Received: 16 February 2021 | Revised: 21 June 2021 | Accepted: 22 June 2021

DOI: 10.1111/apa.16002

REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

# Children with neonatal Hypoxic Ischaemic Encephalopathy (HIE) treated with therapeutic hypothermia are not as school ready as their peers

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**Funding information**
This study was supported by the Sir Halley Stewart Trust, UK.

## Abstract

**Aim:** We aimed to determine whether children with neonatal Hypoxic Ischaemic Encephalopathy (HIE) treated with therapeutic hypothermia (TH) differ from their peers on measures of fine motor skills, executive function, language and general cognitive abilities, factors that are important for school readiness.

**Methods:** We compared school readiness in 31children with HIE treated with TH (without Cerebral Palsy; mean age 5 years 4 months) with 20 typically developing children without HIE (mean age 5 years 6 months).

**Results:** Children with HIE scored significantly lower than typically developing children on fine motor skills, executive functions, memory and language.

**Conclusion:** While general cognitive abilities and attainment were in the normal range, our findings suggest those scores mask specific underlying difficulties identified by more focussed assessments. Children with HIE treated with TH may not be as 'school ready' as their typically developing classmates and may benefit from long-term follow-up until starting school.

KEYWORDS
cognitive ability, motor, neonatal hypoxic-ischaemic encephalopathy (HIE), school readiness, therapeutic hypothermia (TH)

## 1 | INTRODUCTION

It is well known that children with neonatal hypoxic-ischaemic encephalopathy (HIE) are at risk of poorer neurodevelopmental outcome in the early years, that is at toddler and preschool age.[1] A recent systematic review of long-term outcomes at 4 years and older of children with HIE who survived without developing severe neuromotor impairment (Cerebral Palsy, CP) suggests that even after the introduction of TH, children with HIE may experience impairment of motor, cognitive and behavioural abilities.[2] These abilities are important for considering whether a child is ready for school. The concept of 'school readiness' has been defined in many ways. For example, Public Health England (2015) defined school readiness as 'a measure of how prepared a child is to succeed in school cognitively, socially and emotionally' and considers that children are school ready if they have met expected learning goals.[3] UNICEF (2012) defined school

**Abbreviations:** BRIEF, behaviour rating inventory of executive functions; CP, cerebral palsy; FSIQ, full scale IQ; GMFCS, gross motor function classification system; HIE, hypoxic-ischaemic encephalopathy; MABC-2, the movement ABC for children-2; MND, minor neurological dysfunction; TH, therapeutic hypothermia; WIAT-II, Wechsler individual achievement test-II; WPPSI-IV, Wechsler preschool and primary scale of intelligence.

readiness as having two features on three dimensions.[4] The two features are 'transition' and 'gaining competencies', and the three dimensions are 'children's readiness for school', 'schools' readiness for children' and 'families' and communities' readiness for school'. Children who experience difficulties early in life may face a widening gap in cognitive and social skills on starting school, where the cognitive and behavioural demands are greater than they have previously experienced, and specific learning difficulties may be identified.

Prior to TH becoming standard clinical care, HIE was associated with a high incidence of CP. More recent studies, conducted since TH was introduced, that have excluded those with CP, suggest that motor difficulties in the absence of CP persist.[5,6] Fine motor skills are particularly relevant for school readiness: they are important for cognitive development,[7] form part of the range of abilities used to measure school readiness[3] and predict school performance.[8]

Executive Functions—including attention, inhibition, working memory and cognitive flexibility—play an important role in children's school performance.[8] Teachers' surveys suggest that children's ability to self-regulate is an important component of school readiness and achievement.[9] Studies in non-cooled children reported significant difficulties with memory, [10,11] and post-cooling, working memory is worsened in children with HIE.[12] Individual differences in Executive Functions are related to school readiness,[13] and studies from the era prior to TH have reported difficulties in attention in children with neonatal HIE,[12,14–17] but little is known about Executive Functions in children treated with TH, but one study has shown children who were cooled had higher Executive Functions score than children who were not.[17]

Our aim was to investigate whether, on starting school, children with neonatal HIE without major neuromotor impairment (defined here as CP >level 2 on the GMFCS) who received TH differ from their typically developing peers, on measures that are important for school readiness and school success.

**Key Notes**

- On starting school, children with neonatal Hypoxic Ischaemic Encephalopathy (HIE) treated with therapeutic hypothermia (TH) scored lower than control children on fine motor skills, attention, memory and language.
- General cognitive abilities and attainment levels were in the normal range, but composite scores may mask specific underlying difficulties identified by more focussed assessments.
- Children with HIE treated with TH are not as 'school ready' as their typically developing classmates.

## 2 | METHODS

### 2.1 | Participants

Between 01 August 2009 and 31 May 2013, 95 newborns were admitted to the neonatal unit at Princess Anne Hospital (PAH), University Hospital Southampton NHS Foundation Trust, UK, for TH for neonatal HIE (criteria for TH at PAH, see Appendix 1). Infants who did not undergo the whole 72 h of TH ($n$ = 12), who died ($n$ = 14), who had an underlying diagnosis that would make perinatal asphyxia unlikely as the main cause for encephalopathy, had a metabolic, genetic or syndromal disorder ($n$ = 14) are excluded. This leaves 55 infants with neonatal HIE subsequent to perinatal asphyxia; these children were eligible for this study at age 5–7 years. Children with CP were excluded if their gross motor function level was >2 on the GMFCS and their upper limb function level >2 on the Manual Ability Classification System (MACS), $n$ = 3. This left a sample of 52 children. Two of those were lost to follow-up, and thus, 50 families were contacted, of which 62% ($n$ = 31) agreed to participate. Our final study sample consisted of 31 children with neonatal HIE, aged 5-7years. Table 1 compares the demographic and perinatal characteristics of our sample to the whole sample of infants admitted for TH between 01 August 2009 and 31 May 2013 and shows that the study sub-sample was representative of the whole sample.

Typically developing children ($n$ = 20) were recruited using a friends and family approach ($n$ = 4) and from local schools ($n$ = 16). The recruitment strategy was to match for age, gender and postcode area as closely as possible. There was no difference in years of parental education between the HIE group (mean = 15.29, SD = 3.84) and controls (mean = 17.38, SD = 2.39),[18] $t$ = 2.08, $p$ = 0.161.

### 2.2 | Measures

General cognitive abilities were assessed using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)[19]; the Verbal Comprehension Index, Visual Spatial Index and Full Scale IQ (FSIQ) scores are reported. Reading, language and numerical attainment were assessed by the Wechsler Individual Achievement Test-II (WIAT-II).[20] Children's language was assessed using the Clinical Evaluation of Language Fundamentals-2,[21] and we report the Core Language Score and three subtests; Sentence Structure, Word Structure and Expressive Vocabulary. Executive functions were assessed using the NEPSY-II[22]; we report selective auditory attention scores (Auditory Attention), behavioural productivity (Design Fluency), ability to inhibit impulsive responding (Inhibition), motor persistence and inhibition (Statue). Real-world executive functioning at school and home was assessed using parent and teacher ratings from the Behaviour Rating Inventory of Executive Functions (BRIEF).[23] We report eight clinical scales, the Behavioural Regulation Index and Meta-Cognition Index Scores; and an overall Global Executive Composite. Memory was assessed by the Rivermead Behavioural Memory Test[24] and teacher and parent ratings on working memory of the BRIEF.

A simplified version of the Touwen Neurological Examination was used to evaluate posture, muscle tone (passive and active),

**TABLE 1** Comparison Table of Current and Whole Sample

| | [a]Whole sample N = 55 | | | | Study sample N = 31 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | SD | minimum | maximum | M | SD | minimum | maximum | *U* | *z* | *p* |
| Birth Weight (g) | 3387 | 598 | 2200 | 4980 | 3415 | 660 | 2200 | 4980 | 359 | -.22 | .83 |
| Gestational age (wk) | 39.9 | 1.5 | 36.4 | 42.1 | 39.9 | 1.4 | 37.0 | 42.1 | 341 | -.53 | .59 |
| Apgar at 10 min | 4.9 | 2.1 | 0 | 10 | 4.9 | 2.4 | 0 | 10 | 368 | -0.8 | .94 |
| [b]Cord PH or within first 60 min (arterial) | 7.04 | 0.19 | 6.7 | 7.4 | 7.05 | 0.19 | 6.7 | 7.4 | 284 | -.40 | .69 |
| [c]Base Excess either cord BE or within first 60 min (arterial) | −13.7 | 7.1 | −29 | −17 | −13.3 | 6.8 | −28.1 | −3.6 | 228 | -.45 | .65 |
| Neonatal seizures n, (%) | 14 (24.6) | | | | 8 (25.8) | | | | | | |

[a]Whole sample of infants born between 01 August 2009 and 31 May 2013 consists of 95 infants who were admitted for hypothermia treatment for neonatal HIE. Infants who did not undergo the whole 72 h of hypothermia treatment, who had an underlying diagnosis that would make perinatal asphyxia unlikely as the main cause for encephalopathy, and those who died are excluded.

[b]Missing data: pH missing for 5 infants (2 in study sample).

[c]Missing data: Base excess missing for 10 infants (6 in study sample).

tendon reflexes, cranial nerve function, coordination and balance. Findings were classified according to the number of dysfunctional domains: normal neurology, simple minor neurological dysfunction, MND, (one or two domains abnormal) or complex MND (more than two domains abnormal).[25] Cerebral Palsy was diagnosed on the basis of the criteria of the Surveillance of Cerebral Palsy in Europe Working Group.

The Movement ABC for Children-2 (MABC-2) was used to assess motor function.[26] We were principally interested in children's fine motor skills as manual dexterity is particularly important on starting school[8] and linked to later school achievement[27]; however, findings from the other two subscales, that is balance skills, aiming and catching skills, are reported too.

Assessments were conducted either at the hospital or at home. The same assessment pathway was applied to all children. Assessors were not blind to which group the children were in.

### 2.3 | Statistical Analysis

Statistical tests were conducted using IBM SPSS Statistics 25. The Shapiro-Wilk test for normality was used to assess for normal distribution. If the data were normally distributed, differences between groups were assessed with independent samples t test. If data were not normally distributed, group differences were assessed with Mann–Whitney *U* tests. The alpha level was set at 0.05.

### 2.4 | Ethics approval

The study was approved by the NHS Health Research Authority National Research Ethics Committee North West – Lancaster (REC reference 15/NW/0292). Written consent was obtained from parents and assent from children. All procedures were in accordance with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards.

## 3 | RESULTS

### 3.1 | General cognitive abilities, academic achievement measures, attention and executive function measures

We compared the performance of children with HIE treated with TH with control children and these data are presented in Tables 2 and 3. We present data on the proportion of children in FSIQ descriptive categories and NEPSY clinical categories in Table 4, and the proportions in Rivermead Behavioural Memory Test severity groups in Table 5.

For or all three WPPSI-IV composite scores, children with HIE scored lower than controls, but not significantly so (Table 2). All mean scores were in the average range, but some individuals—in both HIE and control groups—scored more than one standard deviation below the mean. This is reflected in the FSIQ Descriptor scores, which shows that the majority of control children scored in the average category or higher, while the majority of children with HIE scored in the average and low average range (Table 4). In addition, the proportion of children in the Extremely Low and Borderline categories was over twice the number in the group of children with HIE compared with controls.

On the WIAT-II, children with HIE had scored slightly lower than controls on all four scales, but not significantly so (Table 2). While mean scores were in the normal range, individuals in both the HIE group and controls scored below the normal range.

On the Clinical Evaluation of Language Fundamentals-2, median scores were lower in children with HIE compared with controls, and significantly so for the Word Structure score (Table 3).

Children with HIE performed similarly to children in the control group on many of the Attention and Executive Function tasks from the NEPSY-II, with the exception of both Auditory Attention Scaled Scores in which their scores were significantly lower than those of controls (Table 3). Distribution across clinical categories (Table 4) shows that 28.6% of children with HIE scores were in the borderline or lower ranges, while only 5% of control children fell in this range.

Memory test performance was significantly worse in children with HIE compared to controls (Table 3). Rivermead Behavioural Memory Test total scores were significantly lower, and there was particular difficulty on both immediate and delayed story recall subtests; while 95% (immediate) and 70% (delayed) of control children were in the normal category, only 23% and 17% of children with HIE fell in the normal range (Table 5). On the BRIEF, scores were higher on Working Memory, for both parent and teacher ratings, in children with HIE indicating more difficulties compared with controls.

### 3.2 | Parental and teachers' executive function rating

Scores were higher in the HIE group for the majority of subscales, indicating problems in these areas, but only significantly higher for Shift.

In contrast, for teacher ratings, scores were significantly higher in the HIE group for Initiate, Shift, Working Memory, Plan/Organise, the Meta-Cognition Index, the Behavioural Regulation Index and the Global Executive Composite, indicating problems in the classroom in these areas.

### 3.3 | Neurology, Vision, Hearing and Neuromotor Measures

All 20 control children were categorised as neurologically normal. In the HIE, group 2 had CP (GMFCS1 and MACS1); 23/29 without CP were categorised as neurologically normal, 4/29 had simple MND, and 2/29 had complex MND. Information on visual and hearing function was retrieved from the child's medical records. The majority of children had normal vision (27 children with HIE, 90%; 13 controls, 65%; 7 control data missing, 35%). A small proportion had vision corrected with glasses (2 children with HIE, 6.7%; 2 controls, 13.3%). One child with HIE (3.3%) had vision not fully corrected with glasses. All of the control children had normal hearing, as did the majority of children with HIE (*n* = 26, 86.7%). Just under 10% of children with HIE had hearing impairment (*n* = 3), which was fully corrected with hearing aids for one of the children and not fully corrected for the other two.

On the MABC-2, children with HIE had significantly poorer performance on manual dexterity tasks compared with control children (Table 3). When analyses were repeated excluding children with CP, there were no changes to the results.

## 4 | DISCUSSION

Children with neonatal HIE performed more poorly than their typically developing peers on measures of executive functions including auditory attention and memory, language and fine motor skills. These differences from their peers suggest that children with a history of neonatal HIE, despite having been treated with TH and in the absence of major neuromotor impairment, are not as ready for school as

**TABLE 2** WPPSI-IV and WIAT-II Scores by Group

| | | Children with HIE | | | Control children | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | M | SD | n | M | SD | n | t | df | p | Cohen's d |
| WPPSI-IV | FSIQ | 93.03 | 13.10 | 31 | 98.65 | 11.59 | 20 | 1.563 | 49 | .125 | 0.45 |
| | Verbal Comprehension Index | 93.10 | 12.27 | 31 | 97.30 | 9.94 | 20 | 1.283 | 49 | .205 | 0.37 |
| | Visual Spatial Index | 88.30 | 17.49 | 23[a] | 97.11 | 15.45 | 19 | 1.710 | 40 | .095 | 0.54 |
| WIAT-II | Word Reading | 105.55 | 12.67 | 29 | 111.95 | 11.17 | 20 | 1.821 | 47 | .075 | 0.53 |
| | Spelling | 101.89 | 13.67 | 27 | 102.95 | 14.93 | 20 | 0.253 | 45 | .801 | 0.08 |
| | Numerical Operations | 97.04 | 10.04 | 28 | 101.00 | 10.37 | 20 | 1.330 | 46 | .190 | 0.39 |
| | Mathematical Reasoning | 97.30 | 12.52 | 27 | 99.05 | 13.09 | 20 | 0.466 | 45 | .644 | 0.14 |

*Note:* Comparisons that were significant at the 0.05 level are in bold.

[a]Visual Spatial Index was omitted for the first few children assessed. The normative mean is 100, and the SD is 15.

**TABLE 3** MABC, Clinical Evaluation of Language Fundamentals-2, NEPSY and BRIEF Scores by Group

| | | Children with HIE | | | Control children | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Median | IQR | *n* | Median | IQR | *n* | U | z | *p* |
| MABC Whole sample | Manual Dexterity Standard Score | 9.00 | 6.00 | 28 | 12.00 | 5.00 | 20 | 132.5 | −3.09 | .002 |
| MABC Excluding children with CP | Manual Dexterity Standard Score | 9.00 | 6.00 | 27 | 12.00 | 5.00 | 20 | 132.50 | −2.97 | .003 |
| Clinical Evaluation of Language Fundamentals−2 | Sentence Structure | 9.00 | 4.00 | 31 | 10.00 | 2.00 | 19 | 230.50 | −1.29 | .197 |
| | Word Structure | 8.00 | 5.00 | 31 | 10.00 | 3.00 | 19 | 162.50 | −2.27 | .008 |
| | Expressive Vocabulary | 10.00 | 3.00 | 31 | 9.00 | 1.00 | 19 | 289.50 | −0.10 | .920 |
| | Overall Standard Score | 92.00 | 20.00 | 31 | 102.00 | 14.00 | 19 | 216.00 | −1.57 | .116 |
| NEPSY-II | Auditory Attention Total Correct Scaled Score | 9.00 | 5.00 | 28 | 11.50 | 4.00 | 20 | 152.50 | −2.69 | .007 |
| | Auditory Attention Combined Scaled Score | 9.50 | 5.00 | 28 | 11.50 | 5.00 | 20 | 123.00 | −3.34 | .001 |
| NEPSY-II | Design Scaled Score | 10.00 | 5.00 | 27 | 10.00 | 3.002 | 20 | 231.00 | −0.85 | .395 |
| NEPSY-II | Inhibition Naming Total completion time scaled score | 11.00 | 2.00 | 26 | 12.00 | 6.00 | 20 | 190.50 | −1.56 | .118 |
| | Inhibition Naming Combined scaled score | 11.00 | 4.00 | 26 | 13.00 | 5.00 | 19 | 189.00 | −1.34 | .179 |
| | Inhibition Total Completion time scaled score | 12.00 | 4.00 | 26 | 11.00 | 4.00 | 20 | 249.00 | −0.25 | .806 |
| NEPSY-II | Statue Scaled Score | 11.00 | 4.00 | 28 | 11.00 | 9.00 | 19 | 249.50 | −0.36 | .718 |
| BRIEF Parent ratings | Inhibit | 45.50 | 15.25 | 30 | 48.00 | 11.50 | 16 | 232.00 | −0.19 | .853 |
| | Shift | 46.00 | 17.00 | 30 | 41.00 | 11.00 | 16 | 128.00 | −2.60 | .009 |
| | Emotional Control | 51.50 | 27.75 | 30 | 47.00 | 12.00 | 16 | 171.50 | −1.58 | .113 |
| | Initiate | 46.00 | 19.25 | 30 | 42.00 | 15.00 | 16 | 190.00 | −1.16 | .246 |
| | Working Memory | 55.50 | 30.25 | 30 | 44.50 | 7.00 | 16 | 161.50 | −1.82 | .070 |
| | Plan/Organise | 50.00 | 22.00 | 30 | 49.00 | 15.00 | 15 | 220.00 | −0.12 | .904 |
| | Organisation of Materials | 46.00 | 14.75 | 30 | 52.00 | 17.00 | 16 | 193.50 | −1.08 | .282 |
| | Monitor | 49.00 | 27.00 | 30 | 45.00 | 7.00 | 16 | 202.50 | −0.89 | .385 |
| | Behavioural Regulation Index | 49.00 | 23.00 | 30 | 46.00 | 13.00 | 15 | 158.00 | −1.62 | .106 |
| | Meta-Cognition Index | 49.50 | 26.50 | 30 | 47.00 | 15.25 | 16 | 232.00 | −0.19 | .853 |
| | Global Executive Composite Score | 50.00 | 23.50 | 30 | 44.00 | 13.50 | 16 | 189.50 | −1.17 | .244 |

(Continues)

**TABLE 3** (Continued)

| | | Children with HIE | | | Control children | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Median | IQR | *n* | Median | IQR | *n* | U | z | *p* |
| BRIEF Teacher ratings | Inhibit | 46.50 | 5.50 | 28 | 45.00 | 5.25 | 20 | 247.00 | −0.73 | .467 |
| | Shift | 48.00 | 14.25 | 28 | 43.00 | 2.25 | 20 | 157.50 | −2.72 | .007 |
| | Emotional Control | 48.00 | 15.50 | 28 | 44.00 | 5.00 | 20 | 213.00 | −1.43 | .152 |
| | Initiate | 55.00 | 17.00 | 27 | 41.00 | 4.00 | 20 | 137.00 | −2.92 | .003 |
| | Working Memory | 51.00 | 20.50 | 28 | 42.00 | 4.50 | 20 | 142.50 | −2.92 | .003 |
| | Plan/Organise | 50.50 | 11.25 | 28 | 44.00 | 5.50 | 20 | 156.00 | −2.62 | .009 |
| | Organisation of Materials | 47.00 | 6.00 | 28 | 46.00 | 2.25 | 20 | 214.00 | −1.45 | .148 |
| | Monitor | 48.50 | 14.00 | 28 | 46.00 | 9.00 | 20 | 188.00 | −1.94 | .052 |
| | Behavioural Regulation Index | 48.50 | 11.75 | 28 | 44.00 | 7.25 | 20 | 181.00 | −2.10 | .036 |
| | Meta-Cognition Index | 50.50 | 23.50 | 28 | 43.00 | 3.50 | 20 | 149.50 | −2.75 | .006 |
| | Global Executive Composite Score | 50.50 | 21.25 | 28 | 43.50 | 5.00 | 20 | 155.50 | −2.61 | .009 |
| Rivermead Behavioural Memory Test | Total Score | 14.00 | 4.00 | 27 | 17.00 | 2.00 | 19 | 101.50 | −3.51 | .001 |

For the MABC-2, scores between the 5th and the 15th centile are indicative of borderline motor problems, scores ≤5th centile are indicative of definite motor problems. There were two children with CP in the HIE group, one of whom refused to complete the MABC-2.

For Clinical Evaluation of Language Fundamentals-2 overall standard scores, the normative mean is 100 and the SD is 15. For the Clinical Evaluation of Language Fundamentals-2 subtest scores and all NEPSY scores, the mean normative score is 10 and the standard deviation is 3. For all of these, a higher score indicates better performance. One control child was too old to complete the Clinical Evaluation of Language Fundamentals-2.

For the BRIEF scores, the normative mean is 50 and the standard deviation is 10. For these scores, higher scores indicate difficulties in these areas. T scores from 60 to 64 are considered mildly elevated, scores from 65 to 69 are considered potentially clinically elevated and T scores at or above 70 are considered clinically elevated.

For the Rivermead Behavioural Memory Test, the total score is the sum of subtest scores and a higher score indicates better performance. Note, this test is reported only for 5- to 6-year-old children (one control child omitted).

**TABLE 4** Number and percentage of children in WPPSI-IV FSIQ Descriptive Categories and NEPSY Clinical Categories Group

| | | Children with HIE | | Control Children | |
|---|---|---|---|---|---|
| | Category | *n* | % | *n* | % |
| WPPSI-IV FSIQ Descriptor Labels | Extremely Low | 1 | 3.3 | 0 | 0 |
| | Borderline | 3 | 10.0 | 1 | 5.6 |
| | Low Average | 9 | 30.0 | 2 | 11.1 |
| | Average | 14 | 46.7 | 11 | 61.1 |
| | High Average | 2 | 6.7 | 2 | 11.1 |
| | Superior | 1 | 3.3 | 2 | 11.1 |
| | Very Superior | 0 | 0 | 0 | 0 |
| NEPSY Attention/Executive Subtests Clinical Categories | Well below expected | 1 | 3.6 | 0 | 0 |
| | Below expected | 2 | 7.1 | 0 | 0 |
| | Borderline | 5 | 17.9 | 1 | 5.0 |
| | At expected | 18 | 64.3 | 13 | 65.0 |
| | Above expected | 2 | 7.1 | 6 | 30.0 |

**TABLE 5** Number and percentage of children in Rivermead Behavioural Memory Test severity groups

| Rivermead Behavioural Memory Test Subtests | Children with HIE | | | | | | Control Children | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normal | | Borderline | | Impaired | | Normal | | Borderline | | Impaired | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Belonging | 25 | 83.3 | 2 | 6.7 | 0 | 0 | 19 | 95.0 | 0 | 0 | 0 | 0 |
| Pictures | 21 | 70.0 | 1 | 3.3 | 5 | 16.7 | 17 | 89.5 | 1 | 5.0 | 1 | 5.0 |
| Story Immediate recall | 7 | 23.3 | 3 | 10.0 | 17 | 56.7 | 19 | 95.0 | 1 | 5.0 | 0 | 0 |
| Story Delayed recall | 5 | 16.7 | 6 | 20.0 | 16 | 53.3 | 14 | 70.0 | 3 | 15.0 | 3 | 15.0 |
| Faces | 23 | 76.7 | 2 | 6.7 | 2 | 6.7 | 17 | 85.0 | 2 | 10.0 | 0 | 0 |
| Route Immediate Recall | 27 | 90.0 | 1 | 3.3 | 0 | 0 | 19 | 95.0 | 1 | 5.0 | 0 | 0 |
| Route Delayed Recall | 26 | 86.7 | 1 | 3.3 | 0 | 0 | 18 | 90.0 | 2 | 10.0 | 0 | 0 |
| Message | 27 | 0 | 0 | 0 | 0 | 0 | 19 | 95.0 | 1 | 5.0 | 0 | 0 |
| Orientation | 20 | 66.7 | 4 | 13.3 | 3 | 10.0 | 20 | 100 | 0 | 0 | 0 | 0 |

their peers who did not experience neonatal HIE. Their general cognitive abilities and attainment levels were in the normal range, but our findings suggest that composite scores are masking specific underlying difficulties identified by more focussed assessments. This may lead to more divergence between children with HIE and their peers as they age, on both specific cognitive processes and attainment, as the concepts and learning in schools become more complex.

Children with HIE performed more poorly than controls on language assessments, specifically the Clinical Evaluation of Language Fundamentals-2 Word Structure subtest that evaluates children's knowledge of grammatical rules in a sentence completion task. Currently, there are few studies examining the language skills of children with HIE treated with TH. Instead, studies have focussed on more global assessments of language, such as Verbal IQ scores which, while they correlate with scores on language assessments[21] and measure quite different skills.[28] Existing studies show conflicting results. In two studies of 6- to 7-year-old children with HIE treated with TH, one reported VIQ scores in the normal range,[17] while a second reported mean VIQ scores in the low to normal range.[29] Studies in younger children have reported that a minority have language difficulties, for example a study of 2-year-old children reported that 4.2% had deficits in language development assessed via the Bayley Scales of Infant and Toddler Development 3.[6] Two-year-old children with HIE treated with TH, when compared to test norms, scored significantly lower on tests of expressive language and visual reception, but not on tests of receptive language[18] and speech output and complexity.[30] Currently, few studies have examined the long-term (i.e., beyond toddler age) impact of HIE on language. Future work should continue to fully evaluate potential long-term effects on language production, processing and understanding in children with HIE treated with TH.

In our sample, children with HIE performed similarly to controls on many of the NEPSY-II Attention and Executive Functions tasks, but significantly lower on both Auditory Attention scores. Performance on these Auditory Attention subtests assesses the ability to sustain selective auditory attention and set-shifting, which requires inhibition of previously successful responses, aspects of cognitive control important for school readiness,[8] both for classroom behaviour[9] and long-term attainment.[13] Furthermore, behaviour ratings of executive dysfunction in 'the real world' were higher in children with HIE compared to controls, particularly in the case of teacher ratings. It is likely that teacher ratings suggest more impacted behaviour because the classroom is a more challenging environment. In the limited literature on Executive Functions in children with HIE treated with TH, difficulties with sustained attention have been reported in cooled children[16] and in attention before cooling became the standard treatment for neonatal HIE.[10,14,15,31] The persistence of difficulties with attention in the era of TH suggests that cooling is not wholly protective of these functions. Intervention studies in children born preterm suggest improvements in Executive Functions and may also improve the Executive Functions of children with HIE treated with TH.[32]

Children with HIE in our study had significant difficulties with memory, both on objective measures (Rivermead Behavioural Memory Test) and parent and teacher ratings of real-life behaviour. The effect size for the Rivermead Behavioural Memory Test comparison was 'large' and was the largest effect size observed in our study; this suggests more focused follow-up on memory difficulties is warranted. Parents and teachers might observe working memory difficulties in children in their care by the children forgetting instructions, losing track of what they are doing, or forgetting the purpose of an errand. Without an awareness that children with HIE treated with TH might have a specific difficulty with memory, they may be consider to lack care and attention in their behaviour, and perhaps, as was the case in a very low birthweight cohort, to be considered 'naughty'.[33]

The difficulties observed in children with HIE on fine motor skills are consistent with previous studies, for example.[5,12] One child with mild CP completed the MABC-2, but this child's performance did not unduly influence the results, which remained when this child's data were excluded from the analysis. Difficulties with fine motor skills might have impacted on performance on the other cognitive tests. The present study requires replication in a larger sample with a more detailed assessment of motor skills and, indeed, motor abilities. Nonetheless, our findings highlight that, even in the absence of CP, fine motor behaviour was significantly impaired relative to the control children, which may lead to difficulties with tasks such as handwriting.

Two macroscopic patterns of hypoxic-ischaemic (HI) injury have been described: to the deep grey matter (thalami, basal ganglia, brain stem) after severe acute asphyxia, and, after prolonged partial asphyxia, injury to the paracentral 'watershed' brain regions.[34,35] The first pattern has been associated with severe neuromotor and developmental impairment, the latter with predominantly global cognitive impairment.[36] Neural correlates of cognitive/behavioural impairment in neonatal HIE, in particular in infants without CP, are still poorly understood. Recent animal work suggests that neonatal HI injury disrupts large-scale functional pathways between the prefrontal cortex and hippocampus and that this is linked to cognition,[37] even when morphological macroscopic changes are minor/moderate. The thalamus, often affected in neonatal HIE, is crucial for dynamic routing of information across the brain and is integral to cognitive processes, including attention, memory, cognitive flexibility, movement monitoring and control.[38] The hippocampus is also susceptible to early HI, and hippocampal volumes in children with HI events are associated with later memory impairment.[39] With regard to the observed difficulties in working memory in our sample, we hypothesise that these may be associated with hippocampal injury In the case of language, the watershed pattern of brain injury in children with neonatal encephalopathy and cognitive development at age 2 years,[40] and with verbal IQ at age 4 year.[41] In a follow-up study at 2 years old of children with HIE, treated with TH, cortical/subcortical anomalies observed on neonatal MRI predicted subsequent language difficulties.[30] The Executive Functions and attention difficulties in our sample may be a consequence of widespread alterations in white matter tracts following early hypoxic-ischaemic injury. Imaging studies in typically developing persons indicate that executive functions are controlled by brain networks that involve dorsolateral, prefrontal, anterior cingulate and parietal cortices.[42] Such widespread fronto-cingulate-parietal networks will depend on functioning connecting pathways.[43,44] Routine clinical neonatal imaging, commonly used in clinical routine for early prediction of neurodevelopmental outcome after neonatal HI, or conventional structural MRI later in childhood, will not be sufficiently sensitive to identify possible alternations in brain networks after HIE, and future work should combine specific and focused cognitive and behavioural assessment, alongside advanced neuroimaging for characterisation of anatomical and functional brain networks, in order to consider the neural underpinnings of the findings we report.

There are limitations to this study. The sample size was relatively small, although in line with other studies in children with HIE,[12] and future work should increase this. Assessors were not blind to whether children were in the HIE or control group, and while the use of standardised assessments mitigates the risk of bias, it is possible that some could remain.

In conclusion, in our small clinical cohort of children with HIE treated with TH, and in the absence of major neuromotor impairment, our data suggest that children with HIE treated with TH were not as school ready as their classroom counterparts. However, this requires replication with a larger sample. Educational professionals should be aware of the difficulties these children might face on starting school, enabling them to identify those who would benefit from early interventions. Our findings have implications for long-term follow-up of children with HIE treated with TH, suggesting that this should continue until they start school.

## ACKNOWLEDGEMENTS

We thank children and parents/caregivers for participation, S. Helps for help preparing the ethics application and M. Schreglmann for contributions to study set-up.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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**How to cite this article:** Edmonds CJ, Cianfaglione R, Cornforth C, Vollmer B. Children with neonatal Hypoxic Ischaemic Encephalopathy (HIE) treated with therapeutic hypothermia are not as school ready as their peers. Acta Paediatr. 2021;00:1–10. https://doi.org/10.1111/apa.16002

## APPENDIX 1

Criteria for therapeutic hypothermia for treatment of neonatal HIE following perinatal asphyxia: Gestational age ≥36 weeks; at least one of the following: Apgar score of 5 or less 10 min after birth; continued need for resuscitation, including endotracheal or mask ventilation, 10 min after birth; or acidosis (defined as pH <7 or base deficit >15 mmol/L, or both, in umbilical cord blood or any blood sample within 1 h of birth),[45] and showed signs of moderate-to-severe encephalopathy. Severity of encephalopathy was classified using modified Sarnat and Sarnat staging, including altered state of consciousness, abnormal tone and abnormal primitive reflexes. In line with our centre's clinical protocol, which aims to avoid delay in initiation of TH, amplitude integrated EEG (aEEG) was not used to determine initiation of TH.