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Short Communication

Feasibility of High-Density EEG Mismatch Negativity Paradigm for Assessing Phoneme Processing in Preterm Infants

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Abstract

Owing to excellent time resolution and optimized spatial resolution related to increased number of recording electrodes, high-density electroencephalography allows localization of the sources of cortical activities evoked by specific stimulation. Here we evaluate the feasibility of a high-density EEG mismatch negativity of event-related potentials approach involving auditory cortical processing of phonemes in newborn infants born preterm (28 and 31 weeks' gestation) in a routine clinical set-up. We recorded 64-channel EEG at term age. We identified the classical evoked components and found the amplitude of P1 and N2 to be significantly higher in the deviant (target) condition than in the standard condition. We analyzed the signals using standardized weighted low-resolution brain electromagnetic tomography (swLORETA) on theta, alpha, beta and gamma frequency bands. High theta and alpha power spectrum appeared in the superior and the middle temporal gyrus in following the standard and target stimulation. Additionally, delayed frontal area recruitment was seen after the target stimulation. Beta-gamma event-related synchronization was observed in BA10, BA46 and BA10, more markedly following target than standard stimulation. This suggests ability for auditory memory and change detection in neonates and shows early results in source localization. This approach paves the way for increased understanding of central processes involved during early neurological development. It may contribute to documenting physiological and deviant neurophysiological organization in the wider context of early diagnosis of features associated with preterm birth.

Introduction

Preterm infants are at risk for neurodevelopmental disabilities, including cerebral palsy, sensory impairment, language impairment, behavioural problems and intellectual disability. Yet, early diagnosis and detection of specific impairment remain difficult. In the last few years, advanced neuroimaging techniques, such as those based on magnetic resonance imaging, have improved assessment of the brain maturation in preterm infants and eventual abnormalities. In complement to these structural approaches, high-density electroencephalography (EEG) has opened new non-invasive avenues for assessing brain activities along specific neural pathways. Thanks to excellent time resolution and optimized spatial resolution owing to increased number of recording electrodes over the scalp, high-density EEG allows localization of the sources of locally-synchronous activities in the cerebral cortex. Event-related potentials (ERP) recorded from scalp channel EEG data can be analysed in the time domain and in the frequency domain to estimate the spectral power within a number of frequency bands correspondingto the neural processing of a given stimulation. Pre-attentive detection of changes in stimuli, studied by mismatch negativity [1], is known to emerge early in maturation compared to other ERP component [2]. Here, we test the feasibility of designed a mismatch negativity ERP paradigm of high-density EEG in order to assess auditory cortical processing of phonemes in newborn infants born preterm in a routine clinical set-up.

Methods

Newborn infants born before 32 weeks' gestation were eligible for the study. Exclusion criteria were craniofacial congenital malformations, known genetic syndrome, clinical evidence of neonatal encephalopathy, ultrasound evidence of intraventricular hemorrhage or cystic periventricular leukomalacia and abnormalities in waveform, latency or threshold in brainstem auditory evoked potentials. For this report, 4 newborn infants (3 girls, 1 boy) were included. Median gestational age was 30 week (range 28 to 31). Median birth weight was 1254 g (range 725 to 1608).

Recordings were performed at term age (± 1 week) while infants were asleep. High-density EEG was recorded using the ActiveTwo system (Biosemi) with size-adapted head caps with 64 sintered active Ag/AgCl electrodes positioned according to the 10/20 system. Sampling rate was 2048 Hz. For ERP stimulation, we used an oddball paradigm in which a series of repeated synthesized short [da] sounds were used as standard stimuli (85%) and randomly occurring longer [dɑ] sounds were used as deviant, or target stimuli (15%). The stimuli were delivered binaurally. Summed ear lobe potentials were used as reference. We used a 0.2 Hz high-pass filter and a 48-52 Hz notch filter.

In order to determine whether responses differed significantly from each other in the short [da] sounds and long [dɑ] sounds conditions, we performed Sudent's t-test using a MATLAB script on averaged trials of each subject for each condition. For amplitude calculation, we indexed the difference between the baseline (over 100 msprestimulus) and the peak amplitude for P1 and N2 evoked component. For latency calculation, we indexed the difference between stimulus onset and the lag to the highest amplitude for each considered component. For the Student's t-test analysis, we used epoch extending from 100 ms prior to the onset of stimulus delivery to 1,000 mspoststimulus. We considered significance when p was lower than 0.05.

We then applied the standardized weighted low-resolution brain electromagnetic tomography (swLORETA) mathematical and statistical approach in order to identify source location for the evoked responses. This distributed source method considers a large search space (all the brain cortex) instead of a few selected dipoles. The advantage of swLORETA with respect to the original LORETA is that it provides a statistical non-parametric map which uncovers which brain locations (or voxels population) are significantly activated with respect to the rest of brain locations (or neighboring voxels). Then it is possible to get a significant estimation of cortical activation even for single subjects as the comparison is made between more than one thousand voxels in the same brain cortex. For this analysis, segments of EEG were analyzed using epoch lengths extending from 900 ms prior to the onset of stimulus delivery to 900 ms thereafter. EEG signals were analyzed using swLORETA on discrete frequency bands (alpha, beta and theta), which allows accurate reconstruction of surface and deep current sources in simulated data even in the presence of noise [3].

The study protocol was approved by the local ethics committee and informed consent was obtained from the parents.

Results

Consistent auditory responses were identified in all infants, showing the feasibility of the recording approach. Responses consisted of the classical P1 component at around 300 ms (or P300) followed by the N2 component around 600 ms (Fig. 1). The mean amplitude of the P1 component was maximal at the level of electrode FCz (corresponding to electrode B15 on 64 channels Biosemi layout) on brain topographies. On this electrode, response to short [da] sounds showed average amplitude of 13.1 µV (standard deviation 5.2) and average latency of 287 ms (standard deviation 94) for the P1 component, and average amplitude of -1.1 µV (standard deviation 0.9) and average latency of 611 ms (standard deviation 72) for the N2 component. Responses to the deviant (target) stimulation showed average amplitude of 43.4 µV (standard deviation 13.6) and average latency of 382 ms (standard deviation 78) for the P1 component, and average amplitude of -1.8 µV (standard deviation 0.3) and average latency of 890 ms (standard deviation 158) for the N2 component. Student's t-test confirmed the significant difference in amplitude between the standard and the deviant condition. Though mean latencies were higher in the deviant condition, this difference was not significant.

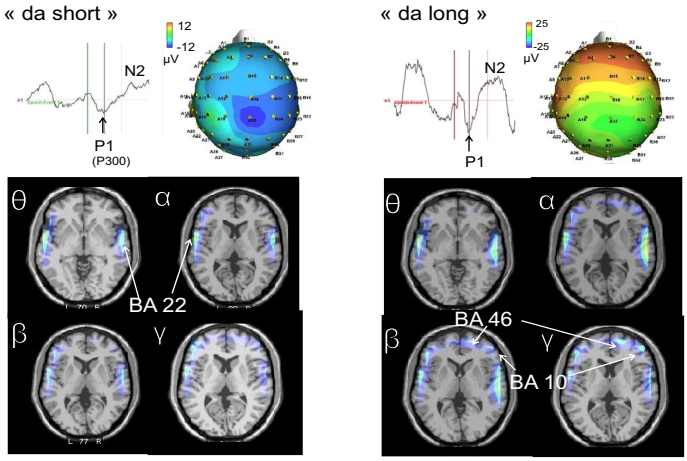

Figure 1. Time-frequency sources of the P1 (P300) auditory component.
On the left short [da] sounds or standard stimulation, on the right long [dɑ] sounds or target stimulation. In the upper part, on the left for each condition, event-related potential with P1 (P300) precedent N2 component. Note bigger P1 amplitude for the target stimulation. In the upper part on the right, for each condition,

scalp potential distribution at the P1 latency. In the lower part of both conditions, time-frequency sources in theta, alpha, beta and low gamma frequency bands. Note the addition of frontal areas (BA46, BA10) for the target stimulation.

We also found that the quality of the obtained EEG signals allowed the application of swLORETA sources modeling. swLORETA analysis showed high power spectrum in the theta and alpha bands in the superior and the middle temporal gyrus in both conditions, namely target stimulation or long sound, and standard stimulation or short sound). Moreover, we observed additional recruitment in the frontal area following the target stimulation in the time window around the P1, i.e. from 0.066s to 0.400s. In the beta-gamma frequency band, event-related synchronization was present in the medial, inferior and superior frontal gyrus (BA10, BA46 and BA10). This event-related synchronization was stronger following the target than the standard stimulation.

Discussion

These results support the feasibility of recording and analyzing mismatch negativity ERP using high-density EEG (64 channels) in newborn infants born preterm in a routine clinical set-up in order to approach auditory cortical processing of phonemes. Given the limited sample in this study, the neurophysiological significance of our findings should be regarded as indicative at this stage and call for future recording and analyses, which can be carried out using this method. Our present findings of auditory ERP elicited in response to a change in the stimulus in the newborn infants illustrate discrimination between similar but different phonemes at term age in infants born prior to 32 weeks' gestation. This suggests ability for both auditory memory and detection of change1. The high-density active electrodes setting allows precise ERP voltage mapping at scalp level and estimation of the cortical sources accounting for it. The generated source models indicate strong dipoles for beta-gamma rhythms in frontal cortical areas. These sources will need to be confirmed in larger samples. Considering the statistical demands of the swLORETA method, spatial pattering of sources underlying the oscillatory brain rhythms showed consistence between alpha, beta and theta range frequency bands. Although gamma oscillation has been related to the general perception of auditory signals [4,5], its role in the P300 component remains unclear. It has been suggested that power differences in the gamma frequency band are dependent on the clinical situation, while delta and theta synchronization are directly related to the amplitude of the P300 component, irrespective of the clinical diagnosis [6]. Interestingly, in infants, gamma band power is known to indicate preferential processing of native over foreign language rhythm and phonemic contrast [7]. In adults, at the scalp level, target stimulation of the auditory P300 component has been related to frontal theta activity, decrease in alpha and beta activity over the posterior and central regions, and decrease gamma activity over the central region [8]. Our study focused on the cortical sources that express perturbation in spectral power during the P300 auditory component. It has, however, been suggested that comprehensive study of spectral dynamics during the discrimination of auditory targets also requires the analysis of phase synchronization [8]. Indeed, in healthy adult subjects gamma synchrony has been found to predict the amplitude of the P300 component [9].

In sum, this approach can be applied in the clinical setting. It may provide valuable tools for better understanding the central processes that are involved during early neurological development. It may contribute to documenting physiological and deviant neurophysiological organization in the wider context of early diagnosis of features associated with preterm birth.

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