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Neurobehavioural functioning in neonatal intensive care unit graduates in late childhood and early adolescence

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Summary

The current study examined memory and executive functioning in a sample of children who were hospitalized in a neonatal intensive care unit (NICU) after birth. Thirty-two children born prematurely and/or with medical complications (NICU children) and 25 control children born at term were assessed with the Cambridge Neuropsychological Testing Automated Battery (CANTAB), a multi-dimensional computer-based measure of memory and executive functioning. Comparisons between the NICU and control groups on the CANTAB subscales indicated that the NICU children had a shorter spatial memory span length and committed more forgetting errors on a spatial working memory task. Correlational analyses demonstrated that the number and extent of medical complications at birth was negatively associated with spatial memory span, planning and spatial recognition memory. Multiple regression models suggested that gestational age was of primary importance in predicting spatial memory span, while neurobiological risk was primary in the prediction of spatial working memory errors. Overall, the current results showed fewer deficits in this group of children than were found in a previous neuropsychological assessment of this cohort. The implications of this finding for discerning the effects of neural plasticity over and above normal brain maturational processes are discussed.

Keywords: brain development; executive functioning; neuropsychology; plasticity; premature birth

Abbreviations: CANTAB = Cambridge Neuropsychological Testing Automated Battery; fMRI = functional MRI; ID/ED = intradimensional/extradimensional; IQ = intelligence quotient; NBRS = Neurobiological Risk Score; NICU = neonatal intensive care unit; SES = socioeconomic status; WISC-III = Wechsler Intelligence Scale for Children—III

Introduction

The neurological sequelae of premature birth are fairly well established and numerous investigators have demonstrated that infants born preterm are generally at risk for cognitive, academic and behavioural problems later in life (e.g. Katz *et al*., 1996; Matthews *et al*., 1996; Rose and Feldman, 1996). In addition, recent longitudinal examinations of the impact of low birth weight have indicated a lasting negative impact on cognitive ability and educational attainment well into young adulthood (e.g. Conley and Bennett, 2000). It is presumed that these global cognitive and behavioural impairments are due at least in part to the sequelae of the medical complications often associated with preterm birth such as hypoxia, intraventricular haemorrhages and respiratory distress syndrome that either directly or indirectly compromise the integrity and/or development of the CNS (Vohr *et al*., 1989). The ensuing neurological abnormalities are believed to be the primary underlying cause of commonly observed cognitive deficits in preterm children, although the exact nature of the association between such abnormalities and specific cognitive impairments in children born prematurely is not well established (Vohr *et al*., 1989, 1991; Huppi *et al*., 1996).

With the recent advent of neuroimaging techniques, which allow direct examination of neuroanatomical substrate, evidence has accumulated indicating that children born preterm do have identifiable brain abnormalities. For example, neuroimaging studies of preterm children during the neonatal period have shown general cerebral abnormalities in preterm infants (e.g. Maalouf *et al*., 1999). Recently, an MRI investigation by Peterson and colleagues demonstrated reduced volumes in several cortical brain regions as

well as in subcortical regions, including the hippocampus, in a sample of 8-year olds who were born preterm compared with a group of matched control children (Peterson *et al*., 2000). Within the group of children who were born preterm, a statistically significant positive correlation among cortical and corpus callosum volume and intelligence quotient (IQ) was found. These volumetric measures were also correlated with gestational age at birth and perinatal medical risk factors. An MRI study of a sample of 14–15-year-old adolescents who were born preterm reported decreased cerebellar volume compared with a group of term-born controls; however, no relationships between motor neurological variables and cerebellar volume were found (Allin *et al*., 2001). However, significant associations were found between cerebellar volume and intelligence and achievement test scores measured at age 8 years in this preterm sample but not in controls (Stewart *et al*., 1999). This suggests that cerebellar abnormalities may be associated with some of the cognitive deficits found in children born preterm earlier in development, but that some process resulting in compensation (i.e. plasticity) may occur over time to diminish the associations between brain abnormalities and neurobehavioural functioning.

In particular, Stewart and colleagues reported that 55% of the MRI scans of this sample of 14–15-year olds were rated as abnormal and 21% had equivocal scans (Stewart *et al*., 1999). The abnormal scans included features such as ventricular dilation, thinning or atrophy of the corpus callosum, and posterior trigonal dilation. All but one of those with equivocal or abnormal MRI scans in this study also had abnormal neonatal ultrasonographic scans at birth. Perinatal factors such as birth weight, gestational age at birth, Apgar score or need for mechanical ventilation did not differentiate between individuals with normal, equivocal or abnormal MRI scans in adolescence. There was also no clear association between brain structural abnormalities detected by MRI scanning and neurological outcomes. However, preterm adolescents with abnormal MRI scans did score worse on a neurobehavioural rating (Stewart *et al*., 1999). Further neuropsychological assessment of this sample has indicated impairment only on a measure of word fluency compared with a group of matched controls, with performance on measures of attention, perceptual skills and executive functioning in the normal range and not statistically different from that of a group of matched controls, regardless of abnormality of MRI scan (Rushe *et al*., 2001).

Evidence of a direct correlation between specific episodic memory deficits (assessed behaviourally) in children born prematurely and hippocampal volume was provided by an anatomically-based MRI study (Isaacs *et al*., 2000). These authors found significantly reduced hippocampal volume bilaterally in a sample of 13-year-old children who were born prematurely compared with a group of matched control children. This correlated with deficits on several behavioural measures of memory.

The hippocampus has long been associated with normal memory function (Zola *et al*., 2000). In addition, Nelson (1995) as well as Seress (2001) have postulated that the hippocampus develops early in life, thus supporting some aspects of explicit memory as early as the first half year of life. More relevant to the current investigation, the hippocampus is in particular vulnerable to adverse perinatal events such as hypoxia-ischaemia, hypoglycaemia and iron deficiency, potentially resulting in memory deficits in children born preterm (Ben-Ari, 1992; Volpe, 1995; Luciana *et al*., 1999; Deregnier *et al*., 2000; Isaacs *et al*., 2000; Nelson *et al*., 2000). The CA1 region of the hippocampus has been found to be most vulnerable to neuronal loss as a result of interruptions in the supply of oxygen and glucose. This is due to the particularly large concentration of *N*-methyl D-aspartate (NMDA) receptors present in the pyramidal neurones comprising this structure and their permeability to Ca^{2+} (Ben-Ari, 1992). Generally, lesion and autopsy studies have shown that an intact hippocampus (particularly the CA1 region) is necessary for proper memory functioning in adults (Scoville and Milner, 1957; Zola-Morgan *et al*., 1986). In animal studies, it has been shown that damage to the hippocampus in monkeys typically leads to memory impairments (Zola-Morgan *et al*., 1992; Alvarez *et al*., 1995; Zola *et al*., 2000). Humans with damage to the hippocampus and amygdala are also impaired on certain memory tasks (Owen *et al*., 1995).

Neuroimaging studies have generally supported an association between hippocampal activity and memory functioning. Hippocampal metabolic rate has been shown to increase as monkeys perform a recognition memory task (Friedman and Goldman-Rakic, 1988). Moreover, several functional MRI (fMRI) studies with humans have indicated that hippocampal activation is related to memory functioning (e.g. Fernández *et al*., 1998; Wagner *et al*., 1998; Elliott and Dolan, 1999; Strange *et al*., 1999; Monk *et al*., 2002).

In addition to the vulnerability of the hippocampus, the head of the caudate nucleus, located along the wall of the lateral ventricles, may be especially vulnerable to necrotic damage from intraventricular haemorrhages often associated with premature birth (Casey *et al*., 1997). Damage to the caudate nucleus in monkeys is associated with impairment in spatial memory tasks (Goldman-Rakic and Rosvold, 1972). Given the combination of lesions that occur in premature infants, episodic and working memory functions (which rely in large part on the interconnections between the prefrontal cortex, caudate nucleus and hippocampus) may be the type that would be particularly compromised in children born prematurely (O'Donnell and Grace, 1995).

Until recently, studies of cognitive functioning of children suffering from neurological insults during the perinatal and neonatal periods have focused primarily on global behavioural measures of cognition such as IQ (e.g. Lobato *et al*., 1995; Sykes *et al*., 1997). Others have examined areas of general neuropsychological functioning such as attention (e.g. Katz *et al*., 1996; Robson and Pederson, 1997) and perceptual-motor functioning (e.g. Klein *et al*., 1989; Hack *et al*., 1994).

Yet other studies have examined general aspects of executive functioning, such as planning and inhibition as measured by the Tower of Hanoi task (Harvey *et al*., 1999). Generally, such studies have demonstrated that children born preterm have worse neuropsychological outcomes compared with term children without neurological insult.

However, memory functioning of preterm children has been examined in some detail. For example, in a follow-up study of a cohort of prematurely born children, Rose and Feldman (1995, 1996) reported that, at age 11 years, these children demonstrated deficits on behavioural measures of immediate and delayed memory, memory for spatial sequence and recognition memory compared with a group of matched control children not born prematurely.

However, the methodologies employed in these studies have not typically allowed for examination of possible linkages between typologies and patterns of neuropsychological deficits and damage to specific neural substrates. In particular, few studies have addressed how specific patterns of memory deficits in preterm children may correspond with damage to neural structures known to be impacted by adverse perinatal events. Luciana and colleagues conducted a study of a cohort of preterm children utilizing the Cambridge Neuropsychological Testing Automated Battery (CANTAB) (Luciana *et al*., 1999), a computer-based neuropsychological test of non-verbal memory and executive functioning (Fray *et al*., 1996). Linkages between specific CANTAB tasks and neuroanatomical systems have been established in neuroimaging studies of adults (Owen *et al*., 1996). Luciana and colleagues demonstrated deficits in non-verbal memory span, spatial working memory and recognition memory in a group of preterm children at 8 years of age compared with a group of matched control children (Luciana *et al*., 1999). The pattern of deficits shown on the CANTAB tasks was consistent with a picture of more global impact of early neurobiological risk factors that adversely affect brain oxygenation and blood flow processes at the level of neural networks devoted to working memory.

The current study followed up a portion of the sample assessed by Luciana and colleagues (Luciana *et al*., 1999) to re-examine memory and executive functioning in these children as they were approaching adolescence. This cohort of children spent time in a neonatal intensive care unit (NICU) after they were born. The majority of children in the sample were born preterm, while others were born at term and suffered from medical complications similar to those experienced by the preterm children (the NICU sample employed in the current study is a very heterogeneous group of NICU graduates, with widely varying degree and severity of medical complications experienced at birth. However, the strength of this heterogeneity is that the findings from this sample may be generalizable to the general population of children who spent time in an NICU after birth in the United States). The rationale for the follow-up assessment was to determine whether or not the deficits found in these children during middle childhood were indicative of a developmental lag in brain maturation. This may resolve as the final phases of brain development and myelination of prefrontal cortical areas, which underlie many of the working memory and executive functioning tasks assessed by the CANTAB proceed. Alternatively, it is possible that subtle deficits in memory and executive functioning will become more apparent in these children as they enter adolescence and experience greater demands on their cognitive resources both in school and life generally. The current study compared this cohort of children who experienced neurobiological adversity during the perinatal period with a group of age-matched control children who did not have medical complications at birth.

Specifically, the following questions were investigated:
(i) Does experiencing medical complications during the perinatal period result in deficits in executive functioning and/or memory during late childhood/early adolescence?
(ii) Will this cohort of children demonstrate recovery from previously observed deficits in memory and executive functioning, and thus demonstrate plasticity, or will the previously observed deficits be manifested in further neuropsychological/behavioural sequelae?
(iii) What are the relative contributions of neonatal health, gestational age (as a proxy for extent of completion of brain development at birth) and measures of current general cognitive functioning to the prediction of executive functioning during late childhood/early adolescence?

Methods

Participants

The total sample for the current study included 57 children, 32 of whom were NICU graduates (NICU sample) and 25 control children matched for age and socio-economic status. Parents provided written informed consent after the study procedures had been fully explained to them. The study was approved by the Institutional Review Board of the University of Minnesota's Research Subjects' Protection Programs. The children in the NICU sample were born between 1987 and 1989, and were part of a selected cohort of 81 families with children treated at birth in a NICU at a large university medical centre. They were recruited soon after birth for general participation in any university-conducted longitudinal research. Children who underwent surgical procedures, had congenital anomalies or who were in the NICU less than 5 days were excluded from the sample. Forty of these children participated in a study of the neurobehavioural sequelae of premature birth in 1996, when they were compared with a group of 92 control children born at term (Luciana *et al*., 1999).

Thirty-two of the 40 children in previous study participated in the current investigation. There were no statistically significant differences on the key perinatal and neonatal medical risk indices between the children who did and did not participate in the current assessment. Twenty-five (78%) of the children in the current NICU sample were born preterm

Table 1 *Perinatal/medical characteristics of the NICU sample*

Parameter	Value (SD)
Mean birth weight (g)	1887.8 (925)
Birth weight groups:	
<1500 g (very low birth weight) (*n*)	15
1500–2500 g (low birth weight) (*n*)	9
>2500 g (normal birth weight) (*n*)	8
Mean gestational age (weeks)	32.3 (4.7)
Range	24–40
Preterm (<37 weeks) (*n*)	25
Mean NICU length of stay (days)	38.5 (33.8)
Range	6–127
Neonatal risk factors:	
IVH (*n*)	17
IVH Grades (I, II, I) (*n*)	4, 8, 5
Respiratory distress syndrome (*n*)	24
Intrauterine growth retardation (*n*)	4
Bronchopulmonary dysplasia (*n*)	7
Neonatal seizures (*n*)	1
Asphyxia/hypoxia (*n*)	8
Mean NBRS	3.5 (3.0)
Range	1–12
12 month Bayley PDI ($n = 16$)	92.4 (10.0)
12 month Bayley MDI ($n = 16$)	104.4 (12.2)

IVH = intraventricular haemorrhage; PDI = psychometer developmental index; MDI = mental development index.

(gestational age <37 weeks). The remaining seven children experienced significant medical complications after birth that were similar to those experienced by the preterm children in the sample. There were no statistically significant differences on perinatal and neonatal medical risk indices between the preterm and term children in the NICU sample. Table 1 summarizes the perinatal and neonatal events experienced by the NICU sample. These include degree of prematurity, presence of intraventricular haemorrhage, intrauterine growth retardation (birth weight *Z*-score < 2), bronchopulmonary dysplasia (marked by the requirement of supplementary oxygen at 28 days) and neonatal seizures.

In addition to the NICU sample, 25 control children were recruited. The primary criteria for inclusion as a control was being born at term, free of medical complications. The control children were close friends of the children in the NICU sample and came to the experimental session with the NICU sample child. As shown in Table 2, there were no statistically significant differences between the NICU sample children and the control children in terms of age and socio-economic status (SES). The NICU group was 44% male and the control group was 48% male. There were statistically equivalent proportions of left and right-handed children in the NICU and control groups. Nineteen percent of the NICU group and 12% of the control group were left-handed ($\chi^2 = 0.48$, not significant). Although every effort was made to get each NICU child to bring a friend to the testing session to serve as a control, seven of the NICU sample children did not bring a friend.

Table 2 *Sample demographic characteristics*

	NICU	Control
n	32	25
Mean age (years)	11.5	11.2
Range	10–14	9–12
Sex	14 male	12 male
	18 female	13 female
Mean Hollingshead SES	42.8	47.3
Handedness	6 left	3 left
	26 right	22 right

Instruments

Executive functioning was assessed using the computerized CANTAB (Sahakian and Owen, 1992). This instrument employs non-verbal tasks to measure aspects of executive functioning that include psychomotor speed and fine motor accuracy, spatial memory span, spatial working memory, set-shifting ability, planning and inhibition, and pattern and spatial recognition memory. Subject responses are recorded using a touch-screen monitor and scoring of the tasks is automated by the software.

Its development guided by the animal experimental literature, the CANTAB was originally designed to assess neurologically normal and impaired adults (Fray *et al*., 1996). The neural correlates of the CANTAB tasks have been extensively studied and validated in neuroimaging studies of adults (e.g. Baker *et al*., 1996; Owen *et al*., 1996). The results of such studies point to the sensitivity of this test to damage in the temporal lobe and the dorsolateral prefrontal cortex. The CANTAB was utilized in a previous study of neurobehavioural functioning in this cohort, which demonstrated its usefulness in assessing working memory deficits in the current cohort at age 8 years (Luciana *et al*., 1999). Subsequent work examining normative developmental data on children aged 4–12 years with this instrument has more firmly established the validity of the CANTAB for children (Luciana and Nelson, 1998, 2002).

The six CANTAB tests administered to the participants in the study are outlined below. A more complete description of these tasks can be found in Luciana *et al*. (1999) and Luciana and Nelson (2002).

Psychomotor screening

This involved a reaction time test measuring psychomotor speed and fine motor accuracy. The letter 'X' appears at a random location on the screen in each of 10 trials, and the respondent is instructed to touch the centre of the 'X' as quickly and accurately as possible.

Spatial memory span

This measures memory for a spatial sequence. For this task, the participant is presented with 10 white squares in random

locations on the screen. During each trial, the squares change colour (and then change back to white again) in increasingly longer sequences. After each series of colour changes, the participant must reproduce the sequence of colour changes in order by touching the squares in the order in which they changed colour. A ceiling is reached that is determined by the individual's success. The neural correlates of this task are reportedly the right ventrolateral prefrontal cortex (Luciana and Nelson, 1998).

Spatial working memory

This assesses working memory for spatial stimuli and requires use of mnemonic information. For this task, the participant is presented with an array of coloured squares on the screen. For each trial, the participant must search for blue squares 'hidden' underneath the coloured squares. The blue squares are found by touching the coloured squares. Once a blue square is found in a particular location, another one will not be found there. Thus, participants must remember the locations of previously found squares, and employ some type of strategy to successfully find all of the squares. Trials progress from two to eight squares. Patients with damage to the dorsal and ventral portions of the prefrontal cortex demonstrate deficits on this task (Owen *et al*., 1995).

Tower of London

This is a measure of spatial planning and behavioural inhibition. For this task, participants must move three coloured 'balls' within a specified number of moves to match a pattern of three coloured balls generated by the computer. The number of moves required progresses from one to five through several trials. An additional motor control portion of each trial involves imitating the moves of the balls made by the computer as quickly as possible. This task has been shown to activate the parietal cortex bilaterally, as well as the left caudate nucleus and left dorsolateral prefrontal cortex (Morris *et al*., 1993).

Intradimensional/extradimensional (ID/ED) set-shifting

This task measures discrimination and reversal learning, and requires attending to shifting patterns of visual stimuli. The task moves through several stages of increasing difficulty. The participant is presented with a symmetrical array of four boxes on the computer screen. Throughout the task, different types of stimuli appear in pairs in two boxes, and the participant must discern a rule for choosing the 'correct' stimulus. After a criterion number of correct responses is reached for the first set of simple line figures, the feedback concerning which stimulus to choose is reversed, so that the one that was formerly 'correct' is now 'incorrect'. The stimuli include simple line figures and progress to more complex figures that include lines with superimposed coloured shapes. This task is similar to the Wisconsin Card Sorting Task. Patients with frontal lobe excisions show significant impairments on this task (Owen *et al*., 1991).

Pattern/spatial recognition

This employs a delayed match-to-sample paradigm to assess recognition memory for visual patterns and spatial locations. The pattern recognition task presents the participant with a series of 12 geometric patterns of varying colours one after another (encoding phase). During the test phase, two stimuli are presented side by side, and the participant is instructed to choose the one that was seen during the previous encoding phase. The pattern recognition task has its putative neural circuitry located in the medial temporal lobe (Owen *et al*., 1995).

During the spatial recognition task, the computer presents a series of five white squares in random locations on the computer screen (encoding phase). During the test phase the computer presents five pairs of squares, one of which is in the same location on the screen as one of the previously presented squares from the encoding phase. The participant must select the square that is in the same location. The spatial recognition task is reportedly correlated with neural circuitry in the medial temporal and parietal lobes, as well as the right dorsolateral prefrontal cortex.

Other tests

In order to obtain a general measure of cognitive ability, the vocabulary, block design, and digit span subscales of the Wechsler Intelligence Scale for Children—III (WISC-III) were administered to the entire sample. The vocabulary and block design subscales were combined to derive a proxy for the full scale IQ score. These two WISC subtests have high correlations with full-scale IQ (typically above 0.9) and are highly reliable (Kilian and Hughes, 1978; Sattler, 1982).

The children in the NICU sample were assessed using the Neurobiological Risk Score (NBRS) (Brazy *et al*., 1991; Oehler *et al*., 1993), which is a composite measure of the presence of neonatal risk factors that would influence brain blood flow and oxygenation (e.g. seizures, intraventricular haemorrhage, etc.) based on a chart review of their treatment in the NICU. A score is derived based on a cumulative tally of adverse medical events during the course of treatment in the NICU, with high scores representing high risk.

Results

Data were analysed with the Statistical Package for the Social Sciences, Version 8.0 (SPSS-PC, SPSS Inc., Chicago, IL, USA). Given that performance on the CANTAB is moderated by chronological age in children younger than 12 years of age, analysis of covariance was employed to examine all between-group differences on the CANTAB tasks with

Table 3 *Performance on CANTAB*

CANTAB task	NICU group mean (SD)	Control group mean (SD)	ANOVA *F* value
Psychomotor motor screening			
Average error	16.8 (4.5)	19.0 (7.1)	2.1
Average response latency	822.1 (130.0)	815.7 (117.3)	0.1
Spatial memory span			
Spatial span	5.6 (1.0)	6.0 (1.5)	3.5*
Spatial working memory			
Forgetting errors			
Three-item searches	0.1 (0.3)	0.1 (0.3)	0.4
Four-item searches	0.6 (0.9)	0.7 (1.3)	0.1
Six-item searches	10.9 (6.1)	7.6 (7.4)	4.2*
Eight-item searches	27.7 (12.9)	22.6 (11.1)	3.9*
Total forgetting errors	39.3 (17.4)	31.1 (17.4)	4.7*
Strategy score	36.3 (3.6)	34.9 (3.7)	2.2
Tower of London			
Average planning time (s)	6063.8 (2922.3)	6769.5 (3092.3)	0.9
Average total moves	23.4 (3.9)	22.7 (4.4)	1.2
% correct minimum move solutions, test trials	66.7 (15.4)	62.3 (18.2)	1.3
Three-move problems	3.2 (0.3)	3.2 (0.5)	0.0
Four-move problems	5.7 (1.1)	6.0 (1.1)	0.4
Five-move problems,	6.8 (1.4)	7.0 (1.6)	0.5
Pattern recognition (% correct)	89.5 (8.6)	92.0 (6.5)	1.3
Spatial recognition (% correct)	66.4 (10.6)	68.4 (12.4)	0.7
ID/ED set-shifting			
Stage reached	8.7 (0.9)	8.7 (1.0)	0.1
EDS minus IDS trials to criterion	2.8 (6.3)	1.8 (9.6)	0.0
EDS minus IDS errors	4.4 (9.4)	3.0 (8.7)	0.5

*$P < 0.05$; EDS = extradimensional shift; IDS = intradimensional shift.

chronological age as a covariate. Likewise, linear associations involving the CANTAB within the NICU sample were partial correlations controlling for age.

Analyses examining possible sex differences in performance on the CANTAB within each group revealed only one statistically significant difference. In addition, only two statistically significant CANTAB performance differences based on handedness status were found. Thus, the variables sex and handedness were not considered further in analyses with CANTAB performance as a dependent variable.

Between-group differences

As can be seen in Table 3, the NICU and control samples differed on two of the CANTAB tasks. The NICU children had a shorter total spatial memory span length than the control subjects [$F(1,54) = 3.5$, $P < 0.05$]. On the spatial working memory task, the total number of memory errors made during each difficulty level of searching (i.e. two, three, four, six and eight item searches) was computed. For searches of two, three and four items, there was no statistically significant difference in the number of memory errors between the NICU and control samples. The children in the NICU sample did, however, make more errors than the control children in six item [$F(1,54) = 4.2$, $P < 0.05$] and eight item [$F(1,54) = 3.9$, $P < 0.05$] searches. In addition, when memory errors were summed across all five search conditions, children in the NICU sample performed with more memory errors than control children [$F(1,54) = 4.7$, $P < 0.05$]. There were no statistically significant group differences between the NICU and control samples on any other individual CANTAB tasks. In addition, there were no statistically significant group differences between the NICU and control samples on the WISC-III subtests (vocabulary, block design, digit span) or extrapolated full-scale IQ, nor were there any within group differences between vocabulary, block design or digit span scores. Both groups had a mean full-scale IQ of approximately 103, with the NICU group scores ranging from a low of 77 to a high of 144, and the control group participants scoring between 71 and 138.

Group differences on four factors derived by Luciana and Nelson (2002) from a factor analytic study of normative CANTAB data on 340 children aged 5–12 years were examined in the current sample. The factors derived from the normative data were:

(i) Memory and efficiency of processing, which includes length of spatial memory span, percent correct on pattern recognition and the number of Tower of London problems solved in the minimum number of moves;

(ii) Working memory/strategic planning, which includes the spatial working memory task strategy score and memory errors on six and eight item searches;

Table 4 *Partial correlations between CANTAB tasks and NBRS, gestational age and WISC-III components*

CANTAB variable	NBRS	Gestational age	Vocabulary	Block design	Full–scale IQ
Psychomotor screening					
Speed	0.10	–0.14	–0.18	–0.09	–0.17
Accuracy	0.19	–0.31†	–0.08	–0.02	–0.07
Spatial memory span	–0.39*	0.36*	0.27	0.20	0.31
Spatial working memory					
Three-item searches	–0.16	0.16	–0.19	–0.23	–0.29
Four-item searches	0.22	–0.37*	0.05	–0.02	0.01
Six-item searches	0.29	0.00	–0.25	–0.35*	–0.41*
Eight-item searches	0.19	0.10	–0.35*	–0.20	–0.35*
Total forgetting errors	0.25	0.06	–0.36*	–0.28	–0.42*
Strategy score	0.19	0.04	–0.19	–0.12	–0.20
Tower of London					
Average total moves	0.29	0.13	–0.31†	0.00	–0.16
% correct minimum move solutions, test trials	–0.36*	–0.16	0.33†	–0.03	0.15
Three-move problems	0.29	–0.21	–0.03	–0.01	–0.03
Four-move problems	0.27	0.04	–0.19	–0.01	–0.10
Five-move problems	0.20	0.16	–0.32†	0.00	–0.18
Average planning time	–0.18	–0.18	0.27	0.10	0.23
Pattern recognition (% correct)	–0.03	–0.05	0.07	0.24	0.23
Spatial recognition (% correct)	–0.35*	0.15	0.22	0.23	0.30
ID/ED set-shifting stage reached	–0.21	0.21	–0.01	0.27	0.17

†$P < 0.10$; *$P < 0.05$.

(iii) Motor learning, which consists of mean latency and error scores from the psychomotor screening task as well as stage reached on the ID/ED set-shifting task;
(iv) Mnemonic aspects of working memory, which includes memory errors on two, three and four item searches of the spatial working memory task.

Scores on tasks for each factor were standardized and then summed across subjects to derive a standard score for each factor. The control group scored significantly lower (in the positive direction with fewer forgetting errors, more use of strategy) on the working memory/strategic planning factor than the NICU group [$F(1,54) = 4.8$, $P < 0.05$]. There were no other group differences on the CANTAB factors.

Correlational analyses

Aside from investigating between-group differences, one of the questions the current study sought to examine was the relation among general intellectual functioning, CANTAB task performance and early biomedical risk factors experienced by the NICU sample. In particular, we sought to ascertain the relative contributions of gestational age and the NBRS to performance on the CANTAB tasks. Gestational age was employed as a proxy for the level of brain development achieved by the children in the NICU sample before birth. Thus, the goal of these analyses was to parse out the relative contribution of immature brain development at birth and ensuing medical complications to the prediction of executive functioning in late childhood.

As shown in Table 4, lower gestational age is associated with a shorter spatial memory span and with more memory errors on four item searches of the spatial working memory task. Increased neurobiological risk during the neonatal period is associated with a shorter spatial memory span, a lower percentage of correct solutions (made at or below the maximum number of allowed moves) to Tower of London problems and more incorrect responses on the spatial recognition memory task.

For the WISC-III, subscale scores obtained from one child in the NICU sample were excluded from analyses, as the examiner determined that the test administration for this child was not valid. There were several statistically significant correlations between the WISC-III scales and CANTAB tasks. Lower extrapolated full-scale IQ was moderately associated with more memory errors in eight item searches as well as more total forgetting errors on the spatial working memory task. Lower scores on the vocabulary subscale were moderately associated with more memory errors in eight item searches and more total forgetting errors on the spatial working memory task. In addition, lower scores on vocabulary were marginally associated with poorer performance on the Tower of London CANTAB task—specifically with more average total moves, more moves required on five-move problems and a decrease in the percentage of problems correctly solved within the maximum number of moves allowed. Lower scores on the block design subscale were associated with more memory errors on six item searches on the spatial working memory task.

There was a moderate statistically significant correlation showing that increased neurobiological risk was associated with lower full-scale IQ ($r = –0.38$, $P < 0.05$), and a marginally significant correlation indicating that increased neurobiological risk was associated with lower block design scores ($r = –0.34$, $P < 0.10$). However, there were no

Table 5 *Partial correlations between NBRS, gestational age and WISC-III components*

	NBRS	Gestational age	Vocabulary	Block design	Digit span	Full–scale IQ
NBRS	1.00	–0.47**	–0.29	–0.34†	–0.33†	–0.32†
Gestational age		1.00	0.18	0.20	0.14	0.18
Vocabulary			1.00	0.36*	0.50**	0.74***
Block design				1.00	0.53**	0.88***
Digit span					1.00	0.59**
Full-scale IQ						1.00

†$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 6 *Multiple regressions predicting spatial memory span and spatial working memory*

Variable	Spatial memory span		Spatial working memory, total forgetting errors	
	R^2 change	Beta	R^2 change	Beta
Chronological age	0.01	ns	0.04	ns
Gestational age	0.13*	0.36*	0.00	ns
NBRS	0.06	ns	0.10†	0.35†
Full-scale IQ	0.12*	0.37*	0.23**	–0.51**

†$P < 0.01$; *$P < 0.05$; **$P < 0.01$; ns = not significant.

statistically significant associations between scores on the WISC-III and gestational age.

Table 5 shows the correlations between neonatal risk factors and individual WISC-III scales. Neurobiological risk correlates moderately with block design, digit span and extrapolated full-scale IQ—with lower scores on these scales associated with higher risk. Gestational age, while correlated with the NBRS, is not associated with IQ.

In order to more clearly explicate the relative contributions of specific perinatal risk factors and current global cognitive functioning to performance on CANTAB tasks, multiple regression analyses were employed. Specifically, spatial memory span served as the dependent variable in the first equation, and total forgetting errors on the spatial working memory task was the dependent variable in the second regression. These two dependent variables were chosen because they most clearly distinguished between the NICU and control groups.

Linear regression equations were employed, with independent variables entered separately at each step. For both regression equations, the first independent variable entered was chronological age due to its strong association with CANTAB performance. The remaining variables were entered in the chronological order of their contribution to the dependent measure. Thus, the second independent variable entered was gestational age, which was considered a proxy for the extent of brain maturation at the time of birth. The next variable entered in the multiple regressions was the NBRS, which is a composite of medical complications that occurred during the child's stay in the NICU. Finally, the full-scale IQ score was entered to examine its contribution to the prediction of the dependent variables after controlling for factors during the perinatal period. All two-way interaction terms were examined, and none contributed to the prediction of the dependent variables, and thus were excluded from the final regression analyses.

As shown in Table 6, gestational age contributes unique variance in the prediction of spatial memory span, after controlling for chronological age. The NBRS does not contribute uniquely to the prediction of spatial memory span after controlling for the previous two independent variables. At the final step of the equation, IQ contributes to the prediction of spatial memory span to approximately the same extent as gestational age.

Table 6 also shows the multiple regression results for the prediction of total forgetting errors on the spatial working memory task. After controlling for chronological age, gestational age does not uniquely contribute to the variance in the prediction of spatial working memory. However, at the next step, the NBRS does uniquely contribute to this prediction, even after controlling for chronological and gestational age. Although the R^2 change and beta are, strictly speaking, not statistically significant at the $P < 0.05$ level ($P = 0.09$), given that there were only 31 subjects with data in the equation, we believe the effect size is of some significance. Finally, after controlling for all of the previous independent variables, IQ uniquely contributes to the prediction of spatial working memory to a moderate degree and more strongly than it does to the prediction of spatial memory span.

Discussion

In an assessment of this cohort of children utilizing the CANTAB ~3 years prior to the current study, Luciana and colleagues found substantial deficits on most of the CANTAB

tasks compared with a group of matched controls (Luciana *et al*., 1999). Consistent with the findings of the previous assessment, the NICU cohort in the current study demonstrated a shorter spatial memory span as well as more forgetting errors on a spatial working memory task. However, in the previous assessment, they also exhibited more errors and longer response latency on the psychomotor screening task, longer average planning time and more average moves on the five-move problems on the Tower of London task, poorer performance on a pattern recognition memory task and poorer use of strategy on the spatial working memory task. Overall, in the previous assessment, the effect sizes of the differences between the NICU sample and controls were substantially larger and the pattern of results more robust and consistent.

In order to interpret more clearly the findings of the current study, it is important to consider the possible reasons for the observed differences in the between-group comparisons across the 3-year assessment interval. One of the original motivations for re-assessing this cohort with the CANTAB was to investigate plasticity of neuropsychological functioning of children who experienced medical adversity during the perinatal period. At first glance, it would appear that these children have recovered substantial functioning relative to a group of control children. However, in order to evaluate this hypothesis, it is important first to consider the possible contribution of some methodological differences between the initial assessment and the current follow-up.

First, the same control group was not used in the two studies. Luciana and colleagues employed a control group that was part of a sample from a normative study of memory development utilizing the CANTAB (Luciana *et al*., 1999). The current study employed a methodology whereby the NICU children brought a friend with them to the experimental session. In each of the studies, the controls were matched with the NICU group on age and sex. One advantage of the bring-a-friend control methodology is that SES can more easily be matched between groups; in the current study, the two groups were statistically equivalent on Hollingshead ratings of SES. One disadvantage of the bring-a-friend method is that children with similar characteristics (including neurocognitive functioning) tend to become friends (e.g. Rubin *et al*., 1994), thus leaving open the possibility that the control group will not be representative of a normal population on the variable of interest.

It is not clear if the control samples across the two studies are comparable on SES, as the SES of the control and NICU groups were not reported in the study by Luciana and colleagues (Luciana *et al*., 1999). However, the relationship between SES and performance on the CANTAB may not be a strong one. It is informative, though, to compare the CANTAB results of the control group from the current study to the CANTAB scores from a normative study of children's performance on the CANTAB (Luciana and Nelson, 2002). This study examined the performance of a normative sample of 4–12-year-old children on the CANTAB. Although statistical comparisons of the data from the current study to the data from Luciana and Nelson (2002) were not possible, a comparison of scores between the 11 to 12-year old children in the normative sample and the current control children reveals no appreciable differences between the groups (see Table 7). In addition, this study found no association between SES and CANTAB performance. Thus, it is possible to conjecture that the control children in the current study were not exceptional and that their performance on the CANTAB was indeed representative.

Thus, it would appear reasonable to interpret the current findings, which revealed fewer deficits of smaller magnitudes in the NICU group than found 3 years earlier, as evidence of neural plasticity in these children. The questions that remain concern not only the type of plasticity but also the mechanisms by which this neural plasticity may come about. Generally, neural plasticity refers to the process by which compensatory neural events, brought about either by endogenous, genetically driven mechanisms or through environmental experience, facilitates change or reorganization in the neural substrate (Curtis and Nelson, 2002). These changes can occur and are observed on one or more levels of analysis, including molecular, cellular, neurochemical, anatomical and at the level of brain systems (Nelson, 1999). It appears that plasticity is an inherent property of the brain (Johnson, 1999) and that this compensatory process, even in the face of catastrophic physical damage to brain tissue, is perhaps normative.

In this respect, the current findings are consistent with the results of the work by Rushe *et al*. (2001), which examined the neuropsychological outcome of a group of 14–15-year-olds who were born preterm. This study found no differences in measures of verbal and visual memory, attention and executive functioning between these children and a group of controls. Control children performed better than the preterm children only on a measure of verbal fluency. In addition, there were no differences between the preterm adolescents in this study with MRI scans classified as either abnormal, equivocal or normal on any test of neuropsychological performance. These scans showed decreased whole brain volume, increased volume of the lateral ventricles and decreased hippocampal volume. This is consistent with the volumetric findings of others (Isaacs *et al*., 2000; Peterson *et al*., 2000).

At age 8 years, this group of preterm children showed some evidence of poor interhemispheric interaction, as evidenced by poorer performance on a battery of neuro-motor assessments designed to test interhemispheric transfer of cognitive information (Kirkbride *et al*., 1994). However, the extensive neuropsychological assessment of these children carried out in adolescence was not performed during childhood. Thus, no direct comparison of their neuropsychological status during childhood and adolescence can be made within this sample. It is striking, however, that the findings of improvement of function in this sample of preterm adolescents, who on

Table 7 *Performance on CANTAB: normative group versus current controls*

CANTAB task	Normative group mean (SD) (Luciana and Nelson)	Control group mean (SD)
Psychomotor motor screening		
Average error	19.1 (7.1)	19.0 (7.1)
Average response latency	873.8 (218.9)	815.7 (117.3)
Spatial memory span		
Spatial span	6.1 (1.2)	6.0 (1.5)
Spatial working memory		
Forgetting errors		
Three-item searches	<0.01 (0.2)	0.1 (0.3)
Four-item searches	0.8 (1.4)	0.7 (1.3)
Six-item searches	10.4 (7.3)	7.6 (7.4)
Eight-item searches	23.9 (10.0)	22.6 (11.1)
Strategy score	37.0 (3.2)	34.9 (3.7)
Tower of London		
Average planning time (s)	6063.8 (2922.3)	6769.5 (3092.3)
Average total moves	23.4 (3.9)	22.7 (4.4)
Three-move problems	3.3 (0.4)	3.2 (0.5)
Four-move problems	5.9 (0.8)	6.0 (1.1)
Five-move problems	7.5 (1.2)	7.0 (1.6)
Pattern recognition (% correct)	90.0 (10.0)	92.0 (6.5)
ID/ED set-shifting		
Stage reached	8.3 (1.7)	8.7 (1.0)

average were of even lower birth weight than the current sample, appear to be remarkably consistent with the findings of the current study.

It is unclear what form neural plasticity may take in children who are born preterm. The consistent evidence of decreased cortical and hippocampal volume in children who do not have severe neuropsychological sequelae may suggest that decreased brain volume *per se* may not severely hinder neurocognitive development. In addition, the finding of no relation between abnormality of MRI brain scan and neuropsychological functioning by Stewart and colleagues seems to indicate that the reorganization that takes place does not occur at the gross neuroanatomical level (Stewart *et al*., 1999). Thus, neural plasticity may compensate for decreased brain volume by increasing the density of synapses and other neurocellular processes, thus maximizing the efficiency of neural wiring in the reduced cortical substrate. At the neural systems level, some re-wiring of connecting circuits may be required in order to maintain normal functioning within the reduced brain volume. These examples should not imply that the processes of neural plasticity in the brain of a preterm individual compensate exclusively for reduced brain volume. However, in the absence of fMRI, there is very little evidence upon which to base hypotheses about neural plasticity.

Normative processes of brain maturation may also contribute to the sparing of function seen in this group of children. The period from middle childhood to the beginning of adolescence is marked by continued protracted maturation of the prefrontal cortex, with myelination of the frontal cortex continuing into early adulthood (Giedd *et al*., 1999; Sowell *et al*., 1999, 2001), as well as evidence to suggest continued development of synapses and neurotransmitter systems into adolescence (Thatcher, 1991; Benes, 2001). Further, behavioural evidence indicates that executive functioning may in fact occur in a stage-like process with distinct levels of maturation and integration at age 6 years, age 10 years and in adolescence (Welsh *et al*., 1991), perhaps reflecting an extended period of maturation of the prefrontal cortex during the first two decades of life.

It is possible that the early neurological insults suffered by children born preterm in some way slow down the normative developmental process in the prefrontal cortex during the first 8–10 years of life. However, by the time children with such injuries reach early adolescence the highly canalized, genetically mediated mechanisms of normal brain maturation may to some degree finally overcome the developmental lag. While these children still show deficits in some aspects of nonverbal memory, the differences between the NICU and control groups are subtle, and there is no behavioural evidence that would indicate frank hippocampal or prefrontal damage in the NICU group. The current study provides evidence of fairly good improvement in memory and executive functioning in this group of children during the 3 years between neurobehavioural assessments. Thus, normal processes of brain maturation and neural plasticity may work in concert to contribute to the to the nearly normative levels of neurobehavioural functioning seen in this group.

Neural plasticity may in fact be mediated by environmental factors. In addition to the direct contribution of normative processes of brain development and plasticity to the attainment of normative functioning in this group of children, environmental factors may also have played a role as a protective factor. Many of the children in the current study came from a middle to upper-middle class socio-economic

background and live in rural areas free of many of the risk factors associated with an urban environment. This is in contrast to NICU children from other follow-up studies (e.g. Rose and Feldman, 1995), in which most such children live in impoverished environments. For example, it is striking that the mean IQ of the preterm children at age 11 years in the study by Rose and Feldman (1995) was 89.6 (nearly a standard deviation below the mean IQ of the current NICU sample), with a mean Hollingshead SES of 26.7, indicating lower SES. Thus, these children are considered to be at risk both biologically and socially (Rose and Feldman, 1995). For the current sample, the advantages of higher SES and the accompanying access to greater educational and remedial opportunities may well serve as a form of environmental enrichment that promotes the processes of neural plasticity.

One of the goals of the study was to examine the possible differential contributions of neonatal risk factors to the prediction of memory and executive functioning in early adolescence. Our results suggest that being born earlier contributed to the prediction of spatial memory span, while the level of neurobiological risk did not (after controlling for gestational age). In contrast, the amount of neurobiological risk experienced during the neonatal period, in particular the presence of factors that influence brain blood flow and oxygenation, does contribute to the prediction of total forgetting errors in the CANTAB spatial working memory task (even after controlling for gestational age). Gestational age does not contribute to the prediction of total forgetting errors after controlling for chronological age. In our analyses, the contribution of neurobiological risk to the prediction of total forgetting errors does not reach the conventional level of statistical significance (an important caveat). However, the pattern of results differentiating the relative contributions of gestational age and neurobiological risk to the prediction of memory functioning in early adolescence is nonetheless striking and may have important implications for brain development and plasticity.

Our results suggest that being born early, and thus without prenatal brain development completed, has some impact on spatial memory span that is independent of the medical complications that may be experienced in conjunction with premature birth. Spatial memory span as measured by the CANTAB, mediated by the right ventrolateral prefrontal cortex and its reciprocal connections with subcortical regions (for a discussion, see Luciana and Nelson, 1998), may be particularly sensitive to the lack of expectant environment that the preterm brain encounters. Our findings suggest that medical complications may not contribute to resultant deficits in spatial memory span beyond those produced by lack of expectant environment for the developing brain. Recent work from our laboratory has demonstrated that 19-month old infants born prematurely but without medical complications demonstrated explicit memory deficits as measured by an elicited imitation task (de Haan *et al*., 2000). Successful completion of this task requires memory for temporal order, not unlike the type of memory required for the CANTAB spatial memory span task. Several risk factors may contribute to memory deficits in low-risk preterm children including nutrition, differences in early physical environments of preterm children and differences in the development of sleep-wake cycles (de Haan *et al*., 2000). In concert, these factors may contribute to inadequate development of grey matter and synaptic interconnections within neural networks subserving memory for spatial sequences. More speculatively, the dramatic increase in synaptogenesis and the accompanying increase in synaptic density during the perinatal period shortly before and after birth may be particularly disrupted as a result of preterm birth, regardless of any medical complications. This process may be sensitive to and impaired by deviations from the expected environment.

The current results, on the other hand, also suggest that performance on the CANTAB spatial working memory task, primarily mediated by dorsal and ventral regions of the prefrontal cortex (Luciana and Nelson, 1998), is not predicted by preterm birth *per se*, but is impacted by neurobiological risk. The areas involved in this task encompass a large portion of the entire cerebral cortex, which implies that the task is mediated by a large network of cortical (and most likely subcortical) areas and the interconnections between them. Behaviourally, the spatial working memory task requires more prefrontal involvement, as it relies heavily on response inhibition, working memory and planning, in addition to explicit memory. Events that compromise the flow of oxygen to the brain, rather than impacting brain development *per se*, may instead have a deleterious effect on already established neural networks. Consistent with the findings of Luciana and colleagues, the current results showed that deficits on the spatial working memory task occurred on the more difficult six and eight item searches. This implied that larger networks, such as those mediating spatial working memory, may function less efficiently under high demand (Luciana *et al*., 1999).

In summary, neurobiological risk may have a wide impact on discrete networks established in the prefrontal cortex, producing the continued deficits in spatial working memory observed in the current results. Lack of the expected environment during brain development, as occurs as a result of premature birth, may result in a process whereby deficits are produced in more discrete, less widespread neural circuitry reflected by deficits seen in spatial memory span. This finding has possibly important implications for interventions with preterm children, suggesting that even if a preterm child does not experience medical complications during the perinatal period, they may still be at risk for cognitive deficits.

The findings of the current study also demonstrate that it is useful to examine specific aspects of executive functioning and memory in this population of children to discern their neuropsychological status more clearly. The IQ scores did not distinguish between the NICU and control samples, but were moderately associated with higher neurobiological risk

during the neonatal period. If the current study had examined only IQ in these two groups of children, the conclusion would have been that while there was some association of IQ with neonatal medical adversity, the NICU and control groups were indistinguishable on IQ. However, the use of the CANTAB, a measure of perhaps more subtle and specific aspects of neuropsychological functioning, did distinguish the groups to some extent. The ability to assess specific deficits in executive and cognitive functioning could have useful application in the design of school-based interventions or early preventive interventions designed to help preterm children compensate for cognitive deficits.

In order to achieve a clearer understanding of the neural correlates of cognitive functioning in children born preterm it will be critical to utilize functional brain imaging. Employing fMRI to study patterns of brain activation will allow examination of whether children born preterm are utilizing alternative, reorganized brain circuits, which might at least partially circumvent compromised areas such as the hippocampus, in order to compensate for perinatal damage. An fMRI case study of a young adult born prematurely with 50% hippocampal volume loss bilaterally has recently been reported (Maguire *et al*., 2001). Although activation of the subject's hippocampus during memory tasks was similar to that of controls, there were differences in patterns of activation, reflected by differences in hippocampal–cortical connectivity. This finding, although for only one subject, appears to offer direct evidence of neural plasticity in an individual with reduced hippocampal volume resulting from complications due to premature birth.

Further work needs to examine more carefully the relation between the typology and severity of specific neurological insults during the perinatal period and specific types of neuropsychological functioning later in life. Future fMRI studies should compare hippocampal and prefrontal functioning in groups of prematurely born children with that of control children. In particular, fMRI would be useful in examining the neural and functional correlates of the apparent improvement of neuropsychological function between childhood and adolescence in this population, despite evidence of structural abnormalities. Utilizing brain imaging techniques to examine the developmental course of brain development in children born preterm would be useful in attempting to establish the important linkage between neurological insult, the mechanisms and form of plasticity, and function.

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