35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

EEG source localization in full-term newborns with hypoxic-ischemia

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Abstract— **The aim of this study was to evaluate EEG source localization by standardized weighted low-resolution brain electromagnetic tomography (swLORETA) for monitoring of full-term newborns with hypoxic-ischemic encephalopathy, using a standard anatomic head model. Three representative examples of neonatal hypoxic-ischemia were included. The method was validated with MRI data. Hypoxic-ischemic areas, visible on MRI, correlated well with swLORETA current density distributions. In addition, neonatal seizure activity may be localized. The calculated current density distributions provide easy-to-interpret localized information about neonatal brain function, which may enable detailed longitudinal monitoring and potential assessment of treatment efficacy.**

I. INTRODUCTION

Perinatal asphyxia is characterized by different degrees of hypoxia-ischemia during labor or delivery, with the outcome depending on the severity of the underlying neuronal damage. Currently, MRI-based techniques, including diffusion-weighted imaging, and longitudinal electroencephalography (EEG) monitoring, including bed-side amplitude-integrated EEG (aEEG), are used as a predictor of adverse neurodevelopmental outcome [1], [2].

Source localization methods of EEG offer an opportunity to combine assessment of brain function with anatomical localization. EEG source localization models intracerebral sources responsible for potentials observed on the scalp by estimating current dipoles in a volume conductor model of the head.The LORETA (low resolution brain electromagnetic tomography) method determines the electric current density distribution inside the brain volume by solving the inverse solution of the electric potentials as measured by EEG [3]. The consistency of LORETA with physiology and localization has been validated for numerous normal and pathological conditions [4]. The source localization method was further improved with the advent of standardized weighted LORETA (swLORETA) [5]. Although EEG source localization is widely used in adults, it is not frequently used in newborns because of technical difficulties such as lack of data concerning the newborn skull [6].

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The objective of this study is to evaluate the feasibility and performance of EEG source localization by swLORETA for monitoring full-term newborns with HIE, using a standard anatomic head model. The method was compared to observations from MRI data.

II. MATERIALS AND METHODS

A. Study population

Three neonates with perinatal hypoxic-ischemia (umbilical cord pH $\leq$ 7.10, 5 min Apgar $\leq$ 6, advanced resuscitation), constituting representative examples encountered in our neonatal intensive care unit, were selected. Two infants suffered severe HIE and one suffered cerebral infarction by occlusion of the middle cerebral artery (MCA).

B. EEG data acquisition

Digital EEG recordings were acquired (NicoletOne; Viasys Healthcare, Conshohocken, PA, USA). After skin preparation, twenty-one Ag/AgCl cup electrodes filled with a conductive paste were placed on the scalp according to the international 10-20 montage system. Electrode impedance was below 10 kΩ. The digital EEG signal was sampled at 512 Hz and stored on hard disk.

C. MRI data acquisition

MRI images were acquired on a 1.0-T MRI unit (Gyroscan; Philips Medical Systems, Best, the Netherlands), with a standard birdcage head coil. The imaging protocol is described by Van Pul *et al*. [2]. In short, MRI consisted of T_1-weighted spin-echo (repetition time TR: 568 ms, echo time TE: 18 ms), T_2-weighted fast spin-echo (TR/TE: 4381/120 ms), and inversion-recovery (TR/TE: 3436/18 ms, inversion time: 400 ms). The protocol also included diffusion-weighted imaging (DWI) with single-shot echo-planar MRI. In the neonatal brain, 20 adjacent transverse slices were recorded with 3595 ms/82 ms and a voxel size of 1.56 x 1.56 x 3 mm. Three b-values (0, 400 and 800 s/mm^2) were used to calculate the apparent diffusion coefficient (ADC). MRI scans were performed within 24-hours from EEG, and were compared to swLORETA source localization maps.

D. Data analysis

The swLORETA method calculates a 3D current density distribution as a solution to the inverse problem of determining the sources of scalp potentials as measured by EEG [5]. This problem has an infinite number of solutions. To limit the number of solutions, maximum synchronization of neighboring neuronal structures is assumed [3]. The optimal current density is estimated from the minimum norm solution. To

solve the inverse problem, an anatomical head model is obtained by segmentation of MRI data. This study was performed using the ASA software package (ANT Software, Enschede, the Netherlands).

Due to low spatial resolution, small scan volume and low image contrast of neonatal MRI scans as acquired within routine clinical protocol, a standard adult T_1-weighted MRI dataset was used for construction of the swLORETA head model (Colin 27, MNI) [7]. This model was created through segmentation of MRI data, resulting in brain, skull and scalp volumes. The compartments had conductivity values of 0.33, 0.0042 and 0.33 S/m, respectively [6]. We used a 0.14 mm mesh with an additional 0.1 mm scalp-rendering for the scalp, and a 0.16 mm mesh for skull and brain. The brain volume of the model consisted of 5902 dipoles at 7 mm isotropic spatial resolution.

The EEG data were high-pass filtered at 0.53 Hz, low-pass filtered at 30 Hz and a 50 Hz notch filter was applied in ASA. The complete EEG recordings, which varied in duration from 25 to 40 min, were subjected to source analysis. Data were divided into non-overlapping 2-s segments to reduce computational load. The swLORETA analysis of EEG data with the anatomical head model resulted in a statistical estimate of current density in each voxel. Results were subsequently averaged over all 2-s segments, and the average current density distribution was displayed within a frame of reference based on MRI images.

III. RESULTS

A. Case 1 - HIE

A full-term neonate was born after an emergency caesarean section because of a placental abruption. Apgar scores were 5 and 6 at five and ten min after birth. Umbilical arterial pH was 6.80. The neonate developed multi-organ failure and HIE with signs and symptoms of neonatal seizures, which were treated with anti-epileptic drugs. A 20-s segment of the EEG at day 6 of life is presented in Fig. 1, with a brief neurophysiological description in the legend. MRI at day 6 of life (Fig. 2) showed extensive damage of the cortical areas, basal ganglia, optic radiation and white matter, consistent with severe HIE. Diffusion abnormalities were observed in corpus callosum and splenium.

The current density distribution resulting from swLORETA analysis of the 35-minute EEG recording showed that maximum current densities were located in the left and right parietal, temporal and occipital lobes (Fig. 2). Current density probability in the central area and frontal lobe was lower. Hence, MRI abnormalities in the basal ganglia and frontal areas correlated with low swLORETA intensity, indicating loss of EEG in this area. The MRI examination also showed damage in the optic radiation and occipital white matter. These abnormalities were not visible in the swLORETA current density distribution.

B. Case 2 - HIE

A full-term neonate was delivered by vacuum extraction, performed because of fetal distress. Apgar scores were 5 and 8 at five and ten min after birth. Umbilical arterial pH was 6.82. The neonate developed multi-organ failure and HIE with neonatal seizures, for which treatment with anti-epileptic drugs was instituted. A 20-s segment of the EEG at day 2 of life is presented in Fig. 3, with a brief neurophysiological description in the legend. MRI at day 2 of life (Fig. 4) showed in the DWI ischemic damage at the cortex (cortical highlighting), posterior limb of the capsula interna, thalamus and caudate nucleus. In addition, MRI showed generalized white matter edema and a focal medio-occipital hemorrhage in the right hemisphere.

The swLORETA current density distribution of the 40-minute EEG recording showed a region of high current density near the right frontal and temporal lobes, corresponding with the Fp_2, F_4, F_8 and T_4 electrodes (Fig. 4). The current density probability in other areas of the brain was distributed homogeneously. The right frontal and temporal hotspots in the swLORETA plot correlated with the EEG recording, showing seizure activity alternating over the left and right frontal lobe, with maximum activity in right hemisphere. MRI showed symmetric bilateral ischemic damage in the frontal lobe. Lowest activity in both the swLORETA plot and EEG recording was observed in the left parietal area. The focal medio-occipital hemorrhage visible on MRI was not observed in EEG and swLORETA data.

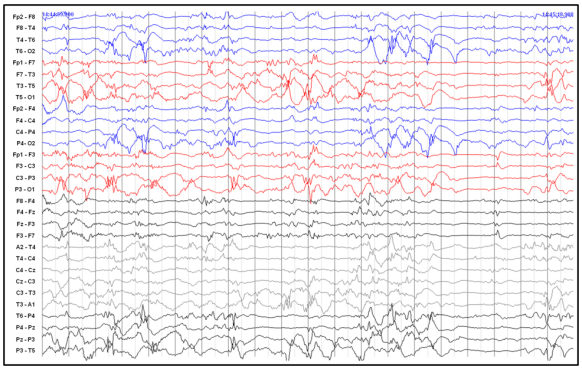

Fig. 1. Representative 20-s EEG segment of patient 1. Recording was performed at day 6 after birth and showed a discontinuous background pattern with increased inter-hemispheric asynchrony. Abnormal activity included delta brushes and rhythmic delta-activity with superimposed short bursts of spikes over the left and right temporal and central regions. No electrographic seizure activity was observed.

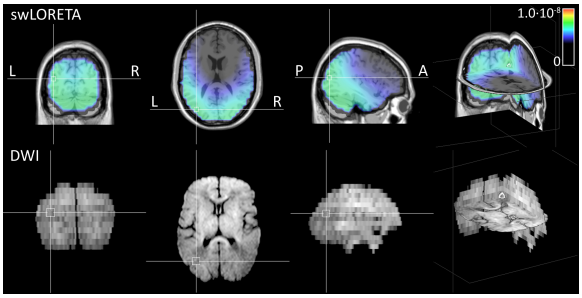

Fig. 2. swLORETA reconstruction of EEG recording with a segment length of 35 min. The color bar indicates current density probability, with red and black representing high and low probability, respectively. Note that the L-R orientation of the MRI image is changed from the international standard to facilitate comparison with the current density distribution.

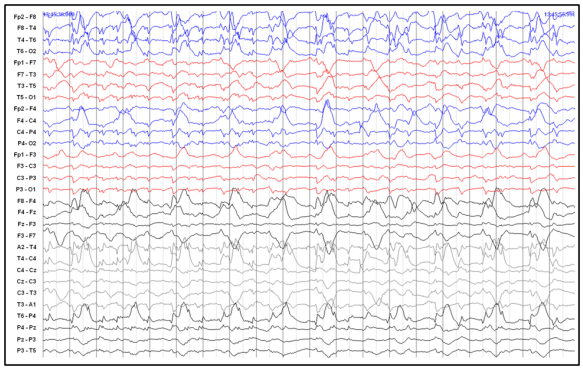

Fig. 3. Representative 20-s EEG segment of patient 2. Initially the EEG recording, performed at day 2 after birth, showed a severely depressed background pattern with continuous slow seizure activity over the frontal and temporal regions. After the administration of midazolam, the background pattern changed to burst suppression, with on average one burst in every ten seconds, often consisting of multiple spikes. The electrographic seizure activity disappeared, but short, sharp spikes over the left and right frontal regions were occasionally present during the suppression periods.

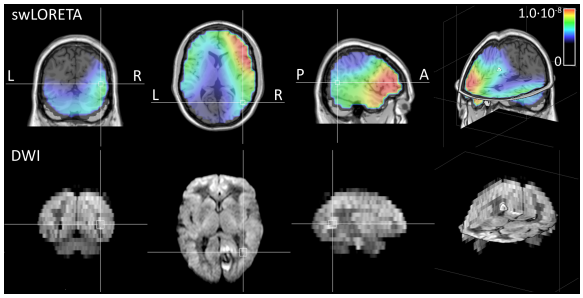

Fig. 4. swLORETA reconstruction of EEG recording with a segment length of 40 min. The color bar indicates current density probability, with red and black representing high and low probability, respectively. Note the L-R orientation of the MRI image, analogous to Fig. 2.

C. Case 3 - Stoke MCA

A full-term neonate with perfect Apgar scores after birth developed incidents of central apnea at 12 hrs of age. CT at day 1 showed a large middle cerebral artery infarction of the right hemisphere. Remarkably, the EEG showed no seizure activity. A 20-s segment of the EEG at day 5 of life is presented in Fig. 5, with a brief neurophysiological description in the legend. MRI at day 4 of life (Fig. 6) showed in the DWI large diffusion abnormalities in the right hemisphere, consistent with an occlusion of the right middle cerebral artery. An additional partial infarction in the right occipital region and agenesis of the right posterior communicating artery were observed. In addition, high signal intensities at the corticospinal tract were visible, suggesting Wallerian degeneration. Reduced diffusion was specifically observed in corpus callosum and anterior and posterior limb of the internal capsule.

The swLORETA current density distribution of the 25-minute EEG recording showed that the activity was mainly located in the left (contralateral) hemisphere (Fig. 6), while the stroke-affected region had a much lower average current density probability. Hence, stroke-induced DWI abnormalities correspond to a region of low signal intensity in the swLORETA images. The resulting regional loss of cerebral function was also evident in the underlying EEG recording.

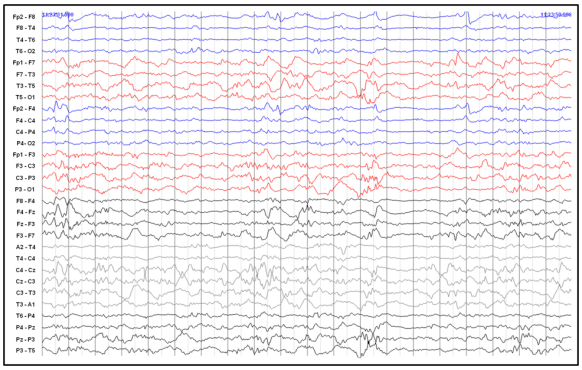

Fig. 5. Representative 20-s EEG segment of patient 3. The EEG recording, performed at day 5 after birth, showed asymmetrical background activity. On the left side, a continuous background pattern was present, mainly consisting of beta-activity and delta-activity. On the right side, background activity was depressed, while frontal sharp transients were present in a large number.

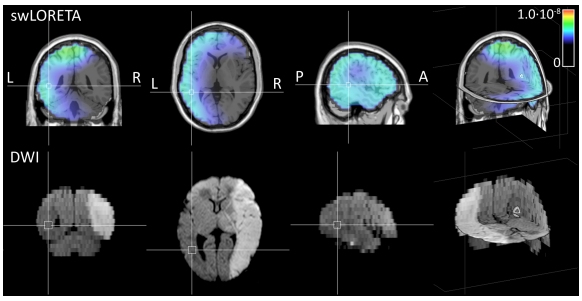

Fig. 6. swLORETA reconstruction of EEG recording with a segment length of 25 min. The color bar indicates current density probability, with red and black representing high and low probability, respectively. Note the L-R orientation of the MRI image, analogous to Fig. 2.

IV. DISCUSSION

A. Case 1 - HIE

The hypoxic-ischemic MRI abnormalities observed in the basal ganglia and frontal areas are correlated with low swLORETA signal intensity, indicating a loss of EEG sources in these areas. This finding is in agreement with Thordstein *et al*. who showed that post-asphyctic full-term neonates have reduced low-frequency EEG power compared to healthy neonates, while high-frequency power remains unchanged [8]. Our implementation of swLORETA visualizes current density distributions for the total EEG frequency spectrum, and consequently does not discriminate changes in low-frequency and high-frequency activity. Frequency decomposition of the current density distribution confirmed reduced low-frequency power in the hypoxic-ischemic regions (preliminary data, not shown).

The MRI examination also showed damage in the optic radiation and occipital white matter, which was not visible in the swLORETA images. Inder *et al*. observed a decreased spectral edge frequency following white matter damage, while the EEG amplitude remained unchanged [9]. This may indicate that swLORETA as implemented in our study is less sensitive for white matter damage. However, frequency decomposition of the current density distribution showed reduced occipital high-frequency power (not shown).

B. Case 2 - HIE

The MRI indicated frontal cortical highlighting, which may be associated with seizure activity observed in EEG and high signal intensity in the swLORETA current density distribution. The focal medio-occipital hemorrhage visible on MRI was not observed in the swLORETA images. Mirkovich *et al*. showed good correlation between the location of hemorrhagic lesions and reconstructed sources of epileptic spikes in neonates for analysis of ultra-short segments (40 ms) centered on the maximum spike value [10]. Localization accuracy was found to decrease for reconstructed sources of surrounding data segments. In our study, we averaged long segments (minutes). Hence, hemorrhagic lesion localization may be hampered. Furthermore, in our study the hemorrhage was located in the white matter, whereas in the study of Mirkovich the lesions were mostly situated in the cortex. Finally, Claassen *et al*. have shown that electrographic seizures only occur in a small percentage of patients with intracranial hemorrhage, and seizure incidence decreased with increasing distance from the cortex [11].

C. Case 3 - Stroke MCA

The large stroke-induced diffusion MRI abnormalities in the right hemisphere corresponded to a region of low signal intensity in the swLORETA current density distribution. The resulting regional loss of cerebral function was also evident in the underlying EEG recording. This finding is in agreement with Koelfen *et al*., who reported an agreement between the site of origin of EEG changes and the location of stroke in neonates [12]. These EEG changes first included focal slowing and later sharp waves or localized voltage reduction. Additionally, Thordstein *et al*. showed that hypoxic-ischemia reduced low-frequency EEG power [8]. This was supported by frequency decomposition of our current density distribution, showing reduced low-frequency power in the stroke-affected region (not shown).

D. Limitations

In this study, swLORETA calculations were performed using a generic head model based on adult MRI data, which differs from the neonatal head. Roche-Labarbe *et al*. studied the influence of different neonatal head models (varying skull thickness and conductivity, with and without fontanels) on current density distributions [6]. Higher accuracy may be expected when using a neonatal head model based on individual neonatal MRI data. However, since anticipated improvements in dipole location are small, the general representation is expected to be similar. Odabaee *et al*. showed that the existence of open fontanels may be ignored [13]. Furthermore, use of a generic head model allows bed-side monitoring at an early stage, before MRI data are available.

Source localization accuracy may decrease from assuming exact positioning of scalp electrodes [3]. For neonates, errors may be up to 15 mm [14]. However, for the swLORETA application described in this study, exact electrode positioning is of limited importance as the visualization of cerebral function is expected to be similar.

By assuming synchronicity between neighboring grid points, swLORETA determines which unique, physiologically meaningful, configuration of current sources best explains the data. This assumption is based on observations from adult subjects, and has not been validated for neonates. In our study, robustness of the swLORETA method was assessed by varying spatial resolution and sub-segment length, which had no relevant effect on dipole positions and resulting current density distributions.

V. CONCLUSIONS

This study demonstrates EEG source localization with swLORETA for monitoring of full-term neonates with hypoxic-ischemia. Hypoxic-ischemic areas visible on MRI correlate well with regions of low current density on swLORETA images. Furthermore, neonatal seizure activity, which is not visible on MRI, may be localized using swLORETA. The method presented in this study simplifies interpretation of the complex EEG signal, visualizing the current density distribution. This method preserves spatial information contained within the EEG, while compressing information in the time domain, and may provide a useful monitoring tool for bed-side visualization of cerebral function, possibly enabling detailed longitudinal monitoring and assessment of treatment efficacy.

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