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Estimating functional brain maturity in very and extremely preterm neonates using automated analysis of the electroencephalogram

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HIGHLIGHTS

- Automated analysis of the EEG provides a widely accessible, noninvasive and continuous assessment of brain activity.
- We developed an automated measure of EEG maturational age in the very and extremely premature neonate.
- Automated estimates of EEG maturational age are correlated with gestational age.

ABSTRACT

Objective: To develop an automated estimate of EEG maturational age (EMA) for preterm neonates.
Methods: The EMA estimator was based on the analysis of hourly epochs of EEG from 49 neonates with gestational age (GA) ranging from 23 to 32 weeks. Neonates had appropriate EEG for GA based on visual interpretation of the EEG. The EMA estimator used a linear combination (support vector regression) of a subset of 41 features based on amplitude, temporal and spatial characteristics of EEG segments. Estimator performance was measured with the mean square error (MSE), standard deviation of the estimate (SD) and the percentage error (SE) between the known GA and estimated EMA.
Results: The EMA estimator provided an unbiased estimate of EMA with a MSE of 82 days (SD = 9.1 days; SE = 4.8%) which was significantly lower than a nominal reading (the mean GA in the dataset; MSE of 267 days, SD of 16.3 days, SE = 8.4%: $p < 0.001$). The EMA estimator with the lowest MSE used amplitude, spatial and temporal EEG characteristics.
Conclusions: The proposed automated EMA estimator provides an accurate estimate of EMA in early preterm neonates.
Significance: Automated analysis of the EEG provides a widely accessible, noninvasive and continuous assessment of functional brain maturity.

1. Introduction

Every year, over two million babies are born very or extremely premature, less than 32 weeks gestational age (GA), and will require admission to a neonatal intensive care unit (NICU) (Blencowe et al., 2012). Neurological complications from prematurity can result in a 10–25 fold increase in annual healthcare costs (Kancherla et al., 2012). While recent progress in

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cardio-respiratory intensive care has increased the numbers of surviving neonates, the proportion of survivors with lifelong neurocognitive disabilities has not significantly declined (Saigal and Doyle, 2008; Sellier et al., 2010). This developmental compromise may originate from neurological complications associated with conditions such as infection, cerebral haemorrhage and lung disease which are acquired during a stay in the NICU (Volpe, 2001). Many of these issues can be treated or prevented by prompt cotside recognition. It is, therefore, important that the neurological function of preterm neonates is carefully monitored in the NICU.

Currently available, noninvasive, tools for monitoring brain function in the NICU include electroencephalography (EEG) and near infrared spectroscopy which can be supplemented with structural information from imaging methods such as cranial ultrasound and magnetic resonance imaging. Clinical work in the 1970's, mostly based on visual EEG interpretation, has established well recognised developmental changes in EEG activity (André et al., 2010; Aminoff, 2012). These visually observed changes in EEG waveforms can be explained in the context of early developmental changes in neuronal networks and their molecular expressions (Vanhatalo and Kaila, 2006). This has informed clinical EEG review of preterm neonates which is based on detecting deviances in EEG maturational age (EMA) from what is expected at a given conceptual or maturational age (MA) (Scher, 1997). A well trained clinical electroencephalographer may be able to visually detect delayed maturation or dysmaturity of approximately two weeks (Parmelee et al., 1968). Such analysis is, however, challenged by several caveats: (1) it is qualitative, (2) the required expertise and access to facilities are limited and (3) assessment is rarely performed in a spatial context.

A device that provides a computational means of tracking EEG brain maturation in preterm neonates, allowing comparison of the recorded and expected EEG maturation, would be a useful tool for clinicians in the NICU (Scher, 1997). Quantitative analyses have suggested a wide variety of signal properties, estimated from automated segmentations of the EEG and measurements of spectral power, amplitude and connectivity, that correlate with MA (Holthausen et al., 2000; Niemarkt et al., 2011; O'Reilly et al., 2012; Koolen et al., 2014; Meijer et al., 2014; Murphy et al., 2015; Saji et al., 2015; Schumacher et al., 2015). These analyses provide a candidate feature set for use in an automated EMA estimator in the very and extremely premature neonate.

In the present work, we developed an "EMA estimator" for preterm neonates, with appropriate EEG for GA, based on automated analysis of the EEG. We used a combination of well studied features that have been shown to correlate with MA extracted from different segments of the EEG recording. The performance of our EMA estimator was then evaluated on a relatively large database of preterm neonates to provide proof of concept evidence for the design of a novel automated EEG maturity index.

2. Method

2.1. Database

2.1.1. Subjects

A database of EEG recordings from 49 preterm neonates with appropriate EEG for GA was used to develop the automated EMA estimator. Neonates with a range of GA from 23 weeks plus 3 days to 32 weeks plus 0 days (164–224 days) were included in the database. The distribution of GA in the database is shown in Fig. 1(A); the mean GA was 28.6 weeks (198 days) with a standard deviation of 16 days. Neonates were enrolled for EEG monitoring from the NICU of the Cork University Maternity Hospital, Ireland from January 2009 to October 2011. Approval for the study was obtained from the Clinical Research Ethics Committees of the Cork Teaching hospitals, Ireland. Written, informed consent was received from at least one parent of each neonate included in the study.

2.1.2. EEG recording

Multi-channel, conventional video-EEG recording was commenced on enrolment (within 72 h of birth) and continued for up to 3 days. A Nicolet One EEG machine (Natus Medical Inc., Pleasanton, CA, USA) was used to acquire the EEG. An array of 10 scalp electrodes were placed according to the International 10–20 system of electrode placement modified for neonates: frontal (F3, F4), central (C3, C4, Cz), temporal (T3, T4), occipital (O1, O2), and a reference. A bipolar montage of 8 channels was used in this study: C4–O2, C3–O1, C4–T4, C3–T3, C4–Cz, Cz–C3, F4–C4, F3–C3. Electrode to scalp impedance was maintained below 5 kΩ when possible. EEGs were recorded with a sampling frequency of 256 Hz. After each EEG was recorded, all identifiable patient information was removed from the recording and the EEG was stored with a unique study number.

2.1.3. EEG review

The EEGs were examined by an experienced neonatal neurophysiologist (GBB) and were included if the EEG was judged to be appropriate for MA (André et al., 2010; Aminoff, 2012) and no clear abnormalities were present on the EEG (Watanabe et al., 1999; André et al., 2010). This resulted in the inclusion of the EEG recordings of 49 out of a possible 80 preterm neonates. The EEG recordings from these neonates were then segmented into three, hour long epochs (147 epochs in total) that were predominantly free of significant artefact.

2.1.4. MA assignment

The EMA estimator was developed with the aim of minimising the error between the EMA and GA. The GA was assigned using the best obstetric estimate, an estimate based on the mother's report of the first day of their last menstrual period (LMP) as well as ultrasound (US) assessment at approximately 12 weeks GA (Engle et al., 2004). The LMP was used as the primary method of attributing a GA unless there was significant (greater than 7 days) deviation between reported LMP and US assessment at which point the US date was used. For analysis, we considered this definition of GA as the MA because the EEG was recorded so close to birth; the median postnatal age of EEG recording was 15 h (interquartile range, IQR: 6–19). More specifically, we assumed that GA was approximately post-menstrual age (PMA) which is a biased estimate of MA, see Fig. 1(B). This minimised any confounding effects from differences between intra-uterine and extra-uterine maturation on the EEG (Nunes et al., 2014; Shany et al., 2014).

2.2. Automated EEG analysis

The automated analysis of the EEG was based on the extraction of features or characteristics of the EEG that have been shown to correlate with MA. These features include spectral power, inter-hemispheric synchrony and inter-burst interval (Aminoff, 2012). Example epochs of preterm EEG are shown in Fig. 2. These features were extracted from segments of EEG that relate to underlying physiological activity. The segmentation of the EEG was based on the model of preterm EEG proposed by Vanhatalo and Kaila (2006), see Fig. 2(C) in the text and Fig. 3 in Vanhatalo and Kaila (2006) for more details. During early brain development, cortical (EEG) activity consists of unique intermittent activity that is considered crucial for brain maturation. This activity is readily observed in the EEG as spontaneous activity transients (SAT), which alternate with periods of gradually increasing continuous cortical activity (inter-SAT). The intrinsic properties of these two