Motor performance and cognitive correlates in children cooled for neonatal encephalopathy without cerebral palsy at school age.

Jary S, Lee-Kelland R, Tonks J, Cowan FM, Thoresen M, Chakkarapani E.

Sally Jary: Senior Research Associate, Translational Health Sciences, Bristol Medical School, University of Bristol, UK

Richard Lee-Kelland: Research Fellow, Translational Health Sciences, Bristol Medical School, University of Bristol, UK.

James Tonks: Paediatric Clinical Neuropsychologist / Honorary Fellow, Translational Health Sciences, Bristol Medical School, University of Bristol & University of Exeter Medical School, UK.

Frances M Cowan: Visiting Professor, Translational Health Sciences, Bristol Medical School, University of Bristol, UK.

Marianne Thoresen: Professor of Neonatal Neuroscience, Translational Health Sciences, Bristol Medical School, University of Bristol. UK. & Professor of Physiology, University of Oslo, Norway.

Elavazhagan Chakkarapani: Consultant Senior Lecturer Neonatology, Translational Health Sciences, Bristol Medical School, University of Bristol, UK.

Corresponding author

Dr Ela Chakkarapani FRCPCH MD

Level D, St Michael's Hospital

Southwell Street, Bristol.

UK. BS2 8EG.

Email: ela.chakkarapani@bristol.ac.uk
https://orcid.org/0000-0003-3380-047X

Aim: To investigate whether motor performance in school-age children without cerebral palsy, cooled for neonatal encephalopathy, is associated with perinatal factors and 18-month developmental scores and to explore relationships between school-age motor and cognitive performance.

Methods: Motor and cognitive performance was assessed in 29 previously cooled children at 6-8 years using the Movement Assessment Battery for Children-2 (MABC-2) and the Wechsler Intelligence Scale for Children (WISC-IV). Associations between MABC-2 scores less than/equal (≤)15th centile and perinatal factors, social/family background, 18-month Bayley-III scores and WISC-IV scores were explored.

Results: Eleven/29(38%) children had MABC-2 scores ≤15th centile including 7(24%) ≤5th centile. No significant perinatal or socio-economic risk factors were identified. Motor scores <85 at 18 months failed to identify children with MABC-2 scores ≤15th centile. MABC-2 scores ≤15th centile were associated with lower Full Scale IQ (p=0.045), Working Memory (p=0.03) and Perceptual Reasoning (p=0.005) scores at 6-8 years and receiving greater support in school (p=0.01).

Conclusion: A third of cooled children without cerebral palsy had MABC-2 scores indicating motor impairment at school-age that was not identified at 18 months by Bayley-III. Most children with low MABC scores needed support at school. Sub-optimal MABC-2 scores indicate need for detailed school-age cognitive evaluation.

Running title: *School-age motor performance cooled children without cerebral palsy*

Key Notes:

- A third of children cooled for neonatal encephalopathy who did not develop cerebral palsy, have low childhood Movement Assessment Battery for Children-2 (MABC-2) scores which are associated with lower Full-scale Intelligent Quotient, Perceptual Reasoning and Working Memory scores and additional support with learning at school.
- Sub-optimal MABC-2 scores may indicate need for detailed school-age cognitive evaluation.
- Perinatal factors and 18-month developmental scores did not predict school-age M~~ovement~~ ABC-2 scores.

Key words: neonatal encephalopathy, therapeutic hypothermia, MABC-2, WISC-IV, Bayley-III

Abbreviations:

aEEG Amplitude integrated electroencephalogram

Bayley-III Bayley Scales of Infant and Toddler Development

CP Cerebral palsy

CI Confidence Interval

IQ Intelligence Quotient

MABC-2 Movement Assessment Battery for Children - Second edition

n Number of participants

WISC-IV Wechsler Intelligence Scale for Children ® - Fourth UK Edition (WISC-IV UK)

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Cohort studies of survivors of neonatal encephalopathy into childhood from the pre-cooling era report a spectrum of impairments that include cognitive, behavioural, attention and memory difficulties as well as motor deficits, mainly reported as cerebral palsy (CP) in about a quarter of survivors.(1-3). Motor deficits in the absence of CP in pre-cooled cohorts are reported to occur in 10-60% of children.(4-8) Since 2010 therapeutic hypothermia has been recommended by the UK National Institute for Clinical Excellence (https://www.nice.org.uk/guidance/ipg347) and the International Consensus on Cardiopulmonary Resuscitation(9) as the standard neuroprotective intervention for neonatal encephalopathy. Therapeutic hypothermia or cooling has been found to reduce death and severe disability(10, 11), including the rate and severity of CP(12), and to increase the proportion of survivors with a full scale IQ >85 into early childhood. (13, 14).

Focus upon neuromotor outcomes in children cooled for moderate/severe neonatal encephalopathy has been largely limited to the presence and severity of CP.(12-15) We recently reported school-age outcomes of cooled infants following neonatal encephalopathy without CP compared to matched controls.(16) Movement Assessment Battery for Children-Second Edition (MABC-2) total scores were found to be significantly lower in cooled compared to control children, even in the absence of severe neuromotor disability. Characterisation of cooled children without CP who have lower MABC-2 scores in terms of the perinatal factors, early development and cognitive profile is currently lacking. For earlier identification and to counsel parents appropriately it is important to identify whether perinatal risk factors or early developmental outcomes are associated with lower MABC-2 scores at school age. Whether there is an association between lower MABC-2 scores and cognitive performance at school age in children cooled for neonatal encephalopathy but without CP is not known. In this subset of children an improved understanding of potential deficits in different developmental domains and their relationship may improve the identification of specific children who might benefit from targeted intervention.

Our objectives were: to identify associations between motor, cognitive and language neurodevelopmental outcomes at 18 months with motor performance at school age and to explore relationships between concurrent motor and cognitive performance at school age; to investigate whether any perinatal clinical risk factors were associated with MABC-2 scores at school age

PATIENTS AND METHODS

Ethical approval was obtained (15/SW/0148) for a school-age follow-up study of children who had been treated with therapeutic hypothermia following neonatal encephalopathy in St Michael's Hospital, Bristol, UK. Criteria for inclusion in this study at 6-8 years, were birth at ≥36 weeks gestation, moderate or severe neonatal encephalopathy following perinatal asphyxia, confirmed by clinical examination and amplitude-integrated electroencephalogram (aEEG) (11, 17), and treatment with whole body-cooling within six hours of birth. Clinical data for surviving children in the target age range (6-8 years born between April 2007 and October 2010 held under a previous ethics approval (09/H0106/3) were screened (R L-K & EC). Children were excluded even if they had moderate to severe neonatal encephalopathy but were <36 weeks gestation at birth, had major intracranial haemorrhage or structural brain abnormality seen on neonatal MRI scan, had received Xenon as part of a neuroprotective feasibility study, had been found to have a metabolic or genetic disorder, had started cooling late, were cooled for <3 days, had no 18 month developmental assessment or had developed CP identified by 2 years of age. Families who agreed to participate in the study attended the Clinical Research and Imaging centre (CRIC) Bristol, for a full day of assessments (detailed below) and a neurological examination (RL-K) to exclude later presentations of CP or any other neurological problems not previously identified. Informed consent for participation was obtained from parent(s) of assessed children as well as each participant's assent.

School age assessment at 6-8 years

Motor assessment

Motor performance was assessed using the MABC-2(18) which is a valid and reliable measure of motor competence(19) for this age group. It is relatively quick to administer with normative data derived from a typically developing sample of children from 2005 to 2006 in the UK. It consists of 8 items divided into three different components: Manual Dexterity, Aiming and Catching, and Balance. Raw scores for each item are then converted into 8 item standard scores based on the child's age from normative data test standardisation tables. Item standard scores are combined to provide a component score, standard score and percentile equivalent for Manual Dexterity, Aiming & Catching and Balance. In addition, the sum of the 8 item scores can be converted into a total test standard score and equivalent percentile rank. All standard scores have a mean (standard deviation) (SD) of 10(3). Test developers recommend the use of MABC-2 total test scores ≤5th centile to indicate significant motor difficulty and scores between the 6th and 15th centiles to indicate a high risk for motor difficulty.(18) The MABC-2 was administered by one assessor (RL-K), who had not been previously involved in the patient's care or follow-up. The assessment was videoed and subsequently double scored by a second assessor from the anonymised recordings (SJ). Only 3 differences in item scoring were identified and these were agreed by consensus.

Psychometric assessment

Cognitive testing was undertaken using the Weschler Intelligence Scale for Children 4th Edition (WISC-IV) by psychologists (JT, EB) who also had not previously been involved in the child´s care. The WISC-IV summarises raw score performance from 10 subtests into 10 scaled scores. These scaled scores are summed in four domains: Verbal Comprehension, Perceptual Reasoning, Processing Speed and Working Memory which are converted into composite scores with mean (SD) of 100(15) and equivalent percentile rank. The sum of scaled scores in each domain are combined from which a full scale IQ [mean(SD) of 100(15)] is derived.

Data were also collected regarding any formal or private extra tuition received by the child at home or school, family social class defined as A, B C1, C2, D, E groups based on the national

readership survey (http://www.nrs.co.uk/nrs-print/lifestyle-and-classification-data/social-grade) and level of maternal education (left school at 16 years, further education, university education).

Perinatal Data

Clinical variables included gestation at birth, sex, birth weight, Apgar score at 10 minutes, pH and base excess from cord blood gas or worst arterial blood gas recorded in the first hour after birth, most severe background aEEG pattern(20) in the first 3 hours after birth and clinical grade of neonatal encephalopathy prior to commencement of cooling.

Developmental data at 18 months

All children had undergone regular developmental follow-up until the age of 24 months and all (except one, who had cognitive testing only) had an assessment of motor, cognition and language skills using the Bayley Scales of Infant & Toddler Development (Bayley-III)(21) at 18 months of age. Bayley-III generates distinct Cognitive Composite, Language Composite, and Motor Composite scores from raw scores, which have a normative mean(SD) of 100(15). In addition, scaled scores for Cognition, Gross Motor and Fine Motor development and Receptive and Expressive Language can be derived with a normative mean(SD) of 10(3).

Statistical analysis

Continuous variables are presented as mean/median (95% Confidence Interval (CI) and categorical variables as proportions. All 2-way comparisons were undertaken using the Student's t test for normally distributed variables or Mann Whitney U test for non-parametric data. Three group comparison of proportions was undertaken using the Kruskal-Wallis test and 2 group comparisons using the "N-1" Chi-squared test or Fisher's exact test.

We compared perinatal clinical risk factors and 18-month developmental outcomes between assessed children and those not assessed at 6-8 years.

Perinatal risk factors including the demographic characteristics, clinical severity of asphyxia and early aEEG pattern were compared between children with MABC-2 total test scores $\leq 5^{th}$, 6-15^{th}

centile and >15th centiles. Subsequent analyses were compared in children with MABC-2 total scores either above or equal/below 15th centile.

Mean WISC-IV scores and the proportion of children with WISC-IV scores < 85 (1SD below mean), the need for informal extra school support and/or formal educational support at 6-8 years, level of maternal education and family socio-economic status were compared between children with MABC-2 total test scores <15th and >15th centile.

Relationships between Bayley-III Composite and domain scaled scores at 18 months with MABC-2 component standard scores at 6-8 years and between MABC-2 percentile score equivalents and WISC-IV subscales at 6-8 years, were explored using Spearman's Rho. Bonferroni correction was used to account for multiple testing. A threshold p value of 0.007 was calculated for the seven Bayley Motor and Language Composite score comparisons with MABC-2 scores and 0.012 for the four Bayley Cognitive and MABC-2 score comparisons. For the three comparisons between subscales of WISC-IV and MABC-2 subscales, a p threshold of 0.016 was used.

Other analysis was undertaken using SPSS version 23(www.ibm.com/DataStatistics/SPSS), using a 0.05 level of significance.

RESULTS

Twenty-nine children were assessed at 6-8 years. Of the 33 other surviving children, seven were diagnosed with CP, six had been in a Xenon feasibility study and eight were cooled outside RCT criteria(22) and therefore did not fulfil the entry criteria for this study. A further seven children were not contactable or lost to follow-up, four families declined to be involved and one child did not have outcome data at 18 months. (Figure S1.)

There was no statistical difference in the early clinical variables between the assessed study cohort (n=29) and the children without CP not reviewed at 6-8 years (n=26). Bayley-III Composite scores were all lower in the non-assessed group compared to the assessed group however this did not reach significance. (Table S1.)

MABC-2 outcomes and perinatal risk factors

The mean (95% CI) MABC-2 total 8(7-9) Manual Dexterity 8(6-9), Aim & Catch 8.5(7-9) and Balance 9(8-10) component standard scores were all below the mean score of 10 in the test standardisation sample. Eleven of the 29 children (38%) had MABC-2 total scores $\leq 15^{th}$ centile including seven (24%) with scores $\leq 5^{th}$ centile. There were no significant differences in the early clinical characteristics between children with MABC-2 scores $>15^{th}$ centile and those with scores between 6^{th} and 15^{th} and $\leq 5^{th}$ centiles. (Table 1.) However, none of the children with MABC-2 scores $>15^{th}$ centile had severely abnormal aEEG background prior to cooling compared to 3/11(27%) children with MABC-2 scores $\leq 15^{th}$ centile. No significant differences were found in levels of maternal education or socioeconomic status between children with MABC-2 scores above or $\leq 15^{th}$ centile. (Table S2.)

Relationship between Bayley-III and MABC-2 scores

There was no significant relationship between 18-month Bayley-III Motor Composite scores and MABC-2 total test score percentile (rho = -0.01, p=0.9). Bayley-III Motor composite scores <85 (1SD below mean) at 18 months only identified one child with total MABC-2 scores $\leq 5^{th}$ centile at 6-8 years. (Figure 1.) There were also no significant correlations between the Bayley-III Fine Motor or Gross Motor scaled scores and MABC-2 total test standard score, or with any of the MABC-2 subscale standard scores at 6-8 years.

There was no significant relationship between Bayley-III Cognitive Composite Score and MABC-2 total test percentile score (rho = 0.2, p=0.3), Bayley-III Language Composite score was moderately associated with MABC-2 total test percentile score (rho =0.5, p = 0.01), (Figure 1.) Bayley-III Expressive Language scaled scores were moderately associated with Manual Dexterity standard scores (rho=0.42; p=0.03) and Balance standard scores (rho=0.48; p=0.01). Bayley-III Receptive Language scaled scores were moderately associated with MABC-2 Manual Dexterity standard score (rho=0.4; p=0.04). However, none of the relationships between

Bayley-III Language Composite and subscale scores remained significant following Bonferroni correction. Neither Bayley-III Motor nor Cognitive composite scores were significantly different for children with MABC-2 scores ≤15th or >15th centile at 6-8 years. Mean (95% CI) Bayley-III Language composite score was significantly lower in children with MABC-2 scores ≤15th centile compared to those with higher scores [93(85-100) versus 106(99-113), p=0.02].

School age MABC-2 and WISC-IV scores.

Exploration of relationships between individual MABC-2 and WISC-IV subscale percentile scores at school age indicated significant positive correlations across the sample (n=29) between WISC-IV Perceptual Reasoning and MABC-2 Manual Dexterity (rho=0.6, p=0.001)., and MABC-2 Aim & Catch (rho=0.4, p=0.02). These relationships were found to only be significantly related in the subset of children with MABC-2 scores ≤15th centile (rho=0.8, p=0.01; rho = 0.6, p=0.04). In addition, WISC-IV Working Memory Scores had a strong significant correlation with MABC-2 Manual Dexterity score, also only apparent in the subset with MABC-2 total scores ≤15th centile. These associations remained significant after Bonferroni correction for multiple testing. (Table 2., Figure 2.) There were no significant associations between WISC-IV Verbal Comprehension or Processing Speed and MABC-2 scores.(Table 2.) Children with MABC-2 scores ≤15th centile had significantly lower Full Scale IQ, Working Memory, Perceptual Reasoning and Verbal Comprehension scores compared to those with MABC-2 scores >15th centile and significantly more children with MABC-2 scores ≤15th centile had Working Memory, Perceptual Reasoning and Verbal Comprehension scores <1SD below the mean. (Table 3)

School performance at 6-8 years

Seven children (64%) with MABC-2 scores ≤15th centile required additional support (reading, writing and/or maths) in lessons at school, significantly more than the 3/18 (17%) children with higher MABC-2 scores (relative risk: 3.83, p=0.01). (Table S2.)

DISCUSSION

Even in the absence of CP, over a third of children cooled for neonatal encephalopathy were found to have MABC-2 scores $\leq 15^{th}$ centile, a level considered to be a clinically important indicator of motor difficulties(18) and which was associated with a need for extra support at school. We found no significant differences in perinatal risk factors, socioeconomic status or level of maternal education between children with MABC-2 scores above and equal/below the 15^{th} centile at 6-8 years, however 27% of children with MABC-2 scores $\leq 15^{th}$ had severely abnormal aEEG background when assessed prior to cooling compared to none of the children with MABC-2 scores $>15^{th}$ centile.

Bayley-III Motor Composite score <1SD below the mean (<85) at 18 months only identified one child with low MABC-2 scores at 6-8 years and a score <95 only identified one more child. (Figure 1.) The poor predictive ability of Bayley-III Motor Composite Score is consistent with reports in other cohorts including term infants with neonatal hypoglycaemia,(23) and non-cooled infants with mild/moderate hypoxic-ischaemic encephalopathy at varying ages up to 42 months.(7) Previous studies of non-cooled infants have also found a lack of association between early neuromotor outcomes and later motor impairment.(4, 8) This suggests that, in children without early overt neurological impairment, more subtle motor difficulties only become evident with age with the increasing complexity and demands of motor tasks.

Neither did we find any evidence of a relationship between the Bayley-III Cognitive Scaled scores at 18 months and MABC-2 total or subscale scores at 6-8 years and, after conservative correction for multiple comparisons, there was no significant association between Bayley-III Language and MABC-2 scores. Mean Bayley-III Language scores at 18 months were in the typical range both for children with MABC-2 scores above and below 15th centile, but were significantly lower in children with MABC-2 scores $\leq$15 centile. A recent study did find an association between language development and early changes in brain structure in a cohort of infants diagnosed with NE, the majority of whom were cooled. Early regional brain volumes at 6

months were found to be significantly associated with Bayley-III Language but not with Motor or Cognitive Composite scores at 30 months in children without functional motor impairment.(24) However, as our numbers are small and language scores may not be reliable at such an early age, our findings should be viewed with caution. We did not specifically test language ability at school-age however, by 6-8 years there was no difference in WISC-IV Verbal Comprehension scores between children with MABC-2 scores above and below <15th (Table 3.)

Assessments of motor performance at school age following neonatal encephalopathy from the pre-cooling era, using the first edition of the MABC, show a wide range of motor impairment rates in the absence of CP.(4-7) This is probably as a result of differences in the severity of encephalopathy in the different cohorts. The only estimate to date of motor impairment in cooled infants without CP at school age is from the cooled arm of the NICHD hypothermia trial, which recruited infants with moderate/severe neonatal encephalopathy.(13) In this study only 5% of cooled children without CP were found to have motor difficulties following assessment of everyday and complex motor function and fine motor function tests of co-ordination. In contrast, in our study using the MABC-2, a standardised test of motor performance, we identified 38% of our cohort surviving moderate/severe neonatal encephalopathy without CP to have MABC-2 scores $\leq$15 centile.

Our unexpectedly greater proportion of children with low MABC-2 scores could be because the MABC-2 does not only assess motor skills. A range of physical, motor-based abilities and neuro-cognitive factors need to be integrated in order to complete the tasks of the MABC-2. Hayes et al(7) assessed a non-cooled cohort of children following mild/moderate neonatal enceophalopathy and identified around 10% of children to be at high-risk of motor impairment using the MABC-2. They suggest this may result from difficulty with timed tests and processing of instructions. Our finding of significant correlations between MABC-2 Manual Dexterity scores and WISC-IV Perceptual Reasoning and Working Memory scores in the subset of children at 6-8 years with total MABC-2 scores $\leq 15^{th}$ centile, supports this association. MABC-2 Manual Dexterity activities in particular require the ability to process instructions visuo-

spatially and perceptually, as well as the ability to plan and execute correct motor performance. Children with developmental co-ordination difficulties, who score poorly in motor coordination tasks, commonly demonstrate considerable variation in in perceptual, visual-motor integration and visual-spatial processing tasks.(25). Such difficulties are commonly observed in localising objects in space and are linked to the eye movement mechanisms involved in selective attention necessary for executing accurate motor functions.(25) Earlier, alternative theoretical models, suggest a link between visuo-spatial processing skills, motor abilities and socio-emotional executive functioning.(26) Similar findings have been reported in children with acquired brain injury. Tonks et al suggest links between early developing visual-spatial processing and later emerging socio-emotional executive function deficits.(27) Whether cooled children, who perform poorly on the MABC-2, will ultimately go on to develop a similar profile of difficulties, is not yet known. Further longitudinal studies in larger cohorts of cooled children across the span of childhood and adolescence are therefore needed.

Our cohort differs from that of Hayes et al (7) in that our participants had a greater severity of encephalopathy and were treated with cooling. Cooling is known to lessen severe disability, particularly the rate and severity of CP. We have previously reported lower mortality and less severe CP outcomes in a larger sample of this cooled cohort in comparison to both historical and cooling trial outcomes.(15) Of the 7/62(11%) survivors diagnosed with CP excluded from this study, all but one were independently mobile at school age. Therefore, the evolution of motor disability mediated by cooling observed as reduced rate and severity of CP may also manifest itself as an increase in children with low MABC-2 scores at school age. However, numbers are small and our findings remain to be confirmed in other cohorts.

Importantly, children with MABC-2 scores $\leq 15^{th}$ centile are 3.8 times more likely to be receiving additional support at school. The need for special educational support services or delayed school year progression has been identified in both cooled and non-cooled children.(28) Some of these children may go on to fulfil diagnostic criteria for Developmental Co-ordination Disorder, Attention Deficit Hyperactive Disorder or Deficits in Attention and Motor Performance.

Therefore, serial assessment continues to be important in children treated with cooling to at least school age, even in those with developmental scores in the typical range at 18 months. The MABC-2 is enjoyed by children, is relatively easy to administer and our findings suggest that low scores at school-age could be used to trigger more in-depth assessment of skills in other areas. Longer term follow-up of this cohort using the MABC-2 is indicated to both assess the impact of lower school-age MABC-2 scores on motor function and life skills at later ages and to establish the predictive validity of MABC-2 beyond 8 years of age. (29) The strengths of this study are the careful selection of participants who had moderate-to-severe encephalopathy and the use of a standardised motor tool to assess motor performance. Our findings are limited by the small sample size which limits extrapolation of the results. However, findings describe the interrelation of potential deficits that a subset of children, who survived moderate and severe neonatal encephalopathy without CP, may face at school age. Further research is indicated in larger cohorts of cooled children and also in school age cohorts of children who sustained mild degrees of hypoxic ischaemic encephalopathy in the neonatal period.

Conclusion

Over a third (11/29) of children following moderate and severe neonatal encephalopathy treated with cooling had MABC-2 scores $\leq$15th centile at early school age despite not having CP and having had no evidence of motor problems at 18 months. Having MABC-2 scores $\leq$15th centile was independent of family social class, level of maternal education and all perinatal factors examined, except having low voltage EEG after birth. MABC-2 scores $\leq$15th was associated with lower working memory, perceptual reasoning and IQ scores and a 3.8 times greater need for additional support at school. Greater risk of receiving additional support at school in children with MABC-2 scores <15th centile indicates the relationship between sub-optimal test scores on actual academic performance in daily life.

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Conflict of Interest

There are no conflicts of interest.

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Table 1. Comparison of perinatal characteristics between children with MABC-2 scores ≤5th centile, 6th to 15th and > 15th centiles at 6-8 years (* data missing for one child)
(aEEG = amplitude integrated electroencephalography; BE= Base excess; CI = confidence interval MABC-2 = Movement Assessment Battery for Children 2nd edition)

Early clinical data (n(%) or median (95% CI)	**≤5th centile n = 7**	**6th to 15th centile n = 4**	**>15th centile n = 18**	**>15th versus ≤ 5th & 6th to 15th centiles** *p*
Sex no. male	5(71)	2(50)	12(66)	*0.8*
Apgar score at 10 minutes	6(1-10)	6(1-7)	7(5-8)	*0.5*
Clinical Grade of encephalopathy (prior to active cooling) 1= mild, 2= moderate, 3= severe	2(2-2)	2(2-3)	2(1-3)	*0.6*
Worst pH (cord/1st hour)	6.9(6.7 -7.2)*	6.97(6.87-7.2)	6.9(6.8-7.0)	*ns*
Worst BE (cord/1st hour)	-26.8 (-31 to -9.8)	-18.25 (-26.4 to -12)	-16.1 (-20.8 to -11.1)	*0.8*
aEEG voltage (prior to active cooling)				
Moderately Abnormal	5(71)	3(75)	18(100)	
Severely Abnormal	2(29)	1(25)	0	*0.07*

Table 2. Relationships between MABC-2 subscale centiles and WISC-IV subscale centiles at 6-8 years for whole sample (n=29) and according to those children with MABC-2 total scores above (n = 18) and below (n=11) 15th centile.
(MABC-2 = Movement Assessment Battery for Children 2nd Edition, WISC-IV = Weschler Intelligence Scale for Children 4th Edition)
**not significant after Bonferroni correction for multiple testing*

		MABC-2 centile scores at 6-8 years								
Spearman Rho *(p)*		Manual Dexterity			Aim & Catch			Balance		
		All n = 29	≤ 15th centile n = 11	>15th centile n=18	All n = 29	≤ 15th centile n = 11	>15th centile n=18	All n = 29	≤ 15th centile n = 11	>15th centile n=18
WISC-IV centile scores at 6-8 years	Verbal Comprehension	0.2 *(0.4)*	0.1 *(0.7)*	0.1 *(0.7)*	0.3 *(0.1)*	0.3 *(0.4)*	0.5 *(0.04)**	0.4 *(0.06)*	0.2 *(0.6)*	0.4 *(0.1)*
	Perceptual Reasoning	0.6 ***(0.001)***	0.8 ***(0.01)***	0.1 *(0.7)*	0.4 *(0.02)**	0.6 *(0.04)**	-0.1 (*0.6)*	0.1 *(0.5)*	-0.5 *(0.1)*	-0.3 *(0.9)*
	Working Memory	0.4 *(0.06)*	0.8 ***(0.01)***	-0.1 *(0.7)*	0.5 *(0.01)**	0.5 *(0.09)*	0.2 *(0.4)*	0.1 *(0.5)*	-0.5 *(0.1)*	0.1 *(0.6)*
	Processing Speed	0.2 *(0.4)*	0.6 *(0.1)*	-0.4 *(0.9)*	-0.01 *(0.9)*	-0.1 *(0.7)*	0.1 *(0.9)*	0.1 *(0.8)*	-0.3 *(0.9)*	-0.3 *(0.9)*

Table 3. Comparison of mean WISC-IV scores between children with MABC-2 total scores above and below 15th centile at 6-8 years. (CI= Confidence Interval; Movement ABC-2 = Movement Assessment Battery for Children 2nd Edition, WISC-IV = Weschler Intelligence Scale for Children 4th Edition) (* WISC-IV data missing for one child)

WISC-IV scores at 6-8 years	MABC-2 total scores		
	>15th centile n = 18	**≤15th centile n = 11**	*p*
Mean (95%CI)			
Full Scale IQ	95(90-99)	86(78-94)*	***0.045***
Processing speed	96(89-102)	95(85-106)*	*0.9*
Working memory	99(94-103)	86(76-97)	***0.03***
Perceptual reasoning	94(90-98)	82(75-89)	***0.005***
Verbal comprehension	96(92-99)	91(84-98)	*0.25*
No (%) of children with WISC-IV scores <85			
Full Scale IQ	3/18(17)	4/11(36)	*0.25*
Processing speed	2/18(11)	3/11(27)	*0.3*
Working memory	1/18(5)	6/11(55)	***0.003***
Perceptual reasoning	2/18(11)	7/11(64)	***0.003***
Verbal comprehension	0/18(0)	3/11(27)	***0.045***

Table S1. Comparison of early clinical data and 18-month developmental outcomes between the assessed cohort (n=29) and children not assessed (n = 26) at 6-8 years.
(# Worst pH data missing for 1 child)
(Bayley-III = Bayley Scales of Infant and Toddler Development; ns = non significant; BE= base excess; aEEG = amplitude-integrated electroencephalogram)

Table S2. Comparison of level of maternal education and family social class between children with MABC-2 total scores above and below 15th centile at 6-8 years. *(CI= Confidence Interval; NRS = National Readership Survey)*

Figure S1. Flow chart of study participants assessed at 6-8 years (n = 29) and children without cerebral palsy, not assessed at 6-8 years (n = 26)
(CP = cerebral palsy, aEEG = amplitude integrated electroencephalography)

Figure 1. Scatter plot of Bayley-III Composite scores at 18 months versus MABC-2 percentile scores at 6-8 years.
(n = 28 for Bayley-III Motor & Language Composite scores as one child, who had MABC-2 scores less than or equal to 15th centile, only had cognitive testing at 18 months)

Figure 2. Scatter plots of WISC-IV Perceptual Reasoning and Working Memory centile scores with MABC-2 Manual Dexterity scores at 6-8 years.
(MABC-2 = Movement Assessment Battery for Children, 2nd Edition; WISC-IV = Wechsler Intelligence Scale for Children ® - Fourth UK Edition)