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Neuropsychological development in infancy: Insights from the study of preterm infants[1].

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Introduction

Rapid progress has occurred in the neuro-sciences in the past 20 years, however until recently relatively little attention was paid to the neuro-psychological development of infants and young children. Although the dramatic developmental changes which occur during the first few years of life suggest rapid neurological development little direct evidence has been available on the actual patterns of brain development. Beliefs about the functioning of the different parts of the brain during the early years have been derived primarily from downward extensions of evidence from adult clinical patients together with indicators from animal studies.

Improved neural imaging technology such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), along with neuro-physiological techniques, which allow specific areas of the brain to be temporarily inactivated through the use of low temperatures or drugs, have given access to more sophisticated information about the functioning of the brain. However, these techniques remain costly and most of the research has continued to focus on adults because of the difficulty of assessing infants and young children. Never the less it has become possible to study the development of neural pathways in more detail than ever before. This research has suggested that within the brain neuronal connections are made between information received through the sense organs and responses to that stimulation. The proliferation of synaptic connections seems to be at its height during the first three years of life although new connections continue to be made at a slower rate throughout childhood and possibly throughout life. The pathways that are layed down become strengthened through repeated utilisation of the stimulus-response links and at the same time pathways that are not made use of are pruned away. Thus the architecture of the brain is established on the basis of the stimuli which are received from everyday experiences and responses to them (Cynader & Frost, 1999). Most of this research has focused on the functioning of subcortical structures which regulate emotional responses to environmental stimuli, although Thatcher (1991) and Bell and Fox (1992) provided evidence of increased synaptogenesis in the frontal cortex during infancy

It is postulated that these neural pathways once established are difficult to change and therefore experiences early in life are likely to have a profound effect on behaviour

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into adult life (Power & Hertzman, 1997). This evidence from brain research has been used to explain the long term adverse outcomes of children who suffer abuse or neglect during infancy and early childhood (Perry, 1993; 1996).

The suggestion that environmental events early in life have a significant effect on the architecture of the brain, and that this, in turn, influences developmental and behavioural outcomes in later childhood and adult life, has attracted wide media attention in recent years. The neuro-sciences research has also been popularised through publications such as *The Early Years Report* (McCain & Mustard, 1999) and *Rethinking the Brain* (Shore, 1997). This has had the beneficial effect of alerting both the public and policy makers to the importance of the early years of life and interest in the neuro-psychological development of infants and young children has gained prominence. It would however be wise to insert a word of caution, as there has been a tendency in some quarters to over-interpret and over-extend the results from a very limited number of research studies. Furthermore most of these studies were conducted on animals (Cynader & Frost 1999; Suomi, 1997) and few of them followed their subjects into adult life. As the brain structure of animals is different to that of humans care must be taken in applying the results of research on animals to humans. Furthermore although the evidence suggests that experiences in early life may *influence* subsequent development and behaviour there is no evidence to show that they *determine* outcomes. Little is known about the plasticity of the brain and some children appear to be highly resilient and to show no adverse effects despite exposure to extremely unfavourable environments early in life (Werner & Smith, 1992). Furthermore, there is a danger that interpreting the evidence from brain research in a deterministic fashion will undermine the positive effects that can result from appropriate intervention. Whilst no-one would deny the advantages of a good start in life, it is important to remember that there is much that can be done to repair the scars suffered by less fortunate children (McCormick, McCarton, Tonascia, & Brooks-Gunn, 1993).

Research in neuro-psychology has also contributed to an understanding of early brain development. The pioneering work of Diamond (1989; 1991) and Goldman-Rakic (1987) for example clearly demonstrated that areas of the cortex which had hitherto been thought to be dormant during infancy and early childhood were in fact active even in quite young infants although they continued to mature throughout childhood and adolescence. Bell and Fox (1992) found that EEG patterns of infants who were able to find a hidden object were more mature than those of infants who were unable to perform this task. Thus confirming a link between frontal lobe activity and cognitive development in infancy. Further evidence of early cortical activity has also come from studies of planning and problem solving by infants (Sun & Mohay, 2000; Willatts, 1989; 1997; 1999).

This burgeoning of research in the neuro-sciences has led to a reframing of many long held beliefs about brain development. Shore in her book *Rethinking the Brain* summarised current thinking as follows:

> "How a brain develops hinges on a complex interplay between the genes you are born with and the experiences you have.

Early experiences have a decisive impact on the architecture of the brain, and on the nature and extent of adult capacities.

Early interactions don't just create the context, they directly affect the way the brain is "wired".

Brain development is non-linear: there are prime times for acquiring different kinds of knowledge and skills

By the time children reach age three, their brains are twice as active as those of adults. Activity levels drop during adolescence."

(Shore, 1997)

Evidence from studies of preterm infants

Preterm infants are a particularly interesting population. Their immaturity at birth and consequent exposure to environmental stimuli at a time when other infants would still be *in utero* provides a unique opportunity to examine the effects of both biological factors and environmental events on subsequent development. In Australia approximately 6% of births occur preterm (ie at <37 weeks gestation) with approximately 1% occurring prior to 28 weeks gestation. Preterm infants are often described in terms of their birth weight. A birth weight of <2,500 grams is referred to as low birth weight (LBW), a birth weight of <1500 grams as very low birth weight (VLBW), and one of <1000grams as extremely low birth weight (ELBW).

Since 1978 the development of all surviving ELBW infants who were cared for in the Neonatal Intensive Care Unit of the Mater Mothers' Hospital, Brisbane, Australia, has been monitored systematically by a multi-disciplinary team of researchers in the Growth and Development clinic at the Mater Children’s Hospital. Most of the data that I will present in the remainder of this chapter comes from studies which my colleagues and I have conducted through this clinic.

I will first present some overall data on survival and disability rates and then some evidence on neurological development.

Survival data

The survival of preterm infants in all birth weight categories has increased dramatically in the past twenty years and in recent years this has been most evident in the ELBW group. Thus increasing numbers of ever smaller and more preterm infants are surviving. For example in 1977 only one ELBW infant survived at the Mater Mothers' Hospital whereas in 1999 over fifty such infants survived.

This increase in the number of surviving preterm infants has resulted largely from advances in medical knowledge and technology that have allowed more fragile and sick infants to be kept alive. The figures have also been boosted to some extent by an increase in the numbers of preterm births resulting from population growth in the area served by the hospital, and by an increase in the number of preterm multiple births resulting from IVF pregnancies (Mohay et al., 2000). Similar increases in survival rates have been reported by most of the major centres in the world which have intensive care facilities for preterm infants

Disabilities

Preterm infants have a significantly increased risk of developmental disabilities; the most common of which are cerebral palsy and intellectual impairment. As neurosensory disabilities are relatively unaffected by psychosocial or socioeconomic factors they provide some indication of the extent of biological risk to which preterm infants are exposed. Disabilities of this type may be due to the immaturity of the organism at birth and its inability to adequately cope with the demands of the external environment. They may also result from the treatment required to keep the infant alive, or they may be due to prenatal events that may also have precipitated the preterm birth. The importance of the latter as a significant cause of cerebral palsy in preterm infants has been increasingly recognised in recent years (Stanley, Blair & Alberman, 2000).

A number of studies have reported an inverse relationship between birth weight and disability rate (Hack, Klein & Taylor 1995; Holst, Andersen, Phillip & Henningsen, 1989; McCormick, 1989). These results are however compounded by the increased risk of medical complications in smaller and more immature infants (Klebanov, Brooks-Gunn, & McCormick, 1994).

In general, the increased survival rate of preterm infants does not appear to have been accompanied by any significant increase in the frequency of disabilities in the preterm population as a whole (Aylward, Pfeiffer, Wright & Verhulst, 1989; Tudehope, Burns, Gray et al., 1995), although there has been considerable variation in disability rates reported by different Centres. (A summary of data from recent reports of disability rates for low birth weight infants from tertiary care centres in the Unites States, Canada, Australia, and Western Europe, is presented in Table 1)

Table 1. Surviving LBW Infants with One or More Major Handicaps

Birthweight (g)	Mean % of Infants with Developmental Disabilities
LBW 1501-2500	8 (Range 5-20)
VLBW 1001-1500	15 (Range 5-30)
ELBW ≤1000	25 (Range 8-40)

The wide discrepancy in reported disability rates is largely due to differences in the populations served by different hospitals, disparities in the age at which outcomes were assessed and a lack of commonly agreed criteria for defining disabilities (Hack, Klein & Taylor, 1995). These problems make it difficult to interpret data on disabilities however it is widely accepted that approximately 25 percent of ELBW infants will have identifiable disabilities, although most of these will fall within the mild category.

Use of Chronological Age v Corrected age for developmental assessment

The early identification of disabilities, especially developmental delay, is fraught with even greater difficulty than usual when working with preterm infants. To identify a developmental delay the infant's development must be compared with an age norm. How we calculate the age of a preterm infant has been the subject of considerable debate (Caputo, Goldstein & Taub, 1979; Hunt & Rhodes, 1977**;** Miller, Dubowitz & Palmer, 1984; Ungerer & Sigman, 1983). If the infant's age is calculated from date of birth virtually all ELBW infants will appear to be developmentally delayed, at least during the first two years of life. However, if the infant's age is calculated from the expected date of delivery, ie, a correction is made for the number of weeks preterm, then their development, in most cases, is comparable to that of a full term infant of the same age. Some people have argued that making a correction for prematurity leads to an overestimation of the child's abilities and a failure to identify developmental anomalies (Miller, Dubowitz & Palmer 1984). However most clinicians favour correcting for gestational age until at least two years of age when assessing the development of very preterm infants, and most research supports this decision (DePietro & Allen, 1991). This verdict is highly significant in terms of understanding infant brain development, as it suggests that the basic pattern of central nervous system development is set in place at the time of conception and runs its course whether the child is *in utero* or exposed to external stimulation. What is more, this seems to apply to all areas of development including both those which might be expected to be regulated by the myelination of nerves, eg, gross motor development, and those which might be expected to be more strongly influenced by environmental factors eg, language development. It is however important to note that the assessment tools which have generally been used in follow-up studies have only been capable of measuring gross developmental patterns and fine grain differences may therefore have been missed. Never the less, results from these standard developmental assessment tests suggest that biological factors strongly influence overall development during the first one to two years of life after which environmental factors appear to have an increasingly important effect on developmental outcomes (Hack, Klein & Taylor 1995).

Developmental delay

Comparison of the developmental assessments of preterm and term infants at various ages in infancy and early childhood has repeatedly shown that although the mean scores for preterm infants fall within the average range in all areas of development they are never-the-less consistently below those of term infants (Aylward, et al., 1989; Hack, Friedman & Fanaroff, 1996; Kalmar 1998, O'Callaghan, et al.,1995)

There is then an association between preterm birth and some mild delays in development, and this is especially so when prematurity is associated with other biological and/or social risk factors (Sansavini, Rizzardi, Alessandroni & Giovanelli, 1996). A significant relationship exists between preterm birth and conditions such as maternal poverty, smoking, drinking, drug taking, poor nutrition and inadequate antenatal care (Sameroff, 1982; Sansavini et al., 1996) all of which are associated with adverse long term outcomes for the infant. Hence the biological vulnerability of these frail infants is frequently compounded by detrimental socioeconomic and psychosocial circumstances (Escalona, 1982) which increase the risk of adverse developmental outcomes, although these may not become apparent until school age (Grigoroiu-Serbanescu, 1984; O’Callaghan et al., 1996a; Saigal, Hoult, Streiner et al., 2000). Failure to recognise these more subtle developmental problems at an early age may be due to a lack of sensitivity of standard assessment tools to neuro-psychological dysfunction in infancy and early childhood

Learning difficulties

At school age, children who had extremely low birth weights, but who have no diagnosed neurological abnormalities, continue to have a two to three-fold greater risk of learning difficulties than their full term peers, even when IQ is controlled for (Klebanov, Brooks-Gunn, & McCormick, 1994; Nickel, Bennett, & Lamson, 1982, Taylor, Klein, & Hack, 1994; Taylor, Klein, Minich & Hack, 2000). A recent study of our population of school age ELBW infants who were cared for in the Neonatal Intensive Care Unit of the Mater Mothers' Hospital, Brisbane, we found that 46% had required remedial help at school, and 21% had repeated a grade (O'Callaghan et al., 1996a). An increase in behavioural disorders, such as attention deficit disorders, which are frequently associated with learning difficulties have also been reported in children who were born preterm (Klebanov et al., 1994; Lah, Michie, Starte, Gibson, Bowen & Ma, 1995) although we did not find this in our own case control study (O'Callaghan et al., 1996b). Other studies have found an increase in a range of other behavioural and emotional disorders (Brandt, Magyary, Hammond, & Barnard, 1992; McCormick, Gortmaker, & Sobol, 1990; Mohay, et al., 1989; Szatmari, Saigal, Rosenbaum, et al., 1990). Whilst behavioural and emotional problem may arise as a result of learning difficulties it is also possible that they are the cause the learning problem, or that both the learning difficulties and behavioural problems emerge from the same underlying neuro-psychological deficits.

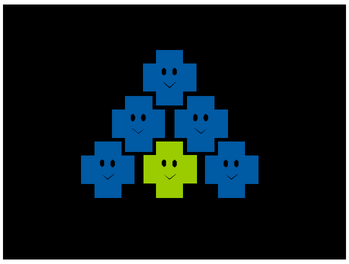
Information processing, attention and executive function

To date it has proved difficult to disentangle the web of interacting risk factors affecting the developmental outcomes of preterm infants and no accurate indicators of later learning abilities have been identified. The standard developmental assessments carried out in infancy or early childhood have been repeatedly shown to be poor predictors of educational achievements in the school years. A number of researchers (eg. Fagan, Singer Montie & Shepherd,1986; Rose & Feldman, 1997: Slater, 1997) have therefore been directing their attention to measures which address the abilities underlying academic learning, in the hopes that these will provide better predictors of outcomes and ultimately allow intervention to occur at an early age to prevent school failure.

Considerable research has suggested that children who have learning problems at school show deficits in attention and/or in one or more of the major components of executive function ie working memory, response inhibition, and planning (Furster, 1997; Pennington & Welsh 1995). Executive function is thought to be under the control of the prefrontal cortex, which is a late developing part of the brain. It therefore seems reasonable to hypothesise that this part of the brain will be particularly immature and vulnerable to damage in preterm infants and that this may explain the increased frequency of learning disabilities in this population. In our recent research we have therefore attempted to compare the abilities of preterm and term infants and young children on a number of measures related to attention and executive function, which might be adversely affected by subtle damage of the prefrontal cortex.

Our first study (Harvey, O'Callaghan & Mohay, 1999) compared a group of apparently normal ELBW 4 year olds and a matched group of full term peers on a simplified version of the Tower of Hanoi (a classic test of executive function requiring working memory, planning, and inhibition of a prepotent response), a motor planning task, and a clapping task which required inhibition of a natural response. Even when differences in intelligence were controlled for, we found that the performance of the ELBW children was inferior to that of the children born at term on all the measures of executive function, with the greatest difference being on the Tower of Hanoi task.

Having found that we could assess executive function satisfactorily in 4 year olds we recently extended our research to infants. Our first infancy study (Freiberg & Mohay, 2000; 2001) compared the ability of healthy ELBW and term infants at 4 months corrected age to inhibit attention to non-salient stimuli in an information processing task. To do this we used a visual pop-out paradigm. Visual pop-out is the phenomenon that occurs when one component of a display differs from the other components along a particular dimension eg. colour (see Figure 1).



In this array the green target stimulus stands out and captures the observer's attention in the primary (familiarisation) stage of visual processing, and the processing of the blue background stimuli (distracter) is inhibited. Thus if the infant has responded to the pop-out (target) stimulus it should be processed more completely than the distracter items.

Figure 1 Familiarisation stimulus

Subsequently when paired with a novel stimulus, a stimulus that has been processed should hold attention for less time than the novel stimulus. Conversely, a stimulus that has not been processed and the new stimulus should have equal novelty and hold attention for the same amount of time. Using this paradigm it is possible to assess which components of a display infants have attended to.

The results, shown in Table 2, suggest that the full term infants did, on average show a classic "pop-out" response ie they spent significantly more time looking at the novel stimulus when it was paired with the target stimulus than when it was paired with the distracter. Preterm infants did not respond in the same way. In fact their mean scores show that the percentage of time spent looking at the novel stimulus was very close to the chance level irrespective of whether it was paired with the target or distracter stimulus

Table 2 Mean percentage of time spent looking at the novel stimulus when paired with the target and the distracter stimulus

	Full Term	Preterm
Novel v Target test trial	72.78	52.26
Novel v Distracter test trial	57.07	52.49

These results suggests that the preterm infants did not processing the stimuli in the same way as the full term infants, indeed at first glance, it would seem that the preterm infants had not processed either the target or the distracter stimuli. However, when we further examined the data we found that the infants could be divided into four groups:

- **Group 1** showed a classic pop-out effect and looked at the novel stimulus for more than 55% of the time when it was paired with the target stimulus but less than 55% of the time when it was paired with the distracter stimulus ie they had attended to and processed the target and inhibited attention to the distracter during the familiarisation trials.

- **Group 2** looked at the novel stimulus for more than 55% of the time when it was paired with either the target or the distracter stimulus ie they appeared to have processed information rapidly so that both the target and the distracter were processed during the familiarisation trials.

- **Group 3** looked at the novel stimulus for less than 55% of the time irrespective of whether it was paired with the target or the distracter ie they did not appear to have processed either the target or the distracter. This suggests that they may have been processing information very slowly. (This would be in keeping with Rose and Feldman's (1996) finding that preterm infants process visual information more slowly than term infants.) Alternatively these infants may have been unable to inhibit attention to the distracter and switched attention between the target and distracter making it impossible to adequately process either stimulus.

- **Group 4** looked at the novel stimulus for more than 55% of the time when it was paired with the distracter but not when it was paired with the target stimulus ie they appear to have processed the distracter and not the target stimulus. This suggests that they were unable to inhibit attention to the distracter and attended to this preferentially.

Table 2 Number of full term and preterm infants in Groups 1-4

	Group 1 Novel v Target > 55%	**Group 2** Novel v Target + Novel v Distracter >55%	**Group 3** Novel v Target + Novel v Distracter <55%	**Group 4** Novel v Distracter >55%
FullTerm	12	15	4	1
Preterm	10	6	7	9

Table 2 shows that half of the preterm infants behaved in much the same way as the majority of term infants ie they were in Group 1 or Group 2 and showed normal information processing patterns. The remaining 50 % of preterm infants showed atypical patterns of information processing compared to 15% of the term infants. (It is of interest to note that previous research has suggested that approximately 50% of ELBW graduates from our neonatal intensive care nursery experience learning problems at school compared to approximately 12% of children who were born at term (O'Callaghan et al., 1996a)).

The preterm infants in this study were healthy and developmental normal. None had had adverse events during their time in the intensive care nursery. They were therefore all regarded as having low biological (medical) risk. There were no differences between preterm infants in Groups 1 and 2 and those in Groups 3 and 4 with regards to birth weight or gestational age. At 12 and 24 months corrected age all of the preterm infants were routinely assessed on the Griffiths Scale of Mental Development at the Growth and Development Clinic at the Mater Children's Hospital. At 12 months the mean GQ score of the infants who had been in Groups 1 and 2 was significantly higher than that for the infants in Groups 3 and 4 (GQ 105 and 96 respectively). At two years of age no difference in GQ was found between these groups. It remains to be seen whether the pop-out effect test has enabled us to identify the children who have learning problems when they enter school.

Currently we are conducting an ambitious project to compare the three components of executive function (problem solving, inhibition and working memory) and sustained attention in ELBW and term infants at 8 months corrected age (Sun & Mohay 2000). All of the executive function tasks start at an easy level, which all infants can pass, and get progressively more demanding. The problem solving task is based upon the work of Willatts (1997; 1999) and requires infants to carry out an increasing numbers of steps to attain an attractive object. The one step task involves pulling a cloth to retrieve the object; the two step task requires the removal of a barrier before the cloth can be pulled to retrieve the object and so on. Scoring of the task requires the infant's attempts to retrieve the object to be goal directed (ie to show a significant degree of planning).

The working memory and inhibition measures are based on the classic A not B research paradigm in which an attractive object is hidden under one of two cups and increasing delays are imposed before the infant is allowed to search for it (Diamond & Goldman-Rakic, 1989).

The sustained attention task is based on the work of Ruff (Ruff & Rothbart, 1996) and measures the duration of attention and the range of activities engaged in with a series of novel objects. The level of difficulty of this task does not change

Potential confounding factors such as socioeconomic status, maternal education and maternal depression were controlled for, and no difference was found between the preterm and term infants on the Mental Development Index of the Bayley Scales of Infant Development or the Infant Temperament Questionnaire (Sanson, Prior,& Oberklaid, 1985).

Preliminary analysis of the results of the executive function measures indicates that at each level of difficulty, except the simplest, more term infants than preterm infants were able to successfully complete these tasks. The overall score on each component of executive function was significantly higher for term infants than for preterm infants. These differences remained when preterm infants who had any significant adverse events during the perinatal period were removed from the sample ie even low risk preterm infants had poorer performance than term infants on measures of executive function.

Sustained attention is not considered to be a component of executive function nor is it believed to be primarily under the control of the prefrontal cortex however some studies have linked a failure of sustained attention to learning problems at school age. No difference was found between the full term and preterm infants on measures of sustained attention.

The findings from these studies which have used more sophisticated method to explore early cognitive functioning appear to show that even preterm infants who had an uneventful course in the perinatal period may show deficit in cognitive functioning which are not apparent on standard developmental assessments. It is important to note that not all preterm infants show these deficits and much more research is required to identify the causal pathways. Furthermore it remains unclear whether these signs of cognitive dysfunction in infancy are persistent and whether they will have any influence on future learning abilities.

Conclusions

The study of preterm infants provides opportunities to examine a number of issues related to early brain development. The fact that preterm infants appear to reach all the major developmental milestones at the same age post-conception as infants who are born at term, strongly suggests that the broad pattern and timing of development is layed down genetically, and is only disturbed by quite severe insults to the central nervous system. Standard developmental assessments measure only overall patterns of development, therefore whilst they may be useful for the identification of significant disabilities they fail to detect more subtle problems which become apparent when children enter school.

At school age even preterm infants who show no evidence of neurological abnormalities, had no significant trauma during the neonatal period and who score within the average range on intelligence tests, have an increased risk of learning disabilities. Tests which assess aspects of cognitive functioning thought to underlie later learning abilities are able to identify deficits in planning ,working memory, and inhibition (which are components of executive function) in some preterm infants during the first few months of life. Future research must examine the relationship between these early deficits and later learning abilities. Further research is also required to identify the causal pathways of these deficits. The prefrontal cortex which is a late maturing part of the brain and therefore particularly vulnerable to damage in preterm infants is thought to govern these particular skills but why should this area of the brain be damaged in some infants and not in others when none appeared to be subjected to significant CNS trauma. The answer may lie in their genetic make up which may make some infants more vulnerable to even mild insults than others, or there may be cumulative damage from a number of minor adverse events. Prenatal events might also be responsible for damage and may simultaneously precipitate the preterm birth. There is growing evidence to suggesting that this is the aetiology in at least some cases of cerebral palsy (Stanley, Blair & Alberman, 2000). Maybe it is also the case for learning disabilities .

If the tests of infant cognitive functioning are able to accurately identify those children who will have learning difficulties at school, early intervention to alleviate these difficulties will be become possible. As the population of preterm infants is so prone to learning difficulties it is an ideal population in which to search for the cause of these problems. Only when this has been identified will be possible to seek ways of preventing these problems occurring.

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