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The suppression curve as a quantitative approach for measuring brain maturation in preterm infants

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HIGHLIGHTS

- We apply the suppression curve for automated detection of maturational changes in multichannel preterm EEG.
- The suppression curve reflects the decrease in EEG discontinuity with advancing postmenstrual age in healthy preterm infants.
- Interburst intervals values are calculated automatically and correlated with postmenstrual age.

ABSTRACT

Objectives: We apply the suppression curve (SC) as an automated approach to describe the maturational change in EEG discontinuity in preterm infants. This method allows to define normative values of interburst intervals (IBIs) at different postmenstrual ages (PMA).
Methods: Ninety-two multichannel EEG recordings from 25 preterm infants (born $\leqslant$32 weeks) with normal developmental outcome at 9 months, were first analysed using the Line Length method, an established method for burst detection. Subsequently, the SC was defined as the 'level of EEG discontinuity'. The mean and the standard deviation of the SC, as well as the IBIs from each recording were calculated and correlated with PMA.
Results: Over the course of development, there is a decrease in EEG discontinuity with a strong linear correlation between the mean SC and PMA till 34 weeks. From 30 weeks PMA, differences between discontinuous and continuous EEG become smaller, which is reflected by the decrease of the standard deviation of the SC. IBIs are found to have a significant correlation with PMA.
Conclusions: Automated detection of individual maturational changes in EEG discontinuity is possible with the SC. These changes include more continuous tracing, less amplitude differences and shorter suppression periods, reflecting development of the vigilance states.
Significance: The suppression curve facilitates automated assessment of EEG maturation. Clinical applicability is straight forward since values for IBIs according to PMA are generated automatically.

1. Introduction

Despite cardiorespiratory advances in perinatal and neonatal intensive care, premature infants are still at high risk for neurological disabilities (Aarnoudse et al., 2009; Back and Miller, 2014; Larroque et al., 2008; Mwaniki et al., 2012). Early identification of at risk infants can improve short-term neuroprotective measures, and can ameliorate supportive measures in future life. Intensive brain monitoring in this vulnerable period of care, can help to

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identify the influence of various endogenous and exogenous disturbances on cortical activity and maturation (Chau et al., 2013; Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010; Victor et al., 2005b; Wikström et al., 2008).

Early cortical brain activity alternates between two activity modes. Periods of relative quiescence (interburst intervals) are interrupted by spontaneous activity transients (SATS or bursts) (Tolonen et al., 2007; Vanhatalo and Kaila, 2006). Bursts and interburst intervals (IBIs) will change with development and are influenced by medication as well as brain lesions (Hellström-Westas and Rosén, 2005; Iyer et al., 2015; Malk et al., 2014). Discontinuous activity (tracé discontinue) is the characteristic EEG pattern below 30 weeks postmenstrual age. Gradually, the electroencephalographic patterns evolve into a more continuous pattern (tracé continue) as a marker of maturation towards term age (André et al., 2010; Hayakawa et al., 2001; Scher, 1996; Vecchierini et al., 2003). Abnormal discontinuity for age (also referred as IBI duration) is the most studied feature in the preterm infant, associated with cerebral pathology, immaturity and adverse neurological outcome (Biagioni et al., 1994; Conde et al., 2005; Holmes and Lombroso, 1993; Menache et al., 2002; Wikström et al., 2012). However, accurate outcome prediction based on one single parameter may not be robust enough due to both physiological and technical shortcomings, and therefore, additional objective maturational parameters would fill the gap. Brain function can be transiently or permanently disturbed by various factors. To understand better physiological and pathological maturational processes in the preterm brain, continuous, consecutive and multichannel EEG measurements are essential. However, visual EEG interpretation requires expertise, and there are no standardized classification methods. A quantitative analysis of EEG activity, including automated analysis of selected maturational features of cortical function, would create a more objective and accurate classification scheme for preterm EEG.

Different burst detection algorithms for multichannel EEG are described in the literature (Jennekens et al., 2011; Koolen et al., 2014a; Murphy et al., 2015; Palmu et al., 2010). These studies were intended to improve algorithm performance and compared with interobserver agreement. Based on these automated algorithms, a possibility has been opened to study the developmental changes in the level of EEG discontinuity, and this without human intervention. Niemarkt et al. (2010) tested the maturational trend with an interburst/burst ratio algorithm in 18 healthy preterms, however this study used only one bipolar EEG signal (C3–C4). No further studies have been performed on a larger dataset with consecutive, multichannel EEG recordings to verify the performance of any of these algorithms to assess global maturational changes in the discontinuous EEG pattern.

We apply a method, which quantitatively describes the maturational changes in EEG discontinuity in preterm infants with normal neurodevelopmental outcome at the corrected age of 9 months. This quantitative metric, the suppression curve, uses a single feature, the Line Length (LL). It has been shown in previous work to accurately detect high activity epochs (burst) and suppressed parts (IBIs) in long EEG recordings (Koolen et al., 2014a). In the present study, we want to assess whether the global developmental changes in the level of discontinuity, detected by the suppression curve, are robust enough to use it as a maturational feature. Second, we will improve the clinical applicability by presenting age-specific values for interburst intervals.

2. Methods

2.1. Data acquisition

The study was performed at the Neonatal Intensive Care Unit of the University Hospitals of Leuven, Belgium during the period from February 2013 to September 2014 and approved by the Ethics Committee of the University Hospitals of Leuven, Belgium. All preterm infants with gestational age (GA) $\leqslant$32 weeks were eligible to enter this EEG study. Preterm infants were consecutively enrolled in the study after informed parental consent. The main dataset consisted of 149 recordings in 41 infants (GA $\leqslant$ 32 weeks) and all included infants had at least 2 consecutive recordings to assess brain development. From this larger dataset, 25 premature infants were retrospectively selected based on strict inclusion criteria: (1) normal neurodevelopmental outcome score at 9 months corrected age (Bayley Scales of Infant Development-II, for mental and motor function >85), (2) no use of any sedative or anti-epileptic medication during EEG registration and (3) the absence of a severe cerebral lesion (normal cerebral ultrasonography or intraventricular hemorrhage (IVH) grade $\leqslant$II, no periventricular leukomalacia or ventricular dilatation >p97).

2.2. EEG monitoring

The first EEG measurements were obtained as soon as the infant was clinically stable, between the first and the third week of life and then one EEG recording every 2 weeks up to transfer or discharge at home. These time points are a compromise between the accuracy of an identification of developmental features and the minimization of drop outs of the very preterm and critical sick newborns in the initial postnatal period. All infants underwent at least two and a maximum of six EEG recordings, depending on their stay at our NICU, resulting in 92 recordings, ranging from postmenstrual age (PMA, gestational age + postnatal age) 27–42 weeks.

The optimal recording time we aimed for was 4 h to record multiple vigilance states: mean 381 min (median (IQR) 254 min (219–316) min, minimum 115 min, maximum 1558 min). Feeding and care were carried out according to normal routine of the NICU, preferentially before and after the EEG measurement. Kangaroo Care was allowed and encouraged during the recordings as part of the application of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP). Occasionally, in some infants, minimal duration of EEG recording was reduced due to clinical contingencies, but a complete sleep cycle was always acquired, in according to neonatal EEG surveillance guidelines (André et al., 2010).

All EEG measurements were recorded at 250 Hz, with a filter bandwidth of 0.27–70 Hz and 8 electrodes (Fp1, Fp2, C3, C4, T3, T4, O1, O2) placed according to the 10–20 standard locations and reference electrode Cz (BRAIN RT, OSG equipment, Mechelen, Belgium). Polygraphic monitoring included a channel for respiratory activity, electrocardiogram and oxygen saturation.

2.3. Automated analyses

Preprocessing the data involved applying a 50 Hz Notch filter and a 1–20 Hz band pass filter to capture the interesting burst information present in this frequency range, no additional artefact correction was performed on these recordings. Multichannel EEG recordings in unipolar mode were further analysed using the Line Length method, which includes the characteristics of both amplitude and frequency content, and serves for automatic burst detection (Koolen et al., 2014a). In the first part of the algorithm, each EEG channel is divided into consecutive segments of 1 s (with an overlap of 0.12 s). Next, the Line Length value is calculated for each 1 s segment and then normalized by dividing through the total line length of a 150 s window. Normalization is necessary to average out the effect of amplitude differences between EEG channels due to different electrode placement. After normalization, the median value over all 8 EEG channels is obtained for each segment: L_n.