Published in final edited form as:

Memory. 2014 August ; 22(6): 605–615. doi:10.1080/09658211.2013.809765.

Neonatal Brain Abnormalities and Memory and Learning Outcomes at 7 Years in Children Born Very Preterm

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Abstract

Using prospective longitudinal data from 198 very preterm and 70 full term children, this study characterised the memory and learning abilities of very preterm children at 7 years of age in both verbal and visual domains. The relationship between the extent of brain abnormalities on neonatal magnetic resonance imaging (MRI) and memory and learning outcomes at 7 years of age in very preterm children was also investigated. Neonatal MRI scans were qualitatively assessed for global, white-matter, cortical grey-matter, deep grey-matter, and cerebellar abnormalities. Very preterm children performed less well on measures of immediate memory, working memory, long-term memory, and learning compared with term born controls. Neonatal brain abnormalities, and in particular deep grey matter abnormality, were associated with poorer memory and learning performance at 7 years in very preterm children, especially global, white-matter, grey-matter and cerebellar abnormalities. Findings support the importance of cerebral neonatal pathology for predicting later memory and learning function.

Keywords

Very preterm – VPT; Gestational age – GA; Neonatal brain abnormalities; Memory and learning

Introduction

Very preterm (VPT; <32 completed weeks of gestational age [GA]) birth accounts for approximately 2% of births world-wide (World Health Organisation, 2012). While most VPT infants now survive, up to 60% of survivors will show later cognitive (Anderson & Doyle, 2003), motor (Williams, Lee & Anderson, 2009), academic (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever & Oosterlaan, 2009) and behavioural (Bhutta, Cleves, Casey, Craddock, & Anand, 2002) problems. One area that has not received much attention in VPT children is memory and learning. Given evidence suggesting impaired memory and learning in children born preterm compared with term born controls (Taylor, Klein, Minich & Hack, 2000; Rose, Feldman & Jankowski, 2005), and the high risk of brain pathology in this population (Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Woodward, Anderson, Austin, Howard, & Inder, 2006), further investigation of memory and learning outcomes and the association with brain pathology in preterm children is warranted especially within those born VPT.

Memory is a complex construct. Information initially enters a temporary storage system, or immediate memory. The capacity to manipulate and process this information while in temporary storage is referred to as working memory. Processes such as articulatory rehearsal (Baddeley, 1996) and attentional refreshment (Barrouillet & Camos, 2001) enable information to be transferred from temporary storage into the more durable long term memory. Long term memory can be broken down into subdivisions; explicit (declarative) and implicit (procedural) memory (Tulving, 1972; Strauss, Sherman, & Spreen, 2006). Explicit memory can be further subdivided into memory for specific events or experiences (episodic memory) and memory for facts (semantic memory) (Tulving, 1972). Immediate and working memory have both been associated with the prefrontal cortex (PFC), anterior cingulate, and parietal and occipital regions (Cabeza & Nyberg, 2000), whereas structures of the medial temporal lobe, including the hippocampus and related cortices (perirhinal, entorhinal and parahippocampal) have vital implications for the retention, storage and retrieval of information (Moscovitch & Umiltà, 1990; Nadel, Samsonovitch, Ryan, & Moscovitch, 2000).

Studies show that preterm children have difficulties with multiple components of memory. The majority of research has focused on immediate and/or working memory with preterm children exhibiting deficits in both visual (Isaacs et al., 2000; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Rose et al., 2009; Rose, Feldman, Jankowski & Van Rossem 2011; Woodward et al., 2005) and verbal (Böhm, Smedler, & Forssberg, 2004; Isaacs et al., 2000) modalities when compared to term controls. With regards to explicit memory, 12 month old preterm infants have shown deficits in the reproduction of action sequences (Rose et al., 2009), and children with very low birth weight (VLBW; <1500 g) have demonstrated reduced list learning, delayed recall, inaccurate recall (Taylor et al., 2000), and visual recall (Taylor, Minich, Klein, & Hack, 2004) compared with term controls. Additionally, poorer everyday memory (Isaacs et al., 2000) and recognition memory (Rose et al., 2005; Rose, Feldman & Jankowski, 2009; Rose, Feldman, Jankowski, & Van Rossem, 2011) have been reported in preterm cohorts.

Cognitive deficits in VPT children, such as memory, may be associated with neonatal brain injury and disrupted brain development (Ment, Hirtz, & Huppi, 2009). Historically, the major neuropathologies associated with VPT birth have been high-grade intraventricular haemorrhage (IVH) and cystic periventricular leukomalacia (PVL), both of which are easily detected on cranial ultrasound. These pathologies have been associated with moderate to severe cognitive and motor impairments (De Vries, Van Haastert, Rademaker, Koopman, & Groenendaal, 2004; Sherlock, Anderson & Doyle, 2005), but are now uncommon due to

improved obstetric and neonatal care (observed in fewer than 10% of VPT survivors; Volpe, 2009). While most VPT infants avoid significant brain injury, magnetic resonance imaging (MRI) studies have revealed that the majority of VPT infants have diffuse white-matter abnormalities (Inder et al., 2003; Back, 2006; Boardman & Dyet, 2007), including enlarged lateral ventricles, white matter signal abnormalities and volume loss, thinning of the corpus callosum, and delayed myelination (Inder et al., 2003; Woodward et al., 2006). Grey matter abnormalities, such as delayed gyration, increased subarachnoid space, and decreased cerebral grey matter volume, have also been detected in VPT infants (Inder, Huppi, Warfield, Kikinis, Zientara, et al., 1999; Woodward et al., 2006), and may be at least partly related to white matter abnormalities (Inder et al., 1999). Qualitative scoring systems for neonatal brain MRI (Inder et al., 2003; Miller, Ferriero, Leonard, Piecuch, Glidden, et al., 2005; Woodward et al., 2006) suggest that approximately one fifth of VPT infants have moderate to severe white matter abnormalities and 50% have mild abnormalities (Inder et al., 2003; Miller et al., 2005).

Despite the recognition of brain abnormalities in VPT infants, few studies have examined the association between neonatal brain injury and later cognitive functioning in VPT children. Moderate-severe white matter abnormality has been reported to predict early cognitive delay, cerebral palsy and neurosensory deficits (Woodward et al., 2006), as well as executive functioning at preschool age (Woodward, Clark, Pritchard, Anderson, & Inder, 2011). At school age, mild and moderate-severe white matter abnormalities have been found to predict visual and verbal working memory deficits (Clark & Woodward, 2010) and motor impairment (Spittle, Cheong, Doyle, Roberts, Lee, et al., 2011). Similarly, grey matter abnormalities have been associated with early cognitive and motor delays (Woodward et al., 2006), and later impairments to visual working memory (Clark & Woodward, 2010).

In summary, although there is some evidence of memory deficits in VPT infants, a better understanding of memory and learning in VPT children is required, especially given the importance of these skills to academic progress and vocational success (Hornby & Woodward, 2009). Furthermore, it is unclear how memory and learning deficits reported in this population are related to neonatal brain abnormalities. As such, this study aims to: 1) characterise memory and learning performance in both verbal and visual domains in 7 year old children born VPT compared with term controls, and 2) evaluate the association between neonatal brain abnormalities and memory and learning functioning at 7 years of age in VPT children.

Materials and Methods

Participants

Participants were prospectively recruited into the Victorian Infant Brain Studies (VIBeS) cohort from the Royal Women's Hospital in Melbourne, Australia from July 2001 to December 2003. Eligible VPT infants were born <30 weeks' GA and/or <1250 g, without congenital abnormalities that would impair neurological function, and survived the neonatal period. In total, 227 VPT infants were recruited although 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 VPT infants. A control group of 77 term (37 to 42 weeks' GA) and normal birth weight (>2500 g) 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 centres. Previous follow-up assessments of VPT and control children 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 5-year follow-up the VPT children exhibited poorer immediate/working memory

compared to the term controls (Roberts, Lim, Doyle, & Anderson, 2011). At the 7-year follow-up, 198 of the 224 VPT children (88% of infants) and 70 of the 77 control children (91%) were assessed.

Procedure and Measures

Approval for the study was obtained from the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital in Melbourne. Written informed consent was obtained from parents.

VPT infants had a brain MRI scan at term equivalent age, while the 46 term controls recruited in the neonatal period were scanned within 2 weeks of birth. T₁ (1.2 mm coronal slices; repetition time 35 msec; echo time 9 msec; flip angle 45°; field of view 210×158 mm; matrix 256×192) and T₂ weighted structural MR images (1.7-3.0 mm coronal slices; repetition time 4000 msec; echo time 60/160 msec; flip angle 90°; field of view 22×16 cm; matrix 256×192, interpolated 512×512) were acquired with a 1.5 Tesla General Electric MRI scanner at Melbourne's Royal Children's Hospital. Infants were fed, settled and fitted with earmuffs before being scanned without sedation. Using T₁ and T₂ weighted scans, cerebral abnormality was rated by a neonatal neurologist using a system described by Kidokoro, Neil, & Inder, (2012, in press), which is an adaptation of a procedure applied previously (Inder et al., 2003; Woodward et al., 2006). This scoring system rates the presence and severity of white matter abnormality (WM; cystic lesions, signal abnormality, myelination delay, callosal thinning, lateral ventricular volume, white matter volume), cortical grey matter abnormality (CGM; extracerebral space, signal abnormality, gyral maturation), deep grey matter abnormality (DGM; signal abnormality, deep grey matter volume) and cerebellar abnormality (signal abnormality, cerebellar volume) on a scale from 0 to 4. These four subscales are also summed to generate a global abnormality score (scores ranged from 0-40).

Memory and learning were assessed at 7 years of age, corrected for prematurity, as part of a larger neuropsychological battery of standardized tests, including a measure of intelligence (IQ; Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999). We selected standardized memory tests that are used widely both in clinical and research settings.

Working Memory Test Battery for Children (WMTB-C; Pickering & Gathercole, 2001)—Three subsets from the WMTB-C were administered. 1) Forward Digit Recall, which assesses immediate verbal memory. Participants are read a series of numbers and required to recall each sequence in original order. Number sequences increase from 1 digit to 9 digits, with 6 trials per sequence length. 2) Backward Digit Recall, which assesses verbal working memory. Participants are required to repeat sequences of numbers in the reverse order. 3) Block Recall, which assesses immediate visual-spatial memory. Blocks on a three-dimensional board are tapped in a sequence by the examiner, and participants are required to tap them in the same sequence. A total score for each subtest reflects the number of trials completed correctly.

California Verbal Learning Test – Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994)—The CVLT-C assesses verbal memory and learning. Participants are read a 15-item word list (list A), which they are asked to immediately recall. This procedure is repeated 5 times, deriving a learning score. A second or distracter list (list B) is administered, and immediately followed by a short-delay free recall of List A. After approximately 20-minutes, long-delay free recall and recognition trials of List A are administered. Outcome measures include: verbal working memory (number of words

recalled on trial 1 of list A), verbal learning (total number of words recalled across trials 1-5), and number of words recalled after short and long delays.

Dot Locations subtest from the Children's Memory Scale (CMS; Cohen, 1997)

—The Dot Locations subtest assesses visual-spatial memory and learning. Participants are presented with an array of 6 dots for 5 seconds on a 3×3 grid and are required to learn their spatial location. Next, participants are asked to place 6 plastic dots on a blank 3×3 grid in the same array as just seen. This procedure is repeated another 2 times. Following these 3 learning trials, a second (or distracter) dot array is presented followed by a short-delay recall trial of the original dot array. A long-delay recall trial is administered approximately 20 minutes later. Performance measures of interest in this study were visual learning (total trials 1-3 of the first array), and visual memory after short and long delays.

Social Risk—There is a tendency for preterm cohorts to be of higher social risk than term-born cohorts, and higher social risk has been associated with an increased risk of developmental problems (Largo, Graf, Kundu, Hunziker, & Molinari, 1990; Roberts, Howard, Spittle, Brown, Anderson, et al., 2008; Wang, McGlynn, Brook, Leonard, Piecuch, Hsueh et al., 2006). Preterm infants with moderate to high social risk are at increased risk of developmental problems (Hack, Breslau, Aram, Weissman, Klein, & Borawski-Clark, 1992) and are less likely to receive early intervention (Roberts, et al., 2008). As part of the 7 year assessment, parents completed a questionnaire to assess social risk based on family structure, language spoken at home, education of the primary caregiver, occupation and employment status of the primary income earner, and maternal age at birth (Roberts et al., 2008). Scores ranged from 0 – 12, with higher scores being reflective of greater social risk.

Statistical Analyses—Data were analysed using Stata 12 (StataCorp, 2011). Given the restricted age range of the children at follow-up, raw data were used. Scores were recorded as 'missing' if children were either too impaired to complete tasks, refused to complete tasks, or there was a problem with the assessment equipment (e.g. missing components of a task).

Firstly, linear regression was used to examine differences between birth groups (VPT and term) on all outcome measures. Each model was fitted using generalised estimating equations (GEEs) with an exchangeable correlations structure and robust standard errors to allow for correlations between twins/triplets in the study, and included adjustment for age at testing. Subsequent analyses also controlled for social risk, and excluded children with a full-scale IQ<70 to determine the extent to which these factors explained the difference in performance between the groups. Impairment on each scale was classified as 1 standard deviation (SD) below the control group mean. Unadjusted logistic regression (fitted with GEEs) was used to compare the odds of impairment between the two groups on outcome measures.

Linear regression was also used to examine the relationship between the presence of brain abnormality (as continuous variables) at term and memory and learning outcomes at 7 years in the VPT group. The models were fitted using GEEs, and controlling for age at testing, social risk, and excluding children with IQ<70. Semi partial correlations (sr^2) were used to assess the percentage of variance accounted for by each independent predictor.

Results

Sample Characteristics

Table 1 shows the characteristics for the VPT and control groups. The gender ratio was similar between the VPT and term groups, although there was evidence of differences between groups for age at assessment ($p=0.002$) and social risk ($p=0.001$).

Group Differences on Memory and Learning Outcomes at 7 years

Table 2 shows that VPT children on average performed lower than term-born children on all measures of memory and learning, with the exception of CVLT-C trial 1 and long delay. While subsequent analysis adjusted for social risk and excluding children with $IQ<70$ resulted in some attenuation of results, evidence of group differences remained in the majority of outcomes.

Table 3 displays the proportion of children with impairment in the VPT and control groups for all outcome measures, and highlights that a higher proportion of the VPT group have impairments compared with the control group (i.e. performing more than one SD below the control group mean). There was evidence that the impairment rate was higher in the VPT group across all memory measures, with odds ratios ranging from 2.1 to 3.5.

Neonatal Brain Pathology and Memory and Learning Outcomes in Children Born VPT

Figure 1 shows the presence of neonatal brain abnormalities as a predictor of memory and learning performances at 7 years in VPT children. The general trend is that increasing severity of neonatal brain abnormality is associated with reduced performance on memory and learning tasks in VPT children. Deep grey matter abnormality appeared to be the strongest predictor of memory functioning, associated with poorer scores for the majority of outcomes, although there were large overlaps in the 95% confidence intervals across the measures. Of the measures used, the CVLT-C total trials 1-5 was the most strongly predicted by neonatal brain abnormality. For the other outcomes, the association with brain abnormalities were generally weak, with the exception of deep grey matter abnormality. Sr^2 controlling for age at assessment, social risk, and excluding children with $IQ<70$, indicate that neonatal brain injury accounts for only a small amount of variance in the outcomes presented (1.93% to 8.36%).

Discussion

In this prospective, longitudinal study, children born VPT performed consistently less well than term children across all measures of memory and learning in both the verbal and visual modalities at 7 years of age. Children born VPT had higher social risk than their term-born counterparts, and this contributed to poorer performance on a number of outcome measures. Given that VPT children with higher social risk are more susceptible to developmental difficulties and are less likely to receive early intervention than VPT children with low social risk (Roberts et al., 2008), we expected an attenuation of results on outcome measures when social risk was controlled for. We also found evidence of an association between neonatal brain abnormalities and poorer memory and learning outcomes at 7 years in VPT children, especially with the presence of deep grey matter abnormality. Verbal learning appeared to be most vulnerable to neonatal brain pathology.

Understanding the mechanisms behind memory and learning deficits in VPT children improves the capacity to detect high-risk children at a young age. This is particularly important given the contribution of these skills to academic progress and success (Colom, Escorial, Shih, & Privado, 2007; Hornby & Woodward, 2009; Swanson, 1994), and has

implications for enrolling children in early intervention programs that target memory enhancement. White matter abnormalities observed on neonatal MRI in VPT infants has been reported to be predictive of early developmental delay (Woodward et al. 2006), visual working memory at 6 years (Clark et al., 2010), executive functioning at age 4 years (Woodward et al., 2011), motor impairment at age 5 (Spittle et al., 2011), and language functioning at age 7 years (Reidy, Morgan, Thompson, Inder, Doyle, 2012 in press). The current study contributes to the literature by examining neonatal brain abnormalities more generally, not just white matter injury, and demonstrates that qualitative neonatal MRI is predictive of memory and learning at 7 years.

Although it is unclear whether the memory and learning impairments identified in this VPT sample reflect developmental delay or deficit at this stage of development, findings are consistent with other studies reporting memory outcomes in children and adolescents born VPT (Taylor et al., 2000; Böhm et al., 2004; Taylor et al., 2004; Woodward et al., 2005; Taylor et al., 2011; Clark & Woodward, 2010). VPT children in the current study have previously been reported to have working memory deficits compared to their term born peers at 5 years of age (Roberts, Lim, Doyle, & Anderson, 2011). In the current study, immediate and working memory in VPT children were characterised by deficits in the initial acquisition of visual information as well as the manipulation of verbal material when compared with term controls. Relative to term controls, the efficacy of the learning process for visual formation was reduced, and there was a trend for a higher risk of impaired verbal learning in the VPT population. A discrepancy between the groups in recall after short and long delays was also present – recall following a short delay was reduced for both verbal and visual material in the VPT group, but only reduced for recall of visual information after a long delay. Overall, recalling of visual information appears to be more impaired in VPT children than verbal information. This may be due to the use of different memory networks for these modalities, suggesting a higher vulnerability of visual networks to neonatal brain injury in VPT birth.

Consideration of memory models may provide insight into the processes underlying memory and learning impairments experienced by VPT children. An issue of long-standing debate has been whether immediate/working memory and long term memory systems are separate entities, or whether they act independently but are linked in parallel (Hebb, 1949, Baddeley, 1997). Most recent evidence supports the latter view (Baddeley 2000; Baddeley, 2003; Hodges, 2007) because patients with immediate phonological impairments have also been found to display specific deficits in long term phonological learning (Baddeley, Papagno, & Vallar, 1998). Consistently, verbal memory and learning skills in our VPT group was characterised by impaired immediate/working memory and short delay recall, with relatively preserved long delay recall. This pattern of impairment may reflect a primary impairment of immediate and/or working memory. In contrast, visual memory and learning impairments in the VPT cohort were more generalised, suggesting more extensive deficits to underlying networks.

An important finding in the current study was that across each memory outcome approximately 30% of VPT children performed at least 1 SD below the control group mean. Odds ratios showed that the VPT group had approximately 3 times greater odds of impairment than the full-term sample. This highlights the high frequency of memory impairments in VPT children, which is a significant concern given that memory is a core cognitive skill that underlies other cognitive domains (Swanson, 2008). Memory and learning deficits have also been associated with academic success such as mathematical and grammatical abilities (Sansavini et al., 2006; Bull, Espy, & Wiebe, 2008). Based on our findings, we would strongly advocate that a detailed assessment of memory and learning is

incorporated into the surveillance programs of VPT children in early school or preschool age.

Increased global abnormality score (the sum of pathology in cerebral white matter, cortical grey matter, deep grey matter and cerebellum) was associated with poorer memory outcomes in the VPT group, particularly immediate visual memory, learning in visual and verbal modalities, and ultimately the consolidation of visual and verbal material in long term memory. This finding highlights the potential impact that neonatal brain abnormalities observed on MRI associated with VPT birth can have on later memory and learning. Deep grey matter abnormality, which in this case refers to the basal ganglia and thalamus, was the strongest predictor of memory and learning performance. The basal ganglia play an important role in memory and learning, with simultaneous activation of its structures and the medial temporal lobe systems during learning tasks (Seger, 2006; Packard & Knowlton, 2002). Similarly, lesions to the thalamus can result in amnesia, supporting its vital role in memory (Aggleton & Brown, 1999; Moscovitch, Rosenbaum, Gilboa, Addis, Westmacott, 2005), and bilateral lesions have been associated with memory impairments to verbal and non-verbal material (Cipolotti, Husain, Crinion, Bird, Khan, et al., 2008). Recent findings suggest that both basal ganglia and thalamic activations are present during verbal immediate/working memory (Moore, 2012 in press). As such, deep grey matter abnormalities may compromise a number of structures that have a role in memory and learning.

White matter, cerebral grey matter and cerebellum abnormalities were only weakly associated with poorer performance on memory measures at age 7 years, and the relationships often failed to reach statistical significance. Total number of words recalled on the CVLT-C appeared to be most strongly associated with MRI defined neonatal brain abnormality, and was associated with all scales with the exception of cortical grey matter. These findings suggest that extensive networks throughout the brain may subserve more complex tasks, such as verbal learning, in VPT children.

One of the strengths of the current study was the use of measures which assess multiple components of memory and learning. This contrasts much of the previous literature that has tended to have a narrow focus. Although this has helped improve our understanding of the memory and learning difficulties many VPT children endure, methodological issues remain to be addressed. First, there were unequal sample sizes, with more children in the VPT group than in the term group, and second, the two birth groups were not entirely matched with respect to socioeconomic status – the VPT group having greater social risk than the term group.

Findings from the current study extend our understanding of memory and learning impairments in VPT children, and substantiate the predictive value of the neuropathological processes that underlie these difficulties. This information is important for VPT children and their parents in order to understand the child's potential and limitations, and to make appropriate educational and vocational choices. It also aids educators in developing interventions to minimise the impact of memory and learning impairments on academic achievement, and helps us understand the biological mechanisms behind these impairments. Further research examining ways to reduce the rate of cerebral abnormalities in VPT infants is essential for improving their long-term outcome.

Acknowledgments

We would like to acknowledge the input of the entire 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.

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Figure 1. Association between brain injury at term and memory and learning at 7 years. The figure shows the linear regression coefficient and its 95% Confidence Interval (CI), which represents the change in memory and learning outcome per one unit change in brain abnormality score.

Table 1

Demographic and perinatal characteristics of the sample assessed at 7 years of age for the current study.

	Very Preterm sample <i>n</i> = 198	Term sample <i>n</i> = 70
GA (weeks), <i>M</i> (<i>SD</i>)	27.4 (1.9)	39.1 (1.3)
Age at assessment (years), <i>M</i> (<i>SD</i>)	7.5 (0.02)	7.6 (0.04)
Birth weight (g) , <i>M</i> (<i>SD</i>)	960 (222)	3323 (508)
Social risk, <i>M</i> (<i>SD</i>)	2.2 (1.8)	1.4 (1.4)
Small for gestational age, %	8.6	2.3
Male gender, %	52.3	48.6
Singleton, %	57.4	94.3
Antenatal corticosteroids, %	87.3	0
Postnatal corticosteroids, %	8.7	0
Bronchopulmonary dysplasia, %	33.1	0
Cystic periventricular leucomalacia, %	4.1	0
Intraventricular haemorrhage grades 3/4%	3.5	0

GA = gestational age

M = mean

SD = standard deviation

Table 2
Associations between birth group and memory and learning outcomes at age 7 years

Outcome	N	M(SD)	N	M(SD)	Term	Adjusted for age only	Adjusted for age and social risk ^a	Adjusted for age, social risk, excluding children with IQ < 70 ^b
Immediate Memory								
Digits Forward	191	25.70(4.67)	69	27.09(3.68)		-1.36(-2.51, -.22)	.02	.31
Block Recall	186	20.63(4.74)	69	23.30(3.97)		-2.49(-3.71, -1.26)	<.01	<.01
Working Memory								
Digits Backward	177	9.03(3.29)	68	10.97(3.50)		-1.96(-2.97, -.94)	<.01	<.01
CVLT-C Trial 1	187	5.28(2.00)	69	5.70(1.86)		-.43(-.97, .10)	.11	.14
Memory/Learning								
CVLT-C								
Total Trials 1-5	187	37.31(10.04)	69	41.75(9.78)		-3.85(-6.73, -.97)	<.01	.04
Short Delay	187	6.76(3.04)	69	8.32(2.55)		-1.37(-2.11, -.62)	<.01	<.01
Long Delay	186	7.34(3.24)	69	8.16(2.90)		-.65(-1.49, .19)	.13	.47
Dot Locations								
Total Trials 1-3	185	14.51(2.97)	69	15.93(2.08)		-1.27(-1.95, -.59)	<.01	<.01
Short Delay	186	4.90(1.31)	69	5.54(0.83)		-.64(-.94, -.34)	<.01	<.01
Long Delay	185	4.92(1.33)	69	5.48(0.95)		-1.27(-1.95, -.59)	<.01	.01

VPT = very preterm

CVLT-C = California Verbal Learning Test – Children's Version

b = coefficient for group from the linear regression model representing the difference in means between the VPT and term groups.

CI = confidence interval

M = mean

SD = standard deviation

^a = 12 participants with missing data on social risk hence not included in the adjusted analysis.

^b = 15 participants with missing data on social risk hence not included in the adjusted analysis.

Table 3

Frequency of children who performed in the impaired range (>1.0 standard deviation below the term group mean) on memory and learning outcome measures

	VPT Sample (n=198)%	Term Sample (n=70)%	Odds Ratio (95% CI)	<i>p</i>
Immediate Memory				
Digits Forward	27.8	10.1	3.20(1.39, 7.40)	<.01
Block Recall	39.3	18.4	2.91(1.47, 5.76)	<.01
Working Memory				
Digits Backwards	36.2	16.2	2.97(1.43, 6.16)	<.01
CVLT-C Trial 1	19.3	10.1	2.11(0.88, 5.11)	.09
Memory and Learning				
CVLT-C				
Short Delay	30.0	11.6	3.25(1.44, 7.35)	<.01
Long Delay	26.9	14.5	2.13(1.00, 4.51)	.05
Total Trials 1-5	28.3	10.1	3.49(1.48, 8.24)	<.01
Dot Locations				
Short Delay	31.2	13.04	3.12(1.45, 6.69)	<.01
Long Delay	40.8	15.2	2.31(1.07, 5.00)	.03
Total Trial 1-3	30.3	14.5	2.49(1.20, 5.13)	.01

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

VPT = very preterm

CVLT-C = California Verbal Learning Test – Children's Version

CI = confidence interval