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EEG functional connectivity in term age extremely low birth weight infants ☆

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ABSTRACT

Objective: The hypothesis is tested that electrocortical functional connectivity (quantified by coherence) of extremely low birth weight (ELBW) infants, measured at term post-menstrual age, has regional differences from that of full term infants.
Methods: 128 lead EEG data were collected during sleep from 8 ELBW infants with normal head ultrasound exams and 8 typically developing full term infants. Regional spectral power and coherence were calculated.
Results: No significant regional differences in EEG power were found between infant groups. However, compared to term infants, ELBW infants had significantly reduced interhemispheric coherence (in frontal polar and parietal regions) and intrahemispheric coherence (between frontal polar and parieto-occipital regions) in the 1–12 Hz band but increased interhemispheric coherence between occipital regions in the 24–50 Hz band.
Conclusions: ELBW infants at term post-menstrual age manifest regional differences in EEG functional connectivity as compared to term infants.
Significance: Distinctive spatial patterns of electrocortical synchrony are found in ELBW infants. These regional patterns may presage regional alterations in the structure of the cortex.

1. Introduction

There has been a steady rise in the rate of extreme preterm birth (gestational age <30 weeks; birth weight <1250 g), which accounted for 2.3% of all births in 2003 (Martin et al., 2005). These infants are at high risk for poor neurodevelopmental outcome, including cerebral palsy, mental retardation (Furman et al., 1996; Hall et al., 1995; Piecuch et al., 1997; Stewart and Kirkbride, 1996; Whitaker et al., 1997), attention deficit hyperactivity and anxiety disorders, schizophrenia (Ichiki et al., 2000), learning disabilities (Sykes et al., 1997; Whitaker et al., 1997), sudden infant death (Sahni et al., 2007) and cognitive dysfunction during adolescence (Saigal, 2000). An extensive literature has linked premature exposure to the extrauterine environment and disruption of normal brain development (Hubel and Wiesel, 1963; McEwen, 2001; Mower et al., 1982; Pham et al., 2003; Wiesel and Hubel, 1965). Severe abnormalities measured by head ultrasound exam, including interventricular hemorrhage and periventricular leucomalacia, are robust predictors of cerebral palsy. Nonetheless, more than 75% of all surviving extremely low birth weight (ELBW) infants have a normal head ultrasound exam and yet persist in having an increased incidence of cerebral palsy and/or poor cognitive outcome (Fanaroff et al., 2007; Laptook et al., 2005). Thus, our research is focused on the ELBW infants with normal ultrasonic findings with an overall goal to detect changes in electrocortical function early in the neonatal period that are predictive of the neurodevelopmental outcome.

This report describes our initial research in this area, namely to determine if there are differences in electrocortical function between ELBW infants, at term-equivalent age, and full term infant controls. We hypothesized that there are regional differences in EEG function between these groups because recent MRI studies have found regional differences in brain anatomy (Inder et al., 2005; Peterson, 2003; Peterson et al., 2003; Thompson et al., 2006); (Boardman et al., 2006; Srinivasan et al., 2007). The EEG is used to evaluate brain function between groups because it is a

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valuable tool for studies of cortical development (Mizrahi and Kellaway, 1987).

For this study spontaneous EEG from sleeping infants was recorded and processed to quantify brain function. The sources of spontaneous EEG are localized groups of neurons within the cerebral cortex, most likely pyramidal cells, that fire synchronously to form electric current dipoles that produce electric potentials measurable on the surface of the scalp (Buzsaki and Draguhn, 2004; Pedley, 1997). The dipoles that contribute most significantly to the spontaneous EEG are superficial radial dipoles within cortical gyri in close physical proximity to the recording electrode (Nunez, 1981; Salek-Haddadi et al., 2003; Srinivasan et al., 1998). Synchronous firing of neurons within a local cortical group produces increased EEG power at that site. Similarity in the population averages of neural firing across two spatially remote locations produces synchrony in the time-varying behavior of EEG waveforms recorded at those sites (Fingelkurts et al., 2005; Friston et al., 1996; Horwitz, 2003; Koenig et al., 2005; Sporns et al., 2004; Stam, 2004; Valdes-Sosa et al., 2005). Therefore, functional connectivity (as contrasted with neural connectivity) between brain regions can be inferred by quantifying the synchrony of EEG waveforms with use of measures such as the correlation function (Marmarelis, 1978) or coherence (Nunez, 1981; Nunez et al., 1999; Nunez et al., 1997). Various temporal frequencies in the EEG reflect different neural sources that subserve different brain functions (Buzsaki and Draguhn, 2004; Pedley, 1997). Thus, spectral power, an index of local neural synchrony, and coherence, an index of electrocortical functional connectivity, are measured in various EEG frequency bands.

Previously, researchers attempted visual analysis of the EEG from preterm and term infants but were unable to discern differences between the groups of infants (Ferrari et al., 1992; Nunes et al., 1997). Another group found similar EEG spectral power in the delta band of preterm infants (GA < 32 wks) compared with term infants, but significantly less power at higher frequencies in the preterm group, with the largest differences in the left parasagittal region (Scher et al., 1994). Other research from the same group assessed the correlations of EEG waveforms across multiple pairs of electrodes in term and preterm infants and found significantly higher correlations in the preterm group, particularly in the left parasagittal region, without assessment of the increased probability of false positive findings (Scher et al., 1996; Scher et al., 1997). Healthy infants born close to term were found to have greater coherence between the frontal and occipital regions at 10 Hz and between the left central and temporal regions at 6–24 Hz than prematurely born infants (Duffy et al., 2003). Our previous research developed and validated methods for localization of regional differences in EEG power and coherence in term infants with 128-lead, high density EEG technology (Fifer et al., 2006; Grieve et al., 2005, 2007). We have applied these methods in the present study.

2. Methods

2.1. Subjects

This study was approved by the Institutional Review Board at Columbia University Medical Center. The subjects were infants in the well baby nursery and the Neonatal Intensive Care Unit of the Morgan Stanley Children's Hospital of New York-Presbyterian. With prior permission from attending physicians, informed consent was given by the parent(s) of each infant studied. High density (128-lead) EEG data were then collected between postnatal days 2–4 from 8 healthy term infants at 39.7 ± 0.8 wks post-menstrual age (mean ± SD) with birth weight of 3119 ± 329 g and 5 male subjects. Table 1 summarizes the characteristics of this group. One pregnancy was complicated by a positive test for tuberculosis and treated with Isoniazid. There were no other complications. Cesarean delivery was indicated by a breech presentation in 1 pregnancy, suspected fetal distress in 1, and repeat procedures in 4. All infants had a normal neurological exam. Physical findings were all normal except one infant had an undescended testis.

EEG data were also collected at 40.1 ± 3.8 (mean ± SD) wks post menstrual age in 8 ELBW infants born at 25.4 ± 1.5 wks, with birth weight of 786 ± 158 g and 5 male subjects. Table 2 summarizes the characteristics of this group. Entry criteria included birth weight ⩽1250 gm, gestational age at birth ⩽30 weeks, and the absence of maternal complications of pregnancy other than premature labor or rupture of fetal membranes. Two infants were the second born of twin gestations and two mothers were treated with antibiotics (urinary tract infection and vaginal culture positive for group B Streptococcus). None of the women had a history of ethanol, tobacco or drug use in pregnancy. In all ELBW infants there was an

Table 1
Summary of the clinical characteristics of the eight full term infants (mean ± SD).

Maternal age (y)	26.4 ± 6.9 (18–39)
Gravidity (#)	2.9 ± 1.4 (1–5)
Use by history	
Tobacco	Negative 8 of 8
Drugs	Negative 8 of 8
ETOH	Negative 8 of 8
Pregnancy	Uncomplicated 8 of 8
Delivery	
Vaginal	1 of 8
Cesarean	7 of 8
Apgar score 1 min	⩾8 for 8 of 8
Apgar score 5 min	⩾9 for 8 of 8
Gestational age (wk)	39.7 ± 0.8 (39–41)
Newborn	
Sex	3 female and 5 male
Birth weight (gm)	3119 ± 329 (2875–3575)
Head circ. (cm)	33.7 ± 1.1 (32–35.5)
Length (cm)	49.2 ± 1.3
Growth (AGA = appropriate for gestational age)	AGA 8 of 8
Neurological exam	Normal 8 of 8
Breast feeding	6 of 8

Table 2
Summary of the clinical characteristics of the 8 ELBW infants (mean ± SD).

Pregnancy	
Gravidity	2.5 ± 1.3 (range 1 to 5)
Multiple gestation	2 of 8 (Twins)
Assisted fertility	2 of 8
Premature labor	6 of 8
Fetal membrane rupture	5 of 8
Prenatal steroids	6 of 8
Delivery	
Vaginal	3 of 8
Cesarean	5 of 8
Apgar 1 min	5.4 ± 2.4 (range 2–8)
Apgar 5 min	7.5 ± 0.7 (range 7–9)
Gestational age (wk)	25.4 ± 1.5 (range 24–28.3)
Newborn	
Sex	3 Females and 5 males
Birth weight (gm)	786 ± 158 (range 620–1120)
Head circ. (cm)	23.4 ± 1.7 (range 21.5–26.5)
Medical course	
Respiratory distress	8 of 8 (6–8 severe)
Documented sepsis	3 of 8
Patent ductus arteriosis	7 of 8 (ligation 5–7)
Bronchopulmonary dysplasia	3 of 8 (at discharge 1 of 3)
Necrotizing enterocolitis	1 of 8 (ruled out in 3 of 7)
Retrolentilfibroplasia	4 of 8 (2 of 4 laser surgery)
Parenteral nutrition (d)	43.9 ± 27.8 (range 11–104)
Hospitalization (d)	121.5 ± 37.4 (range 75–185)