The motor profile of preterm infants at 11 y of age

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BACKGROUND: Preterm infants are at a higher risk for poor motor outcome than term infants. This study aimed to describe the long-term motor profile in very preterm born children.

METHODS: A total of 98 very preterm infants were included. Volumetric brain magnetic resonance imaging (MRI) was performed at term age, and the Movement Assessment Battery for Children—Second Edition (The Movement ABC-2) was employed at 11 y of age. The diagnosis of Developmental Coordination Disorder (DCD) was determined at 11 y of age according to the International Classification of Diseases.

RESULTS: Eighty-two of 98 (84%) very preterm infants had normal motor development at 11 y of age. In these children, the mean percentile for the total test score in the Movement ABC-2 examinations was 42 (SD 20). Eight (8%) children had DCD. The mean percentile in these children was 4 (SD 2). Eight (8%) children had CP. Their mean percentile was 6 (SD 14). Decreased volumes in all brain regions associated with lower Movement ABC-2 total scores.

CONCLUSION: The majority of the very preterm infants had normal motor development at 11 y of age. Volumetric brain MRI at term age provides a potential tool to identify risk groups for later neuromotor impairment.

Preterm infants are at a higher risk for poor motor outcome than term infants (1–5). While the incidence of CP has slightly decreased due to vast advances in perinatal and neonatal care over the past decades (6), the rate of milder motor problems is reported to be significantly high in prematurely born children (7). Furthermore, these problems seem to continue when entering adulthood (8). The Developmental Coordination Disorder (DCD) is defined as a motor impairment that appears in the absence of any obvious neurological and structural abnormality or intellectual disability that would interfere with activities of daily living or academic performance (9). The prevalence of DCD in school-aged children is 5–6%, the reported prevalence being higher in children born at very low birth weight or very preterm, from 9.5 to 51% (4,7,9,10).

The Movement Assessment Battery for Children is the most commonly used and best validated tool for detecting DCD (9), also in a high-risk population of very preterm infants (11). The structural validity of its revised version (The Movement Assessment Battery for Children—Second Edition, The Movement ABC-2) has recently been established (12). The Developmental Coordination Disorder Questionnaire 2007 (DCDQ'07) is a parent report developed to assist in the identification of DCD. The sensitivity and the specificity of this revised questionnaire are 89 and 76%, respectively, in the age group of 10–15 y (13).

Even though the predictive value of magnetic resonance imaging (MRI) for short-term outcome is established (14), there is little data on the predictive value of MRI on long-term outcome. The existing data suggest that motor impairment in children with perinatal adversities is especially related to white matter abnormalities MRI (15). We have previously shown the predictive value of structural brain MRI at term age for neurosensory, cognitive and neurological outcome in very preterm born children at 2, 5, and 11 y of age (16–18). A recent study did not find correlations between brain volumes at term age and the Movement ABC-2 scores at age 5.5 y (19). We have recently published the associations between brain volumes at term age and neurological performance at 11 y of age in very preterm born children (18).

The objective of this study was to describe the long-term motor profile of very preterm infants at 11 y of age. The motor assessment was completed by using the Movement ABC-2 to identify children with movement difficulties. An additional aim was to study the associations between volumetric neonatal brain MRI and long-term motor outcome in very preterm infants.

RESULTS

The neonatal characteristics of the 98 very preterm infants are shown in **Table 1**. Of all infants, 96 (98%) were examined by brain MRI at term age. The mean age at the time of MRI examination was $40^{0/7}$ (SD 2.6 d, (minimum $39^{1/7}$, maximum $41^{3/7}$)). All the children without CP (n = 90) were examined using the Movement ABC-2 at 11 y of age, and all their parents were interviewed according to the DCDQ'07. Seven (88%) of the eight children with CP could be examined. The mean age at the time of examination was 11 y and 2 mo (SD 4 mo, (10 y and 6 mo, 11 y and 9 mo)). All the neonatal characteristics (**Table 1**) of the study infants and drop-outs (n = 23) (**Figure 1**) were

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Table 1. Neonatal characteristics of the very preterm infants ($n = 98$)

Characteristics	Children with normal motor outcome ($n = 82$)	Children with DCD ($n = 8$)	Children with CP ($n = 8$)
Birth weight, mean (SD) (minimum, maximum), grams	1,087 (258) (580, 1,500)	792 (338) (400, 1,490)	1,031 (306) (560, 1,500)
Gestational age at birth, mean (SD) (minimum, maximum), weeks	29 0/7 (2 5/7) (24 0/7, 35 6/7)	26 3/7 (2 1/7) (23 0/7, 30 1/7)	28 0/7 (3 1/7) (25 5/7, 35 1/7)
Males, *n* (%)	34 (41)	8 (100)	5 (63)
Cesarean section, *n* (%)	48 (59)	4 (50)	5 (63)
Small for gestational age, *n* (%)	32 (39)	3 (38)	2 (25)
Bronchopulmonary dysplasia, *n* (%)	9 (11)	3 (38)	3 (38)
Sepsis, *n* (%)	17 (21)	3 (38)	3 (38)
Necrotizing enterocolitis, surgical, *n* (%)	1 (1)	1 (13)	2 (25)
Retinopathy of prematurity, laser treated, *n* (%)	1 (1)	1 (13)	0 (0)
Structural brain MRI findings at term age (data missing for two infants)			
Normal findings	52 (65)	3 (38)	1 (13)
Minor pathologies	18 (23)	2 (25)	0 (0)
Major pathologies	10 (13)	3 (38)	7 (88)

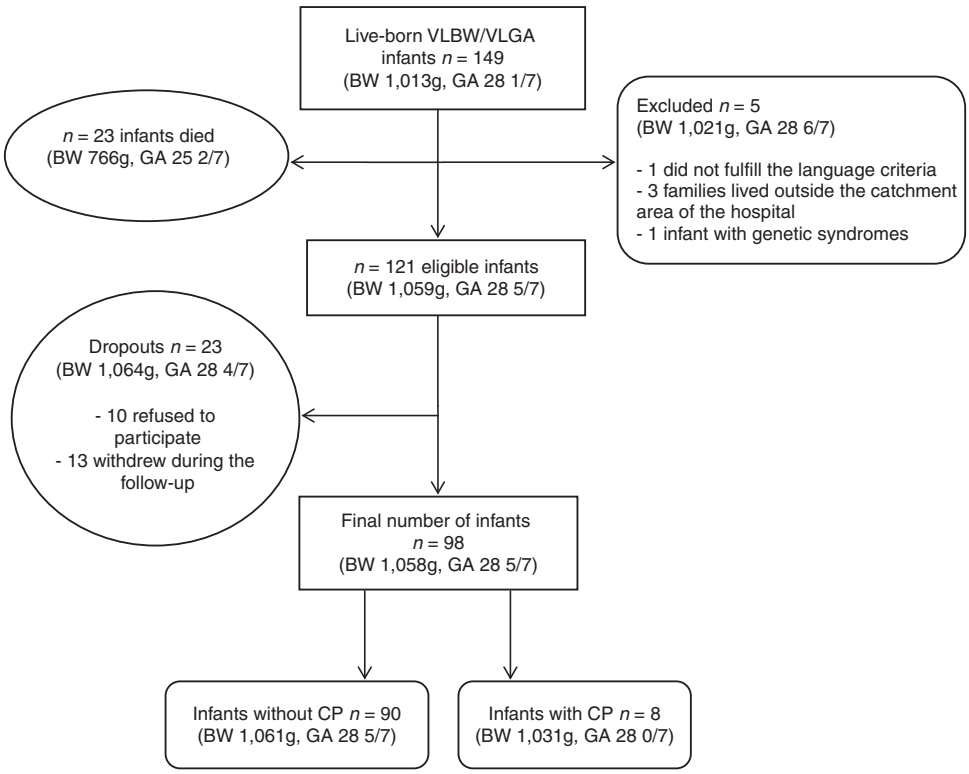

Figure 1. The flow chart of the participants, mean birth weights and gestational ages in weeks.

compared. The only statistically significant finding was that children lost to follow-up were more often born by cesarean section than the study children ($P = 0.01$).

The number of children with normal motor outcome was 82 (84%). Of these children, 79 (96%) had a total test score >67 (>15th percentile), and 3 (4%) had a total test score of 57–67 (>5th-15th percentile) in the Movement ABC-2. The mean total score of the parental questionnaire DCDQ'07 for these children was 67 (SD 7, (46, 75)), and 7 (9%) children had a total score ≤57 indicating risk for DCD. Fifty-two (63%) of the children with normal motor outcome participated regularly in after-school sporting activities. Eight (8%) children had scores ≤56 (≤5th percentile) in the Movement ABC-2 and were diagnosed with DCD. The mean total score of the DCDQ'07 for these children was 52 (SD 14, (35, 74)), and 4 (50%) had a total score ≤57, indicating risk for DCD. Two (25%) of the children

with DCD participated regularly in after-school sporting activities. There were eight (8%) children with CP. The mean total score of the DCDQ'07 for these children was 49 (SD 10, (37, 68)), and 6 (86%) had a total score ≤57. One (14%) of the children with CP participated regularly in after-school sporting activities. The mean values of the three domains and the total test score of the Movement ABC-2 in all children are shown in **Table 2**. The distribution of the total test scores in children with and without CP is shown in **Figure 2**.

Brain MRI explained 17.8% of the variation in the Movement ABC-2 total scores ($P < 0.001$) in all children and 7.8% in children without CP ($P = 0.03$). Major brain pathologies on MRI reduced the Movement ABC-2 total scores compared to normal findings ($b = -3.5$ for minor pathologies and $b = -25.2$ for major pathologies in all children, and $b = -3.6$ for minor pathologies and $b = -17.9$ for major pathologies in children without CP). The negative predictive value of normal findings or minor pathologies in brain MRI and positive predictive value of major pathologies for DCD was 93.3 and 23.1%. The negative predictive value and positive predictive value of brain MRI for CP was 98.7 and 35.0%. Decreasing volumes in all brain regions associated with lower Movement ABC-2 total scores as shown in **Table 3**. All the associations remained statistically significant when excluding the children with CP. The mean values of brain volumes at term age in very preterm born children with normal motor outcome, DCD, and CP are shown in **Table 4**.

Of the other background characteristics shown in **Table 1**, gestational age ($r = 0.26$, $P = 0.01$), birth weight ($r = 0.25$, $P = 0.01$), and bronchopulmonary dysplasia ($R^2 = 0.07$, $P = 0.009$) were significantly associated with the Movement ABC-2 total scores. The DCDQ'07 total scores correlated with the Movement ABC-2 total scores ($r = 0.43$, $P < 0.001$).

Table 2. The mean values (SD, median, and interquartile range) of the three domains and the total test score of the Movement ABC-2 in percentiles in very preterm born children with normal motor outcome ($n = 82$), DCD ($n = 8$), CP ($n = 8$), and all children ($n = 97$)

Domain	Mean	SD	Median	Interquartile range
Manual dexterity				
Children with normal motor outcome	41	22	37	25–50
Children with DCD	11	16	7	1–13
Children with CP*	13	15	5	0–25
All children*	36	23	37	16–50
Aiming and catching				
Children with normal motor outcome	36	26	37	16–50
Children with DCD	10	10	5	2–21
Children with CP*	3	3	2	1–5
All children*	32	26	25	9–50
Balance				
Children with normal motor outcome	59	27	50	37–91
Children with DCD	11	12	9	4–13
Children with CP*	13	34	0	0–1
All children*	52	32	50	25–91
Total test score				
Children with normal motor outcome	42	20	37	25–63
Children with DCD	4	2	5	4–5
Children with CP*	6	14	1	0–2
All children*	36	23	37	16–50

*Data missing for one child.
CP, cerebral palsy; DCD, developmental coordination disorder.

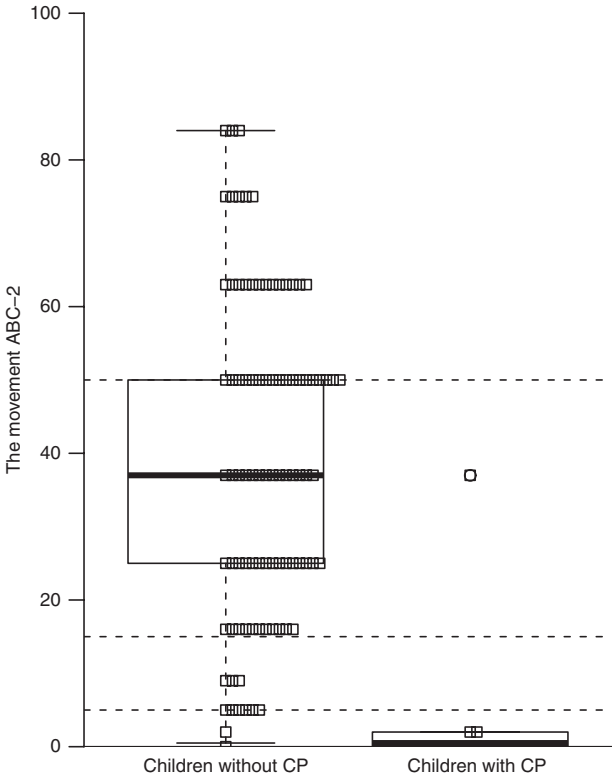

Figure 2. Combined dotplot and boxplot of the percentiles for the total test scores of the Movement ABC-2 examinations in very preterm born children with CP ($n = 8$) and without CP ($n = 90$). Horizontal dashed lines of the percentiles 5, 15, and 50 show the cut-offs of significant movement difficulty, risk of having a movement difficulty, and the mean of the norm population, respectively.

Table 3. The associations between brain volumetric findings at term age and the Movement ABC-2 total scores in very preterm born children at 11 y of age

	The Movement ABC-2 *b* (95% CI)	*P*
Total brain tissue	0.20 (0.10–0.30)	<0.001
Ventricles	−0.23 (−6.80–6.33)	0.94
Cerebrum	0.20 (0.10–0.30)	<0.001
Frontal lobes	0.32 (0.12–0.51)	0.002
Basal ganglia and thalami	1.65 (0.85–2.45)	<0.001
Cerebellum	1.16 (0.21–2.11)	0.02
Brain stem	2.13 (0.53–3.73)	0.01

The analysis was adjusted for gestational age, small for gestational age status, gender, and MRI categories.

Table 4. The mean values (SD) of brain volumes (ml) at term age in very preterm born children with normal motor outcome ($n = 82$), DCD ($n = 8$), and CP ($n = 8$) at 11 y of age

	Normal motor outcome	DCD	CP
Total brain tissue	399.2 (44.7)	374.3 (62.7)	359.1 (36.8)
Ventricles	16.1 (9.2)	14.4 (10.4)	44.1 (48.4)
Cerebrum	366.0 (43.0)	346.8 (58.4)	330.5 (33.4)
Frontal lobes	136.9 (22.2)	125.5 (17.0)	113.9 (19.2)
Basal ganglia and thalami	26.7 (5.2)	23.5 (4.0)	22.4 (3.4)
Cerebellum	25.4 (4.6)	21.1 (7.0)	21.4 (2.8)
Brain stem	7.7 (2.9)	6.4 (2.2)	7.2 (2.7)

CP, cerebral palsy; DCD, developmental coordination disorder.

DISCUSSION

This prospective follow-up study of a regional cohort of very preterm infants showed that the majority of children performed within the lower range of normal variation considering motor outcome at 11 y of age. Decreasing regional brain volumes at term age associated with poorer motor outcome even when excluding children with CP.

The skills to aim and catch a tennis ball were the most commonly impaired in very preterm born children. Interestingly, others have found the most prominent problems to be in balance skills (2), whereas the present study found also manual dexterity skills to be impaired more often than balance skills. This difference may partly be explained by the use of a previous version of the Movement ABC examination and the inclusion of only extremely low-birth-weight or very preterm infants. In addition, it would be interesting to know the regional brain volumes in different populations of very preterm infants. Different care practices may have different effects especially on the vulnerability of the basal ganglia and cerebellum, which modify the profile/quality of movement in motor performance. Another difference compared to previous literature was that no effect of gender or small for gestational age status on the motor performance was found (4,9,10). This is consistent with our previous results of similar outcomes in small for gestational age infants (20–22).

The neonatal characteristics that associated with poorer motor outcome were gestational age, birthweight, and bronchopulmonary dysplasia. A previous study of perinatal and neonatal predictors for DCD in very low birthweight children has shown that male sex, lower gestational age, lower birthweight, postnatal steroid exposure, longer duration of ventilation, more days of oxygen, retinopathy of prematurity, and hyponatremia were associated with poorer motor outcome. Of these variables, only male sex, low birthweight and postnatal steroid exposure remained significant with the addition of neonatal factors (10).

Interestingly, children with DCD seemed to have even lower gestational age and lower birthweight than children with CP in this study. Also the structural brain MRI findings differentiated the children with DCD and the children with CP. The majority of children with CP had major pathologies, whereas of the children with DCD, fewer had major pathologies compared to children with CP. According to volumetric findings, children with CP had significantly larger ventricles than children with DCD. Even though all children with DCD in the present study were boys, the small number of children with DCD and CP did not enable reliable statistical analysis.

We found increased prevalence of DCD in children born preterm as shown earlier. However, our prevalence was lower compared to previous studies (4,7,9,10). The possible reasons for these differences include different patient populations with different inclusion and exclusion criteria, and different age point at testing, as the present study is unique in having such a long follow-up time. There are also studies using different cut-off levels in the Movement ABC examination, and studies using the DCDQ as the only diagnostic instrument, which is in disagreement with the latest diagnostic recommendations (9).

It is noteworthy that more than half of the very preterm infants with normal motor development participated regularly in organized after-school sports, which might potentially have supported normal motor development. Having regular after-school sporting activities indicates sufficient motor outcome for participating in peer-group physical activities and, potentially, supports not only motor but also social development. It is also known that sporting activities are associated with higher quality of life (23). As for the children with DCD, only a quarter of them had after-school sport activities, which is in agreement with a previous study showing that fewer children with motor impairment participate in organized sporting activities outside school compared to children with normal motor development (24).

The present study showed that decreased volumes in all brain regions at term age associated with poorer Movement ABC-2 total scores at 11 y of age. In contrast to our results, a recent study with shorter follow-up time of 5.5 y found no correlations between automatically segmented brain volumes at term age and motor outcome in very preterm born children (19). The difference might be explained by the fact that our study included more major brain pathologies and also more children with CP. Our study also had higher follow-up rate. It is possible that motor problems manifest more clearly with increasing age. In addition, the brain volumes were measured manually in our study. We have previously shown an association between reduced volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum and poor neurological outcome at the age of 11 y (18). The present study strengthens these previous results suggesting that brain volumes are potentially valuable in finding the risk groups for later neuromotor impairment. However, clear cut-off values would require large normative samples.

A possible technical limitation is the MRI equipment of the study period. More advanced and accurate imaging techniques are plausible to improve the prediction of abnormal outcome. In addition, T2-weighted images were obtained, but they were not used for the volume measurements, since there was a gap in the T2-weighted images between slices. Accordingly, the

continuous T1-weighted images were used. Although the slice thickness was rather thick (5 mm) on T1-weighted images, this, however, allowed sufficient signal to noise ratio for interpretation. It is possible that partial volume effect may have caused some error on the volume measurements; however, the error would be similar in all infants. Another limitation is the lack of a control group.

The strengths of this study included a high coverage of the examinations at term age and at 11 y of age. Furthermore, the latest versions of the Movement ABC and the DCDQ were used. The results of the DCDQ'07 were only used to support the results of the MABC-2 as the DCDQ'07 is not designed to be used alone to identify DCD. Instead, the diagnosis also requires valid clinical measures (13). The presence of DCD was defined according to International Classification of Diseases (ICD)-10), which is used in many countries. These criteria are also comparable with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

This study, showing normal motor outcome in the majority of very preterm infants, supports recent research on the improving outcome of preterm infants. Brain growth seems to play a pivotal role, since smaller regional brain volumes predict a poorer motor outcome.

METHODS

This study is part of the multidisciplinary PIPARI Study (The Development and Functioning of Very-Low-Birth-Weight Infants from Infancy to School Age), a prospective study of very low birth weight or very low gestational age infants born to Finnish- or Swedish-speaking families between 2001 and 2006, at Turku University Hospital, Finland. The inclusion criteria was a birth weight ≤1,500 g in preterm infants born <37 gestational weeks, from 2001 to the end of 2003. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 wk, regardless of birth weight. Only the infants born between January 2001 and April 2004 were included in this study because the MRI equipment was upgraded thereafter. The flow chart of the participants is shown in **Figure 1**. Written informed consent was obtained from all children and parents for the follow-up study. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of South-West Finland in December 2000 and in January 2012.

Magnetic Resonance Imaging of the Brain

The brain MRI was performed at term age. One neuroradiologist (R.P.) analyzed the images and manually performed volume measurements blinded to the clinical information of the infant. Axial T2-weighted images, coronal three-dimensional T1-weighted images and coronal T2-weighted images of the entire brain were obtained using the MRI equipment of an open 0.23 Tesla Outlook GP (Philips Medical, Vantaa, Finland) equipped with a multipurpose flexible coil fitting the head of the infant. All of the sequences were optimized for the imaging of a term infant brain. To evaluate the relationship between the brain pathology and the motor outcome, the infants were categorized into three groups based on the structural MRI findings: (i) Normal findings consisted of normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum, and posterior fossa structures), width of extracerebral space <5 mm, ventricular/brain (V/B) ratio <0.35, (ii) Minor pathologies consisted of consequences of intraventricular hemorrhages grade 1 and 2, caudothalamic cysts, width of the extracerebral space of 5 mm and V/B ratio of 0.35, and (iii) major pathologies consisted of consequences of intraventricular hemorrhages grade 3 and 4, injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5 mm, V/B ratio >0.35, ventriculitis or other major brain pathology (infarcts).

Volume measurement was performed on T1-weighted images by visually separating the cerebrospinal fluid from the brain tissue image by image. The anatomical differentiation of the brain was based both on anatomical landmarks and signal intensity differences of the brain structures. The volumes of the total brain tissue (total brain volume minus ventricle volumes), the cerebrum, the cerebellum, the frontal lobes, the brain stem (medulla oblongata together with pons), the basal ganglia together with the thalami, and ventricles (lateral ventricles, third and fourth ventricles) were measured. The reproducibility of these measurements was assessed by repeated volume measurement of 20 children, performed by another neuroradiologist, who was blinded for the results of the first measurement. These methods have been previously described in detail (16–18,20,25).

Outcome Classification

For this study, normal motor outcome was defined as a total test score ≥57 (>5th percentile). The diagnosis of DCD was defined as a total test score ≤56 (≤5th percentile) according to ICD-10. A further requirement was that the diagnosis was not solely explicable in terms of general intellectual disability or of any specific congenital or acquired neurological disorder (9). The diagnosis of CP, including the grading of functional severity by Gross Motor Function Classification System (26), was ascertained by a child neurologist (L.H.) at 2 y of corrected age after a systematic clinical follow-up. Data concerning the children's regular participation in after-school sporting activities was acquired during the follow-up visit at 11 y of age.

The Movement Assessment Battery for Children—2

The motor assessment was completed at 11 y of age by using the Movement ABC-2 to identify children with movement difficulties (27). The clinical examination was performed by the author (S.S.). The Movement ABC-2 included three domains: manual dexterity (three items), aiming and catching (three items), and balance (three items). All the items were scored according to best attempt to receive raw scores. These were then further calculated to standard scores equating to percentiles of each domain and total test score, accordingly. A total test score ≤56 (≤5th percentile) denoted a significant movement difficulty. A total test score of 57–67 (>5th to 15th percentile) suggested the child was at risk of having a movement difficulty (monitoring required). Any total test score >67 (>15th percentile) indicated that there was no movement difficulty. The age band 3 (11–16 y) was used and the test was scored according to the norms for 11-y-old children as we wanted to use identical test tasks and references for all children even if some children had not yet turned 11 y at the time of the examination.

The Developmental Coordination Disorder Questionnaire 2007

Parents were asked to compare their child's motor performance to that of his/her peers to support the diagnosis of the DCD concerning the interference of motor difficulties in everyday functional activities. The DCDQ'07 consisted of 15 items, which were further grouped into three distinct factors: control during movement, fine motor and handwriting, and general coordination (13). The questionnaire was completed by interview (author S.S). All the items were scored using a 5-point Likert scale. Total scores were calculated by summing up item scores. The total score varied from 15 to 75. Scores from 15 to 57 indicated DCD.

Data Analysis

Pearson's correlation was used to study the univariate associations between two continuous variables. Univariate associations between continuous Movement ABC-2 percentile and categorical predictor variables were studied using regression analysis. Associations between brain volumes and continuous Movement ABC-2 percentile were studied using regression analysis controlling for brain pathology, gender, small for gestational age status, and gestational age. The regression equation for the associations between the total scores of the Movement ABC-2 and background characteristics was 3.88+0.19*gestational age in days-22.36*major pathologies in brain MRI-2.27*minor pathologies in MRI-0.19*small for gestational age status-2.52*male gender. All the results of regression analyses remained the same when controlling

for the age at the time of brain MRI examination. Continuous variables are presented with mean (SD) (minimum, maximum). Main results were analyzed both in all children and excluding children with CP. Continuous variables were compared between study infants and drop-outs using the Mann–Whitney *U*-test and comparisons between two categorical variables were done using the v2 test or Fisher's exact test, as appropriate. Statistical analyses were performed using SAS for Windows version 9.3. and *P* values below 0.05 were considered as statistically significant.

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