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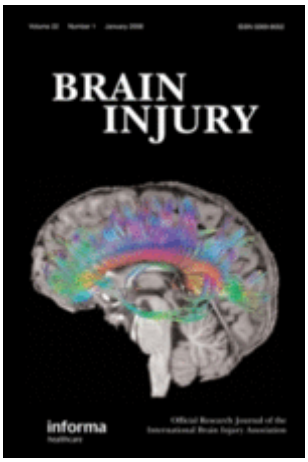

Attention and visuo-spatial function in children without cerebral palsy who were 'cooled' for neonatal encephalopathy: a case-control study.

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Abstract:

Objectives: Dorsal-stream functions are vulnerable to early brain injury associated with neonatal encephalopathy (NE) following perinatal asphyxia, even in children not developing cerebral palsy (CP). Since therapeutic hypothermia (TH) became the standard treatment for NE, the incidence of CP is reduced but the impact on dorsal-stream functions is unknown. We aimed to compare dorsal-stream functions in TH-treated survivors of NE, without CP, with those of matched controls.

Methods: We administered tests of dorsal-stream function to 29 case children aged 6-to-8 years treated with TH for NE and without CP, and 20 age, sex and social class matched controls. We used the Conner's Continuous Performance Test (CPT) 2nd Edition to assess attentiveness, based upon Hit Reaction Time (HRT) percentile score and HRT standard error percentile, the CPT HRT block change measure to assess sustained attention and the NEPSY-II block construction and arrows tests to assess visuo-spatial performance and mental rotation.

Results: Case children performed significantly worse than controls on measures of attention and visuo-spatial function.

Conclusions: Children given TH treatment for NE can have subtle attention difficulties with slower reaction times and reduced visuo-spatial processing. These findings illustrate the continued vulnerability of dorsal-stream functions following NE despite the use of TH.

INTRODUCTION

Neonatal encephalopathy (NE) secondary to intrapartum events affects nearly 1.15 million babies worldwide. (Lee et al., 2013). Children with NE are at an increased risk of developing motor, cognitive and visuo-spatial, sensorimotor, attention and executive impairments (Marlow et al., 2005). Clinical trials have shown that moderate cooling following NE,

(reducing the core temperature to 33-34°C within 6 hours of birth for three days - termed therapeutic hypothermia (TH)) reduces death and disability at 18 months (Jacobs et al., 2013), the incidence and severity of cerebral palsy (CP) (Jary et al., 2015) and furthermore, survival with an IQ>85 is increased (Azzopardi et al., 2014). TH is now the standard care for infants with NE (NICE, May 2010).

In one of the two clinical trials of TH known as 'the Toby trial,'(Azzopardi et al., 2014) the infants who received TH, compared to the non-cooled group, had higher attention and executive function scores and comparable visuo-spatial function assessed using the "NEuroPSYchological" Assessment second edition-NEPSY-II) (Holcomb and Davis, 2011). In the other clinical trial, the NICHD trial (Shankaran et al., 2012), the proportion of children with attention and executive function or visuo-spatial scores (below a standard score of 70) did not differ between the TH and non-cooled groups. Both studies included children with and without CP and compared the attention, executive and visuo-spatial scores to the test norm. Although cooling reduced the occurrence of severe disabilities, it is not known whether subtle impairments in attention and visuo-spatial function will remain in cooled children without severe disabilities such as CP.

It is methodologically problematic that both of these studies reported only index scores (created from amalgamating individual tests designed to assess separate sub-components of executive function and attention). Executive functions include a range of abilities, such as assigning priority to tasks, sequencing, planning, initiation, inhibition, fluency emotional regulation, processing speed and managing the resources of attention. Separate tests are used to assess these discrete components of executive function, but then they are commonly collapsed in assessment tools (as index scores) to create a single index score of executive function and attention. Lower-scores are then commonly 'smoothed-out' by the averaged, or amalgamated index-score. Such an approach can inflate Type II error rates (Tonks et al., 2014). Thus in both

of the studies to date, reporting only index scores could have masked more subtle strengths and weaknesses in the neuropsychological profiles of these groups. We further note that the attention tasks used in the studies were of relatively short duration, and so placed low demands upon sustained attention.

One theory of relevance in understanding how NE may affect attention and visuo-spatial functions is the Dorsal Stream Vulnerability model (Atkinson et al., 2003, Atkinson & Braddick, 2011). Visual processing is divided into two specialized extra-striate streams; a ventral stream, or 'what' stream projecting from the visual cortex to temporal lobe structures, which is integral to object processing; and a dorsal stream, or 'where' stream projecting from the visual cortex to the parietal lobe, which is essential in spatial processing (Felleman and Van Essen, 1991, Young, 1992, Milner and Goodale, 2006). Selective, rapid visual attention processes in location and movement of objects, and visuo-spatial functions (such as spatial transformation and visuo-spatial relations) are dependent on the "dorsal stream" pathway in the brain (Spencer et al., 2000, Atkinson and Braddick, 2011). Previous studies have indicated that abilities that we now associate with dorsal stream function do appear to be affected by perinatal brain injury, and particularly hypoxic-ischemic injury (Mercuri et al., 1997, Mercuri et al., 1999). It is therefore reasonable to hypothesize that children cooled for NE who do not have problems severe enough to cause CP could still have effects on dorsal stream functions, despite treatment. Children with early (though not neonatal) brain injury commonly have problems with visuo-spatial relations, which often become more apparent at around 10 years (Tonks et al., 2009a). That is, visual-spatial tests are sensitive in differentiating between healthy children and children after brain injury. Similar findings have been reported in relation to attention difficulties which can also become more evident from 10 years, with attention-switching skills having some interdependence with later developing executive function (Tonks et al., 2011).

In summary, little is known about subtle visual attention processing, and visuo-spatial abilities associated with dorsal-stream function in children who were cooled as standard care for NE. In this study we compared performance on tests of attention and visuo-spatial function, between children aged 6-8 years who were cooled for NE and did not develop CP, and matched 'healthy' control children, in order to determine whether there is evidence of subtle, enduring brain injury effects.

METHOD

This was a prospective case-control study conducted between October 2016 and October 2017 within the University of Bristol, UK with ethics approval from the North Bristol Research Ethics Committee (REC ID:15. SW.0148) and the Health Research Authority.

Participants:

Cases: Eligibility criteria were as follows: gestation at birth ≥36 weeks, treatment with TH as standard clinical care, based on TOBY trial eligibility criteria including signs of perinatal asphyxia and moderate to severe encephalopathy confirmed by amplitude integrated electroencephalogram (aEEG)(Azzopardi et al 2009). All the children had English as their primary language and did not have an additional medical diagnosis other than NE.

Cases were selected from the cohort of children who received TH for NE between 2008 and 2011. These data are maintained by the Bristol Neonatal Neurosciences group at St Michael's Hospital, Bristol, UK. A diagnosis of CP was ruled-out from the assessment at 2 years and reconfirmed at 6-8 years assessment. Forty potential cases were identified after inclusion/exclusion criteria were applied.

Controls: The study sample was compared to a control group of children matched for age, sex and socio-economic status (SES). SES was defined based on the national readership survey (NRS) A, B, C1, C2, D and E criteria (2015). Exclusion criteria included children born before 36 weeks gestation, any history of NE or other medical issues of a neurological nature, and English not being the primary language. Children who were best matched to the case in terms of age, sex and social class were invited to participate in the study.

Procedure and measures

Cases and controls attended for a single day of testing at the Clinical Research and Imaging Centre (CRIC), Bristol. Written informed consent was obtained from the parents and the participants. We administered selected, standardised tests that assess performance in visuo-spatial function and attention (details of each test are provided below). Each participant was tested individually in a quiet testing room by assessors who were unaware of case/control status.

Measures.

Attention Measures:

The Conners Continuous Performance Test (CPT) 2nd Edition (16) (Conners et al, 2004) assesses attention-related problems in individuals from 6-years through to adulthood. During a 14-minute, 360 trial administration, children are required to respond by clicking a computer mouse when any letter appears on a computer screen, except the non-target letter "X." By assessing the participant's response times across the test (and comparing the participant's mean-score to the mean score of the published normative sample), it is possible to understand

performance in areas of inattentiveness, and/or sustained attention. Three CPT measures that provide percentile scores for response time were focused upon for this study. These were:

- ***Overall Hit Reaction Time (HRT)***: Each time a trial is presented to the participant and they correctly respond, a response time is recorded. The overall HRT is the mean correct response-time from the 360 trials, which is given as a percentile for comparison against the population norm. It provides an indication of efficiency in selectively processing targets and can therefore index inattentiveness. Higher scores indicate worse performance.
- ***HRT Standard Error of the Mean***: this is a measure of response speed consistency for correct items throughout the administration of the test. The higher the overall standard error (SE) of mean percentile, the greater the inconsistency in the response speed. Response speed inconsistency is indicative of inattentiveness and can indicate when a participant is less engaged or processing stimuli less efficiently during parts of the test-administration. The mean percentile for both overall HRT and HRT SE of the Mean is 50. One standard deviation (SD) is a score of 84, 2 SDs is 98.
- ***HRT by Block (HRT Block Change)*** HRT Block Change measures change in reaction time across the duration of the test. High values of HRT Block Change indicate a substantial slowing in reaction times. Low values indicate that responses got quicker as the test progressed. If reaction times slow down, as indicated by a higher HRT Block Change score, the participant's information processing efficiency declines, and a loss of sustained attention is indicated.

Visuo-spatial mental rotation and visual discrimination:

The NEPSY-II Block construction test (Korkman et al., 2007) was used to assess visual-spatial performance in a task of mental rotation/transformation. Participants were presented with images of block designs (towers and other forms) and blocks for design construction. Each image depicts complex arrangements of various numbers of 3D cubes positioned in structures. The task is to visualise and construct the designs based upon studying the image before them. Scaled-scores were utilised.

The NEPSY-II Arrows' test (Korkman et al., 2007) was administered as a measure of visual discriminatory skill. Participants were presented with images of arrows around a target. Only two arrows were on a trajectory to directly hit the target. The task is to identify the arrows that will hit the centre of the target. Scaled scores were utilised. Average scaled scores range from 8 to 12, scores <7 are 1SD below the mean, scores of 5 are considered borderline for impairment and scores of 4 or less are considered to represent impairment.

Study size

Forty eligible case children were identified. Seven families could not be traced and 4 families were not willing to participate in the study leaving 29 participants in the case group. One of the case-participants did not complete the CPT-2 test leaving 28 case children for the analysis of CPT performance. The control children were recruited from schools in and around the Bristol area. We contacted 133 schools to ask if study information could be put in their school-newsletter. In accordance with Ethics protocols, schools were excluded if any case participant was a pupil. Fifty-one families volunteered to participate. We best-matched 20 control children with the case group based on age, sex and social class. Two of the control-participants refused to complete the CPT-2 test leaving 18 control children for the analysis of CPT performance.

The NEPSY-II Block construction and the Arrows test were completed by all 29 cases and 20 control children.

Statistical methods

Checks for *departure from normality* were undertaken on all data for analysis using Shapiro-Wilk's test. Checks of *homogeneity of variance* were undertaken using Levene's test. We used independent *t-tests* with group (case/controls) as the independent variable. Analysis 1 was undertaken with HRT Block Change as the dependent variable, analysis 2 was undertaken with visuo-spatial (Block construction) results as the dependent variable, and analysis 3 was undertaken with visual discrimination (NEPSY-II Arrows) as the dependent variable. Two further analyses were undertaken (in considering Overall HRT and HRT SE of the mean) using Mann-Whitney U testing on mean ranks due to unequal variance and departure from normality. All analyses were performed using IBM SPSS version 24 (IBM Corp., Armonk, NY, USA). All reported p values are two tailed and $p < 0.05$ was considered as significant.

Results

In case children the median (IQR) Apgar score at 10 mins was 6 (5, 8). Median (IQR) pH value within 1 hour of birth was 6.9 (6.8-7.1). The aEEG patterns were moderately abnormal in 93% (27/29) and severely abnormal in 7% (2/29).

Cases were matched with controls for age (mean (SD): 7.0 years(0.5) versus 7.0 years (0.6)), sex (males: 69% versus 60%) and social class (upper middle class: 14% versus 15%; middle class: 28% versus 30%; lower middle class 21% versus 20%; skilled working class 24% versus 25%; working class: 10% versus 10% and casual worker or unemployed: 3% versus 0%).

Differential Performance in attention:

Comparison of the mean rank of the overall HRT percentiles indicated significantly slower response-times in the case children (84.1, Mean Rank 27.0) compared to the control children, (67.3, Mean Rank 17.89), [U=151.5, p=.024]. Similarly, HRT SE of the mean indicated greater variability in performance in case children (Mean Rank 26.8) compared to the control children (Mean Rank 18.2), [U=157, p=.032]. Figure 1 shows the distribution of scores for cases and controls on these measures, where higher percentiles indicate slower response-times (and therefore worsening score). A larger number of cases compared to controls performed poorly on these tests; the proportion of case and control children below 2SD (98th percentile) were 32% versus 11% respectively for HRT, and 18% versus 11% respectively for HRT SE. Additionally, many more cases than controls performed below 1SD (84th percentile), specifically, 57% versus 33% for HRT percentile and 50% versus 33% for HRT SE.

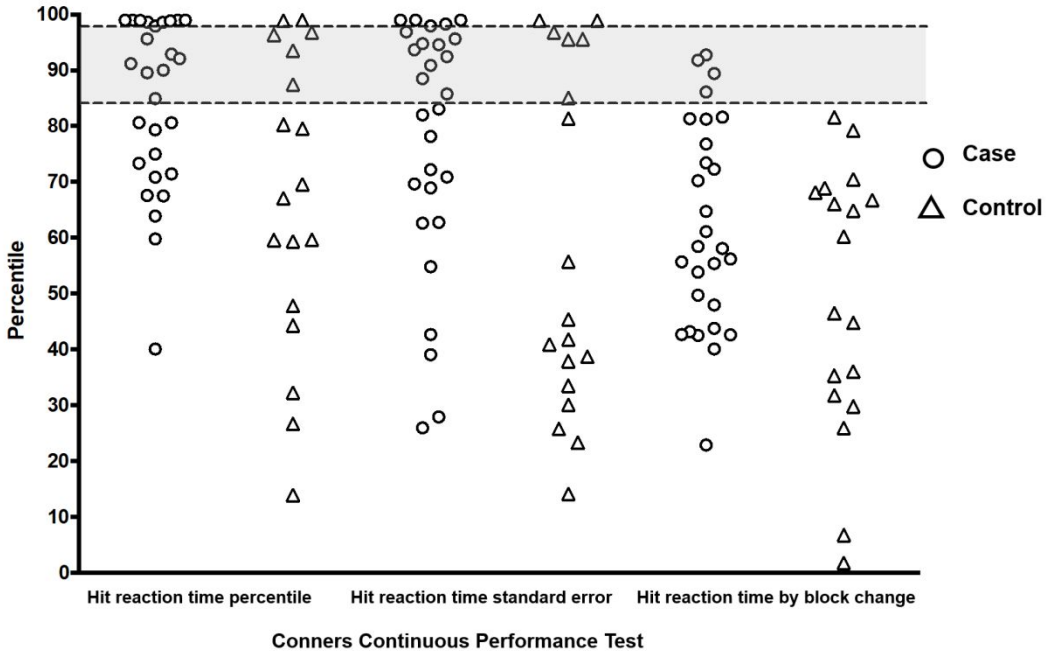

***Figure 1**: Distribution of scores for cases and controls: Overall Hit Reaction Time (HRT), HRT standard error of the mean and HRT change across each block of the Conner's Continuous Performance Test. Dotted lines mark 1 and 2 SD cut-offs.*

In considering HRT by block, the control group mean was marginally below the 50th percentile (M=49.1, SD 23.9) while the mean for the case children was higher (M=61.9, SD 18.4) indicating that they had worse (slowed) performance as the assessment progressed. This difference was significant [t (44)=-2.04, p = .047]. Figure 1 shows the distribution of scores for cases and controls for HRT by block, where a higher percentile indicates slower response-times (and therefore worsening score). Again, more cases (14%) than controls (0%) perform below 1SD (84th percentile).

Differential performance in visual-spatial mental rotation, and visual discrimination tests:

Case children had significantly worse scores than control children for visual discrimination [$t(47)=2.02$, $p=.049$] and for the visuo-spatial mental rotation task [$t(47)=-2.18$, $p= .034$]. (Figure 2) More cases than controls performed below 1SD (scaled score <7) (Visual Discrimination: Cases 10% Controls 5%. Visuo-spatial mental rotation: Cases 17%, Controls 5%).

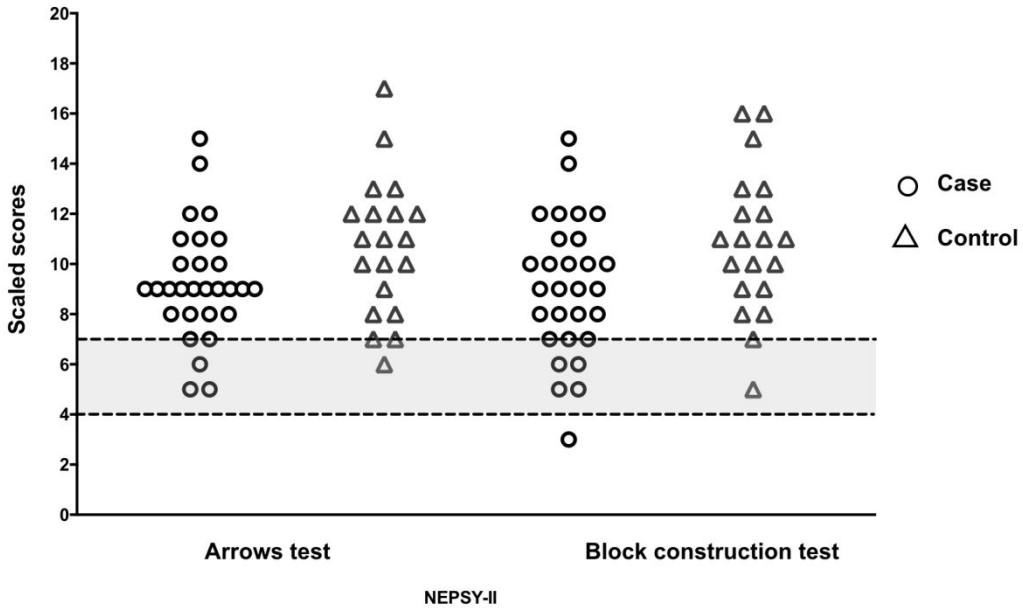

***Figure 2**: Distribution of scores for cases and controls: Scaled scores for the Arrows Test and Block Construction Test from the NEPSY-II. Dotted lines mark 1 and 2 SD cut-offs.*

DISCUSSION

We undertook tests of attention ability and visual-spatial processing in children treated with TH after NE who did not develop CP and compared them to matched controls. In summarising our findings in relation to attention, we note that the case children compared to the controls had higher response speed percentiles indicating slower response times, greater inconsistency in their response speed and worsening reaction times over the duration of assessment. Taken together these results are indicative of reduced efficiency in attention processing, and loss of sustained attention at a rate that is significantly different to age-matched control peers. Analysis of group differences in visual-spatial function, similarly showed that the case group performed significantly worse than same age peers.

Attention problems have been reported in the pre-cooling era for children who were defined as having moderate to severe NE based on a broad clinical definition and who did not develop CP. Of those children nearly 11% were reported to have attention problems assessed using the NEPSY-II and Child Behaviour Checklist at 5-16 years (Hayes et al., 2018). At 6.5-9 years children with medical histories of severe encephalopathy had significantly lower attention and executive scores assessed using the NEPSY than children with moderate encephalopathy and a control group. Additionally, the moderate encephalopathy group had lower scores than a matched control group (Marlow et al., 2005). At 15-19 years, children who have had moderate encephalopathy were compared to control children and were noted to score higher on the Inattention subscale of the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale-IV (Lindström et al., 2006).

The school age (6-7 years) follow-up data from the clinical trials of TH for NE (including children with CP) reported varying results, with the TOBY trial finding higher attention and executive scores in the cooled group than the non-cooled group (Azzopardi et al., 2014) and the NICHD trial reporting similar scores between the cooled and control group (Shankaran et

al., 2012). The clinical trials combined attention and executive function into a single measure in order to understand the effects of TH as did the studies in the 'pre-hypothermia era'. Given that executive functions develop across the span of childhood and adolescence, with most significant advances arising with pre-frontal cortex development after 10-to-12 years in healthy maturation (Tonks et al., 2017), it seems probable that any immediate, but subtle attention-based difficulties could have been concealed by the methodological approach used, which did not base test selection on early brain injury models of post-injury attention and visuo-spatial development. We compared performance differences between healthy children and children treated with TH after NE, focusing more specifically upon the dorsal-stream vulnerability hypothesis in exploring outcome after TH. Our approach recognises a temporal (early vs late) evaluation of the effects of NE, which considers the effect of brain growth and the changing nature of neuropsychological abilities as children mature. Dorsal-stream functions of visuo-spatial mental rotation and attention efficiency in terms of response-times were focussed upon here, based upon the current age of the sample, and the patterns of neuropsychological difficulty that might be predicted after NE. Mean HRT is shown to be associated with hyperactivity and mean HRT SE is related to hyperactive-impulsive and inattention symptoms in a cohort of children with attention deficit hyperactivity disorder (Epstein et al., 2003).

In non-cooled children without CP, visuo-spatial function was reported to be impaired in nearly 5% of children aged 3-4 years (Hayes et al., 2018), and children who have had severe NE had significantly lower scores than children with moderate encephalopathy at 6.5-9 years (Marlow et al., 2005). In children aged 6-7 years (including children with CP) who underwent TH the visuo-spatial processing scores did not differ from the non-cooled group (Azzopardi et al., 2014, Shankaran et al., 2012). Our findings support the dorsal-stream vulnerability model in this age group and our findings indicate that sustained attention and visual-spatial processing

can be negatively affected in children with NE following TH, much as can be observed in children who had NE and who have received no treatment.

Our study is limited by sample-size. Future research utilizing a longitudinal approach with larger samples is needed in order to enhance understanding of outcome, particularly in the context of age-related brain maturation.

In conclusion, based upon this preliminary study, despite therapeutic cooling, children who have had NE can have problems with attention and visuo-spatial function even in the absence developing severer problems such as CP. It, therefore remains important to maintain a temporal approach in following-up children treated with TH after NE, seeking to remediate difficulties that might emerge for individuals.

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Disclosure statement

The authors do not have any conflicts of interest to disclose.

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