Prefrontal lobe functioning and its relationship to working memory in preterm infants

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Abstract: This study investigated working memory in preterm and full-term infants at 8 months after expected date of delivery. A case-control study design was used for the study. Thirty-seven preterm infants without identified disabilities and 74 full-term and gender matched healthy full-term infants participated in the study. All infants were assessed on working memory tasks at 8 months after the expected date of delivery (when preterm infants were actually 10-11 months chronological age). The findings of the study showed that preterm infants performed significantly more poorly than full-term infants at 8 months after the expected date of delivery on measures of working memory. The results suggest that the effects of maturation are greater than the effects of exposure to extraterine environmental stimuli on the development of working memory. Furthermore, the preterm infants were divided into two subgroups on the basis of (a) low or high medical risk factors, (b) birthweight of < 1000 g versus 1000-1500 g, and (c) gestation age of < 28 weeks versus 28-32 weeks, in order to assess the effects of these variables on the performance of working memory. Medical risk, lower birthweight and lower gestation age were all found to adversely affect performance on working memory. The present study provides further insights into the emergence of working memory in infants and the feasibility of evaluating these abilities in infants who are at risk for further learning difficulties and attention deficits.

Keywords: Prefrontal lobe functioning, working memory, preterm infants, full-term infants

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INTRODUCTION

Advances in medical technology continue to improve the survival rate of preterm infants, so that increasing numbers of children who weigh <1000g at birth are surviving and entering the school system (1,2). These at-risk children have been the focus of much research and many follow-up studies have identified a strong relationship between birthweight and learning development at school age (3). Confounding this relationship, with the fact that as birthweight declines, the number and severity of perinatal
complications experienced by infants is likely to increase, and the increased chance of having learning problems (4).

Extensive attempts have been made to identify sensitive predictors of later learning problems in both term and preterm children (5,6). It has been accepted that learning problems have multiple determinants, and it is important to consider the interactions of biological factors (such as medical complications and genetic endowment), environmental factors (such as demographic factors, quality of educational experience, socioeconomic, and psychosocial factors), and developmental factors (such as specific cognitive abilities and general development) (7). Frequently there is an association between perinatal risk and poor social circumstances. Several studies have demonstrated that social factors, particularly low educational level of the parents and socioeconomic status, play an important role in the intellectual outcome of both healthy full-term and preterm infants and those who had perinatal medical complications (8,9).

The population of Very Low Birthweight (VLBW, birthweight between 1001-1500 grams) and Extremely Low Birthweight (ELBW, birthweight less than 1000 grams or 750 grams) infants is known to be at increased risk for a broad spectrum of health and developmental problems, and also an increased incidence of psychosocial disadvantages (e.g., poverty, single parenthood, youthful maternal age, and limited parental education), producing a “doubly vulnerable” population, which places their development in even greater jeopardy (10). The assessment of subtle developmental and behavioural delays in infants is complicated, and currently there are few sensitive measures available for the early identification of learning problems in infants. Conventional developmental assessment tools, such as the Bayley Scales of Infant Development, (11) only provide global indicators of development and fail to measure specific skills that may provide sensitive predictions of later learning.

The assessment of specific cognitive skills, in particular working memory, rather than a global development score in infancy, has been advocated by a number of investigators (12,13). Working memory is defined as “the ability to maintain an appropriate problem solving set for the attainment of a future goal” (1). Working memory deficits have been linked to a range of developmental problems, including attentional deficit disorder (ADD), learning difficulties, and autism, all of which are more prevalent in children born preterm (14). Studying a group of infants at high-risk for learning difficulties should make it easier to identify factors that are predictive of later learning problems. This may lead to a greater understanding of the etiology of these problems in all children.

In Welsh and Pennington’s model of working memory, certain information remains at the forefront of cognition, despite distraction, and hence is active for the purpose of guiding appropriate responses. An important characteristic of working memory is that it is prospective, that is, its purpose is to attain a goal. Fuster (15) suggested that this is achieved not only by holding information in mind, but also by guiding goal directed actions. Graham and Harris (16) stated that working memory is also necessary in tasks which require strategy selection, monitoring, and revision of actions. This implies that working memory not only enables information to be held in mind but also to be manipulated. It is generally agreed that these behaviours are governed by the prefrontal cortex of the brain (17). This part of the brain is late in developing and therefore may be particularly vulnerable to damage in preterm infants.
The development of frontal lobe in human infants

The prefrontal cortex is one of the last regions of the central nervous system to undergo full myelination, and developmental changes originating from frontal lobe development are evident in several periods of life (20). The most active periods of development of the prefrontal cortex appear to be in the first 2 years of life, then between 7 and 9 years, and finally in adolescence. The development of the frontal lobe in infants deserves particular mention because during this period remarkable and rapid changes occur in both the neural physiology and the behaviour of the human being. For the frontal cortex, the period of maximum synaptic excess appears to be in the second half of the first year (21), after which there occurs a protracted period of decline in synaptic density through selective elimination of little used pathways. Recent studies of human brain activity using Positron Emission Tomography (PET) documented developmental changes in rates of glucose metabolism (22). These changes are characterised by a rise in metabolism in the frontal region at approximately 6-8 months of age, followed by a prolonged period of decline in rates of metabolism which parallels the decline in synaptic density (22). Thus, it seems that the significant and rapid changes related to anatomy and function of the frontal lobe occur in the second half of the first year after birth and continue more slowly after this early period.

There is ample evidence that working memory also develops dramatically during the second half of the first year of life. For example, infants can hold information in mind for increasing periods of time and use this information to direct and regulate their responses. Behaviours of this type have been shown in numerous studies to be related to the prefrontal cortex. Bell and Fox (23) further demonstrated a relationship between working memory and prefrontal lobe functioning and showed individual differences in frontal-brain electrical activity, as shown in EEG recordings and performance on the AB task which measures working memory. Infants at eight months of age who succeeded on the AB task exhibited greater power values in the frontal EEG during baseline recordings than infants who were unable to do the task (24).

Additional evidence for the importance of prefrontal cortex maturation for the development of working memory abilities has come from studies of children with phenylketonuria (25). Even when treated, this genetically transmitted error of metabolism can have the specific consequence of reducing the levels of the neurotransmitter dopamine in the dorsolateral prefrontal cortex. This results in impaired performance on tasks thought to measure working memory, such as the AB task (26). The standard AB task was originally described by Piaget (27) to measure the changes in the concept of object permanence in human infants. In Piaget’s AB task, an infant sits before two identical hiding places, often referred to as occluders (e.g., two identical cloth covers or two identical lids) that are separated by a small distance. While the infant watches, a desired object is hidden in one location (A). After a delay, the infant is allowed to reach and search for the object. This hiding and search at location A is repeated. Then while the infant watches, the object is hidden at the second location (B). After the delay, the infant is allowed to reach and search for the object. Infants frequently make the error of searching again at location A, committing what is known as the classic AB error. Thus both electrophysiological and behavioural data provide support for the relation between the development of
the prefrontal cortex and the emergence of working memory in the first year of life.

During this important maturation process, any damage or disturbance to the development of the prefrontal cortex due to disease, trauma, or conditions associated with perinatal risk factors (i.e., medical complications, extremely low birthweight, shorter gestation age) may lead to working memory dysfunction. Diamond and Goldman-Rakic (28) used animal models to examine whether lesions of the dorsolateral prefrontal cortex would have the same effect on infant monkeys as on adult monkeys. Two of the infant rhesus monkeys were tested longitudinally on the AB and the DR tasks. They received bilateral lesions of the dorsolateral prefrontal cortex at 5½ months. They were then tested on the AB task at 6 months. The findings showed that the infant monkeys that had the prefrontal lesions displayed poorer performance on the AB task than their age mates who did not have the prefrontal lesions. The lesions produced the same effect in infant monkeys as they did in adult monkeys with prefrontal lesions: they all reached incorrectly when the delay increased to 2-5 seconds after the toy changed to the new hiding position.

Damage to the prefrontal lobe due to trauma and disease in infancy may have lifelong effects on working memory abilities, and may cause learning difficulties during school years (29). In comparison with adults, childhood frontal lobe lesions produce a more pervasive impairment, interfering with the acquisition of age-appropriate working memory skills. Most studies on the relationship between working memory development and frontal lobe damage in children are based on older children (30). However, a recent case study by Anderson, Damasio, Tranel, and Damasio (31) reported that an infant who had right frontal region damage at 3 months showed severe learning difficulties and behavioural problems at school, and failure in career development in adulthood despite average intelligence (as measured by traditional intelligence tests at school age and during adulthood). The study found that the impairments largely reflected a failure to develop working memory. These findings are consistent with the notion that early damage to prefrontal regions can lead to severe disruption of working memory, while not significantly affecting many aspects tapped by standard intelligence tests. They also suggest that the prefrontal cortex may have limited neuronal plasticity which contributes to poor working memory if the damage occurs early. This may be due to disruption to the laying down of the neural architectures which are viewed as the foundation of cognitive development. A detailed examination of the relationship between prefrontal cortex development and the development of working memory in a large sample of human infants has not been possible because of the relative lack of obvious prefrontal lesions in infants and the expense and lack of availability of neural imaging technology.

The prefrontal cortex of infants who are born preterm is even more immature and prone to damage from the multitude of adverse medical complications to which these frail infants may be exposed. Lesions or atypical development of the prefrontal cortex occurring as a consequence of these hazardous events may have a detrimental effect on the development of working memory which may have long-term consequences in terms of learning difficulties at school age. Indeed it has been found that children born preterm are at an increased risk for learning difficulties and attentional deficits when they reach school age and it has been suggested that this may be
due to early abnormality in the development of the prefrontal cortex and consequently of working memory (32, 33).

Failure of working memory has therefore been shown to underlie learning difficulties and attention deficits in children and these problems are particularly common in children born preterm. Historically, the assessment of working memory in infants was thought impossible. However, recent neuropsychological research has suggested that the AB task provide avenues for research on working memory.

This study was undertaken to compare the performance of preterm and full-term infants of the same corrected age (8 months) age and 10-11 month chronological age on tests related to working memory. Specifically the study tested two hypotheses:

- Hypothesis 1: There will be significant difference between preterm and full-term infants of the same chronological age in the performance of working memory task (i.e., exposure to extrauterine environmental stimuli is the key factor influencing the development of working memory.
- Hypothesis 2: There will be significant difference between preterm and full-term infants of the same corrected age in the performance of working memory task (i.e., maturation of the central nervous system from the time of conception is the key factors influencing the development of working memory).

METHODS
This research involves the comparison of a cohort of ELBW infants (n = 37) and two comparison groups of full-term infants (n = 37 in each group) matched for gender and the age since expected date of delivery. The purpose of having two full-term comparison groups is to increase the statistical power. All infants were assessed on the working memory task. This measure formed the dependent variable. Infants were also assessed on the confounding factors that include the following perinatal variables: medical complications, birthweight, and gestation age. All infants were assessed on the above variables at 8 months after the expected date of delivery (preterm infants were 10 to 11 months chronological age at this time). Term infants were reassessed at an age equivalent to the chronological age of the matched preterm infants at the time of the first assessment. This retest provided a comparison with the preterm infants on the basis of chronological age.

Participants
Participants consisted of two groups – preterm and fullterm infants.
1. Preterm infants: The mothers of 41 preterm infants, who attended the Growth and Development Unit at Mater Children’s Hospital in Brisbane, Australia, responded to an invitation to participate in this study. These preterm infants were all born at the Mater Mothers’ Hospital, Brisbane, Australia, between May 1998 and July 1999. Inclusion criteria for preterm infants were:
   - < 1500 g birthweight,
   - < 32 weeks of gestation,
   - eight months of age after expected date of delivery,
• no evidence of severe visual, auditory or neurological impairment, or severe congenital anomalies,
• living in the Brisbane metropolitan area, and
• mother was English-speaking.

Of the 41 preterm infants, 37 were included in the study group. Two infants were excluded from the study due to severe intellectual and neurological problems and two other infants were excluded from the data analysis due to errors in the administration of some of the test items. There were two sets of twins and one set of triplets. A “high medical risk preterm infant” was further defined as an infant who had one or more of the following perinatal medical complications, previously identified as associated with poor outcomes. (40, 41). These were: Home Oxygen Dependency, Cerebral Ventricular Hemorrhage, Ventricular Dilatation, and Periventricular Hemorrhage-Intraventricular Hemorrhage.

2. Full-term Infants: Names and addresses of potential full-term comparison infants who were the same sex as the matched preterm infants, born at the Mater Mothers’ Hospital on the same expected date of delivery, were obtained from medical records at the hospital. Parents were then contacted by a letter, and provided with an information sheet, and a follow-up telephone call. A total of 207 letters were sent, and of these 74 mothers of infants with birth weights of > 2500g were selected to match the corresponding preterm infants on a first-come basis. Inclusion criteria for full-term infants were:

• > 2500 grams birthweight,
• 38-42 weeks of gestation,
• same sex as matched preterm infant,
• born on the same expected date of delivery as the matched preterm infant,
• no evidence of perinatal complications or congenital abnormalities,
• living in the Brisbane metropolitan area,
• mother was English speaking, and
• developmentally normal

In summary, all infants recruited into this study were born at the same hospital and tested at eight months (+ or - 2 weeks) after the expected date of delivery. Full term infants were reassessed when they were 10-11 month chronological age. All infants lived within a 50-kilometre radius of the Mater Mothers’ Hospital and did not have identifiable disabilities at the time of assessment.

Participation in the project was voluntary and informed consent was obtained from at least one parent of each child. Ethical approval for the project was obtained from the Mater Children’s and Mater Mothers’ Hospital Ethics Committees, and the Queensland University of Technology Research Ethics Committee.

**Working memory task**

The assessment of working memory was based on a task derived from the AB and DR tasks which have been described in the literature (26, 34). In the AB task, an infant sits before two identical hiding locations (e.g., cloth covers, cups or wells) that are separated by a small distance. While the infant
watches, a desired object is hidden in one location, location A. After a delay, the infant is allowed to reach and search for the object. This hiding and searching at location A is repeated. Then while the infant watches, the object is hidden at the second location, location B. After a delay, the infant is allowed to reach and search for the object. Infants frequently make the error of searching again at location A committing what is known as the classic AB error. The sequence of hiding locations in the DR task is random, whereas the hiding locations in the AB task are determined by the number of correct searches at location A.

Procedure
The administration procedure is described below.
1. Materials. The following materials were used for the Infant Working Memory task: one yellow cup (used to cover the toys), two red cups, three blue cups, and three small toys for hiding under the cups.
2. Pre-test. This involved the experimenter putting a toy on the table in front of the infant while the infant was watching. The infants were allowed to retrieve the toy immediately to test whether they could reach it. If it was unclear whether the infant had reached for the toy (e.g., if the infant showed an interest in the examiner or waited for several seconds before reaching to the toy), this procedure was repeated.

Ability to successfully retrieve the hidden objects is influenced by the infant’s interest in and attention to the task (35). To maintain infant’s attention to the task, the colours of the occluders (the cups under which the goal objects were hidden), were changed at set points in the test administration.

Administration of the infant working memory task
1-cup task. The Infant Working Memory task started with a 1-cup task. One yellow opaque cup and three small round toys were used. A toy was placed directly in front of the infant, at a distance of approximately 20 cm. While the child watched, the opaque yellow cup was placed by the examiner over the toy so that the toy was invisible. For this trial and all subsequent trials the mother was asked to prevent the infant from reaching by gently holding him/her whilst the object was being covered and also during the imposition of a delay between hiding and retrieving the object. She was instructed, prior to the task, to release her child when the examiner said “find the toy.” The infant’s ability to remove the occluder and reach for the object underneath was then noted. Three trials were given for each of the delay periods (0, 4 and 10 seconds).

2-cup task. For the 2-cup task, two red opaque cups and the same three toys were used. One cup was positioned 11 cm to the right of the infant’s midline, at a distance of 20 cm from the infant. The other was positioned 11 cm to the left, also at a distance of 20 cm from the infant. Testing began by positioning the goal object in front of the cup on the infant’s left hand side. The cup was then moved to cover the object. The infant was then permitted to retrieve the object and allowed a few seconds to play with it. The toy was hidden in the following positions: right, right, left, left, and right for the remaining 5 trials. Then the delay time between hiding the object and retrieving was increased to 2 seconds. For the 2 seconds delayed period trial, the order for hiding the toy was: right, left, left, right, right, and left. The hiding locations for the 4 s delay was the same as that of the 0 s delay and the
hiding locations for the 10 s delay was the same as for the 2 seconds delayed time condition.

3-cup task. In the 3-cup task, three blue cups and the same toys were used. In this condition, the toy was always hidden to the left and the right side of the infant and never in the middle. The order for the hiding location was the same as for the 2-cup condition. For the 2- and 3-cup difficulty level, the toy was always hidden on the left side first, because perseverative reaching has been demonstrated to be more common on an infant’s right side (36).

For the 1-cup task, three trials were presented at each time delay of the task. From the 2-cup to 3-cup Infant Working Memory task, six trials were presented at each time delay of the task. Three round toys with three colours (red, yellow, and blue) were used as objects for hiding under the cups. These three toys were used for each trial each for the first three trials at each time delay level based on the colour sequence of red, yellow, and blue. The procedure for the presentation of toys were the same for the second three trials at each time delay level. During the inter-trial (i.e., between infant’s retrieval and the preparation of next trial) interval, the experimenter gave the hidden toy to the infant to play with for approximately 20 s while the next trial was prepared. The inter-trial interval was about 20 seconds. A summary of the tasks is presented in Table 1.

Table 1

Criteria used for termination and continuation of the task
Each infant was tested on the 1-cup, 2-cup, and 3-cup tasks. In each of these conditions, the infant started from the easiest level of time delay, 0 seconds. If the infant failed to reach to the appropriate occluder on three consecutive trials at any delay level, the next trial was administered with one extra cup and 0 s delay, otherwise testing continued at the next level of delay with the same number of cups. The criteria used for terminating the task or moving to the next level are described in more detail below.

1. 1-cup task. Three presentations of this task could be given at each time delay (0, 4, 10 s). If the infant succeeded in removing the cup and obtaining the object underneath within the time limit on at least two of three presentations, then the task was administered at next level of time delay. If the infant failed to obtain the object on all three trials at a given time delay, following completion of three trials at 10 s delay the examiner moved on to the 2-cup task with a 0 s time delay.

2. 2-cup task. Six presentations of the 2-cup task were given at each delay time. There were four delay times (0, 2, 4, and 10 s), making a total of 24 trials. If the infant succeeded in reaching to the correct position on at least three consecutive trials on a given time delay, the next level of time delay was then presented. During the 2-cup task, if the infant failed to reach to the appropriate occluder on three consecutive trials at any delay level, testing of the 2-cup task was terminated, and the 3-cup task was administered with 0 s time delay.

3. 3-cup task. The criterion to pass this task was the same as in the 2-cup task. In this condition, if the infant failed to retrieve the toy on three consecutive trials at any delay level, the tester stopped the testing.

Scoring scheme for working memory
As shown in Table 2, finding a hidden object in the 1-cup task requires infants to remember the hidden object rather than a location, and to be able to reach
the hidden object. These are the criteria for the infants to perform the Infant Working Memory task. Finding a hidden object in location A in the 2- and 3-cup tasks requires working memory for location. Increasing the delay time between hiding and retrieval increases the difficulty of the task for infants (37).

Therefore working memory was scored on the memory for location, and this was scored on the basis of the 2- and 3-cup tasks in location A. A score of one was awarded if the infant remembered the location of the toy on the first trial of both 2- and 3-cup tasks, and on subsequent trials when the hiding position was the same position as on the previous trial (i.e., all the A trials which are the ones not in bold type in Table 2). The task administration was organised so that this was always the 1st, 3rd and 5th trial at each time delay level. The total number of correct trials from all A trials attempted was then calculated. Possible scores ranged from 0-12 for both the 2- and 3-cup tasks (i.e., a possible overall total range of 0-24).

Data analysis
All data were analysed using the SPSS package version 17.0. Each preterm infant had two comparison term infants matched for gender and age. The comparison between the study group and comparison groups on working memory tasks at eight months corrected age and 10-11 months chronological age was analysed by multivariate analysis of variance to test Hypothesis 1 and Hypothesis 2.

If there was a significant difference between preterm and full-term infants, the confounding variables which may explain this difference were examined. Perinatal variables which might confound the effects of prematurity, such as medical risks, birthweight, and gestation age, were also examined using ANOVA to compare the differences between the two preterm and one full-term infant groups.

RESULTS
The aim of this analysis was to compare the performance of preterm and full-term infants of the same chronological age (i.e., 10-11 months after expected date of delivery) and the same corrected age (i.e., eight months after expected date of delivery) on working memory task. Table 2 provides the results on the comparison of preterm and full-term infants on working memory tasks at 10-11 months chronological age and eight months corrected age.

Table 2

The univariate ANOVAs showed that each of the components of working memory contributed significantly to the differences between groups for working memory measure. There was a significant difference between the preterm group and full-term infants group on the working memory task.

There were significant differences between preterm and full-term infants at 10-11 months chronological age in the performance of working memory. Preterm infants showed significantly poorer performance than the full-term infant groups on working memory. These results supported Hypothesis 1, which stated that there will be significant difference between preterm and full-term infants of the same chronological age in the performance of working memory task (i.e., exposure to extrauterine
environmental stimuli is the key factor influencing the development of working memory.

It was also found that there were significant differences between preterm and full-term infant groups at eight months corrected age on working memory. Specifically, preterm infants as a group had significantly poorer performances on working memory compared with the full-term infant groups at eight months corrected age. These results supported Hypothesis 2, which stated that the performance of preterm infants is different to full-term infants of the same corrected age on measure of working memory.

The next part of this study examined performance of infants at 8 months corrected age, and aim to identify those factors which might contribute to the differences in performance on working memory task between preterm and term infants. It is possible that some factors associated with being preterm affected performance of working memory more than prematurity per se. These factors include medical complications, lower birthweight and shorter gestation age. Further analyses were conducted to assess the effect of perinatal variables which might have significantly affected preterm infants’ performance on the working memory measures.

Preterm infants were firstly grouped on the basis of their severity of medical complication as follows. None of the full term infants had serious perinatal complications and they were combined to form one group.

1. high-risk preterm group (n = 18), group 1;
2. low-risk preterm group (n = 19), group 2; and,
3. no medical complications (term infants n = 74), group 3.

The results of high risk preterm infants, low-risk preterm infants and full term infants are shown in Table 3.

Table 3

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<th>Group Description</th>
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<td>High-risk preterm</td>
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<tr>
<td>Low-risk preterm</td>
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<td>No medical</td>
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The preterm infants who had a high medical risk in the perinatal period performed worse than those who did not have these medical risk factors on working memory, although the differences in performance were not statistically significant. The scores of both the preterm infant groups were lower than those of full-term infants on working memory measure. These differences reached statistical significance between both groups of preterm infants and full-term infants on working memory. The difference between preterm infants who had high medical risk and full-term infants was greater than that between low-risk infants and full-term infants on working memory, suggesting that medical risk influences the development of working memory. Preterm infants were grouped on the basis of their birthweights as follows. None of the full-term infants was low birthweight and they were combined to form one group:

1. < 1000 g birthweight (n = 21), group 1;
2. 1000-1500 g birthweight group (n = 16), group 2; and,
3. normal birthweight group (term infants, n = 74), group 3.

The results of infants with less than 1000g birthweight, infants with 1001-1500g birthweight and normal birthweight infants are shown in Table 4.

Table 4

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<td>&lt; 1000 g birthweight</td>
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<td>1000-1500 g birthweight</td>
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<td>Normal birthweight</td>
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The preterm infants who had < 1000 g birthweight performed worse than those who had ≥ 1000 g birthweight on working memory although the differences in performance were not statistically significant. The scores of both groups of preterm infants were poorer than those of full-term infants on working memory. These differences were statistically significant between both groups of preterm infants and full-term infants on working memory. Thus the differences between the preterm infants who had < 1000 g birthweight and full-term infants appear greater than that between the infants with ≥ 1000 g birthweight and full-term infants on working memory, suggesting that ELBW may significantly influence the development of working memory.

Preterm infants were grouped on the basis of their gestation age. None of the full-term infants had low gestation age and they were combined to form one group.

1. 28 weeks gestation age (n = 15), group 1;
2. 28 to 32 weeks gestation age (n = 22), group 2; and
3. normal gestation age (full-term infants, n = 74), group 3.

Table 5 shows that scores were poorer for the infants < 28 weeks gestation than for the preterm infants with ≥ 28 weeks gestation on working memory, and the scores of both groups of preterm infants were poorer than those of full-term infants on working memory. These differences reached statistical significance between preterm infants and the group of full-term infants on working memory.

Table 5

DISCUSSION

Preterm and full-term infants of the same chronological age and same corrected age were compared on measures of working memory in order to assess the differential effects of maturation (biological maturity) and length of exposure to extrauterine environmental stimuli on the development of these abilities. Although a number of studies suggest that global development seems to be largely the result of maturational influence (38), others have reported that “neural sculpting” occurs as the result of exposure to environmental influences (39). Currently little is known about the impact of the environment on the development of brain mechanisms that mediate specific cognitive abilities, such as working memory.

It was found that preterm infants were inferior to full-term infants on working memory tasks at both the same chronological age and the same corrected age, but the differences in performance were much less when the infants were compared at the same corrected age. This suggests that maturation had a greater impact than exposure to environmental stimuli on the development of working memory. However, as differences between the preterm and full term infants remained even when they were compared on corrected age, other factors must also have impact on the development of working memory in these infants. It was also found that high-risk perinatal complications, extremely low birthweight (<1000 g) and very low gestation age (< 28 weeks) were associated with poor performance on working memory task.

Preterm infants represent a heterogeneous population which varies with respect to gestation age, birthweight, adequacy of interuterine growth,
and the diversity of medical complications to which they may have been exposed. All too often in the literature these differences have been ignored and data from preterm infants has been lumped together. It is however essential to consider the effect which these factors may have over and above the effects of prematurity per se.

The perinatal risk factors examined in the present study were high medical risk, extremely low birthweight, and shorter gestation age. VD did not occur in any of the infants in the present study so it was not used for the analysis. Eighteen infants fell into this “high medical risk” category, and the remaining 19 preterm infants were defined as “low medical risk.”

ELBW was defined as birthweight < 1000 g. Preterm infants in the < 1000 g birthweight group did not differ from the preterm infants with > 1000 g birthweight group with regards to medical risk status. Two gestation age groups comprised infants with gestation age < 28 weeks and preterm infants with ≥ 28 weeks gestation age. Infants with gestation age < 28 weeks were regarded as having shorter gestation age. Likewise, preterm infants born at < 28 weeks gestation were not significantly different to those with 28-32 weeks gestation in terms of medical risk status. There was therefore an opportunity to consider the effect of birthweight and gestation age independent of medical complications.

In each case, the high-risk group (i.e., the medical complications group, the <1000 g birthweight group, and the < 28 weeks gestation group) performed more poorly than their low risk counterparts (i.e., the low medical risk group, the > 1000 g birthweight group, and the > 28 weeks gestation group) on working memory measure although these differences did not reach statistical significance. The performance of both the high risk and low risk preterm groups on measure of working memory were also consistently poorer than that of the full-term group, and this reached levels of statistical significance more frequently for the high risk preterm groups than for the low risk groups. The results of the effects of perinatal factors on the performance of working memory are summarised in Table 6 below. These findings suggest that medical risk, lower birthweight, and lower gestation age adversely affect performance on working memory measure.

Table 6

The findings of this study are consistent with those of other researchers, who have reported that perinatal risk factors influence cognitive development during the first year of life (42). Similar deficits in working memory have also been reported in studies of school age children who were born preterm and who experienced high medical risk (43). For example, Luciana et al [33] found that preterm born children at 7 to 9 years of age who had high medical risk differed from full-term infants on working memory tasks, and Taylor et al (44) also suggested that medical risk may influence the long term developmental outcomes of preterm infants.

The results are also consistent with previous studies of children with extremely low birthweight, whether defined as birthweight < 1000 g (32) or < 750 g (43), which have reported lower scores on the performance of working memory tasks. However the children in these studies were older than the children in the present study. The effect of Small for Gestational Age (SGA) may also influence the performance of working memory in the preterm infants with < 1000 g birthweight group in the current study. For example,
the poorer performance of the ELBW infants on working memory may have been due to the fact that there were eight SGA infants in the ELBW group. Several studies, such as that of McCarton et al (45) have reported that SGA preterm infants tend to perform more poorly than their AGA counterparts on general developmental assessment measures. In the current study, SGA preterm infants tended to show poorer scores on the working memory measure than AGA preterm infants, but these differences did not reach statistically significant differences as the number of SGA infants in the present study was too small. Evidence for direct central nervous system effects of intrauterine undernutrition is primarily based on animal studies. Laboratory studies in rats and guinea pigs that have experienced intrauterine growth retardation have shown decreased brain weight, and reduced amount of brain DNA, protein, and myelin lipids (46). While extrapolation from animal studies is questionable this does raise the possibility that SGA infants may experience cognitive impairments as the result of reduced brain growth. This study appears to be the first to examine the effect of gestation age on the performance of working memory. The effects of gestation age on subsequent cognitive development has been the topic of considerable debate. Many studies have included a heterogeneous group of preterm infants with a wide range of gestation ages. The effects of gestation age on subsequent development have consequently often been confounded by a higher incidence of perinatal complications and poor psychomotor development in the infants of lower gestation age (47, 48). In this study, both preterm infants with < 28 weeks gestation and infants with 28-32 weeks gestation had lower scores than the full-term infants on working memory. The differences between both preterm groups and full-term infants reached statistical significance on measure of working memory. This suggests that a shorter gestation age is no more detrimental to performance in these areas than prematurity per se.

There is considerable evidence that tasks which require the holding of information in memory involve the dorsolateral prefrontal cortex (49,50). The deficits in working memory observed in the high perinatal risk groups may be associated with the adverse effects of these perinatal risk factors on the prefrontal cortex which is very immature and sensitive in the preterm infants (51). Mouradian, Als and Coster (52) suggested that deficits in working memory might be due to late maturing cortical organization, particularly of the prefrontal regions. Myelination of the brain has been demonstrated to occur in a systematic fashion starting at the end of the first trimester and continuing at least until the end of the second year (53). Between 23 and 32 weeks of gestation, structural differentiation of the central nervous system is at its most rapid (i.e., neuronal differentiation, glial cell growth, myelination, axonal and dendritic growth and synapse formation). The preterm infants in the present study were born between 24 to 32 weeks gestation just at this time of brain development. Most of these preterm infants were in the Neonatal Intensive-care Unit for up to three months after they were born. The environment in the Neonatal Intensive-care Unit may not be conducive to the development of the brain and the perinatal risk factors which occurred during this period may have further adversely affect brain development. The prefrontal cortex, which appears to play a central role in regulating working memory, is a late maturing area of the brain, and is consequently likely to be particularly vulnerable to damage in preterm infants (54). Those preterm infants with these detrimental perinatal events are at particular risk for the abnormal prefrontal cortex functioning, hence the deficits in working memory.
The deficits of working memory observed in preterm infants may have long term consequences in terms of learning difficulties at school age. During school years, children born preterm who experienced high perinatal risks (i.e., high medical risks, extremely low birthweight, shorter gestation age) during the perinatal period have been found to have higher rates of deficits in cognitive and neuropsychological abilities, mathematics achievement, and adaptive behaviours, as well as higher rates of special education placements as compared with their full-term counterparts (2,33,44, 55). It is possible that this is due to early abnormality in the development of the prefrontal cortex and consequent working memory impairment. Anderson et al (31) suggested that this might possibly result in inability to ever acquire aspects of working memory.

In summary, there were significant differences between preterm and full-term infants’ scores on working memory at both 10-11 month chorological age and eight month corrected age. Medical risk factors, extremely low birthweight, and shorter gestation age confounded the effects of prematurity for working memory.

Limitation of the study
There are several limitations of this study. First, due to the restricted timeframe, long-term outcomes cannot be assessed. Hence a link cannot be made between the deficits in working memory in preterm infants found in the present study and learning difficulties in school. Second, the examiner was not blind to the preterm/term status of the infants and this may have affected the administration and coding of the tests. Third, the relatively small sample of preterm infants who could be recruited within the time constraints for the present study restricted the range of statistical analyses that could be carried out and thus limited their power. Finally, the strict selection criteria chosen to yield a group of relatively healthy preterm infants may have biased the sample and made it unrepresentative of the general population of every preterm infant. For the above reasons the results should be interpreted with some caution.

CONCLUSIONS
Differences were found between preterm and full-term infants on measures of working memory at both the same corrected and same chronological age. Maturation was found to be an important factor influencing the development of working memory. However other factors associated with prematurity were also found to affect performance on working memory measure. The present research examined the factors which may significantly affect the differences between preterm and full-term infants. In particular, high medical risk, lower birthweight, and shorter gestation age all affected the differences between preterm and full-term infants on of working memory measure.

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