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Brain and cognitive-behavioural development after asphyxia at term birth

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Abstract

Perinatal asphyxia occurs in approximately 1–6 per 1000 live full-term births. Different patterns of brain damage can result, though the relation of these patterns to long-term cognitive-behavioural outcome remains under investigation. The hippocampus is one brain region that can be damaged (typically not in isolation), and this site of damage has been implicated in two different long-term outcomes, cognitive memory impairment and the psychiatric disorder schizophrenia. Factors in addition to the acute episode of asphyxia likely contribute to these specific outcomes, making prediction difficult. Future studies that better document long-term cognitive-behavioural outcome, quantitatively identify patterns of brain injury over development and consider additional variables that may modulate the impact of asphyxia on cognitive and behavioural function will forward the goals of predicting long-term outcome and understanding the mechanisms by which it unfolds.

Introduction

Perinatal asphyxia (PA) occurs in approximately 1–6 per 1000 live full-term births (Hill, 1991; Pierrat, Haouari, Liska, Thomas, Subtil & Truffert, 2005; Thornberg, Thiringer, Odeback & Milsom, 1995). It has long been recognized that its occurrence can be associated with brain damage and subsequent motor, cognitive and behavioural impairments, though there is still debate as to the nature and range of severity of outcomes (American College of Obstetricians and Gynecologists, 2004; Low, Galbraith, Muir, Killen, Pater & Karchmar, 1988; Marlow, Rose, Rands & Draper, 2005; Miller, Ramaswamy, Michelson, Barkovich, Holshouser, Wycliffe, Glidden, Deming, Partridge, Wu, Ashwal & Ferriero, 2005). This review will begin with a brief description of PA, follow with an overview of patterns of brain damage resulting from such episodes, and discuss the possible links between hippocampal damage caused by PA and two different long-term consequences, cognitive memory impairment and the psychiatric disorder schizophrenia.[1]

What is birth asphyxia?

The World Federation of Neurology Group defines asphyxia as 'a condition of impaired blood gas exchange leading, if it persists, to progressive hypoxemia and hypercapnia' (Bax & Nelson, 1993). Severe asphyxia can occur in infants around the time of birth for several reasons, including compression of the umbilical cord, abruption of the placenta, abnormal uterine contractions, or failure of the neonate to successfully begin breathing.

A newborn who has experienced an acute episode of PA may show clinical features such as fits, abnormal movement and alterations in tone, sometimes resulting in persistently low Apgar scores[2] or the diagnosis of neonatal encephalopathy (see below). Other indicators of PA are: (i) abnormal EEG, (ii) signs of disrupted energy metabolism including acidosis or atypical levels of certain metabolites (e.g. lactate, phosphorous metabolites), (iii) history of fetal distress (e.g. late decelerations in heart rate), (iv) necessity for resuscitation and/or (v) a signal event occurring during labour (e.g. ruptured

[1] For a broader overview of outcome after perinatal asphyxia see: Cowan, 2000; Dilenge, Majnemer & Shevell, 2001; Robertson & Finer, 1993.

[2] Low Apgar scores are sometimes used as an indicator though they can also be obtained for other reasons.

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uterus). Of these signs, neonatal encephalopathy is perhaps the most important because its presence is considered to signal the occurrence of asphyxia potentially severe enough to cause brain damage (Hill, 1991). This condition is diagnosed on the basis of neurological signs appearing within seven days after birth.[3] Typically it is described in three stages of increasing severity (Sarnat & Sarnat, 1976): *Stage 1* or 'Mild' is characterized by hyperalertness and hyperexcitability, *Stage 2* or 'Moderate' by lethargy, hypotonia and suppressed primitive reflexes and *Stage 3* or 'Severe' by stupor, flaccidity and absent primitive reflexes.

Accurately defining asphyxia is important with respect to outcome studies, as their conclusions may depend somewhat on how cases are identified. For example, one review found that the estimate of severe impairments (severe developmental delay, cerebral palsy) varied from 5 to 100% across studies with varying definitions of asphyxia (Dilenge, Majnemer & Shevell, 2001). A recent study showed that up to 90% of infants with neonatal encephalopathy (with or without seizures) show evidence of acute brain injury, i.e. acquired brain injury that did not pre-exist before birth (Cowan, Rutherford, Groenendaal, Eken, Mercuri, Bydder, Meiners, Dubowitz & de Vries, 2003; see Pierrat *et al.*, 2005, for similar results; but see Badawi, Kurinczuk, Keogh, Alessandri, O'Sullivan, Burton, Pemberton & Stanley, 1998). These results support the idea that the presence of neonatal encephalopathy is a relatively good indicator of acute perinatal injury.

Neuroimaging can also provide potentially valuable information with respect to determining the timing of events leading to brain damage. This is because the pattern of brain injury following asphyxia is not static but evolves over time. For example, magnetic resonance spectroscopy (MRS) in neonates with PA shows that temporo-parietal phosphorus spectra are normal on the first day of life but become abnormal by the second to fourth day (Wyatt, Edwards, Azzopardi & Reynolds, 1989; reviewed in Cady, 2001). Similarly, diffusion weighted imaging can detect abnormalities within 24 hours of asphyxiation (Cowan, Pennock, Hanrahan, Manji & Edwards, 1994) that become more widespread by 30 hours (Soul, Robertson, Tzika, du Plessis & Volpe, 2001). As the time course of such changes is increasingly characterized, the timing of the episode causing the damage can begin to be confirmed with imaging methods.

[3] Neonatal encephalopathy is difficult to define in infants less than 34 weeks gestation unless seizures are present, because most of its characteristics are part of the normal preterm course.

Patterns of brain damage

Although asphyxia is a global insult, it affects some brain regions more than others, with the pattern of spared and impaired areas determined in part by factors such as the maturity of the brain at the time of the incident and the duration and severity of the asphyxia (reviewed in Sie, van der Knaap, Oosting, de Vries, Lafeber & Valk, 2000). Since the pattern of brain injury may relate to long-term outcome, its accurate characterization is important. The discussion below will focus on patterns of brain injury observed in full-term asphyxiated infants, and is based primarily on radiological inspection of neuroimaging findings within the first days to months after the episode, but also on autopsy findings of infants who did not survive such episodes (Squier & Cowan, 2004).

1. Brain stem/thalamus

In some cases of PA, damage occurs primarily in the brain stem nuclei and thalamus with other regions relatively spared. Many of these infants do not survive (Barkovich & Truwitt, 1990; Squier & Cowan, 2004). This pattern is most commonly seen after acute, profound asphyxia such as might occur in cardiac arrest.

2. Basal ganglia, thalamus and cortex

Another pattern involves damage to the basal ganglia, thalamus and brain stem with the cerebral cortex and white matter relatively spared (Cowan *et al.*, 2003; Hunt, Neil, Coleman, Kean & Inder, 2004; Miller *et al.*, 2005; Natsume, Watanabe, Kuno, Hayakawa & Hashizume, 1995; Pasternak & Gorey, 1998; Pasternak, Predey & Mikhael, 1991; Roland, Hill, Norman, Flodmark & MacNab, 1988; Roland, Poskitt, Roderiguez, Lupton & Hill, 1998; Voit, Lemburg, Neuen, Lumenta & Stork, 1987). A recent study examining infants with PA defined as showing either neonatal encephalopathy or evidence of metabolic acidosis or an Apgar score of less than or equal to 5 at five minutes found that this pattern of injury was seen in 25% of infants (Miller *et al.*, 2005).

3. Parasagittal injury

Injury to the grey matter and underlying white matter in parasagittal areas is observed in a proportion of asphyxiated term neonates in many studies (Baenziger, Martin, Steinlin, Good, Largo, Burger, Fanconi, Duz, Buchli & Rumpel, 1993; Barkovich & Truwit, 1990; Campistol, Poo, Alvarez, Fernandez & Carratala, 1999; Kuenzle, Baenziger, Martin, Thun-Hohenstein, Steinlin, Good,

Fanconi, Boltshauser & Largo, 1994; Miller *et al.*, 2005; Westmark, Barkovich, Sola, Ferriero & Partridge, 1995). Blood flow to this region has also been found to decrease during the period of acute illness (Volpe, Herscovitch, Perlman, Kreusser & Raichle, 1985). A recent study suggests that this is the most frequent pattern, occurring in 45% of infants asphyxiated at term (Miller *et al.*, 2005). This pattern of damage to the parasagittal region is typically observed if the asphyxia is less severe but is chronic or repeated (Squier & Cowan, 2004). Additional damage to grey matter may also appear in one of two patterns: (i) cortical grey matter injury prominent in the depths of cortical sulci rather than the crests of the gyri (Squier & Cowan, 2004) or (ii) a mild basal ganglia-thalamic injury.

4. Widespread white matter damage with or without relative cortical sparing

White matter damage with relative cortical sparing is commonly associated with premature birth (Sie *et al.*, 2000; Squier & Cowan, 2004), but infants asphyxiated at term also show this pattern (Cowan *et al.*, 2003; Hunt *et al.*, 2004), sometimes accompanied by widespread cortical grey matter injury (Hunt *et al.*, 2004).

5. Hippocampus

Several studies of infants asphyxiated at term report injury to the hippocampus (Barkovich, 1992; Cowan *et al.*, 2003; Rademakers, van der Knaap, Verbeeten, Barth & Valk, 1995; Sie *et al.*, 2000). Injury to this structure is typically not observed in isolation, but in association with damage to the basal ganglia and thalamus (approximately 50% of infants with hippocampal damage; Sie *et al.*, 2000; Cowan *et al.*, 2003) and/or more widespread grey and white matter damage (approximately 90% of these infants; Sie *et al.*, 2000; Cowan *et al.*, 2003).

Patterns of cognitive-behavioural outcome and their relation to pattern of brain injury[4]

Approximately 15–20% of infants with PA die in the neonatal period (Robertson & Finer, 1993; Vannucci & Perlman, 1997). For those who survive, outcomes have traditionally been divided into a dichotomy of impaired–nonimpaired: approximately 25% of infants show major neurological impairments, while the remaining 75% do not and thus are often classified as having a 'normal' outcome (Vannucci & Perlman, 1997). This dichotomous view has originated in part due to the notion that there is a critical threshold of asphyxia beyond which brain damage occurs (Low, 1993). However, there is an increasing appreciation that a more continuous range of outcomes might be possible, and a focus on how such varying outcomes might be predicted. An interesting question is whether the different patterns of brain injury described in the previous section are related to particular cognitive-behavioural profiles. As yet there is relatively little information on this point as investigators are only more recently beginning to take advantage of quantitative neuroimaging methods to better characterize patterns of brain injury and to measure cognitive-behavioural outcomes at a more specific level.

Many investigators have attempted to link the severity of the episode of asphyxia, typically classified as the most advanced stage of neonatal encephalopathy, to outcome (reviewed in Roberston & Finer, 1993). This provides an indirect assessment of how extent of brain injury contributes, since the extent of neonatal brain injury increases with increasing severity of encephalopathy (Malik, Pandey, Kumar, Chawla, Rathi & Gupta, 2002). The general conclusion is that outcomes are poorer for those with more severe asphyxia. For example, one study found that general intellectual abilities, academic progress and visuo-motor integration were impaired at 8 years of age in those who showed moderate or severe neonatal encephalopathy compared to those who suffered mild or no encephalopathy (Robertson, Finer & Grace, 1989). A more recent study found that 7-year-old children who suffered severe neonatal encephalopathy (but no motor disability) were impaired on measures of general intellectual abilities, attention and executive function, language, memory and visuo-spatial abilities compared to controls, with only sensorimotor skills unaffected (Marlow *et al.*, 2005). When compared to children who had experienced moderate neonatal encephalopathy, the severe group performed more poorly on general intellectual abilities (especially non-verbal), attention and executive function and memory (Marlow *et al.*, 2005).

Other investigations have examined whether classifying brain injuries by clinical radiological inspection of brain scans relates to outcome. Such studies have shown that injury involving the brain stem, thalamus and/or basal ganglia regions is typically associated with poor outcome including death and severe disability (Kuenzle *et al.*, 1994; Roland *et al.*, 1998) and greatly reduced head growth (Kuenzle *et al.*, 1994). Other MRI studies show that: (1) there is a relation between signal intensity

[4] Only a small number of children with cerebral palsy showed signs of perinatal asphyxia or neonatal encephalopathy (Blair & Stanley, 1988; Gaffney, Flavell, Johnson, Squier & Sellers, 1994), thus cerebral palsy will not be discussed further here (see Phelan, Martin & Korst, 2005, for discussion).

in frontal watershed areas and scores on a general test of mental development at 12 months (Coskun, Lequin, Segal, Vigneron, Ferriero & Barvovich, 2001), (2) there is a link between injury to the posterior limb of the internal capsule and motor outcome (Hunt *et al.*, 2004; Rutherford, Pennock, Counsell, Mercuri, Cowan, Dubowitz & Edwards, 1998) with low values for the apparent diffusion coefficient in this area possibly reflecting degeneration of motor pathways following injury to parasagittal areas (Hunt *et al.*, 2004), and (3) proton MRS performed within a few days of birth can predict short-term 'good' versus 'poor' neurological outcome (L'Abee, de Vries, van der Grond & Groenendaal, 2005) and phosphorus MRS can predict neuromotor impairment and scores on general tests of mental development at 1 (Roth, Edwards, Cady, Delpy, Wyatt, Azzopardi, Baudin, Townsend, Stewart & Reynolds, 1992) and 4 years of age (Roth, Baudin, Cady, Johal, Townsend, Wyatt, Reynolds & Stewart, 1997).

Hippocampal injury and cognitive-behavioural outcome

While the above findings are interesting, they mostly related to broad measures of outcome rather than specific cognitive skills, often did not include quantitative measures of brain abnormality, and did not examine brain–behaviour relationships beyond the neonatal or early infancy period. The following sections will focus on two specific long-term outcomes, cognitive memory impairment and the psychiatric disorder schizophrenia, that have been linked to hippocampal damage resulting from birth asphyxia.

Memory impairments

Adults who experience hypoxia can show signs of memory impairment (Beatty, Salmon, Bernstein & Butters, 1987; O'Reilly, Grubb & O'Carroll, 2003; Parkin, Miller & Vincent, 1987; Quamme, Yonelinas, Widaman, Kroll & Sauve, 2004; Volpe & Petito, 1985) and associated abnormality of the hippocampus (Gale & Hopkins, 2004; Volpe & Petito, 1985), a structure known to be involved in memory function. It is worth noting that selective damage to the hippocampus is observed in only 18% of adult cases, with a similar percentage showing selective impairments in memory (Caine & Watson, 2000).

There is evidence that infants and children who experience PA can also show memory impairments in association with bilateral hippocampal abnormalities. One study of five children aged 12–16 years who experienced PA (Gadian, Aicardi, Watkins, Porter, Mishkin & Vargha-Khadem, 2000; see also Vargha-Khadem, Gadian, Watkins, Connelly, van Paesschen & Mishkin, 1997, case Beth) found bilateral reductions of the hippocampus with volumes ranging from 43% to 71% of normal. Voxel-based morphometry of the whole brain confirmed reduced grey matter bilaterally in the hippocampus without additional abnormality in the temporal lobe. There were, however, additional abnormalities in the putamen, ventral thalamus and brain stem, a pattern consistent with asphyxia (see also Vargha-Khadem, Salmond, Watkins, Friston, Gadian & Miskin, 2003). This pattern of brain injury was associated with a specific memory impairment: severe difficulties with episodic memory (context-rich memory for events, as assessed by tests of everyday memory and visual and verbal delayed recall) but semantic memory (context-free memory for facts, as measured by subtests of verbal IQ), working memory and academic attainments in the low average range or above. A volume reduction in the hippocampus of at least 20–30% on each side appears necessary to produce this particular memory profile (Isaacs, Vargha-Khadem, Watkins, Lucas, Mishkin & Gadian, 2003), termed developmental amnesia. Neither the amnesic profile (in terms of the deficit in everyday memory and delayed recall) nor the pattern of neuropathology (in terms of the bilateral reduction of grey matter in the hippocampus, putamen and thalamus) is affected by whether the hypoxic-ischaemic event occurs early (<1 year of age) or later (6–14 years) in childhood (Vargha-Khadem *et al.*, 2003). A motor or cognitive-behavioural correlate of the basal ganglia damage in these children has not yet been identified.

An interesting characteristic of developmental amnesia is that, in the cases where injuries are sustained perinatally, memory difficulties do not become apparent until later in life when children are approximately school aged (Gadian *et al.*, 2000; Vargha-Khadem *et al.*, 1997, 2003). One possible explanation is that semantic memory (dependent on temporal lobe cortex surrounding the hippocampus; see Mishkin, Suzuki, Gadian & Vargha-Khadem, 1997, for review) develops first and normally in both healthy children and those with selective, bilateral hippocampal pathology. Episodic memory, by contrast, emerges later during childhood in healthy individuals, but fails to develop normally in those with early-onset hippocampal damage, because hippocampal pathology curtails its progressive development (see Mishkin *et al.*, 1997). Another possibility is that subtle signs of memory impairment in individuals with hippocampal damage can be detected early in life, but they become increasingly noticeable with age. Whatever the explanation, it seems that some of the cognitive-behavioural consequences of PA may only become noticeable long after the period of acute injury.

While these studies of developmental amnesia are informative and suggest that PA can lead to bilateral hippocampal injury and memory impairment, they do not directly address the question of long-term outcome of asphyxia at term. This is because these studies included both children born preterm and those born full-term and included cases with a suggestion of prenatal pathology (e.g. two cases with macrosomy, one associated with maternal diabetes, a condition that may also be associated with hippocampal pathology; see Nelson, Wewerka, Thomas, Tribby-Walbridge, de Reginer & Georgieff, 2000). In addition, these cases were identified by their memory impairment, and asphyxia was only later identified as the probable cause. Thus, it is not clear whether memory impairments are a common outcome following PA.

Two studies have examined groups of adolescents all of whom were born full-term and all of whom had clinical and/or biochemical evidence of PA. The first study (de Haan, Wyatt, Roth, Gadian, Vargha-Khadem & Mishkin, 2002) examined memory abilities in 12 adolescents (12–18 years of age) who had all shown biochemical (base excess in cord blood or arterial blood taken shortly after delivery of less than −15 mmol/L) and/or neurological signs (including fits, abnormal movement and altered tone) of asphyxia at term birth but who had shown no signs of major neurological impairment when followed up at 4 years of age (Roth *et al.*, 1997). Group means fell within the normal range for all cognitive tests including those of intelligence, episodic memory and semantic memory. Only one case, with the lowest hippocampal volumes in the group, showed a cognitive profile that might have been a mild form of developmental amnesia. A subsequent study of 13 cases with an average age of 16 years who showed moderate neonatal encephalopathy found bilateral reduction in hippocampal volumes (size 89% of normal) and impaired delayed, but normal immediate, verbal memory relative to IQ-matched controls (visual memory was not tested; Mañeru, Serra-Grabulosa, Junqué, Salgado-Pineda, Bargalló, Olondo, Botet-Mussons, Tallada & Mercader, 2003; see also Mañeru, Junqué, Botet, Tallada & Guardia, 2001). An additional neuropsychological study of a larger group (28 patients and 28 controls) showed that visual delayed (but not immediate) memory is also impaired along with aspects of frontal lobe function (motor skills, response inhibition and verbal fluency; Mañeru *et al.*, 2001). These findings suggest that impairments in delayed verbal (and possibly visual) memory with intact immediate memory and semantic memory can occur together with hippocampal volume loss as a long-term consequence of PA. However, the severity of the memory impairment and hippocampal volume loss appears milder than in developmental amnesia. Further long-term investigations are needed to more fully understand the nature of memory deficits following PA, the circumstances under which they emerge as a specific problem, and whether they represent a form of developmental amnesia.

Schizophrenia

Schizophrenia, a condition in which a person suffers from distorted thinking, disorganized behaviour, hallucinations and a reduced ability to feel normal emotions, is a chronic and disabling mental disorder affecting about 1% of the population. There is a large literature documenting reductions in hippocampal volume (Antonova, Sharma, Morris & Kumari, 2004) and impairments in hippocampal-mediated cognitive function in schizophrenia (Antonova *et al.*, 2004; Cirillo & Seidman, 2003).[5]

A large body of research links obstetric complications to schizophrenia (e.g. Lewis & Murray, 1987; McNeil, 1995). One meta-analysis of 18 studies (Geddes & Lawrie, 1995) indicates that obstetric complications double the likelihood of developing schizophrenia, with further studies suggesting a particular link with early-onset (~ between 7 and 13 years of age) schizophrenia (Rosso, Cannon, Huttunen, Huttunen, Lonnqvist & Gasperoni, 2000; Van Erp, Saleh, Rosso, Huttunen, Lönqvist, Pirkola, Salonen, Valanne, Poutanen, Standertskjöld-Nordenstam & Cannon, 2002; but see Ordoñez, Bobb, Greenstein, Baker, Sporn, Lenane, Malaspina, Rapaport & Gogtay, 2005). Studies which have examined whether certain types of obstetric complications are specifically implicated have found links with several features including maternal infection and pre-eclampsia (Brown, Begg, Gravenstein, Schaefer, Wyatt, Bresnahan, Babulas & Susser, 2004; Cannon, Jones & Murray, 2002a; Dalman, Allebeck, Cullberg, Grunewald & Koster, 1999; Van Erp *et al.*, 2002), but the most consistent link observed is with hypoxia at birth (Cannon *et al.*, 2002a; Dalman, Thomas, David, Gentz, Lewis & Allebeck, 2001; Rosso *et al.*, 2000; but see Ordoñez *et al.*, 2005). It is important to note, however, that more than 90% of individuals who experienced birth asphyxia do not go on to develop schizophrenia (Cannon *et al.*, 2002b; Rosso *et al.*, 2000).

The link between birth asphyxia and schizophrenia may at least in part be mediated via the hippocampus, as birth asphyxia can result in hippocampal abnormalities (reviewed above) and schizophrenic patients show reductions in hippocampal volume (reviewed in Antonova *et al.*, 2004). However, to date there is still some debate

[5] Other structural abnormalities have also often been reported (reviewed in Antonova *et al.*, 2004; Boog, 2004), but this discussion will focus on hippocampal abnormalities as these have been most consistently studied in relation to the contribution of birth asphyxia in the development of schizophrenia.

as to what extent the hippocampal abnormalities observed in schizophrenia reflect environmental factors such as obstetric complications versus genetic factors. For example, recent evidence suggests that allelic variation within the DISC1 (Disruption-In-Schizophrenia 1) gene increases the risk for schizophrenia by a mechanism involving structural and functional alterations in the hippocampus (Callicott, Straub, Pezawas, Egan, Mattay, Hariri, Verchinski, Meyer-Lindenberg, Balkissoon, Kolachana, Goldberg & Weinberger, 2005). A possibility is that birth asphyxia interacts with schizophrenia susceptibility genes (reviewed in Boog, 2004). In support of this view, one study found an interactive effect whereby hippocampal volumes decreased with increasing genetic load for schizophrenia and this effect was related to birth asphyxia only for those with schizophrenia (Van Erp *et al.*, 2002).

Conclusions and future directions

There are few long-term studies of brain structure or cognitive-behavioural function in survivors of PA. This is in contrast to the relatively larger body of literature examining patterns of brain injury and neurological or general developmental status in infants in the hours to months after an episode of asphyxia. Studies of long-term outcome have largely focused on neurological status and general cognitive and academic progress and have typically not assessed brain structure. These studies do suggest that children with severe or moderate asphyxia (likely reflecting more extensive brain damage) have poorer long-term outcomes than those with mild asphyxia. There is some suggestion from longer-term studies that damage to the hippocampus resulting from PA might contribute to two different outcomes that only become apparent some time afterwards: cognitive memory impairment and the psychiatric disorder schizophrenia. However, it remains unclear how the initial brain injury affects subsequent brain and cognitive-behavioural development and contributes to these outcomes.

The evidence linking PA to memory impairment is preliminary in that there are few studies and relatively small groups have been tested. It is also unclear whether and which additional factors might add to or interact with PA to lead to memory impairments. The observation that memory impairments in children with PA do not appear as severe as those in individuals with developmental amnesia suggests that additional factors may play a role in the emergence of the latter condition. It is also unclear whether the pattern of memory impairment differs if hypoxia occurs at term compared to preterm birth. Memory impairments together with hippocampal volume reduction have also been reported in children who were born preterm and with birth complications including anoxia (Giménez, Junqué, Narberhaus, Caldú, Salgado-Pineda, Bargalló, Segarra & Botet, 2004) or need for prolonged ventilation (Isaacs. Lucas, Chong, Wood, Johnson, Marshall, Vargha-Khadem & Gadian, 2000), and some cases of developmental amnesia experienced asphyxia with preterm birth (Gadian *et al.*, 2000; Vargha-Khadem *et al.*, 1997). No studies to date have directly compared memory skills in relation to brain injury in the two groups.

PA has also been linked to a different long-term outcome, schizophrenia. A large body of literature demonstrates abnormalities in the structure and function of the hippocampus in patients with schizophrenia (Antonova *et al.*, 2004). Moreover recent studies link these abnormalities to PA (Cannon, van Erp, Rosso, Huttunen, Lonnqvist & Pirkola, 2002b; Dalman *et al.*, 2001; Rosso *et al.*, 2000). However, genetic factors also play an important role and may interact with PA to contribute to this outcome (Van Erp *et al.*, 2002). The details of how these factors might interact to contribute to the development of schizophrenia are unclear.

Neither memory impairments nor schizophrenia are apparent immediately following PA but emerge later in childhood. This raises two points for further investigation: (i) identifying the factors mediating the timing of emergence of these impairments and (ii) considering whether precursors of these problems are identifiable earlier in development. While there has been some progress made in this regard with respect to schizophrenia (Rapoport, Addington, Frangou & Psych, 2005), less is known with respect to memory disorders.

Understanding the long-term cognitive-behavioural consequences of PA will be advanced as future studies increasingly begin to include a focus on more specific cognitive and behavioural profiles rather than only more general measures (such as overall neurological status or intelligence scores). Linking these observed outcomes with the pattern of brain injury will rely on advances in neuroimaging methods for accurately quantifying such injuries, as well as an understanding of how, in the developing child, the impact of such acute injuries on brain and cognitive development may evolve over time.

References

American College of Obstetricians and Gynecologists (2004). ACOG Committee opinion #303: Inappropriate use of the terms fetal distress and birth asphyxia. *Obstetrics & Gynecology*, **104**, 903.

Antonova, E., Sharma, T., Morris, R., & Kumari, V. (2004). The relationship between brain structure and neurocognition

in schizophrenia: a review. *Schizophrenia Research*, **70**, 117–145.

Auer, R.N., & Siesjo, B.K. (1999). Biological differences between ischemia, hypoglycaemia and epilepsy. *Annals of Neurology*, **24**, 699–707.

Badawi, N., Kurinczuk, J.J., Keogh, J.M., Alessandri, L.M., O'Sullivan, F., Burton, P.R., Pemberton, P.J., & Stanley, F.J. (1998). Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *British Medical Journal*, **317**, 1554–1558.

Baenziger, O., Martin, E., Steinlin, M., Good, M., Largo, R., Burger, R., Fanconi, S., Duc, G., Buchli, R., & Rumpel, H. (1993). Early pattern recognition in severe perinatal asphyxia: a prospective MRI study. *Neuroradiology*, **35**, 437–442.

Barkovich, A.J. (1992). MR and CT evaluation of profound neonatal and infantile asphyxia. *American Journal of Neuroradiology*, **13**, 959–972.

Barkovich, A.J., & Truwitt, C.L. (1990). Brain damage from perinatal asphyxia: correlation of MR findings with gestational age. *American Journal of Neuroradiology*, **11**, 1087–1096.

Bax, M., & Nelson, K.B. (1993). Birth asphyxia: a statement. World Federation of Neurology Group. *Developmental Medicine and Child Neurology*, **35**, 1022–1024.

Beatty, W.W., Salmon, D.P., Bernstein, N., & Butters, N. (1987). Remote memory in a patient with amnesia due to hypoxia. *Psychological Medicine*, **17**, 657–665.

Blair, E., & Stanley, F.J. (1988). Intrapartum asphyxia: a rare cause of cerebral palsy. *Journal of Pediatrics*, **112**, 515–519.

Boog, G. (2004). Obstetrical complications and subsequent schizophrenia in adolescent and young adult offsprings: is there a relationship? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **114**, 130–136.

Brown, A.S., Begg, M.D., Gravenstein, S., Schaefer, C.A., Wyatt, R.J., Bresnahan, M., Babulas, V.P., & Susser, E.S. (2004). Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Archives of General Psychiatry*, **61**, 774–780.

Cady, E.B. (2001). Magnetic resonance spectroscopy in neonatal hypoxic-ischaemic insults. *Child's Nervous System*, **17**, 145–149.

Caine, D., & Watson, J.D. (2000). Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. *Journal of the International Neuropsychological Society*, **6**, 86–99.

Callicott, J.H., Straub, R.E., Pezawas, L., Egan, M.F., Mattay, V.S., Hariri, A.R., Verchinski, B.A., Meyer-Lindenberg, A., Balkissoon, R., Kolachana, B., Goldberg, T.E., & Weinberger, D.R. (2005). Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proceedings of the National Academy of Sciences, USA*, **104**, 8627–8632.

Campistol, J., Poo, P., Fernandez Alvarez, E., & Carratala, F. (1999). Parasaggital cerebral injury: magnetic resonance findings. *Journal of Child Neurology*, **16**, 299–300.

Cannon, M., Jones, P.B., & Murray, R.M. (2002a). Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry*, **159**, 1082–1092.

Cannon, T.D., van Erp, T.G., Rosso, I.M., Huttunen, M., Lonnqvist, J., Pirkola, T. *et al.* (2002b). Fetal hypoxia and structural brain abnormalities in schizophrenia patients, their siblings and controls. *Archives of General Psychiatry*, **59**, 35–41.

Cirrilo, M.A., & Seidman, L.J. (2003). Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychology Review*, **113**, 43–77.

Coskun, A., Lequin, M., Segal, M., Vigneron, D.B., Ferriero, D.M., & Barkovich, A.J. (2001). Quantitative analysis of MR images in asphyxiated neonates: correlation with neurodevelopmental outcome. *American Journal of Neuroradiology*, **22**, 400–405.

Cowan, F. (2000). Outcomes after intrapartum asphyxia in term infants. *Seminars in Neonatology*, **5**, 127–140.

Cowan, F., Rutherford, M., Groenendaal, F., Eken, P., Mercuri, E., Bydder, G.M., Meiners, L.C., Dubowitz, L.M., & de Vries, L.S. (2003). Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet*, **361**, 736–742.

Cowan, F.M., Pennock, J.M., Hanrahan, J.D., Manji, K.P., & Edwards, A.D. (1994). Early detection of cerebral infarction and hypoxic ischemic encephalopathy in neonates using diffusion-weighted magnetic resonance imaging. *Neuropediatrics*, **25**, 172–175.

Dalman, C., Allebeck, P., Cullberg, J., Grunewald, C., & Koster, M. (1999). Obstetric complications and the risk of schizophrenia: longitudinal study of a national birth cohort. *Archives of General Psychiatry*, **56**, 234–240.

Dalman, C., Thomas, H.V., David, A.S., Gentz, J., Lewis, G., & Allebeck, P. (2001). Signs of asphyxia at birth and risk of schizophrenia: population-based case-control study. *British Journal of Psychiatry*, **179**, 403–408.

de Haan, M., Wyatt, J., Roth, S., Gadian, D., Vargha-Khadem, F., & Mishkin, M. (April, 2002). Effects of birth asphyxia on memory development and hippocampal volume during childhood. Poster presented at the meeting of the Cognitive Neuroscience Society, San Francisco, CA.

Dilenge, M.-E., Majnemer, A., & Shevell, M.I. (2001). Long-term developmental outcome of asphyxiated term neonates. *Journal of Child Neurology*, **16**, 781–792.

Gaffney, G., Flavell, V., Johnson, A., Squier, M., & Sellers, S. (1994). Cerebral palsy and neonatal encephalopathy. *Archive of Diseases in Childhood*, **70**, F195–F200.

Gadian, D.G., Aicardi, J., Watkins, K.E., Porter, D.A., Mishkin, M., & Vargha-Khadem, F. (2000). Developmental amnesia associated with early hypoxic-ischaemic injury. *Brain*, **123**, 499–507.

Gale, S.D., & Hopkins, R.O. (2004). Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. *Journal of the International Neuropsychological Society*, **10**, 60–71.

Geddes, J.R., & Lawrie, S.M. (1995). Obstetric complications and schizophrenia: a meta-analysis. *British Journal of Psychiatry*, **167**, 786–793.

Giménez, M., Junqué, C., Narberhaus, A., Caldú, X., Salgado-Pineda, P., Bargalló, Segarra, D., & Botet, F. (2004).

Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. *Neuroimage*, **23**, 869–877.

Hill, A. (1991). Current concepts of hypoxic-ischemic cerebral injury in the term newborn. *Pediatric Neurology*, **7**, 317–325.

Hunt, R.W., Neil, J.J., Coleman, L.T., Kean, M.J., & Inder, T.E. (2004). Apparent diffusion coefficient in the posterior limb of the internal capsule predicts outcome after perinatal asphyxia. *Pediatrics*, **114**, 999–1003.

Isaacs, E.B., Lucas, A., Chong, W.K., Wood, S.J., Johnson, C.L., Marshall, C., Vargha-Khadem, F., & Gadian, D.G. (2000). Hippocampal volume and everyday memory in children of very low birthweight. *Pediatric Research*, **47**, 713–720.

Isaacs, E., Vargha-Khadem, F., Watkins, K.E., Lucas, A., Mishkin, M., & Gadian, D.G. (2003). Developmental amnesia and its relationship to degree of hippocampal atrophy. *Proceedings the National Academy of Sciences*, *USA*, **100**, 13060–13063.

Kuenzle, C., Baenziger, O., Martin, E., Thun-Hohenstein, L., Steinlin, M., Good, M., Fanconi, S., Boltshauser, E., & Largo, R.H. (1994). Prognostic value of early MR imaging in term infants with severe perinatal asphyxia. *Neuropediatrics*, **25**, 191–200.

L'Abee, C., de Vries, L.S., van der Grond, J., & Groenendaal, F. (2005). Early diffusion-weighted MRI and 1H-magnetic resonance spectroscopy in asphyxiated full-term neonates. *Biology of the Neonate*, **88**, 306–312

Lewis, S.W., & Murray, R.M. (1987). Obstetric complications, neurodevelopmental deviance and risk of schizophrenia. *Journal of Psychiatric Research*, **21**, 413–421.

Low, J.A. (1993). Relationship of fetal asphyxia to neuropathology and deficits in children. *Clinical and Investigative Medicine*, **16**, 133–140.

Low, J.A., Galbraith, R.S., Muir, D.W., Killen, H.I., Pater, E.A., & Karchmar, E.J. (1988). Motor and cognitive deficits after intrapartum asphyxia in the mature fetus. *American Journal of Obstetrics & Gynecology*, **158**, 356–361.

Malik, G.K., Pandey, M., Kumar, R., Chawla, S., Rathi, B., & Gupta, R.K. (2002). MR imaging and in vivo proton spectroscopy of the brain in neonates with hypoxic-ischemic encephalopathy. *European Journal of Radiology*, **43**, 6–13.

Mañeru, C., Junqué, C., Botet, F., Tallada, M., & Guardia, J. (2001). Neuropsychological long-term sequelae of perinatal asphyxia. *Brain Injury*, **15**, 1029–1039.

Mañeru, C., Serra-Grabulosa, J.M., Junqué, C., Salgado-Pineda, P., Bargalló, N., Olondo, M., Botet-Mussons, F., Tallada, M., & Mercader, J.M. (2003). Residual hippocampal atrophy in asphyxiated term neonates. *Journal of Neuroimaging*, **13**, 68–74.

McNeil, T.F. (1995). Perinatal risk factors and schizophrenia: a selective review and methodological concerns. *Epidemiologic Reviews*, **17**, 107–112.

Marlow, N., Rose, A.S., Rands, C.E., & Draper, E.S. (2005). Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, **90**, 380–387.

Miller, S.P., Ramaswamy, V., Michelson, D., Barkovich, J., Holshouser, B., Wyclifee, N., Glidden, D.V., Deming, D., Partridge, J.C., Wu, Y.W., Ashwal, S., & Ferrrero, D.M. (2005). Patterns of brain injury in term neonatal encephaolopathy. *Journal of Pediatrics*, **146**, 453–460.

Mishkin, M., Suzuki, W.A., Gadian, D.G., & Vargha-Khadem, F. (1997). Hierarchical organization of cognitive memory. *Philosophical Transactions of the Royal Society of London*, *B Biological Sciences*, **352**, 1461–1467.

Natsume, J., Watanabe, K., Kuno, K., Havakawa, F., & Hashizume, Y. (1995). Clinical, neurophysiologic, and neuropathological features of an infant with brain damage of total asphyxia type (Myers). *Pediatric Neurology*, **13**, 61–64.

Nelson, C.A., Wewerka, S., Thomas, K.M., Tribby-Walbridge, S., de Regnier, R.A., & Georgieff, M.K. (2000). Neurocognitive sequelae of infants of diabetic mothers. *Behavioural Neuroscience*, **114**, 950–956.

O'Reilly, S.M., Grubb, M.R., & O'Carroll, R.E. (2003). In-hospital cardiac arrest leads to chronic memory impairment. *Resuscitation*, **58**, 73–79.

Ordoñez, A.E., Bobb, A., Greenstein, D., Baker, N., Sporn, A., Lenane, M., Malaspina, D., Rapaport, J., & Gogtay, N. (2005). Lack of evidence for elevated obstetric complications in childhood onset schizophrenia. *Biological Psychiatry*, **58**, 10–15.

Parkin, A.J., Miller, J., & Vincent, R. (1987). Multiple neuropsychological deficits due to anoxic encephalopathy: a case study. *Cortex*, **23**, 655–665.

Pasternak, J.F., & Gorey, M.T. (1998). The syndrome of acute near-total intrauterine asphyxia in the term infant. *Pediatric Neurology*, **18**, 391–398.

Pasternak, J.F., Predey, T.A., & Mikhael, M.A. (1991). Neonatal asphyxia: vulnerability of basal ganglia, thalamus and brainstem. *Pediatric Neurology*, **7**, 147–149.

Phelan, J.P., Martin, G.I., & Korst, L.M. (2005). Birth asphyxia and cerebral palsy. *Clinics in Perinatology*, **32**, 61–76.

Pierrat, V., Haouari, N., Liska, A., Thomas, D., Subtil, D., Truffert, P., on behalf of the Groupe d'Etudes en Epidemiologie Perinatale (2005). Prevalence, causes and outcomes at 2 years of age of newborn encephalopathy: a population-based study. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, **90**, 257–261.

Quamme, J.R., Yonelinas, A.P., Widaman, K.F., Kroll, N.E., & Sauve, M.J. (2004). Recall and recognition in mild hypoxia: using covariance structural modeling to test competing theories of explicit memory. *Neuropsychologia*, **42**, 672–691.

Rademakers, R.P., van der Knaap, M.S., Verbeeten, B. Jr., Barth, P.G., & Valk, J. (1995). Central cortico-subcortical involvement: a distinct pattern of brain damage caused by perinatal and postnatal asphyxia in term infants. *Journal of Computer Assisted Tomography*, **19**, 256–263.

Rapoport, J.L., Addington, A.M., Frangou, S., & Psych, M.R. (2005). The neurodevelopmental model of schizophrenia: update 2005. *Molecular Psychiatry*, **10**, 434–449.

Robertson, C.M., & Finer, N.N. (1993). Long-term follow-up of term neonates with perinatal asphyxia. *Clinics in Perinatology*, **20**, 483–500.

Robertson, C.M., Finer N.N., & Grace, M.G. (1989). School performance of survivors of neonatal encephalopathy

associated with birth asphyxia at term. *Journal of Pediatrics*, **114**, 753–760.

Roland, E.H., Hill, A., Norman, M.G., Flodmark, O., & MacNab, A.J. (1988). Selective brainstem injury in an asphyxiated newborn. *Annals of Neurology*, **23**, 89–92.

Roland, E.H., Poskitt, K., Rodriguez, E., Lupton, B.A., & Hill, A. (1998). Perinatal hypoxic-ischemic thalamic injury: clinical features and neuroimaging. *Annals of Neurology*, **44**, 161–166.

Rosso, I.M., Cannon, T.D., Huttunen, T., Huttunen, M.O., Lonnqvist, J., & Gasperoni, T.L. (2000). Obstetric risk factors for early-onset schizophrenia in a Finnish birth cohort. *American Journal of Psychiatry*, **157**, 801–807.

Roth, S.C., Baudin, J., Cady, E., Johal, K., Townsend, J., Wyatt, J.S., Reynolds, E.O.R., & Stewart, A.L. (1997). Relation of deranged neonatal cerebral oxidative metabolism with neurodevelopmental outcome and head circumference at 4 years. *Developmental Medicine and Child Neurology*, **39**, 718–725.

Roth, S.C., Edwards, A.D., Cady, E.B., Delpy, D.T., Wyatt, J.S., Azzopardi, D., Baudin, J., Townsend, J., Stewart, A.L., & Reyonolds, E.O. (1992). Relation between cerebral oxidative metabolism following birth asphyxia, and neurodevelopmental outcome and brain growth at one year. *Developmental Medicine and Child Neurology*, **34**, 385–395.

Rutherford, J.A., Pennock, J.M., Counsell, S.J., Mercuri, E., Cowan, F.M., Dubowitz, L.M., & Edwards, A.D. (1998). Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. *Pediatrics*, **102**, 323–328.

Sarnat, H.B., & Sarnat, M.S. (1976). Neonatal encephalopathy following fetal distress. *Archives of Neurology*, **33**, 696–705.

Sie, L.T.L., van der Knapp, M.S., Oosting, J., de Vries, L.S., Lafeber, H.N., & Valk, J. (2000). MR patterns of hypoxic-ischemic brain damage after prenatal, perinatal or posnatal asphyxia. *Neuropediatrics*, **31**, 128–136.

Soul, J.S., Robertson, R.L., Tzika, A.A., du Plessis, A.J., & Volpe, J.J. (2001). Time course of changes in diffusion-weighted magnetic resonance imaging in a case of neonatal encephalopathy with defined onset and duration of hypoxic-ischemic insult. *Pediatrics*, **108**, 1211–1214.

Squier, W., & Cowan, F. (2004). The value of autopsy in determining the cause of failure to respond to resuscitation at birth. *Seminars in Neonatology*, **9**, 331–345.

Thornberg, E., Thiringer, K., Odeback, A., & Milsom, I. (1995). Birth asphyxia: incidence, clinical course and outcome in a Swedish population. *Acta Paediatrica*, **84**, 927–932.

Van Erp, T.G., Saleh, P.A., Rosso, I.M., Huttunen, M., Lönqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutanen, V.P., Standerskjold-Nordenstam, C.G., & Cannon, T.D. (2002). Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. *American Journal of Psychiatry*, **159**, 1514–1520.

Vannucci, R.C., & Perlman, J.M. (1997). Interventions for hypoxic-ischemic encephalopathy. *Pediatrics*, **100**, 1004–1014.

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*, **277**, 376–380.

Vargha-Khadem, F., Salmond, C.H., Watkins, K.E., Friston, K.J., Gadian, D.G., & Mishkin, M. (2003). Developmental amnesia: effect of age at injury. *Proceedings of the National Academy of Sciences, USA*, **100**, 10055–10060.

Voit, T., Lemburg, P., Neuen, E., Lumenta, C., & Stork, W. (1987). Damage of thalamus and basal ganglia in asphyxiated full-term neonates. *Neuropediatrics*, **18**, 176–181.

Volpe, B.T., & Petito, C.K. (1985). Dementia with bilateral medial temporal lobe ischemia. *Neurology*, **35**, 1793–1797.

Volpe, J.J., Herscovitch, P., Perlman, J.M., Kreusser, K.L., & Raichle, M.E. (1985). Positron emission tomography in the asphyxiated term newborn: parasaggital impairment of cerebral blood flow. *Annals of Neurology*, **17**, 287–296.

Westmark, K.D., Barkovich, A.J., Sola, A., Ferriero, D., & Partridge, J.C. (1995). Patterns and implications of MR contrast enhancement in perinatal asphyxia: a preliminary report. *American Journal of Neuroradiology*, **16**, 685–692.

Wyatt, J.S., Edwards, A.D., Azzopardi, D., & Reynolds, E.O. (1989). Magnetic resonance and near infrared spectroscopy for investigation of perinatal hypoxic-ischaemic brian injury. *Archives of Disease in Childhood*, **64**, 953–963.