Published in final edited form as:
Neuropsychology. 2014 July ; 28(4): 552–562. doi:10.1037/neu0000071.

Neonatal Brain Pathology Predicts Adverse Attention and Processing Speed Outcomes in Very Preterm and/or Very Low Birth Weight Children

Andrea L Murray[1,2], **Shannon E Scratch**[1], **Deanne K Thompson**[1,4], **Terrie E Inder**[1,3], **Lex W Doyle**[1,5,6,7], **Jacqueline F. I. Anderson**[2,8], and **Peter J Anderson**[1,3,5]

[1]Victorian Infant Brain Studies, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, VIC, 3052, Australia

[2]Melbourne School of Psychological Sciences, The University of Melbourne, Grattan Street, Parkville, VIC, 3010, Australia

[3]Department of Pediatrics, Washington University in St Louis Medical School, St Louis, MO, USA

[4]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Grattan Street, Parkville, VIC, 3010, Australia

[5]Department of Paediatrics, The University of Melbourne, Royal Children's Hospital, Flemington Road, Parkville, VIC, 3052, Australia

[6]Research Office, The Royal Women's Hospital, Grattan Street, Parkville, VIC, 3052, Australia

[7]Department of Obstetrics & Gynaecology, The University of Melbourne, Royal Women's Hospital, Grattan Street, Parkville, VIC, 3052, Australia

[8]Department of Psychology, The Alfred, Alfred Health, Commercial Rd, Melbourne, VIC, 3004, Australia

Abstract

Objective—This study aimed to examine attention and processing speed outcomes in very preterm (VPT; <32 weeks' gestational age) or very low birth weight (VLBW; <1500 g) children, and to assess the ability of brain abnormalities measured by neonatal magnetic resonance imaging (MRI) to predict outcome in these domains.

Methods—A cohort of 198 children born <30 weeks' gestational age and/or <1250 g and 70 term controls were examined. Neonatal MRI scans at term equivalent age were quantitatively assessed for white matter, cortical gray matter, deep gray matter, and cerebellar abnormalities. Attention and processing speed were assessed at 7 years using standardized neuropsychological tests. Group differences were tested in attention and processing speed, and the relationships between these cognitive domains and brain abnormalities at birth were investigated.

Corresponding Author: Dr. Peter Anderson, Address: Victorian Infant Brain Studies (VIBeS), Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria, 3050, Telephone number: +61 3 99366704, peter.anderson@mcri.edu.au, Fax: +61 3 93481391.

The information in this manuscript and the manuscript itself has never been published either electronically or in print, and there are no conflicts of interest.

Results—At 7 years of age, the VPT/VLBW group performed significantly poorer than term controls on all attention and processing speed outcomes. Associations between adverse attention and processing speed performances at 7 years and higher neonatal brain abnormality scores were found; in particular, white matter and deep gray matter abnormalities were reasonable predictors of long-term cognitive outcomes.

Conclusion—Attention and processing speed are significant areas of concern in VPT/VLBW children. This is the first study to show that adverse attention and processing speed outcomes at 7 years are associated with neonatal brain pathology.

Keywords

VPT; very preterm; *VLBW*; very low birth weight; *MRI*; magnetic resonance imaging; attention; processing speed

Introduction

Since the 1980s, the survival rate of very preterm (VPT; <32 weeks' gestational age [GA]) newborns has been steadily increasing due to improvements made in obstetric and neonatal care (Saigal & Doyle, 2008). Children born VPT are at increased risk of a spectrum of neurosensory impairments including cerebral palsy, deafness and blindness (Arpino et al., 2010). These disabilities are, however, relatively uncommon, and the VPT child is instead more likely to suffer from cognitive, educational and behavioral problems (P. J. Anderson & Doyle, 2003; Aylward, 2005; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Hutchinson et al., 2013; Salt & Redshaw, 2006). Attention and processing speed deficits, in particular, are a major area of concern for children born early as these skills form the building blocks from which other cognitive skills develop (Rose, Feldman, Jankowski, & Van Rossem, 2008, 2011). While no study to date has looked at whether these deficits have an underlying structural basis, given the high risk of brain pathology in this population (Cheong et al., 2009; Inder, Wells, Mogridge, Spencer, & Volpe, 2003; S. P. Miller et al., 2005) it is predicted that a link might exist between neonatal pathology and later cognitive functioning in the preterm child.

In the developing brain, any inefficiencies in the more elementary abilities, such as attention and processing speed, can have substantial influence over the development of other, more complex cognitive abilities (Rose, et al., 2008). Because these skills form the basis from which other cognitive abilities develop (V. Anderson, Northam, Hendy, & Wrennall, 2001; Rose, Feldman, & Jankowski, 2011), it is important to identify early problems within each of these domains in order to potentially limit more widespread cognitive deficits.

While early models of attention conceptualized the construct as a single entity (Broadbent, 1958; Deutsch & Deutsch, 1963), it is now widely accepted that attention is a complex cognitive domain, made up of numerous components. The two most influential neuropsychological models of attention were proposed by Mirksy and colleagues and Posner and colleagues (P. J. Anderson et al., 2011). Mirsky's model is made up of four factors (selective attention, sustained attention, shifting and encoding), which are based on principal component analysis of neuropsychological test scores (Mirsky, Anthony, Duncan, Ahearn,

& Kellam, 1991; Mirsky & Duncan, 2001). *Selective attention* is described as the capacity to focus on relevant stimuli and ignore irrelevant information, whereas *sustained attention* is defined as the maintenance of a focused and alert state. *Shifting* is described as the ability to transfer attention from one activity to another, while *encoding* is defined as the capacity to hold information in mind while performing other cognitive tasks. Miller's school neuropsychological conceptual model (D. C. Miller, 2007, 2010) extended on Mirsky's work by adding a fifth attention factor known as *divided attention*. Divided attention is a higher-order attention ability, similar to shifting, which requires the individual to respond to multiple stimuli simultaneously. Posner's model is similar in many respects, but divides attention into three functional domains (orienting, alerting, and executive control), each with its own underlying structural network (Petersen & Posner, 2012; M. I. Posner & Petersen, 1990; Posner & Peterson, 1990; M.I. Posner, Sheese, Odludaş & Tang, 2006). The *orienting* network, similar to selective attention, prioritizes sensory input by focusing attention to relevant stimuli. The *alerting* network, similar to sustained attention, is responsible for acquiring and maintaining an alert state, and the *executive* network broadly controls top-down regulation of tasks and higher-order attentional capacity.

Van de Weijer-Bergsma et al. (2008) reviewed the literature on attention development in young preterm (<37 weeks' GA) children. They concluded that early orienting, alerting and executive attention skills were less optimal in preterm infants compared with term controls, and that these differences increased over the first four years of life. A meta-analysis conducted by Mulder et al. (2009) examined the attention skills of older preterm children in comparison with term born controls and found marked impairment in selective and sustained attention, but inconsistent findings for shifting ability. Divided attention has received little consideration in the preterm literature. While Anderson et al. (2011) found poorer divided attention capacity in a large representative sample of extremely preterm (EPT; <28 weeks' GA) children compared with full term controls at 8 years, no other study has assessed this ability in the preterm child.

Processing speed refers to the ability to process information quickly and efficiently (Lezak, Howieson, & Loring, 2004) and has also been found to be deficient in preterm children. Deficits in processing speed have been found as early as 5 months and persist throughout the first year of life (Rose, Feldman, & Jankowski, 2002, 2009). Cognitive slowing has also been documented in later childhood, with studies showing processing speed deficits in low birth weight (<2500 g)(Rose & Feldman, 1996), very low birth weight (VLBW; <1500 g) (Bohm, Smedler, & Forssberg, 2004) and EPT/extremely low birth weight (<1000 g) (P. J. Anderson & Doyle, 2003; Marlow, Wolke, Bracewell, Samara, & Grp, 2005) cohorts compared with term controls.

Because attention and processing speed are intimately connected, many assessment tools used to measure performance within these domains fail to isolate the two processes from one another. In a recent meta-analysis investigating attention performance in preterm children, Mulder et al., (2009) discussed the problem of task impurity within the context of prematurity. They argued that, in the present literature, a depressed performance on a task will often reflect impairment in multiple abilities rather than a single, specific difficulty. They cautioned that, when selecting measures to assess development in preterm children, it

is important to choose measures with minimal contamination, so that genuine difficulties can be identified.

A likely contributor to inattention and slowed processing speed in preterm children is brain pathology incurred in the perinatal period. While the most severe neuropathology associated with prematurity is high-grade intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (PVL), the most prevalent form of pathology affecting VPT infants is non-cystic or diffuse PVL (Back, Riddle, & McClure, 2007; Boardman & Dyet, 2007; Inder, Wells, et al., 2003). On MRI, diffuse PVL is reflected in white matter signal abnormalities, enlarged lateral ventricles, white matter volume loss, delay in myelination, and thinning of the corpus callosum (Inder, Anderson, Spencer, Wells, & Volpe, 2003; Inder, Wells, et al., 2003; Woodward, Anderson, Austin, Howard, & Inder, 2006). MRI studies show evidence of diffuse PVL and its associated neuronal/axonal deficits in approximately 50% of VPT infants (Cheong, et al., 2009; Inder, Wells, et al., 2003; S. P. Miller, et al., 2005). This pathology often results in impaired myelination and failure of axonal development, leading to reduced white matter volume and enlargement of the lateral ventricles (Inder, Wells, et al., 2003; Maalouf et al., 1999; Woodward, et al., 2006). In addition, dysfunctional growth and development occurs within interacting structures of the brain, including the cerebral cortex, thalamus, basal ganglia, brainstem and cerebellum (Volpe, 2009).

The rate of brain pathology (particularly diffuse PVL) in VPT infants is relatively consistent with the percentage of VPT children that later present with neurobehavioral problems, leading to speculation that the former might be predictive of the latter (Boardman & Dyet, 2007). Limited studies have examined the impact of brain pathology on functioning in the preterm population and most have reported on short-term outcomes only. Previous studies have found associations between white and gray matter abnormalities on MRI at term equivalent age and motor and neurosensory impairment (Aida et al., 1998; Kwong, Wong, Fong, Wong, & So, 2004; Mirmiran et al., 2004; Spittle et al., 2011; Woodward, et al., 2006), executive dysfunction (Beauchamp et al., 2008; Clark & Woodward, 2010; Edgin et al., 2008; Woodward, Clark, Bora, & Inder, 2012; Woodward, Clark, Pritchard, Anderson, & Inder, 2011; Woodward, Edgin, Thompson, & Inder, 2005), memory (Omizzolo et al., 2013), and global developmental delay (Dyet et al., 2006; Inder, Warfield, Wang, Huppi, & Volpe, 2005; S. P. Miller, et al., 2005; Peterson et al., 2003; Woodward, et al., 2006). Longer-term follow-up is necessary to determine which neurodevelopmental functions remain deficient over time. Despite the known influence that attention and processing speed abilities have on other cognitive domains (Rose, et al., 2008; Rose, Feldman, Jankowski, et al., 2011), these basic functions are yet to be fully characterized in the VPT child. Further, few studies have examined the potential neural mechanisms that underlie these cognitive impairments. This study aims to characterize the attention and processing speed profiles of VPT/VLBW children. It will also examine the relationship between abnormal MRI findings at term equivalent age and attention and processing speed outcomes at 7 years.

Materials and Methods

Participants

Two hundred and twenty seven VPT/VLBW participants were included in the Victorian Infant Brain Studies (VIBeS) cohort, originally recruited at birth from the Royal Women's Hospital, Melbourne, Australia, during July 2001 to December 2003. In order to target the highest risk infants, selection criteria included either a gestational age prior to 30 weeks or a birth weight of <1250 g. Although 227 VPT/VLBW participants were recruited, two children died in early childhood and one was later excluded due to a late diagnosis of congenital infection known to affect developmental outcome, leaving 224 infants. A control group of 77 term (37-42 weeks' GA) and normal birth weight (≥2500g) children were also recruited; 46 were recruited during the neonatal period from the Royal Women's Hospital and the remaining 31 were recruited at 2 years of age from maternal-infant health centers. Previous follow-up assessments have been performed at ages 2 and 5 years, corrected for prematurity (Thompson, Wood, Doyle, Warfield, Lodygensky, et al., 2008; Roberts, Lim, Doyle, & Anderson 2011; Treyvaud, Doyle, Lee, Roberts, Lim, et al., 2012). At the 7 year follow-up, 198 VPT/VLBW (88%) and 70 control (91%) children were assessed. The Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital approved the study. Informed consent was obtained from the parents or guardians of all participants.

Procedure and Measures

T_1 and T_2 imaging occurred at term-equivalent age (37-42 weeks' GA) on 222 VPT/VLBW and 46 term born infants at the Royal Children's Hospital, Melbourne, with a 1.5 Tesla MRI scanner (Signa LX Echospeed System; General Electric, Milwaukee, WI). Two VPT/VLBW infants were scanned outside the term-equivalent window and were excluded from the imaging analysis. In order to reduce motion, infants were placed in a Vac Fix beanbag unsedated (S&S Par Scientific, Odense, Denmark). Brain abnormality was determined using a rating system described previously (Kidokoro, Neil, & Inder, 2013). The scoring system gives an overall rating of white matter, cortical gray matter, deep gray matter and cerebellar abnormality, with individual items scored on a scale of 0 to 4. These scales are summated to generate an overall global score (ranging from 0-40), where higher values indicate more brain abnormality. Ratings were made by an experienced neonatal neurologist.

Participants also underwent comprehensive neuropsychological assessment at 7 years' corrected age at the Royal Children's Hospital which included measures of general intellectual function, language, visuoperceptual reasoning, memory, and executive function in addition to attention and processing speed. A psychologist or post-graduate psychology trainee conducted the neuropsychological assessment. All assessors were blinded to medical information and group membership. Primary caregivers were also asked to complete a set of questionnaires about the child and the family dynamics. Attention, processing speed and social risk measures were taken from a larger assessment battery and are outlined below.

The Test of Everyday Attention for Children (TEA-Ch) (Manly, Robertson, Anderson, & Nimmo-Smith, 1999)

The TEA-Ch is a reliable and valid battery of nine subtests designed to measure attention processes in children (Manly et al., 2001; Manly, et al., 1999). Four subtests were administered. 1) Sky Search, which assesses visual selective attention, requires participants to circle targets among distracters under time constraints. The number of correct targets identified (maximum=20) was the variable used in this study. 2) Score!, which assesses auditory sustained attention, requires participants to count the number of intermittent tones presented on an audiotape. The variable of interest was the number of correct counting trials (maximum=10). 3) Creature Counting, which assesses shifting ability, is a task where children are required to count visual targets. Participants are required to inhibit a previous response (e.g., counting forward) when presented with a signal (up or down arrow) and switch to a new response type (e.g., counting backward). The number of correct trials (maximum =7) was the variable of interest for this task. 4) Sky Search Dual Task (DT), which assesses divided attention, requires participants to perform activities similar to the Sky Search and Score! tasks simultaneously. Performance on this task was judged using an algorithm that takes into account accuracy on both tasks (P. J. Anderson, et al., 2011).

CogState Research (CogState Ltd., Melbourne Australia)

CogState is a reliable and valid computerized battery of cognitive tests designed for repeatable use within research and clinical settings (Collie, Maruff, Darby, & McStephen, 2003; Maruff et al., 2009). Two of the tests, Detection and Identification, were selected for use, which are suitable for participants aged 6 to 106 years. The Detection task is a simple measure of psychomotor function and processing speed. Participants are presented with the back of a playing card in the center of the computer screen and they respond (by pressing the “yes” key) upon seeing the face of the card. The Identification task measures visual attention and vigilance in addition to processing speed. The back of a single playing card is presented in the center of the screen; participants respond to the question “Is the card red?” by pressing the “yes” or “no” key when the card turns over. The unit of measurement for these tasks is the log10 of the reaction time recorded in milliseconds as these responses are generally non-normally distributed. As such, the variable of interest from these two tasks was the mean of the log10-transformed reaction times for correct responses.

Social Risk

A questionnaire was used to determine social risk based on a number of indicators: family structure (0 = family intact, 1 = separated/dual custody or cared for by another intact family member such as grandparents, 2 = single caregiver or foster care), education of the primary caregiver (0 = tertiary, 1 = completed year 11 or 12, 2 = completed below year 11), occupation of the primary income earner (0 = skilled/professional, 1 = semi-skilled, 2 = unskilled), employment status of the primary income earner (0 = full-time, 1 = part-time, 2 = unemployed/pension), dominant language spoken in the home (0 = English only, 1 = some English, 2 = no English), and maternal age at birth (0 = >21 years, 1 = 18-21 years, 2 = <18 years). Each child received a social risk score ranging from 0-12, a higher score indicating greater social risk (Roberts et al., 2008).

Statistical Analyses

All data from the neonatal period and 7 year follow-up were analyzed in Stata 12.0 (StataCorp, College Station, Texas). Differences between the VPT/VLBW and term groups on demographic and perinatal characteristics were analyzed using simple linear regressions or Mann-Whitney U tests (conducted for variables with skewness values > or < than 0 and kurtosis values > or < 3) for continuous variables, and χ^2 analyses or Fisher exact tests for categorical variables. For the primary analyses, children were excluded if the task could not be completed due to external factors (e.g., faulty equipment) or if a child was too cognitively impaired to complete the task (e.g., did not meet the minimum requirements or did not understand the task). Bivariable (unadjusted) and multivariable (adjusted) linear regression models were used to examine group differences on outcome measures and the relationships between these measures and brain abnormality. Multivariable models controlled for age at testing, social risk, gender and severe intellectual disability by excluding children with an IQ<70 (n = 3). These children were excluded to ensure that group differences and/or associations were not due to a small number of significantly impaired children in the VPT group. These covariates were included because the VPT and term groups differ on these variables and/or they are known to influence outcome measures of attention (Frazier, Demaree, & Youngstrom, 2004; Pascualvaca et al., 1997; Salt & Redshaw, 2006). Secondary analyses were also performed, in which children who were too cognitively impaired to assess were assigned a score of 3 standard deviations below the mean of the term group. These analyses increased the sample sizes of the subtests by 3-19% (Sky Search = 3% increase, Score! = 7% increase, Creature Counting = 19% increase, Sky Search DT = 11% increase, Detection task = 5% increase, Identification task = 6% increase). Given the large proportion of twins and triplets in the sample, the Huber/White/Sandwich method was used, which assumes independence across families but not within. This model is the preferred modeling technique for twin/triplet data and it alters the standard error but not the primary parameters of the model (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005). The odds of impairment on the outcome measures, defined as more than 1 standard deviation below the term group mean (P. J. Anderson, et al., 2011; Omizzolo, et al., 2013), were compared between the two groups using unadjusted logistic regression (clustering using the Huber/White/Sandwich method). Rather than relying solely on p values, results were interpreted based on the profile and magnitude of group differences and associations.

Results

The demographic and perinatal characteristics of the sample are displayed in Table 1. As expected, the VPT/VLBW group differed from the term group on perinatal medical variables such as Apgar score, episodes of sepsis, patent ductus arteriosus, bronchopulmonary dysplasia, length of hospital stay, as well as antenatal and postnatal corticosteroids. The VPT/VLBW sample also had a lower proportion of singletons and a higher level of social risk compared with the term group.

The VPT/VLBW group significantly underperformed on all attention and processing speed measures compared with the term control group (Table 2). Group differences remained significant on all but one measure (Identification task) after controlling for age at testing,

social risk, gender and IQ. A similar pattern of results was found when children unable to be tested because of cognitive impairment were included (data not shown).

Impairment rates for the VPT/VLBW group ranged from 38-52% on the attention measures, with the rate of impairment being 2.9 to 3.5 times greater in the VPT/VLBW group compared with the term group (Table 3). The rate of impairment on the measures of processing speed for the VPT/VLBW group ranged from 18-24%, but this did not differ to the rate observed in the term group (Table 3). Again, a similar pattern of results was found in secondary analyses in which children too cognitively impaired to complete the task were included (data not shown).

Neonatal brain MRI abnormality scores were predictive of adverse attention and processing speed performances in the VPT/VLBW children at 7 years of age (see Figure 1). There was evidence for an association between higher deep gray matter abnormality and poorer performance across all attention domains and the choice reaction time task (Identification), and these associations became stronger in the secondary analyses, which included the children who were unable to complete these tasks. There was also some evidence that higher white-matter abnormality scores were associated with poorer attention and slower processing speed, particularly in the secondary analyses. Finally, there was evidence that cerebellar abnormality was associated with poorer sustained, shifting and divided attention.

Discussion

In the current study VPT/VLBW children performed significantly less well than their term born peers on all measures of attention and processing speed at 7 years of age. Uniquely, we also found significant associations between qualitative measures of brain abnormality on MRI at term equivalent age and adverse attention and processing speed outcomes at 7 years among VPT/VLBW children.

Our findings of poorer attention and slower processing speed in VPT/VLBW children compared with term born children are consistent with previous work. While lower-order domains of attention, such as selective and sustained attention, are consistently shown to be impaired during infancy and childhood (Mulder, et al., 2009; van de Weijer-Bergsma, et al., 2008), the literature has been inconclusive or limited when investigating higher-order domains of attention, such as shifting and divided attention. Our study adds weight to the literature reporting poorer shifting performance in the preterm population (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Mulder, Pitchford, & Marlow, 2011b; Ni, Huang, & Guo, 2011; Rose, Feldman, & Jankowski, 2011; Woodward, et al., 2011). It also contributes to the scarce literature on divided attention (P. J. Anderson, et al., 2011), highlighting impairment within this subdomain in a VPT/VLBW group compared with a healthy term control group. The finding of reduced processing speed in the VPT/VLBW children is also consistent with previous research (P. J. Anderson & Doyle, 2003; Bohm, et al., 2004; Marlow, et al., 2005; Rose & Feldman, 1996; Rose, et al., 2002, 2009). These results highlight that attention and processing speed are significant areas of concern in the VPT/VLBW child. Further follow-up of this cohort will help to determine

whether this group demonstrates catch-up over time, or whether their deficits persist or worsen with time.

This study is the first to show that impaired attention and processing speed is associated with brain pathology observed on neonatal MRI. Specifically, the results showed that white matter and deep gray matter brain abnormalities were predictive of both attention and processing speed outcomes. Cerebellar abnormality was also predictive of the majority of the attention outcomes. While many trending associations between brain abnormality and outcome were observed in the primary analyses, these associations became more robust in the secondary analyses when lower functioning children were included. These results suggest that neonatal brain pathology has important consequences for longer-term, adverse cognitive functioning in VPT/VLBW children.

Based on these findings we can speculate that white matter, deep gray matter and cerebellar abnormalities at birth may be the neural mechanisms underlying the longer-term attention and processing speed impairments that are typically observed in the preterm population. The association between white matter abnormality and neurocognitive function is not at all surprising given the high rate of diffuse PVL that exists in this population (Cheong, et al., 2009; Inder, Anderson, et al., 2003; S. P. Miller, et al., 2005). Attention problems are known to occur as a result of white matter abnormality, as evidenced by research into the clinical syndrome of attention deficit hyperactivity disorder (ADHD). A meta-analysis conducted by Valera et al. (2007) reported global reductions in white matter in the brains of ADHD patients and a number of studies have identified specific white matter pathways as being dysfunctional in ADHD, such as the cingulum bundles (Konrad et al., 2010; Makris et al., 2008), the superior longitudinal fasciculi (Hamilton et al., 2008; Makris, et al., 2008), and the corpus callosum (Cao et al., 2010). Cognitive slowing is also a characteristic pattern that occurs in a number of clinical syndromes that are known to affect white matter, such as multiple sclerosis (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004) and traumatic brain injury (Mathias & Wheaton, 2007).

The deep gray matter and cerebellar associations are perhaps more puzzling but might also be logical in light of the effects following diffuse white matter pathology. Diffuse white matter lesions are thought to have secondary effects on other brain regions, occurring as a result of degeneration following axonal deafferentiation (Volpe, 2009). In fact, a study of VPT infants found that those with diffuse white matter lesions had more widespread neuroanatomical abnormalities, particularly in the deep gray matter regions of the brain (Boardman et al., 2006). Diffuse white matter lesions cause marked astrogliosis and microgliosis, and in particular, a decrease in preoligodendrocytes (pre-OLs). This decrease in pre-OLs is followed by an increase in oligodendroglial progenitors that fail to differentiate into mature myelin producing cells. A lack of mature oligodendrocytes causes impairment in myelination and a failure of axonal development (Boardman & Dyet, 2007; Volpe, 2009). The neuronal/axonal disease accompanying diffuse white matter pathology has been shown to affect interconnected regions of the brain, including the thalamus, basal ganglia, and cerebellum (Pierson et al., 2007). Deep gray matter and cerebellar abnormalities might be caused by problems with the microstructural organisation of large white matter pathways, such as thalamocortical, frontostriatal and frontocerebellar tracts,

connecting these structures with the cortex. Further, many of the white matter tracts passing through deep gray matter and cerebellar regions have been found to relate to attention and processing speed deficits (Ashtari et al., 2005; Casey et al., 2007; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Turken et al., 2008).

As mentioned previously, many studies attempting to look at attention and/or processing speed in the preterm population have used assessment techniques that fail to separate these fundamental cognitive abilities from one another (Mulder, et al., 2009). The selected measures of attention in the current study were chosen because they use accuracy instead of speed of response as the outcome measure. From the current study, we can conclude that both domains of attention and processing speed are problematic in the VPT/VLBW child. The TEA-Ch was also selected because of its ability to assess each of the attention subdomains independently. Previous studies have shown inconsistent findings when profiling the subdomains of attention that are impaired in preterm cohorts relative to controls. Some studies find deficits in all subdomains tested (P. J. Anderson, et al., 2011; Hack et al., 1994; Mikkola et al., 2005; Snyder, Davis, Burns, & Robinson, 2007), while other studies find impairment in only some of the subdomains of attention (Bayless & Stevenson, 2007; Cserjesi et al., 2012; Mulder, Pitchford, & Marlow, 2011a; Olsen et al., 1998; Pizzo et al., 2010; Taylor, Hack, & Klein, 1998). The current study was able to show that both lower-order and higher-order subdomains of attention were impacted by prematurity. Finally, while previous studies have demonstrated associations between the presence of white and gray matter abnormalities on MRI at term equivalent age and the subsequent risk of neurological (Aida, et al., 1998; Kwong, et al., 2004; Mirmiran, et al., 2004; Spittle, et al., 2011; Woodward, et al., 2006) or global cognitive impairment (Dyet, et al., 2006; Inder, et al., 2005; S. P. Miller, et al., 2005; Peterson, et al., 2003; Woodward, et al., 2006), our study found MRI imaging at birth also has predictive value for later attention and processing speed outcomes.

A proportion of the VPT/VLBW children were unable to complete some of the attention tasks because of either an inability to understand the task instructions or an inability to meet the cognitive demands of the task. This raises the question as to whether the TEA-Ch is suitable for the assessment of attention in samples of high-risk children with considerable heterogeneity. To our knowledge, there is no other attention test that will characterize lower functioning individuals without compromising the ability of the test to also characterize higher functioning children. Further, while the TEA-Ch does indeed report ceiling and floor effects in their subtests even in the normative sample, there is no other test that allows assessment of all of the subdomains of attention (Manly, et al., 2001). To address the possible overestimation of ability in the VPT/VLBW group a secondary round of analyses were conducted, which included estimate scores for all children too cognitively impaired to complete the task. However, because these scores were imputed, greater emphasis has been placed on the findings from the primary analyses.

In sum, findings from the current study have helped to characterize the nature of the attention and processing speed inefficiencies that exist in VPT/VLBW children. Results also demonstrated that these inefficiencies have an underlying structural basis. The findings suggest that crude measures of brain abnormality found on neonatal MRI scans can be used

to predict subsequent problems with attention and processing speed. Measures of brain abnormality may be used clinically by any experienced neonatal neurologist to predict which children are at risk of later adverse outcomes, without having to resort to other more experimental neuroimaging techniques, such as complex volumetric analyses. The detection of high-risk children is critically important given the impact that these abilities have on the other developing cognitive domains (Rose, et al., 2008). Short- and long-term deficits resulting from the brain abnormality associated with prematurity have been documented, thus it is important for future research to determine ways of reducing the effects of preterm birth on the brain and for clinicians to identify vulnerable children for which remedial strategies may be beneficial.

Acknowledgments

We would like to acknowledge the input of the VIBeS research team, and all the families who participated in this study. This study was funded by Australia's National Health & Medical Research Council (Project Grants (237117 & 491209), Early Career Award (1012236 to D.T.), Senior Research Fellowship (628371 to P.A.)), National Institutes of Health (HD058056), and the Victorian Government's Operational Infrastructure Support Program.

References

Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-Analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009; 124(2):717–728. Review. 10.1542/peds.2008-2816 [PubMed: 19651588]

Aida N, Nishimura G, Hachiya Y, Matsui K, Takeuchi M, Itani Y. MR imaging of perinatal brain damage: comparison of clinical outcome with initial and follow-up MR findings. AJNR. American journal of neuroradiology. 1998; 19(10):1909–1921. [PubMed: 9874547]

Anderson PJ, De Luca CR, Hutchinson E, Spencer-Smith MM, Roberts G, Doyle LW. Attention Problems in a Representative Sample of Extremely Preterm/Extremely Low Birth Weight Children. Developmental Neuropsychology. 2011; 36(1):57–73. Article. 10.1080/87565641.2011.540538 [PubMed: 21253991]

Anderson PJ, Doyle LW. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. Journal of the American Medical Association. 2003; 289(24): 3264–3272.10.1001/jama.289.24.3264 [PubMed: 12824207]

Anderson, V.; Northam, E.; Hendy, J.; Wrennall, J. Pediatric Neuropsychology: A Clinical Approach. London: Psychology Press; 2001.

Arpino C, Compagnone E, Montanaro ML, Cacciatore D, De Luca A, Cerulli A, Curatolo P. Preterm birth and neurodevelopmental outcome: a review. Childs Nerv Syst. 2010; 26(9):1139–1149.10.1007/s00381-010-1125-y [PubMed: 20349187]

Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Ardekani BA. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. Biological psychiatry. 2005; 57(5):448–455.10.1016/j.biopsych.2004.11.047 [PubMed: 15737658]

Aylward GP. Neurodevelopmental outcomes of infants born prematurely. Journal of Developmental and Behavioral Pediatrics. 2005; 26(6):427–440.10.1097/00004703-200512000-00008 [PubMed: 16344661]

Back SA, Riddle A, McClure MM. Maturation-dependent vulnerability of perinatal white matter in premature birth. Stroke. 2007; 38(2):724–730. Article; Proceedings Paper. 10.1161/01.str.0000254729.27386.05 [PubMed: 17261726]

Bayless S, Stevenson J. Executive functions in school-age children born very prematurely. Early Human Development. 2007; 83(4):247–254. Article. 10.1016/j.earlhumdev.2006.05.021 [PubMed: 16837146]

Beauchamp MH, Thompson DK, Howard K, Doyle LW, Egan GF, Inder TE, Anderson PJ. Preterm infant hippocampal volumes correlate with later working memory deficits. Brain. 2008; 131(Pt 11):2986–2994.10.1093/brain/awn227 [PubMed: 18799516]

Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm - A meta-analysis. Jama-Journal of the American Medical Association. 2002; 288(6):728–737. Review. 10.1001/jama.288.6.728

Boardman JP, Counsell SJ, Rueckert D, Kapellou O, Bhatia KK, Aljabar P, Edwards AD. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. Neuroimage. 2006; 32(1):70–78.10.1016/j.neuroimage.2006.03.029 [PubMed: 16675269]

Boardman JP, Dyet LE. Recent advances in imaging preterm brain injury. Minerva Pediatr. 2007; 59(4):349–368. [PubMed: 17947841]

Bohm B, Smedler AC, Forssberg H. Impulse control, working memory and other executive functions in preterm children when starting school. Acta Paediatrica. 2004; 93(10):1363–1371.10.1080/08035250410021379 [PubMed: 15499959]

Cao Q, Sun L, Gong G, Lv Y, Cao X, Shuai L, Wang Y. The macrostructural and microstructural abnormalities of corpus callosum in children with attention deficit/hyperactivity disorder: a combined morphometric and diffusion tensor MRI study. Brain Research. 2010; 1310:172–180. Research Support, Non-U.S. Gov't. 10.1016/j.brainres.2009.10.031 [PubMed: 19852946]

Carlin JB, Gurrin LC, Sterne JA, Morley R, Dwyer T. Regression models for twin studies: a critical review. Int J Epidemiol. 2005; 34(5):1089–1099.10.1093/ije/dyi153 [PubMed: 16087687]

Casey BJ, Epstein JN, Buhle J, Liston C, Davidson MC, Tonev ST, Glover G. Frontostriatal connectivity and its role in cognitive control in parent-child dyads with ADHD. American Journal of Psychiatry. 2007; 164(11):1729–1736. Article. 10.1176/appi.ajp.2007.06101754 [PubMed: 17974939]

Cheong JL, Thompson DK, Wang HX, Hunt RW, Anderson PJ, Inder TE, Doyle LW. Abnormal white matter signal on MR imaging is related to abnormal tissue microstructure. AJNR. American journal of neuroradiology. 2009; 30(3):623–628.10.3174/ajnr.A1399 [PubMed: 19131414]

Clark CA, Woodward LJ. Neonatal cerebral abnormalities and later verbal and visuospatial working memory abilities of children born very preterm. Dev Neuropsychol. 2010; 35(6):622–642.10.1080/87565641.2010.508669 [PubMed: 21038157]

Collie A, Maruff P, Darby DG, McStephen M. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. Journal of the International Neuropsychological Society : JINS. 2003; 9(3):419–428.10.1017/s1355617703930074 [PubMed: 12666766]

Cserjesi R, Van Braeckel K, Butcher PR, Kerstjens JM, Reijneveld SA, Bouma A, Bos AF. Functioning of 7-Year-Old Children Born at 32 to 35 Weeks' Gestational Age. Pediatrics. 2012; 130(4):E838–E846. Article. 10.1542/peds.2011-2079 [PubMed: 22945414]

Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex. 2012; 48(2):194–215.10.1016/j.cortex.2011.04.007 [PubMed: 21575934]

DeLuca J, Chelune GJ, Tulsky DS, Lengenfelder J, Chiaravalloti ND. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? Journal of Clinical and Experimental Neuropsychology. 2004; 26(4):550–562. Article; Proceedings Paper. 10.1080/13803390490496641 [PubMed: 15512942]

Dyet LE, Kennea N, Counsell SJ, Maalouf EF, Ajayi-Obe M, Duggan PJ, Edwards AD. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics. 2006; 118(2):536–548. Research Support, Non-U.S. Gov't. 10.1542/peds.2005-1866 [PubMed: 16882805]

Edgin JO, Inder TE, Anderson PJ, Hood KM, Clark CAC, Woodward LJ. Executive functioning in preschool children born very preterm: relationship with early white matter pathology. Journal of the International Neuropsychological Society. 2008; 14(1):90–101. [PubMed: 18078535]

Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology. 2004; 18(3):543–555.10.1037/0894-4105.18.3.543 [PubMed: 15291732]

Hack M, Taylor HG, Klein N, Eiben R, Schatschneider C, Mercuriminich N. School-age outcomes in children with birth weights under 750 g. New England Journal of Medicine. 1994; 331(12):753–759.10.1056/nejm199409223311201 [PubMed: 7520533]

Hamilton LS, Levitt JG, O'Neill J, Alger JR, Luders E, Phillips OR, Narr KL. Reduced white matter integrity in attention-deficit hyperactivity disorder. Neuroreport. 2008; 19(17):1705–1708. Article. 10.1097/WNR.0b013e3283174415 [PubMed: 18841089]

Hutchinson EA, De Luca CR, Doyle LW, Roberts G, Anderson PJ, Group, f. t. V. I. C. S. School-age Outcomes of Extremely Preterm or Extremely Low Birth Weight Children. Pediatrics. 201310.1542/peds.2012-2311

Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. AJNR. American journal of neuroradiology. 2003; 24(5):805–809. [PubMed: 12748075]

Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics. 2005; 115(2):286–294. Article. 10.1542/peds.2004-0326 [PubMed: 15687434]

Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. The Journal of pediatrics. 2003; 143(2):171–179.10.1067/s0022-3476(03)00357-3 [PubMed: 12970628]

Kidokoro H, Neil JJ, Inder TE. New MR Imaging Assessment Tool to Define Brain Abnormalities in Very Preterm Infants at Term. AJNR. American journal of neuroradiology. 201310.3174/ajnr.A3521

Konrad A, Dielentheis TF, El Masri D, Bayerl M, Fehr C, Gesierich T, Winterer G. Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. The European journal of neuroscience. 2010; 31(5):912–919.10.1111/j.1460-9568.2010.07110.x [PubMed: 20374289]

Kwong KL, Wong YC, Fong CM, Wong SN, So KT. Magnetic resonance imaging in 122 children with spastic cerebral palsy. Pediatr Neurol. 2004; 31(3):172–176.10.1016/j.pediatrneurol.2004.02.005 [PubMed: 15351015]

Lezak, M.; Howieson, D.; Loring, D. Neuropsychological Assessment. 4th. New York: Oxford University Press; 2004.

Maalouf EF, Duggan PJ, Rutherford MA, Counsell SJ, Fletcher AM, Battin M, Edwards AD. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. The Journal of pediatrics. 1999; 135(3):351–357. [PubMed: 10484802]

Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, Seidman LJ. Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections. Cerebral Cortex. 2008; 18(5):1210–1220.10.1093/cercor/bhm156 [PubMed: 17906338]

Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. The differential assessment of children's attention: The test of everyday attention for children (TEA-Ch), normative sample and ADHD performance. Journal of Child Psychology and Psychiatry. 2001; 42(8):1065–1081. [PubMed: 11806689]

Manly, T.; Robertson, IH.; Anderson, V.; Nimmo-Smith, I. TEA-Ch: The Test of Everyday Attention for Children. Bury St. Edmunds, England: Thames Valley Test Company; 1999.

Marlow N, Wolke D, Bracewell MA, Samara M, Grp EPS. Neurologic and developmental disability at six years of age after extremely preterm birth. New England Journal of Medicine. 2005; 352(1):9–19.10.1056/NEJMoa041367 [PubMed: 15635108]

Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, Pietrzak RH. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol. 2009; 24(2):165–178.10.1093/arclin/acp010 [PubMed: 19395350]

Mathias JL, Wheaton P. Changes in attention and information-processing speed following severe traumatic brain injury: a meta-analytic review. Neuropsychology. 2007; 21(2):212–223.10.1037/0894-4105.21.2.212 [PubMed: 17402821]

Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, Fellman V. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. Pediatrics. 2005; 116(6):1391–1400.10.1542/peds.2005-0171 [PubMed: 16322163]

Miller, DC. Essentials of school neuropsychological assessment. Hoboken, NJ: Wiley; 2007.

Miller, DC. Best practices in school neuropsychology: Guidelines for effective practice, assessment, and evidence-based interventions. Hoboken, NJ: Wiley; 2010.

Miller SP, Ferriero DM, Leonard C, Piecuch R, Glidden DV, Partridge JC, Barkovich AJ. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. The Journal of pediatrics. 2005; 147(5):609–616.10.1016/j.jpeds.2005.06.033 [PubMed: 16291350]

Mirmiran M, Barnes PD, Keller K, Constantinou JC, Fleisher BE, Hintz SR, Ariagno RL. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Pediatrics. 2004; 114(4):992–998.10.1542/peds.2003-0772-L [PubMed: 15466096]

Mirsky AF, Anthony BJ, Duncan CC, Ahearn MB, Kellam SG. Analysis of the elements of attention: a neuropsychological approach. Neuropsychology review. 1991; 2(2):109–145. [PubMed: 1844706]

Mirsky AF, Duncan CC. A nosology of disorders of attention. Ann N Y Acad Sci. 2001; 931:17–32. [PubMed: 11462740]

Mulder H, Pitchford NJ, Hagger MS, Marlow N. Development of Executive Function and Attention in Preterm Children: A Systematic Review. Developmental Neuropsychology. 2009; 34(4):393–421.10.1080/87565640902964524 [PubMed: 20183707]

Mulder H, Pitchford NJ, Marlow N. Inattentive behaviour is associated with poor working memory and slow processing speed in very pre-term children in middle childhood. British Journal of Educational Psychology. 2011a; 81(1):147–160.10.1348/000709910x505527 [PubMed: 21391967]

Mulder H, Pitchford NJ, Marlow N. Processing speed mediates executive function difficulties in very preterm children in middle childhood. Journal of the International Neuropsychological Society. 2011b; 17(3):445–454. Article. 10.1017/s1355617711000373 [PubMed: 21439114]

Ni TL, Huang CC, Guo NW. Executive function deficit in preschool children born very low birth weight with normal early development. Early Human Development. 2011; 87(2):137–141. Article. 10.1016/j.earlhumdev.2010.11.013 [PubMed: 21194855]

Olsen P, Vainionpaa L, Paakko E, Korkman M, Pyhtinen J, Jarvelin MR. Psychological findings in preterm children related to neurologic status and magnetic resonance imaging. Pediatrics. 1998; 102(2):329–336.10.1542/peds.102.2.329 [PubMed: 9685434]

Omizzolo C, Scratch SE, Stargatt R, Kidokoro H, Thompson DK, Lee KJ, Anderson PJ. Neonatal brain abnormalities and memory and learning outcomes at 7 years in children born very preterm. Memory. 201310.1080/09658211.2013.809765

Pascualvaca DM, Anthony BJ, Arnold LE, Rebok GW, Ahearn MB, Kellam SG, Mirsky AF. Attention performance in an epidemiological sample of urban children: The role of gender and verbal intelligence. Child Neuropsychology. 1997; 3(1):13–27.10.1080/09297049708401365

Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annual Review of Neuroscience. 2012; 35:73–89.10.1146/annurev-neuro-062111-150525

Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, Ment LR. Regional Brain Volumes and Their Later Neurodevelopmental Correlates in Term and Preterm Infants. Pediatrics. 2003; 111(5):939–948. [PubMed: 12728069]

Pierson CR, Folkerth RD, Billiards SS, Trachtenberg FL, Drinkwater ME, Volpe JJ, Kinney HC. Gray matter injury associated with periventricular leukomalacia in the premature infant. Acta Neuropathol. 2007; 114(6):619–631.10.1007/s00401-007-0295-5 [PubMed: 17912538]

Pizzo R, Urben S, M VDL, Borradori-Tolsa C, Freschi M, Forcada-Guex M, Barisnikov K. Attentional networks efficiency in preterm children. Journal of the International Neuropsychological Society : JINS. 2010; 16(1):130–137. Research Support, Non-U.S. Gov't. 10.1017/S1355617709991032 [PubMed: 19849881]

Posner MI, Petersen SE. The attention system of the human brain. Annual Review of Neuroscience. 1990; 13:25–42. Review. 10.1146/annurev.ne.13.030190.000325

Posner MI, Peterson SE. The attention system of the human brain. Annual Review of Neuroscience. 1990; 13:25–42.

Posner MI, Sheese BE, Odludaş Y, Tang Y. Analyzing and shaping human attentional networks. Neural Networks. 2006; 19:1422–1429. [PubMed: 17059879]

Roberts G, Howard K, Spittle AJ, Brown NC, Anderson PJ, Doyle LW. Rates of early intervention services in very preterm children with developmental disabilities at age 2 years. J Paediatr Child Health. 2008; 44(5):276–280.10.1111/j.1440-1754.2007.01251.x [PubMed: 17999667]

Rose SA, Feldman JF. Memory and processing speed in preterm children at eleven years: A comparison with full-terms. Child Development. 1996; 67(5):2005–2021. Article. 10.1111/j.1467-8624.1996.tb01840.x [PubMed: 9022226]

Rose SA, Feldman JF, Jankowski JJ. Processing speed in the 1st year of life: A longitudinal study of preterm and full-term infants. Developmental Psychology. 2002; 38(6):895–902.10.1037//0012-1649.38.6.895 [PubMed: 12428702]

Rose SA, Feldman JF, Jankowski JJ. Information Processing in Toddlers: Continuity from Infancy and Persistence of Preterm Deficits. Intelligence. 2009; 37(3):311–320.10.1016/j.intell.2009.02.002 [PubMed: 20161244]

Rose SA, Feldman JF, Jankowski JJ. Modeling a cascade of effects: the role of speed and executive functioning in preterm/full-term differences in academic achievement. Developmental Science. 2011; 14(5):1161–1175. Article. 10.1111/j.1467-7687.2011.01068.x [PubMed: 21884331]

Rose SA, Feldman JF, Jankowski JJ, Van Rossem R. A cognitive cascade in infancy: Pathways from prematurity to later mental development. Intelligence. 2008; 36(4):367–378. Article. 10.1016/j.intell.2007.07.003 [PubMed: 19122757]

Rose SA, Feldman JF, Jankowski JJ, Van Rossem R. Basic information processing abilities at 11 years account for deficits in IQ associated with preterm birth. Intelligence. 2011; 39(4):198–209. Article. 10.1016/j.intell.2011.03.003 [PubMed: 21643482]

Saigal S, Doyle LW. Preterm birth 3 - An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008; 371(9608):261–269. Review. 10.1016/s0140-6736(08)60136-1 [PubMed: 18207020]

Salt A, Redshaw M. Neurodevelopmental follow-up after preterm birth: follow up after two years. Early Human Development. 2006; 82(3):185–197.10.1016/j.earlhumdev.2005.12.015 [PubMed: 16530991]

Snyder EH, Davis DW, Burns BM, Robinson JB. Examining attention networks in preschool children born with very low birth weights. Journal of Early Childhood and Infant Psychology. 2007; 3:185–203.

Spittle AJ, Cheong J, Doyle LW, Roberts G, Lee KJ, Lim J, Anderson PJ. Neonatal white matter abnormality predicts childhood motor impairment in very preterm children. Developmental Medicine and Child Neurology. 2011; 53(11):1000–1006. Article. 10.1111/j.1469-8749.2011.04095.x [PubMed: 22014319]

Taylor HG, Hack M, Klein NK. Attention deficits in children with < 750 gm birth weight. Child Neuropsychology. 1998; 4(1):21–34.

Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage. 2008; 42(2):1032–1044.10.1016/j.neuroimage.2008.03.057 [PubMed: 18602840]

Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biological psychiatry. 2007; 61(12):1361–1369. Article; Proceedings Paper. 10.1016/j.biopsych.2006.06.011 [PubMed: 16950217]

van de Weijer-Bergsma EV, Wijnroks L, Jongmans MJ. Attention development in infants and preschool children born preterm: A review. Infant Behavior & Development. 2008; 31(3):333–351.10.1016/j.infbeh.2007.12.003 [PubMed: 18294695]

Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. The Lancet Neurology. 2009; 8(1):110–124.10.1016/S1474-4422(08)70294-1

Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm children. New England Journal of Medicine. 2006; 355:685–694. [PubMed: 16914704]

Woodward LJ, Clark CA, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. PLoS One. 2012; 7(12):e51879. [PubMed: 23284800]

Woodward LJ, Clark CAC, Pritchard VE, Anderson PJ, Inder TE. Neonatal White Matter Abnormalities Predict Global Executive Function Impairment in Children Born Very Preterm. Developmental Neuropsychology. 2011; 36(1):22–41. Article. 10.1080/87565641.2011.540530 [PubMed: 21253989]

Woodward LJ, Edgin JO, Thompson D, Inder TE. Object working memory deficits predicted by early brain injury and development in the preterm infant. Brain. 2005; 128:2578–2587.10.1093/brain/awh618 [PubMed: 16150850]

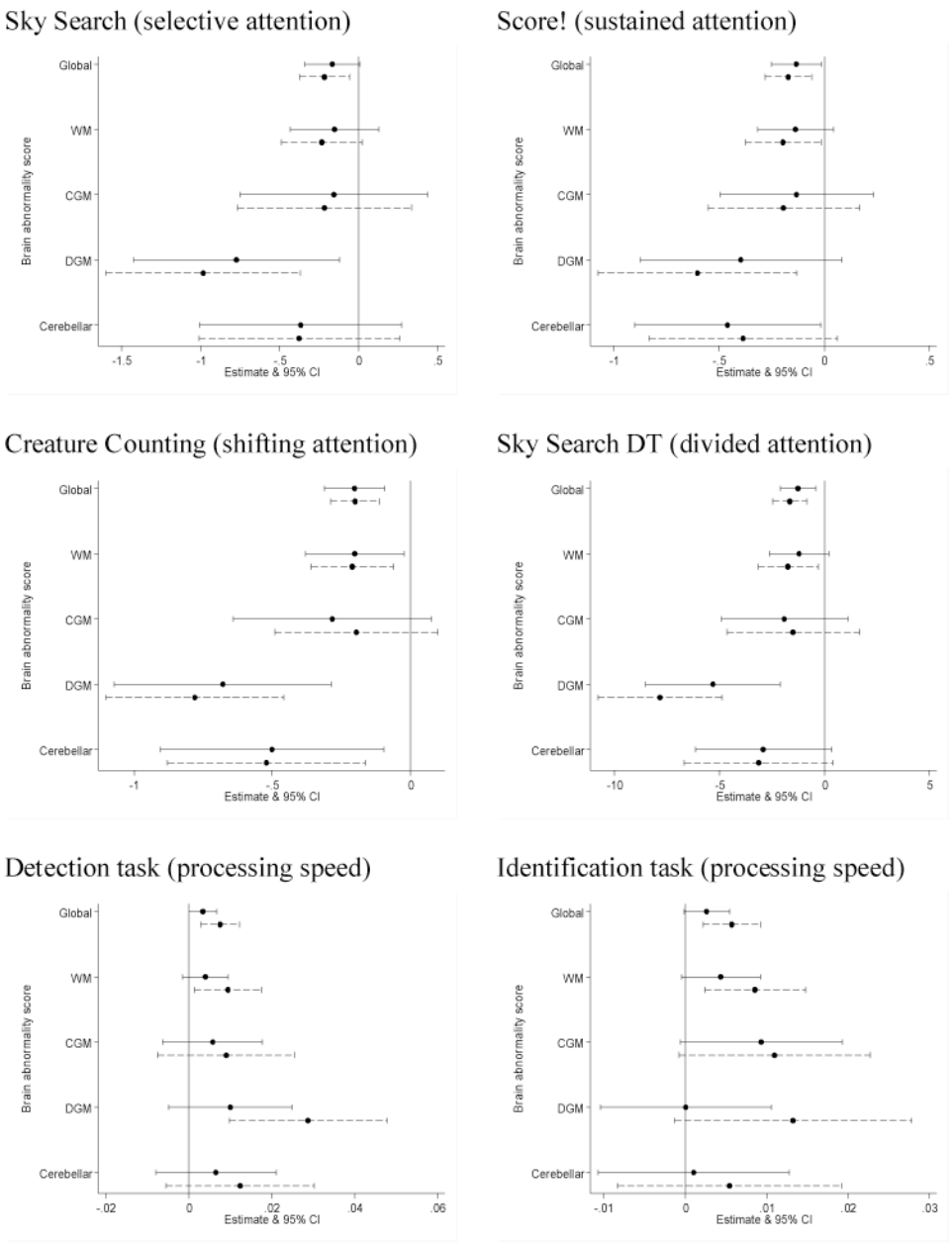

Figure 1.

Adjusted associations between MRI abnormalities and attention and processing speed outcomes at 7 years. The solid line represents the primary analyses and the broken line represents the secondary analyses. For Sky Search, Score!, Creature Counting, and Sky Search DT lower scores indicate worse functioning. For the Identification and Detection tasks higher scores indicate worse functioning.

WM, white matter; *CGM*, cortical gray matter; *DGM*, deep gray matter

Table 1
Demographic and perinatal characteristics of the sample

	VPT n* = 198	Term n* = 70	OR (95% CI)	p
GA (wk), M (SD)	27.4 (1.9)	39.1 (1.3)	-	<**.001**
Birth weight (g), M (SD)	960 (222)	3322 (508)	-	<**.001**
Male, n %	104 (52.5)	34 (48.6)	0.9 (0.5, 1.5)	0.57
Singleton, n %	114 (57.6)	66 (94.3)	12.2 (4.3, 34.7)	<**.001**
SGA, n (%)	17 (8.6)	1 (2.3)[a]	4.0 (0.5, 30.5)	0.13
Apgar score at 5 mins, median (25th & 75th %ile)	8 (8-9)	9 (9-10)[a]	-	<**.001**
Episodes of sepsis, n %	88 (44.4)	1 (2.3)[a]	-	<**.001**
Patent ductus arteriosus, n %	99 (50.0)	0[a]	NA	<**.001**
Necrotising enterocolitis, n %	21 (10.6)	0[a]	NA	0.10
Bronchopulmonary dysplasia, n %	69 (35.0)	0[a]	NA	<**.001**
LOS (d), median (25th & 75th %ile)	82 (68-104)	5 (4-6)[a]	-	<**.001**
Antenatal corticosteroids, n %	173 (87.8)	0[a]	NA	<**.001**
Postnatal corticosteroids, n %	17 (8.6)	0[a]	NA	**0.03**
Cystic PVL, n %	9 (4.6)	0[a]	NA	0.17
Grade III/IV IVH, n %	7 (3.6)	0[a]	NA	0.26
WMA, n %	134 (67.7)	6 (8.6)	-	<**.001**
Maternal age at birth (y), M (SD)	30.4 (5.7)[b]	31.4 (4.5)[b]	-	0.20
Social risk score, median (25th & 75th %ile)	2 (1-3)[c]	1 (0-2)[c]	-	<**.001**
Age at 7 years (yrs), M (SD)	7.52 (0.25)	7.65 (0.31)	-	<**.001**
FSIQ at 7 years, M (SD)	97.09 (13.76)[d]	107.21 (12.76)	-	<**.001**

GA, gestational age; *M*, mean; *SD*, standard deviation; SGA, small for GA (below the 10th percentile for GA); *LOS*, length of hospital stay; *PVL*, periventricular leukomalacia; *IVH*, intraventricular hemorrhage; *WMA*, white matter abnormality (mild, moderate or severe); *FSIQ*, Wechsler Abbreviated Scale of Intelligence full scale intelligence quotient.

Some sample sizes are less than the total sample because of missing data.

[a] Term n = 43

[b] VPT n = 197; Term n = 68

[c] VPT n = 187; Term n = 69

[d] VPT n = 190

NA = OR could not be calculated because of a 0 value in 1 of the cells.

Bold text indicates statistically significant values.

Table 2

Differences between the VPT and term children on attention and processing speed outcomes at age 7 years

	VPT Group		Term Group		Unadjusted		Adjusted for age, social risk, gender and excluding children with IQ < 70[a]	
Outcome	**N**	**M(SD)**	**N**	**M(SD)**	**Est(95% CI)**	***p***	**Est(95% CI)**	***p***
Attention								
Sky Search	191	15.70 (3.97)	69	17.77 (2.50)	-2.07(-2.90, -1.24)	**<.001**	-1.71(-2.59, -0.83)	**<.001**
Score!	182	6.03 (2.63)	69	7.10 (1.90)	-1.07(-1.66, -0.48)	**<.001**	-0.76(-1.38, -0.14)	**0.02**
Creature Counting	160	3.29 (2.30)	69	4.57 (1.97)	-1.27(-1.85, -0.69)	**<.001**	-1.18(-1.77, -0.59)	**<.001**
Sky Search DT	175	69.78 (20.03)	69	78.95 (16.18)	-9.17(-14.08, -4.26)	**<.001**	-6.28(-11.43, -1.13)	**0.02**
Processing Speed								
Identification Task	178	2.90(0.07)	69	2.87(0.08)	0.03 (0.00, 0.05)	**0.03**	0.02(-0.00, 0.04)	0.06
Detection Task	179	2.70 (0.09)	69	2.67(0.11)	0.03 (0.01, 0.06)	**0.02**	0.04 (0.01, 0.06)	**0.01**

VPT, very preterm; *M*, mean; *SD*, standard deviation; *Est*, estimate of regression coefficient representing the difference in means between the groups; *CI*, confidence interval.

[a] = up to 11 participants with missing data on social risk and up to 3 participants with IQ<70 not included in these analyses.

Bold text indicates statistically significant values.

Table 3

Frequency of children whose attention and processing speed scores fell below -1 SD of the term group mean

	VPT Group n* =198 (%)	Term Group n* =70 (%)	Odds Ratio (95% CI)	*p*
Attention				
Sky Search	76/191 (39.8)	11/69 (15.9)	3.5(1.7, 7.1)	**<.001**
Score!	69/182 (37.9)	12/69 (17.4)	2.9(1.5, 5.8)	**.003**
Creature Counting	83/160 (51.9)	17/69 (24.6)	3.3(1.8, 6.2)	**<.001**
Sky Search DT	71/175 (40.6)	13/69 (18.8)	2.9(1.5, 5.8)	**.002**
Processing Speed				
Identification Task	43/178 (24.2)	13/69 (18.8)	1.4(0.7, 2.8)	0.37
Detection Task	32/179 (17.9)	13/69 (18.8)	0.9(0.5, 2.0)	0.86

VPT, very preterm; *CI*, confidence interval.

*Some samples are less than the total sample due to missing data.

Bold text indicates statistically significant values.