatal characteristics of the cases have been published elsewhere (Stewart *et al.*, 1999).

Subjects born very pre-term had abnormal neurological examination results compared with term-born controls. Upper limb co-ordination was impaired on clinical testing in the pre-term cases, but eye movements were not affected. The mean full-scale WISC-R IQ score at 8 years was 103.8 (SD = 15.3). WISC-R data was only collected on the very pre-term-born cases. There was a significant difference in category fluency, administered at 14–15 years, between cases (mean = 34.8, SD = 9.0) and controls (mean = 44.4, SD = 10.3) [$F(1,111) = 27.76$; $P < 0.001$]. There were no significant differences between cases and controls in the other cognitive data collected in both groups at 14–15 years. These cognitive tests were verbal fluency (FAS), Boston naming test, Schonnel reading and spelling age and digit span.

MRI scans

Of the 76 cases seen, four refused MRI examination on the day. Five of the scans obtained were subsequently excluded from analysis because of technical problems with the images. The volume of the whole cerebellum was determined in 67

Table 2 Results of ANOVA comparing whole brain, grey matter and white matter volumes between cases and controls

	Mean volume in cm ³ (SD)	F	d.f.	P
Whole brain				
Cases	1306.1 (111.9)	13.91	1109	<0.001
Controls	1387.1 (115.6)			
White matter				
Cases	467.7 (73.6)	0.039	1108	0.843
Controls	470.6 (81.1)			
Grey matter				
Cases	624.3 (84.2)	26.57	1108	<0.001
Controls	707.6 (83.8)			

cases and 50 controls. The volumes of whole brain, used as covariate in the analyses, and volumes of grey and white matter, were measured using the same technique (Nosarti *et al.*, 1999); these results are presented in Table 2.

Cerebellar volume

The volume of the cerebellum was smaller in pre-term-born cases (mean = 135.3 cm³, SD = 16.5) than controls (mean = 147.2 cm³, SD = 11.9); Student's *t*-test revealed that this difference was statistically significant [$t(1,115) = 4.31$; $P < 0.001$]. Statistical significance was still present after ANCOVA, with cerebellar volume as dependent variable and whole brain volume, gender and socioeconomic status as covariates [$F(1,97) = 13.2$; $P < 0.001$].

Linear regression analyses

No relationship was demonstrated between any motor neurological variables at 1 or 14–15 years and the volume of the cerebellum. However, there were significant relationships between various cognitive variables measured at 4, 8 and 14–15 years and cerebellar volume in the cases of patients born very pre-term, notably the full-scale WISC-R IQ score and the K-ABC. The verbal IQ subscale of the WISC-R demonstrated a trend-level relationship with cerebellar volume (which did not reach statistical significance), but the performance IQ did not show any such relationship. Three individual subtests, similarities, block design and object assembly, were related to cerebellar volume. The sequential processing, simultaneous processing and achievement scales of the K-ABC were all significantly related to cerebellar volume. These results are presented in Table 3.

No relationships were revealed between cognitive variables and cerebellar volumes in the controls, but cognitive data were only available for controls at 14–15 years; these data therefore did not include WISC-R or K-ABC.

The same variables were subjected to linear regression analyses with whole brain volume, total white matter volume

Table 3 Results of linear regression analyses for associations between cerebellar volume and cognitive tests in cases of subject born very pre-term

Test	Standardized regression coefficient (β)	d.f.	P
WISC-R full-scale IQ at 8 years	0.244	65	0.048*
WISC-R verbal IQ at 8 years	0.224	65	0.071
Information subtest	0.205	64	0.807
Similarities subtest	0.312	65	0.011*
Vocabulary subtest	0.186	64	0.138
Comprehension subtest	0.220	64	0.078
WISC-R performance IQ at 8 years	0.179	65	0.150
Arithmetic subtest	-0.031	64	0.807
Picture completion subtest	0.103	65	0.411
Picture arrangement subtest	0.067	65	0.596
Block design subtest	0.265	65	0.031*
Object assembly subtest	0.260	65	0.035*
K-ABC at 8 years			
Mental processing component	0.331	64	0.007†
Sequential	0.285	64	0.021*
Simultaneous	0.260	65	0.035*
Achievement	0.382	64	0.002†
Riddle interpretation	0.257	65	0.037*
Reading-decoding	0.300	65	0.014*
Reading-understanding	0.298	65	0.015*
Verbal fluency (FAS) at 14–15 years	0.202	63	0.107
Category fluency at 14–15 years	0.139	64	0.273
Boston naming test at 14–15 years	0.102	63	0.421
Schnnell reading age at 14–15 years	0.295	62	0.019*
Schnnell spelling age at 14–15 years	0.180	63	0.155
Digit span at 14–15 years	0.250	66	0.046*

d.f. = degrees of freedom. * $P < 0.05$; † $P < 0.01$.

Table 4 Results of linear regression analyses with whole brain volume, cerebral white matter volume or cerebral grey matter volume as dependent variable

	Whole brain volume		White matter volume		Grey matter volume	
	β (d.f.)	P	β (d.f.)	P	β (d.f.)	P
K-ABC achievement	0.321 (59)	0.012*	0.266 (59)	0.040*	0.100 (59)	0.448
Digit span	0.252 (59)	0.052	0.376 (59)	0.003†	-0.055 (59)	0.674

K-ABC achievement score administered at age 8 years; digit span administered at age 14–15 years. β = standardized regression coefficient; d.f. = degrees of freedom. * $P < 0.05$; † $P < 0.01$.

and grey matter volume as dependent variables. Significant relationships were defined for the K-ABC achievement score (at 8 years) and the digit span (at 14–15 years). The results are presented in Table 4. All other relationships demonstrated in Table 3 were specific to the cerebellum.

Discussion

We have demonstrated that individuals born very pre-term have significantly smaller cerebella than their term-born peers and that this difference remains statistically significant after controlling for whole brain volume and other potentially confounding variables. We are not aware of any other published volumetric studies of the cerebellum in a comparable subject group.

Despite its large size, the cerebellum has been relatively neglected in imaging studies. There are, however, good grounds for suspecting that it may be involved in the motor and cognitive problems associated with very pre-term birth. Acute lesions of the cerebellum in children and adults produce a well recognized motor syndrome (Adams *et al.*, 1997), which has some overlap with the ‘developmental co-ordination disorder’ of pre-term-born individuals (Hadders-Algra *et al.*, 1988; Hall *et al.*, 1995; Goyen *et al.*, 1998; Johnston, 1998; Snider, 1998). The mammalian cerebellum is known to be in a vulnerable state around the time of birth, since this is a period of active proliferation and migration of the cerebellar granule cells. Potentially harmful events around the time of birth or during a post-natal period of intensive care may therefore interfere with the development of this

cell population (Sohma *et al.*, 1995; Johnston, 1998). Other cell populations of the cerebellum may then have their own development altered because of disordered, or absent, interactions with granule cells (Jacobson, 1991). The most plausible candidates for such noxious environmental influences are hypoxia-ischaemia and under-nutrition. Cerebellar lesions of probable hypoxic-ischaemic aetiology have been found at post mortem (Sohma *et al.*, 1995; Tsuru *et al.*, 1995) and on follow-up MRI (Mercuri *et al.*, 1997) in pre-term individuals.

The reduced size of the cerebellum that we demonstrate may thus reflect a relative loss of cell populations or abnormal ultrastructural development—such as dendritic branching or synaptogenesis—as a result of a neonatal insult. That ultrastructural brain abnormalities are present in pre-term-born individuals may be inferred from abnormal distribution of neuronal markers such as parvalbumin (Iai *et al.*, 1999) and altered ratios of neural metabolites on magnetic resonance spectroscopy (Huppi *et al.*, 1991).

Previous study of this cohort has shown a relationship between brain MRI abnormality (qualitatively rated by a neuroradiologist) and behaviour (Stewart *et al.*, 1999), but did not find a relationship between brain abnormality and neurological examination or cognitive assessments. The study of Stewart *et al.* was not a volumetric study, but our findings are in agreement in that we demonstrate no relationship between motor neurological signs and cerebellar volume. This may be a reflection of functional compensation that has occurred in the 14 years since the birth of our pre-term-born subjects. The motor consequences of acute cerebellar lesions in adults are known to improve over time (Schmahmann and Sherman, 1998), so our finding of a lack of relationship may represent developmental plasticity of the cerebellum or of cortico-cerebellar circuits. Alternatively, it may be that the neurological examination undertaken was insufficiently detailed to detect subtle signs of motor cerebellar dysfunction. Neurophysiological assessments of cerebellar function, such as testing of the vestibulo-ocular reflex, smooth pursuit eye movements and electronystagmography were not performed, but could be used to evaluate further this cohort in the future. This study did not divide the cerebellum into regions along anatomical boundaries, which might have helped to clarify more precise structure–function relationships. For example, pathology confined to the posterior lobe of the cerebellum might be expected to impair cognitive rather than motor function.

Although there was no relationship to motor signs, we did find significant associations between a number of cognitive measures and cerebellar size. Multiple linear regression tests were performed, with the inherent likelihood that some results may be due to chance. However, the large number of significant relationships revealed is unlikely to be explained solely by chance effects. Also, the same linear regression analyses carried out using whole brain volume or cerebral white or grey matter volume as dependent variables did not show a similar pattern. Another potential limitation of the

analysis, which may reduce the significance of some of the findings, is that assessment of the WISC-R and the K-ABC was carried out at 8 years, whereas the MRI scans were performed at 14–15 years. In addition, since WISC-R and K-ABC were not administered to a control group at 8 years, it is not possible to exclude the possibility that cerebellar volume might also be associated with these measures in a control population. However, other cognitive test variables (Schonnel reading age and digit span) that were performed at the time of scanning also showed significant relationships with cerebellar volume and these relationships were specific to the cases of subjects born very pre-term.

Although our findings do not prove a causal relationship they do add to the accumulating body of evidence implicating the cerebellum in cognition (Grafman *et al.*, 1992; Appollonio *et al.*, 1993; Molinari *et al.*, 1997; Rao *et al.*, 1997; Schmahmann and Sherman, 1998; Levisohn *et al.*, 2000; Riva and Giorgi, 2000), language (Leiner *et al.*, 1993; Cole, 1994; Silveri *et al.*, 1994) and attention (Townsend *et al.*, 1999) in addition to its motor functions. Focal cerebellar lesions in both adults (Schmahmann and Sherman, 1998) and children (Levisohn *et al.*, 2000; Riva and Giorgi, 2000) produce a characteristic cognitive-affective syndrome consisting of deficits in executive function, visuospatial cognition and language and blunting of affect, or disinhibited or inappropriate behaviour. The overall result of these deficits is an overall decline in cognitive performance. Our results are consistent with this in that we find reduced cerebellar volume to be associated with reduced WISC-R and K-ABC scores in the subjects born very pre-term. More specifically, we find reduced cerebellar size to be associated with deficits in executive and visuospatial function (the block design and object assembly subtests of the WISC-R), and language (the Schonnel reading age, the similarities subtest of the WISC-R and the riddle interpretation, reading-decoding and reading-understanding subtests of the K-ABC). Our findings are therefore broadly consistent with the cerebellar cognitive-affective syndrome. However, there are some areas of discrepancy, e.g. Schmahman and Sherman (1998) reported deficits in the Boston naming test and the FAS verbal fluency test in their adult subjects with focal cerebellar lesions, whereas we find no association between these tests and cerebellar volume. The differing results may be a consequence of the different pathological processes at work in the two subject groups. In particular, the acute, focal, destructive lesions of the cerebellum described in relation to the cerebellar cognitive-affective syndrome are rather different from the more diffuse, chronic cerebellar pathology of the group of subjects born very pre-term.

The cognitive deficits associated with pre-term birth may therefore be related to dysfunction in several neural systems, which include the cerebellum. There are anatomical connections from the cerebellum, via the thalamus, to sensorimotor cortex, dorsolateral and dorsomedial prefrontal cortex, Broca's area and limbic and parahippocampal areas. Leiner *et al.* (1993) suggest that the function of the cerebellum

is to aid the performance of any area of the brain to which it has reciprocal connections. Subtle cerebellar abnormality causing a degree of cerebellar hypofunction could thus underlie the reduced performance of pre-term-born individuals in a number of different cognitive domains. It is also possible that basal ganglia abnormality may play a role in the motor and cognitive deficits of the individuals born very pre-term, given what is known about the function of these structures. The basal ganglia have not been assessed in this study and this may therefore also represent an avenue for further research.

A relationship between reduced cerebellar volume and cognitive performance is also reported in other conditions of developmental aetiology (Ciesielski *et al.*, 1997). In fragile X (chromosome) syndrome, the size of the posterior vermis predicts full-scale, verbal and performance IQ scores (Mostofsky *et al.*, 1998). In schizophrenia, the aetiology of which has been linked to obstetric problems (O'Callaghan *et al.*, 1992), abnormalities of the cerebellum have also been found to correlate negatively with measures of cognitive and language function (Martin and Albers, 1995; Levitt *et al.*, 1999; Nopoulos *et al.*, 1999).

In summary, we conclude that the smaller cerebellar volume of adolescents born very pre-term reflects a disruption of the normal development of this structure. We have not demonstrated a link between cerebellar volume and motor signs, possibly because of developmental compensation. We have, however, noted a relationship between cerebellar volume and performance on cognitive tests, including some tests of language function. This suggests that cerebellar pathology may, at least in part, underlie the cognitive impairments seen in those born very pre-term. In addition it provides further evidence in support of the general role of the cerebellum in cognition.

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