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Original article

Drug effects on endogenous brain activity in preterm babies

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Abstract

Background: Animal experiments have suggested that the quality of the early intermittent brain activity is important for shaping neuronal connectivity during developmental phase that corresponds to early prematurity. This is a pilot study aiming to assess whether spontaneous activity transients (SAT) in the early preterm babies are affected by drugs that are routinely used in neonatal intensive care. *Methods:* We collected retrospectively seventeen EEG recordings (15 babies, conceptional age 26–33 weeks, no brain lesions) that were divided into groups according to drug administration at the time of EEG: phenobarbital, fentanyl, theophylline, and controls. SATs were extracted from the EEG for further analysis with several advanced time-series analysis paradigms. *Results:* The visual appearance of SATs was unaffected by drugs. Phenobarbital reduced the total power of the SAT events. Both fentanyl and phenobarbital reduced the length of SATs, and enhanced the oscillations at higher frequencies. Theophylline reduced the oscillatory activity at middle frequencies during SAT, but enhanced oscillations at higher frequencies during time-period prior to SAT. *Conclusions:* Our findings suggest, that (i) all drugs examined affect brain activity in ways that are not seen in the visual EEG interpretation, and that (ii) both acute and long term (i.e. developmental) effects of these drugs on brain may warrant more attention as a part of optimizing preterm neurological care.

Keywords: Neonatal EEG; Preterm EEG; SAT; iSAT; Drug therapy

1. Introduction

Increasing number of ELBW (extremely low birth weight) premature babies are surviving and the focus of attention in neonatal care is now shifting to their neurological outcome, because several studies on ex-preterm babies have reported later neurocognitive problems in NICU (neonatal intensive care unit) graduates [1,2]. It is now generally accepted that conditions associated with prematurity, or even treatment during NICU may account for the subsequent neurocognitive sequelae [3–10].

The time of NICU stay of ELBW babies corresponds to the early third trimester of pregnancy. This period coincides with the growth of long-range brain connections, which are instrumental in brain's ability to carrying out high cognitive functions. Defects in these structures (i.e. white matter) are assumed to underlie neurocognitive problems in ex-premature babies

Abbreviations: EEG, electroencephalography; aEEG, amplitude integrated electroencephalography; ELBW, extremely low birth weight; SAT, spontaneous activity transient; iSAT, inter-SAT; F-C, fronto-central derivation; NICU, neonatal intensive care unit; TF, time–frequency analysis; RMS, root mean square; F, fentanyl; PH, phenobarbital; TP, theophylline; GABA, γ-aminobutyric acid; CO_2, carbon dioxide

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[11–13]. Interestingly, growth of brain connectivity at this age is believed to be guided by the early form of brain activity [14–18] which is seen in the EEG as intermittent bouts of activity, also called spontaneous activity transients [14,19,20].

Neonatal EEG is a powerful, non-invasive tool for detecting these events, especially after little technical modifications that enable visualization of the whole signal [22]. While the earlier EEG studies on drug effects on neonatal EEG have focused on the 'changes in the EEG continuity' [23–26], a large body of more recent work in basic science [14,21,27,28] and in human neonates [29,30] suggests that the developmentally meaningful effects should be searched from the early intermittent events rather than the somewhat ill-defined 'overall continuity'. Our group has recently coined the term spontaneous activity transient (SAT), which refers to the family of intermittent EEG events in the preterm and early fullterm EEG that have previously have previously been called by a number of inherently ambiguous terms, such as delta brush, burst or temporal theta (for details, please see Table 1 in Ref. [21]). In this context, it is intriguing that: (i) several experimental studies have shown a high sensitivity of the SAT-type activity to several environmental modulators (e.g. drugs) [31,32], (ii) this activity is necessary for a normal brain [14,21], and (iii) human preterm babies are exposed to a considerable load of such treatments during the early weeks of NICU stay [5]. There are as yet no studies that would assess whether common drug treatments affect the intrinsic characteristics of the early intermittent brain activity. This study was set out as a pilot study to see whether potential effects of drugs on SAT activity can be seen when analysed from a retrospectively collected dataset.

2. Materials and methods

We studied seventeen EEG recordings from fifteen preterm infants at 26–33 weeks of conceptional age, with no lesions detectable by ultrasound (for details of subjects, see Table 1). Recordings were made for clinical purposes at the neonatal intensive care unit of Helsinki University Central Hospital. The EEG recordings used in our study were identified retrospectively from the department archives, starting from a search of all preterm EEGs of this age group during years 2001–2003, and subsequently excluding those babies with a detected ultrasound lesion ($n = 5$ exclusions). All recordings were collected with a NicOne EEG device (M40 amplifier, Cardinal Healthcare, Madison, WI, USA; sampling rate 256 Hz; 10 s time constant) using a standard International 10–20 electrode system modified for neonates (eight EEG electrodes and polygraphic channels). The original recordings were approximately 1 h long, and included at least one cycle of quiet sleep or a clear epoch of 'trace discontinue'.

The patient records were reviewed for the following data: the conceptional age, clinical symptoms indicating the EEG recording, specific neurological symptoms, medications during the time of recording, ultrasonographical findings as well as possible respirator treatment during recording and diagnosis. The recordings were then divided into four drug-treatment groups: phenobarbital ($n = 4$), fentanyl ($n = 2$), theophylline ($n = 9$), and controls ($n = 2$). Ketamine was also considered to be a drug of interest in this study. Since we could only find one recording with ketamine treatment without ultrasound lesion, it was excluded from the study. In this retrospective data, no drug levels were available, unfortunately. Patients did not receive other brain-acting drugs at the same time, and no major ultrasound abnormalities were seen. The patients may have received other drugs (e.g. antibiotics, vitamins, or calcium supplementation) that are not expected to affect brain activity. All drugs were given for clinical indications, which were usually respiratory care (theophylline), seizure treatment (phenobarbital) or pain treatment (fentanyl). See Table 1 for details of the patient group. This study was approved by the Ethics Committee of Hospital for Children and Adolescents, Helsinki University Central Hospital.

2.1. EEG analysis

Twenty minutes of artefact free EEG-recording was included into the analysis from each patient. The 'continuity of EEG' was first quantified by visually marking the SATs (equivalent to 'bursts', see e.g. [29,39], and 'inter-SAT' periods (equivalent to 'inter-burst interval'). We collected a database of the first 5–8 visually identified SAT events from each recording. The SATs were extracted as 12-s-long epochs and centered to the visually identified onset of SAT, which thus contained 6 s of inter-SAT (i.e. 6-s of signal prior to SAT), as well as the first 6-s after SAT onset. The EEG signal was low pass filtered at 30 Hz. No high pass filter was used in the review or analysis software (i.e. signal was filtered by the amplifier only). The right centrooccipital (C4-O2) derivation was used for further analyses. Comparison of the incidence or quality of the SATs showed no difference between left and right, hence we chose to use right side only. Our recent study [33] has shown that visual marking of clear SAT (i.e. bursts) epochs is reliable, hence no formal assessment was made about inter- or intrarater reproducibility.

Analysis of the SAT waveforms was done by following methods (for details of rationale behind this analysis, see also [34]: first, the raw signal was averaged and the variation of the waveform was analyzed by standard deviation (see Fig. 2). Second, we assessed the magnitude of the signal by calculating its amplitude envelope with Hilbert transformation, which is a standard