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Neonatal White Matter Abnormalities Predict Global Executive Function Impairment in Children Born Very Preterm

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Neonatal White Matter Abnormalities Predict Global Executive Function Impairment in Children Born Very Preterm

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Using prospective longitudinal data from 110 very preterm and 113 full term children, this article describes the executive functioning abilities of very preterm children at age 4, and examines relations between the extent of white matter abnormality on neonatal magnetic resonance imaging (MRI) and later executive function outcomes. Very preterm children performed less well than full term children on measures of planning ability, cognitive flexibility, selective attention, and inhibitory

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control. Executive impairments at age 4 were confined to preterm children with mild or moderate—severe white matter abnormalities on MRI. Findings support the importance of cerebral white matter integrity for later executive function.

Children born very preterm are at an increased risk for global cognitive impairment. They obtain IQ scores that are on average 10.9 points lower than their full term peers (Anderson & Doyle, 2008; Aylward, 2002; Bhutta, Cleves, Casey, Cradock, & Anand, 2002), and up to 50% will be subject to significant cognitive delay by school age (Doyle & Saigal, 2009; Johnson, 2007; Saigal & Doyle, 2008). These high rates of cognitive impairment and their effects on school achievement have become a focus of wide international concern. As a result, research efforts have increasingly sought to clarify the specific cognitive difficulties associated with preterm birth, as well as the neural mechanisms that place some very preterm children at risk of cognitive impairment while others remain relatively spared. Such knowledge is vital for preventative efforts and the development of appropriately targeted interventions to improve the cognitive, educational, and psychological well being of children born very preterm.

The most common form of brain injury affecting children born very preterm consist of diffuse non-cystic white matter abnormalities (Back, 2006; Back, Riddle, & McClure, 2007; Boardman & Dyet, 2007; Inder, Wells, Mogriddle, Spencer, & Volpe, 2003). These abnormalities, which are readily detected with conventional magnetic resonance imaging (MRI) in the neonatal period, include white matter signal abnormalities, enlargement of the lateral ventricles, white matter volume loss, delay in myelination, and thinning of the corpus callosum (Inder, Anderson, Spencer, Wells, & Volpe, 2003; Inder et al., 2003; Maalouf et al., 1999; Woodward, Anderson, Austin, Howard, & Inder, 2006). Recent estimates from MRI studies suggest that about a fifth of infants born very preterm are subject to moderate to severe white matter abnormalities and a further 50% to mild white matter abnormalities (Cheong et al., 2009; Inder et al., 2003; Miller et al., 2005). These high and relatively stable rates of diffuse white matter abnormalities stand in marked contrast to recent declines in other forms of brain injury associated with preterm birth and poor outcome, such as periventricular haemorrhagic infarction (PHI) and cystic periventricular leukomalacia (PVL) (Boardman & Dyet, 2007; Volpe, 2009). Furthermore, these rates are fairly comparable with the later risks of cognitive impairment in this group (Boardman & Dyet, 2007).

Diffusion tensor imaging (DTI) studies provide support for the validity of conventional MRI measures as markers of early white matter pathology (Cheong et al., 2009; Huppi & Dubois, 2006; Huppi et al., 2001; Inder, Warfield, Wang, Huppi, & Volpe, 2005; Miller et al., 2002; Rose et al., 2008; Skranes et al., 2007). For example, in a recent sample of 111 very preterm infants, Cheong et al. (2009) found that more extensive white matter signal abnormalities on conventional MRI were linearly related to concurrent changes in a number of diffusion parameters. Specifically, compared with infants with no or only focal white matter signal abnormalities, infants with more extensive abnormalities showed significantly higher levels of radial diffusion (water movement perpendicular to the axon) across sensorimotor regions bilaterally and in the right internal capsule. Radial diffusion, which is a marker of myelination and the integrity of oligodendroglial cells, is known to be vulnerable with preterm birth. Corresponding declines in fractional anisotropy values were also found within the internal capsule, and right frontal and occipital regions, suggesting that preterm infants with more extensive white matter signal abnormalities were characterized by less mature fiber tract organization.
In line with these findings, a serial DTI study found that infants without white matter abnormalities showed developmentally appropriate increases in anisotropy from birth to near term (Miller et al., 2002). In contrast, these increases were not seen in very preterm infants with moderate white matter abnormalities. Infants with mild white matter abnormalities were found to also share some of these risks, but in a more regionally specific way, with the absence of anisotrophic gains seen only in frontal white matter. These results suggest that as cerebral development proceeds, early white matter injury in the preterm infant may adversely impact connectivity and myelination beyond the site of the initial injury, with some regions being potentially more vulnerable than others.

Collectively, these studies provide valuable insight into the effects of white matter injury on axonal development and myelination, as well as helping to confirm the validity of clinically useful, conventional MRI measures of cerebral white matter abnormality in the high risk preterm neonate (Boardman & Dyet, 2007; Huppi et al., 2001; Volpe, 2009). They also raise the possibility that early neonatal exposure to white matter abnormalities could play an important role in the evolution of later cognitive impairments known to affect a substantial proportion of children born very preterm.

To date, very few studies have examined the impact of these early white matter abnormalities on later cognitive functioning (Hart, Whitby, Griffiths, & Smith, 2008). Those that do exist have reported on short term outcomes only (Beauchamp et al., 2008; Miller et al., 2005; Nagy et al., 2003; Woodward et al., 2006). There has also been a tendency for studies to focus on severe impairment or disability without considering the risks of less severe but clinically relevant neurocognitive impairments (Aylward, 2002). Nonetheless, converging evidence from a diverse set of studies provides increasing support for the importance of cerebral white matter abnormalities as an independent and important predictor of severe cognitive delay (Hack & Taylor, 2000; Miller et al., 2005; Woodward et al., 2006).

One important aspect of cognitive functioning that has been shown to be impaired in preschool and school aged children born very preterm is executive function (Aarnoudse-Moens, Smidts, Oosterlaan, Duivenvoorden, & Weisglas-Kuperus, 2009; Anderson, Howard, & Doyle, 2010; Mulder, Pitchford, Hagger, & Marlow, 2009). Executive function skills that are highly reliant on the integrity of white matter tracts within sub-cortical and cortical regions (Filley, 2001) enable an individual to manage, self-regulate, and engage in goal-directed behavior (Anderson, 2002; Lezak, 2004). Key components of executive function include inhibitory control, working memory, and cognitive flexibility, as well as more complex planning and organized search abilities involving the integrated coordination of these core components (Baughman & Cooper, 2007; Huizinga, Dolan, & van der Molen, 2006; Miyake et al., 2000). Importantly, these skills have also been shown to be predictive of children’s later educational achievement (Blair & Razza, 2007; Clark, Pritchard, & Woodward, 2010; Marlow, Hennessy, Bracewell, & Wolke, 2007).

Although relatively few studies have examined the development of executive function abilities in preschool children born very preterm, existing studies do suggest that, as a group, these children are at elevated risk for executive impairments (see Howard, Anderson, & Taylor, 2008). Observed impairments in executive function from preschool to early school age have been found in working memory (Clark & Woodward, 2010; Edgin et al., 2008; Espy et al., 2002; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004; Woodward, Edgin, Thompson, & Inder, 2005), inhibitory control (Aarnoudse-Moens et al., 2009; Edgin et al., 2008; Espy et al., 2002), planning, switching, and attention (Anderson & Doyle, 2004; Espy et al., 2002; Taylor, Minich, Klein,
& Hack, 2004; Vicari et al., 2004), with effect sizes in the small to medium range (Howard et al., 2008). Few studies, however, have examined linkages between the extent and severity of cerebral white matter abnormalities on neonatal MRI and the development of executive functioning skills during the preschool period. Of those that have considered this issue, most have tended to focus on a single component of executive functioning such as working memory (Clark & Woodward, 2010; Woodward et al., 2005) or inhibitory control (Edgin et al., 2008). Although informative, these analyses provide limited information about the specificity or pervasiveness of executive impairments among children born very preterm. Given the multidimensional nature of executive functions, a comprehensive evaluation of a broad range of skills is needed to fully understand the profile of executive functions in this population. Late preschool age represents an appropriate time to attempt a comprehensive assessment of this kind since most executive skills have begun to emerge and are developing rapidly (Garon, Bryson, & Smith, 2008). By this age, children also have sufficiently sophisticated language and motor skills to enable the assessment of a broad range of executive skills.

The overall objectives of the present study were to describe the executive functioning profile of preschool children born very preterm, and to examine the relationship between the severity of cerebral white matter abnormalities on term MRI and a range of executive functions. The specific aims and hypotheses of the study were as follows.

1. To compare very preterm and full term children’s performance on a range of executive processes assessed at age 4 years (corrected for the extent of prematurity). These processes included response inhibition, cognitive flexibility and set shifting, planning, organized visual search, and goal-directed behavioral regulation. We hypothesized that very preterm children would demonstrate impairment across all executive processes.

2. To examine the relationship between the severity of white matter abnormalities on MRI at term equivalent age and very preterm children’s performance on measures of executive function at 4 years of age. We hypothesized that very preterm children with white matter abnormalities on term MRI would demonstrate global executive impairment relative to full term children, with the degree of this impairment being linearly related to the severity of earlier neurological pathology.

**METHODS**

**Participants**

The study sample consisted of two groups of children who are being followed as part of a prospective longitudinal study of the neurodevelopmental consequences of very preterm birth. These two study groups are described below.

**Very preterm.** The first group was a cohort of 110 children born very preterm ($\leq$32 weeks gestation) who were admitted consecutively into a level III neonatal intensive care unit at Christchurch Women’s Hospital, New Zealand from November 1998 to December, 2000. During the two-year recruitment period, 129 very preterm infants met study criteria. In total (10 deaths, 4 missed, 5 refusals), 92% of all eligible infants were recruited at birth, leaving a total $n$ of 110
infants. Exclusion criteria included congenital abnormalities and non-English speaking parents. Of those children surviving to corrected age 4 years, 98% \((n = 107)\) were seen at followed up. Three further children were excluded from this analysis due to blindness \((n = 1)\), severity of cognitive impairment \((n = 1)\), and lost MRI data \((n = 1)\).

**Full term.** The comparison group comprised 113 children born full term (37–41 weeks) who were recruited at age 2 and followed to age 4 years. These children were identified from hospital birth records \((N = 7,200)\). For each very preterm child born and recruited, the second previous or second next child on the hospital delivery schedule was identified and the parents invited to participate in the study. Children were matched for gender. Of those identified, 62% \((n = 113)\) were recruited. Reasons for non-participation included: untraceable (47%), moved overseas (12.5%), refused (12.5%), and agreed but unable to schedule an appointment within the 2-week assessment window due to illness or family circumstances (28%). No significant differences were found between recruited and non-recruited infants on measures of birth weight, gestation, gender, socioeconomic status, family type, or ethnicity. Comparison of the socioeconomic profile of families in the full term group with regional census data also showed that these families were highly representative of the region from which they were recruited. Retention to age 4 was 96% \((n = 108)\). Of these children, three were not included due to incomplete data. Table 1 describes the infant clinical and family background characteristics of the two study groups.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics of the Sample</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Infant Clinical Characteristics</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Full Term</strong> ((N = 105))</td>
</tr>
<tr>
<td>M (SD) Gestation</td>
</tr>
<tr>
<td>M (SD) Birth weight</td>
</tr>
<tr>
<td>% Male</td>
</tr>
<tr>
<td>% Multiple birth</td>
</tr>
<tr>
<td>% Small for gestational age</td>
</tr>
<tr>
<td>% Chronic Lung Disease</td>
</tr>
<tr>
<td>% Sepsis</td>
</tr>
<tr>
<td>% Maternal fever &gt; 38°C</td>
</tr>
<tr>
<td>% Postnatal steroids (Dexamethasone only)</td>
</tr>
<tr>
<td>% Grade III/IV Intraventricular haemorrhage</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia</td>
</tr>
<tr>
<td><strong>Family Social Background</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Full Term</strong> ((N = 105))</td>
</tr>
<tr>
<td>M (SD) Maternal age</td>
</tr>
<tr>
<td>% European ethnicity</td>
</tr>
<tr>
<td>% Mother no formal educational qualifications</td>
</tr>
<tr>
<td>% Semi/unskilled SES status</td>
</tr>
<tr>
<td>% Single parent</td>
</tr>
</tbody>
</table>
Measures

*Magnetic Resonance Imaging (Term)*

In addition to comprehensive clinical data collected throughout the hospital period, all children born very preterm had a structural MRI scan at term equivalent age. Unsedated infants were settled, wrapped, and placed in a Vac Fix bean bag and then scanned using a 1.5T GE Signa System with previously documented sequences (Inder et al., 2003). Each infant’s scan was graded using a standardized scoring system consisting of five 3-point scales assessing the nature and extent of white matter signal abnormality, periventricular white matter volume loss, the presence of cystic abnormalities, ventricular dilation, and thinning of the corpus callosum. All scans were scored by a blinded pediatric radiologist, and independently reviewed by a pediatric neurologist (TI). Inter-rater agreement was 95%, with discrepancies resolved by consensus. Based on their total white matter abnormality scores, preterm infants were classified as follows: (1) no abnormalities (score of 5–7, $n = 22$), (2) mild abnormalities (score of 8–10, $n = 61$), or (3) moderate to severe abnormalities (score > 10, $n = 19$). Further details regarding this scoring system are available in the online supplement to Woodward et al. (2006).

*Executive Function Measures (4 Years)*

At age 4 years (corrected for the extent of prematurity), all participants were invited to attend a neurodevelopmental assessment at our university-based research house. As part of this assessment, children completed a short form of the Wechsler Preschool and Primary Scales of Intelligence (WPPSI–R) and a battery of four executive function tasks. The WPPSI–R short form consisted of two verbal subscale tests (Comprehension, Arithmetic) and two Performance subscale tests (Picture Completion, Block Design). All measures were administered in a fixed order to minimize the confounding influence of fatigue. All procedures and measures were approved by the regional ethics committee and written informed consent was obtained from all parents/guardians. The four executive function tasks were as follows.

**Tower of Hanoi.** The three disk version of the Tower of Hanoi provided a measure of planning ability (Simon, 1975; Welsh, 1991). The task apparatus consisted of two identical platforms (30 cm long and 9 cm wide), one used by the examiner and the other by the child. Each platform held three equal sized upright pegs. Placed on these pegs were 2 to 3 disks of varying size that allowed for five different pattern configurations across the three pegs. The task involved the examiner showing the child a series of model configurations and asking them to copy the examiner’s model by transferring their own disks from the start home peg to the other pegs. Three rules had to be followed: (1) disks could not rest anywhere but on the pegs, (2) only one disk could be moved at a time, (3) a larger disk could not be placed on top of a smaller disk. Before beginning the task, each child’s understanding of the task rules was checked on two training trials. Once this was confirmed, test trials commenced, with the child asked to replicate a series of increasingly difficult disk configurations (Levels 2 to 7) in as few moves as possible. The number of moves required to complete a configuration ranged from 2 (Level 2) to 7 (Level 7). At each move level (2, 3, 5, and 7) there were two trials, resulting in a total of 8 potential trials overall. Levels 2 to 3 used only two disks. At level 5, a third disk was introduced and the task rules were reiterated.
Children were recorded as passing a trial if they reproduced the required configuration in as few moves as possible without breaking a rule. When children failed two consecutive trials at one level, the task was discontinued. Task performance was assessed using two measures: successful passing of the two training trials and the highest move level at which the child passed both test trials.

**Flexible Item Selection Task.** The Flexible Item Selection Task (FIST) was used to assess concept formation and cognitive flexibility (Jacques & Zelazo, 2001). The task consisted of nine stimulus cards. Each card contained three pictures that varied in terms of shape, color or size. One picture within this triad was able to be matched with the two other pictures on one of the above dimensions (e.g., it could be matched with one of the other pictures in terms of shape and the other in terms of color or size). Each task trial consisted of two phases. During the first phase (pre-switch), the examiner asked the child to “show me two pictures that are the same in one way,” necessitating the recognition that two pictures could be matched on one dimension (e.g., color). This phase provided a measure of concept formation and/or abstraction. In the second phase of each trial (switch), children were asked to now “show me two pictures that are alike in a different way,” necessitating a recognition two pictures could also be matched according to a different dimension (e.g., shape). This phase provided a measure of cognitive flexibility and/or shifting. Two practice trials were administered to allow children to become familiar with the task. If children did not demonstrate an understanding of the concept of selecting pictures that were the “same” or “different” during these practice trials the task was discontinued. Following practice trials, the test trials were administered. These were ceased if a child failed more than two consecutive trials. Two measures of task performance were recorded: the total number of correct abstractions (score range: 0–9) and the total number of correct cognitive flexibility trials (score range: 0–9).

**Visual Search.** A Visual Search task was used to assess selective attention and organized search (Welsh, 1991). The task consisted of a series of black and white line drawings that were presented on A3-sized sheets of paper. The objective of the task was for the child to correctly find as many target items \( N = 8 \) within the stimulus array as quickly as possible. The stimulus array also included 32 distractor items. An example of the target item for each trial was presented at the top of the array. Children were administered eight trials in which they were required to select eight target items (e.g., bananas). The child was asked, “What is this”? (with the examiner pointing to the picture). When the child had successfully identified the item, they were told, “Find all the _____ as quickly as you can. Tell me when you are finished.” The examiner timed the length of each search trial using a stopwatch. To minimize the motor demands of the task, children were asked to identify the targets by pointing and then the examiner placed a mark across the stimulus. Total errors were recorded (e.g., child pointing to the same item twice or selecting a non-target item). An efficiency score for each trial was calculated by dividing the total correct by the total search time (in seconds). Per trial efficiency scores were then averaged to produce an overall mean efficiency score (Welsh, 1991), with higher scores reflecting greater searching efficiency.

**Shape School.** The Shape School task for preschoolers was used to measure inhibition and cognitive flexibility (Espy, 1997). The task follows a storybook format, depicting cartoon
drawings of colored, shape figures (red, yellow, and blue; circles and squares) as response stimuli. There are four task conditions, which are presented in order of increasing difficulty: control, inhibit, switch, and inhibit/switch. Because children younger than 4 years typically under perform in the inhibit/switch condition (see Espy, 1997), the data for this condition are not reported here (see also Aarnoudse-Moens et al., 2009). Prior to each test condition, children were required to respond correctly to a set of practice stimuli. If they were unable to do so, the task was discontinued. In the first control condition, study children were asked to name as quickly as possible the colors of 15 shapes that were arranged on a page in three rows of five. In the inhibit condition, children were told that shapes with happy faces were ready to go for school lunch, whereas those with sad faces were not. Children were asked to name as quickly as possible the color names of all the figures who were ready for lunch (i.e., the happy-faced shapes, \( N = 8 \)), but not the color names of those that were not ready (i.e., the unhappy-faced shapes, \( N = 7 \)). In the switch condition, six of the shape figures were shown wearing hats, while nine were without hats. Children were asked to name figures with hats by their shape and figures without hats by their color. Successful responding in this condition required the children to switch between two different response rules. Each condition was timed and errors recorded. For the inhibition and switch conditions, an efficiency score was calculated (efficiency = (number correct – number of errors)/time taken). The control condition served primarily as a baseline measure of processing speed (see Espy et al., 2006). The proportion of children who were unable to pass this condition due to non-compliance and/or color unfamiliarity was also examined.

Executive function composite. To obtain an overall measure of children’s executive function performance, principal components analysis was used to assess whether the four tasks described above loaded on a single common factor of executive function. A key variable from each task was identified for inclusion in this analysis based on two criteria: (1) the score that best captured the executive demand/s of the task and (2) the score that most discriminated between very preterm and full term children. These measures were: the highest move level achieved on the Tower of Hanoi; the total number of FIST switch trials passed; the overall Visual Search efficiency score; and the efficiency score for the Shape School inhibit condition. Children who had been unable to complete a task were allocated the minimum score achieved for the task. Results of this analysis showed that all four measures loaded onto a single common factor that explained 52% of the variance. Factor loadings were all above .6 and communalities were acceptable (> .4). Based on this analysis, an executive function composite score was computed for each study child by summing z-scores (based on the mean and SD of the full term group) for each task and standardizing to a mean of 10 and standard deviation of 2.

Statistical Analysis

Data analysis proceeded in three stages. First, the performance of children born very preterm and full term was compared on the WPPSI–R and on each of the four executive function tasks in addition to the composite executive function measure using either a chi-squared test of independence for dichotomous outcomes or a multivariate analysis of variance (ANOVA) for continuous outcomes. Multivariate ANOVA was used instead of t-tests in order to minimize Type 1 errors arising from multiple significance testing. These analyses were then extended to examine the extent to which any between group differences in task performance might be accounted for,
either in part or in full, by differences in family socioeconomic status (SES). This involved statistically adjusting all bivariate associations between group status and each executive function outcome for the effects of family SES using multivariate analysis of covariance (MANCOVA), logistic or ordinal regression models.

In the second stage of analysis, relations between the extent of earlier white matter abnormalities and later executive function outcomes were examined. For this analysis, all children in the very preterm group were classified on the basis of the severity of their cerebral white matter abnormalities on neonatal MRI (none, mild, moderate–severe). The task performance of these three preterm groups was then examined in relation to the task performance of children in the full term comparison group. This involved first examining the overall relationship between the severity of white matter abnormality and EF task performance using either the Mantel Haenszel Chi squared statistic or multivariate ANOVA, with tests for linear trends. Also examined were contrasts between each of the three preterm groups and the full term group.

In the final stage of the analysis, a multiple regression model was fitted to examine the extent to which the severity of cerebral white matter abnormalities on term MRI independently predicted global executive outcome in the very preterm children after all other social and medical risk factors shown in Table 1 were taken into account. This analysis was limited to the very preterm group given that few of the clinical risk factors associated with preterm birth were relevant for children born full term. Global executive outcome was measured using the composite executive function score described above. Model fitting was conducted using both forwards and backwards variable selection to identify the best fitting and most parsimonious model.

**RESULTS**

**Extent of Cerebral White Matter Abnormalities and Global Cognitive Delay Among Children Born Very Preterm**

On MRI at term equivalent, 23% (24/103) of very preterm infants showed no white matter abnormalities, 58% (60/103) showed mild, 15% (16/103) moderate and 3% (3/103) severe white matter abnormalities. Given the small number of children with severe cystic white matter abnormalities, children in the moderate and severe white matter abnormality groups were combined in all subsequent analyses.

At 4 years corrected age, children born very preterm obtained lower mean IQ scores than their same age full term peers (preterm: 95.4 ± 14.7 SD; term: 104.6 ± 13.5 SD, p < .0001), using a short form of the WPPSI–R. Examination of rates of overall cognitive delay showed that 25% of the very preterm group met criteria for mild cognitive delay, that is, IQ > 1 SD but < 2 SD below the full term group mean, and 8.7% for severe cognitive delay, that is, IQ > 2 SD below the full term group mean, compared to 11.4% and 1.9% for the full term group, respectively.

**Executive Functioning Profile of Children Born Very Preterm at Age 4 Years**

Table 2 provides a descriptive profile of the performance of the very preterm and full term groups on the four executive function tasks and the executive function composite measure. Across all
TABLE 2

Performance of Full Term and Very Preterm Groups on Executive Function Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Full Term (N = 105)</th>
<th>Very Preterm (N = 104)</th>
<th>p</th>
<th>Adj. p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tower of Hanoi†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Passed training trials</td>
<td>95.2</td>
<td>89.0</td>
<td>.10</td>
<td>.25</td>
</tr>
<tr>
<td>Mean (SD) Highest move level achieved</td>
<td>1.96 (1.38)</td>
<td>1.41 (1.29)</td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td>Flexible Item Selection Task</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Passed criterion trials</td>
<td>87.6</td>
<td>78.8</td>
<td>.09</td>
<td>.19</td>
</tr>
<tr>
<td>Mean (SD) Correct abstractions</td>
<td>6.98 (1.97)</td>
<td>6.51 (2.33)</td>
<td>.08</td>
<td>.07</td>
</tr>
<tr>
<td>Mean (SD) Correct cognitive flexibility</td>
<td>3.44 (2.19)</td>
<td>2.83 (2.14)</td>
<td>.04</td>
<td>.07</td>
</tr>
<tr>
<td>Visual Search</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Completed all task trials</td>
<td>98.1</td>
<td>91.3</td>
<td>.03</td>
<td>.05</td>
</tr>
<tr>
<td>Mean (SD) Total correct</td>
<td>6.71 (1.00)</td>
<td>6.28 (1.24)</td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td>Mean (SD) Efficiency score</td>
<td>.25 (.15)</td>
<td>.21 (.16)</td>
<td>.04</td>
<td>.03</td>
</tr>
<tr>
<td>Shape School</td>
<td></td>
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</tr>
<tr>
<td>% Completed control condition</td>
<td>99.0</td>
<td>87.5</td>
<td>.001</td>
<td>.01</td>
</tr>
<tr>
<td>Mean (SD) total correct on inhibit condition</td>
<td>13.49 (2.33)</td>
<td>12.79 (2.63)</td>
<td>.06</td>
<td>.07</td>
</tr>
<tr>
<td>Mean (SD) Inhibit efficiency score</td>
<td>.43 (.27)</td>
<td>.33 (.27)</td>
<td>.02</td>
<td>.02</td>
</tr>
<tr>
<td>Mean (SD) Total correct on switch condition</td>
<td>8.46 (3.67)</td>
<td>8.80 (3.28)</td>
<td>.53</td>
<td>.87</td>
</tr>
<tr>
<td>Mean (SD) Switch condition efficiency score</td>
<td>.04 (.16)</td>
<td>.05 (.15)</td>
<td>.65</td>
<td>.56</td>
</tr>
<tr>
<td>Executive function composite</td>
<td>10.52 (1.86)</td>
<td>9.46 (2.01)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Adj. for household socioeconomic status, †1 very preterm child excluded due to testing error.

measures, very preterm children performed less well than full term children. Effect sizes were generally small for individual tasks ($d < .4$), but in the moderate range for the executive function composite measure ($d = .54$).

**Tower of Hanoi.** There was a tendency ($p = .10$) for very preterm children to have more difficulty understanding the rules of the Tower of Hanoi task than children born full term. Very preterm children were also less likely to graduate to the higher move levels of the task, suggesting that these children engaged in less planning and displayed more impulsive problem solving ($p = .01$, $d = .34$). This between group difference remained significant after adjustment for family SES ($p = .01$).

**Flexible Item Selection Task (FIST).** After exclusion of those children who failed the task criterion trials (full term $n = 14$, very preterm $n = 22$), results showed the very preterm group tended to perform slightly worse on abstraction or concept formation trials ($p = .08$; $d = .22$) than the full term group. Both groups experienced difficulties on the cognitive flexibility or switch trials, with children in the very preterm group being less able to match a second set of pictures according to a new dimension ($p = .04$, $d = .31$). After adjustment for family SES, this between group difference on the switch phase of the task was reduced slightly ($p = .07$).

**Visual Search.** Results from this task revealed that very preterm children experienced greater difficulty selectively identifying target stimuli and using an efficient search strategy. Specifically, they were less likely to be able to stay on task to complete all test trials ($p = .03$), and when they did, correctly identified fewer target stimuli ($p = .01$) and obtained lower mean
search efficiency scores than their full term peers \( (p = .04) \). Effect size comparisons indicated small effect sizes for group differences in the number of correct items nominated \( (d = .38) \) and the efficiency of searching \( (d = .30) \). This pattern of results was robust to statistical adjustment for the effects of family SES.

**Shape School.** On the Shape School task, very preterm children were less likely to pass the control condition \( (p = .001) \) or to be able to complete all three task conditions \( (p = .02) \) than full term children. A MANOVA including the groups’ efficiency scores also revealed that Shape School performance was less efficient in the very preterm group \( (\text{Wilk's } \lambda = .96, F(3,169) = 3.41, p = .02) \), with condition-specific comparisons indicating that the very preterm group obtained lower mean efficiency scores on the inhibit condition \( (p = .02, d = .38) \) but not the switch condition \( (p = .65) \). Closer inspection of the performance of both groups on the switch condition suggested the presence of a developmental floor effect since almost all children obtained low efficiency scores. These findings remained largely unchanged after adjustment for the effects of family SES.

**Executive function composite.** Consistent with the findings for each of the individual executive function tasks, very preterm children as a group obtained lower performance scores than their full term peers on the composite executive function measure \( (d = .54, p < .0001) \). Also in line with previous findings, this difference remained after statistical adjustment for family SES \( (p < .0001) \).

Executive Functioning Outcomes of Very Preterm Children With Varying Degrees of Cerebral White Matter Abnormalities

Table 3 describes the executive task performance of very preterm children with no, mild, and moderate–severe white matter abnormalities relative to their full term peers. As shown, there was clear evidence of a relationship between the extent of cerebral white matter abnormalities and children’s task performance on the Tower of Hanoi (planning), Visual Search (selective attention), Shape School (inhibitory control), and executive function composite measure. Very preterm children in the moderate–severe white matter abnormality group exhibited the most impaired performance on these four measures, followed by those children with mild abnormalities. Very preterm children without white matter abnormalities appeared to obtain similar scores to children in the full term group. While significant associations between group and FIST task performance were not observed, except with respect to the proportion of children passing criterion trials and thus capable of completing the task, a generally similar pattern of findings was still evident across the four study groups despite attenuated numbers.

Further statistical evaluation of between group contrasts confirmed the absence of any performance differences between very preterm children without earlier white matter abnormalities and their full term peers across all measures. In contrast, very preterm children with moderate–severe white matter abnormalities were characterized by the most impaired executive functioning performance, with performance impairments found across almost of the primary executive function measures relative to their full term peers at age 4. The only exceptions were abstraction and cognitive flexibility scores on the FIST and the Shape School switch condition. These were too
## TABLE 3
Executive Functioning Outcomes of Children Born Very Preterm Children with No, Mild, and Moderate–Severe White Matter Abnormalities in Relation to Children Born Full Term

<table>
<thead>
<tr>
<th>Measure</th>
<th>Full Term (FT) (n = 105)</th>
<th>Very Preterm (VPT)</th>
<th>p Values</th>
<th>FT vs. Moderate–Severe WMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Passed training trials</td>
<td>95.2 (1.38)</td>
<td>95.8 (1.32)</td>
<td>.03</td>
<td>.01</td>
</tr>
<tr>
<td>Mean (SD) Highest move level achieved</td>
<td>1.96 (1.38)</td>
<td>1.43 (1.27)</td>
<td>.90</td>
<td>.88</td>
</tr>
<tr>
<td>% Passed criterion trials</td>
<td>87.7 (2.09)</td>
<td>73.3 (2.68)</td>
<td>.004</td>
<td>.02</td>
</tr>
<tr>
<td>Mean (SD) Correct abstractions</td>
<td>6.90 (2.15)</td>
<td>2.68 (2.34)</td>
<td>.01</td>
<td>.11</td>
</tr>
<tr>
<td>Mean (SD) Correct cognitive flexibility</td>
<td>3.40 (2.15)</td>
<td>2.57 (2.28)</td>
<td>.01</td>
<td>.30</td>
</tr>
<tr>
<td>% Completed all task trials</td>
<td>98.1 (1.00)</td>
<td>67.9 (9.5)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean (SD) Total Correct</td>
<td>6.71 (1.00)</td>
<td>5.59 (2.01)</td>
<td>.02</td>
<td>.05</td>
</tr>
<tr>
<td>Mean (SD) Efficiency score</td>
<td>0.25 (0.11)</td>
<td>0.14 (0.20)</td>
<td>.43</td>
<td>.25</td>
</tr>
<tr>
<td>% Completed control condition</td>
<td>99.0 (2.33)</td>
<td>89.7 (2.65)</td>
<td>&lt;.0001</td>
<td>.43</td>
</tr>
<tr>
<td>Mean (SD) Total correct on inhibit condition</td>
<td>13.49 (2.33)</td>
<td>12.50 (2.11)</td>
<td>.30</td>
<td>.30</td>
</tr>
<tr>
<td>Mean (SD) Inhibit condition efficiency score</td>
<td>.43 (0.25)</td>
<td>.25 (0.13)</td>
<td>.03</td>
<td>.03</td>
</tr>
<tr>
<td>Mean (SD) Total correct on switch condition</td>
<td>8.46 (3.67)</td>
<td>9.60 (1.96)</td>
<td>.04</td>
<td>.04</td>
</tr>
<tr>
<td>Mean (SD) Switch condition efficiency score</td>
<td>.04 (.16)</td>
<td>.08 (.06)</td>
<td>.61</td>
<td>.78</td>
</tr>
<tr>
<td>Executive function composite</td>
<td>10.52(1.86)</td>
<td>8.07 (2.49)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

= Magnetic resonance imaging data lost for one very preterm child. WMA:
difficult for most children and therefore discriminated poorly between groups. In general, children with mild white matter abnormalities on term MRI also performed less well than their full term peers, although their performance difficulties appeared to be less marked than children with moderate–severe white matter abnormalities. Specifically, children with mild white matter abnormalities were less likely to graduate to the higher move levels of the Tower of Hanoi or complete all three Shape School task conditions. They were also less likely to understand the task requirements of the FIST (concept formation) and those that did were somewhat poorer in shifting rules (cognitive flexibility). In addition, despite demonstrating efficiency scores on the Visual Search task that were comparable to their full term peers and reflective of an efficient search time, they were less accurate in their identification of target stimuli.

Predictors of Executive Function Outcome Among Children Born Very Preterm

To examine the extent to which the presence and severity of cerebral white matter abnormalities detected on term MRI made a unique and independent contribution to later executive function risk for children born very preterm, the above analysis was extended to include a number of other medical and social risk factors associated with both preterm birth and executive functioning outcomes. For this analysis the primary outcome was the executive function composite score. The results of this linear regression analysis showed that after taking into account all of the infant medical and social risk factors shown in Table 1, white matter abnormality status at term equivalent remained a strong independent predictor of overall executive function performance at age 4 years ($\beta = -0.34$, $p = .0001$). The only other significant net predictor was child gender ($\beta = 0.28$, $p = .002$), with females performing better than males. No significant interaction was found between white matter abnormality status and gender. Jointly these two factors explained 19% of the variance in children’s executive performance, suggesting a moderate level of prediction. This analysis suggests that early cerebral white matter abnormalities place very preterm children at increased risk of executive function impairment during the preschool years over and above other clinical and social background factors.

DISCUSSION

This prospective, longitudinal study of children born very preterm examined a number of key executive functioning processes at age 4. Of particular interest, was the extent to which any identified executive impairments or delays were explained by the presence and severity of cerebral white matter abnormalities that are commonly found on neonatal MRI in children born very preterm. This study extends our understanding of the neuropsychological effects of preterm birth in a number of key ways. First, the examination of a diverse range of executive skills offers valuable information about the profile of emerging strengths and difficulties in specific aspects of executive function for this cognitively and educationally high risk group of children. Second, in contrast to existing neuroimaging studies, which have typically employed cross sectional designs, the availability of neonatal MRI measures of early brain injury combined with prospective follow-up data is helpful in clarifying the longer term neuropsychological implications of early neurological injury in the preterm infant. Finally, given that many preschool measures of
executive function do not have good age-based norms, the inclusion of a large, regionally repre-
sentative, cohort of full term born comparison children of the same age represents an important
methodological strength. The major findings from this study and their implications are discussed
below.

Consistent with existing research, our results demonstrate that children born very preterm
are at elevated risk of later executive difficulties, with these difficulties observable by age 4
(Bohm, Smedler, & Forssberg, 2004; Edgin et al., 2008; Espy et al., 2002; Matthews, Ellis, &
Nelson, 1996; Vicari et al., 2004). Furthermore, extending on previous studies that have tended
to adopt a narrow focus on a specific component of executive function such as working memory
(Beauchamp et al., 2008; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Woodward et al.,
2005), our results suggest that impairment may indeed be more pervasive, affecting a range of
executive abilities, similar to the findings reported by Anderson et al. (2004) in their school-aged
cohort. Specifically, findings revealed adverse impacts of very preterm birth on the development
of children’s planning abilities, selective attention, inhibitory control, and to a lesser extent cog-
nitive flexibility. However, it is important to acknowledge that the observed effect sizes were
largely in the small to moderate range. While these small effect sizes could potentially reflect,
at least to some extent, the effects of measurement error, this would seem unlikely to account
for all our findings given the consistent pattern of results across multiple measures. Rather, it
would seem more likely that early impairments in executive function may be relatively subtle, at
least at this early stage of development. Findings also highlight the potential benefit of employ-
ing multiple measures of a construct to improve measurement precision especially with younger
children.

With respect to the finding that cognitive flexibility appeared to be somewhat less impaired
than other aspects of executive functioning within our cohort of very preterm preschoolers, it is
important to note a substantial number of children were unable to follow task requirements.
For example, whereas only 12% of full term children failed the control condition, 27% and
32%, respectively, of preterm children with mild and moderate–severe white matter abnormal-
ities were unable to complete the task due to an inability to master task demands. In addition,
it is important to note that cognitive flexibility also represents a higher order executive skill
that relies on the simultaneous engagement of several executive abilities. For instance, the FIST
places demands on working memory as well as requiring the simultaneous inhibition of incorrect
response tendencies. Findings from other studies examining cognitive flexibility in children born
very preterm have tended to yield mixed results, with some demonstrating clear performance
impairments on measures of shifting and spatial reversal (Aarnoudse-Moens et al., 2009; Bayless
& Stevenson, 2007; Taylor, Klein, Minich, & Hack, 2000) and others finding no differences
(Curtis, Lindeke, Georgieff, & Nelson, 2002; Espy et al., 2002). Given the complex and chang-
ing nature of this skill over the course of childhood, it is possible that these differences in results
may reflect the age of children at follow-up and/or the relative developmental immaturity of this
complex skill at younger ages. Indeed, although it has been shown that the ability to suppress a
task irrelevant response can be reliably assessed by age 3 years in typically developing children
(Carlson & Wang, 2007; Diamond & Taylor, 1996), the ability to switch flexibly from one stim-
ulus dimension to another appears to be an emergent skill, making its accurate assessment below
the age of 4 years somewhat problematic (Diamond, Carlson, & Beck, 2005; Jacques & Zelazo,
2001). This may be particularly true in the case of high risk samples where there is often wide
variability in development and in turn, considerable heterogeneity in children’s task performance.
While it is unclear whether these observed impairments in executive functioning reflect developmental delay or a true deficit, our findings are consistent with studies reporting executive function outcomes of very preterm children in middle childhood (Anderson & Doyle, 2004), adolescence (Taylor, Minich, Bangert, Filipek, & Hack, 2004), and early adulthood (Nosarti et al., 2007). Further follow-up of this representative cohort should help clarify how individual differences in executive functioning develop with age in this high-risk population.

The most important finding from this study is that executive impairments appear to be associated with white matter pathology observed on neonatal MRI. More specifically, the results showed that across all executive outcomes assessed, impairments were confined to those very preterm children who had either mild or moderate—severe white matter abnormalities at term equivalent. Importantly, very preterm children without MRI white matter abnormalities were indistinguishable from their full term peer in terms of their performance on tests of planning, cognitive flexibility, selective attention, and inhibitory control. This finding suggests that, at least during the preschool years, very preterm children who escape diffuse white matter abnormalities may well be spared the adverse cognitive consequences commonly associated with being born too early. Although it is unfortunate that these children represent a relatively small proportion (approximately a quarter) of the total population of children born very preterm, this observation does offer considerable hope for parents. It also suggests that reducing white matter injury during the neonatal period needs to be an important target for neonatal interventions aimed at reducing longer term cognitive and educational morbidities associated with preterm birth.

The observation that risks of later executive impairments increased with worsening severity of neonatal white matter abnormalities is of particular relevance here, given the known relations between executive function and educational achievement. Preterm children with the most severe and pervasive executive impairments tended to be those with moderate to severe white matter abnormalities. A larger proportion of these children were likely to fail practice and criterion trials on each task, suggesting that they did not understand task instructions or were unable to meet the basic motor or cognitive demands of the task. For those able to complete the tasks, they were more likely to struggle across all measures. In contrast, while children with mild white matter abnormalities were also characterized by more executive difficulties than their full term peers, their task completion rates were higher and their performance impairments less severe.

The importance of intact cerebral white matter development for cognition function has been well documented (Filley, 2001; Geschwind & Kaplan, 1962; Skranes et al., 2008, 2009). As highlighted by Skranes et al. (2008), whereas executive dysfunction is commonly attributed to structural or functional frontal pathology, the prefrontal cortex relies on the integrity of several white matter tracts that connect it to other brain regions. Our findings suggest that early disturbances to the development and microstructure of white matter tissue may adversely impact longer term connectivity, placing very preterm children at increased risk of pervasive impairments in executive functioning.

One promising finding to emerge from these results for those responsible for monitoring the development of these children is that executive problems can be identified prior to school entry, thus allowing for the implementation of intervention programs and remediation strategies. This is important since it is well established that executive impairments impact a child’s academic achievement (Bull, Espy, & Wiebe, 2008; Clark et al., 2010) and social functioning (see Riggs et al., 2006, for a review). Intervening at an early age, therefore, may help to equip these children with skills and strategies that reduce the risk of later educational and social difficulties.
Although this study sheds light on some of the challenges facing very preterm children, as well as the predictive value of neonatal white matter abnormalities in the development of these difficulties, several methodological limitations should be acknowledged. The first concerns the challenge of measuring children’s executive skills during the preschool period, and in particular, the reliance on unstandardized measures with limited psychometric evaluation (Carlson, 2005). This reflects the state of the field, but there is clearly an urgent need for closer evaluation of what constructs these tasks measure, as well as their reliability and predictive validity. Compounding these challenges is the fact that many of these executive skills are relatively immature in preschool aged children, posing measurement and interpretation challenges. Second, the inability of many of the very preterm children to complete all executive function tasks likely served to reduce our statistical power to detect group differences. This also raises questions as to whether these tasks are suited for testing executive function in children with diverse ability levels. Third, no neonatal MRI was available for children in the full term comparison group. As a result, the extent of cerebral white matter abnormalities in these children is not known. However, unpublished estimates suggest that around 5–10% of the general population may exhibit mild white matter abnormalities, with moderate and severe abnormalities rarely seen. Fourth, given the exclusive focus of this analysis on executive function, the degree to which white matter abnormalities might influence general cognitive development, and more importantly, educational under-achievement has yet to be determined. Finally, the extent to which these observed executive function impairments might be secondary to deficits in lower-level information processing, perceptual and motor skills also remains unclear.

Nonetheless, study findings do extend our understanding of the nature of the executive function difficulties experienced by children born very preterm and lend further support to the role of early white matter abnormalities in the evolution of later neurodevelopmental risk in the very preterm infant (Clark, Woodward, Horwood, & Moor, 2008; Woodward et al., 2006; Woodward, Mogridge, Wells, & Inder, 2004). Further, these findings have a number of implications for educators and neonatal care providers. First, for educators, it may be important to recognize that although very preterm children with severe neurological abnormalities will typically be identified and monitored from an early age, others may also experience subtle executive impairments that although undetected, will pose challenges for learning and classroom management. This is important given the clear links between executive functioning and educational achievement in general population samples (Blair & Razza, 2007; Bull et al., 2008; Clark et al., 2010). Thus, a potentially important avenue for future research would be to assess the extent to which newly emerging, intensive executive function training strategies might assist very preterm children in developing core executive skills (Diamond, Barnett, Thomas, & Munro, 2007; Klingberg et al., 2005; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009) that will support children’s learning, behavior, and social development. Second, for neonatal service providers, findings suggest that reducing rates of white matter injury among preterm survivors needs to be an urgent priority if longer term outcomes are to be improved. Neonatal brain monitoring may also be helpful in ensuring that cerebral injuries are detected early and appropriate follow-up services implemented to address the needs of these children and their families.
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REFERENCES


