The role of spectral edge frequency monitoring in neonatal intensive care

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Abstract

Conventional multi-channel electroencephalograms (EEGs) may assist with outcome prediction in newborn infants, but are often logistically difficult and require specialist interpretation. Cotside EEGs using reduced numbers of electrodes generate quantitative parameters such as spectral edge frequency (SEF), but it is not yet clear if these are clinically useful.

The aim of our studies was to test the hypothesis that SEF and other quantitative parameters obtained from two channel cotside EEGs in preterm infants and term infants at risk of seizures predict long-term neurodevelopmental outcome.

We recruited 120 preterm infants <32 weeks gestation. SEF from early cotside EEGs did not predict outcome. However continuity measures were weakly related to motor development at 18 months. There were weak relationships between early quantitative neurophysiological parameters and early illness severity scores, cranial ultrasound scans and pre-discharge neurological examinations. A neurophysiologist reviewing the two channel raw EEG predicted outcome slightly more accurately than the continuity measures.

In normal preterm infants there was a characteristic pattern of changes in EEG parameters after birth, with the SEF patterns suggesting delayed maturation in the most immature infants. Low cerebral blood flow and low blood pressure in the first 48 hours were associated with changes in EEG parameters that persisted for some hours after the cardiovascular perturbations. Surfactant administration and opiate boluses were associated with reduced EEG continuity.

We recruited 24 term infants with, or at risk of, clinical seizures. The background amplitude-integrated (a)EEG pattern was the best EEG predictor of neurodevelopmental outcome. However, magnetic resonance imaging was a better predictor than either cotside or conventional EEG. When convalescent cotside and conventional EEGs were compared, there was moderate agreement between the neurophysiologist's report on the conventional EEG and the background pattern of the aEEG, but not between assessments of sleep state cycling.

Our data suggest that two channel cotside EEGs are not clinically useful for outcome prediction in preterm infants, but can assist in term infants. Future software development may increase their clinical utility. Cotside EEGs may also provide useful information regarding changes in neurophysiology after birth, cerebral responses to clinical interventions and postnatal cortical maturation in preterm infants.

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I have given much thought to this section of my thesis. In many ways it seems the most important section, and such a small place to thank the many people who helped me reach this point.

I have decided to use first name alphabetical order – as how can a student rank one person's input over another's? A small comment at a dinner table may be the turning point of a discussion, a comment over a poster at a conference may lead to another line of questioning…. The people named here are those whose names I recall – there are many unnamed, and to those I apologise for not acknowledging their immense input. I want to thank all those who listened to my thoughts, smiled at me as I pushed my machines down the corridors, and of course those who handed me tissues…without you I could never have made it through this process.

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1 Literature Review

1.1 Outcome for infants admitted to Neonatal Intensive Care Units

Parents hope to have a normal, healthy infant who grows and develops into a child, and subsequently an adult, who enjoys good health in the widest definition. While this outcome can never be guaranteed, there are groups of infants who are at increased risk of falling short of this goal.

Infants admitted for neonatal intensive care treatment are at increased risk of death and long-term neurodevelopmental disability. There are a wide range of disabilities which may be increased such as mental deficiency, tone and motor problems including cerebral palsy, vision and hearing impairments, learning difficulties and behavioural problems. The increased morbidity occurs over the entire spectrum of infants admitted, but is particularly marked in extremely premature infants and in term infants suffering from neonatal encephalopathy. Certain other groups of infants are also at increased risk such as those with congenital anomalies and those with chromosomal defects.

Outcome can be measured at a number of time points. Each point provides unique information relevant to a particular group of infants. Knowledge about these outcome measures is invaluable to the medical staff. It can be used when counselling parents whose infant may be delivered prematurely and, subsequently, during the course of an infant's hospitalisation and follow-up. Relevant outcome measures for a population of neonates include:

- Number of infants born alive at a particular gestational age or birthweight;
- Survival to Neonatal Intensive Care Unit (NICU) admission;
- Survival to NICU discharge;

- Survival to NICU discharge with normal newborn neurodevelopmental examination;
- Survival to 18 months with normal neurodevelopmental examination (intact survival);
- Intact survival to adolescence; and
- Intact survival, including normal educational and behavioural outcomes, to adulthood.

While information can be presented for the entire spectrum of infants admitted to the neonatal unit, it is more informative to break down the data into more homogeneous groupings. The data are frequently presented in groups related to gestational age, birthweight categories or major diagnosis such as neonatal encephalopathy.

When attempting to interpret outcome data it is important to be aware of the source of certain apparent inconsistencies within the literature. Firstly, as noted above, there are a number of ways of categorising the data. At the extreme ends of viability the data set is usually broken down into groups based on gestational age (usually in completed weeks measured from the start of the last menstrual period) or birthweight (Hack & Fanaroff, 2000), resulting in two slightly different, but overlapping, sets of data. Using gestational age is valuable to ensure infants with similar organ maturity are being compared. However the estimation of gestational age is dependent on accurate data from last menstrual period, early ultrasound scanning or clinical examination after birth. It is known that these estimates may be up to two weeks out in their evaluation of gestational age. In contrast, birthweight can be accurately determined but there is a distribution of weight at each gestational age. Thus, a female infant with a birthweight of 700g may represent an average 24 week infant (50^{th} centile), a large for gestational age 22 week infant (97^{th} centile), or a growth restricted 29 week infant (3^{rd} centile). Unfortunately birthweight cannot be accurately predicted before birth and therefore this information is not available when counselling parents antenatally.

The second source of inconsistency in the literature arises from the fact that information regarding outcomes in extremely premature infants involves

relatively small numbers of infants. Thus results from one institution may not be stable over time. Studies of infants from a whole country include more infants, but different management strategies in different units may influence outcomes. Studies from larger institutions and regional studies have the benefit of increased numbers and are more likely to reflect similar practices, but still need to have data collected over several years to provide adequate numbers.

The third source of inconsistency is that neonatal intensive care is a rapidly evolving field. Over relatively short time periods new treatment modalities are introduced and these changes may have substantial impact on outcome measures. Reports comparing outcomes in time periods before and after these changes have been instituted can assist in determining the extent of this impact (Doyle, Anderson, & Victorian Infant Collaborative Study, 2005; Doyle, Betheras, Ford, Davis, & Callanan, 2000). However, subtle changes of practice are regularly occurring and these may have just as large an impact as the more obvious changes.

The fourth source of inconsistency is the different definitions of disability. This difference can be illustrated by comparing the definitions used for mild disability. In the National Women's Hospital Annual Clinical Report (Knight & Kuschel, 2005) mild disability, category III, was defined as presence of a tone or motor disorder, but adjusted Mental score within the average range. A motor disorder is defined as a Bayley Motor Score more than one standard deviation below the mean. In comparison Doyle's Melbourne study of follow-up at 14 years of age(Doyle, Casalaz, & The Victorian Infant Collaborative Study, 2001) defined mild disability as one of the following:

1. Ambulatory cerebral palsy with minimal limitation of movement; or
2. Intelligence Quotient (IQ) between one and two standard deviations below the mean for the normal birthweight control participants using Full, Verbal and Performance Scales of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R).

Thus, mild cerebral palsy without cognitive delay is classified as mild disability in the Melbourne study but moderate disability in the National Women's Annual

Report (Knight & Kuschel, 2005). In the following discussion adverse neurodevelopmental outcome is presented as a single quantity at each level of severity. However, within each level of severity there are more infants with mental deficiency than infants with tone or motor abnormalities. In addition, the most severely disabled infants tend to have multiple disabilities.

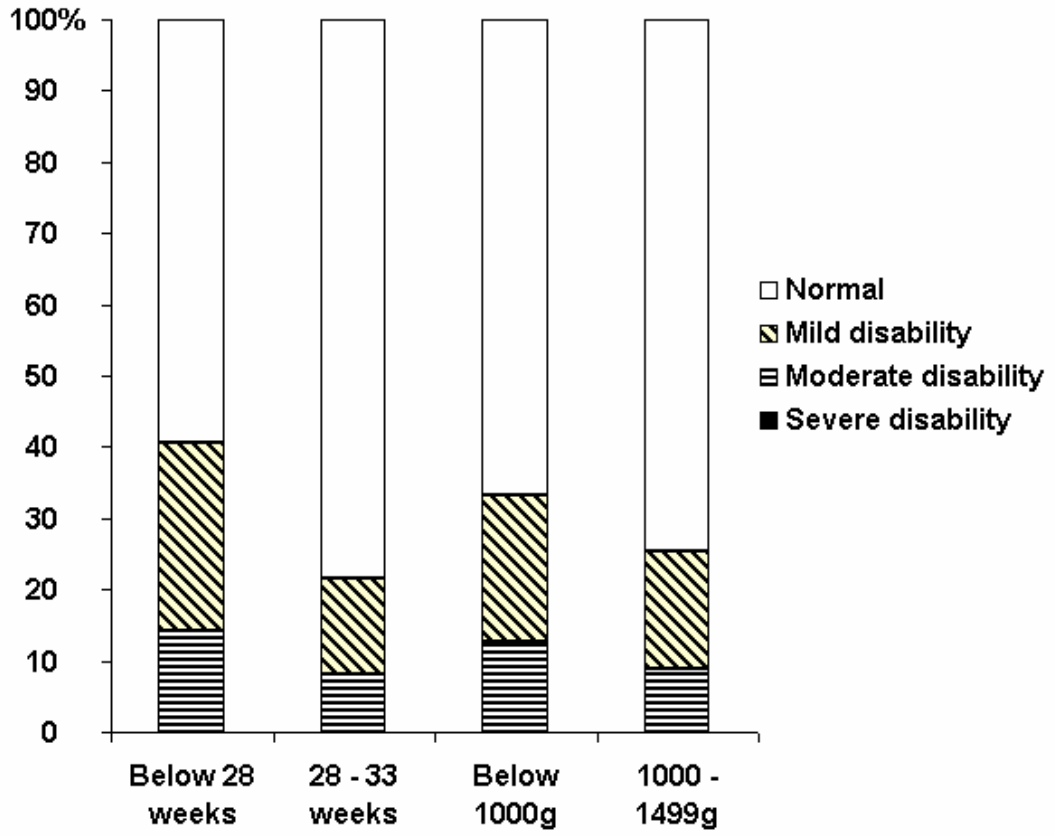
Finally, length of follow-up will influence reported outcomes. Tone and motor abnormalities are not static over childhood. They do, however, become more stable as the infants grow older (Doyle et al., 2001; Doyle & Victorian Infant Collaborative Study, 2001). Diagnosing cerebral palsy before the age of five years can be difficult and there can be changes in motor handicap over time in some children (Ford, Kitchen, Doyle, Rickards, & Kelly, 1990; Ross, Lipper, & Auld, 1985; Stanley, 1982), whereas from five years of age the diagnosis becomes more stable. Similarly, the accuracy of categorisation of educational ability levels improves with increasing the age at follow-up, and determination of behavioural problems will benefit from regular assessment throughout childhood, and indeed into adolescence. However, as the length of follow-up increases there are increasing problems related to more individuals being lost to follow-up and decreasing relevance of the results to current practice (Doyle et al., 2001).

As there is a substantial body of literature available regarding outcome, with a range of outcome data, this review will focus on the results from five reports to present a rounded perspective. The data will be presented according to gestational age groups, and subsequently by birthweight groups as not all data are broken down into both categories.

The first report on outcome is National Women's Health Annual Clinical Report 2004 (Knight & Kuschel, 2005). This report provides local data, relevant to the population of infants we are studying, according to both gestational age and birthweights (figure 1-1). Data are collected on all infants admitted to the NICU, with detailed information on morbidity, mortality and outcome. Although the report is limited in numbers as it reports outcomes from a single unit, it should be noted that National Women's Health has one of the largest NICUs in the

Australian and New Zealand Neonatal Network (ANZNN) (Abeywardana, 2005). The criteria used for outcome categories in the National Women's Health Annual Clinical Reports are shown below (table 1-1).

Figure 1-1
Neurodevelopmental outcome at 18 months for infants cared for in National Women's Hospital Neonatal Intensive Care Unit in 2002.



A second report provides a New Zealand national perspective (Darlow, Horwood, N, & RS, 1997) on long-term follow-up of a cohort of very low birthweight (<1500grams) NICU graduates from 1986. All infants with a birthweight of less than 1500 grams admitted to neonatal units throughout New Zealand in 1986 were part of a prospective audit of acute retinopathy of prematurity. When they reached seven to eight years of age their parents were invited to participate in a study to determine sensorineural outcome. Of survivors resident in New Zealand 96% were assessed. However, infants studied were treated more than 15 years ago and there have been a number of substantial practice changes occurring since this cohort was treated.

Table 1-1
Outcome categories for infants under 30 months of age used at National Women's Health

Category of disability	Definition
Severe	One or more of the following: (i) Sensorineural deafness (requiring hearing aids) (ii) Bilateral blindness (iii) Severe cerebral palsy (iv) Developmental delay (Bayley Mental Score 2 or more standard deviations below the mean)
Moderate	One or more of the following: (i) Bayley Mental Score between 1 & 2 standard deviations below the mean (ii) Mild-moderate cerebral palsy without developmental (cognitive) delay (iii) Impaired vision requiring spectacles
Mild	Presence of tone disorder or motor delay Bayley Motor Score more than 1 standard deviation below the mean but adjusted Mental score within average range
Nil	Normal development: (i) No apparent tone disorder, and (ii) No apparent developmental delay (Bayley Mental and Motor Scores within average range or above)

From 2004 National Women's Health Annual Clinical report(Knight & Kuschel, 2005)

A second report provides a New Zealand national perspective (Darlow, Horwood, N, & RS, 1997) on long-term follow-up of a cohort of very low birthweight (<1500grams) NICU graduates from 1986. All infants with a birthweight of less than 1500 grams admitted to neonatal units throughout New Zealand in 1986 were part of a prospective audit of acute retinopathy of prematurity. When they reached seven to eight years of age their parents were invited to participate in a study to determine sensorineural outcome. Of survivors resident in New Zealand 96% were assessed. However, infants studied were treated more than 15 years ago and there have been a number of substantial practice changes occurring since this cohort was treated.

A third report is the 2003 report of ANZNN (Abeywardana, 2005). This provides complete survival data from all Australian and New Zealand neonatal nurseries for infants who were born at less than 32 completed weeks' gestation, or less than 1500 grams birthweight, or those who received assisted ventilation for four or more hours or received major surgery. It is a large, complete data set but lacks information about outcomes beyond discharge.

A fourth set of reports are from Melbourne, Australia (Doyle, Anderson et al., 2005; Doyle et al., 2001; Doyle & Victorian Infant Collaborative Study, 2001). These reports provide complete, relevant, population-based data from this region. Data are provided for long-term outcomes and include information about relevant practice changes including use of antenatal corticosteroid therapy.

A final report is the EPICure study (Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000) from the United Kingdom and Republic of Ireland. This gives recent data regarding outcomes of infants up to 25 weeks completed gestation. This study provides the most up-to-date complete national data set for these very small infants with the outcome data provided for assessment at a median corrected age of 30 months (Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000) and at six years (Marlow, Wolke, Bracewell, Samara, & Group, 2005).

1.1.1 Outcome for infants born up to 24 weeks completed gestation

Infants born before 24 weeks completed gestation are at the current limit of viability. It is difficult to obtain information about numbers of deaths in labour. There is more information about numbers of infants born alive, those who die in the delivery room and those admitted to the NICU. At this gestation 38% of liveborn infants were admitted for intensive care at National Women's Health (Knight & Kuschel, 2005). The Melbourne data showed an admission rate of 46% (Doyle & Victorian Infant Collaborative Study, 2001) and the EPICure study 51% (Costeloe et al., 2000).

Not all infants admitted to NICU survive until discharge, particularly at the lower gestational ages and birthweight. National Women's Health data (Knight &

Kuschel, 2005) showed 33% of infants admitted in this gestational age group survived to discharge. The ANZNN (Abeywardana, 2005) and Melbourne data (Doyle & Victorian Infant Collaborative Study, 2001) showed similar rates of survival to discharge of 55 and 46%, respectively. However, the EPICure study had lower rates of survival with only 23% of infants admitted being discharged alive (Costeloe et al., 2000).

Information about the numbers of infants discharged with normal neurodevelopmental examinations at around term corrected gestation is currently lacking.

At 18 months corrected postnatal age the survival figures are similar to those at discharge from NICU. A small number of the survivors will have died in the interim. National Women's data, grouped to include all infants born at less than 28 weeks completed gestation, indicates that severe disability is found in none of the survivors tested (figure 1-1). Moderate levels of disability were found in 14% and mild disability in 26% of those assessed. No disability was detected in 60% of infants assessed (Knight & Kuschel, 2005). In contrast, the National Women's Health 2001 – 2003 report shows that 8% of infants under 28 weeks had severe disability, 16% had moderate disability, 21% had mild disability and 55% had no disability (Knight & Kuschel, 2004). This illustrates the inconsistency of results obtained from single institutions over short time periods due to the relatively small numbers of infants studied at any one time.

Less information is available regarding later follow-up. The reported outcome from the Melbourne regional cohort at five years of age (Doyle & Victorian Infant Collaborative Study, 2001) showed 65% of infants discharged home survived to five years without major disability. In the EPICure study 78% of surviving infants were assessed at six years (Marlow, Wolke et al., 2005). Of the 97 infants born before 25 weeks gestation who were assessed at six years 13% had no disability, 33% had mild disability, 26% moderate disability and 28% severe disability (Marlow, Wolke et al., 2005).

1.1.2 Outcome for infants born between 25 and 27 weeks completed gestation

As gestational age increases there is a general trend for each of the outcome measures to improve. This is most marked at the earliest viable gestational ages. National Women's Health data show that 100% of infants born between 25 and 27 weeks completed gestation are admitted to NICU (Knight & Kuschel, 2005). The Melbourne report (Doyle & Victorian Infant Collaborative Study, 2001) shows an admission rate of 97% while the EPICure study (Costeloe et al., 2000) has a similar rate of 92% for infants born at 25 weeks gestation. Rates of survival to discharge are also improved with a survival rate for admitted infants of 89% for National Women's Health data, over 85% for ANZNN data, 73% for the Melbourne data and 52% for the EPICure study.

Outcome data from the National Women's Hospital are outlined above, with data combined for all infants born at gestations less than 28 completed weeks (figure 1-1). At five years of age the Melbourne study found 72% of infants assessed to be free of major disability (Doyle & Victorian Infant Collaborative Study, 2001). At six years of age the EPICure study found 24% of infants born at 25 weeks gestational age had no disability (Marlow, Wolke et al., 2005).

1.1.3 Outcome for infants born between 28 and 31 weeks completed gestation

For infants born at these gestational ages the majority of live born infants are admitted to NICU, 97% from National Women's Health 2004 data (Knight & Kuschel, 2005). Survival to discharge remains consistently high at 98% of infants admitted at National Women's Health, 97% for ANZNN data (Abeywardana, 2005).

Neurodevelopmental examinations performed at 18 months of age showed that at gestations between 28 and 35 weeks no infants had severe disability, 8% moderate disability and 13% mild disability (figure 1-1) (Knight & Kuschel, 2005). Data from the 2001 – 2003 report from National Women's Health showed that for infants born between 28 and 36 weeks gestation 3% had severe disability, 7% had moderate disability, 13% had mild disability and 77%

had no disability when examined at 18 months chronological age (Knight & Kuschel, 2004).

1.1.4 Outcome for infants born between 32 and 36 weeks completed gestation

As infants approach term they continue to have high survival rates to discharge from hospital. The admission rate to NICU actually declines below the discharge rate from the hospital as not all infants at 35 to 36 weeks gestation require admission to the NICU. National Women's data shows that only 53% of infants born alive at these gestations were admitted to NICU, ranging from 100% of infants born at 33 weeks to 28% at 36 weeks (Knight, 2005). However 99% of liveborn infants at these gestations who required admission to NICU were discharged home alive (Knight & Kuschel, 2005). The ANZNN report shows that 96% of infants born at this gestation who fulfil the criteria for this database (only those who needed assisted ventilation or major surgery would qualify at this gestation) survived to discharge (Abeywardana, 2005).

1.1.5 Outcome for infants born with birthweight below 1000g

The improved outcome seen with increasing gestational age is also demonstrated with increasing birthweight. Data from National Women's Health (Knight & Kuschel, 2005) for infants born weighing less than 1000 grams shows that 80% are admitted for NICU care and 92% of those admitted survive to discharge home. ANZNN data (Abeywardana, 2005) show a similar rate of survival to discharge for this weight range of 80%. The New Zealand national cohort did not report survival to discharge for infants with birthweight less than 1000g separately, but 82% of the entire study group survived to discharge (Darlow et al., 1997).

Neurodevelopmental outcome of infants assessed at 18 months at National Women's Health (Knight & Kuschel, 2005) shows that of 39 infants assessed none had severe disability, 13% had moderate disability, 20% had mild disability and 67% had no disability (figure 1-1).

Out of the New Zealand national cohort neurodevelopmental data was available for 79 children alive in New Zealand whose parents accepted assessment (92%

of all survivors born at less than 1000 grams) (Darlow et al., 1997). Severe disability was found in 9%, moderate disability in 4%, mild disability in 16% and no disability was found in 71% of those evaluated.

The Melbourne group reported outcome at eight and 14 years for infants born at less than 1000g (mean gestational age 27 weeks) (Doyle, Anderson et al., 2005; Doyle et al., 2001). Of 89 infants born in 1979 – 80, 87 (98%) were followed up at eight years (Doyle, Anderson et al., 2005). Severe neurological disabilities were found in 14%, moderate disabilities in 12% and mild disabilities in 32%. Of 88 infants from the 1979 – 80 cohort alive at 14 years, 79 were assessed (90% of all survivors) (Doyle et al., 2001). Severe neurosensory disabilities were found in 14% of surviving infants. A further 15% had moderate and 25% had mild disabilities detected. Cerebral palsy was found in 10% of those tested (severe in 2.5%), blindness in 6%, deafness in 5% and intellectual impairment (verbal intelligence quotient more than one standard deviation below the mean) in 46% of those tested.

1.1.6 Outcome for infants born with birthweight between 1000g and 1499g

The outcome for infants with birthweights between 1000 and 1499g was better than that for infants with lower birthweights, with National Women's Health showing an admission rate of 97% of liveborn infants, 93% of whom were discharged home (Knight & Kuschel, 2005). ANZNN reports 95% survival of infants admitted at these weights (Abeywardana, 2005).

Neurdevelopmental outcome of infants assessed at 18 months at National Women's Health (Knight & Kuschel, 2005) shows that of 91 infants assessed none had severe disability, 9% moderate disability, 16% mild disability and 75% without disability (see figure 1-1).

In report on the New Zealand national cohort 221 children with birthweights between 1000 and 1499g were assessed at between seven and eight years (91% of survivors). Severe disability was found in 4%, moderate disability in 5%, mild disability in 15% and no disability in 76% of those tested (Darlow et al., 1997).

Long-term outcome data for extremely premature infants is sparse. Hack (Hack et al., 2002) reported outcomes in young adulthood for very low birthweight infants (birth weight < 1500g, mean gestational age at birth 29 weeks). She reported a lower mean intelligence quotient, lower academic achievement scores and higher rates of neurosensory impairments, and subnormal height in the preterm infants when compared with normal birth weight controls. Men in the very low birthweight group were significantly less likely to be enrolled in post-secondary educational study. The preterm infants also had less alcohol and drug use and lower rates of pregnancy at 20 year of age normal birthweight controls (Hack et al., 2002). Cooke (Cooke, 2004) reported outcomes of a cohort of very low birthweight preterm infants without major disability at 19 – 22 years. He also found that the preterm infants had fewer further education qualifications, lower alcohol intake and were shorter and lighter than normal birthweight controls. While preterm infants were more likely to be living at home, they had similar levels of social interaction and sexual activity (Cooke, 2004).

1.1.7 Other factors known to impact outcome

There are many factors other than birthweight and gestation that can influence the outcome of premature infants.

Adverse neonatal outcome, including cerebral palsy in both preterm and term infants, has been linked to clinical and histologic chorioamnionitis and elevated amniotic fluid and umbilical cord plasma interleukin-6 levels (Wu et al., 2003; Yoon et al., 2000; Yoon et al., 1996).

Socio-economic status also influences neurodevelopmental outcome. Its impact is less in the first year but increases over the subsequent years (Dezoete & MacArthur, 2000; Weisglas-Kuperus, Baerts, Smrkovsky, & Sauer, 1993). At five years of age Fawer (Fawer, Besnier, Forcada, Buclin, & Calame, 1995) showed by multiple regression analysis that socio-economic status was the most important factor affecting the General Intellectual Index. The authors

concluded that as children grow older environmental factors seem to overshadow perinatal factors.

The use of antenatal steroids to increase lung maturation in premature infants results in a significant reduction in mortality, respiratory distress syndrome and intraventricular haemorrhage (Crowley). There is no evidence of this treatment causing neurodevelopmental abnormality, despite increasing the survival of lower gestational age infants and concerns related to brain growth. Follow-up of infants treated with antenatal steroids and control infants at 36 months (Collaborative Group on Antenatal Steroid Therapy, 1984) and four years (MacArthur, Howie, Dezoete, & Elkins, 1981) showed no treatment effect on developmental outcomes. Further assessment of the second group at six years of age (MacArthur, Howie, Dezoete, & Elkins, 1982) showed that, after careful matching, steroid treated infants scored lower than control infants in only one of the battery of cognitive tests administered. One study followed up subjects at 20 years of age (Dessens, Haas, & Koppe, 2000) and showed that one course of antenatal steroids does not have adverse effects on general health and sexual development. The results from thirty year follow-up of the adult offspring whose mothers took part in the original trial of antenatal steroids have recently been published. These have shown that prenatal exposure to a single course of betathasone does not affect adult quality of life, cognitive functioning, psychiatric morbidity (Dalziel, Lim et al., 2005) or cardiac risk factors (Dalziel, Walker et al., 2005).

The use of corticosteroids postnatally has been extensively studied. For infants who are ventilator dependent because of chronic lung disease the administration of steroids facilitates extubation but there are concerns about the risk:benefit ratio. Cochrane Systematic Reviews of postnatal corticosteroid use conclude the early use (at <96 hours of age) (Halliday, Ehrenkranz, & Doyle, 2003b) and delayed use (at > three weeks of age) (Halliday, Ehrenkranz, & Doyle, 2003a) may have more adverse effects than benefits, while moderately early use (at 7 – 14 days of age) (Halliday, Ehrenkranz, & Doyle, 2003c) reduces neonatal mortality and chronic lung disease with short term adverse effects. In all three reviews the authors comment about the limited evidence

available related to long term neurodevelopmental outcome, and the methodological limitations in some of the studies. The reviews of early and delayed corticosteroid use found no increase in the combined outcome of death or major neurosensory disability. A recent review has stratified infants by their risk of chronic lung disease (Doyle, Halliday, Ehrenkranz, Davis, & Sinclair, 2005). For infants with a low risk (<35%) of chronic lung disease the risk of death or cerebral palsy was increased with the use of postnatal corticosteroids. However, for infants with a very high (>65%) risk of death or cerebral palsy the use of postnatal corticosteroids reduced this risk (Doyle, Halliday et al., 2005).

1.1.7.1 Impact of chronic illness

In addition to the neurodevelopmental outcomes, outlined in the sections above, there are some additional sequelae that impact on the general health and wellbeing of these infants (Doyle, Ford, & Davis, 2003). There is a significant burden from on-going chronic illness on the infants, their families and society. Two of the common sources of chronic illness affecting infants requiring NICU admission are illustrated here.

1.1.7.1.1 Chronic Lung Disease

The first common illness is that of chronic lung disease. This is defined as an on-going requirement for supplemental oxygen at 36 weeks corrected gestation. The National Women's Hospital data show 27% of infants born at <1000g who survive to 36 weeks corrected gestation have chronic lung disease. This drops to a rate of 9% for infants born between 1000g and 1499g (Knight & Kuschel, 2005). Some infants diagnosed with chronic lung disease still need supplemental oxygen at the time of discharge. This places restrictions on family mobility above and beyond those of having a relatively fragile infant moving home after a protracted hospitalisation. In addition to potential home oxygen requirements, infants diagnosed with chronic lung disease are at risk of respiratory decompensation with upper respiratory tract infections. These infants experience more episodes of bronchiolitis, and require more hospital admissions for treatment of respiratory illnesses and poor growth in the first year of life (Chye & Gray, 1995). These admissions have a major impact on the family of the infant. If admissions (after the NICU admission) are frequent and

prolonged there may be an impact on the developmental achievements of the infant. Several longitudinal studies have shown that very low birth weight infants with chronic lung disease have worse neurodevelopmental outcomes, particularly motor outcomes, than similar birthweight infants without chronic lung disease (Majnemer et al., 2000; Singer, Yamashita, Lilien, Collin, & Baley, 1997).

1.1.7.1.2 Failure to thrive

The second illness that commonly impacts on these infants is failure to thrive. Any number of factors may operate in any premature infant to cause growth failure. However, continuing difficulty with feeding and growth often leads to a multidisciplinary team becoming involved and potentially invasive procedures, such as gastrostomy formation. Adverse effects on intellectual outcomes have been found in both unselected groups of infants with failure to thrive (Corbett & Drewett, 2004) and also in low birthweight preterm infants with failure to thrive (Kelleher et al., 1993). The impact of nutritional deficiencies and sub-optimal growth on long-term neurodevelopmental outcome can be difficult to quantify, but there are data to show the impact of various micronutrient deficiencies on development, for example sodium deficiency (Al-Dahhan, Jannoun, & Haycock, 2002).

1.1.8 Outcome for term infants born with neonatal encephalopathy

Neonatal encephalopathy, particularly when related to perinatal hypoxic-ischaemic events (hypoxic-ischaemic encephalopathy, which this discussion will focus on) results in substantial morbidity and mortality. Infants with moderate-to-severe encephalopathy (table 1-2 for staging criteria) require admission to NICU for support of the encephalopathy in addition to the multi-organ failure resulting from the precipitating event. Other end-organ damage is common in encephalopathic infants after asphyxial events (Martin-Ancel et al., 1995; Shah, Riphagen, Beyene, & Perlman, 2004). While multiorgan dysfunction has the potential to influence the infant's final outcome, either due to further effects on perfusion and oxygenation of the infant's central nervous system or because of associated pathophysiological mechanisms impacting on the ability of the infant to survive in the extra-uterine environment, no

relationships have been found between organ involvement and long-term outcome (Shah et al., 2004).

Table 1-2
Staging of Hypoxic-Ischaemic Encephalopathy

Signs	Mild encephalopathy (Stage 1)	Moderate encephalopathy (Stage 2)	Severe encephalopathy (Stage 3)
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalography	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hrs (if progresses) otherwise may remain normal	24 hrs to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Modified from Sarnat and Sarnat (Sarnat & Sarnat, 1976)

Infants diagnosed with hypoxic-ischaemic encephalopathy have variable outcomes. The available literature on outcome in these infants has a number of shortcomings (Dilenge, Majnemer, & Shevell, 2001). The first of these is the paucity of recent outcome studies. The recent literature has focussed on outcome prediction for encephalopathic infants and the implications for managing these infants, rather than determining the outcome of the encephalopathic process.

The second shortcoming is related to defining the population of infants to be studied as over the last 40 years the definition of perinatal asphyxia has evolved. Two consensus statements have relatively recently developed criteria for defining asphyxia. In the 1992 joint statement of the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists

(reported in (Committee on Fetus and Newborn, American Academy of Pediatrics, Committee on Obstetric Practice, & American College of Obstetricians and Gynecologists, 1996)) the essential characteristics of perinatal asphyxia include all of the following:

1. Profound metabolic acidosis (pH < 7.00);
2. Persistence of an Apgar score of zero to three beyond five minutes;
3. Clinical neurologic sequelae in the immediate neonatal period; and
4. Evidence of multiorgan system dysfunction in the immediate neonatal period.

The 1999 International Cerebral Palsy Task Force (MacLennan, 1999) definition of an acute intrapartum hypoxic event causing subsequent cerebral palsy requires:

1. Metabolic acidosis (pH <7.00);
2. Early onset of severe or moderate neonatal encephalopathy in infants of ≥34 weeks gestation; and
3. Cerebral palsy of spastic quadriplegic or dyskinetic type.

Other useful criteria in this consensus statement (supportive but not essential) include:

1. A sentinel event;
2. A sudden, rapid and sustained deterioration of the fetal heart rate;
3. An Apgar score below six after five minutes;
4. Early evidence of multisystem involvement; and
5. Early evidence of acute cerebral abnormality.

It has become generally accepted that single markers are insufficient to determine the level of asphyxial insult to which any infant has been exposed.

The third shortcoming is the shortage of long-term (ie beyond school entrance) studies of outcome (Marlow, Rose, Rands, & Draper, 2005; C. M. Robertson, Finer, & Grace, 1989). As noted above, subtle neurodevelopmental disabilities are often only evident as the child reaches school age. Behavioural and learning difficulties are also increasingly evident as the child matures.

The final shortcoming is the fact that most of the studies have focussed on severe outcome measures (including death, cerebral palsy and mental

retardation) ignoring the impact which relatively minor disabilities, such as learning difficulties and behavioural problems, have on the life of the infant, their families and communities (Marlow, Rose et al., 2005). Those studies addressing these issues have used a number of outcome measures, many of which are not described or standardised .

Studies that classify outcomes according to the severity of hypoxic-ischaemic encephalopathy show uniformly poor outcomes for those with severe hypoxic-ischaemic encephalopathy at all ages assessed. The eight year follow-up data from a Canadian study (C. M. Robertson et al., 1989) showed 82% of the 28 infants with severe encephalopathy died and the remainder were severely disabled. The report on seven year follow-up from a British study showed that children who had had neonatal encephalopathy had lower scores for cognitive, educational and behavioural assessments than classmate controls, and that these were found to be more severe in infants diagnosed with severe encephalopathy (Marlow, Rose et al., 2005). There are infrequent reports of infants with normal development after severe hypoxic-ischaemic encephalopathy in the literature from before cooling trials (Shankaran, Woldt, Koepke, Bedard, & Nandyal, 1991). Currently available outcome data from cooling trials only report data for death or severe disability (Gluckman et al., 2005; Shankaran et al., 2005) and it is not evident whether more infants with severe encephalopathy had normal development, although this does not appear likely.

Nearly all infants with mild hypoxic-ischaemic encephalopathy were normal when assessed after variable periods of follow-up. Those with disability were relatively mildly affected. In the initial report on outcome of a Canadian cohort of asphyxiated infants at a mean age of 19 months (Finer, Robertson, Richards, Pinnell, & Peters, 1981) six infants out of 25 infants with stage 1 hypoxic-ischaemic encephalopathy were reported to have mild handicap. Mild handicap was defined as variations from normal on neurologic or developmental examination without a specific diagnosis. Further reports by the same group showed all 66 infants with mild hypoxic-ischaemic encephalopathy followed up at three and a half years were free of handicaps (C. Robertson & Finer, 1985).

A further report by this group at eight years of age with multiple psychology and educational testing showed infants with mild hypoxic-ischaemic encephalopathy at birth have similar test scores to the control group (C. M. Robertson et al., 1989). Data from Sweden show similar results with none of the 36 infants with mild hypoxic-ischaemic encephalopathy being disabled at 18 month follow-up (Thornberg, Thiringer, Odeback, & Milsom, 1995).

In contrast to the polarised neurodevelopmental outcomes noted above, infants who suffer from moderate hypoxic-ischaemic encephalopathy have a wide spectrum of outcome. The Canadian data showed that of infants with moderate HIE, 46% had a normal outcome, 36% had moderate to severe handicap and 18% had died before first follow-up (mean age 19 months) (Finer et al., 1981). The Swedish data also showed that 47% of infants with moderate hypoxic-ischaemic encephalopathy had some level of disability at 18 month follow-up (Thornberg et al., 1995). The eight year follow-up of the Canadian cohort showed that 5% of those with moderate hypoxic-ischaemic encephalopathy were dead, 15% were disabled and the remainder performed at lower levels on all the tests, generally one year below the control subjects (C. M. Robertson et al., 1989). The British data showed that although infants with moderate encephalopathy at birth had testing scores closer to the control group they had special educational needs identified more frequently than the control group (Marlow, Rose et al., 2005) indicating an increased risk for subtle cognitive impairments even when motor impairments are not present.

These data suggest that early categorisation of term infants with hypoxic-ischaemic encephalopathy has important long-term prognostic significance.

1.1.9 Who should report outcome?

Reports of outcome measures use data generated by professionals such as Psychologists, Physiotherapists, Developmental Paediatricians and teachers. These data are often supplemented by the results of interviews or questionnaires with the parents of the children involved to give a perspective on the impact of various factors on the infant's life (Saigal et al., 2000).

There have been some reports on the perception of NICU graduates regarding their quality of life. Saigal et al reported data from 141 extremely low birthweight survivors compared to 124 controls at between 12 and 16 years of age (Saigal et al., 1996). As a group the low birthweight infants rated their health-related quality of life as significantly lower than control teenagers. However, the majority felt that their health-related quality of life was quite satisfactory.

One study showed that objective quality of life measures had improved for young adults who had been very low birthweight infants born in 1980 – 1982 compared with a previous cohort born in 1971 - 74, although not as much as the normal control group (Dinesen & Greisen, 2001). Interestingly, while objective quality of life measures were lower in very low birthweight infants there were no differences in subjective quality of life measures. They conclude that in a free society, the final judgement of quality of life must rest with the individual (Dinesen & Greisen, 2001). Cooke also found no difference between early adults born very preterm and term controls in self-reported quality of life (Cooke, 2004).

1.1.10 Wider aspects of outcome

It is important to consider the impact of a sick infant on the broader context of the family unit. Having a small sick infant has lasting impact on some family relationships. The birth of extremely low birthweight infants caused crisis reactions in 85% of mothers and 65% of fathers (Stjernqvist, 1992). The families of these infants showed increased strain on the husband-wife relationship over the first year. Longer term follow-up has shown increased financial burden, familial/social impact and personal strain, particularly in families with children left with functional handicap when compared with full-term infants (Cronin, Shapiro, Casiro, & Cheang, 1995). Furthermore the effect on family stress, up to seven years after the birth, are compounded by socio-demographic status, severity of neonatal illness and ongoing infant health problems (Taylor, Klein, Minich, & Hack, 2001). On the other hand, parents of very low birthweight infants reported heightened appreciation of their child, irrespective of the presence of neurologic sequelae (Rivers, Caron, & Hack, 1987).

1.2 Vulnerability of the neonatal brain to injury

As shown above newborn infants requiring admissions for intensive care are at increased risk of long-term neurodevelopmental disabilities. The preterm infant's brain is particularly vulnerable to injury due to the developmental stage of the neuronal proliferation and migration, myelination and vascularity. The underlying mechanism of injury in the perinatal period for both preterm and term infants is hypoxic-ischaemic damage leading to activation of glutamate receptors, accumulation of cytosolic calcium and generation of free radicals (Inder & Volpe, 2000; Volpe, 2001). In term infants the most common injury is selective neuronal necrosis (Ferriero, 2004; Inder & Volpe, 2000; Volpe, 2001) while in preterm infants damage to immature oligodendrocytes and white matter injury, particularly to subplate neuron (Ferriero, 2004), occurs more commonly (Inder & Volpe, 2000; Volpe, 2001). In preterm infants altered cerebral perfusion also predisposes to germinal matrix haemorrhage and venous infarction (Inder & Volpe, 2000).

Hypoxia refers to insufficient oxygen supply to tissues. Ischaemia refers to insufficient blood flow to supply nutrients to tissues and to remove toxic by-products of metabolism. In the presence of severe hypoxaemia metabolic changes occur as anaerobic metabolism of glucose and glycogen causes impaired production of high energy phosphate and increased production of lactate. Increased glucose uptake from the blood occurs in an attempt to provide sufficient substrate for the inefficient energy production. When significant ischaemia occurs the glucose supply to the brain is substantially reduced and alternative sources are activated. There also appears to be a regional vulnerability with white matter being more easily compromised than grey matter (Duffy, Cavazzuti, Cruz, & Sokoloff, 1982). Despite glycogenolysis the brain glucose concentrations fall rapidly, lactate levels rise and energy levels fall. The energy depletion in the cerebral tissues does not need to be profound for the ensuing cascade of events leading to cell death (Volpe, 2001). As cell death occurs after the insult there are likely to be other influences in the post-ischaemic period which impact on the final outcome for each cell including hypoperfusion as a result of impaired autoregulation of cerebral blood flow. Owing to the time lag between the hypoxic-ischaemic insult and cell death there

is also a window of opportunity for neuroprotective interventions to avert cell death.

In preterm infants the subplate neurons are particularly vulnerable to hypoxic-ischaemic insults (Ferriero, 2004). Subplate neurons migrate early, peaking between 22 and 34 weeks gestation, before the major neuronal migration that forms the cortical plate region. Subplate neurons form synapses with axons from the thalamus and other cortical sites until their neuronal targets in the cortical plate have arrived and matured. Without subplate neurons these connections would degenerate which would significantly impact upon cortical organisation (Kanold, Kara, Reid, & Shatz, 2003).

Decreased cerebral blood flow may also result in hypoxia and/or ischaemia to the germinal matrix, which is supplied by end-arteries and therefore vulnerable to flow changes. This insult could result in damage to the fragile endothelial lining of the vascular channels. When cerebral blood flow increases, in an unregulated fashion in the absence of autoregulation, the combination of endothelial damage and loose supportive tissue enables haemorrhage to occur. Histologic features of intraparenchymal haemorrhages suggest that they occur as a result of venous infarction. The infarctions result from obstructed venous drainage of the periventricular tissue due to germinal matrix haemorrhages rather than directly as a result of cerebral hypoperfusion or direct extension of the germinal matrix haemorrhage (Gould, Howard, Hope, & Reynolds, 1987).

1.3 Prediction of outcome

As discussed above there is a substantial literature describing many of the outcomes of infants requiring NICU treatment. Knowledge of these data allows clinicians to make some predictions regarding both survival and neurodevelopmental outcomes for individual infants. In spite of decades of research our current ability to predict an individual infant's likely outcome has significant deficiencies, particularly before birth and in the critical first hours and days of their admission to NICU. In addition, as the available data are all related to populations of infants it is difficult to extrapolate this information to an

individual infant. When multiple sources of information are combined the overall picture is clarified and the ability to predict outcome is often improved.

There are a number of techniques available for clinicians to gain information that may help prediction of long-term outcome. These include various imaging techniques, including cranial ultrasonography, magnetic resonance imaging, a variety of advanced neurophysiological techniques, including standard and amplitude-integrated electroencephalography (aEEG) and illness severity scores such as the CRIB score. In addition there are a number of methods for assessing cerebral perfusion available which may give additional prognostic information. The information available to most neonatologists when predicting outcome will be discussed below.

1.3.1 Gestational Age

The outcome for infants born through the spectrum of viable gestations was discussed in sections 1.1.1 to 1.1.4. While there are potential inaccuracies related to the determination of the gestational age of a fetus, this information is often the most accurate information available to a paediatrician before an infant is delivered. A further limitation of the predictive value of gestational age is the broad spectrum of reported outcome data at each gestation. Whenever possible it is most useful to use data from one's own institution, or one with similar outcomes, to counsel parents.

1.3.2 Birthweight

Prior to delivery rough estimates of fetal weight can be made from ultrasound data, but an accurate measure of weight can only be obtained at birth. Sections 1.1.5 and 1.1.6 outline the range of outcomes experienced by very low birthweight infants. This information can be added to that derived from the gestational age of the infant to refine outcome predictions early in the course of the NICU admission.

1.3.3 Ultrasound imaging

Ultrasonography is a non-invasive technique which can give the clinician valuable information for planning management strategies as well as assisting in

the prediction of outcome. It is widely available within obstetric and neonatal units.

1.3.3.1 Antenatal ultrasonography

Antenatal ultrasonographic measurements are able to give an estimation of fetal weight. However, these are relatively inaccurate (Chauhan et al., 1998). Information is often available about the status of the brain, heart, bones, lung size and the presence or absence of hydrops fetalis. Details about associated anomalies present in a fetus can assist with refining outcome prediction.

1.3.3.2 Postnatal Cranial Ultrasonography

Cranial ultrasounds are performed routinely in NICUs on premature infants, and selected term infants. Ultrasound machines can be taken to the infant's room and scans performed with minimal handling, allowing the most medically fragile infants to undergo scanning. In premature infants cranial ultrasound's main value is in the detection of germinal matrix - intraventicular haemorrage (GM-IVH) and periventricular leucomalacia (PVL). In term infants cranial ultrasound is used to detect major anatomical anomalies, haemorrhage, significant midline shift from fluid collections and in the investigation of hydrocephalus.

In premature infants a grading system for GM-IVH was developed by Papile (Papile, Burstein, Burstein, & Koffler, 1978) (table 1-3). Grade 4 GM-IVH, involving bleeding into the brain parenchyma, is significantly associated with long-term neurodevelopmental disability. Unfortunately the more common lesser grades of GM-IVH do not have the same predictive value. Multiple studies show that severe neurodevelopmental delays can occur in 10 – 35% of very low birthweight infants with a normal cranial ultrasound scan at one month post delivery (Ng & Dear, 1990). Infants with isolated germinal matrix haemorrhage (grade 1 IV-GMH) have a similar outcome to those with a normal ultrasound (Tudehope et al., 1989). In summary, grade 4 GM-IVH is associated with poor outcome while a normal scan, or low-grade IVH, is not consistently associated with a good long-term neurodevelopmental outcome.

Table 1-3
Papile grading of germinal matrix-intraventricular haemorrhage.

Grade	Definition
1	Haemorrhage confined to germinal matrix
2	Blood present in the ventricular cavity without ventricular dilatation
3	Ventricular cavity enlarged and full of blood
4	Parenchymal haemorhage

From Papile et al (Papile et al., 1978)

Several groups have highlighted inconsistencies in the interpretation of images obtained by cranial ultrasound (Corbett et al., 1991; Harris et al., 2006; Harris et al., 2005; O'Shea, Volberg, & Dillard, 1993; Reynolds, Dale, & Cowan, 2001). Within each study interobserver agreement was reasonable for classification of scans into two major prognostic categories; Grade 0 to 2 GM-IVH versus Grade 3 to 4 GM-IVH. O'Shea (O'Shea et al., 1993) concluded that the lack of agreement was sufficient to result in substantial misclassification bias when used for clinical research. Reynolds performed a clinical audit of 59 neonatal units from one region of United Kingdom (Reynolds et al., 2001). They found accurate identification of six images illustrating important neonatal abnormalities by a group of neonatal registrars, neonatologists and radiologists was only 59%. They concluded that the findings raise significant doubts about the accuracy of local interpretation of cranial ultrasound scans in multicentre research. Harris reported variations between interpretation of cranial ultrasound scans reported to a neonatal network by local neonatologists, and reports on the same scans generated by three reviewers (Harris et al., 2006; Harris et al., 2005). However, ultrasound remains useful for providing some information for outcome prediction, particularly as it is portable and easily performed on unstable infants. A further benefit is that it can be used serially to assess the progression of abnormalities.

It is not possible to directly measure cerebral volumes for assessment of cerebral atrophy using cranial ultrasound scanning. However, it is possible to measure the subarachnoid space as an indirect measure of brain growth within

the skull (Govaert, Pauwels, Vanhaesebrouck, De Praeter, & Afschrift, 1989; Lui et al., 1990) and normal values for preterm infants have been determined (Armstrong, Bagnall, Harding, & Teele, 2002). Further investigation regarding the clinical utility of this measurement is required.

Comparing Magnetic Resonance Imaging (MRI) and cranial ultrasound shows that MRI is considerably more sensitive than ultrasound in demonstrating white matter injuries in both premature and term infants (Childs et al., 2001; Inder, Anderson, Spencer, Wells, & Volpe, 2003; Rademaker et al., 2005) with up to three times as many lesions being detected. However, the authors note that MRI will never replace cranial ultrasound due to logistic and economic factors, and the American Academy of Neurology practice parameter on neuroimaging for very low birthweight preterm infants recommends cranial ultrasound scanning for outcome prediction (Ment et al., 2002).

Correlation of cerebral ultrasound changes with post-mortem examination changes show that ultrasound does not detect all bleeding or white matter injury (Adcock, Moore, Schlesinger, & Armstrong, 1998; Paneth et al., 1990). Some of the inconsistencies are related to the timing of ultrasound, with lesions felt to have occurred after the last ultrasound, or due to the small size of the lesion being undetectable by ultrasound. However, these factors do not explain all inconsistencies. The limited capacity of ultrasound to detect all white matter injury may explain why infants with normal cranial ultrasound scans still have a 10 – 35% chance of developing severe neurodevelopmental delays.

1.3.4 Computerized Tomography Scanning

Compared with cranial ultrasonography and Magnetic Resonance Imaging (MRI), Computerized Tomography (CT) scanning has been less widely utilised by Neonatologists. In general the amount of information gained by CT scans does not add sufficient information of management or prognostic value over ultrasound images, and CT scans require substantially more infant handling.

The main indication for obtaining a CT scan is in term encephalopathic infants to determine at an early stage whether haemorrhage is the cause of the

neurological impairment (Ment et al., 2002). For term encephalopathic infants a normal CT scan at one week of age has been shown to predict good neurodevelopmental outcome (M. R. Battin, Gunn, O'Connor, Teele, & Hope, 2001). Basal ganglia lesions at this age predicted a poor outcome, but other abnormalities were less able to predict long-term outcome. The information is only available relatively late in the course as the initial cerebral oedema needs to settle to obtain maximal information. As discussed below MRI scans are usually preferred due to the greater detail obtained from the images.

Neuroimaging, other than cranial ultrasound scans, are more difficult to obtain in infants cared for in NICU. Very few NICUs have dedicated imaging machines easily accessible to their facilities. This means that infants need to be transported to remote facilities, which can be detrimental to their care. Medically fragile infants are even more difficult to transfer, with multiple drug infusions and ventilatory requirements that may not be able to be continued during transport. To obtain maximal information from the scan the infant must lie still which may require a general anaesthetic. It is important that information gained by imaging the infant, particularly when unwell, impacts substantially on the care provided by refining the diagnosis or providing important prognostic information. Often the scans can only be obtained relatively late in the course of the illness, which may decrease the value of the information.

1.3.5 Magnetic Resonance Imaging

Substantial research has been performed regarding the utility of MRI for infants in NICU. While MRI does not detect haemorrhage as well as CT, it provides more detailed information about structure and tissue differentiation within the brain.

MRI scanning in term infants with neonatal encephalopathy has prognostic value. Damage to the posterior limb of the internal capsule (M. A. Rutherford et al., 1998), or to the basal ganglia – thalamus (Kuenzle et al., 1994; M. A. Rutherford, Pennock, Schwieso, Cowan, & Dubowitz, 1995) is predictive of severe long-term neurodevelopmental disablities. However, these infants are

often extremely unwell which can restrict the value of this scanning modality for developing acute management options.

As noted above MRI images show significantly more white matter damage than is evident by ultrasound scanning. Advanced processing techniques combined with higher-powered machines provide many forms of images that are improving our knowledge of normal and abnormal brain development. Three-dimensional reconstruction images allow quantification of various volumes of intracranial tissue and fluid (Inder, Warfield, Wang, Huppi, & Volpe, 2005). Changes in premature infants' brain volumes have been demonstrated when imaged at full-term, compared with normal full-term infants (Inder et al., 1999). Information obtained by MRI technology is being investigated to explore the altered mechanisms underlying the pertubations of brain development experienced by premature infants (Counsell, Rutherford, Cowan, & Edwards, 2003; Neil & Inder, 2004; Volpe, 2003). At this point the data linking MRI changes to long-term neurodevelopmental outcome are limited, but do indicate some relationships with neuromotor outcome at 18 months (Valkama et al., 2000) and memory at two years (Woodward, Edgin, Thompson, & Inder, 2005). However, further studies are required to assess how useful the detailed information from the MRIs will be in predicting outcome.

The utility of MRI is limited by problems related to provision of intensive care to neonates during the scan as well as the need to move them to the MRI facility. It is possible to perform MRI on many infants without a general anaesthetic, but this requires expert staff to settle the infant in special supports while ensuring continued monitoring and care.

1.3.6 Clinical Examination

Physical examinations are performed routinely on infants in NICU. Several research teams have explored specific methods for the examination of the neurological system for prediction of outcome.

A system of neurological examination has been developed by clinicians at Hammersmith Hospital, London, that assess six main areas of function: posture

and tone; tone patterns; reflexes; movements; abnormal signs/patterns and orientation and behaviour (Dubowitz, Dubowitz, & Mercuri, 1999). The Hammersmith Neonatal Neurological Examination (HNNE) has been used in both premature and term infants. Extensive work over nearly two decades using this tool has enabled neurological profiles gestation to be developed for normal term infants and preterm infants from 28 weeks. Assessment of 224 well term infants was used to develop an optimality score. The score sheet for the examination was designed so easily identifiable patterns could be correlated with lesions present on neuroimaging. The authors felt that the development of a quantitative scoring system, particularly for research, would enable the severity of the neurological findings to be correlated with insults and the extent of lesions found on imaging. Optimality score systems have been developed to assess term infants at term (Dubowitz et al., 1999), and at 12 - 18 months (Haataja et al., 1999). These have also been shown in preterm infants examined between nine and 18 months of age to predict locomotor function at two years of age (Frisone et al., 2002). However, preterm infants examined at term equivalent cannot have their examination scored using the term optimality score as they have different tone patterns as a result of their period of extra-uterine life. Information has been published with the median and range of scores found in preterm infants born at different gestations and examined at term corrected gestations(Mercuri et al., 2003). As only small numbers of infants have been examined from each gestational group optimality scores have not been developed for these infants.

Disadvantages of this form of examination are that fragile babies, in particular those born at less than 28 weeks gestation, cannot tolerate the handling required to complete the examination, training is required to achieve acceptable inter-observer variability, and repeated examinations over time are required to show stability of patterns and to enhance prognostication. Extremely premature infants are often not stable enough to tolerate the examination, and ventilated or sedated infants are also not able to undergo the testing. As a result the information is only obtained relatively late in the course of the infant's hospitalisation and is not available for early outcome predictions.

In the 1960's Prechtl generated interest in the neurological examination of newborn infants. The influence of the infant's degree of wakefulness on the examination findings was highlighted. More recently Prechtl has developed an alternative method of examination. Close observation at the cotside, or video recordings of the infant, are used to assess the quality of the general movements (the most frequent and complex spontaneous movement patterns) (Prechtl, Fargel, Weinmann, & Bakker, 1979). This has been shown to be robust and valid (Cioni et al., 1997). When comparing general movement assessment with neurological examination (by either Prechtl or Hammersmith protocol) the sensitivity of the general movement assessment is similar for preterm, term and young infants (Einspieler, Prechtl, Ferrari, Cioni, & Bos, 1997). The specificity of the general movement assessment is age-dependent due to spontaneous recovery of early dysfunction in some infants (Cioni et al., 1997; Einspieler et al., 1997).

The main advantage of these examinations is that they can be performed in the infant's incubator / cot. Disadvantages relate to the need for handling infants (which varies depending on the system used), training to ensure inter-observer reliability and the need for repeated examinations to determine stability of findings and to refine prognostication.

1.3.7 Illness severity scores

Over the last decade a number of scoring systems have been developed for sick neonates in order to predict short term outcomes, particularly mortality, and to compare outcomes between units. These systems vary in their complexity and the time period over which the observations are made.

Eriksson used four different scoring systems to retrospectively assess over 200 infants to determine the ability of these scores to predict long-term neurodevelopmental outcome (Eriksson, Bodin, Finnstrom, & Schollin, 2002). Neonatal Therapeutic Intervention System (Gray, Richardson, McCormick, Workman-Daniels, & Goldmann, 1992) assesses multiple items over the first 24 hours of admission under the following headings: respiratory; cardiovascular; drug therapy; monitoring; metabolic/nutrition; transfusion; procedural and

vascular access. Score for Neonatal Acute Physiology (SNAP) and its modification SNAP-Perinatal Extension (SNAP-PE) were developed in the United States of America. The SNAP score includes measures of cardiovascular, respiratory, haematologic, neurologic, renal and electrolyte status over the first 24 hours (Richardson, Gray, McCormick, Workman, & Goldmann, 1993) with SNAP-PE including birthweight, five minute Apgar and small-for-gestational age items (Richardson, Phibbs et al., 1993). Clinical Risk Index for Babies (CRIB) was developed in the United Kingdom and includes items scored over the first 12 hours of life (Cockburn et al., 1993). Scores are assigned according to birthweight, gestation, the presence of congenital malformations, the maximum base excess and the maximum and minimum appropriated oxygen requirement. SNAP-PE and CRIB were better at predicting hospital mortality than birthweight or gestational age, but none could predict adverse outcome at four years of age (Eriksson et al., 2002).

It is important to note that these scoring systems all require data from the first day of the infant's life in addition to their condition at birth. These data will allow the NICU's management protocols to impact on the score in addition to the condition of the infant. More recently the CRIB (Parry, Tucker, Tarnow-Mordi, & Group, 2003) and SNAP-PE (Richardson, Corcoran, Escobar, & Lee, 2001) scores has been updated to determine whether modifications to the original scoring systems could provide a valid method of risk adjustment on measures obtained within the first 12 hours to reduce the potential for early treatment bias. Both the CRIB and CRIB-II scores have been shown to have better discrimination for predicting death before discharge when compared with the SNAPPE-II score (Gagliardi et al., 2004). However, illness severity scores are now used more for benchmarking between hospitals rather than for prediction of outcome for individual infants ("International Neonatal Network, Scottish Neonatal Consultants, Nurses Collaborative Study Group. Risk adjusted and population based studies of the outcome for high risk infants in Scotland and Australia.," 2000).

1.3.8 Effects of cerebral perfusion on cerebral injury

Blood flow to the body is required for the supply of oxygen and glucose and for the removal of carbon dioxide and lactate. To maintain homeostasis the supply of compounds must be sufficient to maintain the metabolic requirements of the organ and removal of metabolic by-products must occur before they reach levels toxic to the surrounding cells. These requirements vary between organs, as does the ability of organs to cope with insufficient flow for different lengths of time.

The brain is one of the most sensitive organs to deficient blood flow as it is almost entirely relies on aerobic metabolism of glucose for energy production. Glycogenolysis occurs when insufficient glucose is available, and aerobic glucose metabolism maintains energy levels for a period of a few minutes, but these mechanisms rapidly fail to provide sufficient energy. There also appears to be a regional vulnerability with white matter being more easily compromised than grey matter (Cavazzuti & Duffy, 1982; Duffy et al., 1982).

1.3.8.1 Measures of cerebral perfusion

Monitoring in NICU enables blood pressure to be measured on all infants with either episodic Doppler cuff blood pressure measurements, or invasive continuous monitoring, using indwelling catheters in the aorta via the umbilical arteries or in a peripheral artery. Normal ranges of mean arterial blood pressures have been published (Lee, Rajadurai, & Tan, 1999; Low et al., 1991; Versmold, Kitterman, Phibbs, Gregory, & Tooley, 1981) and many babies receive inotropic medications within the first days of their NICU admission to maintain their blood pressure in the normal range. While this is a readily available measurement, the impact of vascular resistance in both the arterial and venous systems as well as the ability to divert blood away from certain organs and the impact of ductus arteriosus steal means that adequate tissue blood flow cannot be assumed even when the blood pressure is in the normal range.

A number of different techniques have been used to examine the cerebral blood flow in the newborn infant because of the apparent significance of

abnormal cerebral haemodynamics for morbidity and mortality (Pryds & Edwards, 1996). Measurements can be divided into quantitative, semi-quantitative and non-quantitative methods. Quantitative methods used in newborn infants include ^{133}Xe clearance, positron emission tomography, Xenon computed tomography, near infrared spectroscopy and venous occlusion plethysmography. Non-quantitative methods include single photon computed tomography and Doppler ultrasonography of the cerebral vessels. In our NICU we are exploring the use of semi-quantitative echocardiography measuring superior vena cava blood flow as a surrogate for cerebral blood flow. The methods used most often in research, and those currently under investigation will be briefly described.

Quantitative methods of measuring cerebral blood flow are based on the Fick principle (the rate of accumulation of a marker is the difference between the rate the marker is delivered and the rate it is removed from the organ). In NICU research the ^{133}Xe clearance has been widely used as it can be performed at the bedside (Greisen, 1986; Jayasinghe, Gill, & Levene, 2003; Lou, Skov, & Pedersen, 1979; Ment et al., 1984). ^{133}Xe may be given via the carotid artery, in the inspired gas of a ventilator or via a vein. It is not metabolised, is fully diffusible across the blood-brain barrier and 90% is excreted during each pass through the lungs. Each measurement gives total body irradiation equivalent to one or two chest x-rays. Measurements occur over several minutes so that rapid changes in blood flow are unable to be detected.

A second quantitative method used in the NICU setting is near infrared spectroscopy (NIRS). As tissue is relatively transparent to light of the near infrared spectrum, oxyhaemoglobin can be used as a tracer because it absorbs the light. Brief increases in inspired oxygen concentration cause an increase in the concentration of oxyhaemoglobin which is measured by NIRS (Edwards et al., 1988). The data allow other information about cerebral haemodynamics and oxygenation to be derived simultaneously. NIRS can be performed in incubators and allows faster measurements which can be repeated without irradiation (Meek, Tyszczuk, Elwell, & Wyatt, 1998; Tyszczuk, Meek, Elwell, & Wyatt, 1998). For the calculations using this technique it must be assumed that

the cerebral blood volume and oxygen extraction remain constant during the measurement. NIRS has been validated by comparison with the ^{133}Xe clearance method (Skov, Pryds, & Greisen, 1991), so these assumptions appear to be valid.

Doppler ultrasonography of the cerebral vessels enables determination of the velocity of blood passing through them, but as the diameter of the vessels are too small to be accurately measured, flow cannot be derived from the recordings. This technique has been validated, and while not quantitative it may provide useful information on trends in cerebral blood flow (Boylan et al., 1999; Hansen, Stonestreet, Rosenkrantz, & Oh, 1983).

Echocardiography can be performed in the infant's incubator without disruption of cardiorespiratory status (Groves, Kuschel, Knight, & Skinner, 2005) and measurements can be made of the left and right ventricular output in premature infants (Evans & Kluckow, 1996a). This can give important information about the adaptation of the heart to the extrauterine environment but shunting through the ductus arteriosus makes extrapolation to distal organ flow patterns inaccurate. Recently interest has been generated in echocardiographic measurements of superior vena cava (SVC) flow as this is a central vessel of sufficient diameter to enable measurements of not only blood velocity by Doppler, but also diameter. It is estimated that 70-80% of SVC flow is from the brain (Drayton & Skidmore, 1987) and it has been shown that middle cerebral artery mean velocity is significantly associated with SVC flow in very preterm infants (Evans, Kluckow, Simmons, & Osborn, 2002). Low SVC flow over the first 24 hours after delivery has been found to be associated with increased risk of GM-IVH (Kluckow & Evans, 2000a), developmental disability and death (Hunt, Evans, Rieger, & Kluckow, 2004). Cerebral blood flow increases over the first three days of life (Kluckow & Evans, 2000b; Meek et al., 1998), so it is important to take this into account when interpreting measures of flow with adverse events.

Despite much research regarding cerebral blood flow there is still much speculation on whether dynamic autoregulation of cerebral blood flow occurs in

preterm infants (Greisen, 2005). Impairment of autoregulation can affect the brain through exacerbation of ischaemia during hypotensive periods, and exposure to excessive blood flow during hypertensive periods has the potential for rupture of vessels and haemorrhage into surrounding tissues. The disparity between studies examining cerebral blood flow autoregulation in newborn infants is due to a combination of factors including the degree of prematurity of the population, the postnatal age at which the infant was studied, the time period elapsed since any significant hypoxic-ischaemic event, and the method used to study flow rates (Greisen, 2005). Boylan showed that minute-to-minute regulation of cerebral blood flow (dynamic autoregulation), using Doppler middle cerebral artery velocity as a proxy measure, was absent in high-risk term infants and all preterm infants compared to control term infants (Boylan, Young, Panerai, Rennie, & Evans, 2000). In contrast, Tyszczuk demonstrated the presence of adequate cerebral blood flow over a range of mean arterial blood pressures in preterm infants examined on the first day after delivery using near infrared spectroscopy indicating the presence of steady-state autoregulation (Tyszczuk et al., 1998). It is likely that autoregulation is present to some extent in the steady-state for well infants, but not for those with evidence of hypoxic-ischaemic brain injury. In addition, it appears that dynamic autoregulation is not operating in preterm infants and that a relationship between blood pressure and cerebral blood flow should not be assumed (Greisen, 2005).

1.3.8.2 Alterations in cerebral perfusion, intraventricular haemorrhage and white matter injury

Alterations in cerebral blood flow are believed to play a significant role in the development of intraventricular haemorrhage. Measurements of cerebral blood flow have been recorded early in the course of infant's intensive care and then repeated serially, along with repeated head ultrasounds, to detect haemorrhage. Infants with normal initial head ultrasounds who subsequently developed intraventricular haemorrhage had an early period of decreased cerebral blood flow (Kluckow & Evans, 2000a; Meek, Tyszczuk, Elwell, & Wyatt, 1999), and the haemorrhage developed after the cerebral blood flow increased to normal levels or beyond (Kluckow & Evans, 2000a).

The immediate impact of alterations in cerebral blood flow on the development of white matter injury in newborn infants is more difficult to demonstrate in the NICU setting. This is because white matter injury is seldom evident on routine head ultrasonography until many weeks after precipitating events. However, animal models have been developed to enhance our understanding of the pathophysiology of white matter. One useful model is neonatal rats that have one common carotid artery ligated (reducing ipsilateral perfusion) followed by a systemic hypoxic insult (Vannicci et al., 1999). The current understanding of the pathophysiology of white matter injury in preterm infants is that it is the result of oxidant mediated damage resulting from ischaemia (Back & Rivkees, 2004; Inder & Volpe, 2000).

1.3.9 Electroencephalography

Electroencephalograms (EEG) have been studied in newborn infants since the 1970s. A range of different techniques for obtaining, processing and representing the EEG have been developed. The techniques used most commonly in NICU research and routine management will be discussed below.

One of the main uses for EEG is seizure detection. Infants requiring admission to NICU have an increased risk of seizure activity from a variety of causes. In older infants, children and adults the gold standard for seizure detection and classification is video recording during standard EEG assessment. In NICU seizure detection mainly relies on observation of infants' movements and physiologic parameters (heart and respiratory rates and blood pressure) as most NICUs do not have EEG facilities readily available, and interpretation of the standard EEG is difficult and is not often provided at the time of the recording.

1.3.9.1 Standard EEG

EEGs obtained using multiple channel polygraphs (between eight and 22 channels) have been used in many centres. The electrodes are placed according to a modified International 10-20 system. The interpretation of data from this form of EEG requires special training. Neonatal EEGs are different

from those of the older paediatric population, and change with increasing maturity in premature infants. As a result it is essential that the neurophysiologist reading the EEG is aware of these factors. The complexity of both electrode application and interpretation of the data make this form of EEG less available and useful for routine clinical use.

1.3.9.1.1 Premature Infants

In spite of the technical difficulties in lead attachment, skin integrity and medical fragility, several groups have investigated the use of standard EEG recordings in premature infants. Both normal patterns and pathological changes have been documented.

1.3.9.1.1.1 Maturity

The normal EEG background pattern of extremely premature infants is discontinuous (Biagioni et al., 1994; M. Hayakawa et al., 2001; Selton, Andre, & Hascoet, 2000). In discontinuous EEG bursts of activity are separated by low voltage activity of <30μV for more than five seconds. Bursts are defined as EEG activity with amplitudes more than 100μV lasting for 2 – 20 seconds in any channel (M. Hayakawa et al., 2001). With increasing maturity discontinuity decreases, bursts last longer, and the background pattern becomes more continuous. EEG has been shown to have constant and reproducible patterns in normal very premature infants (down to 26 weeks gestational age). Sleep/wake cycles begin to develop from 26 weeks gestation. These are cyclic shifts of EEG activity depending on the level of arousal or depth of sleep of the infant (Selton et al., 2000).

1.3.9.1.1.2 Seizure Detection

Premature infants have the highest risk of seizures. Using standard EEG Scher found an incidence of EEG-confirmed seizures of 1:25 in their population of infants 30 or less weeks gestation, falling to 1:67 for infants between 30 and 37 weeks gestation (Scher et al., 1993). Gestation exerts a strong influence on the rate of seizures confirmed by EEG. The increase in confirmation rates ranges from 37 - 63% at 30 weeks or less to 53 – 79% at term (Scher et al., 1993; Sheth, 1999). Scher found 45% of premature infants with seizures had IVH with

or without white matter injury and a further 39% had cerebral infarction (Aso, Abdab-Barmada, & Scher, 1993).

1.3.9.1.1.3 Outcome Prognostication

Standard EEG recordings from infants between 28 and 32 weeks gestation can often add clinically useful prognostic information. Mortality is increased in preterm infants with confirmed seizures compared with term infants with seizures, but in those surviving the incidence of subsequent epilepsy was the same irrespective of gestational age (Scher et al., 1993).

Specific EEG patterns such as positive rolandic sharp waves are more frequent in infants who subsequently have abnormal motor development (Baud et al., 1998; Marret et al., 1997). Abnormalities of the background EEG pattern are common in very premature infants, but are more numerous in infants who die (Marret et al., 1997). During the development of intraventricular haemorrhage there is depression of background activity and epileptic seizures frequently occur. These EEG changes may precede ultrasound evidence of bleeding (J. Connell et al., 1988).

Serial recordings over time have been used to assess the timing of damage resulting in development of PVL (F. Hayakawa, Okumura, Kato, Kuno, & Watanabe, 1999; Itakura et al., 1996). Hayakawa defined acute and chronic changes in early EEG recordings. Chronic changes present on the initial infant EEG were felt to represent antenatal injuries. Acute changes on the first EEG, followed by chronic changes were felt to indicate peripartum injury, whereas an initially normal EEG followed by changes reflected postnatal injury (F. Hayakawa et al., 1999).

Early continuous EEG monitoring with a reduced number of electrodes can provide information regarding the development of lesions and their prognosis for ultrasonographically demonstrated intraventricular haemorrhage (J. Connell et al., 1988) and white matter echodensities (J. Connell et al., 1987).

Difficulties in interpretation of standard EEGs in very premature infants occur because certain patterns of activity may be defined as abnormal only by the frequency of their occurrence rather than their presence or absence. As with many of the tools available to assist in prognostication, early single EEG recordings made at very early gestational ages add information but require serial measurements to enable changes to be assessed for stability of patterns.

1.3.9.1.2 Term Infants

In term infants EEG has been used routinely in clinical assessment and management of infants with seizures and for prognostication with neonatal encephalopathy of presumed hypoxic-ischaemic aetiology.

1.3.9.1.2.1 Seizures

Standard EEG is the gold standard in assessment of probable seizure activity in infants. In complex or atypical cases video recording of the infant's movements during the recording can add further information for refinement of the diagnosis. Pyridoxine dependent seizures are a classic example of using standard EEG diagnostically. In this form of seizures an EEG shows complete abolition of refractory seizures at the time of intravenous administration of pyridoxine (Baxter, 2001).

Some authors state that EEG confirmation of abnormal movements is essential for the diagnosis of seizures (Painter & Alvin, 2001). Others stress the importance of EEG in differentiating seizures from non-seizure events but acknowledge that the confirmatory rate increases with the length of EEG recording (Sheth, 1999). Sheth's study to examine EEG confirmatory rates in infants treated for neonatal seizures showed the initial EEG revealed epileptiform discharges in 60% of infants with seizures, increasing with gestational age. Subsequent EEGs confirmed the diagnosis in a further 15% and 17% of infants who had isolated background abnormalities without epileptiform discharges on their first EEG.

Follow-up of infants at risk of seizures or with suspected seizures showed that the seizures did not correlate with outcome at either one month or one year.

The EEG background was a significant predictor of survival in the first month but not beyond this time (Bye, Cunningham, Chee, & Flanagan, 1997).

1.3.9.1.2.2 Neonatal encephalopathy of presumed hypoxic-ischaemic aetiology

Standard EEG obtained within 48 hours of birth in infants admitted with presumed perinatal asphyxia has been shown to have a sensitivity of 95% and specificity of 68% for prediction of unfavourable outcome. The background activity is noted to be the most important prognostic indicator (Selton & Andre, 1997). The duration of background disturbances has prognostic importance. Resolution of mild background changes by one week is highly suggestive of normal outcome (Selton & Andre, 1997). Repeated standard EEG is recommended if abnormalities are seen, to refine the outcome prediction. This was confirmed by Biagioni who showed that early EEG distinguishes between infants with a normal or abnormal outcome. In cases with an abnormal early EEG a MRI at one week gave more specific information about the type of outcome to be expected (Biagioni et al., 2001).

1.3.9.2 Amplitude-integrated EEG

Amplitude integrated integrated EEG (aEEG) is a single-channel EEG signal obtained from biparietal electrodes. Recordings can be made using either needle or surface electrodes. Frequencies <2 Hz and >15 Hz are filtered selectively and the amplitude-integrated signal is recorded onto an integral printer (al Naqeeb, Edwards, Cowan, & Azzopardi, 1999; Maynard, 1979). Compared with standard EEG this modification is a reliable tool for monitoring both background patterns and seizure activity (Toet, van der Meij, de Vries, Uiterwaal, & van Huffelen, 2002).

1.3.9.2.1 Background Activity

As with other forms of EEG it is important that the person interpreting the data is aware of the maturational changes of infant EEGs from extreme prematurity to term gestation. The aEEG reflects these background changes with an increase in the lowest amplitudes recorded, decreasing discontinuity and increased definition of sleep/wake cycles as gestational age increases (Thornberg & Thiringer, 1990; Verma, Archbald, Tejani, & Handwerker, 1984). Due to the simplification of the EEG signal produced by aEEG it can be difficult

to differentiate normal maturational patterns of preterm infants from pathologic discontinuity and burst suppression.

aEEG has been used for assessment of sick term infants in many studies. Background activity patterns have been described which have prognostic implications for the infant (al Naqeeb et al., 1999; Toet, Hellstrom-Westas, Groenendaal, Eken, & de Vries, 1999; Toet et al., 2002). These patterns vary between authors but include:

3. Continuous normal voltage (CNV). Maximum voltage 10 - 50μV with periods of increased variability due to quiet sleep;
4. Mainly continuous normal voltage with periods of more discontinuous intermittent low voltage activity (DNV). No burst suppression;
5. Discontinuous background pattern / burst suppression (BS). Periods of very low voltage (inactivity) intermixed with bursts of higher amplitude;
6. Continuous background pattern of very low voltage (CLV). Background around or below 5 μV; and
7. Very low voltage, flat trace (FT). Mainly inactive trace below 5 μV.

After an acute hypoxic-ischaemic event the infant's EEG is often depressed. The severity of the insult is reflected in the degree of change in background activity and the length of time that these changes persist. Background activity of burst suppression, CLV or FT are consistent markers of significant brain damage in term infants (Azzopardi et al., 1999; Hellstrom-Westas, Rosen, & Svenningsen, 1995; Toet et al., 1999). For term infants aEEG recordings have been shown to correlate strongly with standard EEG for assessment of both background activity and seizure activity (Toet et al., 2002).

While aEEG has been used less in premature infants Griesen has demonstrated depressed aEEG patterns around the time of bleeding into the germinal matrix in infants born below 32 weeks gestation (Greisen, Hellstrom-Westas, Lou, Rosen, & Svenningsen, 1987; Hellstrom-Westas, Klette, Thorngren-Jerneck, & Rosen, 2001).

One further aspect of the background activity shown on the aEEG is the presence or absence of sleep state cycling. On the continuous normal aEEG trace the broad bands represent quiet sleep and the narrow bands represent active sleep and wakefulness (Viniker, Maynard, & Scott, 1984). Changes in definition of sleep state cycling with increasing maturation have been documented (Thornberg & Thiringer, 1990; Verma et al., 1984; Viniker et al., 1984). The time taken for sleep state cycling to become evident in term infants with asphyxial events has been shown to assist with prediction of neurodevelopmental outcome (Osredkar et al., 2005).

1.3.9.2.2 Seizure Detection

The availability of aEEG bedside monitoring has allowed clinicians to include assessment of electrical evidence of seizure activity in the diagnosis of seizures. Seizure activity in the aEEG can often be detected as there is a transitory change of frequency and amplitude in the background activity. In general there is a transient rise in the background activity with a rapid rise of both the upper and lower margins of the tracing. Repeated seizures may demonstrate a saw-tooth pattern (Hellstrom-Westas, de Vries, & Rosen, 2003; Thornberg & Ekstrom-Jodal, 1994). The aEEG is also useful in documenting the efficacy of medication used to control seizure activity. Detection of seizures in paralysed infants can also occur with aEEG monitoring.

While the aEEG enables clinicians to have access to electrophysiologic data that can be interpreted at the time of data acquisition it does have some limitations that need to be kept in mind. Firstly, brief seizure activity may not be detectable due to the compressed nature of data collection. Secondly, continuous seizures may not be detected due to a persistently raised baseline. Thirdly, only a limited part of the brain activity is recorded so that focal seizures may not be detected. In newborn infants the lack of myelination may mean that seizure activity in the deep structures may not be conducted to the surface of the brain and remains undetected by surface electrodes. Finally, handling of the infant may cause a change in the arousal state of the infant which could be misdiagnosed by the clinician. All procedures should be noted on the recording to allow for changes in aEEG as a result of arousal or medication, and technical

artifacts from movement of electrodes. Up to 50% of neonatal seizures may be missed using single channel aEEG recordings alone, and there may be substantial variation in interobserver agreement on classification of seizure activity (Rennie et al., 2004). Whenever possible a standard EEG should be obtained to make a complete assessment.

1.3.9.2.3 Selection criteria for Interventional Trials

Investigation of novel neuroprotective treatments in infants requires a uniform cohort of infants at high risk of serious adverse outcome (death or severe longterm neurodevelopmental disability) to be identified within a realistic time frame. This allows the novel treatment to be given over the time when the infant receives maximal expected benefit for minimal cost. In term infants at risk of significant hypoxic-ischaemic damage from birth asphyxia the background activity of an aEEG within six hours of birth has been shown to predict outcome correctly in 91.5% of infants (Hellstrom-Westas et al., 1995). Infants who fulfil clinical criteria for peripartum asphyxial events can be screened to assess the electrophysiologic sequelae of the event. Parents of infants with evidence of significant brain damage from the precipitating event can be approached about relevant trials and a more uniform cohort randomised. This approach allows smaller numbers of affected infants to be enrolled while producing high quality evidence for the effect, or lack thereof, of the novel treatment. aEEG has been used extensively in selection of candidates for trials of head and whole body cooling (Gluckman et al., 2005; TOBY).

1.3.9.2.4 Limitations

The aEEG has many applications in the NICU setting, but clinicians using it need to understand its limitations. In addition to those outlined above the effects of drug administration and common causes of artifact need to be known when interpreting the tracing. Many aEEG recorders do not have the ability to simultaneously record the raw EEG data obtained. This limits the potential to examine the raw EEG for evidence of artifacts and seizures.

Whenever there is on-going concern about the infant, or when the aEEG trace is unexpected or uninterpretable, a standard EEG and further neuroimaging should be obtained.

1.3.9.3 Spectral Edge Frequency

Spectral analysis of a segment (for example four seconds) of the raw EEG allows quantification of intensity against frequency. When these are plotted the area under the curve is proportional to the power of the EEG segment analysed. The spectral edge frequency (SEF) is the frequency below which a specified percentage of the power of the EEG resides (for example 90% of the power). The SEF needs to be defined so as to minimise the effect of artifact from movement or nearby electrical interference.

1.3.9.3.1 Animal Trials

Measurements of SEF in fetal sheep have shown an increase in SEF with increased gestational age (Szeto, 1990). SEF has also been used in fetal baboon studies where it could differentiate between EEG changes related to sleep states (Myers et al., 1993). Fetal sheep SEF monitoring has been used extensively to examine the neurologic effects of hypoxic-ischaemic injuries and the neuroprotective effect of head cooling after such events (De Haan, Gunn, Williams, & Gluckman, 1997; Gunn, Gunn, de Haan, Williams, & Gluckman, 1997; Gunn, Gunn, Gunning, Williams, & Gluckman, 1998; Tan et al., 1996).

1.3.9.3.2 Human Trials

Spectral analysis of EEG recordings has been used for many years to monitor the level of anaesthesia in adults. The SEF decreases in a dose-dependent fashion with many intravenous and inhaled anaesthetics and SEF has been used to monitor the “depth” of anaesthesia (Schwender, Daunderer, Klasing, Finsterer, & Peter, 1998; Schwender et al., 1996).

Power spectral analysis of infant EEGs was first reported in 1968 (Nolte, Schulte, Michaels, & Jurgen, 1968). This form of analysis has been used to examine differences between healthy term and term-corrected preterm infants (Scher, Steppe, Sclabassi, & Banks, 1997; Scher et al., 1994). The spectral analysis during episodes of apnoea show a reduction of amplitude in all frequency bands with a decrease in absolute power (Schramm et al., 2000).

More recently SEF has been assessed as a measure which may indicate the state of white matter, with injury reflected by a decreased SEF. Increasing gestational age is associated with a progressive increase in SEF (Bell, McClure, McCullagh, & McClelland, 1991b). In very low birth weight infants increasingly severe white matter injury, detected by MRI at term, is correlated with progressively lower SEF (Inder, Buckland et al., 2003).

Investigation of SEF changes from fetal EEG obtained during labour has shown decreased SEF during episodes of fetal distress (Thaler, Boldes, & Timor-Tritsch, 2000). While this reinforces the concept of SEF measurements indicating the health of the brain there are significant technical limitations for fetal EEG recordings and this area of research is limited.

1.3.10 Avenues for Improving Outcome Prediction

Neurological outcome for preterm infants remains difficult to predict. Improving bedside methods of assessment, particularly those applicable early in the infant's hospitalisation, are essential if management strategies to prevent or reduce brain injury are to be developed, tested and integrated into routine care.

Cotside EEG recordings are able to be performed at an infant's bedside for even the smallest and sickest infants early in their course in NICU. Preliminary data show that quantitative neurophysiological parameters, including SEF, from these recordings are likely to facilitate refinement of outcome prediction compared with currently available tools. In this thesis I present the results of cotside EEG recordings in the NICU exploring the ability of this tool to improve outcome prediction and to help optimise the management of infants during their period in NICU.

2 Methods

2.1 Patient recruitment

2.1.1 Preterm Cohort

Infants born before 32 weeks gestation and admitted to National Women's Hospital, Auckland, New Zealand, between March 2002 and February 2004 were eligible to be recruited. Parents of eligible infants were approached either before delivery, or as soon as possible after delivery. The study was explained to the parents and they were provided with a written information sheet. Written informed parental consent was obtained before commencing EEG recordings.

2.1.1.1 Protocol 1

Infants recruited to protocol 1 had one two channel cotside EEG recording within 48 hours of delivery, a second at one week after delivery, and in some a third EEG was requested after recovery from an acute deterioration. Infants continued to be recruited to this study after the commencement of protocol 2 in December 2002 as some parents only wanted two EEGs performed.

2.1.1.2 Protocol 2

Infants recruited to protocol 2 had four two channel cotside EEG recordings over the first week after delivery, a fifth EEG two weeks after delivery and then fortnightly EEGs until 36 weeks corrected gestation or discharge, whichever occurred first. If parents consented to both protocols then the first EEG was done in the first 48 hours after delivery and the fourth at one week of age. Some EEGs were not performed as scheduled due to acute deteriorations in the infant's clinical status. When the infant recovered EEGs were again performed according to schedule, with catch-up EEGs in some infants.

2.1.2 Term cohort

2.1.2.1 Infants at risk of seizures

Infants born at 35 or more weeks gestation who were considered either to be at risk of seizures, or to have clinical seizures and were admitted to National Women's Hospital, Auckland, New Zealand, between June 2004 and July 2005 were recruited to this study. Parents of eligible infants were approached about the study as soon as there were concerns that their infant was at risk of seizures or that their infant was having seizures. One EEG was performed as soon as feasible after obtaining consent and a second EEG approximately a week later at the time that a conventional EEG was obtained for routine clinical assessment.

2.1.2.2 Term normal controls

Infants born at 35 or more weeks gestation after uneventful pregnancies and deliveries were eligible for recruitment. Eligible infants were referred by one independent midwife, one private paediatrician and from personal contacts of the researcher. Parents of eligible infants were contacted before, or shortly after, the delivery and given information regarding the study. The researcher liased with parents consenting to the study to perform either one EEG within the first three days after delivery, one EEG towards the end of the first week after delivery, or both.

2.2 Ethics Committee Approval

Auckland Ethics Committee X and ADHB granted ethical approval for each of these projects with the following numbers:

2001/161 Prediction of neonatal white matter injury by EEG;

AKX/02/00/242 Temporal changes in electrencephalography and prediction of neonatal white matter injury by spectral edge frequency;

AKX/04/02/029 Modified electrencephalography monitoring for term and near term infants at risk of seizures.

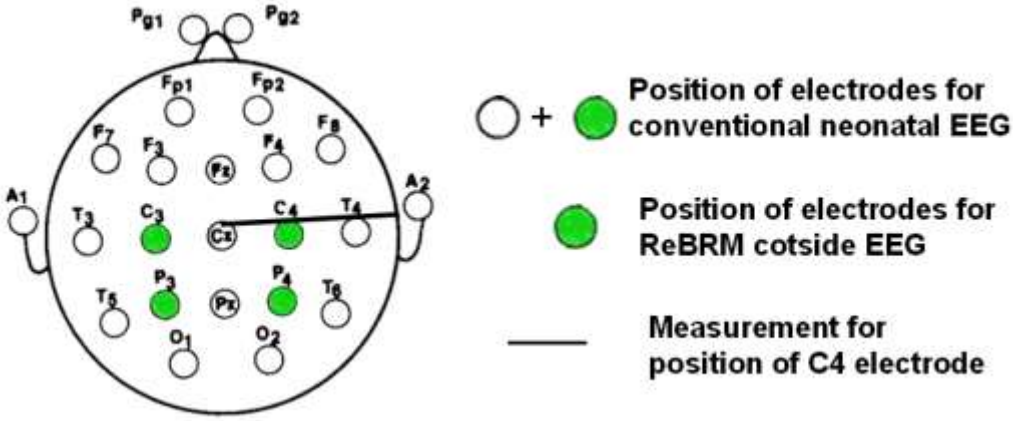
2.3 EEG recording

2.3.1 EEG placement for preterm cohorts

Recordings were obtained using hydrogel electrodes (Hydrospot neonatal electrodes, Physiometrix Inc, North Billerica, MA) placed on the C3, P3, C4 and P4 regions as defined by the modified international 10-20 system after skin preparation appropriate to gestational age. The electrode positions were determined as follows:

1. The distance from the tragus to the midline of the cranial vault was measured (figure 2-1). The C3 and P3 positions were located by calculating 60% of this distance measured up from the tragus.
2. The hemi-head circumference was measured at the level of the C3 / C4 electrode position, parallel to the maximal occipito-frontal head circumference line (ie through F4, C4 and P4 on figure 2-1). The P3 / P4 positions were calculated as 20% of the distance from the centre of the forehead to the centre of the occiput behind C3 / C4.

Figure 2-1
Electrode placement for EEG.



For infants born at less than 28 weeks gestation minimal skin preparation was required for EEGs performed in the first month after delivery. A cotton-tipped swab with a very small amount of Nuprep (Nuprep, D O Weaver & Co, Aurora, CO) was used to remove any blood or skin debris and to move the hair aside to provide a clean, hair-free area for electrode placement. The Nuprep was removed with a piece of damp gauze and the area was dried with a piece of gauze. The electrode was placed on the prepared area and held in position with hydrogel tape (Klear-Tape, Cas Medical Systems, Branford, CT). Skin

preparation for infants of higher gestation, and for very preterm infants later in their NICU course, was similar except that the skin often required more cleaning. Some infants required a small film of Nuprep or Ten20 conductive EEG paste (D O Weaver and Co, Aurora, CO) left under the electrode to improve the impedance. From 33 weeks gestation some infants required stronger fixation of the electrodes because of increased head movement and longer hair. In these infants the electrodes were held in position with EC2 electrode cream (Grass product group, Astro-Med Inc, West Warwick, RI). When this was used the maximum recording time was three hours to allow electrode removal before the cream hardened excessively. After both electrodes were positioned on one side of the head they were covered by a piece of gauze to provide further support and padding around the electrodes. A fifth electrode, the ground electrode, was applied behind the ear on the second side of electrode attachment. A stretch cotton head wrap was closed firmly with micropore tape to finally stabilise the electrodes. If the infant was requiring continuous positive airway pressure (CPAP) respiratory support the gas tubing and chin strap were attached to the head wrap with tape.

2.3.2 EEG placement for term cohorts

Recordings were obtained using commercial electrode configuration designed by BrainZ Instruments Ltd, Auckland, New Zealand. In the commercial package there is a ruler to locate the electrode positions. This was used for location of the C3 and C4 electrodes. However, the ruler positioned the P3 and P4 electrodes only 2.5cm posterior to the C3 / C4 ones which is close to the international modified 10-20 measurement in preterm infants, but is substantially less than the 3.4 to 4.0cm measurement that had been found on the preterm cohort at corrected term gestation. Therefore the positions of the P3 / P4 electrodes were determined by measuring the hemi-head circumference as for preterm infants. The ground lead was placed on the posterior shoulder most accessible at the start of the recording.

Skin preparation in term infants consisted of cleaning the appropriate areas with water, moving the hair aside to provide an appropriate area for electrode application, drying and using a small amount of Nu-prep for skin cleansing until

acceptable impedances were obtained. The skin cleansing for term infants was substantially more vigorous than for preterm infants. The cotton head-wrap and assistance with respiratory support were used as for the preterm population.

2.3.3 Clinical management of infants during EEG

Preterm infants' EEGs were recorded on one of two ReBRM2 EEG machines (research BRM, BrainZ Instruments Ltd, Auckland, NZ) over 2 – 12 hour periods. Term infants had EEGs recorded on the ReBRM3 EEG machine (research BRM, BrainZ Instruments Ltd) over 2 – 24 hour periods. Respiratory support was provided according to the infant's clinical status, and appropriate changes were made as required during the EEG recordings, according to standard nursery protocols. Other clinical procedures were also performed as necessary. Examples of these include intubation, administration of surfactant, placement of intravenous and central venous lines and insertion of an intercostal drain.

2.3.4 Recording sheet

For every EEG a recording sheet was completed with the infant's name, identification label, cot number within the NICU, time of starting the recording, time as displayed on the monitoring device, machine number and their current weight, corrected gestation, medication, respiratory support, ventilator settings (if ventilated), inspired oxygen concentration at the start of the recording and the electrical devices surrounding the infant (such as phototherapy lamps and medication pumps). At the end of the recording the file name allocated to the data was written on the top of the recording sheet. This information was used to track the EEG data and to match physiologic download and EEG data. The clinical data were included to allow a snap-shot of the infant's clinical status over their admission and to determine whether there were any medications which may influence the interpretation of the EEG. Information regarding electrical devices around the infant was used as an indication of potential electrical interference.

Routine nursing procedures were performed as required and documented on the recording, as was handling by doctors, parents and visitors. Episodes of physiological instability, drug administration and blood sampling were also

marked on the recording. After marking the event on the EEG trace the nurse wrote the nature of the event on the recording sheet. Marking the events allowed for analysis of segments of the data for the effects of drug administration etc, and also allowed for the EEG and physiology download data to be linked for analysis.

2.4 Calibration of second EEG recorder (preterm population)

From July 2003 a second EEG recorder was available for use with the preterm infant cohorts. In order to be certain that the two recorders could be used interchangeably eight recordings were started using one recorder and continued on the other recorder, ensuring there was at least one hour of recording adequate for analysis before or after the change. The recordings were analysed for the hour immediately before or after the change for SEF, amplitude, hum and impedance, and the results compared using Wilcoxon signed rank tests. There were no statistically significant differences between the two recorders (table 2-1). Neither were there any significant differences between the first and second portions of EEG irrespective of which machine was used for each time period (machine 1 was used first in five infants and machine 2 was used first in three infants), data not shown.

Table 2-1
Quantitative measures for EEG recorded serially on two EEG recorders, n = 8.

Quantitative parameter	Machine 1 : median (range)	Machine 2: median (range)	Wilcoxon signed rank p-value
Left SEF (Hz)	10.9 (9.9-12.9)	11.0 (10.2-12.3)	0.78
Right SEF (Hz)	11.1 (10.0-12.2)	11.2 (10.4-11.9)	0.62
Left amplitude (μV)	7.3 (5.3-11.2)	8.0 (5.0-9.9)	0.26
Right amplitude (μV)	7.0 (5.1-11.0)	8.1 (5.8-10.2)	0.21
Left intensity (μV^2)	20.1 (8.9-50.5)	19.8 (7.4-40.0)	0.99
Right intensity (μV^2)	20.2 (7.5-47.2)	20.7 (11.2-31.6)	0.58
Left impedance (kΩ)	3.3 (1.7-9.4)	3.5 (1.5-9.5)	0.89
Right impedance (kΩ)	5.4 (1.8-10.6)	5.2 (1.6-10.3)	0.33
Left hum (μV)	6.2 (1.9-22.7)	4.1 (2.6-60.4)	0.99
Right hum (μV)	6.1 (1.6-11.7)	2.9 (1.0-31.0)	0.64

2.5 EEG analysis

2.5.1 Primary analysis

Right and left EEG signals were amplified 5000 times and band-pass filtered with a first-order high-pass filter with -3 dB, frequency at 1Hz and a fourth-order low-pass Butterworth filter at -3 dB frequency at 50 Hz. The signal was digitised by the computer at a sampling rate of 256 Hz, and the intensity spectra and derived parameters were calculated from four second epochs of the digitised signal (Williams & Gluckman, 1990). The total EEG intensity (μV^2) was calculated on the intensity (power) spectrum between 2 and 20 Hz. SEF was calculated as the frequency below which 90% of the intensity was present (Inder, Buckland et al., 2003).

The amplitude was calculated from the bandpass filtered and rectified signal with an algorithm that generates minimum, maximum and median amplitudes that are functionally equivalent to the Cerebral Function Monitor (Maynard, 1979). Continuity measures were determined as the percentage of each minute during which the amplitude of the raw EEG (assessed at two second intervals) was above the determined threshold amplitude (10, 25, 50 or 100μV). The EEG intensity, amplitude, continuity and spectral edge measurements were averaged and stored to disk at one minute intervals.

The averaged signals were analysed off-line using customised software (Chart analyser, Liggins Institute, Auckland, New Zealand). EEG data were defined as valid and included in the analyses if the electrode impedance was <15 kOhm per pair and the continuous data epoch was ≥120 minutes.

Sixty minute segments were analysed and median values of each quantitative variable recorded. The times were chosen to avoid marked events whenever possible. If a prolonged period of EEG without event marks was available, a 60 minute portion in the middle of the “quiet” period was chosen. If there was no 60 minute period of EEG without events then a 60 minute period in the middle of the recording was chosen. The same time period of raw EEG was analysed for each of the quantitative measures. For each recording this 60 minute

segment was chosen to represent the baseline analysis, and is identified as "baseline analysis" in the following chapters.

For the analyses examining the relationships between quantitative EEG data and blood flow and blood pressure measurements the hour directly before or after each echocardiogram was analysed for quantitative EEG measurements.

2.5.2 Secondary analyses

Minimum amplitude was determined as the median value of the lower limit of the amplitudes for the period analysed (corresponding to the lower border of the aEEG trace). This algorithm was produced by Mark Gunning, NeuronZ, Auckland, New Zealand.

Continuity measures were determined as the percentage of each minute during which the amplitude of the raw EEG (assessed at two second intervals) was above the determined threshold amplitude (10, 25, 50 or 100μV). This algorithm was provided by Dr Michael Navakatikyan, BrainZ Instruments Ltd, Auckland, New Zealand.

2.5.3 Sleep state cycles

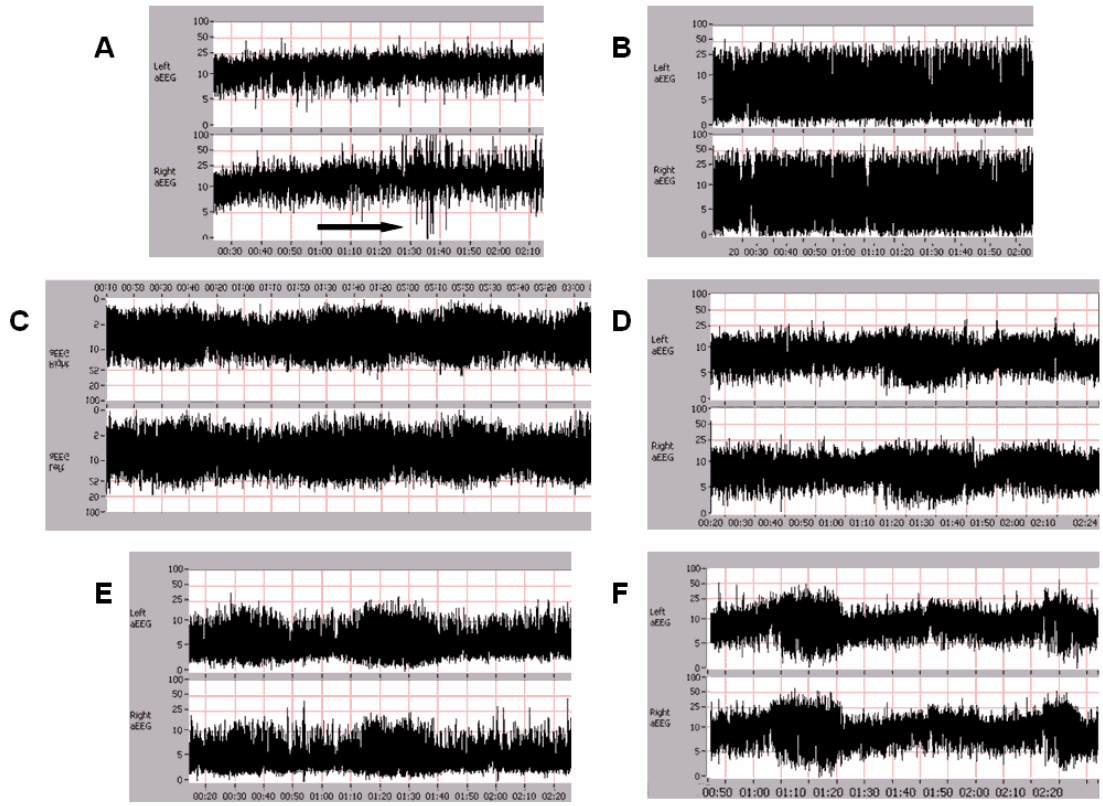
For term infants at risk of seizures, healthy term infants and preterm infants with EEGs recorded at 36 – 38 weeks gestation we analysed EEGs during both 'quiet' and 'active' sleep.

The sleep state was defined as 'quiet' sleep when the aEEG trace broadened, and 'active' sleep when the aEEG trace narrowed. The clarity of sleep state changes varied between EEG recordings and we used the following criteria for each EEG:

1. Level one – no evidence of sleep state cycling (figure 2-2A and B);
2. Level two – indistinct sleep states present on aEEG trace (figure 2-2C);
3. Level three – sleep states present on aEEG trace, but less evident on either:
   a) the lower margin (figure 2-2D) or
   b) the upper margin (figure 2-2E); and

4. Level four – clear sleep states present on aEEG trace with the onset of 'quiet' sleep marked by both an increase in upper margin of aEEG and by a decrease in the lower margin of the aEEG (figure 2-2F)

Figure 2-2
Illustrative aEEG examples of level one sleep state cycling (A, arrow indicates period of artefact, and B), level two (C), level three-a (D), level three-b (E) and level four sleep state cycling (F). Top half of each trace is from the left side of the head and bottom half of each trace is from the right side.



2.5.4 Choosing EEG portions for quantitative assessment

2.5.4.1 Time from start of recording

Analyses of EEG data were performed for inclusion in the database when infants were resting quietly. A second research group, based out of Christchurch and then Melbourne, using the ReBRM machines to evaluate their utility in the preterm population, had a slightly different strategy for EEG placement and analysis. In the Auckland cohort the researcher approached the bedside nurse regarding the timing of EEG placement as well as the ability of the infant to tolerate the procedure. Some infants had the EEG placed before

the oropharyngeal cares were performed, and some after the cares. In other infants the EEG was positioned just before extubation to CPAP, and in one infant a pneumothorax requiring drainage was found as the EEG placement was completed. In all cases the EEG device was switched on before the electrode placement began and in some cases there was a short delay from switching on the device until the start of electrode placement. Therefore, there was a variable time delay and degree of handling of the infants after the EEG recording began.

In the Melbourne cohort the EEG was placed after the completion of cares and the infant was resting quietly for at least the subsequent two hours. In addition, the EEG device was switched on only after the ground lead and the first side of the EEG were in place. The sixty minute period for analysis was chosen to commence 30 minutes after the EEG device was switched on.

The effect of varying the time of analysis was examined on a group of 10 EEGs recorded in Melbourne and 10 recorded in Auckland. For each of the infants the data were analysed by both protocols. The first 60 minute period analysed (Time 1) was chosen to commence 30 minutes after the machine was switched on for infants from Melbourne, and 30 minutes from the first event marking for infants from Auckland (expected to be only 5 – 10 minutes later for infants from Auckland compared with infants from Melbourne). The second 60 minute period analysed (Time 2) was chosen as a time with minimal or no marked events. For the Auckland infants this was taken as their baseline analysis period used in all their analyses. For the Melbourne infants no information was available about the events which were marked, so all events were avoided if possible.

The 20 EEGs were analysed, with simple regression and Bland-Altman plots (Bland & Altman, 1986, 1995), to determine differences in quantitative neurophysiological measurements between the protocols. The measurements analysed included left and right values for SEF, median amplitude, impedance and hum.

There was a median (range) time difference between the start of the two segments analysed (Time 2 – Time 1) of 20 (-19 to 145) minutes.

Table 2-3
Regression analyses for quantitative neurophysiological analyses performed 30 minutes after commencing EEG (Time 1) and at a time chosen when the infant was resting (Time 2), n = 20.

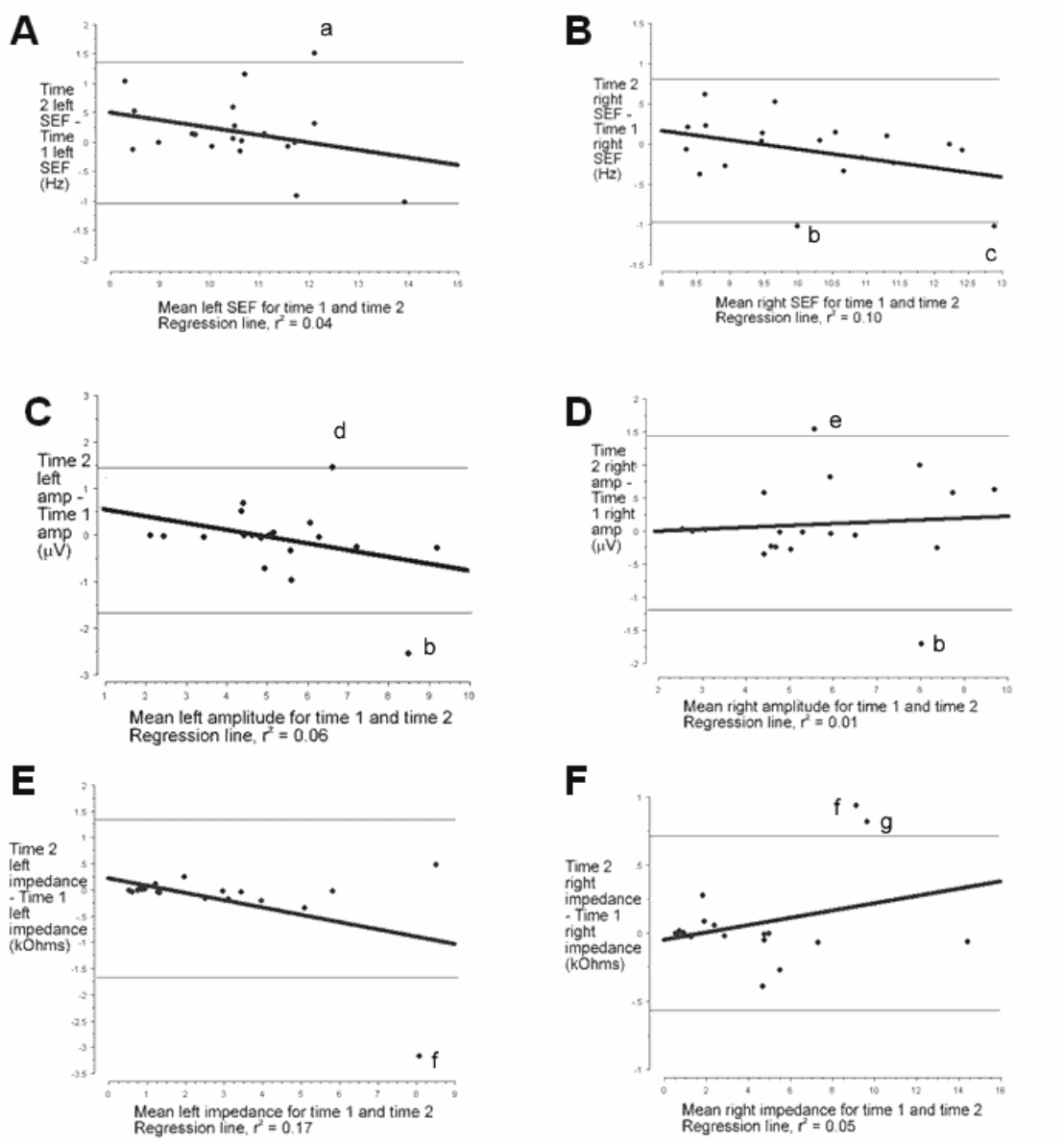
Quantitative measure	Time 1 Median (range)	Time 2 Median (range)	Simple regression (Time 1 vs Time 2)	
			r^2	p
Left SEF	10.9 (7.8 – 14.4)	10.6 (8.4 – 13.4)	0.85	<0.0001
Right SEF	10.9 (8.3 – 13.4)	10.1 (8.3 – 12.3)	0.92	<0.0001
Left median amplitude	5.2 (2.1 – 9.7)	5.1 (2.1 - 9.0)	0.85	<0.0001
Right median amplitude	4.8 (2.8 – 8.9)	5.6 (2.6 – 10.0)	0.90	<0.0001
Left impedance	3.2 (1.3 – 9.6)	1.7 (0.5 – 8.7)	0.93	<0.0001
Right impedance	5.3 (1.3 – 14.5)	2.6 (0.5 – 14.4)	0.99	<0.0001
Left hum	6.6 (4.0 – 124.0)	6.5 (2.1 – 73.6)	0.96	<0.0001
Right hum	5.4 (0.8 – 52.7)	4.8 (0.7 – 52.8)	0.98	<0.0001

Simple regression analyses (table 2-3) and Bland-Altman plots (figure 2-3) indicate that there were no systematic differences between quantitative analyses performed at Time 1 with those performed at Time 2. Seven of the 20 recordings had quantitative measures outside the mean +/- two standard deviation plots (table 2 –4).

Table 2-4
Description of EEGs with points outside mean +/- 2 standard deviations on Bland-Altman plots.

	Time difference Time 2 – Time 1 (mins)	Measures falling outside mean +/- 2 standard deviations
Infant a	15	Left SEF
Infant b	59	Right SEF, left and right amplitude
Infant c	145	Right SEF
Infant d	17	Left amplitude
Infant e	-19	Right amplitude
Infant f	78	Left and right impedance
Infant g	60	Right impedance

Figure 2-3
Bland-Altman plots showing 95% limits of agreement and regression lines for spectral edge frequency (A and B), amplitude (C and D) and impedance (E and F) measurements comparing set time analysis with periods when infant has minimal handling. Points "a" to "g" represent individual infants (see table 2-4).



The two protocols for choosing the EEG period to be analysed do not produce systematic differences in quantitative neurophysiological parameters. The EEG recordings that had more than one parameter outside the mean +/- two standard deviations on Bland-Altman plots had the time periods separated by 59 minutes or more. Therefore, analyses from the two centres can be considered comparable without reanalysing the data using different time parameters.

2.5.4.2 Analysis of EEG when infant resting vs active interventions

To examine the effect of significant handling episodes on the quantitative neurophysiological measurements, 25 EEGs with more than six hours of continuous data were analysed during the time in which the baby was handled (Time 3) in addition to the hour in which they were quiet (Time 2). Examples of handling of the infants include intubation, administration of surfactant, suctioning of the endotracheal tube, oral suctioning, echocardiography and general cares (including taking the temperature, changing the nappy and adjusting head and body position). The results were compared using Wilcoxon signed rank tests (table 2 –5).

The time difference between the start of the two segments analysed (time 3 – time 2) was 111(-127 to 276) minutes. The only significant difference in measurements between periods with the infant resting quietly and when actively handled was in the left SEF measurements, which were higher during handling. Therefore, we chose the periods for EEG analysis when infants were resting quietly, unless otherwise stated. The results may have been slightly different if shorter periods were analysed, such as the period during which the surfactant was administered and five to ten minutes after this, as this is the period one would anticipate the maximum effect on physiological and neurophysiological parameters. The advantage of obtaining quantitative measurements as the median value over 60 minutes is that any such short-term variations are smoothed out.

Table 2-5
Difference in quantitative measures for EEG analysed when the infant was resting quietly and when the infant was handled, n = 25.

Quantitative parameter	Time 2 (quiet): median (range)	Time 3 (handling): median (range)	Wilcoxon signed rank p-value
Left SEF (Hz)	10.6 (8.2 – 15.5)	11.0 (8.7 – 16.6)	0.0009
Right SEF (Hz)	10.7 (8.8 – 15.3)	10.7 (8.9 – 15.1)	0.06
Left amplitude (μV)	5.2 (2.1 - 43.5)	5.1 (2.7 – 12.0)	0.13
Right amplitude (μV)	4.8 (1.7 – 10.7)	4.9 (2.4 – 11.1)	0.14
Left intensity (μV^2)	8.8 (1.5 – 50.2)	9.2 (2.6 – 40.0)	0.08
Right intensity (μV^2)	7.7 (1.8 – 42.5)	9.0 (1.6 – 40.1)	0.49
Left impedance (kΩ)	3.4 (0.6 – 10.7)	3.3 (0.5 -11.6)	0.95
Right impedance (kΩ)	3.6 (0.8 -13.2)	3.8 (0.6 – 13.5)	0.51
Left hum (μV)	6.8 (2.1 – 73.6)	5.8 (1.8 – 69.2)	0.05
Right hum (μV)	4.6 (0.4 – 46.5)	3.7 (0.7 – 58.2)	0.16

2.6 Physiology data acquisition and analysis

2.6.1 Marquette data download

After 17 February 2003 many infants in the Level 3 part of NICU had recordings of their physiologic variables downloaded every 61 seconds using Marquette Solar 8000 monitors (GE medical systems, Wisconsin, USA) and Bedmaster V1.3 software (Excel Medical Electronics Inc, Florida, USA) as part of their routine NICU monitoring. Physiologic data for each infant included continuous SaO_2 monitoring and heart rate monitoring (from SaO_2 monitoring, and cardiorespiratory chest leads in most infants) and in many infants also included respiratory rate and continuous invasive blood pressure monitoring.

Each epoch of available data was exported to an Excel file with the same file name as the corresponding EEG to allow for cross-referencing of the data. In addition to the period of the EEG, a one hour period before the EEG recording was included in the epoch. The following times were marked by colour codes on the individual Excel files: the time the EEG was switched on, the time that the EEG electrodes were felt to be adequately applied for the start of the recording (one colour when the Marquette monitor time had been recorded, or

a second colour when the time was deduced from the marking on the EEG recording), and the time when the baseline 60 minute analysis period began.

2.6.1.1 Blood pressure

Infants with invasive blood pressure (BP) monitoring had recordings of BP downloaded every 61 seconds (Groves et al., 2005). This recorded BP value is an average of the BP monitored over the previous six seconds. If available these measures of BP were then entered into the physiology database. Intermittent BP measures obtained by Doppler measurement using the Marquette monitors with appropriately sized cuffs, were recorded in the physiology database the first time a new BP recording was taken (that is only for the first minute after a new recording) if invasive BP readings were not available.

2.6.1.2 Heart rate, respiratory rate and oxygen saturation recordings

Every 61 seconds the electrocardiography, respiratory and oxygen saturation inputs were recorded by the Bedmaster software as the last measurements on the Marquette monitor. The heart rate is averaged over the previous three seconds from the electrocardiograph tracing. The oxygen saturation is averaged over the previous six seconds from the saturation probe tracing. The data were downloaded into an Excel file for each cot space. Recordings of heart rate, respiratory rate and oxygen saturation were extracted from the downloaded data by the use of formulae. When possible the heart rate was obtained from the electrocardiography download. If the chest leads were not in place the heart rate was obtained from the pulse oximeter recording. Episodes of bradycardia or tachycardia were confirmed by cross-checking between download sources whenever possible. If only one download source showed bradycardia, and there was no evidence of apnoea or desaturation then the heart rate between 120 and 180 beats per minute was recorded from whichever source was appropriate. If chest leads were not in place no respiratory rate was available.

Recordings from the oxygen saturation download were excluded if there was a discrepancy of more than 10 beats per minute between the heart rate from the pulse oximeter and that from the chest leads.

2.7 Echocardiographic measurements

All echocardiography was performed by Drs Alan Groves and Carl Kuschel as a part of Dr Alan Groves' MD research study. Between April 2003 and February 2004 we attempted to recruit infants to both EEG and echocardiography studies to enable us to determine the relationships between these measures when performed at the same times on the same infants. Echocardiography was performed as close as possible to 5, 12, 24 and 48 hours after birth, immediately before or after routine nursing cares to minimise the number of discrete handling episodes encountered by each infant.

The following explanation was written by Dr A Groves to describe the techniques used to obtain the echocardiographic measures. Superior vena caval (SVC) flow volume was assessed as described by Kluckow et al (Kluckow & Evans, 2000b). SVC diameter was assessed using an M mode trailing edge-leading edge technique from a high parasternal view. Measurements were taken at the point at which the vessel begins to open up into the right atrium. Maximum and minimum vessel diameters were assessed in five consecutive cardiac cycles, and the mean of these 10 measures taken to be the mean SVC diameter for flow volume quantification. SVC flow velocity was assessed using pulsed wave Doppler from a low subcostal view. The Doppler range gate was placed at the point at which the vessel begins to open up into the right atrium. Measures of SVC flow were averaged over ten consecutive cardiac cycles to minimise the impact of respiratory variation in flow. Any reversed flow in the SVC was quantified and deducted from the measured forward flow.

Right ventricular outflow diameter was assessed by frame-by-frame analysis of the two-dimensional image at the hinge-points of the pulmonary valve from either the parasternal short axis or tilted parasternal long axis views during cardiac systole (Tsai-Goodman, Martin, Marlow, & Skinner, 2001). Pulmonary

systolic velocity time integral (VTI) was assessed using pulsed wave Doppler, with the range gate placed at the level of the tips of the pulmonary valve leaflets when viewed from the parasternal short axis view (Tsai-Goodman et al., 2001).

In all cases volume of flow (expressed as ml/kg/min) was calculated from:

$$\frac{\text{VTI} \times (\text{vessel diameter})^2 \times \text{heart rate} \times \pi}{4 \times \text{birth weight}}$$

where VTI = velocity time integral in cm, π = 3.14159, vessel diameter in cm, birth weight in kg.

2.8 Clinical data collection

At the time of the first EEG information was collected regarding gestational age, birthweight, Apgar scores, early ventilation and metabolic parameters (for calculation of CRIB scores). At each EEG the current respiratory support, including oxygen requirement and medications were recorded on the recording sheet. At the time of discharge copies were made of discharge summaries, growth charts during the admission, cranial ultrasound reports and Hammersmith neonatal neurology examinations (HNNE). At the time of final data collection information was obtained from the Neonatal Database regarding history of antenatal steroid administration, postnatal steroid administration, medical or surgical treatment of a patent ductus arteriosus, and any missing data. Each infant's hospital notes were also obtained electronically to determine the last paediatric outpatient clinic assessment and the date of the last assessment by the psychologist.

Infants transferred to other hospitals had their discharge summaries and other relevant information requested from the discharging unit. Follow-up information was requested from paediatricians, visiting therapists and psychologists.

2.9 Neurodevelopmental follow-up data

Infants with birthweights < 1500g have a Bayley-II examination by a trained psychologist at 18 months chronological age. We accessed the results of the mental and psychomotor developmental indices from these examinations.

Infants born with weights of 1500g or more, and those transferred to other centres had Bayley-II examinations by registered psychologists in the nearest centre with a qualified examiner at, or after, 18 months chronological age.

Infants were examined around the time of the Bayley-II examination by a paediatrician, or paediatric trainee. They performed a brief, structured neurological examination and obtained brief details of medical problems since discharge, with an emphasis on neurological pathologies, injuries, infections and seizures.

When we were unable to arrange for Bayley-II examinations to be performed on an infant we requested information from their regional child developmental service, or paediatrician for an assessment of their motor and mental development.

2.10 Statistical analyses

Analyses were performed using Statview version 5.0.1 (SAS Institute Inc, Cary, NC, USA). Data are reported as median (range), mean (standard deviation) or number (percentage) as appropriate. Comparisons made between two groups were analysed with Student's t-test or Mann-Whitney U test as appropriate. Comparisons between parameters measured at different time points in the same infants were analysed with Wilcoxon signed rank and Freidman tests. Comparisons between continuous variables that approximated a normal distribution were analysed with factorial analysis of variance (ANOVA) with Fisher's post-hoc analyses. Comparisons between subgroups of infants who had EEGs recorded on consecutive days were analysed with repeated measures ANOVA. Comparisons between categorical data were analysed with contingency tables, and Fisher's Exact tests were used when there were small numbers in some cells of the contingency table. Comparisons between multiple Chi-squared statistics in contingency tables with varying cell sizes were analysed with Cramer's V coefficients. Relationships between continuous variables were analysed with simple linear regression, with multiple regression analyses used to further test significant relationships. Relationships between categorical variables were analysed with logistic regression. Receiver operating

characteristic (ROC) curves were used to determine the cut-off value that maximised the sensitivity and specificity for prediction of outcome. P-values < 0.05 were considered to indicate statistically significant results.

3 Results – Electroencephalography patterns in ‘normal’ preterm infants

3.1 Introduction

It is essential to characterise the patterns of quantitative neurophysiological parameters in the preterm population in order to identify the EEG changes that would be expected to occur during the neonatal period. Once these patterns have been determined, the impact of changes from these ‘normal’ patterns due to brain injury, various interventions and illness can be determined. The definition of normality in preterm infant population is problematic because premature delivery is not normal by any standard. However, there are reported patterns of EEG activity, albeit recorded on different forms of EEG machines at different gestations, both around birth and over the time until discharge from intensive care that are defined as normal (J. A. Connell, Oozeer, & Dubowitz, 1987; Eyre, Nanei, & Wilkinson, 1988; Selton et al., 2000; Thornberg & Thiringer, 1990; Vecchierini, d'Allest, & Verpillat, 2003; S. Victor, Appleton, Beirne, Marson, & Weindling, 2005). EEGs from ‘normal’ preterm infants at term corrected gestation have been compared with those obtained from healthy term infants at similar gestations (Scher et al., 1994). Scher found differences between preterm and term infants in spectral analyses of sleep states (Scher et al., 1994). Therefore, it is also important to compare quantitative neurophysiological parameters between normal preterm infants at near-term / term corrected gestation and healthy infants born at similar gestations.

Sleep states have been identified in preterm infants from 27 weeks postmenstrual age using polygraphic recordings, but accurate determination of state is not possible using only two channel EEG recordings (Curzi-Dascalova et al., 1993). Patterns of broad and narrow bands have been noted on aEEG traces that are consistent with the raw EEG changes occurring in quiet and

active sleep. However, it is not possible to differentiate between active sleep and quiet wakefulness on these traces. Due to the uncertainty of sleep state assignment for our EEG data we have chosen to limit state specific analyses to preterm infants with EEGs obtained after 36 weeks postmenstrual age for comparison with healthy term infants.

In this chapter we report:

1. The changes in quantitative neurophysiological parameters over the first week after delivery in a population of preterm infants delivered before 32 weeks gestation who had unremarkable cranial ultrasound scans during their admission;
2. The changes in quantitative neurophysiological parameters in the same group of infants throughout their NICU stay; and
3. The differences between quantitative neurophysiological parameters recorded in preterm infants at 36 – 38 weeks postmenstrual age and healthy near-term / term infants.

3.2 Methods

Infants were considered 'normal at discharge' if they survived to discharge, had no major congenital anomalies and had unremarkable cranial ultrasound scans, ie they had no evidence of white matter injury and either no intraventricular haemorrhage or only germinal matrix haemorrhage (Grade 1 GM-IVH).

Infants recruited under protocol 2 had four cotside EEGs performed over the first week after delivery, and then fortnightly from day 14 until 36 weeks corrected gestation or discharge. Infants recruited under protocol 1 had one EEG within 48 hours of delivery, another one week after delivery and some had a further EEG later in their NICU course after recovery from an acute deterioration.

Quantitative neurophysiological measurements of SEF, median and minimum amplitudes, and continuity at the 10, 25, 50 and 100μV thresholds were

assessed as median values for the 60 minutes of the baseline analysis (section 2.5.1) for each EEG. Left and right sided values were then averaged.

3.2.1 Normal preterm infants over the first week after delivery

We only included infants recruited to protocol 2 in these analyses as we were interested in the changes in neurophysiological parameters over the whole week. Infants recruited to protocol 1 had all their EEGs clustered around days 1 and 2 and days 6 to 8, rather than spread throughout the week. The infants were divided into tertiles of gestational age in order to examine the effect of gestational age at delivery (< 28 weeks, 28 – 29 weeks and 30 – 31 weeks gestational age).

EEG measures were analysed by factorial ANOVA with Fisher's post-hoc correction for multiple comparisons. Repeated measures ANOVA could not be used for the entire group, as a maximum of four recordings were made for each infant over the first week, not always on the same days. However, to confirm that the trends observed were not due to the effects of recordings from different babies on different days, we used repeated measures ANOVA to analyse data from a subgroup of 24 infants who had their first recording within 24 hours of birth and then at least one further recording before 72 hours. Subgroup analyses which reached statistical significance have the p-values included in parentheses. Values are given as median (range).

3.2.2 Normal preterm infants beyond the first week after delivery

We included the infants identified from protocol 2 as 'normal at discharge' and any infants recruited to protocol 1 who fulfilled the same criteria and had an EEG after the first week. The infants included in these analyses are those in section 3.2.1 who remained beyond the first week of life in National Women's Neonatal Intensive Care Unit, or who were transferred to North Shore Hospital Special Care Baby Unit. EEGs were analysed firstly according to postnatal age at which the EEG was performed, and secondly they were grouped according to postmenstrual age at the time of the EEG: <28 weeks, 28 – 29 weeks, 30 – 31 weeks, 32 – 33 weeks, 34 – 35 weeks, and 36 – 38 weeks. EEG measures were analysed by factorial ANOVA with Fisher's post-hoc correction for multiple comparisons. Repeated measures ANOVA could not be used for the entire

group, as not every infant had a technically acceptable EEG in each time period. The effect of gestational age at delivery was examined by examining infants in the tertile groups as in section 3.2.1.

In order to examine how quantitative neurophysiological parameters obtained on preterm infants at term corrected gestations differ from those obtained on infants born near term, we compared EEGs performed between 36 and 38 weeks postmenstrual age in normal preterm infants and with EEGs performed within one week of delivery on healthy infants born at or near term (from 35 weeks gestation). We have limited our sleep state analyses to the most mature infants and included only infants with sleep state cycles of level three and four on their EEGs (section 2.5.3). Each of the quantitative neurophysiological parameters was assessed from sections of EEG of at least 10 minutes for each sleep state. The sleep state was defined as quiet sleep when the aEEG trace broadened, and active sleep when the aEEG trace narrowed with a higher minimum amplitude. For quiet sleep analyses we included all the available EEG identified within one period of quiet sleep, while for active sleep analyses we included up to 60 minutes of EEG from one period of active sleep.

EEG measures were compared between the same infants in quiet sleep and in active sleep using Wilcoxon signed rank tests, and between preterm and term infants using Mann-Whitney U-tests.

3.3 Results

3.3.1 Changes in quantitative neurophysiological parameters in normal preterm infants over the first week after delivery

Between December 2002 and February 2004, 153 infants of less than 32 weeks gestation were admitted. Parents of 98 infants (64%) were approached regarding the study (protocol 2). Informed parental consent was obtained for 79 infants (81% of those approached), and declined for 19 infants (19%). The parents of 55 babies were not approached regarding the study: two infants were unable to be stabilised and died early; five parents/guardians were unavailable for consent; the parents of four infants did not speak English; one infant had a chemical burn on her skin related to central line placement and the

family was not approached, and for 43 either researcher (two infants) or monitor (41 infants) was unavailable. As there was only one researcher and two EEG devices available we were unable to recruit all eligible infants, and therefore sought preferentially to recruit infants born at less than 29 weeks gestation.

Sixty-two of the 79 recruited infants fulfilled the criteria for inclusion in this analysis. Five infants died before discharge, seven infants had evidence of white matter abnormalities on ultrasound scan, four infants had intraventricular haemorrhage > grade 1 on ultrasound scan (two grade 2, one grade 3 and one grade 4) and one infant was withdrawn from the study before a valid EEG was obtained. Of the infants included in the study only four infants had unilateral germinal matrix haemorrhages (two noted on the day 5 ultrasound and four noted at day 28). The infants included had a median gestation of 29 weeks (range 24 – 31) and median birthweight of 1235g (range 540 – 1980). There were 29 boys and 33 girls.

For analysis of neurophysiology measures the first EEG was technically acceptable in 59 infants (95%), the second EEG was acceptable in 58 infants (94%), the third EEG in 57 infants (92%) and the fourth EEG in 57 infants (92%). The first EEG was obtained at a median of 29 hours (range 3 – 93). The fourth EEG was obtained at a median of 156 hours (range 75 - 194).

In order to examine the effect of gestational age at delivery the infants were divided into tertiles of gestational age. Twenty infants were born at less than 28 weeks gestation, 22 infants between 28 and 29 weeks gestation, and 20 infants between 30 and 31 weeks gestation.

Table 3-1
Gestation at recording, changes in continuity, amplitude and frequency measures in electroencephalogram recordings over the first week after birth.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Number of EEGs analysed	28	43	39	29	28	19	31	14
Corrected gestation at EEG [weeks]	28.4 (24.1 – 31.9)	28.9 (24.1 – 32.0)	29.1 (24.4 – 32.0)	30.1 (24.4 – 32.1)	30.0 (24.6 – 32.4)	29.9 (26.0 – 32.6)	29.9 (24.6 – 32.7)	29.1 (25.1 – 31.3)
Continuity at 10μV threshold [%/minute]	100.0 (59.9 – 100)	100.0 (87.4 – 100)	100.0 (87.4 – 100)	100.0 (90.7 – 100)	100.0 (95.0 – 100)	100.0 (92.4 – 100)	100.0 (91.0 – 100)	100.0 (82.8 – 100)
Continuity at 25μV threshold [%/minute]	71.7 (24.8 – 99.2)	79.0 (49.2 – 100.0)	83.6 (53.7 – 99.8)	88.1 (58.8 – 98.7)	89.4 (70.2 – 98.7)	85.7 (56.7 – 100)	85.5 (56.3 – 100)	92.4 (54.4 – 100)
Continuity at 50μV threshold [%/minute]	39.3 (10.2 – 86.5)	47.5 (16.2 – 74.5)	49.4 (15.8 – 73.3)	58.1 (19.7 – 72.9)	56.1 (36.7 – 70.4)	46.4 (29.1 – 81.9)	55.5 (26.7 – 74.1)	64.0 (34.0 – 74.9)
Continuity at 100μV threshold [%/minute]	11.2 (0.0 – 46.8)	14.9 (0.0 – 39.3)	17.1 (1.4 – 45.2)	16.9 (0.0 – 37.2)	16.0 (1.0 – 34.6)	14.3 (0.0 – 48.6)	16.1 (0.0 – 39.3)	18.4 (10.8 – 39.1)
Median amplitude [μV]	5.8 (2.6 – 10.6)	6.4 (2.9 – 10.5)	6.9 (3.9 – 11.0)	7.6 (4.3 – 9.4)	7.5 (5.0 – 9.2)	6.9 (4.1 – 9.3)	7.1 (4.1 – 10.0)	8.3 (7.5 – 10.1)
Minimum amplitude [μV]	2.0 (1.1 – 4.0)	2.3 (1.2 – 4.0)	2.2 (1.1 – 3.9)	2.6 (1.2 – 4.0)	2.9 (1.2 – 4.1)	2.2 (1.4 – 4.8)	2.4 (1.2 – 4.1)	2.9 (1.3 – 4.2)
SEF [Hz]	10.7 (9.3 – 12.9)	10.4 (8.5 – 13.7)	9.9 (8.1 – 12.3)	10.2 (7.8 – 11.9)	10.4 (8.8 – 13.1)	10.2 (9.0 – 13.1)	10.5 (8.7 – 12.6)	10.1 (8.7 – 11.4)

Values are median(range)

Continuity

Analysis of continuity was performed at amplitude thresholds of 10, 25, 50 and 100μV.

At each threshold there was an increase in continuity over the first half of the first week which then stabilised (figure 3-1A, C, E, G). All subgroups showed

similar trends. For infants with early repeated measures the continuity increased significantly over the first three days after birth (figure 3-1B, D, F, H).

At the 10μV threshold there was an increase in percent continuity over the first week ($p = 0.05$, figure 3-1A). All subgroups showed a similar pattern. Results for infants with early repeated recordings showed significant increases in continuity between days 1 and 3 ($p = 0.008$, figure 3-1B).

At the 25μV threshold the percent continuity increased by 29% over the first week ($p < 0.0001$, figure 3-1C). This pattern was also found for boys ($p < 0.0001$), girls ($p = 0.0007$) and each gestational tertile (middle tertile, $p = 0.01$; oldest tertile, $p = 0.007$). Infants with repeated early recordings showed a 13% increase in continuity ($p < 0.0001$, figure 3-1D).

At the 50μV threshold there was a 63% increase in median continuity over the first week ($p < 0.0001$, figure 3-1E and table 1). There was a similar pattern for boys ($p < 0.0001$), girls ($p = 0.008$) and each gestational tertile (middle tertile, $p = 0.03$, figure 3-2). Infants with repeated early recordings showed a 41% increase in continuity between days 1 and 3 ($p = 0.0004$, figure 3-1F).

At 100μV there was a 72% increase in median continuity between days 1 and 8, with a similar pattern for all subgroups (figure 3-1G). However, this did not reach statistical significance ($p=0.06$). Infants with repeated early recordings showed a 52% increase in continuity between days 1 and days 3 ($p = 0.02$, figure 3-1H).

Figure 3-1
Changes in continuity in electroencephalogram recordings over the first week after birth. Box plots show results of continuity at 10μV (A), 25μV (C), 50 μV (E) and 100 μV (G) thresholds for all infants (n=62); p<0.05 for 10, 25 and 50 μV, p=0.06 for 100μV, see text for details. Line graphs show results for individual infants (n=24) with repeated measures between day 1 and day 3 at 10μV (B), 25 μV (D), 50μV (F) and 100 μV (H) thresholds, all p=<0.02, see text for details.

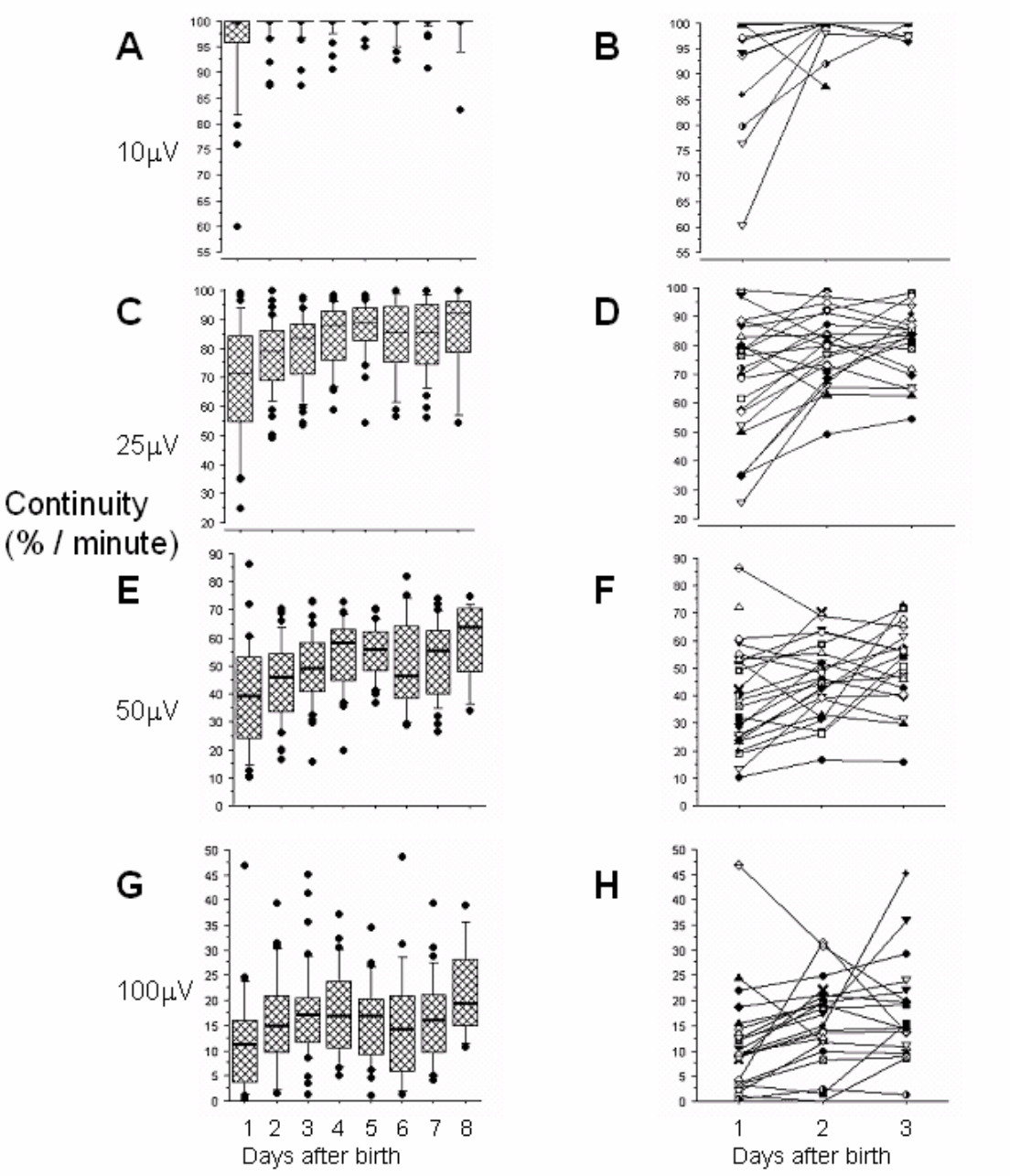
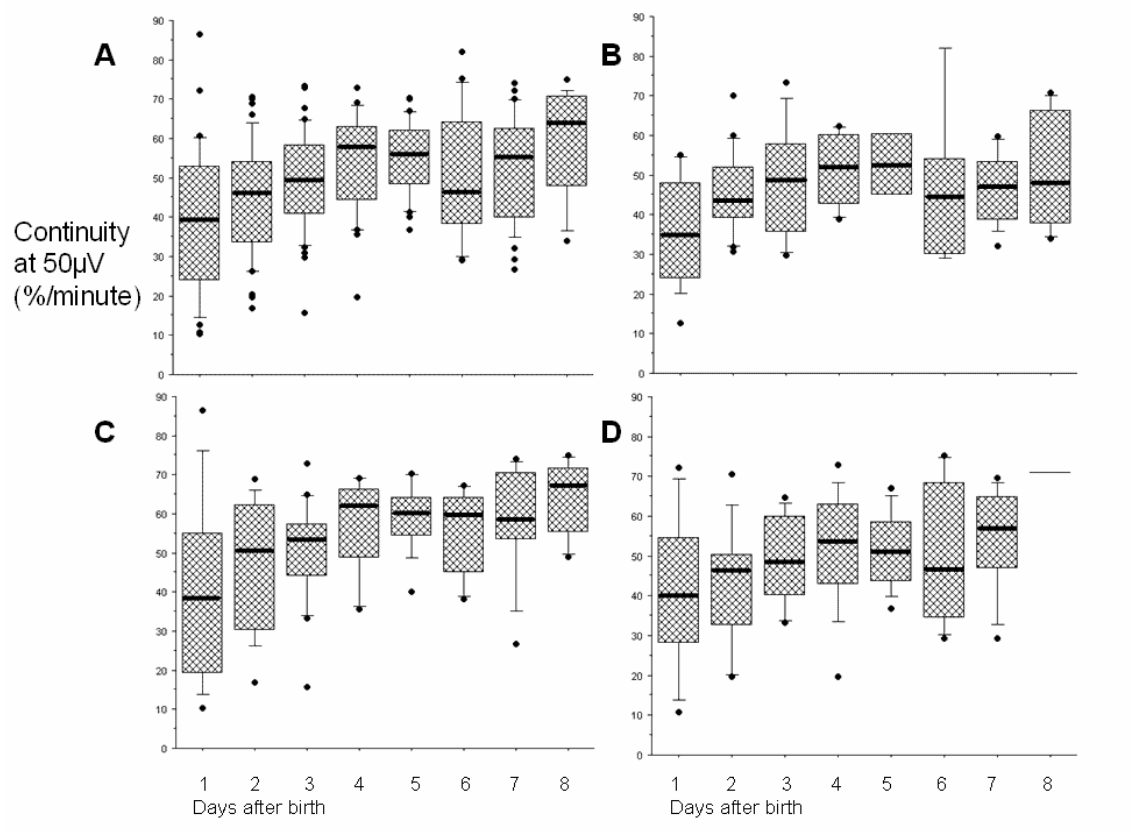


Figure 3-2
Changes in continuity in electroencephalogram recordings over the first week after birth. Box plots show results of continuity at 50μV in the whole cohort (A), the youngest gestational tertile, 24 – 27 weeks gestation (B), the middle gestational tertile, 28 – 29 weeks gestation (C) and the oldest gestational tertile, 30 – 31 weeks (D).



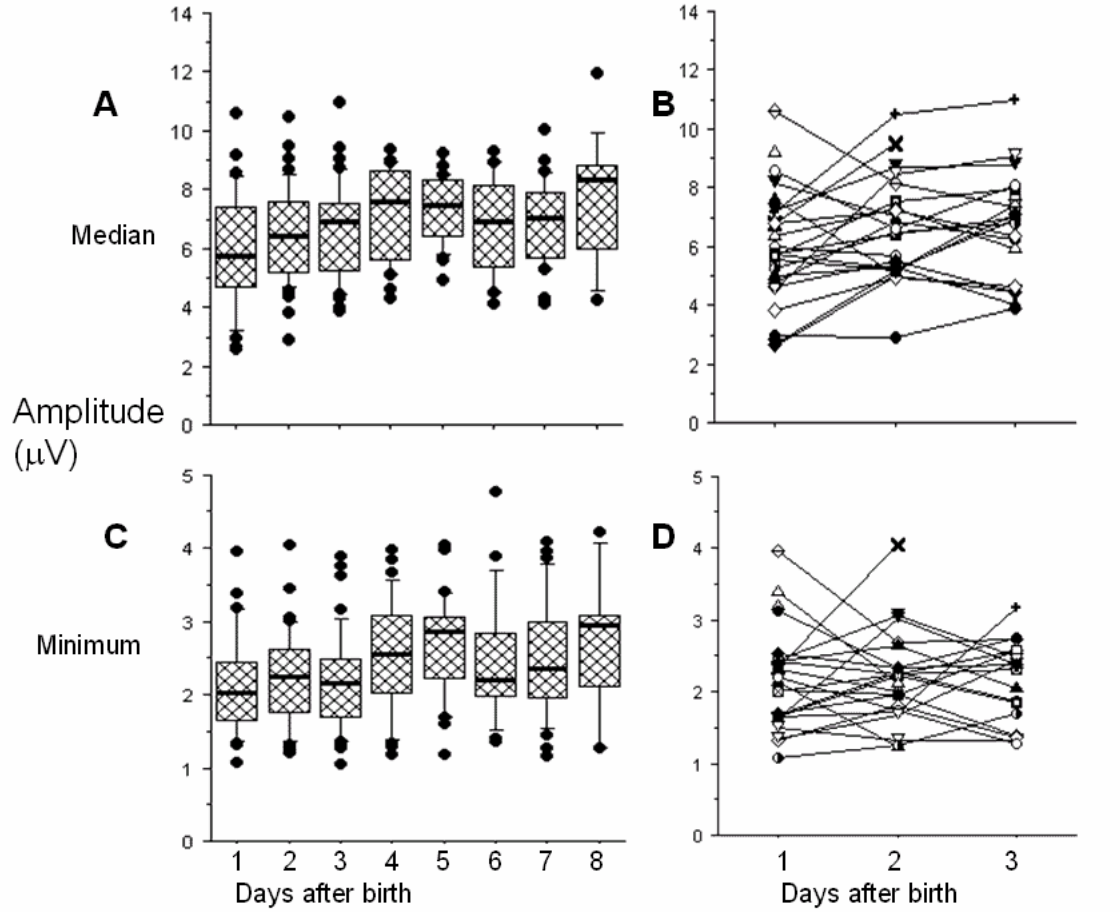
Amplitude

Median amplitude increased by 32% over the first four days from 5.8 (2.6 – 10.6) μV on day 1 to 7.6 (4.3 – 9.4) μV on day 4 before stabilising (p = 0.005, figure 3-3A and table 3-1). Boys (p = 0.004), girls (p = 0.05) and the gestational tertiles all showed similar patterns. Infants with repeated early recordings over the first three days after birth (n = 24) also showed a 17% increase in median amplitude between days 1 and 3 (p = 0.007, figure 3-3B).

The minimum amplitude measures remained stable over the first three days after birth before increasing by 19%, from 2.2(1.1 – 3.9)μV on day 3, to 2.6(1.2 – 4.0)μV on day 4 (p = 0.01, figure 3-3C and table 1). The minimum amplitude was stable over the remainder of the first week. Boys, girls and all tertiles of

infants showed the same pattern. No significant changes over the first three days were seen in infants with early repeated recordings (p = 0.7, figure 3-3D).

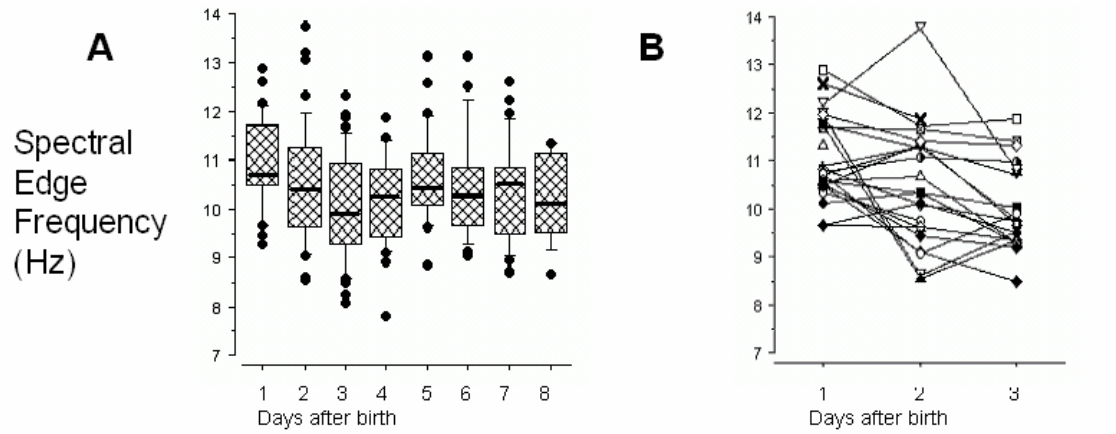
Figure 3-3
Changes in amplitude in electroencephalogram recordings over the first week after birth. Box plots show median amplitude (A) and minimum amplitude(C) for all infants (n=62), all p<0.02, see text for details. Line graphs show median amplitude (B) and minimum amplitude (D) for individual infants (n=24) with repeated measures between day 1 and day 3; median amplitude p=0.007, minimum amplitude p=0.7, see text for details.



Spectral Edge Frequency

Average SEF fell by 8% from a median of 10.7 (9.3 – 12.7) Hz on day 1 to 9.9 (8.1 – 12.3) Hz on day 3 and then stabilised (p=0.06, figure 3-4A and table 3-1). A similar pattern was seen in boys, girls and each gestational tertile (youngest tertile, p = 0.05; middle tertile, p = 0.03). Infants with repeated early measures showed a similar 8% decrease from 10.7 (9.6 – 12.9) Hz on day 1 to 9.8 (8.5 – 11.9) Hz on day 3 (p = 0.001, figure 3-4B).

Figure 3-4
Changes in spectral edge frequency (SEF) in electroencephalogram recordings over the first week after birth. Box plots show overall SEF (A) for all infants (n=62, p=0.06), see text for details. Line graphs show overall SEF (B), for individual infants (n=24) with repeated measures between day 1 and day 3, p=0.001, see text for details.



3.3.2 Changes in quantitative neurophysiological parameters in normal preterm infants over the course of admission to NICU, after the first week

Fifty-five of the 62 infants included in the analysis of first week changes for normal infants at discharge (section 3.3.1) had further EEGs recorded, up to 98 days after delivery. Further EEGs were available on 19 infants born at less than 28 weeks gestation, 22 infants between 28 and 29 weeks gestation, and 14 infants between 30 and 31 weeks gestation. In addition, one infant recruited into protocol 1 fulfilled the criteria for being normal at discharge and had a further EEG during their NICU course, on day 55.

The infants included in these analyses had a median gestation at delivery of 28 (range 24 - 31) weeks and median birthweight of 1165 (range 540 - 1980) grams. There were 25 boys and 31 girls. At each time period between 1 and 46 infants had acceptable EEG recordings (table 3.2). Thirteen EEGs were recorded on 12 healthy term infants during the first week after delivery.

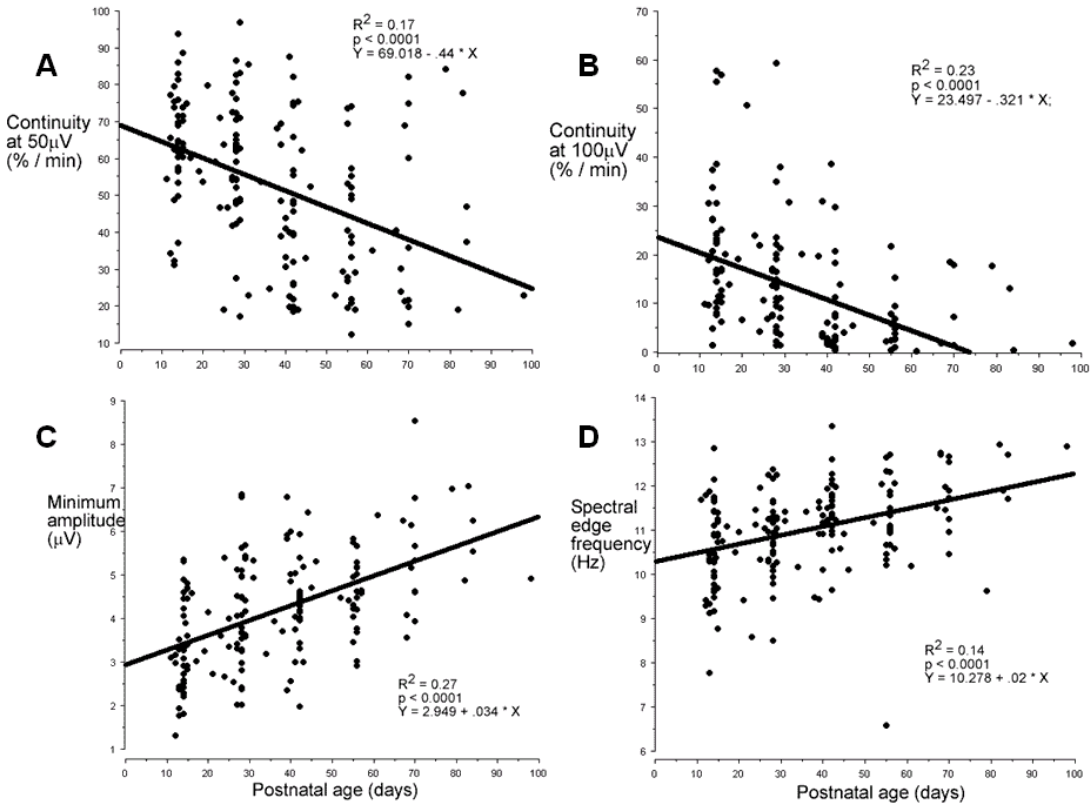
Table 3-2
Demographic data for infants with adequate EEG recordings beyond the first week after delivery, and healthy term infants.

Postnatal age at EEG (weeks)	Number of infants with adequate EEG	Gestation in weeks at delivery	Birthweight in grams	Postnatal age at EEG recording (days)
2	46	28 (24 - 31)	1130 (540 - 1980)	14 (11 - 21)
4	43	28 (24 - 31)	1250 (680 - 1980)	28 (23 - 34)
6	38	28 (24 - 31)	1000 (540 - 1850)	42 (36 - 46)
8	24	27 (24 - 29)	910 (540 - 1480)	56 (52 - 61)
10	12	26 (24 - 27)	820 (540 - 1200)	70 (67 - 70)
12	5	25 (24 - 26)	680 (540 - 850)	83 (79 - 88)
14	1	24	710	98
Healthy Term	12*	38 (35 - 40)	3475 (2340 – 4630)	2 (1 - 8)

Values are median (range)
*one healthy term infant had two EEGs recorded in the first week after delivery

Firstly, we analysed the EEGs according to the postnatal age at which the EEG was performed (table 3-2). There were no relationships between continuity at the 10 and 25μV thresholds or median amplitude and postnatal age ($p = 0.09$, 0.14 and 0.36, respectively). Continuity at the 50 and 100μV thresholds decreased with increasing postnatal age ($p < 0.0001$ for both, figure 3-5 A and B). Minimum amplitude and SEF increased with increasing postnatal age ($p < 0.0001$ for both, figure 3-5 C and D).

Figure 3-5
Relationships between postnatal age in days and continuity at the 50µV (A) and 100µV (B) thresholds, minimum amplitude (C) and spectral edge frequency (D) in electroencephalogram recordings obtained beyond the first week after delivery.



Secondly, we analysed the EEGs according to the postmenstrual age of the infants at the time of the EEG (table 3-3).

Table 3-3
Postmenstrual age at recording, changes in continuity, amplitude and frequency measure in electroencephalogram recordings beyond the first week after delivery until discharge.

Postmenstrual age at EEG	<28 weeks	28 – 29 weeks	30 – 31 weeks	32 – 33 weeks	34 – 35 weeks	36 – 38 weeks
Total number of infants	5	15	31	43	43	25
Infants born at < 28 weeks	5	15	15	16	15	13
Infants born at 28 – 29 weeks			16	16	20	8
Infants born at 30 – 31 weeks				11	8	4
Number of EEGs analysed	5	15	33	45	44	26
Continuity at 10μV threshold [% / minute]	100.0 (93.8-100.0)	100.0 (96.4-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
Continuity at 25μV threshold [% / minute]	79.2 (54.5-91.5)	93.6 (66.6-100.0)	96.8 (82.3-100.0)	97.1 (72.8-100.0)	98.5 (68.4-100)	100.0 (81.1-100.0)
Continuity at 50μV threshold [% / minute]	48.8 (34.3-59.1)	69.3 (32.3-86.0)	69.4 (46.8-96.9)	55.6 (19.1-87.7)	40.6 (12.2-82.7)	36.5 (5.2-84.3)
Continuity at 100μV threshold [% / minute]	23.1 (9.7-27.2)	24.3 (4.8-57.7)	20.8 (6.8-59.4)	7.6 (0.0-38.5)	2.7 (0.0-19.1)	0.8 (0.0-18.0)
Median amplitude [μV]	6.5 (3.8-9.2)	8.7 (5.7-12.0)	8.6 (6.5-14.2)	8.4 (5.2-10.8)	8.5 (5.8-12.8)	8.9 (6.3-13.5)
Minimum amplitude [μV]	1.9 (1.3-3.6)	2.5 (1.8-3.5)	3.2 (2.0-5.4)	4.0 (2.0-5.4)	4.8 (2.6-6.8)	5.4 (3.9-8.5)
SEF [Hz]	9.3 (7.8-12.9)	10.3 (9.1-11.1)	10.7 (8.5-12.3)	11.2 (9.6-12.6)	11.4 (6.6-13.4)	11.4 (9.6-12.9)

Values are median(range)

Continuity

At the 10μV threshold the median continuity was 100% / minute for all postmenstrual age groups (table 3-3). Infants in the lowest gestational tertile had continuity at the 10μV threshold below 100% / minute in two of the five EEGs (40%) recorded at <28 weeks postmenstrual age, and one of 15 EEGs

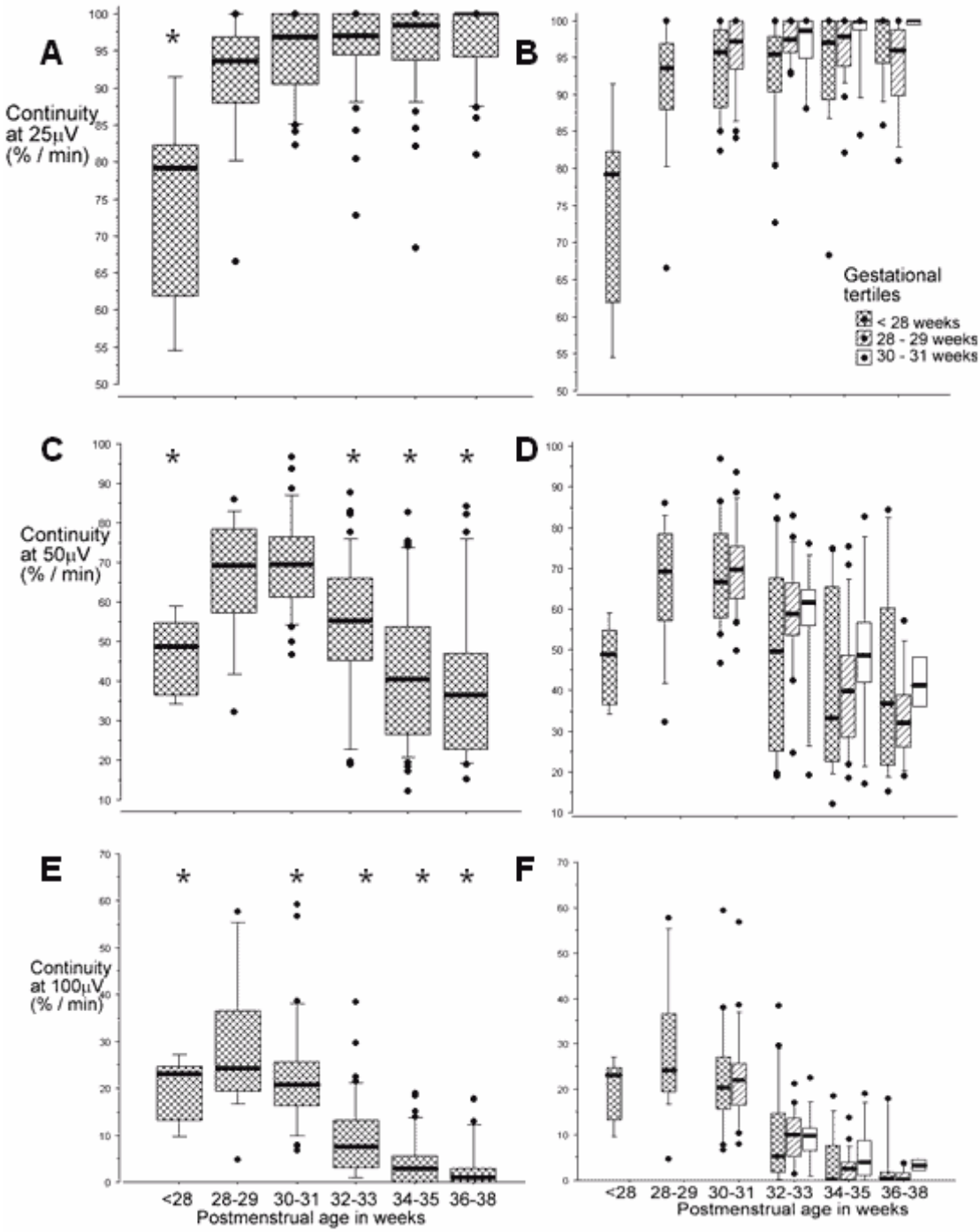
(7%) recorded at postmenstrual ages of 28 and 29. Infants in the middle and oldest gestational tertiles had continuity at the 10μV threshold of 100% / minute in all the EEGs recorded.

At the 25μV threshold the median continuity increased by 26% from recordings obtained at <28 weeks postmenstrual age, reaching 100% / minute at 36 – 38 weeks (overall $p < 0.0001$, table 3-3 and figure 3-6A). Infants in each of the tertiles had similar patterns ($p < 0.0001$ for youngest tertile, figure 3-6B).

At the 50μV threshold the median continuity increased by 42% from recordings obtained at <28 weeks postmenstrual age, reaching 69% / minute at 28 - 31 weeks ($p \leq 0.03$ for post-hoc comparison) before falling to 37% / minute at 36 – 38 weeks postnatal age ($p \leq 0.03$, table 3-3 and figure 3-6C). Infants in each of the tertiles had similar patterns ($p = 0.03$ for increase in youngest tertile; $p < 0.02$ for decreases in youngest and middle tertiles, figure 3-6D).

At the 100μV threshold the median continuity increased by 5% from recordings obtained at <28 weeks postmenstrual age, reaching 24% / minute at 28 – 29 weeks postmenstrual age ($p = 0.03$ for post-hoc comparison) before falling to 1% / minute at 36 – 38 weeks postnatal age (all $p \leq 0.01$, table 3-3 and figure 3-6E). Again, infants in each of the tertiles had similar patterns (decrease in continuity $p < 0.009$ and < 0.005 for youngest and middle tertiles, figure 3-6F).

Figure 3-6
Changes in continuity in electroencephalogram recordings beyond the first week. Box plots show results of continuity at 25µV (A), 50µV (C) and 100µV (E) thresholds for all infants ($p \leq 0.0001$, $= 0.0003$ and < 0.0001, respectively for overall comparisons) and for infants according to tertile of gestational age at delivery (B, D and E for 25µV, 50µV and 100µV thresholds respectively), see text for details. Youngest gestational tertile indicated by cross-hatch, middle by diagonal stripes and oldest gestational tertile indicated by white boxes.



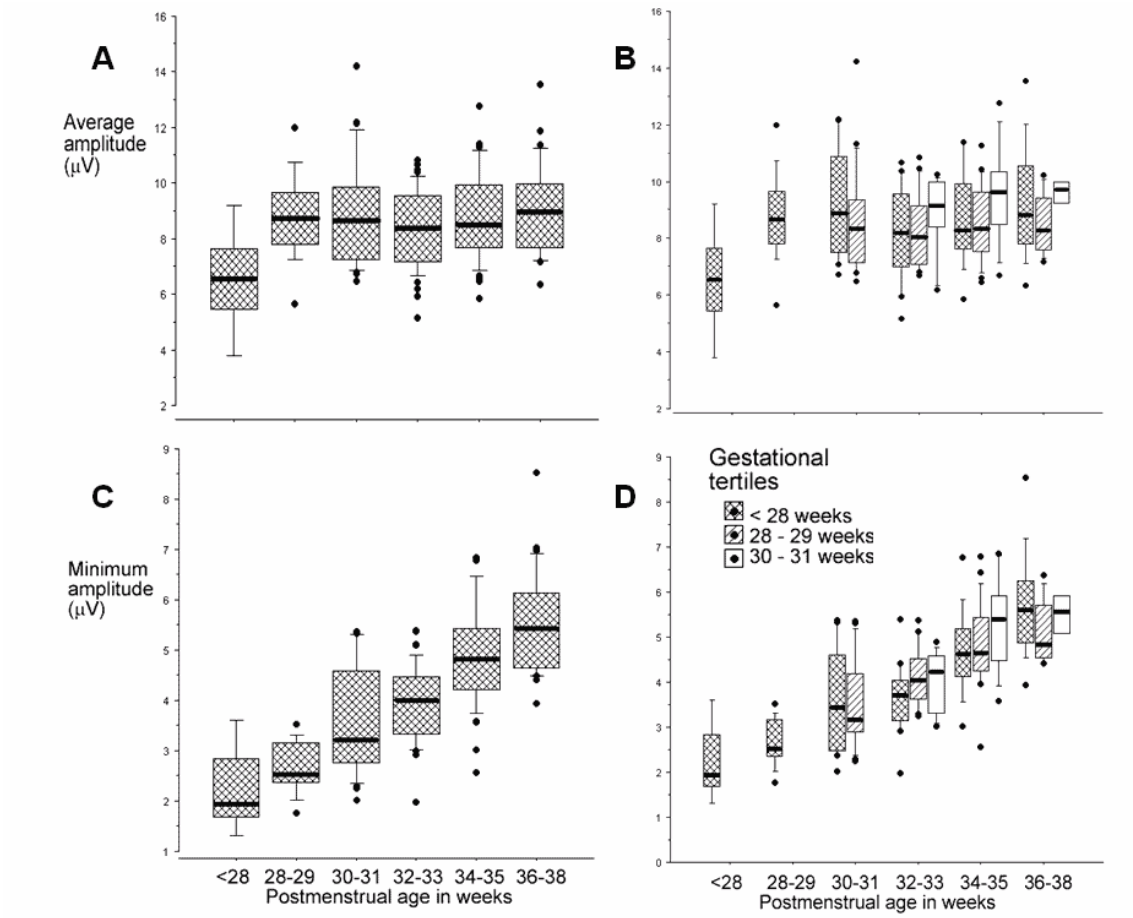
*p < 0.05 for post-hoc comparisons with value at 28 – 29 weeks.

Amplitude

Median amplitude increased by 34% from recordings obtained at <28 weeks postmenstrual age reaching 8.7μV at 28 – 29 weeks postmenstrual age (overall $p \leq 0.02$) and then remained stable (table 3-3 and figure 3-7A). Infants in each tertile had similar patterns ($p = 0.05$ for youngest tertile, figure 3-7A).

Minimum amplitude increased by 280% from recordings obtained <28 weeks postmenstrual age reaching 5.4μV at 36 – 38 weeks postmenstrual age (overall $p < 0.0001$, table 3-3 and figure 3-7C). Infants in each tertile had a similar pattern ($p < 0.0001$, < 0.0001 and $= 0.004$ for youngest, middle and oldest tertiles, figure 3-7D).

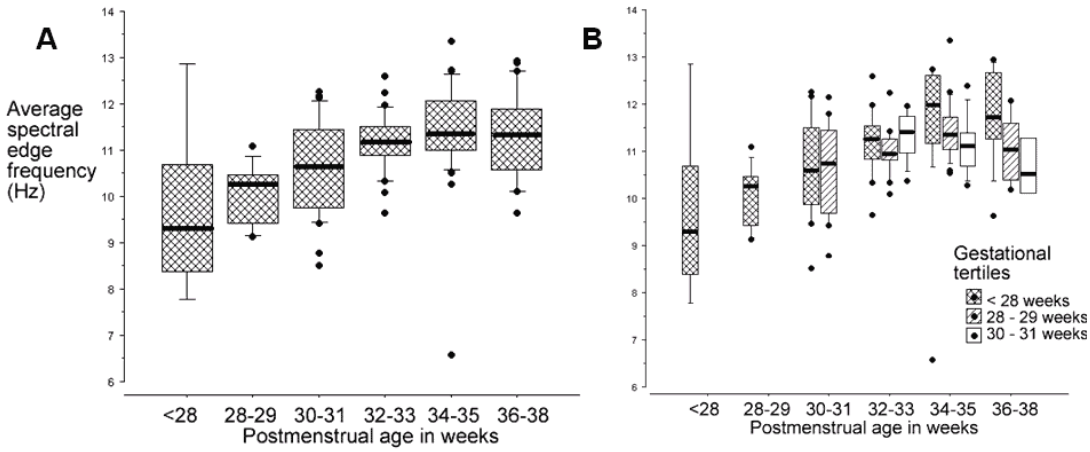
Figure 3-7
Changes in amplitude in electroencephalogram recordings beyond the first week. Box plots show results of in median (A) and minimum (C) amplitude for all infants (overall $p < 0.0001$ for both) and for infants according to tertile of gestational age at delivery (B and D for median and minimum amplitude respectively), see text for details. Youngest gestational tertile indicated by cross-hatch, middle by diagonal stripes and oldest gestational tertile indicated by white boxes.



Spectral Edge Frequency

In the whole cohort SEF increased and then stabilised (overall $p < 0.0001$, table 3-3 and figure 3-8A). This resulted from an increase in SEF up to 32 – 33 weeks (post-hoc comparisons with <28 weeks value all $p \leq 0.03$) and no change between 32 – 33 weeks and 36 – 38 weeks (all $p > 0.30$). The pattern was similar in the youngest (overall $p < 0.0001$) and middle cohorts ($p = 0.008$). The oldest cohort also showed no significant change in SEF between 32 and 38 weeks, but at the latest time (36 – 38 weeks) SEF was lower in this cohort than in the youngest cohort ($p = 0.06$).

Figure 3-8
Changes in spectral edge frequency in electroencephalogram recordings beyond the first week. Box plots show results of spectral edge frequency for all infants (A, p = 0.03) and for infants according to tertile of gestational age at delivery (B), see text for details. Youngest gestational tertile indicated by cross-hatch, middle by diagonal stripes and oldest gestational tertile indicated by white boxes.



3.3.3 Comparison of quantitative neurophysiological parameters in normal preterm infants at 36 – 38 week postmenstrual age and healthy term infants

Twenty-five preterm infants were normal at discharge, and had a technically acceptable EEG between 36 and 38 weeks. There were 13 infants from the youngest gestational tertile (one with two EEGs included), eight from the middle tertile and four from the oldest tertile included in these analyses. These infants had a median (range) gestation of 27 (24 - 31) weeks at delivery, and birthweight of 960 (540 - 1850) grams. These EEGs were performed at 68 (39 - 98) days postnatal age, or 37 (36 – 38) weeks postmenstrual age. The 13

EEGs from healthy term infants were performed at younger postnatal ages (2 [1 – 8] days), and older postmenstrual ages (39 [36 – 41] weeks), both $p \leq 0.001$. For the preterm infants the length of EEG available for analysis in periods of quiet sleep was 16 (11 – 21) minutes and for active sleep was 26 (16 – 60) minutes. Infants in each gestational tertile had similar lengths of EEG analysed for quiet and active sleep. For the term infants the length of EEG available for analysis was shorter for periods of quiet sleep (11 [11 – 21] minutes, $p = 0.02$) but similar for periods of active sleep (21 [11 – 31] minutes).

Table 3-4
Comparison of quantitative neurophysiological measures from EEGs performed on preterm infants near term corrected gestation and healthy term / near-term infants performed in the first week after delivery.

	Preterm infants near term corrected (26 EEGs)		Healthy term / near-term infants (13 EEGs)	
	Quiet sleep	Active sleep	Quiet sleep	Active sleep
Continuity at 10μV threshold [%/minute]	100.0 (96.4 – 100.0)	100.0 (100.0 – 100.0)	100.0 (100.0 – 100.0)	100.0 (100.0 – 100.0)
Continuity at 25μV threshold [%/minute]	80.1 (51.4 – 100.0)*	100.0 (89.5 – 100.0) ‡	90.5 (49.8 – 100.0)	86.9 (19.5 – 100.0)
Continuity at 50μV threshold [%/minute]	30.0 (16.2 – 65.6) ‡	37.0 (12.9 – 97.5) ‡	26.0 (2.8 – 44.9)*	5.6 (0.0 – 32.9)
Continuity at 100μV threshold [%/minute]	1.3 (0.0 – 16.6) ‡	1.7 (0.0 – 23.7) ‡	0.0 (0.0 – 1.8)	0.0 (0.0 – 5.0)
Median amplitude [μV]	7.3 (5.5 – 11.5)*	9.5 (6.6 – 13.1)	9.1 (6.0 – 11.1)	9.4 (5.5 – 10.8)
Minimum amplitude [μV]	2.8 (1.8 – 4.8)*‡	6.1 (4.5 – 8.4)	4.6 (2.1 – 6.9)*	6.5 (3.9 – 7.3)
SEF [Hz]	10.0 (8.0 – 13.6)*‡	11.9 (9.6 – 13.6)	9.2 (8.1 – 11.2)*	11.8 (9.3 – 12.8)

Values are median(range)
*$p < 0.0008$ for differences between quiet and active sleep for the same group of infants
‡$p < 0.03$ for differences between preterm and healthy term infants in the same sleep state

Preterm infants who had EEGs between 36 and 38 weeks postmenstrual age had lower continuity at the 25μV threshold, median and minimum amplitude

and SEF during quiet sleep than during active sleep ($p < 0.0001$ for all analyses, table 3-4). There were no differences in continuity at the 10, 50 or 100µV thresholds between quiet and active sleep for preterm infants. Term infants had higher continuity at the 50µV threshold ($p = 0.007$), lower minimum amplitude ($p = 0.005$) and also lower SEF ($p = 0.002$) during quiet sleep than during active sleep. There were no differences in continuity at the 10, 25 or 100µV thresholds, or median amplitude between quiet and active sleep for term infants.

During both quiet and active sleep, when compared with healthy term infants, preterm infants had higher continuity at the 50 and 100µV thresholds ($p = 0.03$ and 0.007 respectively for quiet sleep, and $p = < 0.0001$ and 0.001 respectively for active sleep). During active sleep preterm infants also had higher continuity at the 25µV threshold ($p < 0.0001$) than healthy term infants, and during quiet sleep preterm infants had lower minimum amplitude ($p = 0.0002$) and higher SEF ($p = 0.004$) than healthy term infants.

3.4 Discussion

3.4.1 Normal preterm infants over the first week after delivery

This study is the first to examine changes in quantitative electrophysiologic measures in preterm infants using a novel cotside EEG monitor over the first week after birth. Our results show that there are significant changes in quantitative measures over this period in a group of preterm infants selected on the basis of reassuring cranial ultrasound scans.

Over the first week after birth there was a 63% increase in the continuity of the EEG traces at the 50µV threshold. There was also a 26% increase in minimum amplitude and a 32% increase in median amplitude, while average SEF fell by approximately 7% over the first three days.

The changes in continuity appear to be pivotal for explaining the changes in quantitative EEG parameters. Since the amplitude reflects the level of synchronous electrical activity in the EEG, an increase in continuity results in an increase in amplitude.

We have analysed our continuity data using four intensity thresholds. At each threshold the range of values shifted towards increased continuity from day 1 to day 8. The increase in percentage continuity over the first week was greatest at the 100μV threshold. However, the data suggest that the 50μV threshold may prove most useful for analysis as the range of values for continuity fell between 10% and 90% at all times, giving the best spread of data. The threshold most useful to discriminate between infants at increased risk of poor outcomes will be discussed further in chapter 6.

Previous studies focussing on aEEG have provided some information on normal patterns of change for preterm infants. Information for extremely preterm infants is scarce (Olischar et al., 2004) compared with that available for infants over 29 weeks gestation (Burdjalov, Baumgart, & Spitzer, 2003; Thornberg & Thiringer, 1990) and includes the study which noted that aEEG patterns may not be established until a few days after birth (Burdjalov et al., 2003). In contrast, our data demonstrate consistent changes in quantitative neurophysiological measures of EEG activity in preterm infants over the first week after birth. These findings are consistent with one other study to report changes over the early part of the first week, which found an decrease in interburst interval and a fall in SEF (S. Victor et al., 2005).

There appear to be at least three possible interpretations for these observations. Firstly, the fall in SEF over the first three days after birth may indicate underlying white matter damage in response to hypoxia-ischemia around the time of birth. An acute fall in SEF occurs in both preterm and near-term fetal sheep after a significant cerebral ischemic event (Reddy et al., 1998; Tan et al., 1996) with a partial recovery over the subsequent 24 to 48 hours. However, in our group the fall was seen over a 72 hour period, perhaps suggesting that low-grade hypoxic-ischemic insults occur over a long period in most infants admitted to NICU. The infants reported here did not have clinical or laboratory evidence of other end-organ damage from ongoing hypoxic-ischemic insults in their early postnatal course, but MRI scans of the brain were not performed to exclude subtle changes. An alternative explanation is that this

demonstrates the response of a preterm infant adapting to delivery and the extra-uterine environment. Superior vena cava flow (Kluckow & Evans, 2000a, 2000b), cerebral blood flow (Meek et al., 1998) and cerebral oxygen extraction (Kissack, Garr, Wardle, & Weindling, 2004) all indicate that cerebral perfusion increases over the first days after birth, and these may be related to the changes in continuity that we observed.

A second possible explanation is that the changes occur as a result of the stress of delivery and the subsequent sensory bombardment of the preterm infant. However, while excessive stimulation of the central nervous system may explain the early elevation of SEF, the increased input would be expected to be associated with a high level of EEG continuity which would fall over the first few days rather than the observed lower level of continuity which rises over the first few days.

A third possibility is that the changes in SEF demonstrated here may be artefacts related to processing of the raw EEG data. During periods of low EEG continuity there is an increase of high frequency, low amplitude artefact components which may potentially produce a falsely elevated initial SEF which would then decrease as the continuity of the EEG increases.

The modified EEG device described here might have potential advantages over the aEEG recordings of the cerebral function monitor and multichannel devices used for earlier studies. These include the computerised analysis of the raw EEG tracing to produce the quantitative measures, allowing simultaneous determination of multiple measures to obtain a broader understanding of the electrophysiology. After initial determination of the segment to be analysed, to ensure valid data, the quantification does not depend on pattern recognition or subjective scoring assessments. In addition, EEG data are recorded from two channels, enabling interpretation of data from each hemisphere independently. We report the average of left and right channels in this paper as the infants had no evidence of significant abnormality on cranial ultrasonography and the patterns were similar for both sides. However, the impact of a significant unilateral insult on ipsilateral electrophysiologic measures in an individual baby

can be assessed when normative values have been determined. Finally, the raw EEG is retained and can be reviewed to assess the elements that have contributed to quantitative measures, or for further analyses.

While this study reports the findings on 63 very premature infants with repeated EEG recordings over the first week after birth, there are several areas which must be highlighted when considering the results. To begin with, the definition of normality for preterm infant studies is always hampered by the fact that premature delivery can never be considered physiologically 'normal'. We have therefore chosen to define our infants by a combination of survival to discharge and head ultrasound information. Infants with isolated germinal matrix haemorrhage were included as their outcomes are not significantly different from infants without evidence of intraventricular haemorrhage (Volpe, 2000).

Furthermore, our study protocol was four EEG recordings to be obtained over the infant's first week after birth. This pragmatic approach was taken to enable repeated periods of monitoring to be performed when the infants were stable. As a result we cannot assess the changes in quantitative measures on individuals throughout the whole of the first week. However, there were sufficient individuals with repeated measure over the first three days after birth to assess the trends in early changes for this subgroup. This confirmed the findings of the analysis for the group as a whole, making it unlikely that our findings were the result of recordings taken from different infants on different days.

Polygraphic recordings, including two channel EEG, and sensors to measure eye, limb and diaphragmatic movement, pulse oximetry and heart rate, can demonstrate early sleep state differentiation from around 27 weeks gestation (Curzi-Dascalova et al., 1993). Changes in sleep state organisation have also been found depending on gestational age at birth (Curzi-Dascalova et al., 1993) and postnatal age (Mirmiran, Maas, & Ariagno, 2003). However, it is difficult to assign sleep state even with polygraphic monitoring up to 34 weeks corrected gestation (Fisch, 1999a), and there is little information available regarding differentiation of sleep states using only two channel EEG recordings

in extremely preterm infants. Curzi-Dascalova found that the use of infant body movement detection altered the classification of sleep state in preterm infants (Curzi-Dascalova et al., 1993). There was an increase of between 40 and 85% in indeterminate sleep when body movement information was used in combination with EEG and eye movements to assign sleep states compared with identical periods assessed using only EEG and eye movements. Our data did not allow for accurate sleep state differentiation, so we assessed 60 minute segments of the EEG recording which would be expected to span a number of sleep state changes as they develop in preterm infants. We assessed portions of the recording away from the time of interventions to minimise any effects these may have on the infant's neurophysiological measurements and sleep state. As our findings were consistent across all gestational tertiles we feel that they are most unlikely to be explained by the development of sleep states over the first week after birth.

3.4.2 Normal preterm infants beyond the first week after delivery

We were also able to demonstrate consistent changes in quantitative electrophysiologic measures from the end of the second week after delivery until 36 – 38 weeks postmenstrual age in preterm infants with unremarkable cranial ultrasound scans.

Continuity at the 25μV threshold increased 26% from <28 weeks postmenstrual age to 36 – 38 weeks postmenstrual age. Conversely, continuity at the 50 and 100μV thresholds peaked at 29 – 31 weeks before declining by 47 and 97% respectively at 36 – 38 weeks. Median amplitude rose slightly, but remained stable from 28 weeks postmenstrual age on, and minimum amplitude increased 280% from <28 weeks postmenstrual age to 36 – 38 weeks. Infants from each tertile showed similar trends over the period until discharge. The increased continuity at the 10 and 25μV thresholds and minimum amplitude are expected from previous studies showing that EEG becomes more continuous with increasing gestational age (Eyre et al., 1988; Goto, Wakayama, Sonoda, & Ogawa, 1992; Hahn, Monyer, & Tharp, 1989). In addition to the EEG becoming more continuous, the high amplitude waveforms become attenuated with increasing gestation, resulting in a decrease in continuity at the 50 and 100μV

thresholds. In particular the delta brush pattern, in which amplitudes up to 200μV occur, appears around 26 weeks postmenstrual age, peaks at around 31 - 32 weeks and then occurs less frequently with increasing postmenstrual age (Lombroso, 1979). The delta brush pattern is a delta frequency transient with a superimposed buzz of 8 – 20 Hz activity. The lack of change in median amplitude can also be expected from these changes; while the minimum amplitude increased there was a decrease in the high amplitude waveforms, leaving the median amplitude stable.

SEF increased until 32 – 33 weeks and then stabilised. The increase in SEF could also be explained by the presence of high amplitude, high frequency delta brush waveforms. Quantitative analysis of conventional EEG by Scher's group has shown increasing total spectral EEG energies up to 36 weeks, with increases in energies of both slow (delta) and fast wave components (alpha and beta) (Scher, Steppe, Banks, Guthrie, & Sclabassi, 1995). Although the SEF was not calculated by this group, the increased energies of two fast components would be expected to result in higher SEF. Bell recorded four channel EEGs on infants three days after delivery, and also found that the SEF increased with increasing gestations ranging from 29 to 41 weeks (Bell, McClure, McCullagh, & McClelland, 1991a).

We found that the SEF of our cohort as a whole was stable from 32 – 33 weeks. This is consistent with the data shown in the diagrams included in Bell's report which show that the SEF stabilised at the higher gestations (Bell et al., 1991a), but her study was not designed to show the changes over time for preterm infants. In addition to the decrease in delta brush activity, maturation of neonatal EEG includes an increase in low amplitude delta waves (low frequency) which continue to develop during infancy. Therefore, the SEF would be expected to stabilise or decrease with increasing postmenstrual age.

Interestingly, we found that the pattern of change of SEF differed among the gestational tertiles as infants approached term corrected gestations. At the 36 – 38 week EEG the infants in the lowest gestational tertile tended to have the highest SEFs. From 36 to 43 weeks Scher's group found that the total spectral

EEG energies and the delta wave energies (low frequency) remained stable, the theta wave energies (moderate frequency) increased, and the alpha and beta wave energies (high frequency) decreased (Scher, Steppe, Banks et al., 1995). This combination of events would result in a fall in SEF over this period. One possible explanation for the difference in SEF we found between gestational tertiles is that it represents a maturational delay in the expected EEG changes such as the decline of delta brush activity in the youngest tertile. The gradient of changes noted between the tertiles would be consistent with this. Recent MRI studies have demonstrated that preterm infants (<32 weeks gestational age) at term corrected gestation had reduced cerebral cortical grey matter volumes compared with normal term controls (Inder et al., 2005). Both the EEG and neuroimaging results may reflect altered central nervous system development, with the most immature infants being particularly vulnerable.

Another possible reason for the difference at 36 – 38 weeks in SEF between the oldest and youngest gestational cohorts is the effect of sleep state on the periods of EEG analysed. In both our preterm and healthy term infants SEF was lower in quiet sleep than in active sleep. Bell also noted that SEF was lower in quiet sleep than in active sleep (Bell et al., 1991a). Therefore, if the infants in the oldest tertile had longer periods of quiet sleep included in the assessment they may be expected to have lower SEFs. However, this is unlikely to explain our results for two reasons. Firstly, when we performed sleep state specific analyses of these same EEGs we were only able to isolate periods of quiet sleep lasting between 11 and 21 minutes, and there were no differences in the lengths of both sleep states between the gestational tertiles. Secondly, as our SEF analyses are the median value for a 60 minute period, and because quiet sleep periods generally last only up to 20 minutes, the SEF values during active sleep predominate in all the analyses.

3.4.3 Comparisons between normal preterm infants at 36 – 38 week postmenstrual age and healthy term infants

In both our preterm and term infants we found differences between quantitative parameters in quiet and active sleep. In our preterm cohort continuity at the 25μV threshold, median and minimum amplitude and SEF were lower during quiet sleep. In the healthy term cohort continuity at the 50μV threshold was

higher in quiet sleep, and minimum amplitude and SEF were lower in quiet sleep. The differences in continuity and amplitude would be expected because of the method used to define sleep state in our population. Quiet sleep was determined on aEEG trace when there was a fall in the lower edge of the trace (which would reduce continuity at the 25μV threshold and minimum amplitude) and increase in the upper edge of the trace (which would potentially increase the continuity at the 50μV threshold and median amplitude). Bell also noted lower SEF in quiet sleep for her cohort of neonates, but did not examine preterm and term infants separately (Bell et al., 1991a).

We found that preterm infants had longer periods of quiet sleep available for analysis than in the healthy term infants. This was consistent with Scher's report of longer sleep cycles with more quiet sleep in preterm infants at term corrected gestation compared with recently born term infants (Scher, Steppe, Dahl, Asthana, & Guthrie, 1992). Scher found that healthy term infants had a non-significant trend towards higher percentage of quiet sleep on day 1 after birth compared with day 2 – 3 (Scher, Steppe, & Banks, 1995), but the day 1 values were still less than those found in preterm infants at term corrected gestation. The difference in length of quiet sleep segments between preterm infants at term and term infants also suggests that prolonged extrauterine life, or altered brain maturation due to prematurity, results in altered neurophysiology.

We also found differences in quantitative parameters between the preterm and term infants. During quiet sleep preterm infants had higher continuity at the 50 and 100μV thresholds, lower minimum amplitudes and higher SEF than healthy term infants. During active sleep preterm infants had higher continuity at the 25, 50 and 100μV thresholds than healthy term infants. In our preterm cohort examined from one week to discharge higher continuities at the 50 and 100μV thresholds and lower minimum amplitude were found in infants with younger postmenstrual and postnatal ages. In addition, as discussed above, higher SEF may also result from delay in normal maturational changes in EEG with gestation. The higher continuity at the 25μV threshold in preterm infants is more difficult to explain, but may be related to the predominance of lower

amplitude waveforms in EEGs at term. These findings are all consistent with an overall picture of delayed maturation of EEG patterns in very preterm infants.

Another possible explanation for the differences between preterm and term EEG parameters, however, is that they are related to the gestation difference at the time of the EEGs rather than as a result of maturational changes. Our preterm infants had their final EEG at a median of 37 weeks while the median age of our healthy term infants was 39 weeks. Scher has found that around 36 weeks postconceptional age (38 weeks postmenstrual age) there are important changes to some sleep state quantitative EEG measures, including continuity (Scher, Steppe, Banks et al., 1995). Unfortunately we do not have data to allow us to make corrections for the discrepancy in postmenstrual ages between our preterm and term infants near term. While we did perform EEGs on four very preterm infants at 41 weeks postmenstrual age, these data have not been included as each infant had a complex neonatal course, as expected by their delayed discharge, and therefore were not representative of the 'normal' preterm population examined in this chapter.

Finally, we are unsure whether healthy term / near-term infants have similar changes in quantitative neurophysiological parameters over the first week after delivery as found in our preterm cohort. Scher studied a cohort of 29 term infants over the first three days after birth and only found differences in percentage of quiet sleep, rapid eye movements and body movements between day 1 and days 2 – 3 (Scher, Steppe, & Banks, 1995), but amplitude, continuity and SEF were not assessed directly in this study. However, any differences in postnatal age are unlikely to explain our findings. If there are changes after delivery, we would expect that the amplitude measures would be lower and SEF measures would be higher when performed at a median of day 2, than if performed later in the week. Therefore, if anything, our results would show smaller differences between the preterm at term and term infants for minimum amplitude and SEF than if the healthy term infants had had EEGs later in the first week.

3.4.4 Summary and implications

There are consistent changes in quantitative neurophysiological measures of EEG activity over the first week after birth in 'normal' preterm infants born at 24 to 32 weeks gestation. The increase in EEG continuity of the recordings over the first week after birth results in an increase in amplitude and the decrease in SEF measures. Determination of normal changes over this period will be valuable when assessing the effects of adverse peripartum events and in the selection of high-risk infants for trials of neuroprotective therapies.

There are also consistent changes in the same quantitative measures in preterm infants during the remainder of their neonatal admission. Continuity at the 25μV threshold, minimum amplitude and SEF increase over this period whereas continuity at the 50 and 100μV thresholds peak around 28 – 29 weeks postmenstrual age before declining. These changes are likely to reflect increasing continuity of the EEG and the appearance and subsequent decline of developmental EEG features including delta brushes. While these changes were seen in a similar pattern for each gestational tertile, there was a trend towards a higher SEF at 36 – 38 weeks in infants from the youngest tertile, potentially reflecting delayed maturation in the least mature infants.

Differences in quantitative parameters were also found between preterm and term infants at near term postmenstrual ages. Preterm infants had higher continuity at the 50 and 100μV thresholds in both sleep states, and lower minimum amplitude and higher SEF in quiet sleep than healthy term infant. These differences may all be consistent with delayed maturation in the preterm cohort. However, we cannot exclude the possibility that some of the differences may be due to differences in postmenstrual ages between our preterm and term cohorts.

4 Results – EEG relationships to early outcome measures in preterm infants

4.1 Introduction

As discussed in Chapter 1, there are a number of tools used early in an infant's NICU course used for prognostication. In this chapter we will be exploring the relationships between early quantitative neurophysiological measures and some of these methods; specifically the Clinical Risk Index for Babies (CRIB) score, cranial ultrasound scans including subarachnoid space measurements, and examination near term using the Hammersmith Neonatal Neurology examination (HNNE).

The CRIB illness severity score was developed and validated in the United Kingdom for prediction of short-term outcomes for preterm infants (Cockburn et al., 1993). Cranial ultrasound examinations have become routine in preterm neonatal care (Ment et al., 2002). In addition to detection of intraventricular haemorrhage and some forms of white matter injury, measurement of the subarachnoid space width gives an indication of relative brain volume within cranial cavity (Anderson et al., 2004; Armstrong et al., 2002). The HNNE is a systematic neurological and state examination of the newborn infant developed by clinicians at Hammersmith Hospital, London (Dubowitz et al., 1999). The HNNE examination has been used to assess preterm infants prior to discharge, at near term equivalent gestations (Dubowitz et al., 1999), and after discharge (Frisone et al., 2002).

4.2 Methods

4.2.1 Quantitative neurophysiological parameters

In this chapter the relationships are examined between quantitative neurophysiological parameters obtained at various time points over the first

week of life and early outcome measures. In addition, the relationships are examined between quantitative neurophysiological parameters obtained around the time of the last cranial ultrasound scans and HNNE examinations and the results of these investigations.

For each EEG recording we assessed the following quantitative neurophysiological parameters over the 60 minute segments chosen as the baseline analysis (Section 2.5.1):

- Spectral edge frequency (SEF)
- Minimum amplitude
- Continuity measured at the 25 and 50μV thresholds.

SEF was chosen for these analyses as it has been shown that in preterm infants early SEF was related to white matter injury on MRI at term corrected gestation (Inder, Buckland et al., 2003).

Minimum amplitude was chosen as this measure has been shown to be useful on aEEG recordings in term infants with neonatal encephalopathy for assessment of the severity of the cerebral dysfunction (al Naqeeb et al., 1999).

Continuity was chosen as this reflects the proportion of each minute when the EEG amplitude is above a threshold, the inverse of discontinuity. Discontinuity of a preterm infant's EEG in excess of gestational norms has been associated with worse neurodevelopmental outcome (J. Connell et al., 1988; Watanabe, Hayakawa, & Okumura, 1999). Continuity measures at the 25 and 50μV thresholds were chosen as the results at these thresholds have a range of values compared with the continuity measures at the 10 and 100μV thresholds which have a clustering of values at the upper and lower percentages respectively. The larger spread of results may allow for better discrimination of useful clinical relationships.

The CRIB score is assessed at 12 hours after delivery. Therefore we analysed only the relationships between the CRIB score and parameters of the first recorded EEG.

For the cranial ultrasound scans and HNNE, performed at around 36 weeks postmenstrual age, we analysed the relationships with these outcome measures and parameters of the first and last EEG performed in the first week after delivery and also EEGs performed within one month and one week of these outcome measures.

We used data from the first EEG to examine whether quantitative measurements from early EEGs could predict these outcome measures. They were examined because we were interested in the ability of early EEG recordings to predict outcome, and cranial ultrasound scans and the HNNE are early surrogate measures for outcome, albeit poor surrogates. Ideally we would have undertaken these analyses on infants with EEGs recorded in the first 12 hours after delivery. However, only 35 infants had their first EEG by 12 hours of age due to constraints of obtaining consent, not interfering with initial care of the infants and the requirements of performing EEGs on other recruited infants with limited equipment. Thus in order to increase the number of infants studied, we analysed data from the first recorded EEG after delivery, (n = 119, median [range] 26 [2 – 114] hours after delivery), of which only eight were more than 72 hours after delivery. Relationships found to be significant in univariate analyses were re-tested using the subset of data from EEGs performed only on day 1 (n = 53), and also from EEGs performed within the first 48 hours (n = 103).

We used data from the last EEG in the first week after delivery to look at the predictive ability of EEGs performed at a time when infants have clinically stablised. Ideally we would have undertaken these analyses on infants with EEGs performed on a specific day at the end of the first week to minimise the variation in neurophysiological parameters found over the first week after delivery. Unfortunately, there were only 59 infants with EEGs performed on day 7 of whom 33 had an HNNE and 35 had a cranial ultrasound scan at 36 weeks

postmenstrual age. We therefore chose to report the data from the last EEG in the first week after delivery (110 infants, median (range) of day 7 [3 – 9] after delivery). Of this larger group of infants 58 had an HNNE and 71 had a cranial ultrasound scan at 36 weeks postmenstrual age, approximately twice the number of infants on day 7 alone. Again, significant relationships were re-tested using subsets of data from EEGs performed only on day 7 (n = 58), and also from EEGs performed on days 5 to 9 (n = 114).

We examined relationships between data from EEGs performed within seven days, and performed within one month of the 36 week cranial ultrasound examination and the HNNE to explore whether contemporaneous EEG parameters were related to imaging and functional assessments.

4.2.2 Clinical Risk Index for Babies (CRIB) score

CRIB scores were determined for each infant from data extracted from the medical records according to the scoring protocol (Cockburn et al., 1993). The CRIB-II score was published during 2003 (Parry et al., 2003). However, we chose to continue collecting CRIB scores as initially planned as there are more data regarding the utility of CRIB scores (Eriksson et al., 2002) and we had already recruited over 50% of our cohort by the time of the CRIB-II publication.

Since gestational age and birthweight are included in CRIB scoring they were not able to be used together with CRIB scores in multiple regression analyses.

4.2.3 Cranial Ultrasound Scans

Our NICU guideline at the time of this research was for routine cranial ultrasound scans to be performed in infants born at <32 weeks gestation or <1500g birthweight. The scans were performed by radiology registrars after teaching by a radiologist or experienced technician and a formal report was written after review with a radiologist. One senior radiologist supervised most of the cranial ultrasound scan reporting over the time of this research. The first cranial ultrasound scan was performed on day 4 - 5 after delivery, the second at one month postnatal age and a discharge cranial ultrasound scan was performed around 36 weeks postmenstrual age. Additional scans were performed as clinically indicated.

Germinal matrix-intraventricular haemorrhage (GM-IVH) was graded according to Papile (Papile et al., 1978). Cranial ultrasound scans were classified as ‘bad’ if they showed grade 3 or 4 GM-IVH or evidence of periventricular leukomalacia (PVL) or porencephalic cyst formation. Cranial ultrasound scans were classified as ‘good’ if they showed grade 0 to 2 GM-IVH and no evidence of cystic white matter injury. We classified the day 5 cranial ultrasound scans according to these criteria, and also classified each infant on their ultrasound scans during their entire admission (ie any classification of ‘bad’ scan vs all scans classified as ‘good’). We chose to classify cranial ultrasound scans in this way as infants with grade 1 and 2 GM-IVH have been found to have a similar incidence of definite neurological sequelae to infants with normal cranial ultrasound scans, whereas those with higher grade GM-IVH, ventricular enlargement and PVL are at increased risk of adverse neurological sequelae (Roth et al., 1993; Whitaker et al., 1996).

We compared the neurophysiological parameters from the first and last EEG in the first week after delivery between the groups of infants with ‘good’ and ‘bad’ day 5 cranial ultrasound scans using Mann-Whitney U tests. We then compared the neurophysiological parameters from the first and last EEGs in the first week after delivery, and from EEGs performed within one week and one month of the last cranial ultrasound scan between the groups of infants with ‘good’ scans throughout their NICU admission and those with one or more ‘bad’ cranial ultrasound scans during their admission.

Subarachnoid space width was measured on coronal views through the anterior fontanelle using a 10MHz linear array transducer on the ATL 3000 scanner (Advanced Technological laboratories, Bothell, Washington, USA) (Armstrong et al., 2002). A generous amount of coupling gel was used to ensure that the views were obtained without pressure. Electronic callipers were positioned perpendicular from the lateral edge of the superior sagittal sinus to the surface of the brain. Measurements, within 0.1mm, were obtained from the right and left sides.

We examined the relationships between subarachnoid space width at around 36 weeks postmenstrual age and neurophysiological parameters from the first week after delivery and around the time of the final cranial ultrasound scan. The subarachnoid space width measurement at 36 weeks postmenstrual age was chosen because there are reference values for preterm infants at this gestation (Armstrong et al., 2002).

The upper limit of the 95% confidence interval of subarachnoid space width in preterm infants at 36 weeks postmenstrual age has been shown to be 5.97mm (mean + two standard deviations) using an identical technique to that used in our cohort of infants (Armstrong et al., 2002). We divided the infants into two groups according to whether their subarachnoid space width at near 36 weeks postmenstrual age was <6.0mm or ≥6.0mm. EEG parameters were compared between the two groups using the Mann-Whitney U test.

Significant relationships from the univariate analyses between neurophysiological parameters and subarachnoid space width at 36 weeks were further tested with multiple regression taking into account gestational age at delivery, birthweight Z-score and corrected gestation at the time of the 36 week cranial ultrasound scan.

4.2.4 Hammersmith Neonatal Neurological Examination

Our NICU guideline is for infants born at <1000g to have an HNNE performed by developmental therapists prior to discharge to assist with allocation of community developmental therapist interventions (Rowley, Kilgour, & Eaton, 2002). In addition, infants recruited to the two research protocols with birthweights above 1000g had an HNNE performed prior to discharge whenever the therapists were available. Tendon jerks and suck were not routinely tested as these were expected to be assessed by the medical staff. Two developmental therapists performed the examination. One of the two therapists was present for all of the examinations performed at National Women's Health.

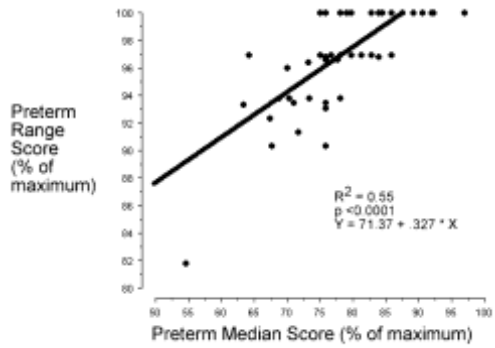
There are data available for the scoring of the HHNE for infants born at term, including optimality scores (Dubowitz et al., 1999). There are also data on outcome prediction using a similar infant examination for preterm infants from nine months postnatal age to predict outcome at two years of life, and optimality scores have been developed for this examination (Frisone et al., 2002; Haataja et al., 1999). However, preterm infants at term equivalent gestations have specific differences in certain elements of the examination, such as muscle tone, when compared with normal term infants, due to their prolonged extrauterine survival. Therefore, preterm infants scoring 'normal' term scores on the HNNE are not necessarily 'normal' (Mercuri et al., 2003) and scoring the examinations against term normal data is not appropriate. Some data have been published on the median and ranges of examination findings expected in preterm infants born at different gestations and examined at near-term corrected gestation (Mercuri et al., 2003). Due to the relatively small number of infants at each preterm gestation, optimality scores have not been developed for preterm infants examined near term.

For our study the original examination record sheet was used to score the examination results in two ways. Firstly, the results were assessed to determine whether each part of the examination was equal to the median score for infants born at a similar gestation (0 = result not equal to the median result; 1 = examination result equal to the median result) (Mercuri et al., 2003). The score was then converted to a percentage of the maximum score for that infant's test, the "Preterm Median Score". Secondly, the examination results were assessed to determine whether they fell within the 90^{th} centile range of scores (Mercuri et al., 2003) for infants born at a similar gestation (0 = result not within the 'normal range' for gestation at delivery; 1 = examination result within the 'normal range' for gestation at delivery). The score was again converted to a percentage of the maximum possible for that infant, the "Preterm Range Score".

The two scoring methods gave results which were poorly correlated, (R^2 = 0.55, $p < 0.0001$, figure 4.1). The Preterm Range Score resulted in clustering of infants with 100% scores while the Preterm Median Scores had a larger spread

with a range from 54.6% to 96.9%. The Preterm Median Score was chosen for the subsequent analyses because of the larger spread of results to optimise discrimination of clinically useful relationships with quantitative EEG measures.

Figure 4-1
Relationship between preterm scoring methods for Hammersmith Neonatal Neurology Examination.



Significant relationships on univariate analyses between neurophysiological parameters and HNNE Preterm Median Scores were further tested with multiple regression taking into account birthweight Z-score and corrected gestation at HNNE examination. Gestational age at delivery was not included in these analyses as this was taken into account when scoring the examination.

4.3 Results

4.3.1 Demographic data

Between March and December 2002, 55 infants of less than 28 weeks gestation were admitted. Parents of 34 (62%) were approached regarding study protocol 1. Informed parental consent was obtained for 32 infants (94% of those approached) and declined for two (6%). The parents of 21 babies were not approached regarding the study: two infants were unable to be stabilised and died early; four parents/guardians were unavailable for consent; the parents of one infant did not speak English and for 14 either researcher (four infants) or monitor (10 infants) was unavailable. Between December 2002 and February 2004, 153 infants of less than 32 weeks gestation were admitted. Parents of 98 infants (64%) were approached regarding the study (protocols 1 and 2 as appropriate). Informed parental consent was obtained for protocol 2 in 79 infants (81% of those approached), in a further 10 infants consent was

obtained for protocol 1 only (two EEGs in the first week) and consent was declined for nine infants (9%). One infant was withdrawn from the study before a valid EEG was obtained. The parents of 55 babies were not approached regarding the study: two infants were unable to be stabilised and died early; five parents/guardians were unavailable for consent; the parents of four infants did not speak English; one infant had a chemical burn on her skin related to central line placement and the family was not approached, and for 43 either researcher (two infants) or monitor (41 infants) was unavailable. As there was only one researcher and two EEG devices available we were unable to recruit all eligible infants, and therefore sought preferentially to recruit infants born at less than 29 weeks gestation.

The 120 infants recruited and studied had a median (range) gestation at delivery of 27 (24 – 31) weeks and birthweight of 990 (420 – 1980) grams. All of the infants had a valid recording for their first EEG, performed at 26 (2 – 114) hours after delivery. Another valid EEG was obtained on day 7 (3 – 9) in the first week after delivery in 110 of the infants. The infants with a valid EEG later in the first week had identical median and range values for gestation at delivery and birthweight to the overall cohort.

Seventy-five infants had cranial ultrasound scans performed at 36 weeks corrected gestation, or just prior to discharge, and subarachnoid space width was measured in 73 of these. These infants had a median (range) gestation at delivery of 27 (24 – 31) weeks, birthweight of 950 (540 – 1975) grams and gestation at time of final cranial ultrasound of 36 (34 – 43) weeks. The first EEG after delivery in these infants was performed at 26 (2 – 114) hours. The last EEG performed during the first week after delivery was performed at 7 (3 – 9) days. The 24 infants with EEGs performed within one week of the final cranial ultrasound were similar to the larger group with a gestation at delivery of 27 (24 – 31) weeks, birthweight of 927 (540 – 1850) grams. These infants had their final cranial ultrasound at 36 (34 - 37) weeks corrected gestation. The 45 infants with EEGs performed within one month of the final cranial ultrasound were also similar to the larger group with a gestation at delivery of 27 (24 – 31) weeks, birthweight of 940 (540 – 1975) grams. These infants had their final

cranial ultrasound at 36 (34 – 39) weeks corrected gestation. All these subgroups were not different from each other, or the overall cohort for basic demographic data.

Of the 120 infants recruited, 59 had a HNNE prior to discharge. These 59 infants had a median (range) gestation at delivery of 26 (24 - 31) weeks and birthweight at delivery of 900 (540 - 1700) grams. The HNNE was performed at a corrected gestation of 36 (34 – 44) weeks and at a postnatal age of 70 (32 – 128) days. The first EEG after delivery was performed at 24 (2 – 91) hours in this group of infants, and the last EEG performed during the first week after delivery was performed at 7 (3 – 9) days. The 24 infants with EEGs performed within one week of the HNNE were similar to the larger group with a gestation at delivery of 27 (24 – 31) weeks, birthweight of 915 (540 – 1550) grams. These infants had their HNNE at 36 (34 - 38) weeks corrected gestation. The 36 infants with EEGs performed within one month of the HNNE were also similar to the larger group with a gestation at delivery of 27 (24 – 31) weeks, birthweight of 885 (540 – 1550) grams. These infants had their HNNE at 36 (34 – 44) weeks corrected gestation. All these subgroups were not different from each other, or the overall cohort for basic demographic data.

4.3.2 CRIB

For 119 of the 120 infants recruited a CRIB score was able to be calculated. The one infant without a CRIB score was transferred from an outlying centre and did not have a blood gas analysis in the first 12 hours after delivery. These 119 infants had a median (range) CRIB score of 1 (0 – 12), birthweight at delivery of 990 (420 - 1980) grams and gestation at delivery of 27 (24 - 31) weeks. Their first EEG was recorded at 26 (2 – 114) hours after delivery.

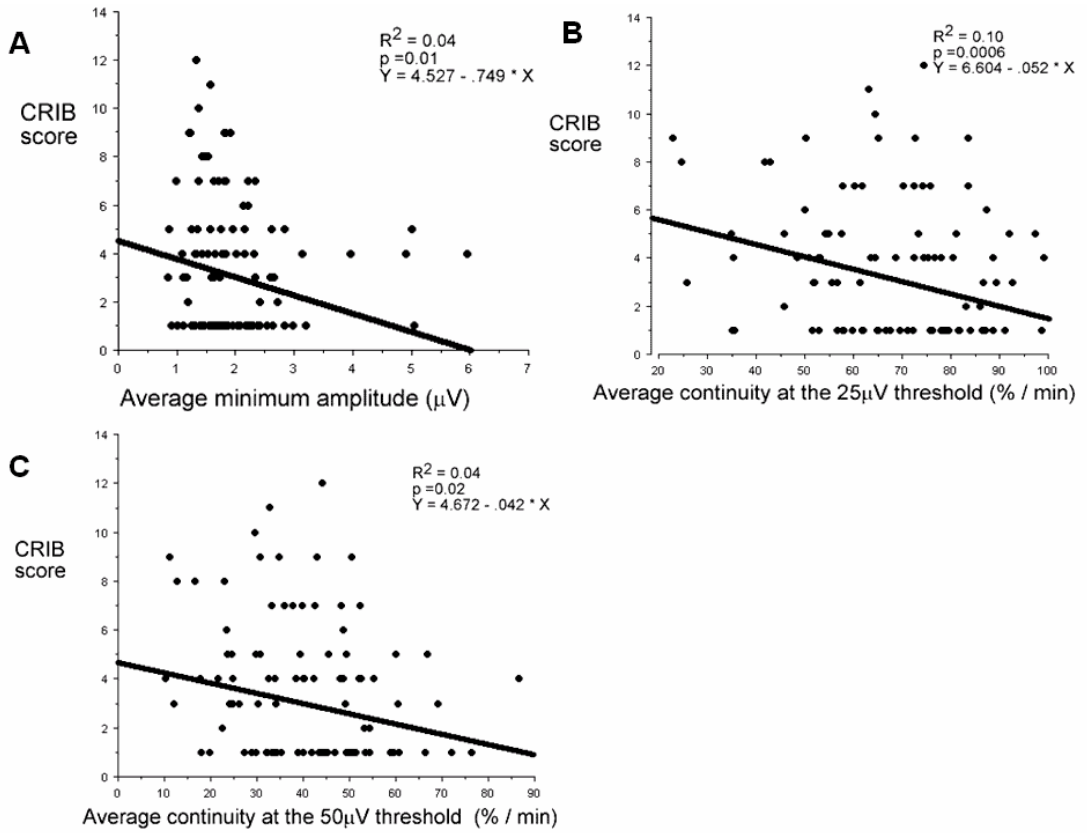
There were very weak but statistically significant relationships between CRIB scores and the following quantitative neurophysiological measures from the first EEG recorded on these 119 infants:

1. average minimum amplitude, $p = 0.01$, $R^2 = 0.04$, coefficient = -0.75, figure 4.2A;

2. average continuity at the 25μV threshold, p = 0.0006, R^2 = 0.04, coefficient = -0.05, figure 4.2B; and
3. average continuity at the 50μV threshold, p = 0.02, R^2 = 0.04, coefficient = -0.04, figure 4.2C.

SEF measurements from the first recorded EEG were not related to CRIB scores.

Figure 4-2
Relationships between CRIB illness severity score and minimum amplitude (A) and continuity at the 25μV (B) and 50μV (C) thresholds from the first recorded EEG after delivery.



We repeated the significant analyses with data from EEGs performed only on day 1 (n = 53), and also with data from EEGs performed within the first 48 hours (n = 103) and found similar results.

4.3.3 Cranial Ultrasound Scans

Early cranial ultrasound scans were performed on 113 infants at a median (range) of 5 (1 – 10) days. They had a median (range) gestation at delivery of

27 (24 – 31) weeks and birthweight of 960 (420 – 1975) grams. All of the infants had a valid recording for their first EEG, performed at 26 (2 – 114) hours after delivery.

Only five infants had 'bad' scans on their day 5 cranial ultrasound scan: one had a unilateral porencephalic cyst; one had bilateral grade 3 GM-IVH with ventricular enlargement, and three had grade 4 GM-IVH (two bilateral and one unilateral). The analyses were repeated excluding the infant with the unilateral porencephalic cyst as the presence of this well defined abnormality on an early cranial ultrasound scan indicates that the injury had occurred well before delivery.

During their NICU admission all infants had at least one cranial ultrasound scan documented. One infant had definite PVL diagnosed, and another had probable PVL diagnosed on the day 28 cranial ultrasound scan. These were classified as 'bad' scans along with those outlined above. Both of these infants' day 5 cranial ultrasound scans were reported as normal.

The mean (standard deviation) of the 73 infants with subarachnoid space widths measured at the 36 week cranial ultrasound scan was 4.1 (1.7) mm on the left and 4.2 (1.7) mm on the right.

4.3.3.1 Germinal matrix – intraventricular haemorrhage

Infants with 'good' cranial ultrasound scans on day 5 had similar neurophysiological parameters to those with 'bad' cranial ultrasound scans. After excluding the infant with the unilateral porencephalic cyst, infants with 'good' cranial ultrasound scans on day 5 had higher continuity at the 25 and 50μV thresholds on the first EEG after delivery than infants with a 'bad' cranial ultrasound scan ($p = 0.02$ and 0.01 respectively, table 4-1), and higher minimum amplitude on the last EEG in the first week after delivery ($p = 0.03$, table 4-2).

Infants with 'good' cranial ultrasound scans throughout their admission had higher SEF and continuity at the 25 and 50μV thresholds on the first EEG after delivery than infants with 'bad' cranial ultrasound scans (p = 0.02, 0.04 and 0.03 respectively, table 4-1). We repeated these analyses with data from EEGs performed only on day 1 (n = 53), and also with data from EEGs performed within the first 48 hours (n = 103) and found similar results.

Table 4-1
Comparison of quantitative neurophysiological parameters from first EEG recorded after delivery between infants categorised as having 'good' and 'bad' cranial ultrasound scans.

	SEF (Hz) – 1st EEG	Minimum amplitude (μV) – 1st EEG	Continuity 25μV (%/min) – 1st EEG	Continuity 50μV (%/min) – 1st EEG
'Good' scan day 5 (n = 106)	10.3 (8.1-15.4)	1.9 (0.8 – 6.0)	74.3 ** (24.8–100.0)	42.2 ** (10.2–86.5)
'Bad' scan day 5* (n = 4)	8.9 (8.4-10.9)	1.5 (1.2 – 1.9)	45.2 (23.0–73.4)	17.3 (11.1–39.4)
All 'good' scans during admission (n = 113)	10.3 ** (8.1-15.4)	1.9 (0.9 – 6.0)	74.5 ** (24.7–100.0)	42.2 ** (10.2–86.5)
≥ 1 'bad scan during admission (n = 7)	9.1 (8.5–10.9)	1.5 (0.8 – 2.8)	48.6 (23.0–97.3)	17.8 (11.1–66.8)

*excluding one infant with unilateral porencephalic cyst
** p <0.05 for comparison between infants with 'good' and 'bad' scans

Infants with 'good' cranial ultrasound scans throughout their admission had higher SEF and minimum amplitude on the last EEG in the first week after delivery than infants with 'bad' cranial ultrasound scans (both p = 0.03, tables 4-1 and 4-2). There were no substantial changes in these analyses if the infant with the unilateral porencephalic cyst detected on the day 5 scan was excluded. We repeated these analyses with data from EEGs performed only on day 7 (n = 58) and with data from EEGs performed on days 5 to 9 (n = 103) and found similar results.

There were no differences in any of the neurophysiological measures on EEGs recorded in either the week or the month before the 36 week cranial ultrasound

scan between infants with 'good' cranial ultrasound scans throughout their admission and infants with 'bad' cranial ultrasound scans.

Table 4-2
Comparison of quantitative neurophysiological parameters from last EEG recorded in the first week after delivery between infants categorised as having 'good' and 'bad' cranial ultrasound scans.

	SEF (Hz) - last EEG in 1st week	Minimum amplitude (μV) – last EEG in 1st week	Continuity 25μV (%/min) – last EEG in 1st week	Continuity 50μV (%/min) – last EEG in 1st week
'Good' scan day 5 (n = 97)	9.9 (8.2 – 13.1)	2.1** (1.0 – 5.1)	81 (51 – 100)	52 (27 – 86)
'Bad' scan day 5* (n = 3)	9.0 (8.7 – 9.4)	1.3 (1.3 – 1.6)	81 (71 – 82)	51 (39 – 53)
All 'good' scans during admission (n = 104)	10.0 ** (8.2–13.1)	2.2 ** (1.0–5.1)	83.1 (54.4 – 100.0)	52.7 (26.7 – 85.8)
≥ 1 'bad scan during admission (n = 6)	9.2 (8.7–9.9)	1.6 (1.3–2.2)	78.6 (60.0 – 82.0)	51.8 (35.0 – 56.4)

*excluding one infant with unilateral porencephalic cyst
** p <0.05 for comparison between infants with 'good' and 'bad' scans

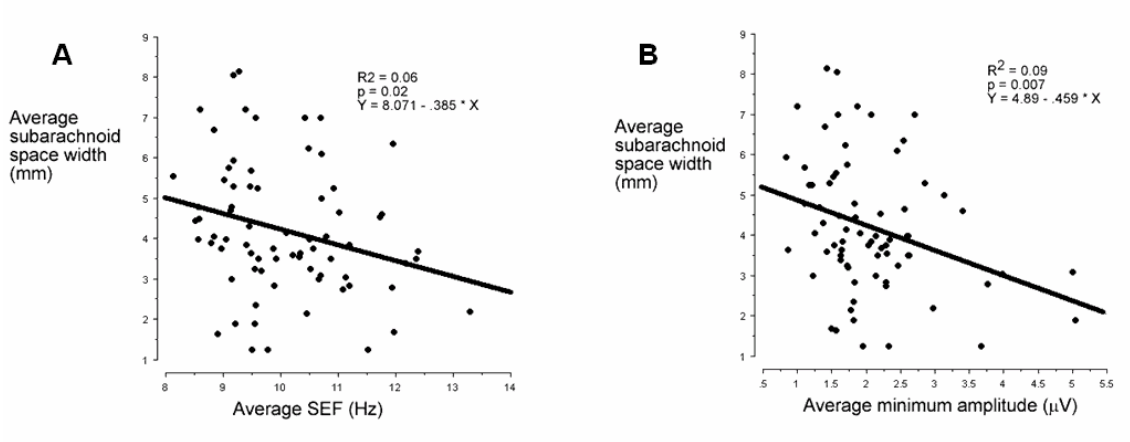
4.3.3.2 Subarachnoid space width measurements

4.3.3.2.1 Univariate analyses

There were statistically significant relationships between the mean subarachnoid space width on the 36 week cranial ultrasound and the following neurophysiological measures from the first EEG recorded after delivery (performed at a median [range] of 24 [2 – 91] hours after delivery), n = 73:

1. average SEF, p = 0.02; R^2 = 0.06, figure 4-3A and
2. average minimum amplitude, p = 0.007; R^2 = 0.09, figure 4-3B

Figure 4-3
Relationships between mean subarachnoid space width on cranial ultrasounds around 36 weeks corrected gestation and SEF (A) and minimum amplitude (B) from the first recorded EEG after delivery.



Continuity measurements at the 25 and 50μV thresholds on the first recorded EEG were not related to subarachnoid space width on the 36 week cranial ultrasound.

We repeated the analyses with data from EEGs performed only on day 1 (n = 53) and also EEGs performed within the first 48 hours (n = 103) and found similar trends.

There were no statistically significant relationships between the mean subarachnoid space width on the 36 week cranial ultrasound and any of the neurophysiological measures from the last EEG recorded in the first week after delivery, n = 69.

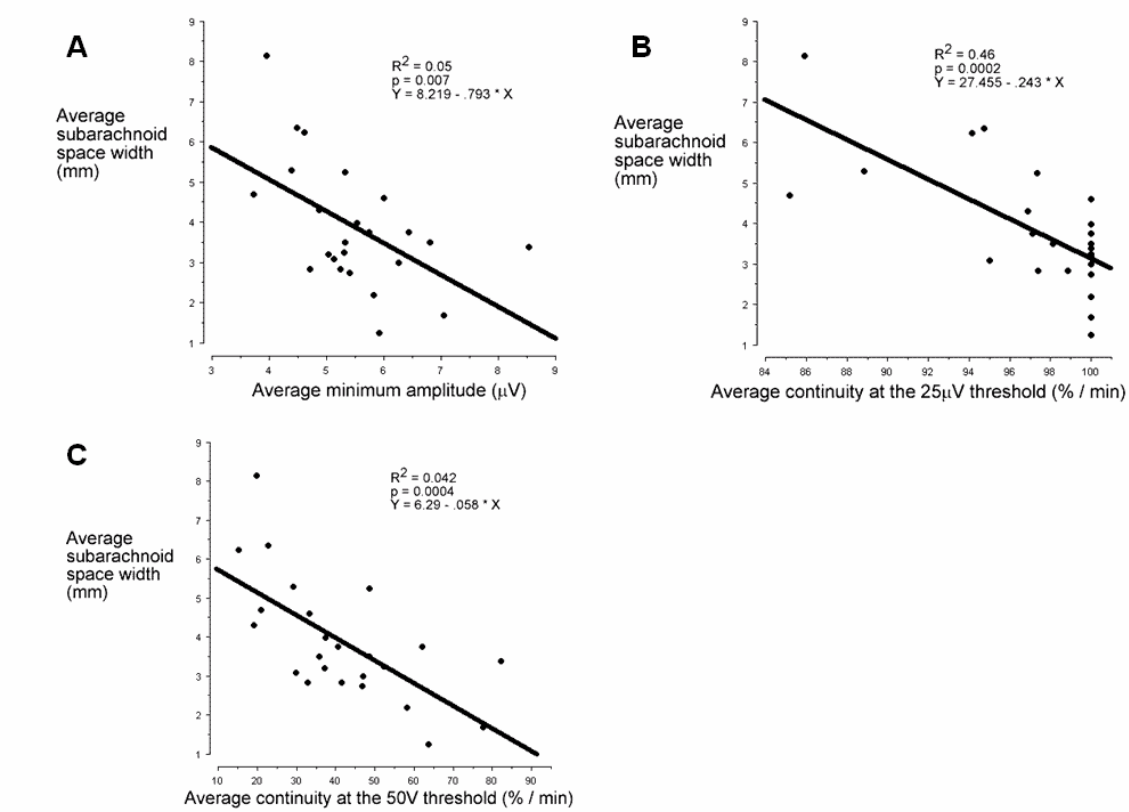
There were stronger relationships between the mean subarachnoid space width on the 36 week cranial ultrasound and the following neurophysiological measures from the 24 EEGs performed within one week of the cranial ultrasound:

1. average minimum amplitude, p = 0.007, R^2 = 0.25, coefficient = -0.79, figure 4-4A;
2. average continuity at the 25μV threshold, p = 0.0002, R^2 = 0.46, coefficient = -0.24, figure 4.4B; and

3. average continuity at the 50μV threshold, p = 0.0004, R^2 = 0.42, coefficient = -0.06, figure 4.4C.

SEF measurements from the EEG performed within one week of the cranial ultrasound were not related to mean subarachnoid space width on the 36 week cranial ultrasound.

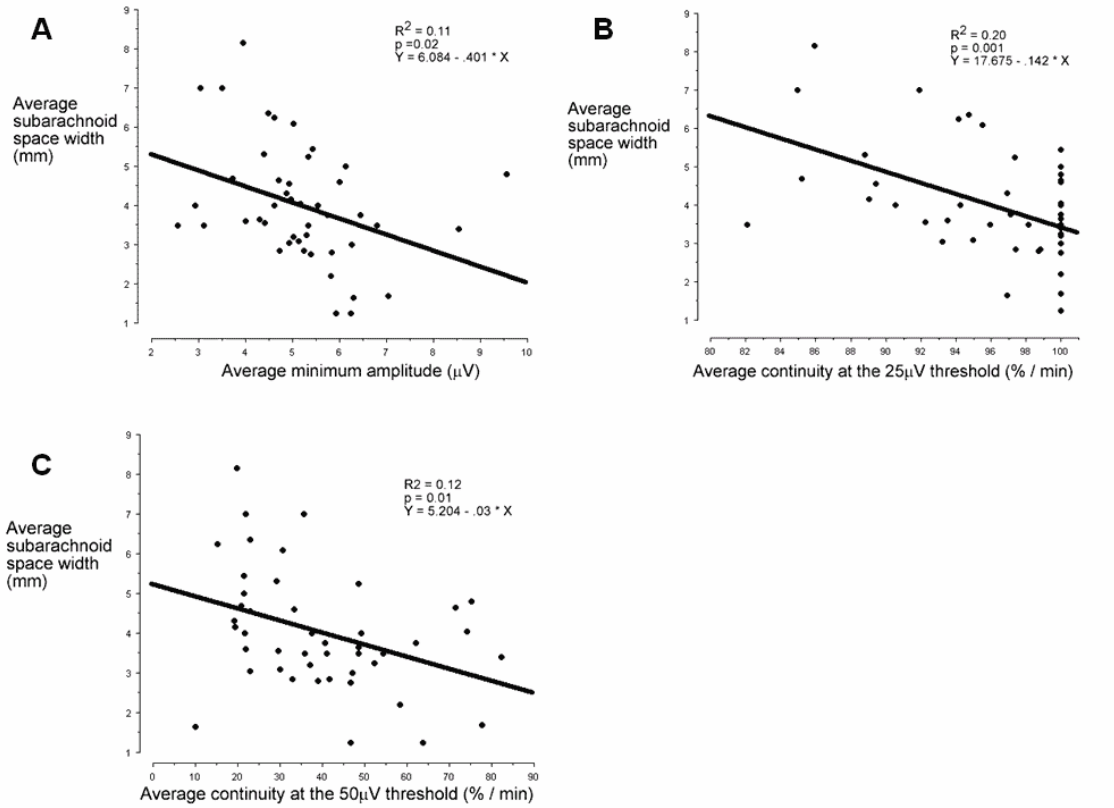
Figure 4-4
Relationships between mean subarachnoid space width on cranial ultrasounds around 36 weeks corrected gestation and minimum amplitude (A) and continuity at the 25μV (B) and 50μV (C) thresholds from an EEG recorded within one week of the cranial ultrasound.



When the analyses were repeated with the 45 infants with an EEG performed within one month of the cranial ultrasound scan the relationships were all similar but weaker:

1. average minimum amplitude, p = 0.02, R^2 = 0.11, coefficient = -0.40, figure 4-5A;
2. average continuity at the 25μV threshold, p = 0.001, R^2 = 0.20, coefficient = -0.14, figure 4-5B; and
3. average continuity at the 50μV threshold, p = 0.01, R^2 = 0.12, coefficient = -0.03, figure 4-5C.

Figure 4-5
Relationships between mean subarachnoid space width on cranial ultrasounds around 36 weeks corrected gestation and minimum amplitude (A) and continuity at the 25µV (B) and 50µV (C) thresholds from an EEG recorded within one month of the cranial ultrasound.



SEF measurements from the EEG performed within one month of the cranial ultrasound were not related to mean subarachnoid space width on the 36 week cranial ultrasound.

4.3.3.2.2 Multiple regression

Neither SEF nor minimum amplitude from the first EEG after delivery remained significant in the multiple regression analysis. The negative relationships between continuity at the 25 and 50µV thresholds for EEGs performed within one week or one month of the cranial ultrasound scan and subarachnoid space width remained statistically significant with similar strength when birthweight Z-score, gestation at delivery and corrected gestation were taken into account, table 4-3. Multivariate analyses weakened the relationship between minimum amplitude for EEGs performed within one month of the cranial ultrasound scan and subarachnoid space width, and the relationship with minimum amplitude

for EEGs performed within one week of the ultrasound scan was no longer significant, table 4-3.

Table 4-3
Coefficients from univariate and multivariate analyses between subarachnoid space width on 36 week cranial ultrasound scan and neurophysiological parameters within one week and one month of the cranial ultrasound scan.

	Coefficient on univariate analysis	Coefficient on multivariate analysis
EEG within one week of cranial ultrasound scan		
SEF (Hz)	0.007	0.20
Minimum amplitude (μV)	-0.79**	-0.65
Continuity at the 25μV threshold (% / minute)	-0.24**	-0.23**
Continuity at the 50μV threshold (% / minute)	-0.06**	-0.06*
EEG within one month of cranial ultrasound scan		
SEF (Hz)	-0.07	0.04
Minimum amplitude (μV)	-0.40*	-0.36*
Continuity at the 25μV threshold (% / minute)	-0.14*	-0.11*
Continuity at the 50μV threshold	-0.30*	-0.28*

*p < 0.05 for each regression analysis
**p < 0.01 for each regression analysis

4.3.3.2.3 Comparison of infants with normal and increased subarachnoid space width

Fifty-eight infants (79%) had normal subarachnoid space widths at 36 weeks postmenstrual age (<6.0mm) and 15 (21%) had increased subarachnoid space widths (≥6.0mm). One infant was excluded from the analyses because he had the cranial ultrasound scan performed at 43 weeks gestation (both left and right subarachnoid space widths were ≥6.0mm). After limiting the analysis to infants with 'good' cranial ultrasound scans throughout their admission, and excluding the infant with cranial ultrasound scans performed after 40 weeks corrected gestation, 20% of infants had subarachnoid space widths above the published upper limit of normal.

Infants with subarachnoid space widths above the normal range had lower minimum amplitude and continuities at both the 25 and 50μV thresholds for EEGs within one week of the cranial ultrasound scan than those with subarachnoid space widths within the normal range (p = 0.02, 0.02 and 0.01 respectively, table 4-4). Only the differences in continuity at the 25 and 50μV thresholds remained significant when EEGs performed within one month of the cranial ultrasound scan were included (p = 0.04 and 0.009 respectively, table 4-4). There were no significant differences between groups in the minimum amplitude and SEF parameters.

Table 4-4
Comparison of quantitative neurophysiological parameters between infants with subarachnoid space width within normal limits and infants with subarachnoid space width above normal limits at 36 weeks corrected gestation.

	Subarachnoid space width <6mm	Subarachnoid space width ≥ 6mm
EEG within one week of cranial ultrasound scan	**(n = 21)**	**(n = 3)**
SEF (Hz)	11.0 (10.1 – 12.9)	11.3 (11.2 – 11.9)
Minimum amplitude (μV)	5.4 (3.7 – 8.5)*	4.5 (3.9 – 4.6)
Continuity at the 25μV threshold (% / minute)	100.0 (85.2 – 100.0)*	94.2 (85.9 – 94.8)
Continuity at the 50μV threshold (% / minute)	41.6 (19.1 – 82.3)*	19.8 (15.2 – 22.9)
EEG within one month of cranial ultrasound scan	**(n = 38)**	**(n = 7)**
SEF (Hz)	11.1 (7.8 – 13.4)	11.3 (11.2 – 11.9)
Minimum amplitude (μV)	5.3 (2.6 – 9.6)	4.5 (3.0 – 6.1)
Continuity at the 25μV threshold (% / minute)	98.8 (82.1 – 100.0)*	94.2 (84.9 – 100.0)
Continuity at the 50μV threshold (% / minute)	40.8 (10.0 – 82.3)*	21.9 (15.2 – 35.6)

* p < 0.05 for comparison between infants with normal subarachnoid space width and infants with subarachnoid space width above the normal range

4.3.4 Results - Hammersmith Neonatal Neurological Examination near term corrected gestation

Preterm Median Scores for the 59 HNNEs had a mean (standard deviation) of 79 (8)%. They had a median (range) gestation at delivery of 26 (24 – 31)

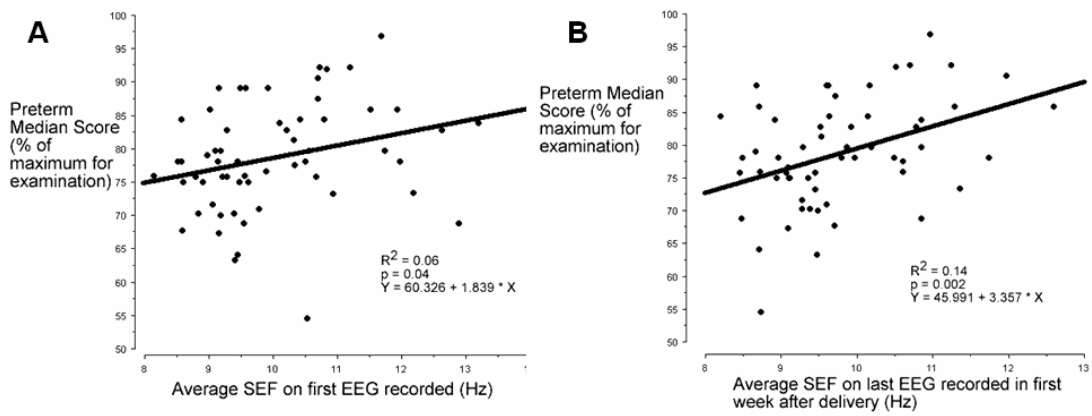
weeks and birthweight of 900 (540 – 1700) grams. All 59 infants had valid EEGs soon after delivery, and 58 had valid EEGs later in the first week after delivery.

4.3.4.1 Univariate analyses

There were weak but statistically significant relationships between the Preterm Median Score and average SEF at the following time points:

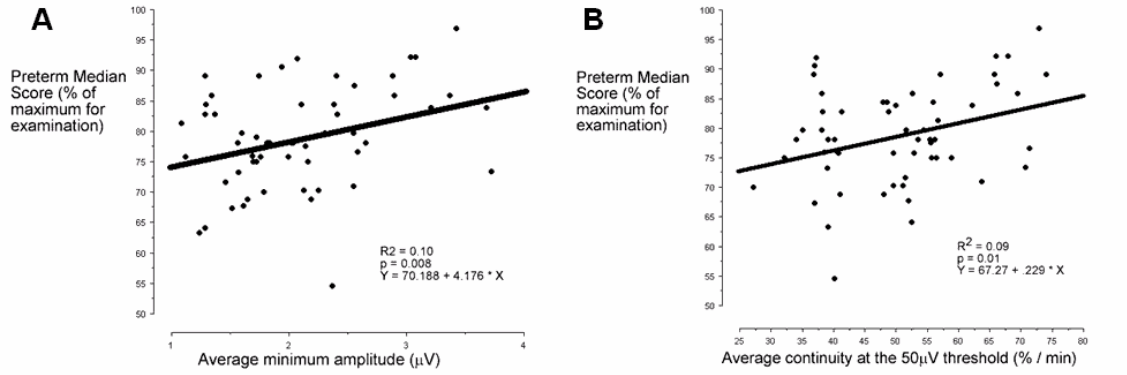
1. the first EEG after delivery, p = 0.04; R^2 = 0.06, figure 4-6A and
2. the last EEG performed during the first week after delivery, p = 0.002; R^2 = 0.14, figure 4-6B.

Figure 4-6
Relationship between Preterm Median Score for Hammersmith Neonatal Neurology Examination and average Spectral Edge Frequency measurements on the first (A) and last (B) EEG recording of the first week after delivery.



There were also statistically significant relationships between the Preterm Median Score and both average minimum amplitude and average continuity at the 50μV threshold at the last EEG performed during the first week, p = 0.008; R^2 = 0.10, figure 4-7A and p = 0.01; R^2 = 0.09, figure 4-7B respectively.

Figure 4-7
Relationship between Preterm Median Score for Hammersmith Neonatal Neurology Examination and average minimum amplitude (A) and continuity at the 50µV threshold (B) measurements on the last EEG recording of the first week after delivery.



There were no significant relationships between the Preterm Median Scores and the following factors:

1. average minimum amplitude at the first EEG performed during the first week after delivery;
2. average continuity at the 25µV threshold on either the first or last EEG recorded within the first week after delivery; and
3. average continuity at the 50µV threshold at the first EEG performed during the first week after delivery.

We repeated any analyses found to be significant analyses for the first EEG with data from EEGs performed only on day 1 and also with data from EEGs performed within the first 48 hours and found similar results. We repeated any analyses found to be significant analyses for the last EEG in the first week with data from EEGs performed only on day 7 and with data from EEGs performed on days 5 to 9 and found similar results.

There were no relationships between Preterm Median Scores and neurophysiological parameters from EEGs performed within one week of the HNNE examination (n = 19), or within one month of the HNNE examination (n = 35).

4.3.4.2 Multiple Regression

The positive relationship between SEF from the last EEG of the first week and Preterm Median Score remained statistically significant when birthweight Z-score and corrected gestation were taken into account (overall $p = 0.005$, $R^2 = 0.17$; p for SEF = 0.007 and coefficient for SEF = 3.0). None of the other relationships remained significant on multiple regression analysis.

4.4 Discussion

This study shows the relationships between investigations currently used for predicting later outcome of preterm infants and quantitative neurophysiological measures obtained during the infant's NICU admission. The strength of the relationships varies depending on the investigation and the timing of the EEG, with many of them having little discriminating value clinically, despite being statistically significant. However, data from early EEGs on asphyxiated term infants (Azzopardi et al., 1999; Hellstrom-Westas et al., 1995) and conventional EEG data on preterm infants have been shown to assist with prediction of long-term neurodevelopmental outcome either alone (Biagioni, Bartalena, Boldrini, Pieri, & Cioni, 2000; Biagioni, Boldrini, Bottone, Pieri, & Cioni, 1996) or in combination with cranial ultrasound scans (Kubota et al., 2002; Marret et al., 1997). Our data suggest that neurophysiological data from EEGs performed within the first week after delivery can provide useful information. However, the weakness of the associations suggest that to be clinically useful combination of neurophysiological data with other investigations such as cranial ultrasound scans will be necessary.

4.4.1 CRIB

We chose CRIB scores as our first early outcome measure as they are obtained very early in the NICU admission, and are associated with early adverse outcomes (Eriksson et al., 2002), and perform at least as well as more complicated illness severity scores (Gagliardi et al., 2004). However, the main use of illness severity scores in NICUs has moved from computing the risk of death for individual infants to determining adjustments for fair comparisons of outcome when benchmarking between hospitals (Gagliardi et al., 2004). Over half of our cohort had been recruited before publication of the CRIB-II score

(Parry et al., 2003). CRIB and CRIB-II scores have been shown to perform nearly identically in assessments of mortality risk in very low birthweight infants (De Felice, Del Vecchio, & Latini, ; Gagliardi et al., 2004).

The relationships between CRIB scores and quantitative neurophysiological measures from their first EEG (minimum amplitude and continuity at the 25 and 50μV thresholds) do not explain much of the variation in results (R^2 values of 0.04) and are unlikely to be clinically relevant. The main reason for the weakness of the relationships is likely to be that CRIB scores are designed to reflect the physiology of the infant while the EEG measures reflect brain function. For example, while high oxygen concentrations in the first 12 hours after delivery leads to high CRIB scores there is likely to be little effect on the neurophysiological measures if normoxaemia is maintained.

A second possible explanation of the weakness of the relationships between early EEGs and CRIB scores is the variation in timing of the first EEG after delivery. While CRIB scores are computed from data obtained within the first 12 hours of delivery the first EEGs were obtained up to four days after delivery. It would be expected that any relationships would become weaker as the time increases between the physiological measurements that contribute to the CRIB score and collection of the EEG recording. However, analyses restricted to infants with EEGs performed within the first 24 hours after delivery did not strengthen the relationships, suggesting that this is unlikely to be an important consideration.

Finally, CRIB scores are heavily influenced by extremely low birthweight (<850 grams), and moderate-to-high oxygen requirements in the first 12 hours after delivery. Gestation influences both CRIB scores and early EEG (Selton et al., 2000; Thornberg & Thiringer, 1990). We found that infants with higher CRIB scores tended to have lower minimum amplitude and continuity measures on their first EEG, consistent with their lower gestation. We are unable to determine from our data set whether the relationships found between EEG parameters and CRIB scores are entirely due to the confounding effects of gestation, but this is likely to be at least part of the explanation.

4.4.2 Cranial Ultrasound Scans

Cranial ultrasound scans are routinely used in neonatal care to provide prognostic information (Ment et al., 2002) and are the only form of neuroimaging routinely used for preterm infants in many NICUs. The presence of significant GM-IVH, ventricular dilatation and PVL are each related to worse prognosis (Thorburn et al., 1981; Weisglas-Kuperus, Baerts, Fetter, & Sauer, 1992). In general early cranial ultrasound scans reveal the presence of significant GM-IVH while later scans are often required to demonstrate whether PVL has developed. Different researchers have used different criteria to group abnormal findings of GM-IVH on cranial ultrasound scans when examining the relationships of scan findings with later neurodevelopmental outcome. Some separated each grade of GM-IVH in analyses (Thorburn et al., 1981) while others grouped low grade GM-IVH (grade 1 and 2) and split grade 3 and 4 separately (Weisglas-Kuperus et al., 1992), and yet others grouped all GM-IVH excluding intraparenchymal extensions (grade 1 to 3) (Roth et al., 1993; Whitaker et al., 1996). The neurodevelopmental outcome of infants with isolated grade 1 GM-IVH (Thorburn et al., 1981) or infants with either grade 1 or 2 GM-IVH (Weisglas-Kuperus et al., 1992) was similar to that of infants with normal cranial ultrasound scans. We chose to divide infants with GM-IVH into two groups: infants with GM-IVH grade 1 and 2 were grouped with infants with normal scans ('good' scans) and infants with GM-IVH grade 3 and 4 were grouped with infants found to have definite or probable PVL ('bad' scans) as we did not have enough infants with grade 2, 3 and 4 GM-IVH to make individual groups for analyses. Infants with probable or definite PVL were included in the 'bad' scans group as PVL is strongly linked to poor neurodevelopmental outcome (Weisglas-Kuperus et al., 1992; Whitaker et al., 1996). None of the infants had PVL diagnosed on the day 5 cranial ultrasound scan and so these infants were only included in the analyses examining EEG parameters between infants with all 'good' scans and those with ≥ 1 'bad' scans.

Distinctive EEG changes have been reported in babies with GM-IVH (Greisen et al., 1987; Hellstrom-Westas et al., 2001) and PVL (Baud et al., 1998; Kubota et al., 2002; Watanabe et al., 1999). Infants with grade 1 GM-IVH have been reported to have depressed background activity (equating to decreased

minimum amplitude) and decreased continuous activity (equating to reduced continuity) on aEEG around the time of the germinal matrix haemorrhage (Greisen et al., 1987). Infants who developed grade 3 and 4 GM-IVH had aEEG changes of decreased burst frequency (equating to reduced continuity) noted on recordings obtained over the first week after delivery (Hellstrom-Westas et al., 2001). Acute changes on conventional EEG of increased discontinuity (equating to reduced continuity), decreased faster frequency components (equating to decreased SEF) and lowered amplitudes (equating to decreased minimum amplitude and decreased continuity at higher continuity thresholds) have been noted soon after delivery in infants who subsequently developed PVL on cranial ultrasound scans (Watanabe et al., 1999). Inder and colleagues (Inder, Buckland et al., 2003) also found that decreased SEF from EEG recordings performed in the first week of life was associated with increased white matter damage on MRI at term corrected gestation. Therefore we anticipated that EEGs recorded in the first week after delivery would show decreased SEF, minimum amplitude and continuity in those infants with abnormal cranial ultrasound scans.

Our results show decreased continuity, consistent with reported aEEG changes, shortly after delivery in infants with grade 3 and 4 GM-IVH on cranial ultrasound scans obtained around five days after delivery. Including the two infants who subsequently had evidence of white matter injury on cranial ultrasound scans gave the expected changes of decreased SEF, minimum amplitude and continuity from early EEGs (Watanabe et al., 1999).

Measurement of the subarachnoid space width by ultrasound has been used as a marker of brain volume within the cranial vault (Armstrong et al., 2002; Lui et al., 1990). At term corrected gestation subarachnoid space widths from cranial ultrasound scans correlate with both total subarachnoid fluid volume and brain volume on MRI scanning (Anderson et al., 2004). However, initial research on subarachnoid space measurements from cranial ultrasound scans found that widened subarachnoid space width was not related to increased developmental impairment (Lui et al., 1990).

Interestingly, we found that increased subarachnoid space width was associated with decreased SEF on the first EEG recorded after delivery. Decreased SEF in the first week after delivery has also been associated with increased severity of white matter injury on MRI at term corrected gestation (Inder, Buckland et al., 2003). Conventional EEG data suggest that changes indicative of acute brain injury include increased discontinuity (or decreased continuity) and lower amplitude traces (Watanabe et al., 1999). Thus our finding that lower minimum amplitude on the first EEG recorded after delivery was associated with increased subarachnoid space width at 36 weeks corrected gestation gives further weight to the hypothesis that these EEG changes may be indicative of early injury leading to decreased cortical growth. Furthermore, the finding that subarachnoid space width at 36 weeks is related to EEG parameters at the beginning but not at the end of the first week after birth supports the current evidence that most preterm brain injury occurs in the period just before, during or shortly after delivery so that EEG changes would be resolving by the end of the first week after delivery (F. Hayakawa et al., 1999; Watanabe et al., 1999). Early cotside EEG recordings with quantitative neurophysiological measures may be able to provide information about which infants are particularly at risk of neurodevelopmental impairment, and which infants may benefit most in trials of neuroprotective agents when these become available.

The relationship between increased subarachnoid space width (≥6.0mm) on the 36 week cranial ultrasound scan and decreased minimum amplitude and continuity at the 25 and 50μV thresholds on EEGs performed either within one week or one month of the cranial ultrasound scan may be explained by the damping effect of the cerebrospinal fluid. The amplitude of scalp EEG decreases with respect to the cortical EEG as a result of changes in the impedance to the electrical impulses from a collection of subdural blood or cerebrospinal fluid (Fisch, 1999c). A fluid collection shunts the currents away (‘short-circuits’) before they reach the recording electrodes. Therefore, the stronger relationships found between quantitative neurophysiological measures on EEGs performed in the week before or after the 36 week cranial ultrasound

scan are unlikely to be clinically useful as larger subarachnoid space widths do not predict impairment (Lui et al., 1990).

It is interesting to note that the previous paper reporting normal subarachnoid space width measurements for preterm infants at 36 weeks corrected gestation found the upper limit of the 95% confidence interval to be 5.97mm (Armstrong et al., 2002). We found 20% of our infants had subarachnoid space widths ≥ 6mm rather than the 2.5% expected from this report. As the two groups of infants were cared for in the same hospital, with recruitment of our cohort starting only 18 months after completion of the Armstrong cohort, it is unlikely that major differences in the management of the infants have caused the changes. The major reason for this over-representation of wide subarachnoid space widths in our population may be the fact that our infants are substantially smaller and lighter than those previously reported. From the previous report it appears that most infants had cranial ultrasound scans performed on days 5 and 28 after delivery. At 28 days after delivery the median gestation of our infants was 31 weeks, with none of the infants being 36 weeks corrected gestation. Therefore, in order to compare our data with that in the previous report we needed to make a correction for a further five weeks of postnatal growth. Armstrong and colleagues found that the subarachnoid space width increased between 0.15 and 0.30mm with each week of increased gestational age on their follow-up scans (Armstrong et al., 2002). Correcting the upper limit of 'normal' subarachnoid space width of the Armstrong data for another five weeks postnatal growth would bring the 'normal' subarachnoid space width to between 6.2 and 7.5mm. Using these cut-offs the percentage of infants with 'good' scans who had subarachnoid space widths above the 95th confidence interval decreased to between 4.5 and 10.4% (between 3 and 7 infants), still well beyond the 2.5% expected.

4.4.3 Hammersmith Neonatal Neurological Examination

The HNNE was chosen to represent an early functional outcome measure. Mercuri's recent publication provides the median and 90th centile range of scores for preterm infants at different gestations examined at term corrected gestation (Mercuri et al., 2003). For research purposes this allows the HNNE

recording sheet to be scored in a meaningful way against reference ranges. In order to provide a spread of results to represent the variety of functional abilities of preterm infants at term, and allow us to examine the relationships of the HNNE with neurophysiological parameters, we chose to score the examination according to whether or not the examination was the same as the median result for infants of a similar gestation at delivery.

To our knowledge there are no data examining the relationships between early EEG data and neurological examination near term in preterm infants. We found weak relationships between average SEF on the first EEG and Preterm Median Score, and between average SEF, minimum amplitude and average continuity at the 50μV threshold on the last EEG performed during the first week after delivery. This is consistent with a previous report that found early EEG changes, but not near-term EEG changes, predicted outcome at 3 years (Biagioni et al., 2000). The lack of any relationships with EEGs performed within either one week or one month of the HNNE suggest that EEG changes shortly after delivery may represent acute injury and be more relevant to functional outcome rather than later EEGs.

It is interesting to note that SEF of the first recorded EEG was related to the Preterm Median Score. This indicates that lowered SEF early in the first week may be associated with both imaging changes (widened subarachnoid space width) and functional changes (lower HNNE scores) at near term corrected gestation.

The positive relationships between Preterm Median Scores and SEF, minimum amplitude and average continuity at the 50μV threshold in the last EEG recorded in the first week after delivery are interesting. One possible reason for the relationships with EEGs recorded later in the first week after delivery is that ongoing subacute insults may result in functional changes near term. The lack of a similar relationship for subarachnoid space width may indicate that the ongoing insult may result in functional outcome without resulting in imaging changes. However, it is possible that we do not have sufficient numbers of

infants to demonstrate the relationships between EEG parameters late in the first week after delivery and cranial ultrasound scan changes near.

4.4.4 Timing of EEG recordings for analyses

We used our data from EEGs performed at different time points over the first week after delivery, and also within one month and one week of the 36 week cranial ultrasound scan and HNNE. We aimed to have the first EEG performed as soon as possible after delivery and another one towards the end of the first week, and aimed to have a spread of data collected throughout the whole of the first week after delivery. Therefore the first and last EEGs in the first week after delivery were clustered around the first 48 – 72 hours after delivery and around days 6 to 8 after delivery.

Analyses using data from the first EEG in the first week after delivery gave similar results to those using data from EEGs performed on day 1, and from EEGs performed in the first 48 hours after delivery. We have chosen to report the results of the first EEG after delivery as these data are more directly related to situations in clinical practice where EEGs cannot necessarily be collected at the same time in every baby for a variety of reasons. It will be important to examine data from more comparable time periods as increasing numbers of infants are recruited into trials using this technology, to determine the importance of timing of early EEGs.

Analyses using only data from either EEGs performed on day seven after delivery, or data from EEGs performed on days five to nine after delivery gave results similar to those using the last EEG in the first week after delivery data. As our results show that EEG parameters in the latter half of the first week had stabilised (section 3.2.4.1) it seems unlikely that the changes in timing as a result of using data from the last EEG in the first week has substantially altered our conclusions.

Finally, analyses were undertaken to examine relationships between EEGs within one week, and EEGs within one month, of either of the 36 week outcome assessments (subarachnoid space widths and Preterm Median Scores).

Results were similar for both times, but the relationships were generally stronger for the EEGs within one week of the outcome assessment despite smaller numbers of infants. With regard to the relationships with subarachnoid space widths this is likely to be because the subarachnoid space width continues to enlarge during infant's NICU admission and EEGs recorded closer in time to the cranial ultrasound scan would reflect the degree of the fluid attenuation more accurately.

4.4.5 Summary and implications

Data from EEGs, CRIB scores and cranial ultrasound scans provide different information about an infant's health status. We have shown that EEGs recorded early in an infant's NICU admission are related to these interim outcome measures. While there are relationships between quantitative neurophysiological parameters from EEGs and CRIB scores, cranial ultrasound scans and predischarge neurological examinations, these are weak and unlikely to be clinically useful on their own. However, some combination of the information contained in these assessments may prove to be useful for prediction of longterm neurodevelopmental outcome. This will be explored further in chapter 6.

5 Relationships between neurophysiological parameters, physiologic measures and therapeutic interventions in NICU

5.1 Introduction

Low cerebral blood flow, measured by intravenous ^{133}Xe clearance, has been associated with discontinuous EEG activity in preterm infants (Greisen & Pryds, 1989). In preterm lambs, EEG activity deteriorated when cerebral oxygen supply decreased below a threshold level (Van Os, Klaessens, Hopman, Liem, & Van de Bor, 2003), and in fetal sheep there were changes in quantitative EEG parameters after an interruption of cerebral perfusion (Reddy et al., 1998). However, direct measures of cerebral blood flow are not available for routine clinical use.

Echocardiographic measurements of ventricular output and superior vena caval (SVC) return have been assessed as surrogate markers of cerebral perfusion. In early postnatal life, estimates of left ventricular output (LVO) and right ventricular output (RVO) are confounded by ductal and atrial shunts respectively. Ductal shunting is felt to be more significant than atrial shunting, so that RVO may be a more reliable indicator of systemic perfusion than LVO (Evans & Iyer, 1995) since it is primarily influenced by systemic venous return. Low SVC flow in the first 24 hours after birth has been associated with periventricular haemorrhage (Kluckow & Evans, 2000a), adverse neurodevelopmental outcome at three years (Hunt et al., 2004), and was a stronger predictor of adverse outcome than arterial blood pressure (BP) (Hunt et al., 2004). However, there are no reports of the relationship between

echocardiographic measurements of blood flow and EEG parameters in newborn babies.

Blood pressure measurements are part of routine care for preterm infants, and efforts are made to maintain the mean systemic arterial pressure (MAP) within widely accepted limits. There are data indicating that MAP is not always directly related to cerebral blood flow (Boylan et al., 2000; Tyszczuk et al., 1998). Therefore we wanted to examine the relationships between blood pressure and quantitative neurophysiological parameters in addition to echocardiographic flow data.

Infants requiring admission to NICU routinely have a number of physiologic parameters monitored. Among these the most common are oxygen saturation (SaO_2), BP (either continuous invasive monitoring, or by oscillometry), heart rate and respiratory rate. While there are some data to suggest that hypotension can cause changes in EEG patterns (Greisen, Pryds, Rosen, & Lou, 1988) the data are limited regarding the extent of perturbation (both in severity of change and length of change) required to change the EEG patterns, or the length of time that EEG changes persist. We planned to explore the interactions between physiologic perturbations commonly occurring in NICU (hypotension and brief moderate desaturations) and neurophysiological parameters to begin to understand the impact of these perturbations on cerebral function.

Some drugs, such as, opiates (Eaton et al., 1992; Young & da Silva, 2000), surfactant (Hellstrom-Westas, Bell, Skov, Greisen, & Svenningsen, 1992) and benzodiazepines (ter Horst, Brouwer, & Bos, 2004) are known to alter EEG parameters. For other drugs, such as indomethacin and caffeine, there are known effects on cerebral blood flow (Hoecker, Nelle, Poeschl, Beedgen, & Linderkamp, 2002; Yanowitz et al., 1998) but no data regarding their effect on EEG parameters. Now that cotside EEG monitoring is increasingly available, it is important to know about the effects of commonly used medication on EEG parameters to assist clinicians with interpretation of both published data and cotside monitoring.

In this chapter we report:

1. relationships between echocardiographic flow data, routinely obtained blood pressure measurements and quantitative EEG data obtained over the first 48 hours after birth in preterm infants;
2. quantitative EEG data before, during and after acute perturbations in physiologic parameters (blood pressure and oxygen saturation); and
3. quantitative EEG data before, during and after administration of common medications known to have the potential to affect brain function (opiates, surfactant, caffeine and indomethacin).

5.2 Methods

5.2.1 Quantitative neurophysiological measurements, blood pressure recordings and echocardiographic measurements of blood flow

Infants reported here were recruited for two different studies; serial echocardiography over the first 48 hours after birth to assess a variety of haemodynamic measurements including SVC flow and RVO, and those recruited for EEG recordings for this thesis. Infants had simultaneous EEG and echocardiography measurements whenever possible. Recording and analysis of echocardiographic and EEG assessments were performed by independent observers unaware of the other's results.

Echocardiography was performed as described in section 2.7. Infants with invasive BP monitoring had recordings downloaded as described in section 2.6. These BP measurements were averaged over the duration of the echocardiography. Intermittent BP measurements were only included if invasive BP readings were not available and if BP readings were taken within an hour of the echocardiogram. Our NICU protocol (Knight) was that infants with MAP below 30mmHg received an initial 10ml/kg bolus of normal saline. Those infants whose MAP remained below 30mmHg were commenced on dopamine infusion 5 -10µg/kg/min, titrated to the BP responses.

Quantitative neurophysiological measurements of median and minimum amplitude, and continuity at the 10, 25 and 50µV thresholds were assessed as

median values for the 60 minutes immediately before or after the echocardiogram was performed. Left and right sided values were averaged.

Simple linear regression was performed for continuous variables which approximated a normal distribution. Firstly, analyses were performed between flow / BP measurements and EEG measurements obtained at each time point. Secondly, analyses were performed between flow / BP measurements at one time point with EEG measurements over the following 24 hours. Analyses with two-tailed p-values ≤0.05 were included in multiple regression analysis using the following independent variables: gestation, birthweight Z-score and CRIB-II score (Parry et al., 2003). To further explore the strength of the relationships between measurements of cardiovascular function and EEG, we also compared EEG measurements between infants having the lowest quartile of blood flow or pressure measurements at each time point, and the remainder of the cohort. As these measurements were not normally distributed they were compared using the Mann-Whitney U test.

5.2.2 Neurophysiological changes and acute changes in physiologic monitoring

In order to document possible changes in neurophysiologic parameters associated with acute changes in physiologic parameters we chose to examine episodes during which infants dropped their diastolic BP below 20mmHg, or their MAP below 30mmHg, or their SaO_2 below 75%.

The diastolic BP threshold of below 20mmHg was used because we wanted to assess infants with very low diastolic BP. Infants in the lowest quartile of diastolic BP 12 hours after delivery in the analyses for the echocardiographic blood flow and BP outlined above had diastolic BPs < 25mmHg (table 5-3). The MAP threshold of 30mmHg was chosen as this is one of the values considered to represent the lower limit of the normal range for preterm infants shortly after delivery (Low et al., 1991; Miall-Allen, de Vries, Dubowitz, & Whitelaw, 1989). More complex nomograms for MAP thresholds, using birthweight, gestation and postnatal age, are available (Lee et al., 1999; Versmold et al., 1981), but their complexity made it difficult for us to isolate relevant EEG sections to be analysed.

Currently there is debate about the target range of SaO_2 levels for extremely preterm infants (Askie, Henderson-Smart, Irwig, & Simpson, 2003; The STOP-ROP Multicenter Study Group, 2000). Our NICU guidelines recommend a target range of 85 – 92% for infants with birthweights below 1500g for the first postnatal month (Knight, Rowley, & Kuschel, 2004). Infants with duct dependent cyanotic congenital heart disease have their SaO_2 maintained above 75% (Kuschel, Gentles, & Beca, 2004). Therefore we chose to identify periods during which infants had their SaO_2 < 75% for at least two minutes. To exclude periods where the SaO_2 recordings were falsely low due to artefact from movement or sensor failure, eligible periods needed to have a similar heart rate on both the SaO_2 probe and the chest leads during the desaturation.

Periods in which the diastolic BP was <20mmHg, the MAP was <30mmHg or the SaO_2 <75% were highlighted in each available Excel file from routine physiologic monitoring (section 2.6.1.2). Each record was searched manually to identify time periods in which the diastolic BP was <20mmHg or the MAP was <30mmHg for at least three consecutive minutes, or the SaO_2 was <75% for at least two minutes consecutively. The identified periods were then checked to find those with at least 10 minutes of EEG recording before or after each episode of the perturbation during which that perturbation did not recur. Segments of EEG that met these criteria were analysed during three time periods:

1. A period of between 10 and 60 minutes before the perturbation;
2. The period of the physiologic perturbation;
3. A period of between 10 and 60 minutes after the perturbation.

These time periods were chosen to minimise the effect of short term variations in the neurophysiologic parameters. Because of this variability our main analyses have been based on 60 minute periods. However, this duration of recording was often not available, and we therefore analysed shorter periods where necessary.

Neurophysiologic parameters were examined using the Freidman test to determine any difference between values before, during and after the physiologic perturbation.

5.2.3 Neurophysiologic changes with administration of medications

Administration of intravenous boluses of opiates, loading infusions of caffeine, infusions of indomethacin and endotracheal administration of surfactant were identified from events marked on the EEG recording sheets. The timing of these was checked against drug administration charts to enhance the accuracy of these analyses.

In our NICU caffeine loading doses are given to infants receiving parenteral nutrition as two intravenous infusions of 12.5mg/kg caffeine base over 30 minutes, one hour apart (Knight, Wilkinson, Hughes, & McFarlane). Indomethacin is given as an infusion of 200 µg/kg/dose over 30 minutes for closure of a persistent patent ductus arteriosus (Knight & Cooper).

For each of the caffeine and indomethacin administrations we analysed:

1. A period of 60 minutes before drug administration;
2. The period of drug administration, 30 minutes; and
3. A period of 60 minutes after the drug infusion.

In addition the following time periods were analysed for some infants:

1. A baseline period of 60 minutes was analysed. If the drug administration occurred less than 60 minutes after the EEG was commenced, the baseline period was chosen as far from the drug administration as possible and at least 60 minutes after the drug had been given.
2. For infants receiving two intravenous caffeine loading doses during the EEG, the period between the loading doses was analysed. These infants had data available before drug administration (or baseline), first drug dose, between drug doses, second drug dose and after drug infusion entered into the database whenever possible.

For infants receiving opiate boluses we analysed a 60 minute period before the bolus was given and a period of 10 - 20 minutes after the administration of the

opiates. The period was also chosen to avoid the interactions of other events that occurred around the time of opiate administration (intubation or chest tube insertion).

For infants receiving endotracheal surfactant we analysed a 60 minute period before surfactant administration (and before the opiate bolus if the child was intubated for the surfactant). We then analysed a 10 and a 60 minute period immediately after the administration of surfactant whenever EEG recordings permitted.

Each of the periods of EEG were analysed to determine SEF, minimum amplitude and continuity at the 25 and 50μV. Left and right sided values were averaged.

Neurophysiologic parameters for the drug administration effects were examined using the Freidman test to determine any difference between values before and during and after drug infusions, and Wilcoxon signed rank test for differences before and after opiates and endotracheal surfactant.

5.3 Results

5.3.1 Relationship between quantitative neurophysiologic measurements, blood pressure recordings and echocardiographic measurements of blood flow

During the study period 155 infants were admitted to the NICU at less than 30 weeks completed gestation. Forty infants had at least one set of paired EEG and blood flow recordings, and 18 had EEG recordings in association with each of their four echocardiographs. Their median (range) gestation was 27(24–30) weeks, and birthweight was 945(510 - 1900) grams (table 1). One hundred and twelve sets of paired data were analyzed. Echocardiographic flow measurements, BP and quantitative EEG parameters were all obtained in between 24 and 30 babies at each time period (tables 5-1 and 5-2).

No infants were receiving opiate infusions, muscle relaxants or sedative medication at the time of these measurements. One infant received a fentanyl bolus for intubation three hours before the 12 hour echocardiograph and one

infant received surfactant immediately after the five hour echocardiograph, at the start of the EEG assessment period. These two infants remained in the analyses as their exclusion did not change the results. The ductus arteriosus was closed in 0, 4, 9 and 12 infants at 5, 12, 24 and 48 hours. No infants received indomethacin prior to the 48 hour assessment.

Table 5-1
Gestation, birthweight, patent ductus arteriosus size, ventilatory support and method of blood pressure measurement for infants with paired flow/blood pressure and EEG data at each time point.

	Infants at 5 hours (n = 24)	Infants at 12 hours (n = 27)	Infants at 24 hours (n = 30)	Infants at 48 hours (n = 31)
Gestation at delivery (weeks)	26 (1.6)	27 (1.6)	26 (1.7)	27 (1.7)
Birthweight (grams)	945 (635-1900)	950 (605-1900)	917 (510-1850)	940 (605-1620)
Patent Ductus Arteriosus diameter >1.5mm	22 (92)	11 (41)	18 (60)	10 (32)*
Ventilatory Support				
Nil	1 (4)	1 (4)	4 (13)	6 (19)
CPAP	7 (29)	9 (33)	9 (30)	14 (45)
Intubated	16 (67)	17 (63)	17 (57)	11 (36)
Blood pressure				
- Invasive	25 (63)	27 (67)	26 (65)	25 (63)
- Doppler	7 (17)	9 (23)	8 (20)	5 (12)
- No recording	8 (20)	4 (10)	6 (15)	10 (25)

Results are mean (standard deviation), median (range) or number (percentage)
*12 (30%) of infants had closed ductus arteriosus

Table 5-2
Echocardiographic flow measurements, blood pressure and quantitative electroencephalographic parameters.

	5 hour	12 hour	24 hour	48 hour
SVC flow [ml/kg/min]	89 (34–186) [n= 40]	97 (21–183) [n=39]	91 (45-169) [n=38]	108 (45-179) [n=40]
RVO [ml/kg/min]	330 (100-616) [n=38]	345 (161-628) [n=40]	426 (192-650) [n=37]	411 (135-655) [n=38]
Mean Arterial Pressure [mmHg]	35 (24-49) [n =32]	35 (22-52) [n=36]	36 (25-59) [n=34]	38 (26-55) [n=30]
Systolic BP [mmHg]	44 (28-67) [n=32]	44 (28-66) [n=36]	46 (33-67) [n=34]	51 (35-71) [n=30]
Diastolic BP [mmHg]	26 (16-38) [n=32]	27 (18-43) [n=36]	27 (19-47) [n=34]	30 (20-45) [n=30]
Continuity at 10µV threshold [%/minute]	100 (56-100) [n=24]	100 (69-100) [n=27]	100 (91-100) [n=30]	100 (94-100) [n=31]
Continuity at 25µV threshold [%/minute]	59 (25-95) [n=24]	64 (29-100) [n=27]	78 (52-97) [n=30]	88 (50-100) [n=31]
Continuity at 50µV threshold [%/minute]	27 (11-64) [n=24]	29 (12-85) [n=27]	45 (15-71) [n=30]	59 (23-80) [n=31]
Minimum amplitude [µV]	1.9 (1.2-4.4) [n=24]	2.1 (1.0-6.5) [n=27]	2.3 (1.1-6.9) [n=30]	2.4 (1.3-3.8) [n=31]
Median amplitude [µV]	5.3 (2.6-9.4) [n=24]	5.0 (2.5-11.4) [n=27]	6.6 (3.1-11.9) [n=30]	7.4 (3.8-11.9) [n=31]

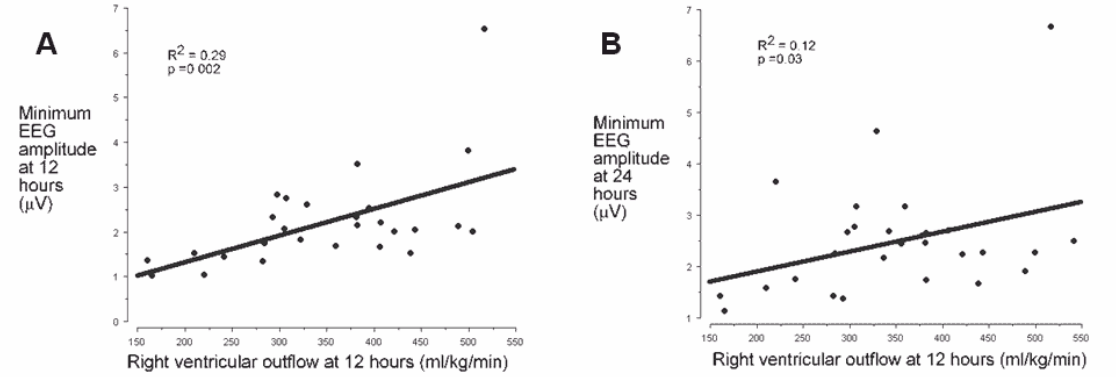
Results are median (range)

5.3.1.1 Blood Flow

5.3.1.1.1 Relationships between blood flow and EEG amplitude

RVO at five hours was not related to EEG amplitude. RVO at 12 hours was positively related to both minimum and median amplitude at 12 hours (R^2 = 0.29, p = 0.002, figure 5-1A and R^2 = 0.18, p=0.02, respectively) and also at 24 hours (R^2 = 0.12, p = 0.03, figure 5-1B and R^2 = 0.15, p=0.009, respectively). There were no significant relationships between RVO at 24 or 48 hours and EEG amplitude measurements.

Figure 5-1
Relationship between right ventricular outflow at 12 hours and minimum EEG amplitude measurements at 12 hours (A, n = 27) and 24 hours (B, n = 30).



SVC flow was not related to EEG amplitude at any of the time points measured.

5.3.1.1.2 Relationships between blood flow and EEG continuity

Only small numbers of infants had EEG continuity at 10μV less than 100%: 10/24 at five hours; 10/27 at 12 hours; 7/30 at 24 hours and 2/31 at 48 hours. As these data were not normally distributed we did not perform linear regression analyses at this threshold.

RVO at five hours was positively related to EEG continuity at the 25μV threshold at 24 hours (R^2 = 0.11, p = 0.05). RVO at 12 hours was positively related to continuity at the 25μV threshold at 24 hours (R^2 = 0.15, p = 0.02). RVO at 24 and 48 hours were not related to EEG continuity.

SVC flow at five hours was positively related to EEG continuity at the 50μV threshold at 24 hours (R^2 = 0.11, p = 0.04). SVC flows at 12, 24 and 48 hours were not related to EEG continuity.

5.3.1.2 Blood Pressure

Approximately two thirds of the infants at each time point had invasive blood pressure monitoring (table 5-1). Invasive blood pressure measurements were lower than those obtained non-invasively, largely because invasive monitoring was undertaken in smaller babies. When gestational age was taken into

account the only significant difference between blood pressure measurements in the invasive and non-invasively monitored group was for MAP at 12 h (mean [standard deviation] 33.5 [5.7]mmHg for invasive montoring and 40.8 [4.9]mmHg for non-invasive monitoring, p = 0.02).

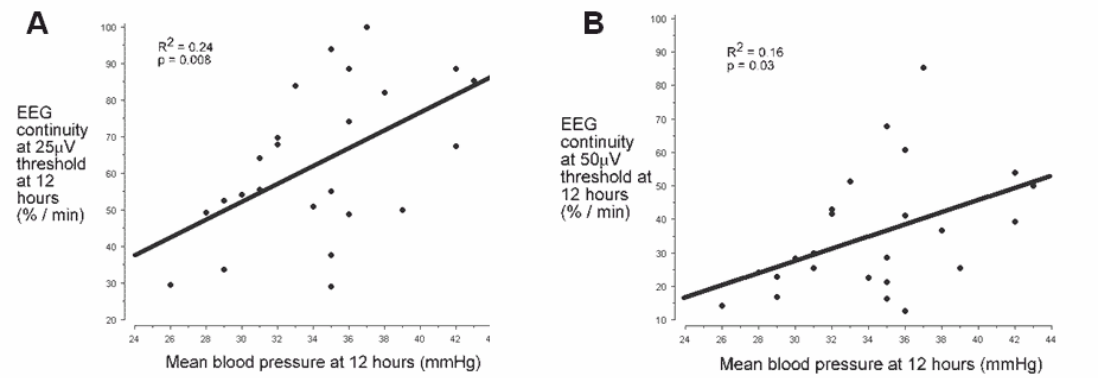
5.3.1.2.1 Relationships between blood pressure and EEG amplitude

Systolic BP, diastolic BP and MAP were not related to EEG amplitude at any time point.

5.3.1.2.2 Relationships between blood pressure and EEG continuity

MAP at five hours was not related to EEG continuity. MAP at 12 hours was positively related to EEG continuity at both the 25µV and 50µV thresholds at 12 hours (R^2 = 0.24, p = 0.008, figure 5-2A and R^2 = 0.16, p = 0.03, figure 5-2B respectively). MAP at 24 hours was related to EEG continuity at the 50µV threshold at 48 hours (R^2 = 0.13, p = 0.04). MAP at 48 hours was not related to EEG continuity.

Figure 5-2
Relationship between mean systemic arterial blood pressure at 12 hours and EEG continuity measurements at 12 hours at the 25µV (A, n = 27) and 50µV (B, n = 27) thresholds.



Systolic BP was not related to EEG continuity at any time point.

Diastolic BP at five and 12 hours was not related to EEG continuity. Diastolic BP at 24 hours was related to EEG continuity at both 25µV and 50µV thresholds at 24 hours (R^2 = 0.19, p = 0.02 and R^2 = 0.21, p = 0.01, respectively), and also to EEG continuity at the 50µV threshold at 48 hours (R^2 = 0.18, p = 0.02). Diastolic BP at 48 hours was not related to EEG continuity.

5.3.1.3 Multiple regression analyses

To explore whether these relationships were simply reflecting severity of neonatal illness, we undertook multiple regression analysis for each of the significant simple regressions, taking into account gestational age, birthweight Z-score and CRIB-II score. Within the narrow range of gestations in this cohort, only continuity measures at the 25μV threshold at 12 hours after birth was significantly related to gestational age on univariate analysis (R^2 = 0.22, p = 0.01), so that colinearity was not considered an important confounder in these analyses.

RVO measured at 12 hours remained independently related to median amplitude measured at 24 hours (overall R^2 = 0.24, p = 0.04, RVO p = 0.01). The relationships between diastolic BP at 24 hours and EEG continuity measured at both the 25 and 50μV thresholds at 24 hours also remained significant in multiple regression models (overall R^2 = 0.38, p = 0.01 with diastolic BP p = 0.003, and R^2 = 0.55, p = 0.0008 with diastolic BP p = 0.0003, respectively).

5.3.1.4 Lowest blood flow quartile and EEG parameters

Infants in the lowest quartile for RVO at five hours (<249ml/kg/min) did not differ from the remainder of the cohort in EEG amplitude. Infants in the lowest quartile for RVO at 12 hours had lower minimum and median amplitude at 12 hours (p = 0.006 and p = 0.0003 respectively, table 5-3) and at 24 hours (p = 0.001 and p = 0.005 respectively, table 5-3). Infants in the lowest quartile for RVO at 24 hours (<349ml/kg/min) did not differ from the remainder of the cohort in EEG amplitude.

Infants in the lowest quartile for RVO at five hours had lower EEG continuity at the 10μV threshold at 24 hours (median[range] 97[91-100]% cf 100[94-100]%, p = 0.03). Infants in the lowest quartile for RVO at 12 hours had lower EEG continuity at the 10, 25 and 50μV threshold at 12 hours (p = 0.02, p = 0.03 and p = 0.08 respectively, table 5-3), and at 24 hours (p = 0.0003, p = 0.01 and p =

0.03 respectively, table 5-3). Infants in the lowest quartile for RVO at 24 hours did not differ from the remainder of the cohort in EEG continuity.

At all times studied, infants in the lowest quartile for SVC flow did not differ from the remainder of the cohort for EEG amplitude. However, infants in the lowest quartile for SVC flow at five hours (<63ml/kg/min) had lower EEG continuity at the 10μV threshold at 24 hours (median[range] 98[91-100]% cf 100[96-100]%, p = 0.01). Infants in the lowest quartile for SVC flow at 12 hours (<64ml/kg/min) also had lower EEG continuity at the 10μV threshold at 24 hours (median[range] 96[91-100]% cf 100[96-100]%, p = 0.02). Infants in the lowest quartile for SVC flow at 24 hours (<77ml/kg/min) did not differ from the remainder of the cohort for EEG continuity.

Table 5-3
Comparison between quantitative EEG measurements in infants in the lowest quartile of right ventricular outflow and blood pressure 12 hours after birth and the remainder of the study cohort.

		Minimum Amplitude µV)		Median Amplitude µV)		Continuity Thresholds (%/minute)					
						10µV		25µV		50µV	
		12 hours	24 hours	12 hours	24 hours	12 hours	24 hours	12 hours	24 hours	12 hours	24 hours
RVO 12 hours	Lowest quartile (<282ml/kg/min)	1.3* (1.0-1.5) (n = 6)	1.5* (1.1-3.7) (n = 8)	3.3* (2.5-5.0) (n = 6)	4.6* (3.8-7.6) (n = 8)	84* (69-100) (n = 6)	96* (91-100) (n = 8)	42* (29-68) (n = 6)	64* (56-96) (n = 8)	20 (14-42) (n = 6)	31* (26-63) (n = 8)
	Remainder (≥282ml/kg/min)	2.2 (1.5-6.5) (n = 21)	2.5 (1.3-6.7) (n = 22)	5.1 (3.4-11.4) (n = 21)	7.4 (3.1-11.9) (n = 22)	100 (91-100) (n = 21)	100 (94-100) (n = 22)	67 (29-100) (n = 21)	79 (52-97) (n = 22)	37 (12-85) (n = 21)	52 (15-71) (n = 22)
Mean systemic arterial pressure 12 hours	Lowest quartile (< 31mmHg)	1.7 (1.0-2.1) (n = 5)	2.0 (1.1-2.7) (n = 6)	4.1 (2.8-4.6) (n = 5)	5.2* (4.5-9.7) (n = 6)	91* (69-96) (n = 5)	100 (91-100) (n = 6)	29* (12-85) (n = 5)	69 (56-90) (n = 6)	23* (14-28) (n = 5)	36 (31-67) (n = 6)
	Remainder (≥ 31mmHg)	2.1 (1.0-6.5) (n = 19)	2.3 (1.4-6.7) (n = 21)	5.1 (2.5-11.4) (n = 19)	6.7 (3.1-11.9) (n = 21)	100 (70-100) (n = 19)	100 (93-100) (n = 21)	49 (30-54) (n = 19)	78 (52-97) (n = 21)	39 (13-85) (n = 19)	52 (15-71) (n = 21)
Diastolic pressure 12 hours	Lowest quartile (< 25mmHg)	2.0 (1.3-2.3) (n = 7)	1.9 (1.4-2.7) (n = 7)	4.1 (2.8-5.0) (n = 7)	5.1 (3.1-9.7) (n = 7)	96* (69-100) (n = 7)	100 (94-100) (n = 7)	53* (30-68) (n = 7)	68 (52-90) (n = 7)	24* (13-42) (n = 7)	35 (15-67) (n = 7)
	Remainder (≥ 25mmHg)	2.2 (1.0-6.5) (n = 17)	2.4 (1.1-6.7) (n = 20)	5.2 (2.5-11.4) (n = 17)	7.1 (3.8-11.9) (n = 20)	100 (70-100) (n = 17)	100 (91-100) (n = 20)	70 (29-100) (n = 17)	79 (56-97) (n = 20)	39 (16-85) (n = 17)	52 (24-71) (n = 20)

*p <0.05 lowest quartile compared with remainder

5.3.1.5 Lowest blood pressure quartile and EEG parameters

Infants in the lowest quartile for MAP at five hours (<30mmHg) did not differ from the remainder of the cohort for EEG amplitude. Infants in the lowest quartile for MAP at 12 hours had lower median amplitude at 12 hours (p = 0.01, table 3). Infants in the lowest quartile for MAP at 24 hours (<32mmHg) did not differ from the remainder of the cohort for EEG amplitude.

Infants in the lowest quartile for MAP at five hours had lower EEG continuity at the 25μV threshold at 24 hours (median[range] 61[56-78]mmHg cf 82[52-97]mmHg, p = 0.02). Infants in the lowest quartile for MAP at 12 hours had lower EEG continuity at the 10, 25 and 50μV thresholds at 12 hours (p = 0.003, p = 0.02 and p = 0.03, respectively, table 5-3). Infants in the lowest quartile for MAP at 24 hours did not differ from the remainder of the cohort for EEG continuity.

Infants in the lowest quartile for diastolic BP at five hours (<23mmHg) did not differ from the remainder of the cohort for EEG amplitude. However, infants in the lowest quartile for diastolic BP at 12 hours had lower median amplitude at 12 hours (p = 0.04, table 5-3). Similarly, infants in the lowest quartile for diastolic BP at 24 hours (<25mmHg) had lower minimum amplitude at 24 hours (median[range] 1.5[1.1-2.2]μV cf 2.5[1.4-6.7]μV, p=0.007 and at 48 hours 1.9[1.3-2.0]μV cf 2.5[1.5-3.8]μV, p = 0.03, respectively).

Infants in the lowest quartile for diastolic BP at five hours did not differ from the remainder of the cohort for EEG continuity. Infants in the lowest quartile for diastolic BP at 12 hours had lower EEG continuity at the 50μV threshold at 12 hours (p = 0.04, table 5-3). Infants in the lowest quartile for diastolic BP at 24 hours had lower EEG continuity at the 25 and 50μV thresholds at 24 hours (median[range] 65[56-78]% cf 79[52-97]%, p = 0.02 and 31[26-46]% cf 52[15-67]%, p = 0.05 respectively).

5.3.2 Neurophysiologic changes and acute changes in physiologic monitoring

Physiologic monitoring data were available for 182 separate EEG recordings obtained from 43 infants. Five episodes of diastolic BP <20mmHg on three infants were available for analysis. These infants had a median (range) birthweight of 765 (680 – 850) grams, gestation at delivery of 26 (24 – 28) weeks and the EEGs were performed on day 1. Four episodes of MAP <30mmHg on four infants were available for analysis. These infants had a birthweight of 850 (680 – 860) grams, gestation at delivery of 25 (24 – 28) weeks and the EEGs were performed on day 1 (1 – 3). Seven episodes of SaO_2 < 75% on five infants were available for analysis. These infants had a birthweight of 765 (635 – 920) grams, gestation at delivery of 26 (24 – 26) weeks and the EEGs were performed on day 7 (1 – 42).

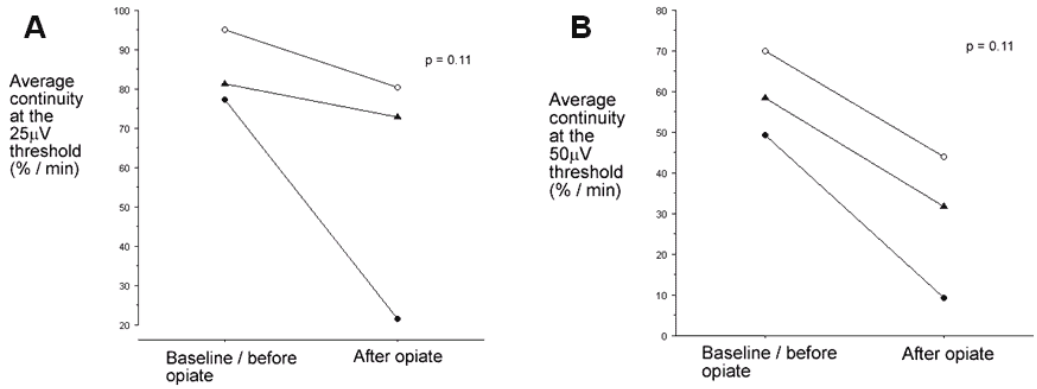
There were no differences between any of the neurophysiologic parameters when measurements before the decreased diastolic BP, MAP or SaO_2 were compared with those during or after the perturbation.

5.3.3 Neurophysiologic changes with administration of medications

EEG data for 12 intravenous infusions of indomethacin on 11 infants were available for analysis. These infants had a median (range) birthweight of 750 (540 – 1115) grams, gestation at delivery of 26 (24 – 29) weeks and the EEGs were performed on day 6 (2 – 8). Nineteen infants had EEG monitoring in place during intravenous infusions of caffeine. These infants had birthweights of 990 (715 – 1700) grams, gestation at delivery of 27 (25 – 31) weeks and the EEGs were performed on day 2 (1 – 7). Three infants had EEG monitoring around the time of opiate boluses, one for chest tube insertion (morphine) and two for elective intubation (fentanyl). These infants had birthweights of 950 (940 – 1700) grams, gestation at delivery of 26 (25 – 29) weeks and the EEGs were performed on day 2 (1 – 2). Nine infants had EEG monitoring at the time of endotracheal surfactant administration, for seven of these it was the second dose of surfactant and for two infants it was their first dose of surfactant shortly after intubation. These infants had birthweights of 1000 (680 – 1320) grams, gestation at delivery of 27 (24 – 29) weeks and the EEGs were performed on day 1 (1 – 2).

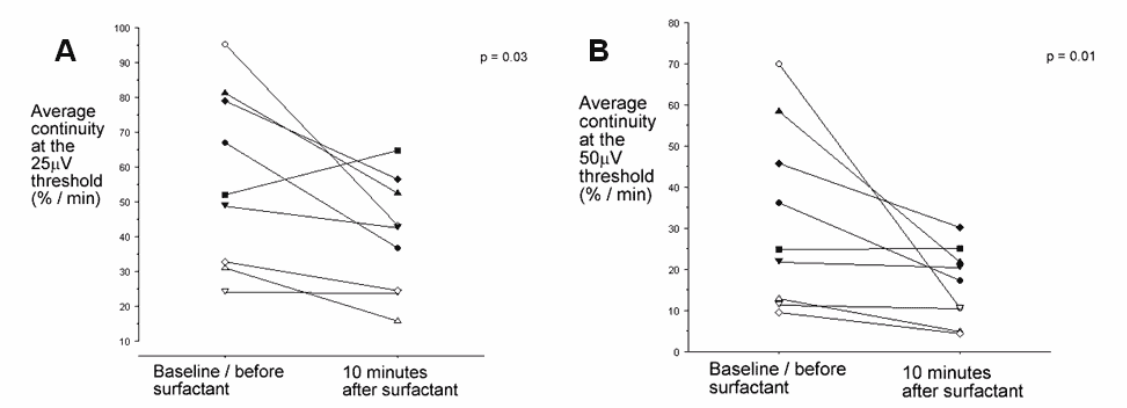
There was a non-significant decrease in the continuity at the 25 and 50µV thresholds after administration of an opiate bolus compared with before the bolus (p = 0.11 for both, figure 5-3 A and B).

Figure 5-3
Continuity at the 25µV(A) and 50µV(B) thresholds before and after administration of an opiate bolus. Lines join values for individual infants.



There was a significant decrease in the continuity at the 25 and 50µV thresholds over the first 10 minutes after administration of surfactant administered via the endotracheal tube (25µV median (range) of 52 (24 - 95) to 42 (16 - 65) % / minute (p = 0.03, n = 9, figure 5-4A, 50µV 25 (10 - 70) to 17 (4 - 30) % / minute (p = 0.01, n = 9, figure 5-4B). The changes in continuity at the 50µV threshold remained significant after exclusion of the two infants receiving an opiate bolus for intubation before administration of surfactant, 15 and 21 minutes respectively, p = 0.03.

Figure 5-4
Continuity at the 25µV(A) and 50µV(B) thresholds before and after administration surfactant via an endotracheal tube. Lines join values for individual infants.



There were no differences in continuity at the 25 or 50µV thresholds measured before, during or after caffeine or indomethacin infusions. There were also no changes in SEF or minimum amplitude with any drug administrations.

5.4 Discussion

5.4.1 Quantitative neurophysiologic measurements, blood pressure recordings and echocardiographic measurements of blood flow

This study demonstrates that, in the newborn preterm infant, some blood flow and BP measurements are related to quantitative EEG measurements, both simultaneously and 12 - 24 hours later. In particular, RVO measured 12 hours after birth was related to both EEG amplitude and continuity at 12 and 24 hours after birth, and BP measurements at 12 and 24 hours were also related to EEG continuity at 12 and 24 hours after birth. These findings are interesting as discontinuous EEG traces, low RVO and SVC flow have all been associated with increased risk of significant intraventricular haemorrhage and poor neurodevelopmental outcome (Evans & Kluckow, 1996b; Hunt et al., 2004; Kluckow & Evans, 2000a; Menache, Bourgeois, & Volpe, 2002).

Although this study reports findings from a small number of infants we demonstrated significant relationships between EEG and physiological measurements. These analyses are only exploratory, and we have performed a large number of comparisons in order to generate the hypotheses, and to test the findings. However, these different analytical approaches all showed

consistent relationships. Multiple regression analyses suggested that these relationships were not just because the smallest, youngest and sickest infants had the lowest blood flow, BP and quantitative EEG measurements.

Conventional multi-channel EEG recordings remain the gold-standard method of assessing cerebral activity, but are difficult to perform in extremely preterm infants; hence new cotside devices are increasingly used. Measurement of EEG amplitude has been previously utilised in the Cerebral Function Monitor. In preterm infants Cerebral Function Monitor traces obtained shortly after birth can predict later outcome of infants with grade 3 or 4 intraventricular haemorrhage (Hellstrom-Westas et al., 2001). Our data show that infants with the lowest RVO at 12 hours of age tended to have lower EEG amplitudes at 12 and 24 hours, raising the possibility that this group may also include those at greatest risk of adverse long-term outcome.

EEG continuity may be potentially useful in clinical practice. Extremely preterm infants have discontinuous EEG traces that become more continuous with increasing gestation (Goto et al., 1992). In encephalopathic term infants persisting EEG discontinuity is associated with adverse neurodevelopmental outcome (Selton & Andre, 1997). Our data show that infants with lower RVO at 12 hours, and also those with lowest quartile of MAP and diastolic BP at 12 and 24 hours had more discontinuous EEGs at 12 and 24 hours, again consistent with the possibility that this group includes infants at greater risk.

Amplitude thresholds ranging from 5μV to 45μV (Biagioni, Bartalena, Boldrini, Pieri, & Cioni, 1999; Menache et al., 2002) have been used to assess discontinuity and interburst interval in EEGs from newborn infants. It is not yet clear which threshold has the most utility for predicting outcome. We therefore examined continuity data at 10, 25 and 50μV thresholds using the ReBRM monitor's continuity algorithm to examine the effects of blood flow and pressure parameters on different levels of EEG attenuation. Our data show similar effects across these thresholds, indicating that these findings are not isolated to the most discontinuous traces.

Our data suggest that the relationships between blood flow, BP and quantitative EEG measurements are most evident between 12 and 24 hours after delivery. The paucity of relationships found at five hours may in part be related to the profound circulatory, metabolic and neurological changes occurring in the period soon after birth. By 12 hours the infant has usually stabilised and any underlying relationship between perfusion and cerebral activity may become more apparent.

Human and animal data support our finding that changes in cerebral perfusion can be related to concurrent EEG changes (Greisen & Pryds, 1989; Reddy et al., 1998; Tan et al., 1996). However, we found that RVO at 12 hours was also related to EEG amplitude and continuity at 24 hours after birth. There are two possible explanations for this apparent delay. Firstly, the infants with low RVO and EEG changes at 12 hours may have been the same infants who had low RVO and EEG changes at 24 hours, resulting in an apparent relationship between the two time points. We were unable to fully explore this possibility as we had too few infants with RVO and EEG data at both 12 and 24 hours. However, we were also not able to convincingly exclude the second possibility: that RVO at 12 hours influenced the EEG obtained up to 12 hours later. Indeed a delay in improvement of amplitude integrated EEG parameters after volume expansion in preterm infants has been reported (Greisen et al., 1988), indicating that cerebral dysfunction is not always rapidly reversible by improved blood flow.

For research purposes radioisotope scans quantify cerebral blood flow more directly than echocardiographic measurements. However, echocardiography is a routine part of NICU practice and flow measurements can be performed by skilled non-cardiologist sonographers. In preterm infants RVO is often a more accurate measure of systemic perfusion than LVO as it is less affected by ductal shunting. SVC flow measurements reflect blood flow returning from the upper body and head, and are not influenced by shunting through an open foramen ovale or ductus arteriosus (Kluckow & Evans, 2000b). The fact that measurements of RVO were more closely related to quantitative EEG measurements than measurements of SVC flow is puzzling. It may be due to

inherent variability in SVC flow measurements, due to the elliptical shape and reduced rigidity of the SVC compared to the right ventricular outflow tract. This variability may make it difficult to discern any relationship with EEG measurements in the small numbers of infants reported here.

BP is routinely measured in NICU and therefore we included measurements of mean, systolic and diastolic pressure in our study. BP and cerebral perfusion have a complex relationship (Greisen, 2005), and BP should not be used alone to assess organ perfusion. While infants with more severe intraventricular haemorrhage have been found to have lower MAP over the first 48 hours after birth (Bada et al., 1990) there are few data to indicate that improving BP measurements improves outcome. We were surprised to find relationships between BP measurements and quantitative EEG measurements at similar times to those found with blood flow measurements. The correlation with diastolic blood pressure at 24 hours was particularly striking in the multivariate analysis (diastolic pressure p=0.0003 for EEG continuity at the 50µV threshold). These data suggest that gestational age, or other factors within the analysis may need to be used to determine thresholds for treatment of diastolic BP. Diastolic BP may be particularly critical in maintaining cerebral perfusion, and may be reduced by the development of early left-to-right ductal shunting.

5.4.2 Neurophysiologic changes and acute changes in physiologic monitoring

In light of the findings above our failure to detect any changes in EEG parameters during or after recorded perturbations in blood pressure and oxygenation is perhaps surprising. Previous reports have shown low burst rates (equating to decreased continuity at higher thresholds) were associated with low MAP in sedated, ventilated infants (Greisen et al., 1988), and these improved in some infants when MAP and cerebral blood flow improved. However, normal EEG can be found in very low birthweight infants with MAP as low as 23mmHg (Weindling & Bentham, 2005). There are few published data on the normal values of diastolic BP (Versmold et al., 1981; Zubrow, Hulman, Kushner, & Falkner, 1995), and none on EEG effects of very low diastolic BP. As diastolic BP is important for maintaining forward flow during diastole we would expect evidence of reduced cerebral electrical function

(reduced minimum amplitude and continuity) to be associated with low diastolic BP. We chose not to evaluate systolic BP as there had been no consistent changes found between systolic BP and EEG in preterm infants. Regarding the EEG changes potentially associated with decreased SaO_2, early work with EEG in preterm infants showed that significant acute hypoxia, as a result of failed extubation attempts, was associated with decreased EEG activity at the 20μV threshold (equating to decreased continuity at lower thresholds) (Roberton, 1969).

The most likely explanation for us not finding significant differences in quantitative neurophysiologic parameters before, during and after physiologic perturbations is that there were insufficient examples of perturbations with appropriate EEG data for analysis. Infants in our cohort had EEGs recorded only when they were deemed stable enough for electrode application by the medical and nursing personnel involved in their care. As a result we are less likely to have recordings from the most medically fragile infants. Automatic download of physiologic monitoring only became available after the first 49 infants had been recruited and was only available for monitoring in the most intensive area of NICU. In addition, physiology download data for over a month was lost due to malfunction of the automatic download. Only 16 episodes of physiologic perturbations with appropriate periods of EEG were available. Some other episodes were unable to be analysed as they lasted throughout the EEG recording, so no baseline comparison was available. Others did not have at least 10 minutes before or after the perturbation for comparisons. Reassuringly, desaturation episodes with SaO_2 below 75% for at least three minutes only occurred three times during the 182 available EEG recordings. Therefore we reduced the criteria to two consecutive minutes for desaturations to be included in the analyses, and four further episodes of low SaO_2 were identified.

We may not have chosen appropriate thresholds for the physiologic perturbations, since EEG changes may only occur with more severe and/or prolonged alterations. We chose our thresholds to represent the levels of perturbations that may be low enough to cause alterations in cerebral electrical

function, while also occurring enough times during NICU care to allow us to identify infants for analysis. While a less extreme threshold may have allowed us to analyse more episodes of physiologic perturbations it is probable that only profound deviations from normal physiology result in acute changes in EEG parameters. This is supported by the reported finding of normal cerebral electrical function with MAP as low as 23mmHg (S Victor, Marson, Appleton, Beirne, & Weindling, 2006; Weindling & Bentham, 2005). In Roberton's report of EEG changes with acute hypoxia the arterial oxygen partial pressure decreased to less than 50% of the value before extubation (Roberton, 1969) and at this level of hypoxaemia there was a decrease in EEG activity in each infant. In addition, many of the perturbations we identified lasted only two or three minutes while the EEG changes reported in fetal sheep were recorded after bilateral carotid artery occlusion lasting 30 minutes (Reddy et al., 1998). If prolonged or severe perturbations are required for acute changes in EEG parameters it is not surprising that we did not identify these changes.

5.4.3 Neurophysiologic changes with administration of medications

Pethidine boluses have been reported to increase EEG discontinuity (equating to decreased continuity), and decrease the variability in discontinuity (Eaton et al., 1992). Morphine infusions have been reported to cause generalised burst suppression patterns (equating to decreased continuity), decreased reactivity and increased seizure activity (Young & da Silva, 2000). Sufentanil boluses and infusions have been shown to increase EEG discontinuity in preterm infants (Nguyen The Tich, Vecchierini, Debillon, & Pereon, 2003). Our finding in infants receiving opiate boluses of a non-significant trend to reduced continuity at the 25 and 50μV thresholds is consistent with previous reports. In each case the EEG analysis was related to the first dose of opiate received by the infants. This is important as the EEG effects of opiate boluses decrease and become less consistent after the first dose (Eaton et al., 1992). We are unable to comment about the effects of opiate infusions on EEG parameters as only one EEG from our whole cohort was performed with an infant receiving an opiate infusion. However, the potential of opiates to affect EEG parameters means

that EEG data must be interpreted with caution by clinicians in NICUs where opiates infusions are routinely used for ventilated infants.

Endotracheal administration of surfactant has been reported to be associated with a transient decrease in burst rate (equating to a decreased continuity) in the 10 minutes following administration (Hellstrom-Westas et al., 1992). Our findings of decreased continuity at the 25 and 50μV thresholds were consistent with this report. In seven of our nine cases we had the EEG in place for the second dose of surfactant. Only two infants were intubated shortly before the surfactant was administered. In our NICU infants receive premedication with atropine, fentanyl and suxamethonium boluses before non-urgent intubation (Kuschel, 2000). Therefore, in two infants an opiate bolus was administered 15 to 21 minutes before the surfactant. The significant changes in continuity at the 50μV threshold after administration of surfactant remained after exclusion of these two infants, suggesting that the results were not only as a result of the combination of opiate and surfactant administration. Surfactant has been shown to cause a decrease in cerebral blood flow of 36% and a drop in MAP of 15% two minutes after administration. The combination of these alterations in cerebral perfusion may explain the acute EEG changes associated with surfactant administration.

While there are no EEG data published regarding the effects of caffeine and indomethacin administration, both these medications may result in decreased cerebral blood flow. Indomethacin administration by rapid injection over one minute, or infused over 30 minutes, consistently results in 30% reductions of cerebral blood flow, as measured by near infrared spectroscopy, associated with a corresponding fall in oxygen delivery of approximately one third (Edwards et al., 1990; Mosca, Bray, Lattanzio, Fumagalli, & Tosetto, 1997). Doppler sonography has shown decreased blood flow velocity for two hours after oral loading doses of caffeine (Hoecker et al., 2002), but not after intravenous loading doses (Saliba et al., 1989). We would expect intravenous infusions of indomethacin and caffeine to potentially cause reductions in continuity, minimum amplitude and SEF. However, we observed no changes in EEG parameters in the infants receiving infusions of indomethacin and

caffeine. This might be because of the relatively small numbers of infants included in the analyses, or because there are no changes to be detected.

5.4.4 Summary and implications

Current techniques used to monitor cerebral perfusion and function in NICU are suboptimal and this hampers the clinician's ability to assess the impact of clinical management on the developing brain. Our data suggest that both low flow and low BP may have an immediate and a prolonged impact on EEG activity. However, these results must be interpreted with caution, and in particular it cannot be concluded from this study alone that the relationship between blood flow or pressure and cerebral function is causal. In addition, some frequently administered drugs affect cerebral function around the time of administration. These changes should be borne in mind by clinicians using EEG monitoring in NICU.

6 Results – Early EEG recordings and long term neurodevelopmental outcome in preterm infants

6.1 Introduction

Parents-to-be generally hope their baby will be healthy. However, for any infant requiring admission to a NICU there is an increased risk of adverse neurodevelopmental outcome compared with healthy term newborn infants (Schermann & Sedin, 2004). While educational and behavioural problems are increased in infants born between 32 and 35 weeks gestation (Huddy, Johnson, & Hope, 2001), it is the extremely preterm infants and term infants with neonatal encephalopathy who are at greatest risk of a adverse neurodevelopmental outcomes (Knight & Kuschel, 2005; Schermann & Sedin, 2004; Weindrich, Jennen-Steinmetz, Laucht, & Schmidt, 2003).

Conventional EEGs have been shown to assist with prediction of long term neurodevelopmental outcome in both preterm (Biagioni et al., 2000; Marret et al., 1997; Maruyama et al., 2002; Watanabe et al., 1999) and encephalopathic term infants (Menache et al., 2002; Selton & Andre, 1997). Modified cotside EEGs obtained during an infant's neonatal admission have also been shown to have some predictive value for both groups of infants (Azzopardi et al., 1999; J. Connell et al., 1988; Hellstrom-Westas et al., 2001; Hellstrom-Westas & Rosen, 2005; Hellstrom-Westas et al., 1995). A system for cotside display and analysis of EEG discontinuity and amplitude was developed for the Oxford Medilog (Wertheim et al., 1991) but this technology has not been incorporated into routine NICU care over the last 15 years. Amplitude integrated EEG obtained from Cerebral Function Monitors has been more widely incorporated into

routine practice for term infants with neonatal encephalopathy, and has been used for prediction of outcome (Hellstrom-Westas et al., 1995), management of seizures, and for entry criteria for recruitment into trials of neuroprotective strategies (Gluckman et al., 2005; TOBY). However, interpretation of the preterm aEEG is more complex as the normal background pattern is discontinuous and most of the reports on outcome prediction are related to variation in the number of bursts in a specified time period (Hellstrom-Westas et al., 1992; Hellstrom-Westas et al., 2001), for which there is no readily available method of analysis.

The EEG system we have used (research BRM, BrainZ Instruments Ltd, Auckland, New Zealand) allows generation of quantitative neurophysiological parameters to assist clinicians who do not have specialist neurophysiologist skills. It is important to critically examine these EEG parameters to determine which of them, if any, may be able to assist with outcome prediction.

In this chapter we report:

1. The relationships between quantitative neurophysiological parameters from two channel EEG recordings performed on preterm infants and Bayley Scales of Infant Development II (Bayley-II) indices obtained at 18 months chronological age; and
2. The ability of a specialist neurophysiologist to predict 'poor' neurodevelopmental outcome from two channel EEG recordings, and the relationship between neurophysiologist and quantitative assessments of the same segments of EEG.

6.2 Methods

6.2.1 Developmental outcome at 18 months chronological age

Infants were assessed by one of five psychologists at 18 months chronological age using the Bayley-II assessment (section 2.9), generating a mental developmental index (MDI) and psychomotor developmental index (PDI). Regression analyses were performed to examine the relationships between MDI and PDI scores and gestation at delivery, birthweight, birthweight Z-scores and corrected age at the time of Bayley-II examination. We included the last of

these analyses as Bayley-II examinations were performed according to the infant's chronological age, so that more preterm infants had their examinations at younger corrected gestations.

Infants were divided into two groups. Those who died or had a MDI or PDI <70 (more than two standard deviations below the mean) were included in a 'poor' outcome category, and those with both MDI and PDI ≥ 70 (not more than two standard deviations below the mean) were included in a 'satisfactory' outcome category. Gestation at delivery and birthweight were compared between groups using Mann-Whitney U tests.

For infants who were followed up, but did not have a Bayley-II assessment, we used the following criteria to assign an outcome category:

1. an alternative formal developmental assessment at or after 18 months chronological age;
2. a Bayley-II assessment before one year of age and specific questioning of their parent; or
3. assessment by a Paediatrician, including assessment of development, at or after 18 months chronological age.

6.2.2 Quantitative neurophysiological measurements

Quantitative neurophysiological measurements of SEF, minimum amplitude, and continuity at the 10, 25 and 50μV thresholds were assessed as median values for the 60 minutes of the baseline analysis (section 2.5.1) for each EEG. Left and right sided values were averaged.

Regression analyses were performed to examine the relationships between SEF, minimum amplitude and continuity at the 25 and 50μV thresholds from the first and last EEGs performed during the first week after delivery, and the PDI and MDI scores. Quantitative neurophysiological measures found to be significant on univariate analyses were further investigated by multiple regression analyses with gestation at delivery and corrected age at Bayley-II assessment included in the model.

In addition, we performed Mann-Whitney U tests to compare SEF, minimum amplitude and continuity at the 25 and 50μV thresholds for the first and last EEG recorded in the first week after delivery between infants with a 'poor' outcome and those with a 'satisfactory' outcome. Neurophysiological parameters that were significantly different between groups were incorporated into a logistic regression model including gestation at delivery and birthweight Z-score.

We constructed receiver operating characteristic (ROC) curves for continuity parameters and found the cut-off value for each continuity threshold that maximised the sensitivity and specificity for prediction of 'poor' outcome. We then determined positive and negative predictive values for these cut-offs with our data set.

We compared the results of cranial ultrasound scans performed five days after delivery with early quantitative neurophysiological parameters in the prediction of outcome category, both alone and in combination with continuity measures below the cut-off values identified by the ROC curves.

The analyses were repeated with a subgroup of infants born at <28 week's gestation to explore whether quantitative neurophysiological parameters performed at least as well in these infants with the highest risk of adverse neurodevelopmental outcome as they did in the overall cohort.

6.2.3 Comparison of outcome prediction by neurophysiologist and quantitative EEG continuity assessment

We compared quantitative neurophysiological parameters with a neurophysiologist's assessment of the same raw EEG using contingency tables. The neurophysiologist reviewed EEG segments recorded on infants <29 weeks gestation who were <48 hours old at the time of the EEG. This gestation was chosen as the same guidelines for EEG analysis can be used for all infants below this gestation (for example interburst interval should generally be <12 seconds, table 6-1). The neurophysiologist reviewed the EEG segment chosen as the baseline analysis (section 2.5.1) for each infant using the EEG viewer developed for the cotside monitor (EEG viewer, version 9.26, BrainZ

Instruments Ltd, Auckland, New Zealand). In addition, she was provided with a list of the marked events for the period analysed. She assessed interburst interval, continuity, seizure activity, amplitude (qualitative assessment) and developmental features (for example, the presence of delta brushes), to categorise the EEGs as normal, within normal limits, mildly abnormal, moderately abnormal and severely abnormal (table 2-2) based on published criteria (Ebersole & Pedley, 2003).

To improve the power of the analyses by increasing the numbers in each group these categories were then grouped as 'within normal limits' (the 'normal', 'within normal limits' and 'mildly abnormal' groups) or 'abnormal' (the 'moderately abnormal' and 'severely abnormal' groups).

Table 6-1
Qualitative assessment of EEG by a neurophysiologist

	Interburst interval (<25μV amplitude)	Seizure activity*	Synchrony between hemispheres	Developmental features of burst **
Normal	<12 seconds	Absent	Present	Present
Within normal limits	Most <12 seconds, rarely up to 20 seconds	Absent	Present	Present
Mildly abnormal	Most <12 seconds, occasional up to 30 seconds	Absent	Present	Present
Moderately abnormal	Frequent > 30 seconds	May be present	May be asynchronous	May be present or asymmetrical
Severely abnormal	Predominantly > 30 seconds, long periods of discontinuity	May be present	May be asynchronous	Absent

* Rhythmic discharge showing evolution for a period of > 10 seconds with frequency <5Hz
** eg delta brush, rhythmic delta and theta activity

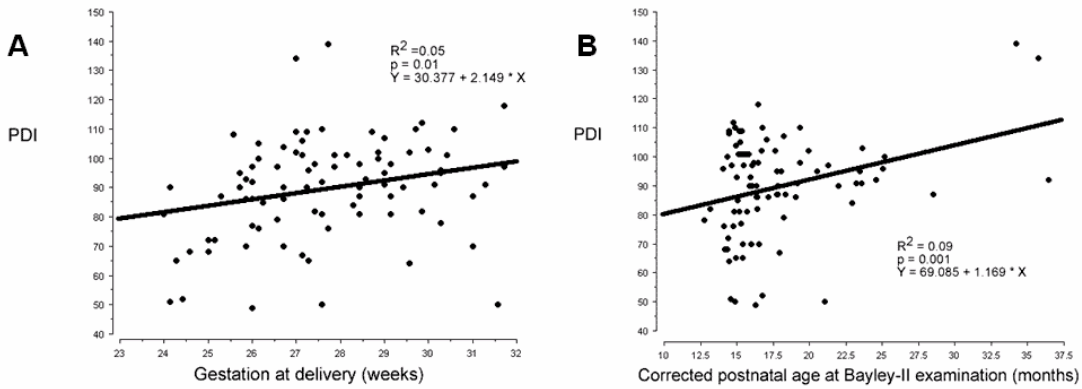
6.3 Results

Ten infants from our cohort died, nine before discharge and one at 10 months chronological age. Compared with the infants alive at discharge, the infants dying before discharge were lighter, (median [range] birthweight 750 [420 – 1190) grams vs 1000 [510 – 1980] grams, p = 0.04) and younger (gestation at

delivery 26 [24 – 28] weeks vs 27 [24 – 31] weeks, p = 0.04). They died at 20 (3 - 101) days after delivery.

Bayley-II examinations performed around 18 months chronological age were available on 98 infants with a mean (standard deviation) score of 95 (14) for the MDI and 90 (16) for the PDI. They were performed at a median (range) chronological age of 19 (15 – 39) months and corrected age of 16 (12 – 36) months. Eighty-eight (90%) of the Bayley-II examinations were performed by two psychologists. Results of the Bayley-II examinations were obtained from the medical records. Infants with Bayley-II examinations had a median birthweight of 1007 (510 - 1980) grams and gestation at delivery of 27 (24 – 31) weeks. Gestation at delivery was related to PDI at 18 months (p = 0.01, figure 6-1A) but not to MDI. Birthweight and birthweight Z-scores were not related to either PDI or MDI at 18 months. Corrected age at the time of the Bayley-II examination was related to the PDI score (p = 0.001, figure 6-1B) but not to the MDI. In these 98 infants the first EEG after delivery was performed at 27 (2 – 114) hours, and the last EEG in the first week after delivery was performed at 7(3 - 9) days. A technically acceptable second EEG was obtained in 95 (97%) of the infants.

Figure 6-1
Relationship between Bayley-II psychomotor developmental index (PDI) score at 18 months chronological age and gestation at delivery (A) and corrected age at Bayley-II assessment (B)



Of the 12 surviving infants without Bayley-II examinations, two had alternative developmental assessments reported as entirely normal, two had normal Bayley-II examinations earlier and continued good progress by report, and two infants were assessed as having normal development by a Paediatrician at

their local base hospital at 21 months corrected age. Six infants could not be assigned an outcome category. One infant had moved to Japan, two infants to the Pacific Islands, one to the Middle East, and two infants were lost to follow-up within New Zealand.

Our outcome analyses were repeated after two infants were excluded. One had a MDI of 75 and PDI of 72 at 14 months corrected age and had neurofibromatosis type 1 diagnosed at two years of age. The second infant died at 10 months chronological age from causes unrelated to prematurity. Exclusion of these infants did not change our results. Therefore, we have reported the results of the whole cohort to most accurately reflect the situation in the NICU, where these later diagnoses are still unknown.

Twenty infants had a 'poor' outcome and 94 infants had a 'satisfactory' outcome. Infants in the 'poor' outcome category were on average one week younger (median [range] gestation at delivery 26 [24 – 31] weeks vs 27 [24 – 31] weeks, p = 0.006) and 250 grams lighter at delivery (birthweight 792 [420 – 1975) grams vs 1056 [510 – 1980] grams, p = 0.01) when compared with infants with a 'satisfactory' outcome.

6.3.1 Prediction of Bayley-II developmental indices by quantitative neurophysiological data

SEF and minimum amplitude on the first (n = 98) and last EEG (n = 92) recorded over the first week after delivery were not related to either PDI or MDI scores in the 98 infants with Bayley-II examinations.

Continuity at both the 25 and 50μV thresholds on both the first and last EEG in the first week were weakly related to PDI scores (figure 6-2). The only significant relationship with MDI was a weak one with continuity at the 25μV threshold on the last EEG recorded in the first week (figure 6-3 A). Each of the quantitative neurophysiological parameters examined showed a wide spread of results around the regression line (figures 6-2 and 6-3).

The relationships between MDI and PDI scores and continuity were no longer significant when adjusted for gestation at delivery and corrected age at Bayley-II examination.

The subgroup of infants born at <28 weeks gestation showed very similar relationships between Bayley-II developmental indices and EEG continuity measures, but only two approached statistical significance. These were relationships between continuity at the 25μV threshold on the last EEG recorded in the first week and both PDI (n = 55, p = 0.03 and coefficient = 0.52) and MDI (n = 55, p = 0.05 and coefficient = 0.36).

Figure 6-2
Relationships between Bayley-II psychomotor and mental developmental indices (PDI, A and B and MDI C and D) and continuity at the 25 and 50μV thresholds measured on the first EEG recorded during the first week after delivery

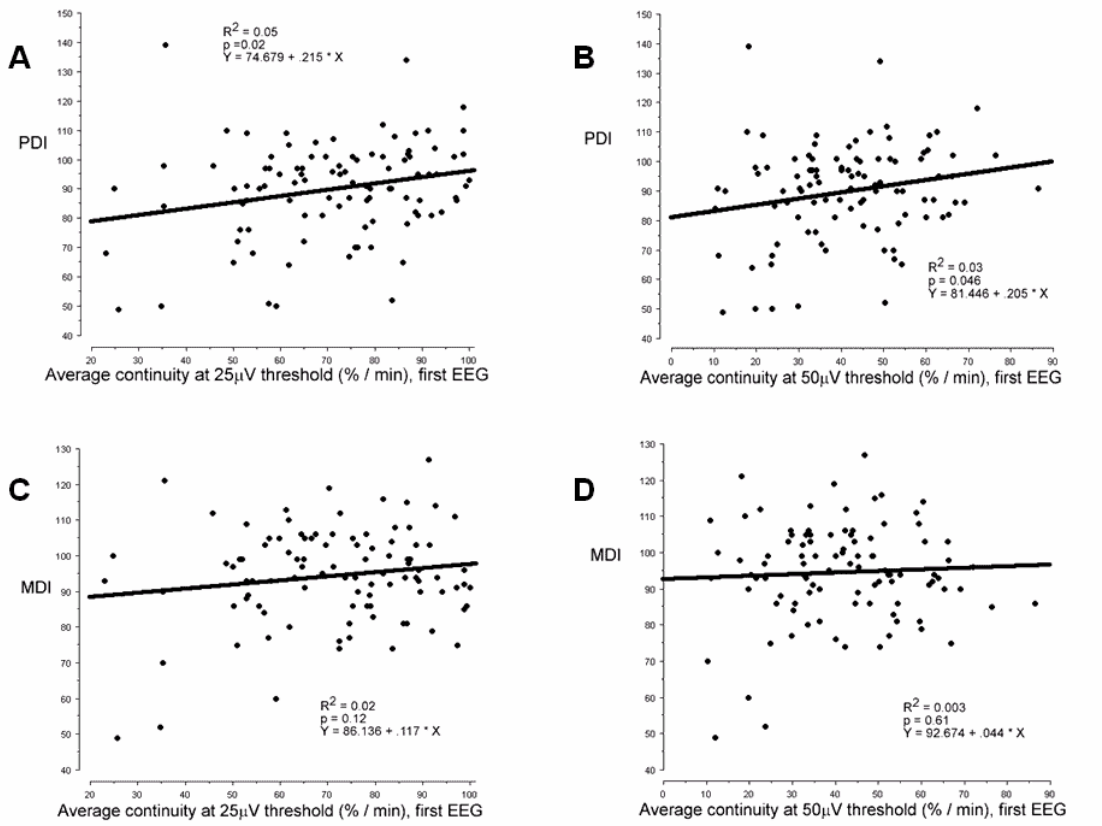
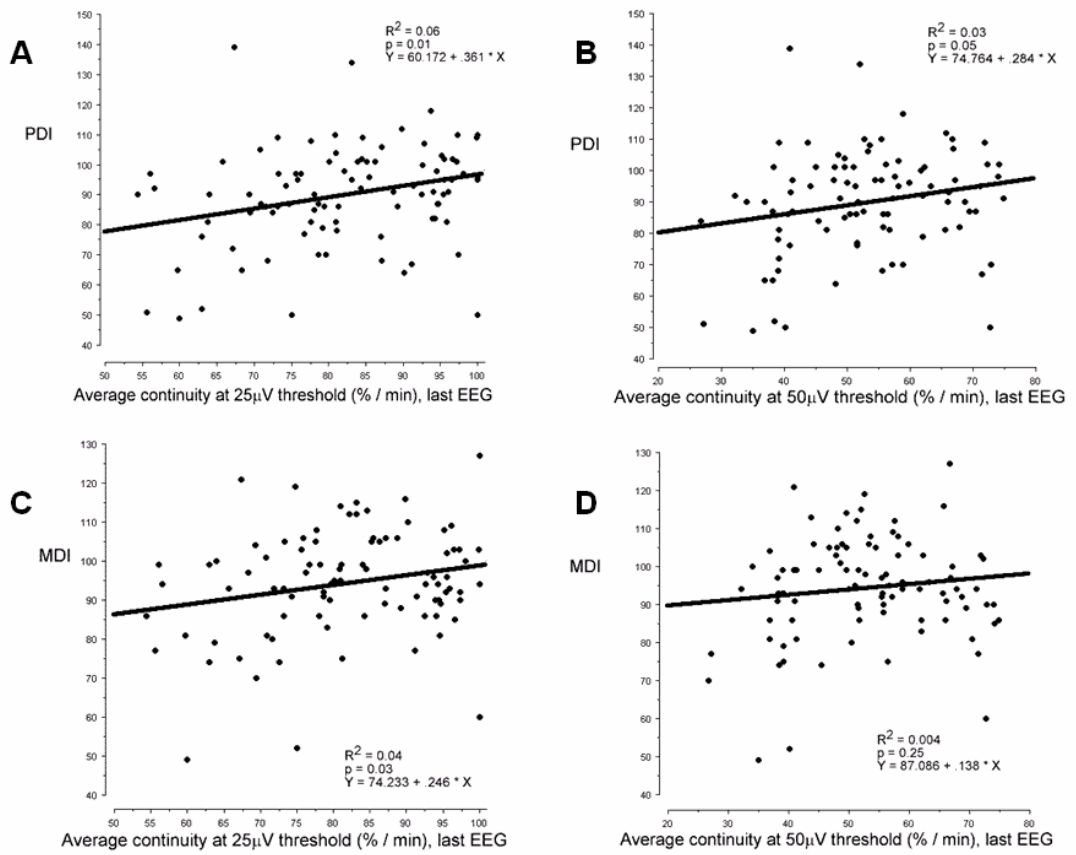


Figure 6-3
Relationships between Bayley-II psychomotor and mental developmental indices (PDI, A and B and MDI, C and D) and continuity at the 25 and 50µV thresholds measured on the last EEG recorded during the first week after delivery



6.3.2 Prediction of infants with 'poor' neurodevelopmental outcome

There were 20 infants in the 'poor' outcome category and 94 infants in the 'satisfactory' outcome category. There were no differences between the two outcome groups for SEF or minimum amplitude on the first EEG after delivery. Infants with a 'poor' outcome had lower continuity at the 10, 25 and 50µV thresholds on the first EEG after delivery (table 6.2, p = 0.01, 0.0008 and 0.003, respectively). There were no differences between the two outcome groups for any quantitative neurophysiological parameters on the last EEG performed in the first week.

For the subgroup of infants born at <28 weeks gestation continuity at the 10, 25 and 50µV thresholds gave similar results to the cohort as a whole.

Table 6-2
Quantitative continuity measurements from the first EEG for infants with 'poor' and 'satisfactory' outcomes

	'Poor' outcome	'Satisfactory' outcome
Continuity at 10μV threshold (% / min)	97 (63 – 100)*	100 (60 – 100)
Continuity at 25μV threshold (% / min)	58 (23 – 86)**	76 (25 – 100)
Continuity at 50μV threshold (% / min)	27 (11 – 54)***	43 (10 – 87)

Results are median (range)
*p = 0.01, **p = 0.0008 and ***p = 0.003 for difference between infants with 'poor' and 'satisfactory' outcomes

The differences between continuity measures for infant with 'poor' and 'satisfactory' outcomes were no longer significant after adjustment for gestation at delivery and birthweight Z-score.

6.3.2.1 ROC curves

ROC curves for prediction of 'poor' outcome using continuity measures on the first EEG (figure 6-4 A to C) showed that while the lower limits of the 95% confidence intervals for each area under the curve were above 0.5, all of the parameters performed poorly (table 6-3).

Although continuity at the 25μV threshold had a slightly larger area under the ROC curve, and slightly higher sensitivity and negative predictive value than continuity at the 50μV threshold, the confidence intervals overlapped, and pairwise comparison of the ROC curves at 25 and 50μV continuity thresholds showed that they were not significantly different (p = 0.4, figure 6-4D).

ROC curves were constructed for the 69 infants born at <28 weeks gestation. These produced cut-off values of ≤87.6% / min for the 10μV threshold, ≤60.3% / min for the 25μV threshold and ≤30.6% / min for the 50μV threshold. Results of sensitivities, specificities and positive and negative predictive values fell within the 95% confidence interval ranges for the whole group (table 6-3) except for specificity at the 10μV threshold, which was higher for infants in the <28 week gestation group than for the whole cohort. Pairwise comparison of

the ROC curves at 25 and 50µV continuity thresholds in this subgroup of infants showed that they were also not significantly different.

Figure 6-4
Receiver operating characteristic curves for prediction of 'poor' outcome at 18 months with continuity measured at the 10µV (A), 25µV (B) and 50µV (C) thresholds for the first EEG recorded after delivery, n = 114. Pairwise ROC comparison of continuity at the 25 and 50µV thresholds for prediction of 'poor' outcome at 18 months (D).

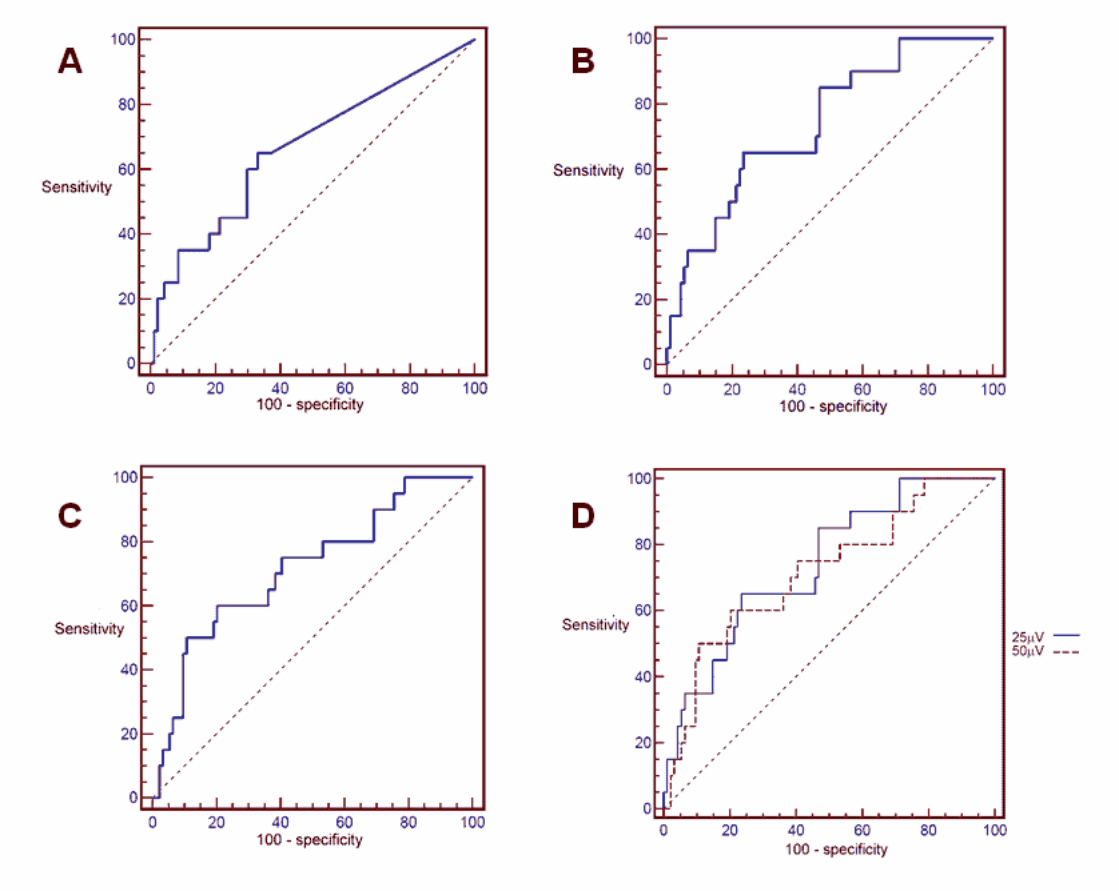


Table 6-3
Prediction of 'poor' 18 month outcome by continuity on the first EEG, using ROC curves to optimise sensitivity and specificity values for continuity at the 10, 25 and 50μV thresholds. Upper half of table shows results for the whole cohort and lower half of table shows results for infants born at <28 weeks gestation.

Continuity threshold	Area under ROC curve	Cut-off value (%/min)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Whole cohort						
10μV (% / min)	0.64 (0.57-0.82)	≤ 98.7	65 (41-85)	67 (57-76)	28 (15-41)	89 (80-98)
25μV (% / min)	0.74 (0.65-0.82)	≤ 61.7	65 (45-82)	77 (67-85)	37 (21-53)	91 (85-97)
50μV (% / min)	0.72 (0.62-0.80)	≤ 30.6	60 (36-81)	80 (70-87)	37 (20-54)	89 (82-96)
Infants < 28 weeks						
10μV (% / min)	0.67 (0.55-0.78)	≤ 87.6	44 (20-70)	89 (77-96)	54 (27-81)	84 (74-94)
25μV (% / min)	0.73 (0.71-0.83)	≤ 60.3	69 (41-89)	74 (60-85)	42 (22-62)	87 (77-97)
50μV (% / min)	0.71 (0.58-0.81)	≤ 30.6	63 (36-85)	77 (64-88)	43 (22-64)	85 (75-95)

Figures in brackets are 95% confidence intervals

The other investigation commonly used for early outcome prediction is cranial ultrasound scanning. Therefore, we determined how well EEG performed compared with day 5 cranial ultrasound scans as a predictor of outcome category in the 105 infants with early cranial ultrasound scans (table 6-4). A 'bad' day 5 cranial ultrasound scan showed evidence of GM-IVH grade 3 – 4 or a porencephalic cyst. All other day 5 cranial ultrasound scans were classified as 'good'. 'Low' continuity at each threshold was defined as a continuity below the cut-off determined by the ROC curve analyses (table 6-3). Finally, we combined the continuity at the 25 or 50μV thresholds from the first EEG after delivery, and the day 5 cranial ultrasound scan to see whether the presence of an abnormality on at least one of these tests would improve the prediction of 'poor' outcome (table 6-4).

Table 6-4
Numbers of infants in each outcome category according with results of day 5 cranial ultrasound scan and continuity analyses at the 25 and 50μV thresholds on the first EEG alone and then in combination.

	'Poor' outcome	'Satisfactory' outcome	Total
'Bad' day 5 cranial ultrasound scan	3	2	5
'Good' day 5 cranial ultrasound scan	14	86	100
'Low' continuity at 25μV threshold on first EEG	13	22	35
'Normal' continuity at 25μV threshold on first EEG	7	72	79
'Low' continuity at 50μV threshold on first EEG	11	19	30
'Normal' continuity at 50μV threshold on first EEG	9	75	84
'Low' continuity at 25μV threshold and / or 'Bad' 5 day cranial ultrasound scan	14	23	37
'Normal' continuity at 25μV threshold and 'Good' 5 day cranial ultrasound scan	6	71	77
'Low' continuity at 50μV threshold and / or 'Bad' 5 day cranial ultrasound scan	12	20	32
'Normal' continuity at 50μV threshold and 'Good' 5 day cranial ultrasound scan	8	74	82

Results are numbers of infants in each category

A 'bad' cranial ultrasound scan alone had a low sensitivity (18%) but a high specificity (98%) for predicting 'poor' outcome (table 6-5). The presence of 'low' continuity at the 25 or 50μV thresholds and / or a 'bad' day 5 cranial ultrasound scan in combination increased the sensitivity for predicting a 'poor' outcome three-to-four- fold (from 18 to 60-70%) but decreased the specificity to 76 - 79%. Addition of day 5 cranial ultrasound scan results did not improve the overall performance of the test above that of EEG continuity alone.

Table 6-5
Comparison of prediction of 'poor' outcome at 18 months by day 5 cranial ultrasound scan, continuity measured at the 25 and 50µV thresholds, and the combinations of day 5 cranial ultrasound scan and continuity measured at the 25 and 50µV thresholds

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
'Bad' Day 5 cranial ultrasound scan	18 *	98 (95-100)	60*	86 (79-93)
Continuity at 25µV threshold ≤ 61.7 % / min	65 (45-82)	77 (67-85)	37 (21-53)	91 (85-97)
Continuity at 50µV threshold ≤ 30.6 % / min	60 (36-81)	80 (70-87)	37 (20-54)	89 (82-96)
'Bad' Day 5 cranial ultrasound scan or 'Low' continuity at 25µV threshold	70 (50-90)	76 (67-75)	38 (22-54)	92 (86-98)
'Bad' Day 5 cranial ultrasound scan or 'Low' continuity at 50µV threshold	60 (39-81)	79 (71-87)	38 (21-55)	90 (84-96)

*sample size too small to calculate confidence intervals
Figures in brackets are 95% confidence intervals

For infants born before 28 weeks gestation the presence of a 'bad' day 5 cranial ultrasound scan or 'low' continuity at the 25µV threshold on first EEG had a sensitivity of 69 (46 -92)%, specificity of 72 (60 - 84)%, positive predictive value of 42 (23 - 61)% and negative predictive value of 88 (78 - 98)% which were similar to the values for the whole cohort.

6.3.3 Prediction of 18 month outcome by qualitative neurophysiologist assessment and quantitative EEG continuity assessment

There were outcome data for 76 infants with gestations <29 weeks who had an EEG within 48 hours after delivery. They had median (range) gestation at delivery of 26 (24 – 28) weeks and birthweight of 910 (420 – 1620) grams. The EEG recording was started at 23 (2 – 48) hours. Nine infants died before discharge. The 67 remaining infants had outcome assessments performed at 15 (13 - 36) months corrected age. Seventeen infants (22%) had 'poor' outcomes (death or MDI / PDI <70) and the remaining 59 had a 'satisfactory' outcome.

Sixteen infants (21%) had 'abnormal' EEGs when assessed by a neurophysiologist. The remainder of the EEGs were 'within normal limits'. The neurophysiologist's assessment of the early EEG had similar sensitivity but higher specificity than continuity measured at the 25μV threshold (tables 6-6 and -7).

Table 6-6
Prediction of outcome at 18 months by qualitative neurophysiologist assessment

	'Poor' outcome	'Satisfactory' outcome
EEG 'within normal limits'	6	54
EEG 'Abnormal'	11	5

Results are numbers of infants in each category

Table 6-7
Comparison of prediction of 'poor' outcome at 18 months by neurophysiologist, and continuity measured at the 25 and 50μV thresholds

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Neurophysiologist	65 (42-88)	92 (85-99)	69 (46-92)	90 (82-98)
Continuity at 25μV threshold	65 (42-88)	73 (62-84)	41 (22-60)	88 (79-97)
Continuity at 50μV threshold	53 (29-77)	78 (67-89)	41 (20-62)	85 (76-94)

Figures in brackets are 95% confidence intervals

6.3.3.1 Seizures and outcome

None of the infants were clinically suspected of having seizures and none received any anticonvulsant medication. Four infants were found to have definite seizures by the neurophysiologist, two had probable seizures and there were possible seizures found in four other infants. Three infants had periods of rhythmic activity on the EEG without evolution that was considered to represent artefact rather than seizure activity.

Three of the four infants with definite seizures died before discharge and the other one developed severe longterm neurodevelopmental disabilities. One of

the infants with probable seizures died at term corrected gestation due to severe respiratory disease and the other had a MDI of 95 and a PDI of 81.

In all of the infants with possible seizures the duration of the observed episodes were ≤10 seconds. Of these infants, one had normal neurodevelopmental assessment (MDI / PDI of 86 / 86), one had a MDI within the normal range but a PDI more than one standard deviation below the mean (90/70), one had MDI and PDI more than one standard deviation below the mean (79/81) and one was lost to follow-up.

6.4 Discussion

This study demonstrates the relationships between cotside EEG data and neurodevelopmental outcome at 18 months chronological age in preterm infants. Quantitative continuity measures from the first EEGs recorded after delivery were able to provide clinicians with information to refine an individual's outcome prediction. For prediction of 'poor' outcome the addition of continuity parameters from an early EEG recording to the results from a day 5 cranial ultrasound scan improved the sensitivity three- to- four- fold. However, a neurophysiologist's qualitative analysis of the raw EEG from a cotside EEG recorded within 48 hours of delivery remained superior to quantitative parameters for prediction of outcome in infants born at <29 weeks gestation.

In chapter 4 we showed that continuity at the 25 and 50μV thresholds from the first EEG were decreased in infants with GM-IVH grade 3 or 4 on the day 5 cranial ultrasound scan compared with infants with GM-IVH grade 0 to 2. Infants with GM-IVH, porencephalic cysts or PVL noted on any cranial ultrasound scan during their NICU admission also had decreased SEF and continuity on the first EEG and decreased SEF and minimum amplitude on the last EEG of the first week compared with infants without these cranial ultrasound scan findings. However, cranial ultrasound scan abnormalities do not predict all infants with poor neurodevelopmental outcome, and there are a wide range of outcomes found for infants with each grade of GM-IVH (Aziz et al., 1995; Thorburn et al., 1981; Whitaker et al., 1996). EEGs may show altered cerebral function in infants without cerebral ultrasound scan changes,

indicating increased risk of adverse long term neurodevelopmental outcome for these infants (F. Hayakawa, Okumura, Kato, Kuno, & Watanabe, 1997).

Infants with ‘satisfactory’ outcomes did not have evidence of significant intracranial pathology on early cranial ultrasound scans (ie the scans had a high specificity for detecting ‘poor’ outcome) but less than one fifth of the infants with a ‘poor’ outcome had ‘bad’ cranial ultrasound scans (ie the scans had a low sensitivity). With the addition of information from an early cotside EEG to the cranial ultrasound scan information the sensitivity was substantially improved, with a more modest decrease in the specificity. These findings are similar to those reported by Biagioni (Biagioni, Bartalena, Biver, Pieri, & Cioni, 1996). In their study 63 infants born before 35 weeks corrected gestation had serial cranial ultrasound scans and early (between days 4 and 14) conventional EEGs examined as prognostic tools for developmental outcome at one year of age. EEG recordings were evaluated manually to determine the degree of dysmaturity of the trace. Severe EEG dysmaturity had a high specificity (94%) but low sensitivity (50%) for predicting severely abnormal outcome. In the same infants severe abnormalities (PVL or grade 4 GM-IVH) found on serial cranial ultrasound scanning had a specificity of 96% and sensitivity of 50%. The combination of early EEG and serial ultrasound scans had a specificity of 90% and sensitivity of 72%, showing a slightly higher specificity than our cohort (76%) but similar sensitivity (70%). Biagioni concluded that EEG and ultrasound scanning appeared to be complimentary in neurological assessment of preterm infants (Biagioni, Bartalena et al., 1996). Of note, our data only included the day 5 cranial ultrasound scan results so the two cases with PVL detected later in the course were not included in the analyses. These findings are in contrast to those reported by Connell (J. Connell et al., 1988) for a group of 54 infants ventilated for respiratory distress. While their study also found that information from manually assessed early EEGs supplemented information from cranial ultrasound scans, they reported a similar sensitivity of 96%, but a specificity of only 14% when using EEG and cranial ultrasound information for predicting death or major neurological abnormality. However, while their group included older and heavier infants, all were ventilated, 20% had intraparenchymal blood noted on serial cranial ultrasound scans and 44% of

the infants died. Therefore, their cohort was more unwell than our cohort, in which <3% had intraparenchymal blood on cranial ultrasound scan and only 8% died.

A previous report showed lower SEF on early EEG in preterm infants was associated with more extensive white matter injury on MRI scans obtained at term (Inder, Buckland et al., 2003). We did not find any relationships between SEF calculated on EEGs recorded in the first week after delivery and subsequent developmental outcome. Both research groups used a similar cotside EEG recording device, with the same method of calculating SEF, and recruited infants of similar birthweights and gestations. However, in the Inder report of the relationship between SEF and MRI only 58% of their EEG data were recorded in the first week after delivery, at a median age of six days (Inder, Buckland et al., 2003). We have shown that in preterm infants the SEF falls over the first four days before stabilising (West, Harding, Williams, Gunning, & Battin, 2006). These changes shortly after delivery may obscure any potential relationships between SEF from the first EEG and neurodevelopmental outcome in our data since the EEGs were recorded in the first four days. However, we also found no relationship between SEF from the last EEG in the first week and 18 month outcome in our cohort, even though the EEGs were performed at a time when SEF measurements had stabilised and at an age similar to that in the Inder cohort. The reason for this apparent discrepancy is not clear, but may reflect the difference in outcome measures (MRI vs Bayley-II assessments) in the two studies. MRI demonstrates abnormalities in the cerebral white matter of a high proportion of preterm infants, whether the scanning is performed serially during the infant's NICU admission (Maalouf et al., 2001), at term corrected gestation (Inder, Anderson et al., 2003) or in adolescence (Stewart et al., 1999). However, there is still uncertainty about the relationship between MRI abnormalities and neurodevelopmental outcome (de Vries, 2000).

In term infants with neonatal encephalopathy the minimum amplitude provides useful information on the background EEG activity, as it represents the lower edge of the aEEG compressed trace and indicates the degree of discontinuity

of the EEG. Prolonged discontinuity (low minimum amplitude) in encephalopathic term infants has been related to poor neurodevelopmental outcomes (Biagioni et al., 1999). However, the normal EEG pattern for preterm infants includes periods of discontinuity (M. Hayakawa et al., 2001; Selton et al., 2000) in which the minimum amplitude would be expected to be low with limited variability. This might explain why minimum amplitude measured in our infants was not related to developmental outcome.

Our finding that infants with worse neurodevelopmental outcomes had lower quantitative measures of continuity early in the NICU course was consistent with other reports of decreased continuity, or increased discontinuity, being associated with poor long term outcomes (Benda, Engel, & Zhang, 1989; Maruyama et al., 2002). Continuity at the 10μV threshold was expected to perform better for outcome prediction as it detects the presence of very low amplitude EEG traces. However, the high false positive rate (23%) is likely to be because of the 'normal' preterm EEG includes periods of discontinuity and therefore portions of very low amplitude trace will be present in many extremely preterm infants who will subsequently have no adverse developmental outcomes (M. Hayakawa et al., 2001). We found that continuity measured at both the 25 and the 50μV thresholds performed similarly for prediction of neurodevelopmental outcome category. However, the weak statistical relationships between Bayley-II developmental indices and continuity measures were most consistent for continuity measured at the 25μV threshold. While these relationships are unlikely to be useful clinically because of their variability, we found in both the continuity measures alone, and also the data combining early EEG continuity measurements with day 5 cranial ultrasound scans that the 25μV threshold had slightly higher sensitivity for prediction of 'poor' outcome. In chapter 3 we proposed that the wider spread of results for the 50μV continuity threshold may result in better discrimination for detection of infants with 'poor' long term neurodevelopmental outcome. However, the data presented in this chapter suggests that continuity at the 25μV threshold performs slightly better than continuity at the 50μV threshold. This is probably because it has a good range of results (50 – 100% / min) while also detecting more discontinuous EEG at this lower amplitude threshold.

Diagnostic test data such as those presented here can be analysed to optimise the sensitivity of the test (for a screening test), or to optimise the specificity (for a diagnostic test). We do not currently have any specific medical or interventional therapies to treat infants identified as being at risk of 'poor' neurodevelopmental outcome. Therefore, we felt it was important to attempt to optimise our data for both sensitivity and specificity. However, when a specific neuroprotective therapy becomes available it will be possible to optimise these, and similar data, towards a diagnostic test, if there are significant potential side-effects, or towards a screening test, if there are minimal potential side-effects.

The expert neurophysiologist was slightly better at predicting the outcome of our preterm infants than the semi-automated quantitative neurophysiological measures when the same periods of two-channel EEG underwent analysis by the two methods. The neurophysiologist's assessment relied on two main factors for assignment of EEG category; the interburst interval and the presence of seizures. Interburst interval can be assessed at a number of different amplitude thresholds in the same way as continuity. However, these two parameters are different. Interburst intervals were manually calculated as the time between two segments of EEG activity above a threshold amplitude. Quantitative continuity measurements reflect the maximum amplitude in two second segments of raw EEG from which the percentage of each minute above a set threshold is calculated. At a set threshold a given continuity can result from several different EEG patterns. For example, 50% / min continuity could be produced by alternating segments of two seconds of low amplitude trace followed by two seconds of burst (higher amplitude) trace, or by 30 seconds of normal (higher amplitude) trace followed by 30 seconds of low amplitude trace. Between these extremes are numerous other possibilities. These two patterns would be interpreted very differently by a neurophysiologist. The first would be within normal limits, whereas the second is pathological at any gestation. This suggests that modification of current continuity algorithms to better reflect interburst interval may improve outcome prediction using quantitative EEG.

The second EEG feature relied upon by the neurophysiologist was the presence of seizures. None of the infants recruited into our preterm cohort were clinically diagnosed as having seizure activity, and none received anticonvulsant medication. However, the neurophysiologist was able to identify four infants with definite seizures. Three of these four infants died and the other had multiple disabilities. Another six infants had probable or possible seizures, and these infants had better outcomes, with only one dying, and none having a PDI or a MDI < 70. Seizures may not be detected by two channel monitoring as it is difficult to determine whether the EEG trace represents abnormal neuronal activity or whether it represents artefact. Without a complete montage of channels to obtain an overall picture of the EEG activity (ie a conventional EEG) the discrimination between these two causes of abnormal EEG may be difficult, and focal seizures may be missed. Although cotside EEG monitoring has been used to assist with identification and treatment of seizures in term infants, even clinicians trained in the interpretation of these traces have been shown to have problems with identification of seizure activity (Rennie et al., 2004). Furthermore, a prototype neonatal seizure detection algorithm developed by the manufacturer of the BRM cotside EEG recording device (EEG Lawnmower version 1.03, BrainZ Instruments Ltd, Auckland, New Zealand) did not detect the seizures identified by the neurophysiologist. However, this algorithm was developed for term infants, in whom seizures may be easier to detect as an alteration in background activity. Seizures in preterm infants may be more difficult to detect by an algorithm because of the discontinuous background. Thus, without the expertise of a sub-specialist neurophysiologist reading the raw EEG, seizures are still very difficult to identify in preterm infants. Further research is required to examine whether these seizures can be detected by an automated system in real time and then whether treatment of these seizures alters prognosis.

Conventional EEG recordings might be expected to perform even better than our modified recordings for outcome prediction as they provide further information in addition to interburst interval and improved seizure detection. The presence of positive rolandic sharp waves in preterm EEG has been associated with subsequent development of cerebral palsy (Baud et al., 1998;

Marret et al., 1997). However, positive rolandic sharp waves cannot be definitely identified on two channel cotside EEG recordings due to the limitations in electrode placement and number. We are not aware of any literature comparing outcome prediction using conventional and two channel EEGs performed on the same infants with expert interpretation.

As expected, we found that infants who died, as well as infants who had a 'poor' outcome at 18 month follow-up tended to be younger and lighter than those who had a better outcome (Knight & Kuschel, 2005). However, only the PDI score of the Bayley-II examination was related to gestation at birth, and age at Bayley-II examination. As our Bayley-II examinations were undertaken at 18 months chronological age this resulted in the infants with the lowest gestations being assessed, in general, at earlier corrected gestations. This relationship may not have been found for the MDI score because development at 18 months chronological age is still predominantly physical and therefore reflected more in the PDI than in the MDI. The reason for the weak associations between individual neurodevelopmental scores and both birthweight and gestation at delivery is likely to be due to the large spread of outcome scores at any given weight or gestation.

Because the youngest, smallest infants have the worst outcomes we wanted to confirm that the neurophysiological parameters performed at least as well for outcome prediction in the subgroup of infants born at <28 weeks gestation. Clinicians already know that these infants are at increased risk of poor neurodevelopmental outcome (Doyle & Victorian Infant Collaborative Study, 2001), so in order to be a useful tool, quantitative EEG parameters must also differentiate between infants that are in this high risk group. As infants born at <28 weeks gestation made up 60% of our cohort it is not surprising that the tests perform similarly in the youngest infants compared with the whole cohort, but it is reassuring that they do not perform worse.

6.4.1 Summary and implications

Quantitative continuity measures from EEGs in the first week after delivery are related to Bayley-II developmental indices at 18 months chronological age. However, these relationships are weak and are not likely to be useful clinically. EEG measures of continuity below a cut-off were more useful but still showed only moderate sensitivity and specificity for prediction of 'poor' outcome. The combination of day 5 cranial ultrasound scan information in addition to EEG measures of continuity did not improve the prediction of outcome above EEG continuity alone. A neurophysiologist's analysis of two channel EEG from infants born before 29 weeks gestation predicted outcome better than continuity measures. Further development of quantitative neurophysiological algorithms, with incorporation of interburst interval assessment and detection of seizures, may be required to improve outcome prediction from quantitative EEG parameters from two channel cotside EEG recordings.

7 Results - Term Infants at Risk of Seizures

7.1 Introduction

Multichannel EEG has been shown to assist with outcome prediction in term infants with neonatal encephalopathy, both alone (Biagioni et al., 1999; Pressler, Boylan, Morton, Binnie, & Rennie, 2001; Sarnat & Sarnat, 1976; Selton & Andre, 1997) and in combination with MRI (Biagioni et al., 2001). Abnormal background EEG activity early in the course of the encephalopathy has been associated with worse outcome, particularly when it does not improve by the end of the first week after delivery (Sarnat & Sarnat, 1976). Manual assessment of interburst interval on multichannel EEG also has prognostic value, with a median interburst interval of more than 30 seconds associated with abnormal neurological outcome (Menache et al., 2002). Term infants with an abnormal neurological outcome have also been shown to have increased positive and negative spikes and sharp waves on early EEG compared with term infants who have a normal outcome (Biagioni, Boldrini et al., 1996). In addition EEG recordings can provide information regarding seizure activity, particularly in infants receiving muscle relaxation.

While conventional EEG monitoring remains the gold standard, many centres do not have on-call neurophysiology technicians and neurophysiologists available for monitoring infants at risk of encephalopathy or with suspected seizures shortly after admission to NICU. Some NICUs also do not have any access to neurophysiologists trained to read neonatal EEG recordings. Therefore, it is important that cotside monitoring devices are compared with conventional EEGs obtained simultaneously, or shortly after each other (Toet et al., 2002). These comparisons will assist delineation of the utility and limitations of recordings from cotside EEGs.

Modified cotside EEG recordings have been studied more extensively in term infants with neonatal encephalopathy than in preterm infants. The background pattern of the aEEG trace from the Cerebral Function Monitor has been shown to help prediction of outcome in term encephalopathic infants (al Naqeeb et al., 1999; Hellstrom-Westas et al., 1995; Klebermass, Kuhle, Kohlhauser-Vollmuth, Pollak, & Weninger, 2001; Thornberg & Ekstrom-Jodal, 1994; Toet et al., 1999). The aEEG traces in these studies were recorded at different times after delivery, from as early as three hours (Toet et al., 1999), up to two days (Thornberg & Ekstrom-Jodal, 1994). Early aEEG criteria have been used to select a more homogeneous population of term encephalopathic infants for recent, and ongoing, trials of hypothermia as a neuroprotective therapy (Gluckman et al., 2005; TOBY).

Interpretation of the cotside EEG monitoring depends on the type of monitor available, and includes analysis of the background pattern and assessment for seizure activity. The gestational age of the infant is the most important factor in determining the expected background activity of an EEG. Therefore, in this chapter we will be confining our discussion to infants with cotside EEG recordings performed after 35 weeks gestational age. These infants are expected to have continuous background activity with well developed sleep state cycling. It is also important to be aware of the potential for some drugs to impact on the background EEG activity (ter Horst, Brouwer et al., 2004; Young & da Silva, 2000) and take this into account in the analysis. Some EEG monitoring systems also allow the raw EEG to be reviewed at the cotside, and this can provide useful confirmatory data, especially with regard to seizure detection.

The aEEG trace provides summary information about the maximum and minimum EEG amplitudes. Continuity measurements obtained from secondary analysis of raw EEG recorded on the BRM monitor are obtained by a different algorithm, but minimum amplitude of the aEEG trace reflects the continuity at the lower amplitude thresholds. There are no normative data published on this continuity algorithm in term infants. While we reported our experience using this form of continuity analysis on a small group of healthy term infants in

chapter 3, we have not used this for comparative analyses with our term infants at risk of seizures as both groups of infants are very small. As there are published data on aEEG traces in both healthy term infants and those at risk of adverse outcome, we have restricted our analyses to assessments of the aEEG traces.

In this chapter we report:

1. The relationship between early cotside EEG and outcome for a cohort of near term infants clinically considered to be at risk of seizures;
2. The relationships between convalescent conventional and cotside EEGs, MRI and outcome for the same cohort of infants; and
3. A comparison between conventional EEG reported by specialist neurophysiologists and cotside EEG interpreted by a neonatologist for convalescent EEGs recorded on the same day in the same cohort of infants.

7.2 Methods

Parents of eligible infants were approached for consent as soon as feasible after the clinical team identified an infant to be having clinical seizures (atypical movements or apnoea) or to be at risk of seizures (a clinical diagnosis of neonatal encephalopathy). Management of infants with anticonvulsant medication was based on clinical criteria and was not delayed until placement of EEG electrodes. One cotside EEG was performed immediately after obtaining consent. A second cotside EEG was performed on the same day as the convalescent conventional EEG. Most infants had an MRI performed on the same day as the conventional EEG. The convalescent EEGs and MRI were performed 5 – 8 days after delivery to assist with prognostication.

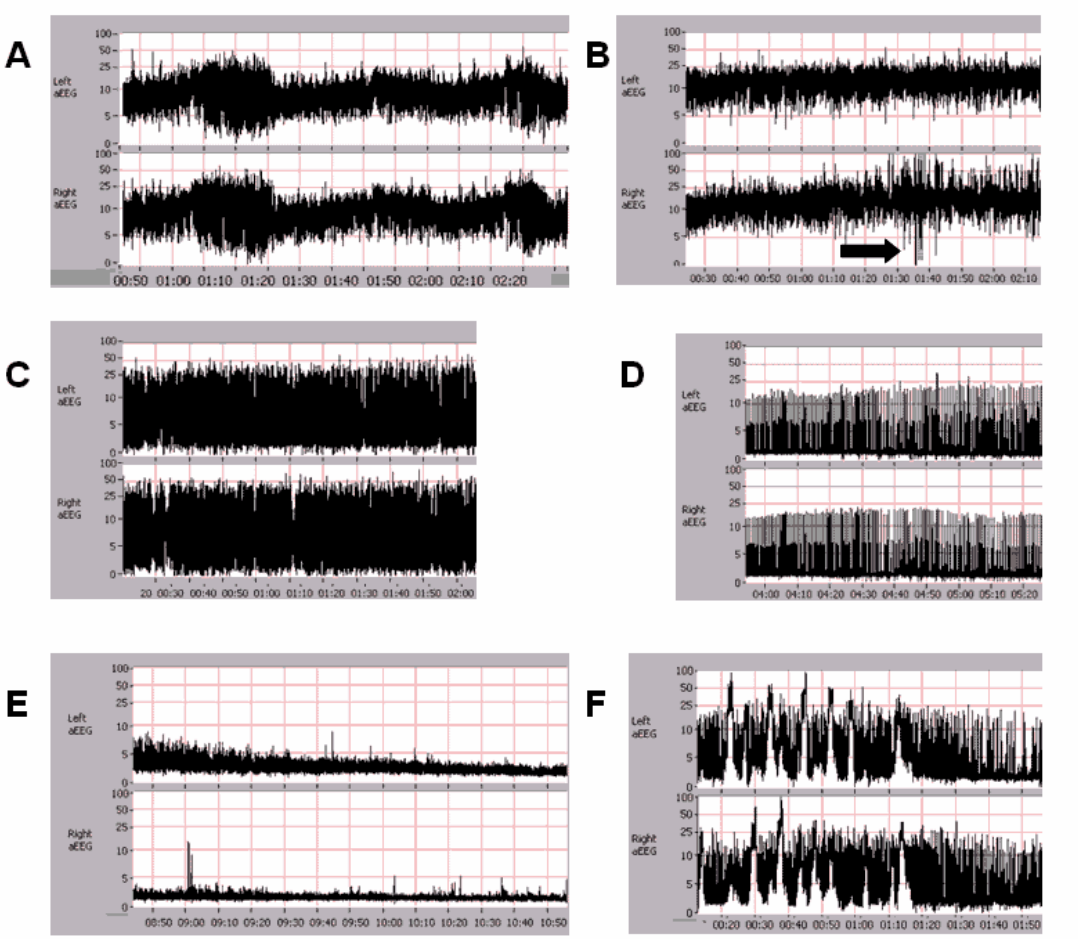
Cotside EEGs were reported independently of conventional EEGs. Each cotside EEG was examined for evidence of sleep state cycling on the aEEG trace (section 2.5.3), and evidence of seizures and increased sharp waves on the raw trace. Minimum amplitude measurements are reported for the different sleep state cycle levels separately as the minimum amplitude would not be expected to be comparable between these groups (see figure 7-1). Infants with

level one or two sleep states had the minimum amplitude assessed for the first hour of the recording. If the baseline decreased subsequently, or if there was recurrent seizure activity over the first hour of the recording, the minimum amplitude was assessed over one hour later in the recording. For infants with level three and four sleep state cycling the minimum amplitude was assessed both for the quiet (broad band) and active (narrow band) sleep states. Values are given for left and right sides separately as term infants at risk of seizures are more likely to have asymmetric recordings than our preterm population. The complete raw EEG was reviewed for the presence of seizures and sharp wave activity using customised Labview software (EEG viewer, version 9.26, BrainZ Instruments Limited, Auckland, New Zealand) starting with standard settings of +/- 100μV and 10 second segments per window.

Assessment of the background activity of the aEEG trace involves pattern recognition, and is a relatively simple skill to learn. There are some variations in terminology applied to background patterns in different reports. However, specific amplitude criteria and illustrations of the patterns result in good agreement between observers after brief periods of training (al Naqeeb et al., 1999). The background EEG pattern was assessed visually from the aEEG trace using a classification based on previous reports (Hellstrom-Westas et al., 1995; Toet et al., 2002) with slight modifications, including the addition of the discontinuous moderate voltage pattern. The classification criteria were:

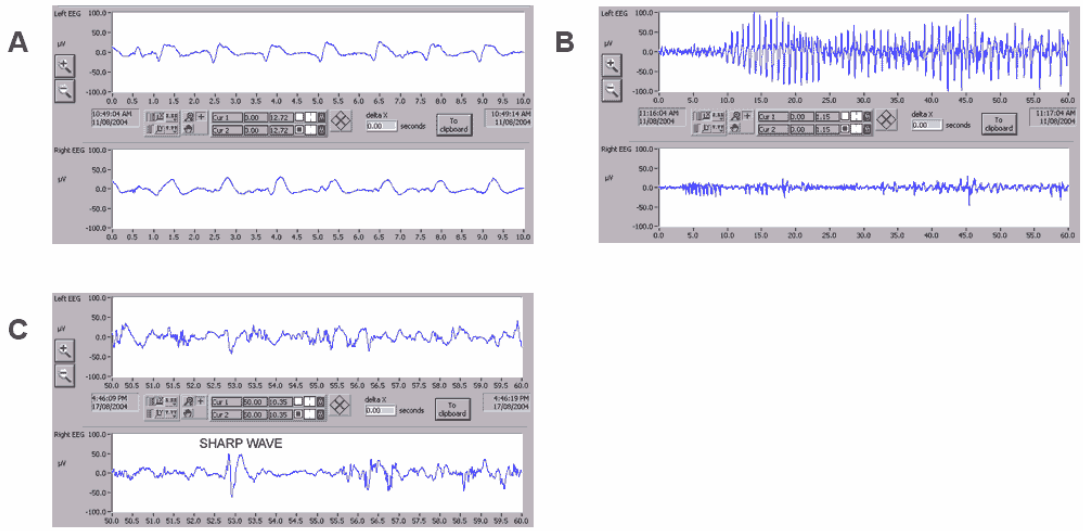
1. Continuous normal voltage – continuous activity with minimum amplitude >5μV either with sleep state cycling (voltage may dip briefly below 5μV during quiet sleep) (figure 7-1A), or without sleep state cycling (figure 7-1B);
2. Discontinuous moderate voltage – broad band of discontinuous activity with minimum amplitude <5μV and maximum voltage >10μV (figure 7-1C);
3. Burst suppression – discontinuous activity with periods of very low amplitudes with bursts of higher amplitudes intermixed (figure 7-1D);
4. Low voltage tracing – narrow band of activity with minimum amplitudes <5μV (figure 7-1E); and
5. Recurrent seizures – sawtooth pattern (figure 7-1F).

Figure 7-1
Amplitude-integrated EEG background patterns. Illustrations show continuous normal voltage with level four sleep state cycling (A) and without clear sleep state cycling (B, arrow indicates period with artifact), discontinuous moderate voltage (C), burst suppression (D), low voltage tracing (right half of E), and recurrent seizure activity, followed by burst suppression (F). Vertical scale is amplitude in microvolts, horizontal scale is time in minutes. In each illustration the top trace is recorded from left side of the head and the bottom trace from the right.



Sharp waves and seizure activity were assessed by review of the cotside raw EEG (figure 7-2). We classified sharp wave activity as 'increased' if >10 sharp waves per minute of raw EEG were detected at any time during the recording. Seizure activity was present if segments of rhythmic discharge lasting at least 10 seconds were seen. Segments of raw EEG with altered waveforms occurring during active handling of the infant, as marked by the bedside nurse, were excluded from analysis of seizure activity. The use of opiates and anticonvulsant medication was recorded.

Figure 7-2
Examples of seizures (A and B) and sharp waves (C) on review of raw EEG from cotside monitor. Vertical scale is amplitude in microvolts, horizontal scale shows 10 seconds of raw EEG per frame for A and C and 60 seconds for B.



Convalescent cotside EEG recordings performed on the same day as the conventional EEG were classified as follows:

1. Normal recordings had level four sleep state cycling with active sleep minimum amplitude above 5μV, and no increase in sharp waves (≤10 / minute on raw EEG);
2. Mildly abnormal recordings had <u>one</u> of the following:
    a. Borderline low minimum amplitude (4 - 5μV),
    b. Sleep state cycling level one to three (b), or
    c. Increased sharp wave activity (>10 / minute on raw EEG);
3. Moderately abnormal recordings had at least two of the following:
    a. Low minimum amplitude (<5μV),
    b. Sleep state cycling level one to three (b), or
    c. Increased sharp wave activity(>10 / minute on raw EEG); and
4. Markedly abnormal readings had either burst suppression or seizures.

The conventional EEGs were reported by neurophysiologists. MRIs were reported by neuroradiologists.

Outcome was assessed from 12 month Ages and Stages questionnaires (Bricker, Squires, & Mounts) completed by the infants' parents, and reports

from visiting neurodevelopmental therapists and paediatric outpatient clinics. Infants with specific abnormalities found on assessment were categorised as having 'suspect' outcome. Due to the strong association between basal ganglia injury on MRI, either with or without thalamic injury, and developmental delay (Biagioni et al., 2001; M. Rutherford, Pennock, Schwieso, Cowan, & Dubowitz, 1996) all infants with evidence of basal ganglia injury on MRI scanning were included in the 'suspect' category unless they had a normal assessment by a Paediatrician at or after 12 months of age.

We compared sleep state cycling, sharp wave activity and reported category of EEG between the convalescent cotside and conventional EEGs using contingency tables. Prediction of outcome category by acute and convalescent cotside EEGs and convalescent conventional EEG were each examined using contingency tables. We report Cramer's V coefficients which indicate the relative strength of association between the two variables in the contingency tables. For 2 x 2 tables we report the Fisher's Exact p value due to the small numbers of infants in some cells. We used logistic regression to examine the relationship between the lowest minimum amplitudes measured on the acute cotside EEG and the outcome category.

7.3 Results

Twenty four infants were recruited between June 2004 and July 2005. One infant was born at 32 weeks gestation, but was recruited to the study at 38 weeks corrected gestation because of unexplained apnoeas. He had a postnatal diagnosis of 8/Y translocation with terminal deletion of 8p, and had also been treated for meningitis. There was clinical uncertainty whether the apnoeas he was having at the time of the study were due to seizure activity. Both of his cotside EEGs showed level four sleep state cycling with no evidence of seizures, and his conventional EEG was within normal limits. His EEGs are not included in the remainder of the results.

The 23 remaining infants were born at a median (range) of 39 (36 - 42) weeks, with birthweights of 3420 (2205 - 4270) grams. Eleven infants were recruited due to clinical concern of seizure activity, and 12 were thought to be at risk of

seizures due to probable hypoxic-ischaemic encephalopathy. Ten infants were transferred to our NICU for tertiary level care, eight from other maternity facilities within the city, one from an intermediate care facility in another centre and one from home on day 3 with dehydration secondary to undiagnosed duodenal atresia. At discharge from NICU, or death, four infants had a diagnosis of stage 1 encephalopathy, 12 had stage 2 and 4 had stage 3 encephalopathy. None of the infants were recruited into head or total body cooling trials.

7.3.1 Early cotside EEG

The cotside EEG recording was started at 14 (2 - 96) hours after delivery and lasted 270 (70 - 1150) minutes. Two infants were receiving opiate infusions at the time the first cotside EEG was recorded, one had had an opiate bolus two hours before the cotside EEG and 11 other infants had received anticonvulsant medication (table 7-1). A further six infants received anticonvulsant medication after the start of the EEG recording, leaving only three infants who received neither opiates nor anticonvulsant medication. From our data it was not possible to determine the impact of medication separately from the underlying condition due to the variation of timing, dosage and combination of medications used.

The first cotside EEG showed level one sleep state cycling in 15 infants, level two in six infants, and level three (b) in two infants (table 7-1).

Of the 15 infants with level one sleep state cycling, one had a continuous normal voltage background pattern (table 7-1, infant 8). Five infants had seizure activity present at the beginning of their EEG recording. In one of these the seizures continued for the seven hour trace despite escalating anticonvulsant therapy (table 7-1, infant 10). In three infants the seizures gave way to a discontinuous moderate voltage background pattern. The background pattern of one of these infants subsequently became a low voltage trace. This infant later died (table 7-1, infant 1). In another of these infants when the seizures stopped the background pattern was burst suppression, and later became discontinuous moderate voltage again. This infant also died before

discharge (table 7-1, infant 4). Nine infants had a discontinuous moderate voltage pattern at the start of the EEG recording. In four of these there was no change over time. One infant subsequently developed burst suppression and then a low voltage trace after treatment of seizure activity. This infant died before discharge (table 7-1, infant 2). Another infant, who also died before discharge, developed a low voltage trace after seizure activity subsided (table 7-1, infant 3). One infant subsequently developed level two sleep state cycling (table 7-1, infant 15), and seizure activity developed in the other two. One of these infant's background activity returned to the discontinuous moderate voltage pattern after the seizure activity ended. The other infant had a period of burst suppression after the seizure activity which then continued as discontinuous moderate voltage (table 7-1, infant 12).

The worst background pattern seen in the 15 infants with level one sleep state cycling was low voltage in three infants, burst suppression in three, recurrent seizures throughout the trace in one, discontinuous moderate voltage in seven and continuous normal voltage in one.

Minimum amplitude could be assessed in the first hour after starting the EEG recording for 10 of the 15 infants with level one sleep state cycling and was 2.9 (0.9 – 7.1) μV on the left and 3.0 (1.5 – 9.8) μV on the right. In three of these infants the minimum amplitude subsequently fell. In five infants the minimum amplitude was not measured over the first hour because they had recurrent seizures, which elevates the minimum amplitude. In the three infants whose minimum amplitude fell over time and the five infants with seizures the minimum amplitudes later in the EEG recording were 2.0 (0.4 – 3.4) μV on the left and 2.0 (0.2 – 3.0) μV on the right.

In the six infants with level two sleep state cycling the minimum amplitude in the first hour after starting the EEG recording was 5.1 (4.0 – 8.3) μV on the left and 5.2 (2.4 – 8.7) μV on the right.

Table 7-1 Summary of cotside and conventional electroencephalography, MRI findings and outcome for term infants at risk of seizures.

Study No	Early cotside EEG				Convalescent cotside EEG				Conventional EEG			MRI lesion	Outcome
	SSC (level)	Backgrd (worst)	Seizures	Anti-convulsant	SSC (level)	Sharps	Backgnd	Category	SSC	Sharps	Category		
1	1	Low volt	+	Pheno, Midaz	ND	ND	ND	ND	ND	ND	ND	ND	Died
2	1	Low volt	+	Pheno, Pheny, Midaz	ND	ND	ND	ND	ND	ND	ND	BGT +Cx	Died
3	1	Low volt	+	Pheno*	ND	ND	ND	ND	ND	ND	ND	ND	Died
4	1	BS	+	Pheno	2	↑	DLV	Moderate	Absent	↑	Abnormal	BGT +Cx	Died
5	1	DLV	-	Pheno*, Pheny*, Midaz*	1	BS	DLV	Marked	Absent	BS	Abnormal	BG	Suspect (MACDD, global delay)
6	1	DLV	+	Pheno, Pheny, Parald	1	↑	CNV	Moderate	Normal	↑	Mild	BGT	Suspect (↑ tone)
7	1	DLV	-	Morphine infusion*	1	↑	CNV	Mild	?	↑	Mild	Nil	Suspect (HP)
8	1	CNV	-	-	2	↑	CNV	Moderate	Normal	↑	Mild	ND	Normal
9	1	BS (short period)	+	Pheno*, Pheny	3b, low baseline	↔	DNV	Moderate	?	↔	WNL, ↓ amp	Cxx	Suspect (HP)
10	1	Recurrent seizures	+	Pheno*, Midaz	4	↑	CNV	Mild	?	↑	Mild	Cx + cyst	Normal
11	1	DLV	-	Morphine bolus	4	↑	CNV	Mild	Normal	↑	Mild	Nil	Normal

12	1	BS	+	Pheno, Pheny	4	↑	CNV	Mild	Poor	↑	Abnormal	Cx	Suspect (↑ tone, deafness)
13	1	DLV	+	Pheno*, Midaz	4	↑	CNV	Mild	Poor	↑	WNL	Nil	Normal
14	1	DLV	+	Pheno*	4	↔	CNV	Normal	Normal	↔	WNL	Nil	No data
15	1	DLV	+	Pheno	4	↑	CNV	Mild	Normal	↑	Mild	BGT	Suspect (no data at 1 yr)
16	2	CNV	+	-	2	↔	DNV	Moderate	?	↔	Normal	BGT	Suspect (TA)
17	2	DLV	-	Pheno*, Pheny*	2	↑	CNV	Moderate	Normal	↑	Mild	Cx	Normal
18	2	DLV	+	Pheno*	4	↑	CNV	Mild	Normal	↔	WNL	Venous infarct	Normal
19	2	DLV	-	Pheno*	4	↔	CNV	Normal	Normal	↔	Normal	BGT	Suspect (no data at 1 yr)
20	2	DLV	-	Morphine infusion*	4	↔	CNV	Mild	Poor	↔	Mild, ↓ amp	BGT +Cx	Suspect (no data at 1 yr)
21	2	DLV	-	Pheno*	4	↑	CNV	Mild	Normal	↑	Mild	Nil	Normal
22	3b	CNV	-	Pheno*	2 (short EEG)	↔	CNV	Mild	Normal	↔	Normal	BG +Cx	Suspect (no data at 1 yr)
23	3b	CNV	-	-	4	↔	CNV	Normal	?	↑	WNL	Cx	Normal

SSC = sleep state cycle; Backgnd = background aEEG pattern; Low volt = low voltage; BS = burst suppression;
DMV = discontinuous moderate voltage; CNV = continuous normal voltage; + = present; - = absent; Pheno = phenobarbitone;
Pheny = phenytoin; Midaz = midazolam; Parald = paraldehyde; * = infant received medication before EEG recording;
ND = Not done; BS = burst suppression; ↑ = increased; ↔ = not increased; Mild = mildly abnormal;
Moderate = moderately abnormal; Marked = markedly abnormal; ↓ amp = decreased amplitude; WNL = within normal limits;
BG = basal ganglia; T = thalami; MACDD = multiple acyl-CoA dehydrogenase deficiency (glutamic acidaemia Type 2);
HP = early hand preference; TA = truncal ataxia.

In the two infants with level three (b) sleep state cycling the minimum amplitudes in quiet sleep were 5.9 and 7.2μV on the left, and 4.9 and 6.4μV on the right, and in active sleep 8.7 and 9.9μV on the left and of 8.2 and 9.9μV on the right.

In the whole cohort the worst background pattern was low voltage in three infants, burst suppression in three, discontinuous moderate voltage in twelve, recurrent seizure activity in one and continuous normal voltage in four.

Seizures were seen on the first cotside EEG in 13 infants. One infant, recruited because of one brief clinical seizure, had not received anticonvulsants before the cotside EEG and had no evidence of seizure activity recorded. She had level three (b) sleep state cycling on her first cotside EEG with increased sharp wave activity.

On the early cotside EEG all infants had increased sharp wave activity (> 10 sharp waves in any one minute segment) on review of their raw EEG.

7.3.2 Convalescent cotside EEG

Twenty infants had convalescent cotside EEG performed at a median (range) of 5 (3 - 26) days after delivery. No infants were receiving opiate or anticonvulsant medication at the time of the convalescent cotside EEG. EEG recordings lasted 140 (70 - 185) minutes.

The convalescent cotside EEG showed sleep state cycling of level one in three infants, level two in five infants, level three (b) in one infant, and level four in 11 infants (table 7-1).

In the three infants with level one sleep state cycling the minimum amplitude in the first hour after starting the EEG recording was 7.5 (2.0 – 9.5) μV on the left and 7.4 (1.6 – 9.6) μV on the right. The five infants with level two sleep state cycling had minimum amplitudes of 6.1 (4.7 – 9.7) μV on the left and 7.3 (4.1 – 10.3) μV on the right. The infant with level three (b) sleep state cycling had a minimum amplitude in quiet sleep of 2.7μV on the left and 2.5μV on the right,

and in active sleep 3.5µV on the left and 2.8µV on the right. The 11 infants with level four sleep state cycling had minimum amplitudes in quiet sleep of 4.6 (2.9 – 6.8) µV on the left and 4.7 (2.7 – 5.8) µV on the right, and in active sleep of 5.8 (5.2 – 9.9) µV on the left and 5.9 (4.0 – 8.3) µV on the right.

The background aEEG pattern for the convalescent cotside EEG was discontinuous normal voltage in four, and continuous normal voltage in 16. There were no seizures seen on the convalescent cotside EEG recordings. Increased sharp wave activity (> 10 / minute) was seen on the raw EEG of 13 infants.

The level of sleep state cycling improved between the first and second cotside EEG in 14 (70%) of infants with two cotside recordings, remained unchanged in five (25%) and decreased from level three (b) to level two in one infant (5%) (table 7-1). However, the infant whose sleep state cycling appeared to deteriorate had the shortest period of EEG recorded (70 minutes). In this infant the conventional EEG was reported to include wakefulness and quiet sleep, which would be anticipated to produce both broad and narrow bands on the aEEG trace.

7.3.3 Convalescent conventional EEG

Twenty infants had conventional EEGs performed on day 5 (2 – 25) after delivery. Seventeen infants had their conventional EEG on the same day as their convalescent cotside EEG, two the day before, and one a day and a half later. The conventional EEG was reported as normal or within normal limits in eight infants, mildly abnormal in nine infants and abnormal in three infants (table 7-1). Additional features commented on in the report included low amplitude traces in two infants, absent or poor sleep state definition in six infants and excess sharp wave activity in 12 infants.

7.3.4 Magnetic Resonance Imaging

Nineteen infants had a MRI performed on day 4(1 - 13) after delivery. Seven (37%) had the MRI performed on the same day as the convalescent EEGs, another eight (42%) had the MRI within two days of the convalescent EEGs.

The MRI was reported as normal in five infants (table 7-1). Evidence of basal ganglia injury, with or without thalamic injury, was found in nine infants, and cortical damage was seen in nine infants. Four infants had evidence both basal ganglia and cortical lesions, and three of these also had thalamic lesions. One infant had a cystic lesion consistent with antenatal injury in addition to evidence of acute cortical ischaemia, and in one infant the cortical damage was caused by an intracranial haemorrhage with venous infarction of the right temporal lobe.

7.3.5 Outcome

Collection of outcome data is ongoing. Follow-up data were available for 17 of the surviving infants at a median (range) of 6 (3 – 16) months after delivery. None of the infants with basal ganglia injury on MRI scanning, with or without thalamic injury, had normal Paediatric assessments at 12 months of age; they either had abnormal neurological findings, or had not reached 12 months of age. From the information available to date eight infants are developing normally, 10 have suspect outcome (six with some degree of neurological abnormality and four with basal ganglia injury on MRI awaiting further review), four are dead (all before discharge) and no data are available for one (tables 7-1 and 7-4).

7.3.6 EEGs and death before discharge

Four infants died before discharge, one after transfer back to the hospital where she was born. These infants all had level one sleep state cycling, recurrent seizures and increased sharp wave activity on their early cotside EEG, two of the four developed burst suppression and three had periods of low voltage during the traces. The infant who survived until transfer had a convalescent cotside EEG that showed continuous background activity with poor sleep wake cycling (level two), minimum amplitudes of 4.7μV on the left and 5.4μV on the right and increased sharp wave activity. Her conventional EEG was reported as abnormal with no evidence of sleep wake cycling, increased sharp waves and immature features including delta brushes. She had a MRI on the day before her convalescent EEGs which showed profound asphyxial changes to the basal ganglia, thalami and cerebral cortex.

The four infants who died before discharge all had minimum amplitudes below 2μV on their early cotside EEG. While these were after treatment with anticonvulsant medication, only three other infants had minimum amplitudes below 2μV on the early cotside EEG. Two of these infants had transient low amplitudes recorded. The convalescent conventional EEG was within normal limits for one infant and showed mild abnormalities in the other. Both of them had normal MRI scans. The last infant had persistent low minimum amplitude measurements on early cotside EEG, an abnormal convalescent conventional EEG, an abnormal MRI (cortical infarction) and had abnormal tone noted on follow-up.

7.3.7 Early cotside EEG and outcome

While our outcome data are not yet complete we have provisional outcome information for 22 (96%) of our infants. This includes four infants placed in the suspect outcome category because of basal ganglia lesions on their MRI who have not yet been followed-up to one year of age.

We found no relationships between the presence of seizures, the use of anticonvulsants at any time during NICU admission, or the level of sleep state cycling and available outcome data (table 7-1). There was also no relationship between increased sharp wave activity (present in all early cotside EEGs) and outcome. There were no relationships between the lowest minimum amplitude and outcome category ($p = 0.14$, $R^2 = 0.31$ for left and $p = 0.17$, $R^2 = 0.25$ for right).

In the 14 infants with level one sleep state cycling and outcome data available, the worst background aEEG pattern from the acute cotside EEG was related to outcome category (table 7-2, Cramer's V coefficient = 0.76, $p = 0.04$). Of note, all the infants with low voltage traces died, and those with burst suppression either died or had suspect outcome. The infant with continuous normal voltage background had a normal outcome, as did the infant with recurrent seizures throughout the EEG recording.

In the whole cohort of infants with outcome data available, the worst background aEEG pattern from the acute cotside EEG was similarly related to outcome (table 7-3, Cramer's V coefficient = 0.70, p = 0.007). However, two infants with continuous normal voltage background pattern had suspect outcome, and suspect outcomes were found after each of the background patterns except for low voltage and recurrent seizures.

Table 7-2
Prediction of outcome for infants with level one sleep state cycling using worst background pattern seen on acute cotside EEG.

		Outcome				TOTAL
		Dead	Suspect	Normal	No data	
Cotside EEG – worst background pattern (level one sleep state cycle only)	Low voltage	3	0	0	0	3
	Burst suppression	1	2	0	0	3
	Discontinuous moderate voltage	0	4	2	1	7
	Recurrent seizures	0	0	1	0	1
	Continuous normal voltage	0	0	1	0	1
TOTAL		4	6	4	1	15

Values are numbers of infants in each category
Cramer's V coefficient = 0.76, p = 0.04 (infant with no data excluded from analysis)

In order to compare our data with previous reports, we calculated the predictive value of a low voltage or burst suppression background pattern for predicting death or suspect outcome in the whole cohort. There was a sensitivity of 43 (95% confidence interval 30 – 56)%, specificity of 100%, positive predictive value of 100 %, and negative predictive value of 50 (37 - 63)% in the whole cohort.

Table 7-3
Prediction of outcome using worst background pattern seen on acute cotside EEG.

		Outcome				TOTAL
		Dead	Suspect	Normal	No data	
Cotside EEG – worst background pattern for all traces	Low voltage	3	0	0	0	3
	Burst suppression	1	2	0	0	3
	Discontinuous moderate voltage	0	6	5	1	12
	Recurrent seizures	0	0	1	0	1
	Continuous normal voltage	0	2	2	0	4
TOTAL		4	10	8	1	23

Values are numbers of infants in each category
Cramer's V coefficient = 0.70, p = 0.007 (infant with no data excluded from analysis)

After excluding the four infants placed in the suspect outcome group because of basal ganglia injury on MRI without follow-up to one year, the predictive value of a low voltage or burst suppression background pattern for predicting death or suspect outcome was slightly better with a sensitivity of 60 (47 – 73)%, specificity of 100%, positive predictive value of 100% and negative predictive value of 67 (53 – 81)% (table 7- 4).

Table 7-4
Prediction of outcome for infants with known outcome by background pattern of acute cotside EEG.

		Outcome		TOTAL
		Dead / Suspect	Normal	
Cotside EEG – worst background pattern for traces	Low voltage / Burst suppression	6	0	6
	Other	4	8	12
TOTAL		10	8	18

Values are numbers of infants in each category
Fisher's exact p = 0.05

7.3.8 Convalescent EEGs and outcome

While our outcome data are not yet complete we have provisional outcome information for 19 of the 20 (95%) infants who had convalescent EEGs. This

includes four infants placed in the suspect outcome category because of basal ganglia lesions on their MRI who have not yet been followed to one year of age.

There was a relationship between the reported category of the conventional EEG and outcome, though this did not reach statistical significance (table 7-5, Cramer's V coefficient = 0.55, p = 0.08). Furthermore, the conventional EEG did not predict outcome with a useful degree of clinical certainty, as infants with suspect outcomes are found in all reported categories of EEG. An abnormal EEG did predict death or suspect outcome, but a normal EEG did not predict a normal outcome. Exclusion of the four infants categorised as having suspect outcome because of their MRI data alone did not change the strength of the relationship (table 7-5, Cramer's V coefficient = 0.54, p = 0.19).

Table 7-5
Prediction of outcome using categories from conventional EEG reports. Top half of table is all infants with convalescent conventional EEG, bottom hasl exclused infants whose outcome is unknown but with basal ganglia injury on MRI.

All infants		Outcome				TOTAL
		Dead	Suspect	Normal	No data	
Conventional EEG final category	Abnormal	1	2	0	0	3
	Mildly abnormal	0	4	5	0	9
	WNL	0	1	3	1	5
	Normal	0	3	0	0	3
TOTAL		1	10	8	1	20
Cohort excluding infants with basal ganglia injury on MRI whose outcome is unknown						
Conventional EEG final category	Abnormal	1	2	0	0	3
	Mildly abnormal	0	2	5	0	7
	WNL	0	1	3	1	5
	Normal	0	1	0	0	1
TOTAL		1	6	8	1	16

Values are numbers of infants in each category
WNL = Within normal limits
All infants – Cramer's V coefficient = 0.55, p = 0.08 (infant with no data excluded from analysis)
Cohort excluding infants with basal ganglia injury on MRI whose outcome is unknown - Cramer's V coefficient = 0.54, p = 0.19 (infant with no data excluded from analysis)

Our classification of cotside EEG into categories using information about the sleep state and minimum amplitude (from the aEEG trace) and sharp wave activity (from review of the raw EEG) showed only a weak relationship with outcome (table 7-6, Cramer's V coefficient = 0.30, p = 0.77). While six of the eight infants (75%) with normal provisional outcome had cotside EEGs categorised as normal or mildly abnormal, six of 10 (60%) with suspect outcome also fell into the same EEG categories. Exclusion of the four infants categorised as having suspect outcome because of their MRI data alone strengthened the relationship, but it was still not statistically significant (Cramer's V coefficient = 0.41, p = 0.54).

Table 7-6
Prediction of outcome using assessment categories from convalescent cotside EEG recordings.

		Outcome				TOTAL
		Dead	Suspect	Normal	No data	
Cotside EEG final category	Markedly Abnormal	0	1	0	0	1
	Moderately abnormal	1	3	2	0	6
	Mildly abnormal	0	5	5	0	10
	Normal	0	1	1	1	3
TOTAL		1	10	8	1	20

Values are numbers of infants in each category
Cramer's V coefficient = 0.30, p = 0.77 (infant with no data excluded from analysis)

Only two background aEEG patterns were found on convalescent aEEG traces in our cohort; the discontinuous moderate voltage and the continuous normal voltage patterns. The relationship between the background pattern of the convalescent aEEG trace and outcome category was of similar strength to that found between the conventional EEG report and outcome (table 7-7, Cramer's V coefficient = 0.58, p = 0.04). Exclusion of the four infants in the suspect outcome group because of basal ganglia injury on MRI strengthened the relationship between background pattern of the convalescent aEEG and outcome (table 7-7, Cramer's V coefficient = 0.70, p = 0.03).

Table 7-7
Prediction of outcome using background pattern of convalescent cotside EEG. Top half of table is all infants with convalescent cotside EEG, bottom half excludes infants whose outcome is unknown but with basal ganglia injury on MRI.

All infants		Outcome				TOTAL
		Dead	Suspect	Normal	No data	
Cotside EEG background pattern	Discontinuous moderate voltage	1	3	0	0	4
	Continuous normal voltage	0	7	8	1	16
TOTAL		1	10	8	1	20
Cohort excluding infants with basal ganglia injury on MRI whose outcome is unknown						
Cotside EEG background pattern	Discontinuous moderate voltage	1	3	0	0	4
	Continuous normal voltage	0	3	8	1	12
TOTAL		1	6	8	1	16

Values are numbers of infants in each category
All infants - Cramer's V coefficient = 0.58, p = 0.04 (infant with no data excluded from analysis)
Cohort excluding infants with basal ganglia injury on MRI whose outcome is unknown - Cramer's V coefficient = 0.70, p = 0.03 (infant with no data excluded from analysis)

7.3.9 MRI and outcome

In the 15 infants with MRIs and outcome data there was a strong relationship between location of MRI lesion and outcome category (table 7-8, Cramer's V coefficient = 0.84, p =0.01). In particular, of the five infants with basal ganglia lesions and follow-up information two had died and three had suspect outcome. The four infants with basal ganglia lesions but without follow-up data to one year were excluded from this analysis.

Table 7-8 Prediction of outcome using MRI data.

		Outcome				TOTAL
		Dead	Suspect	Normal	No Data	
MRI lesion	Basal ganglia +/- thalamic + cortical	2	0	0	0	2
	Basal ganglia +/- thalamic	0	3	0	0	3
	Hypoxic/Ischaemic cortical infarction	0	2	2	0	4
	Venous infarction	0	0	1	0	1
	Normal	0	1	3	1	5
TOTAL		2	6	6	1	15

Values are numbers of infants in each category
Cramer's V coefficient = 0.84, p = 0.01(infant with no data excluded from analysis)

7.3.10 Comparison between convalescent cotside and conventional EEGs

There was poor agreement between sleep state information reported on conventional EEGs and that determined from aEEG patterns (table 7-9).

Table 7-9
Comparison of sleep state cycling between convalescent cotside and conventional electroencephalograms.

		Conventional EEG sleep state		TOTAL
		Absent/Poor	Normal	
Cotside EEG sleep state Level	One, two	3	5	8
	Three, four	3	9	12
TOTAL		6	14	20

Values are numbers of infants in each category
Fisher's exact p value = 0.64

However, the presence of increased sharp wave activity on the report of the conventional EEG was related to >10 sharps / minute on the convalescent cotside EEG (tables 7-1 and 7-10).

Table 7-10
Comparison of increased sharp wave activity between convalescent cotside and conventional electroencephalograms.

		Conventional EEG		TOTAL
		Increased sharps	Normal	
Cotside EEG	>10 sharps / minute	12	1	13
	≤10 sharps / minute	1	6	7
TOTAL		13	7	20

Values are numbers of infants in each category
Fisher's exact p value = 0.001

Comparing the EEG classification between convalescent cotside and conventional EEG reports showed that there was only moderate agreement between these classification systems (table 7-11, Cramer's V coefficient = 0.53, p = 0.08).

Table 7-11
Comparison of reported category between convalescent cotside and conventional electroencephalograms with outcome data as available.

		Conventional EEG			TOTAL
		Normal / Within normal limits	Mildly abnormal	Abnormal	
Cotside EEG final category	Normal	N S ?	-	-	3
	Mildly abnormal	N, N, S	N, N, N, S, S, S	S	10
	Moderately abnormal	S, S	N, N, S	D	6
	Markedly abnormal	-	-	S	1
TOTAL		8	9	3	20

Values are numbers of infants in each category or outcomes for individual infants. N = normal; D = dead; S = suspect outcome; ? = no outcome data.
Cramer's V coefficient = 0.53; p = 0.08

We then repeated the analysis using the background pattern of the convalescent cotside EEGs and the reported category of the conventional EEG.

This showed a similar relationship between the two categories of EEG (table 7-12, Cramer's V coefficient = 0.57, p = 0.04).

Table 7-12 Comparison between background pattern of convalescent cotside EEG and conventional EEG category

		Conventional EEG			TOTAL
		Normal / Within normal limits	Mildly abnormal	Abnormal	
Cotside EEG background pattern	Continuous normal voltage	6	9	1	16
	Discontinuous moderate voltage	2	0	2	4
TOTAL		8	9	3	20

Values are numbers of infants in each category
Cramer's V coefficient = 0.57, p = 0.04

Interestingly, the two infants with discontinuous moderate voltage background patterns on convalescent cotside EEG who had conventional EEGs reported as normal or within normal limits had abnormalities reported on their conventional EEGs which would explain the background patterns. One had a low amplitude trace with some evidence of sleep state cycling on their convalescent cotside EEG, but a low baseline (<2 - 3μV). The other only had quiet sleep recorded and had a broad aEEG trace with poorly defined sleep state cycling (level two), and baseline amplitudes of 4 - 5μV throughout, consistent with quiet sleep. Both of these infants have suspect outcomes (table 7-1, infants 3 and 4).

The infant with an abnormal conventional EEG but continuous normal voltage on cotside EEG had evidence of sleep state cycling (level four) on the convalescent cotside EEG. The conventional EEG was reported as showing no discrimination between sleep wake cycles and multifocal sharps, and the infant has a suspect outcome (table 7-1, infant 12).

7.4 Discussion

We report the results of a heterogeneous group of newborn term infants admitted to NICU because of risk of seizures or for investigation of clinical seizures.

7.4.1 Early cotside EEG and outcome

In our cohort there was a significant relationship between the worst background pattern found on the aEEG of the acute cotside EEG and outcome category. All the infants who had periods of low voltage or burst suppression pattern on their early cotside EEG either died or had suspect outcomes. Infants who died had the worst background patterns and minimum amplitudes of <2μV on their acute cotside EEGs.

These data are in agreement with other studies showing that single channel, cross-head, aEEG traces predict outcome in encephalopathic infants (al Naqeeb et al., 1999; Archbald, Verma, Tejani, & Handwerker, 1984; Hellstrom-Westas et al., 1995; Klebermass et al., 2001; ter Horst, Sommer et al., 2004; Thornberg & Ekstrom-Jodal, 1994; Toet et al., 1999). In those studies the inclusion criteria have been variable, and the numbers of term infants in each cohort have varied. Much of the published literature has focussed on the ability to predict outcome in infants with moderate or severe (Sarnat stage 2 or 3) hypoxic-ischaemic encephalopathy (ter Horst, Sommer et al., 2004; Thornberg & Ekstrom-Jodal, 1994), or neonatal encephalopathy (al Naqeeb et al., 1999; Archbald et al., 1984). We recruited infants based on the occurrence of, or risk of, seizures. However, only 16 of the 24 (67%) infants recruited actually developed moderate or severe hypoxic-ischaemic encephalopathy (Sarnat stage 2 or 3) and four (16%) did not have a diagnosis of neonatal encephalopathy at all. Therefore, it is exciting that in our relatively unselected group the acute cotside EEG can still provide useful prognostic information.

Despite the small numbers in our cohort, we found that a low voltage or burst suppression background pattern on the acute cotside EEG predicted death or suspect outcome with a sensitivity of 43%. This rose to 60% if the infants assigned to outcome category on the basis of basal ganglia injury on the MRI

alone were excluded from the analysis. Previous studies from a more homogeneous group of infants with acute encephalopathy reported a slightly higher sensitivity [93 (88 – 98)% vs 60 (47 – 73)%], similar negative predictive value and slightly lower specificity [70 (61 - 79) vs 100%]and positive predictive value [77 (70 - 84) vs 100%] for predicting adverse outcome (al Naqeeb et al., 1999). Others have reported even higher sensitivities of 85 – 95% for prediction of death or neurological sequelae by a low voltage or burst suppression pattern on very early cotside aEEG in severely asphyxiated infants (Hellstrom-Westas et al., 1995; Toet et al., 1999). These differences may be due to the different inclusion criteria, size of cohorts, and completeness of follow-up data in addition to timing of the EEG. Studies using conventional EEG have also reported a relationship between background pattern on early conventional EEG and outcome (Rose & Lombroso, 1970; Sarnat & Sarnat, 1976; Selton & Andre, 1997). Clinically, the presence of a low voltage or burst suppression pattern on an infant's acute cotside EEG indicates that death or suspect outcome would be expected. However, the outcome for both discontinuous moderate voltage and continuous normal voltage patterns is evenly divided between normal and suspect outcome. This makes it impossible for clinicians to reassure parents about the likelihood of a normal outcome on the basis of an early cotside EEG.

Interestingly, the infant with bilateral recurrent seizure activity throughout her seven hour cotside EEG has no evidence of neurological abnormality to date. This infant had MRI evidence of acute bilateral cerebral infarction. However, she also had evidence of antenatal injury as the MRI also showed an old cystic lesion in the right frontal lobe. The presence of repetitive seizure activity has generally been associated with poor outcome in encephalopathic infants (Hellstrom-Westas et al., 1995; ter Horst, Sommer et al., 2004). However, Selton reported that three of 11 infants (27%) with initial status epilepticus (defined as >30% of the 45+ minute conventional EEG) had a normal outcome at one to eight years of age (Selton & Andre, 1997). While seizure activity has been shown, at least acutely, to affect cerebral blood flow (Boylan et al., 1999) and energy metabolism (Miller et al., 2002) even prolonged seizure activity is not universally associated with significant neurodevelopmental abnormalities.

The lack of relationship between level of sleep state cycling on the acute cotside EEG and outcome is not surprising since aEEG background pattern varied widely within the sleep state groups. Thus, infants with level one sleep state cycling could have any of the aEEG background patterns. Recently the presence of sleep state cycling on aEEG traces of encephalopathic infants has been shown to reflect the clinical severity of the encephalopathy (Osredkar et al., 2005). In addition, infants who showed sleep state cycling within 36 hours of delivery had a better developmental outcome than those who did not (Osredkar et al., 2005). However, as we did not record cotside EEGs for more than 12 hours, and only performed the second EEG on the day of the MRI we do not have comparable data to examine this further.

Our conclusions regarding outcome prediction for this cohort must be regarded as provisional since data collection is ongoing. We chose to include infants with evidence of basal ganglia injury on MRI in the suspect outcome group if they were not yet assessed at one year because of the known risk of abnormal outcome for these infants (Biagioni et al., 2001; M. Rutherford et al., 1996; M. Rutherford, Ward, Allsop, Malamatentiou, & Counsell, 2005). This is consistent with our findings to date that none of the infants with basal ganglia lesions who have follow-up available are normal. The short duration of follow-up currently available also means that we can only comment on the presence of abnormal motor development. Later assessments, perhaps even after beginning school, will be necessary to determine the relationships between the early predictors that we examined and later cognitive function (M. Rutherford et al., 2005).

In our cohort only 10 infants had not received opiates or anticonvulsants at the start of the acute cotside EEG. Unless EEG recordings are commenced as soon as the infant reaches the NICU, many will have received medications before the EEG begins. A lower minimum amplitude has been found in encephalopathic infants given a loading dose of phenobarbitone before the start of an aEEG recording compared with those given no anticonvulsants, despite similar Apgar scores and cord pH (Hellstrom-Westas et al., 1995). Midazolam has been shown to result in reversible burst suppression on aEEG traces in infants with intractable seizures (ter Horst, Brouwer et al., 2004), and

opiates have been shown to decrease continuity, increase sharp wave activity and may also produce reversible burst suppression (da Silva, Alexandrou, Knoppert, & Young, 1999; Young & da Silva, 2000). Ideally cotside EEG monitoring should begin in infants at risk of neonatal seizures before anticonvulsant medication is required. This would enable the clinician to assess the acute effects of anticonvulsants on the background pattern, and take these into account in their interpretation of the trace.

It is important to remember that, in addition to prediction of outcome, early cotside EEGs may have other clinical utility. The ability to assess brain function in infants requiring muscle relaxation, for both background pattern and the presence of seizure activity may assist with clinical management of infants who do not tolerate handling or movement well. The aEEG trace has also been used to assess infants for recruitment into trials of neuroprotective therapies to produce more comparable cohorts and therefore reduce the study size (Gluckman et al., 2005; TOBY) and enhance the application of the results to other settings.

7.4.2 Convalescent EEGs, MRI and outcome

Convalescent EEGs did not predict outcome as well as acute cotside EEGs. Convalescent conventional EEG category predicted outcome better than the convalescent cotside EEG category, but not as well as the background pattern of the convalescent cotside EEG. Only the site of MRI lesions had a stronger relationship with outcome than acute cotside EEG.

Early conventional EEGs have been used for prognostication in asphyxiated term infants since the 1970s. The original Sarnat and Sarnat classification for infants with postanoxic encephalopathy (Sarnat & Sarnat, 1976) included EEG criteria for the three clinical stages, as did Fenichel's revised criteria (Fenichel, 1983). However, as in our NICU, these are not always available acutely, and may be performed later in the first week after delivery.

Despite our NICU guideline recommending conventional EEG in the first week after delivery in infants with stage 2 or 3 neonatal encephalopathy (M. Battin)

there are few studies showing the predictive value of conventional EEG beyond the first 72 hours after delivery. Rose and Lombroso showed that on follow-up EEGs, performed weeks to months after neonatal seizure events, unifocal abnormalities on acute EEGs usually resolved, some multifocal abnormalities resolved and others deteriorated, and no infant with burst suppression or flat traces resolved (Rose & Lombroso, 1970). Sarnat and Sarnat performed conventional EEGs on their cohort until discharge (Sarnat & Sarnat, 1976). They found that a flat trace or burst suppression at any time, increased discontinuity that persisted beyond seven days, or the presence of a low amplitude EEG in the recovery phase was associated with poor prognosis. Watanabe and colleagues showed a strong relationship between the background EEG pattern recorded between days two and seven on infants with perinatal hypoxia, and outcome at a mean age of four years (Watanabe, Miyazaki, Hara, & Hakamada, 1980). Selton and Andre performed repeat conventional EEGs on some of their cohort between two and seven days after delivery. They found that improved background activity from an initial 'intermediate' background indicated a good prognosis, but similar or worse activity was associated with neurological sequelae (Selton & Andre, 1997). Our data also shows a trend towards a relationship between convalescent conventional EEG and outcome. All infants with abnormal conventional EEGs died or had suspect outcome. However, all the infants with normal EEGs had suspect outcomes, and clinicians must therefore be careful not to be falsely reassured by a normal EEG.

The finding that the background pattern of the convalescent cotside EEG predicts outcome at least as well as, if not slightly better than, the conventional EEG is exciting. We expected that the conventional EEG would be a better predictor of outcome, as the neurophysiologist has more information available for interpretation of the recording, including the component frequencies, localisation of abnormal transients and more information about artefact and sleep state (Holmes et al., 1982; Watanabe et al., 1980). This once again points to the aEEG being a valuable tool in the prediction of outcome for at risk term infants, and suggests that a cotside EEG can be performed later in the

first week after delivery, for example on infants transferred from smaller centres, with similar results.

It is interesting to note that our attempt to classify the cotside EEG by analysing the sleep state, minimum amplitude and sharp wave activity did not prove to be any better for outcome prediction than visual assessment of the background pattern of the aEEG trace. In fact, the relationship between our cotside EEG classification and outcome was very poor. The relative simplicity of identifying the background pattern of the aEEG, a skill that can be learnt by interested clinicians from relevant articles (al Naqeeb et al., 1999; Hellstrom-Westas et al., 1995; ter Horst, Sommer et al., 2004; Thornberg & Ekstrom-Jodal, 1994; Thornberg & Thiringer, 1990; Verma et al., 1984) and books (Hellstrom-Westas et al., 2003), further enhances the clinical utility of cotside EEG monitoring in the NICU.

The most confusing aspect of determining the background aEEG pattern of a trace is the different nomenclatures present in the literature. We chose to classify the background pattern into five categories, including recurrent seizures that occurred throughout the trace. The nomenclature for the aEEG pattern with a minimum voltage below 5µV but the maximum voltage is between 25 and 50µV is the most variable. al Naqeeb termed this category moderately abnormal amplitude, Toet used the term continuous normal voltage, slightly discontinuous (Toet et al., 2002) or discontinuous normal voltage (Toet et al., 1999) and Helstrom-Westas showed an illustration of this pattern which was identified in the legend as continuous normal voltage without sleep state cycles (Hellstrom-Westas et al., 1995). al Naqeeb used only three categories (al Naqeeb et al., 1999), normal amplitude (corresponding to our continuous normal voltage), moderately abnormal amplitude and suppressed amplitude (corresponding to our low voltage and burst suppression categories). Seizure activity could accompany each of these. The same three category scheme was used to identify infants for recruitment to the Cool-Cap head cooling trial (Gluckman et al., 2005). Toet had five categories (Toet et al., 1999; Toet et al., 2002), Hellstrom-Westas used five slightly different categories (Hellstrom-Westas et al., 1995), and ter Horst had six (ter Horst, Sommer et al., 2004). Our

categories were most similar to those described by al Naqeeb apart from our choice to separate low voltage and burst suppression categories, and add a recurrent seizure category for the infant who did not exhibit any other background pattern. We chose to categorise burst suppression separately as some studies have found this pattern in infants with normal follow-up (Hellstrom-Westas et al., 1995), whereas infants with low voltage traces consistently have adverse outcome in studies of both conventional and cotside EEGs.

In our cohort MRI was a better predictor of outcome category than any of the EEG recordings. Previous work (Biagioni et al., 2001; M. Rutherford et al., 1996) has also shown the utility of MRI scans performed on encephalopathic term infants in the first week of life for outcome prediction. The severity of basal ganglia and thalamic lesions is related to severity of resultant cerebral palsy in term infants after hypoxic ischaemic insults (Cowan et al., 2003; M. Rutherford et al., 2005; M. A. Rutherford et al., 1998). The American Academy of Neurology has recommended that an MRI should be performed within the first two to eight days of life in term encephalopathic infants to provide predictive data (Ment et al., 2002). We are awaiting our final outcome data to determine whether an EEG at the same time as the MRI provides additional data for outcome prediction.

7.4.3 Comparison of convalescent cotside and conventional EEGs

When comparing the reports of convalescent cotside and conventional EEGs there was excellent agreement regarding the presence of increased sharp wave activity, and moderate agreement regarding background aEEG pattern and conventional EEG category. However, there was less agreement regarding overall reported category between these EEGs, and none regarding assessment of sleep state cycle.

Previous studies have shown strong relationships between background activity on conventional EEGs and background pattern on aEEG traces in encephalopathic infants for both acute (al Naqeeb et al., 1999; Klebermass et al., 2001; ter Horst, Sommer et al., 2004; Toet et al., 2002), and in one study

some later (Toet et al., 2002), EEG recordings. We were unable to obtain acute conventional EEGs in our cohort because the local neurophysiology unit provides a limited acute service, and for the first five months of recruitment our NICU was on a different site. Therefore, we examined the relationship between EEG modalities at the time of the convalescent conventional EEG which is routinely performed in infants with neonatal encephalopathy in our NICU for outcome prediction (M. Battin). Even at this later time, the agreement between conventional EEG report and cotside aEEG background pattern further supports the aEEG trace as a useful way of presenting EEG data for the non-neurophysiologist. Interestingly, the background pattern of the aEEG trace predicted outcome better than the conventional EEG report in the infants with known outcomes.

It is possible that if a single neurophysiologist reviewed conventional EEG traces to report specifically on features that may help predict outcome the results may have been different. However, we chose to use the EEG report provided by the neurophysiologist as part of routine clinical service, as this is the only information currently available to medical staff for outcome prediction. If further information that is relevant for outcome prediction can be provided by the neurophysiologist reading the EEG this needs to be incorporated into the routine report to the clinical team.

We have not attempted to assess the interobserver variability for analysis of either cotside or conventional EEG reporting. Toet and colleagues examined the interobserver agreement for both aEEG traces (read by two neonatologists) and simultaneously acquired conventional EEG (read by two neurophysiologists) (Toet et al., 2002). They found excellent agreement for aEEG interpretation on background activity (κ statistic = 0.92) and good agreement on seizure activity (κ statistic = 0.70). For the conventional EEGs the interobserver agreement about background activity was good (κ statistic = 0.74) and there was complete agreement about seizure activity (κ statistic = 1.0). al Naqeeb and colleagues found similar good agreement for classification of aEEG background pattern between three neonatal doctors (κ statistic = 0.85), and lower agreement for classification of seizures (κ statistic = 0.76) (al

Naqeeb et al., 1999). In contrast, Rennie and colleagues found very poor agreement between four neonatologists for classification of seizures on aEEG traces (κ statistic 0.01 to 0.39) (Rennie et al., 2004). However, it is unlikely that this level of interobserver variability would account for our findings of poor agreement between categories of convalescent cotside EEG and conventional EEG because no seizures were found in either.

The detection of seizure activity by simplified cotside EEG devices is a contentious issue for neonatologists and neurophysiologists. When compared with multichannel video EEG the single channel aEEG monitor was reported to miss around 50% of the seizures, particularly if they were short, focal or low amplitude and there was poor interobserver agreement (κ statistic 0.01 to 0.39) (Rennie et al., 2004). The monitor used in this study has the advantages of having two channels of EEG, one for each side of the head, and the ability to review the raw trace. Therefore, it is possible that more seizures may have been identified correctly when using this monitor. Unfortunately we were unable to further explore this issue as none of the infants had seizure activity on either convalescent EEG.

The close agreement regarding sharp wave activity between the two forms of convalescent EEG indicates that the recognition of specific waveform patterns can be achieved by non-neurophysiologists. We were not able to determine whether a similar number of sharp waves were seen on the two different methods of EEG recording. On conventional EEG recordings it is possible to localise the sharp wave activity, and to be more specific about its directionality ie positive or negative. This cannot be done on review of the raw cotside EEG. On the two channel cotside EEG it is also not possible to determine whether the increased sharp wave activity is due to periodic lateralising epileptiform discharges. However, while increased sharp wave activity in convalescent EEGs performed on encephalopathic term infants is not normal (Biagioni, Boldrini et al., 1996), they do not have the same implications for outcome as positive rolandic sharp waves have in the preterm population. Therefore, the ability to further categorise the sharp wave activity would be anticipated to have minimal effect on outcome prediction.

The lack of any relationship between sleep state cycle assessment on cotside and conventional EEGs is intriguing. Sleep state cycling on the cotside EEG recordings was based on the aEEG patterns (Thornberg & Thiringer, 1990; Verma et al., 1984; Viniker et al., 1984). The aEEG trace is narrow during the more continuous activity associated with active sleep and wakefulness, and broad during the more discontinuous quiet sleep, the *tracé alternant* pattern seen on conventional EEG. Without close observation and documentation during the recording it is not possible to differentiate active sleep and wakefulness from the aEEG trace. Polysomnographic EEG recordings in adults can differentiate six sleep states: wakefulness, rapid eye movement sleep, and sleep stages I to IV (Fisch, 1999b). However, in term infants only awake, drowsy, active and quiet sleep states can be consistently differentiated on conventional EEG (de Weerd & van den Bossche, 2003), although a variable proportion of undifferentiated sleep may also be identified (Scher, Steppe, & Banks, 1995; Scher et al., 1992). Conventional EEG reports from our cohort only differentiated sleep states into awake, quiet and active sleep periods.

During the conventional EEG a technician was present for the whole recording to document sleep state. In addition, during the latter months of the study, video monitoring the entire EEG was incorporated so the reporter could see the infant's movements during review of the EEG. For the cotside monitoring this level of surveillance was not performed, particularly during the convalescent EEG. The nurses were requested to mark the recording to identify when the infant was unsettled, but as they were caring for several infants at one time this could not be assumed to have the same accuracy as the conventional EEG. Therefore, differentiation between wakefulness and active sleep was not possible. Thus the lack of relationship between sleep state cycle assessment on cotside and conventional EEG was not surprising.

7.4.4 Summary and implications

We have shown that in term infants at risk of seizures the aEEG background pattern from acute cotside EEGs is related to provisional outcome category. However, while this relationship is statistically significant it is of limited clinical

utility, since suspect outcome was seen after all the acute aEEG background patterns except for low voltage.

Both cotside and conventional EEGs recorded in the convalescent period were related to outcome, though the aEEG background activity of the cotside EEG was a better predictor than the reported category of the conventional EEG. However, convalescent EEGs did not have better clinical utility than acute cotside EEGs. The location of injury found on convalescent MRI had the strongest relationship with outcome.

When directly comparing the convalescent cotside and conventional EEGs we found that the aEEG background pattern of the cotside EEG was related to the conventional EEG report, but this relationship was only of moderate strength.

The relationship between aEEG background activity on both acute and convalescent cotside EEG recordings and outcome prediction is reassuring for centres that do not have conventional EEG facilities available. Furthermore, cotside EEG can still be useful for outcome prediction when infants are transferred to a NICU for tertiary care some days after delivery.

Complete follow-up data on our cohort will allow us to further analyse whether specific EEG changes are more prevalent in infants with suspect outcomes to allow improved outcome prediction.

We would recommend in term infants at risk of seizures that the best information to assist clinicians with outcome prediction can be obtained from the aEEG background pattern on an early cotside EEG and from an MRI scan later in the first week after delivery.

8 Conclusion

The greatest tragedy of science –
the slaying of a beautiful hypothesis by an ugly fact.

Thomas Henry Huxley, 1894

We began this research to test the hypothesis that SEF measurement from two channel cotside EEG monitoring on newborn infants requiring admission to NICU would be a useful quantitative neurophysiological parameter to assist clinicians with outcome prediction. Our data do not support this hypothesis. However, we extended our analyses to include other quantitative neurophysiological parameters obtained from cotside EEG recordings. These parameters provide additional information on EEG maturation patterns and make some contribution to outcome prediction.

Neurodevelopmental outcome at 18 months corrected age was not related to SEF measurements on early cotside EEGs. We found continuity at the 25 and 50μV thresholds to be the most useful EEG parameters for outcome prediction in preterm infants. However, there was a spectrum of outcomes for each level of continuity, and no clear threshold could be found that could be used for clinically meaningful outcome prediction. Interestingly, a neurophysiologist reviewing the same period of two channel raw EEG was able to predict outcome slightly more accurately than the continuity measures. This improved accuracy appeared to be due to the assessment of interburst interval and seizure activity. Thus, development of software algorithms to assess interburst interval and to detect seizure activity in discontinuous EEG traces may be useful to improve the utility of early cotside EEG for prediction of outcome. Accurate and simple detection of EEG seizure activity would also facilitate

future research regarding the optimal management of preterm infants with seizures.

While we did not show that early cotside EEGs help with outcome prediction, we did find that preterm infants with unremarkable cranial ultrasound scans during their NICU admission had consistent changes in quantitative neurophysiological parameters over the first week after delivery, and throughout the remainder of their admission. Over the first three days after delivery SEF fell, while continuity at the 10, 25 and 50μV thresholds rose. These changes were not limited to preterm infants born at any particular gestational ages. It would therefore be interesting to determine whether term infants show similar changes in neurophysiological parameters after birth. This could be investigated using a protocol of either prolonged, or shorter repeated, EEG recordings starting on the first day after delivery on healthy term infants. If term infants have changes in neurophysiological parameters similar to our preterm cohort this would indicate that the changes are likely to be the result of delivery and the immediate postpartum adaptation. However, if the patterns of change in neurophysiological parameters are unique to preterm infants, further work regarding the impact of peripartum events on cerebral electrical activity would be critical for the understanding of our observations.

During their NICU admission, preterm infants with unremarkable cranial ultrasound scans showed increases in minimum amplitude and SEF, with more complex changes in continuity measures. When preterm infants born at <28 weeks gestation reached 36 – 38 weeks postmenstrual age they tended to have higher SEF measurements than infants born at 30 – 31 weeks gestation while other neurophysiological parameters were similar. We postulate that the differences in SEF at term corrected gestation between the youngest and oldest preterm infants may reflect altered central nervous system development in the most immature infants. We did not perform MRIs in our cohort, which would have allowed further assessment of cortical maturation, but our findings are consistent with recent imaging studies showing reduced cerebral cortical grey matter volumes in preterm infants at term corrected gestation compared with normal term controls. Our data thus raise the interesting possibility that

SEF may warrant further exploration to determine its utility as a cotside measure of cortical maturation in preterm infants.

We found that low cerebral blood flow, as measured by SVC flow, and low blood pressure in the first days after delivery were associated with changes in cotside EEG parameters that persisted for some hours after the cardiovascular perturbations. We also found that endotracheal surfactant administration and opiate boluses were associated with reduced continuity of the cotside EEG trace. We were unable to determine whether these changes were causally related or due to other confounding factors. However these findings suggest that cotside EEG monitoring could be further investigated as a possible tool for assessing the cerebral effects of clinical interventions such as inotrope and analgesic administration.

In term infants at risk of seizures, or admitted with possible seizure activity, we found that the background pattern of the aEEG trace was most useful for outcome prediction. However, the clinical utility of the background pattern was again limited, since it was not possible to predict which infants would have a poor outcome from the background pattern alone. Nevertheless, background pattern from the convalescent cotside aEEG trace performed as well for outcome prediction as the clinical neurophysiology reports from a convalescent conventional EEG. Therefore, a convalescent cotside EEG performed on term infants at risk of seizures may provide useful information regarding prognosis for clinicians practising in neonatal units without ready access to neurophysiology services. We did not record prolonged acute cotside EEGs in our term infants and thus were unable to determine the relationships between the evolution of the background pattern over the days after admission and later neurodevelopmental outcome. However, our data suggest that such an approach may be useful in future studies on term infants at risk of seizures to refine prognostication by taking into account the temporal changes in background EEG patterns as well as the acute effects of drug administration and of clinical interventions, such as hypothermia.

In summary, the research presented in this thesis demonstrates that the quantitative neurophysiological parameters currently available from cotside EEG monitoring using the two channel BRM monitor in preterm infants are not clinically useful for outcome prediction. However, cotside EEG in preterm infants remains a useful research tool that may provide interesting information regarding changes in neurophysiology after birth, in response to clinical interventions and with postnatal maturation. Cotside EEG monitoring in term infants at risk of seizures can provide useful information to assist with outcome prediction, particularly in neonatal units without ready access to conventional neurophysiology services.

We must see the first images which the external world
casts upon the dark mirror of his mind;
or must hear the first words which awaken the sleeping powers of thought,
and stand by his earliest efforts,
if we would understand the prejudices, the habits,
and the passions that will rule his life.

The entire man is, so to speak, to be found in the cradle of the child.

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