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Very preterm children at risk for developmental coordination disorder have brain alterations in motor areas

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Short Title: Brain alterations in very preterm children

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ABSTRACT

Aim

Brain alterations in very preterm children at risk for developmental coordination disorder were investigated.

Methods

Infants born very preterm with gestation age <30 weeks or birthweight <1,250g were recruited from Royal Women's Hospital Melbourne from 2001 to 2003. Volumetric imaging was performed at term equivalent age; at seven years volumetric imaging and diffusion tensor imaging were performed. At seven years, 53 of 162 children without cerebral palsy had scores $\leq 16^{\text{th}}$ percentile on the Movement Assessment Battery for Children-Second Edition and were considered at risk for developmental coordination disorder.

Results

At term equivalent age, smaller brain volumes were found for total brain tissue, cortical grey matter, cerebellum, caudate accumbens, pallidum and thalamus in children at risk for developmental coordination disorder ($p<0.05$); similar patterns were present at seven years. There was no evidence for catch-up brain growth in at risk children. At seven years, at risk children displayed altered microstructural organisation in many white matter tracts ($p<0.05$).

Conclusion

Infants born very preterm at risk for developmental coordination disorder displayed smaller brain volumes at term equivalent age and seven years, and altered white matter microstructure at seven years, particularly in motor areas. There was no catch-up growth from infancy to seven years.

KEYWORDS: Brain alterations, Brain growth, Developmental coordination disorder, Motor areas, Very preterm children

KEYNOTES

- Limited research has examined the neural mechanisms of developmental coordination disorder in very preterm children.
- Children born very preterm at risk for developmental coordination disorder displayed smaller brain volumes particularly in areas associated with motor function, and there was no catch up in brain growth from term equivalent age to seven years.
- Children born very preterm at risk for developmental coordination disorder evidenced altered white matter microstructure at seven years.

INTRODUCTION

Children born very preterm (VPT) are at increased risk of motor impairments (1) and a systematic review conducted in 2010 estimated that 41% of children born VPT without cerebral palsy have motor impairments consistent with developmental coordination disorder (DCD) (2). DCD is characterised by a significant impairment in motor coordination that interferes with activities of daily living and affects academic productivity, prevocational and vocational activities, and leisure and play (3).

Limited research has examined the neural mechanisms of DCD in the VPT population. However, studies have associated motor deficits with brain pathology and structural brain alterations detected by neonatal magnetic resonance imaging (MRI). For example, white matter injury on MRI has been associated with motor impairments in five-year-old children born VPT (4), and neonatal unmyelinated white matter volume has been associated with poorer motor outcomes at 24 months (5). To date, no longitudinal neuroimaging studies in children born VPT with DCD have been reported, so brain growth over time in this vulnerable group of children is unknown. The purpose of this study was to examine: 1) brain volumes at term equivalent age and seven years, 2) brain catch-up growth from term equivalent to seven years, and 3) white matter microstructural organisation at seven years in children born VPT at risk for DCD compared to children born VPT not at risk for DCD.

PARTICIPANTS AND METHODS

From July 2001 to December 2003, 227 children born VPT with gestational age (GA) <30 weeks (M=27.6, SD=1.8, Range=22-32) or birth weight <1,250 g (M=989.7, SD=219.4, Range=414-1425) were recruited at birth from the Royal Women's Hospital in Melbourne, Australia as part of the

Victorian Infant Brain Study cohort; two died and one was later excluded due to a congenital abnormality, leaving a sample of 224. A control group of 77 term and normal birth weight, ≥ 2500 g children was also recruited; however, they were not included as the present study focused on examining associations between risk for DCD and brain alterations in children born VPT. Brain MRI scans were completed at term equivalent age. This study included 162 children who were not diagnosed with cerebral palsy at two years of age and were assessed at seven years on the Movement Assessment Battery for Children-Second Edition. Assessors were blinded to perinatal, neonatal and MRI data. Children were identified as at risk for DCD based on their Total Test score on the Movement Assessment Battery for Children-Second Edition. Children born VPT who scored $\leq 16^{\text{th}}$ percentile on the standardised United Kingdom test norms were classified as at risk for DCD ($n = 53$), consistent with criteria used in previous structural imaging studies of children with DCD (6); 30 of these children scored $\leq 5^{\text{th}}$ percentile and 23 scored between the 6^{th} and the 16^{th} percentile. Children born VPT who scored $> 16^{\text{th}}$ percentile on the Movement Assessment Battery for Children-Second Edition were classified as non-DCD ($n = 109$). Intellectual functioning was assessed using the Wechsler Abbreviated Scale of Intelligence. The standardised US test norms on this measure were used to determine the children's full-scale IQ (FSIQ). Handedness was examined using the Briggs-Nebes modified version of Annett's Handedness Inventory. Scores ranged from -24 to +24 with scores of nine to 24 indicating right-handedness, scores of minus eight to eight indicating mixed-handedness and scores of -24 to minus nine indicating left-handedness. Of the 162 participants, 139 participated in a second brain MRI at seven years. Reasons for nonparticipation in the second MRI scan included contraindications to MRI, difficulty in coordinating a scan time during the assessment visit and children or caregivers not consenting to participate in the scan. Comparison of sample characteristics of those who participated and those who did not revealed no significant differences between groups, except for singleton birth. Children who did not participate in the MRI at seven years were more likely to be a multiple ($p = 0.03$).

The Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, Melbourne, Australia approved the study. Written informed consent was obtained from primary caregivers. Perinatal data were collected from chart review. Birthweight standard deviations scores were computed relative to British Growth Reference data (7).

Brain imaging acquisition

Infants were scanned between 38–42 weeks gestational age at the Royal Children's Hospital, Melbourne with a 1.5 Tesla General Electric MRI scanner without sedation. T_1 weighted (0.8–1.6 mm coronal slices; repetition time 35 ms; echo time 9 ms; flip angle 45° ; field of view $21 \times 15 \text{ cm}^2$; matrix 256×192) and T_2 proton density weighted magnetic resonance images (1.7–3.0 mm coronal slices; repetition time 4,000 ms; echo time 60/160 ms; flip angle 90° ; field of view $22 \times 16 \text{ cm}^2$;

matrix 256 x 192, interpolated 512 x 512) were acquired. At seven years, scans were acquired using a 3 Tesla Trio Siemens MRI scanner (Siemens AG, Germany). Prior to the scan at seven years, children participated in a mock MRI scanning session. Scans were conducted without sedation. A T₁ weighted structural imaging sequence (0.85 mm sagittal slices, flip angle 9°, repetition time 1,900 ms, echo time 2.27 ms, field of view 210 x 210 mm, matrix 256 x 256) and an echo planar diffusion sequence with 25 non-collinear gradient directions and b-values ranging up to 1,200 s/mm² (repetition time 12,000 ms; echo time 96 ms; matrix 144 x 144; field of view 250 x 250 mm; isotropic voxel size 1.7 mm³) were obtained.

Brain imaging analysis

Infant brain volumes for white matter, total brain tissue, intracranial volume, cortical grey matter, cerebrospinal fluid, cerebellum, brainstem, and amygdala were generated using an automatic segmentation method, Morphologically Adaptive Neonate Tissue Segmentation, based on the T₂-weighted images (8). This method has been previously validated against manual segmentations from two independent neonatal datasets (8). Basal ganglia, including the pallidum, putamen, and combined accumbens and caudate, and thalamus volumes were obtained from combined T₂-weighted and proton density-weighted images using the Pediatric Subcortical Segmentation Technique (9). A single operator manually traced the hippocampi on the combined raw T₂- and proton density weighted images. The cross-sectional area of the corpus callosum was manually traced on the mid-sagittal slice of the T₁ weighted image aligned to the anterior-posterior commissure.

At seven years, intracranial volume was obtained from the T₁ images using Functional MRI of the brain Software Library (FSL) brain extraction tool (Analysis Group, FMRIB, Oxford, UK) (10). Volumes for white matter, total brain tissue, cortical grey matter, cerebellum, and brainstem and were derived from the T₁-weighted images using FreeSurfer software (Laboratory for Computational Neuroimaging, Charleston, MA, USA) (11). Volume of the cerebrospinal fluid was calculated as the difference between the intracranial volume and total brain tissue volume. Basal ganglia and thalamus volumes were obtained from the T₁ images using the Pediatric Subcortical Segmentation Technique (12). A single operator manually traced hippocampi on the T₁ scan. Corpus callosum cross-sectional areas were manually traced on the mid-sagittal slice of the structural T₁ scan in alignment with the anterior-posterior commissures.

Diffusion images were motion and eddy current distortion corrected. The diffusion tensor model was fitted to generate fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) images using ExploreDTI (PROVIDI Lab, University Medical Centre Utrecht, The Netherlands) (13). Diffusion tensor images were analysed using tract-based

spatial statistics within FSL, following their pipeline recommended for studies with children (14). Each participant's FA image was non-linearly aligned to every other participant's FA image, to identify the most representative FA image. This image was affine-aligned to Montreal Neurological Institute standard space, and all FA images were brought into this space by combining the non-linear registration to the target with the affine registration to the Montreal Neurological Institute template. A mean FA image was created and thinned to generate the mean FA skeleton, FA threshold 0.2. All aligned FA images were projected onto the skeleton. The original non-linear FA registrations were applied to the AD, RD and MD images, which were projected onto the skeleton.

Statistical analysis

Statistical analyses were performed using SPSS Statistics Version 24 (IBM Corporation, Armonk, NY, USA) and Stata Version 14 (StataCorp, College Station, TX, USA). Sample characteristics were compared between the at risk for DCD and non-DCD groups using analysis of variance or chi-squared tests, as appropriate. Group differences in white matter, total brain tissue, thalamus, putamen, pallidum, hippocampus, corpus callosum, cortical grey matter, cerebellum, brainstem, amygdala, and accumbens and caudate at infancy and 7 years of age were assessed using linear regressions adjusting for sex, age at MRI, birthweight SD score and intracranial volume. These analyses were repeated excluding children with major neonatal brain injury including cystic periventricular leukomalacia ($n = 5$) and intraventricular haemorrhage grade 3 or 4 ($n = 4$), and FSIQ < 80 ($n = 12$). A FSIQ < 80 was chosen as a cut off as children who score below 80 are classified as borderline on the Wechsler Abbreviated Scale of Intelligence. Also, previous imaging studies of children with DCD have used FSIQ < 80 as an exclusion criterion (6). Linear regression was used to assess group differences in brain growth from term equivalent age to seven years. All models were fitted using generalised estimating equations with robust standard errors to allow for clustering of multiple births within a family. Significance was set at $p < 0.05$. Results uncorrected, and corrected for multiple comparisons using false discovery rate, are reported. As this was an exploratory study, interpretation was based on the pattern of findings, including the direction and magnitude of the differences, rather than specific p-values, consistent with modern statistical practice (15).

Group differences in FA, AD, RD, and MD at seven years were investigated, using voxel-wise, non-parametric, permutation-based statistical analysis with Randomise within FSL, the recommended method for statistical analysis of voxel-wise TBSS data (16). All analyses were performed with 5000 permutations, threshold-free cluster enhancement, and family-wise error rate correction; results are reported at $p < 0.05$. Results were localised to white matter tracts using the John Hopkins University white matter atlases within FSL. The primary analyses compared FA, AD,

RD and MD between the group at risk for DCD and the non-DCD group adjusting for age at MRI, sex and birthweight SD score. Analyses were repeated excluding children with major neonatal brain injury and FSIQ < 80.

RESULTS

Sample characteristics

Perinatal characteristics were generally similar between the at risk and non-DCD groups, except that the group at risk for DCD had a lower birthweight SD score (Table 1). Intracranial volume was reduced in the group at risk for DCD relative to the non-DCD group by 3.6% at term equivalent and 3.9% at seven years. At seven years, the group at risk for DCD had a lower FSIQ.

Brain Volumes at Term Equivalent Age

In general, the group at risk for DCD had smaller brain volumes compared with the non-DCD group, with evidence of group differences in white matter, total brain tissue, thalamus, putamen, hippocampus, cortical grey matter, cerebellum, and accumbens and caudate (Figure 1, Table 2). When children with major brain injury and FSIQ < 80 were excluded, the magnitude of the group differences attenuated and were no longer significant after correction for multiple comparisons. However, the general pattern of findings persisted (Figure 1, Table 3).

Brain volumes at seven years

The group at risk for DCD had smaller brain volumes at seven years. A similar pattern to that at term equivalent age was observed, with group differences being most marked for total brain tissue, thalamus, pallidum, cortical grey matter, cerebellum, and accumbens and caudate (Figure 2, Table 4). These group differences did not survive correction for multiple comparisons. Again, group differences attenuated after excluding children with major brain injury and FSIQ < 80 but the general pattern of findings persisted (Figure 2, Table 5).

Brain growth from term equivalent age to seven years

Of the 162 children included in the study, 135 had useable volumetric MRI data at term equivalent age and seven years; 40 in the group at risk for DCD and 95 in the non-DCD group. There was no evidence of catch-up brain growth in the children at risk for DCD between term and seven years. Results revealed that growth was poorer in the pallidum and accumbens and caudate in the children at risk for DCD, after adjusting for sex, corrected age at MRI, birth weight SD score, and intracranial volume (Figure 3, Table 7). These differences did not survive correction for multiple

comparisons. The differences in growth attenuated when children with major neonatal brain injury and FSIQ < 80 were excluded.

White matter microstructure differences at seven years

At seven years, 137 children had usable diffusion tensor imaging data; 39 in the group at risk for DCD and 98 in the non-DCD group. In numerous tracts, FA was lower and AD, RD and MD were higher in children at risk for DCD compared with children without DCD (Figure 4). Differences in FA, RD and MD were found in the: bilateral cerebral peduncle, corticospinal tract, anterior thalamic radiation, uncinate fasciculus, sagittal stratum, inferior and superior fronto-occipital fasciculus, inferior and superior longitudinal fasciculus, posterior thalamic radiation, external capsule, internal capsule, corpus callosum, cingulum, fornix stria terminalis, and corona radiata. Radial diffusivity and MD differences were also found in cerebellar and brainstem white matter tracts including the cerebellar peduncles, pontine crossing tract and medial lemniscus. Differences in AD were generally located in the same tracts as the FA, RD and MD differences, although AD differences were located in more peripheral white matter with fewer AD differences in more central white matter such as the corpus callosum and internal capsule. There were no regions that showed the opposite pattern, where FA was higher or AD, RD or MD lower in those at risk for DCD compared with children without DCD. Analyses excluding the children with major neonatal brain injury and FSIQ < 80 were similar; FA was significantly lower and AD, RD and MD were significantly higher in children at risk DCD compared with children without DCD, but these differences were less widespread throughout the white matter (Figure 5).

DISCUSSION

This study reports longitudinal total brain and regional volume changes from infancy to seven years in a well-characterised cohort of children born VPT who were identified at seven years of age as at risk or not at risk for DCD. At term equivalent age, brain volumes in children born VPT later identified as at risk differed from children born VPT identified as not at risk. Children at risk for DCD displayed smaller brain volumes in white matter, total brain tissue, thalamus, putamen, hippocampus, cortical grey matter, cerebellum and accumbens and caudate. Differences in brain volumes persisted at seven years of age. Importantly, longitudinal analyses revealed that brain growth in children at risk for DCD did not catch up to those without DCD; indeed subtle reductions in growth were observed in the pallidum and accumbens and caudate in the at risk group. This suggests that alterations in brain volumes in the participants born VPT at risk for DCD were present as early as term equivalent age and persisted throughout early childhood, with some evidence that the gap between the at risk and non-DCD groups was widening with increasing age in specific basal

ganglia structures. We also found that seven-year-old children born VPT at risk for DCD displayed altered white matter microstructural organisation, with lower FA and higher MD, RD and AD in numerous white matter tracts associated with motor functions including the corticospinal tracts, cerebellar tracts and corpus callosum (17).

Infant born VPT are vulnerable to a range of complications in utero and following birth that may alter the normal progression of brain development. Of note were our findings that the children at risk for DCD and those without DCD did not differ on any perinatal or neonatal factors with the exception of birth weight SD score. This suggests that the combination of being born VPT and being born small for gestational age may be associated with greater alterations in brain structure.

The smaller volumes of the cerebellum and basal ganglia structures in the children at risk for DCD are consistent with evidence that suggests that DCD could be due to delayed development of these brain structures (18). Behavioral studies of children with DCD in the general population have reported impairments in anticipatory postural activity, postural control, motor adaptation and timing (19), which are thought to reflect cerebellar dysfunction (20,21). Functions associated with the basal ganglia such as force control (22) and motor sequence learning (23), have also been found to be impaired in children with DCD. Our findings revealed that in general, the children at risk for DCD and non-DCD groups showed very similar volumetric increases from term to 7 years, with only subtle differences observed in specific basal ganglia structures, suggesting that in this area brain growth may have fallen further behind. To clarify whether or not children born VPT at risk for DCD catch up to children born VPT without DCD in brain growth in basal ganglia structures, longitudinal imaging studies with larger samples are needed.

The children born VPT at risk for DCD also displayed significantly lower FA and higher diffusivities in white matter tracts than children born VPT without DCD at 7 years of age. These diffusion tensor imaging measures suggested that the children at risk for DCD had altered overall microstructural organisation and coherency of brain white matter, which could reflect underlying cellular differences such as reduced myelination, reduced axon size or density, or less coherent organisation of axons (24,25). The microstructural differences were widespread, in keeping with previous research by our group and others, which showed that infants born VPT had diffuse white matter abnormalities from infancy into adulthood (26–28). Consistent with previous literature that has reported lower FA and higher diffusivities in the white matter of children born VPT who display motor problems (25,29,30), the widespread white matter changes in the children born VPT at risk for DCD appeared to have consequences for motor functioning. The importance of white matter to motor functioning is supported by research that has reported that qualitative abnormalities including white matter signal abnormality, loss of white matter, ventricular dilatation, and thinning of the corpus callosum, are predictive of early motor delay and cerebral palsy (4,26). As expected,

some of the many white matter tracts that differed in the children at risk for DCD included those previously identified to be associated with motor functioning, such as corticospinal tracts, cerebellar tracts and corpus callosum (30–32).

The findings from this study have important implications for children born VPT and their families. Children with DCD experience numerous functional difficulties associated with their motor problems including difficulty dressing, tying shoe laces, using utensils, writing, riding a bike, and playing team sports. Problems in academic achievement, cognitive functions, psychosocial functioning and physical health have also been associated with this disorder. Research identifying risk factors for DCD including MRI, perinatal risk factors and neurobehavioural assessments may help us in recognising children with DCD earlier and in initiating early interventions that could assist in ameliorating these developmental motor problems or assist parents and their children in developing strategies to cope with the functional limitations that they experience. Children born VPT with motor impairments had alterations in brain development as early as term equivalent age that were still evident at 7 years; therefore, early motor assessments throughout childhood may be very important to help identify children who are at risk for DCD early in their development.

Strengths of this study are that it included a large cohort of children born VPT who had an MRI at term and who were prospectively followed from birth to seven years. We also achieved high rates of follow up and assessors were blinded to perinatal and neonatal and MRI data. A limitation was that the sample size was fixed by the recruitment of the families for the original study. A limitation to our imaging analysis was that we were unable to use the same software to segment the neonatal and 7-year-old brain images, as specialised software is required for neonatal tissue classification (8). Neonatal MRI images typically exhibit lower signal to noise ratios, variable intensities within tissue classes, and differing between-tissue intensity contrasts compared with adults due to the incomplete myelination of the neonatal brain (33). In addition, neonatal scans tend to exhibit high variability in brain shape and pathology, particularly in the context of preterm birth, such as enlarged, distorted ventricles, and hyper- and hypo-intense regions are common (34). Another limitation relates to the known limitations of tract-based spatial statistics. Although the skeletonisation step utilised by this method mitigates some of the effects of misalignment between participants, removes the need for data smoothing, and reduces the dimensionality of the data, increasing statistical power, this step also introduces some difficulties in interpreting results (35). The skeletonisation introduces a spatial heterogeneity and orientational dependency of the statistical sensitivity, and has limited anatomical specificity. For example, in regions where multiple fibre structures converge, such as the interface of the superior parts of the corpus callosum and the corticospinal tracts, the skeleton cannot be defined unambiguously (35).

CONCLUSION

These findings are the first to show that children born VPT who are at risk of DCD at 7 years of age displayed smaller brain volumes at term equivalent age, particularly in brain areas associated with motor function. These smaller volumes persisted until 7 years of age and there appeared to be no catch-up growth between infancy and 7 years. Further, at 7 years of age, children born VPT at risk for DCD displayed altered white matter microstructural organisation compared with children born VPT who did not have DCD. Further research is required to examine this association later in development, ideally during adolescence. Future studies should examine whether early intervention reduces the prevalence of motor impairment in VPT populations and promotes development of cerebellar, basal ganglia and white matter tracts in children at risk for DCD.

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CONFLICT OF INTEREST

No competing financial interests exist for any of the authors. No other conflict of interest is declared by the authors.

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LIST OF ABBREVIATIONS

VPT very preterm

DCD developmental coordination disorder

FSIQ full-scale intelligence quotient

FSL Functional MRI of the brain Software Library

SD standard deviation

MRI, magnetic resonance imaging

FA fractional anisotropy

AD axial diffusivity

RD radial diffusivity

MD mean diffusivity

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TITLES AND LEGEND

Figure 1. Percentage mean differences (95% confidence intervals) in brain structures at term equivalent age between the at risk for developmental coordination disorder group (DCD) and non-DCD group.

* Analyses (solid line, dashed line) adjusted for sex, age at magnetic resonance imaging, intracranial volume and birth weight standard deviation score. In the secondary analysis (dashed line) children with significant brain injury and FSIQ <80 were excluded.

WM = white matter, CSF = cerebrospinal fluid, CGM = cortical grey matter, AccCau = accumbens caudate, CI = confidence interval, FSIQ = Full Scale IQ

Figure 2. Percentage mean differences (95% confidence intervals) in brain structures at 7-years of age compared between the at risk for developmental coordination disorder group (DCD) and non-DCD group.

* Analyses (solid line, dashed line) adjusted for sex, age at magnetic resonance imaging, intracranial volume (IVC) and birth weight standard deviation score. In the secondary analysis (dashed line) children with significant brain injury and FSIQ <80 were excluded.

WM = white matter, CSF = cerebrospinal fluid, CGM = cortical grey matter, AccCau = accumbens/caudate, CI = confidence interval, FSIQ = Full Scale IQ

Figure 3. Volumes for caudate pallidum and accumbens and caudate (AccCau) structures at term equivalent age and seven years for the at risk for developmental coordination disorder group (DCD) and non-DCD group.

* Analyses (solid line, dashed line) adjusted for sex, corrected age at MRI, birth weight standard deviation score, and intracranial volume differences. Secondary analyses excluding children with neonatal brain injury and with an FSIQ < 80 revealed similar patterns.

*FSIQ = Full Scale IQ

Figure 4. Comparison of diffusion tensor values between the at risk for developmental coordination disorder group (DCD) and non-DCD group.

* Analyses adjusted for age at scan, sex and birth weight standard deviation score. Regions in red-yellow had lower fractional anisotropy (FA), or higher axial (AD), radial (RD) or mean (MD) diffusivity in the at risk for developmental coordination disorder group (DCD) compared with non-DCD group. FWE= family-wise error rate; TFCE=threshold-free cluster enhancement.

Figure 5. Comparison of diffusion tensor values between the at risk for developmental coordination disorder group (DCD) compared with non-DCD group excluding children with major neonatal brain injury and FSIQ < 80.

*Adjusted for age at scan, sex and birth weight standard deviation score. Regions in red-yellow had lower fractional anisotropy (FA), or higher axial (AD), radial (RD) or mean (MD) diffusivity in the DCD group compared with non-DCD group. FSIQ = Full Scale IQ, FWE = family-wise error rate; TFCE = threshold-free cluster enhancement.

Table 1. Perinatal and seven-year characteristics of children born very preterm in the at risk for developmental coordination disorder (DCD) and non-DCD groups

	DCD n = 53	non-DCD n = 109	Mean Diff (95% CI), OR (95% CI)	P
Perinatal characteristics				
GA at birth (weeks) mean (SD)	27.5 (2.2)	27.6 (1.7)	-0.03 (-0.72, 0.66)	0.93
Birth weight (g) mean (SD)	955 (243)	1007 (206)	-52.73 (-124.24, 20.78)	0.16
Birth weight SD score ^a , mean (SD)	-.69 (1.03)	-.36 (0.85)	-0.32 (-0.65, -0.002)	0.05
GA at term scan (weeks), mean (SD)	40.5 (1.2)	40.6 (1.8)	-0.17 (-0.59, 0.25)	0.42
Intracranial volume (cc), mean (SD)	430.4 (65.0)	446.4 (63.08)	-16.01 (-37.11, 5.09)	0.14
Male, n (%)	32 (60)	53 (49)	1.61 (0.83, 3.14)	0.16
Singleton, n (%)	33 (62)	56 (51)	0.64 (0.33, 1.25)	0.19
Small for GA, n (%)	6 (11)	7 (6)	0.54 (0.17, 1.69)	0.28
Antenatal corticosteroids, n (%)	48 (91)	96 (88)	0.84 (0.28, 2.53)	0.76
Postnatal corticosteroids, n (%)	3 (6)	7 (6)	1.14 (0.28, 4.61)	0.85
Sepsis, n (%)	17 (32)	33 (30)	0.92 (0.45, 1.86)	0.82
Necrotising enterocolitis, n (%)				
- no	47 (89)	98 (90)	0.54 (0.54, 0.56)	0.55
- proven	4 (8)	4 (4)		

- suspected	2 (4)	7 (6)		
Bronchopulmonary dysplasia (oxygen at 36 days), n (%)	19 (36)	33 (30)	0.78 (0.39, 3.56)	0.48
Intraventricular haemorrhage grade III or IV, n (%)	2 (4)	2 (2)	0.48 (0.07, 3.48)	0.46
Cystic periventricular leukomalacia, n (%)	1 (2)	4 (4)	1.98 (0.22, 18.17)	0.54
Seven-year characteristics	n = 40	n = 95		
Age at scan* (years), mean (SD)	7.5 (0.3)	7.5 (0.2)	-0.002 (-0.11, 0.10)	0.98
Intracranial volume (cc), mean (SD)	1366.7 (112.4)	1422.4 (115.8)	-55.68 (-96.96, -14.41)	0.01
Intelligence ^b , mean (SD)	92.1 (12.7)	100.8 (12.7)	-8.75 (-13.09, -4.40)	< 0.001
Intelligence ^b < 80 , n (%)	3 (7.5)	3 (3.2)	0.40 (0.08, 2.08)	0.26
Handedness ^c , (n = 135) (%)				
Right	25 (76)	63 (71)	0.21 (-0.01, -0.22)	0.21
Left	3 (9)	16 (18)		
Mixed	5 (15)	10 (11)		

*corrected for prematurity

GA = gestational age, SD = standard deviation, cc = cubic centimetres; OR= odds ratio; CI= confidence interval.

^a Computed relative to the British Growth Reference data.

^b Wechsler Abbreviated Scale of Intelligence Full Scale IQ

^c Briggs-Nebes modified version of Annett's handedness Inventory

Table 2: Comparison of brain volumes (cm³) and corpus callosum area (cm²) at term equivalent age between the at risk for developmental coordination disorder group (DCD) and non-DCD group

	DCD M (SD) N = 52	non-DCD M (SD) N = 108	Mean Difference (95% CI)	P values	*Benjamin -Hochberg P values
White matter	142.7 (19.5)	150.5 (19.1)	-7.8 (-14.1, -1.5)	0.02	0.04
Total brain tissue	349.3 (51.3)	369.8 (50.0)	-20.6 (-37.2, -4.0)	0.02	0.04
Thalamus	6.71 (0.84)	7.20 (0.93)	-0.48(-0.77, -0.20)	0.001	0.01
Putamen	3.11 (0.42)	3.27 (0.48)	-0.16 (-0.30, -0.02)	0.03	0.049
Pallidum	1.18 (0.15)	1.22 (0.15)	-0.05 (-0.09, 0.002)	0.06	0.09
Hippocampus	2.17 (0.31)	2.30 (0.34)	-.13 (-0.24, -0.02)	0.02	0.04
Cerebrospinal fluid	81.1 (27.8)	75.7 (25.0)	5.4 (-3.5, 14.3)	0.23	0.25
Corpus Callosum	96.0 (23.4)	97.6 (31.1)	-1.6 (-10.7, 7.5)	0.073	0.73
Cortical grey matter	149.7 (26.5)	159.0 (24.7)	-9.3 (-17.8, -0.9)	0.03	0.049
Cerebellum	23.8 (3.5)	25.6 (3.8)	-1.7 (-2.9, -0.5)	0.004	0.02
Brainstem	5.57 (0.58)	5.71(0.73)	-0.15 (-0.36, 0.07)	0.18	0.21
Amygdala	1.29 (0.19)	1.34 (0.21)	-0.05 (-0.12, 0.01)	0.10	0.13

Accumbens caudate	2.56 (0.43)	2.78 (0.41)	-0.21 (-0.35, -0.08)	0.003	0.02
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* False discovery rate correction for multiple comparisons

cm³ = cubic centimetres, cm² = squared centimetres, M = mean, SD = standard deviation, CI = confidence interval

Results have been adjusted for sex, age at MRI, birth weight standard deviation score and intracranial volume

Table 3: Comparison of brain volumes (cm³) and corpus callosum area (cm²) at term equivalent age between the at risk for developmental coordination disorder group (DCD) and non-DCD group with participants with brain injury and FSIQ <80 removed

	DCD M (SD) N = 43	non-DCD M (SD) N = 98	Mean Difference (95% CI)	P values	*Benjamin -Hochberg P values
White matter	143.0 (19.8)	150.3 (19.1)	-7.3 (-14.2, -0.4)	0.04	0.13
Total brain tissue	351.6 (52.9)	369.3 (50.1)	-17.7 (-36.2, 0.8)	0.06	0.16
Thalamus	6.81 (0.85)	7.22 (0.89)	-0.41 (-0.70, -0.10)	0.01	0.13
Putamen	3.16 (0.39)	3.28 (0.49)	-0.11 (-0.27, 0.04)	0.15	0.22
Pallidum	1.18 (0.13)	1.22 (0.20)	-0.04 (-0.09, 0.01)	0.15	0.22
Hippocampus	2.19 (0.33)	2.29 (0.30)	-0.11 (-0.22, 0.01)	0.08	0.17
Cerebral spinal fluid	81.5 (28.4)	75.9 (25.4)	5.6 (-4.3, 15.5)	0.27	0.35
Corpus callosum	95.7 (21.4)	97.6 (32.1)	-1.8 (-11.6, 7.9)	0.71	0.71
Cortical grey matter	151.0 (27.4)	158.7 (25.0)	-7.7 (-17.2, 1.8)	0.11	0.20
Cerebellum	24.2 (3.5)	25.6 (3.8)	-1.4 (-2.7, -0.2)	0.03	0.13
Brainstem	5.60 (0.59)	5.70 (0.79)	-0.09 (-0.31, 0.13)	0.41	0.44

Amygdala	1.30 (0.20)	1.34 (0.20)	-0.04 (-0.11, 0.04)	0.35	0.41
Accumbens caudate	2.62 (0.39)	2.77 (0.39)	-0.15 (-0.29, -0.004)	0.04	0.13

* False discovery rate correction for multiple comparisons

FSIQ =Full Scale IQ, cm³ = cubic centimetres, cm² = squared centimetres, M = mean, SD = standard deviation, CI = confidence interval

Results have been adjusted for sex, age at MRI, birth weight standard deviation score and intracranial volume

Table 4. Comparison of brain volumes (cm³) and corpus callosum area (cm²) at 7 years between the at risk for developmental coordination disorder group (DCD) and non-DCD group

	DCD M (SD) N = 35	non-DCD M (SD) N = 90	Mean Difference (95% CI)	P values	*Benjamin- Hochberg P values
White matter	396.8 (47.1)	410.0 (46.7)	-13.2 (-33.7, 7.2)	0.21	0.34
Total brain tissue	1239.7 (110.3)	1285.6 (116.5)	-45.9 (-94.5, 2.7)	0.06	0.11
Thalamus	14.0 (1.3)	14.6 (1.1)	-0.6 (-1.0, -0.1)	0.03	0.09
Hippocampus	6.62 (0.77)	6.48 (0.74)	0.14 (-0.17, 0.45)	0.38	0.49
Putamen	10.83 (1.07)	10.96 (1.14)	-0.13 (-0.54, 0.28)	0.54	0.54
Pallidum	3.15 (0.36)	3.31 (0.28)	-0.16 (-0.30, -0.03)	0.02	0.10
Cerebral spinal fluid	141.2 (21.0)	127.1 (30.4)	14.1 (3.8, 24.4)	0.007	0.08
Corpus callosum	334.3 (82.8)	345.7 (76.5)	-11.4 (-42.8, 20.0)	0.48	0.52
Cortical grey matter	558.1 (46.5)	579.9 (56.2)	-21.8 (-43.1, -0.5)	0.045	0.10

Cerebellum	143.9 (15.9)	151.5 (13.3)	-7.6 (-14.2, -0.9)	0.03	0.10
Brainstem	16.4 (2.2)	16.8 (1.7)	-0.4 (-1.3, 0.5)	0.42	0.50
Amygdala	3.12 (0.36)	3.20 (0.36)	-0.08 (-0.24, 0.08)	0.31	0.45
Accumbens caudate	8.31 (1.12)	8.80 (1.33)	-0.50 (-0.96, -0.03)	0.04	0.10

* False discovery rate correction for multiple comparisons

cm³ = cubic centimetres, cm² = squared centimetres, M = mean, SD = standard deviation, CI = confidence interval

Results have been adjusted for sex, corrected age at 7-year MRI, birth weight standard deviation score and intracranial volume

Table 5. Comparison of brain volumes (cm³) and corpus callosum area (cm²) at 7 years between the at risk for developmental coordination disorder group (DCD) and non-DCD group with participants with brain injury and FSIQ <80 removed

	DCD M (SD) N = 41	non-DCD M (SD) N = 98	Mean Difference (95% CI)	P Values	*Benjamin- Hochberg P values
White matter	394.9 (46.4)	411.4 (47.8)	-16.4 (-36.8, 4.0)	0.11	0.20
Total brain tissue	1231.1 (119.4)	1287.0 (118.5)	-55.9 (-105.1, -6.6)	0.03	0.08
Thalamus	13.9 (1.7)	14.6 (1.2)	-0.7 (-1.2, -0.1)	0.02	0.07
Putamen	10.7 (1.2)	11.0 (1.1)	-0.3 (-0.7, 0.1)	0.16	0.26

Pallidum	3.11 (0.38)	3.33 (0.30)	-0.22 (-0.35, -0.09)	0.001	0.01
Hippocampus	6.60 (0.77)	6.50 (0.68)	0.10 (-0.19, 0.38)	0.51	0.51
Cerebral spinal fluid	136.8 (30.0)	128.4 (31.9)	8.4 (-3.9, 20.7)	0.18	0.26
Corpus callosum	328.5 (82.4)	347.5 (79.8)	-19.0 (-48.6, 10.5)	0.21	0.27
Cortical grey matter	553.3 (50.0)	580.6 (56.7)	-27.4 (-48.7, -6.0)	0.01	0.04
Cerebellum	143.7 (18.0)	151.1 (13.1)	-7.4 (-14.4, -0.5)	0.04	0.09
Brainstem	16.3 (2.3)	16.8 (1.8)	-0.5(-1.4, 0.4)	0.29	0.31
Amygdala	3.11 (0.38)	3.20 (0.38)	-0.09 (-0.25, 0.07)	0.25	0.30
Accumbens caudate	8.21 (1.09)	8.85 (1.37)	-0.64 (-1.08, -0.21)	0.004	0.03

* False discovery rate correction for multiple comparisons

FSIQ =Full Scale IQ, cm³ = cubic centimetres, cm² = squared centimetres, M = mean, SD = standard deviation, CI = confidence interval

Results have been adjusted for sex, corrected age at 7-year MRI, birth weight standard deviation score and intracranial volume

Table 6. Differences in slopes from term to 7 years for brain volumes (cm³) and corpus callosum area (cm²) compared between infants born very preterm with and without developmental coordination disorder (DCD)

	Differences in slopes (adjusted) ^a				Differences in slopes; participants with brain injury and FSIQ <80 removed (adjusted) ^b			
	B	95% CI	P	*Benjamin-Hochberg P values	B	95% CI	P	*Benjamin-Hochberg P values

White matter	-8.22	-10.30, 26.74	0.38	0.61	-5.05	-12.62, 22.73	0.58	0.75
Total tissue	-33.5	-10.6, 77.6	0.14	0.39	-25.9	-16.0, 67.7	0.23	0.56
Thalamus	-0.15	-0.37, 0.67	0.58	0.69	-0.05	-0.41, 0.51	0.84	0.84
Putamen	-0.09	-0.28, 0.45	0.64	0.69	0.04	-0.37, 0.30	0.83	0.84
Pallidum	-0.15	0.04, 0.26	0.01	0.13	-0.09	-0.02, 0.20	0.09	0.49
Hippocampus	0.17	-0.42, 0.08	0.18	0.39	0.20	-0.47, 0.07	0.15	0.49
Corpus callosum	-12.7	-17.1, 42.6	0.40	0.61	-4.9	-27.0, 36.8	0.76	0.84
Cerebral Spinal Fluid	2.47	-15.39, 10.45	0.71	0.71	7.17	-19.54, 5.19	0.26	0.56
Cortical Grey Matter	-13.9	-5.5, 33.3	0.16	0.39	-9.8	-9.3, 29.0	0.31	0.57
Cerebellum	-5.62	-1.16, 12.40	0.10	0.39	-5.91	-0.40, 12.21	0.07	0.49
Brainstem	-0.36	-0.51, 1.23	0.42	0.81	-0.28	-.057, 1.13	0.52	0.75
Amygdala	-0.04	-0.11, 0.19	0.61	0.69	-0.05	-0.11, 0.20	0.54	0.75
Accumbens caudate	-0.39	0.04, 0.73	0.03	0.20	-0.28	-0.10, 0.66	0.14	0.49

B = regression coefficient, CI = confidence interval, cm^3 = cubic centimetres, cm^2 = squared centimetres, CI = confidence interval

^a Results adjusted for sex, corrected age at MRI, birth weight standard deviation score and intracranial volume; DCD N = 40 , non-DCD N = 95

^b Results adjusted for sex, corrected age at MRI, birth weight standard deviation score and intracranial volume; children with brain injury and FSIQ <80 removed from sample; DCD N = 34; non-DCD N = 87

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