Relationship of EEG Sources of Neonatal Seizures to Acute Perinatal Brain Lesions Seen on MRI: A Pilot Study

Ivana Despotovic,^{1*} Perumpillichira J. Cherian,² Maarten De Vos,^{3,4}
Hans Hallez,¹ Wouter Deburchgraeve,³ Paul Govaert,⁵ Maarten Lequin,⁶
Gerhard H. Visser,² Renate M. Swarte,⁵ Ewout Vansteenkiste,¹
Sabine Van Huffel,³ and Wilfried Philips¹

¹MEDISIP-IPI-IBBT, Ghent University, Sint-Pietersnieuwstraat 41, 9000 Ghent, Belgium

²Department of Clinical Neurophysiology, Erasmus MC, University Medical Center Rotterdam,
's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands

³Department of Electrical Engineering (ESAT) SCD-SISTA and IBBT Future Health Department, KU
Leuven, Kasteelpark Arenberg 10, 3001 Leuven, Belgium

⁴Neuropsychology Laboratory, Department of Psychology, University of Oldenburg, Germany

⁵Department of Neonatology, Erasmus MC-Sophia, Dr. Molewaterplein 60, 3015 GJ, Rotterdam,
The Netherlands

⁶Department of Pediatric Radiology, Erasmus MC-Sophia, Dr. Molewaterplein 60, 3015 GJ,
Rotterdam, The Netherlands

Abstract: Even though it is known that neonatal seizures are associated with acute brain lesions, the relationship of electroencephalographic (EEG) seizures to acute perinatal brain lesions visible on magnetic resonance imaging (MRI) has not been objectively studied. EEG source localization is successfully used for this purpose in adults, but it has not been sufficiently explored in neonates. Therefore, we developed an integrated method for ictal EEG dipole source localization based on a realistic head model to investigate the utility of EEG source imaging in neonates with postasphyxial seizures. We describe here our method and compare the dipole seizure localization results with acute perinatal lesions seen on brain MRI in 10 full-term infants with neonatal encephalopathy. Through experimental studies, we also explore the sensitivity of our method to the electrode positioning errors and the variations in neonatal skull geometry and conductivity. The localization results of 45 focal seizures from 10 neonates are compared with the visual analysis of EEG and MRI data, scored by expert physicians. In 9 of 10 neonates, dipole locations showed good relationship with MRI lesions and clinical data. Our experimental results also suggest that the variations in the used values for skull conductivity

Contract grant sponsor: Flemish Government; Contract grant number: FWO: G.0341.07 (Data fusion), G.0427.10 (EEG-fMRI), IBBT; Contract grant sponsor: Research Council KUL; Contract grant numbers: GOA MANET, PFV/10/002(OPTEC); Contract grant sponsor: Belgian Federal Science Policy Office; Contract grant number: IUAP P6/4(DYSCO); Contract grant sponsor: Alexander von Humboldt stipendium.

*Correspondence to: Ivana Despotovic, MDISIP-IPI-IBBT, Ghent University, Sint-Pietersnieuwstraat 41, 9000 Ghent, Belgium.
E-mail: ivek@telin.ugent.be

Received for publication 7 July 2011; Revised 10 February 2012;
Accepted 13 February 2012

DOI: 10.1002/hbm.22076

Published online 21 April 2012 in Wiley Online Library
(wileyonlinelibrary.com).

or thickness have little effect on the dipole localization, whereas inaccurate electrode positioning can reduce the accuracy of source estimates. The performance of our fused method indicates that ictal EEG source imaging is feasible in neonates and with further validation studies, this technique can become a useful diagnostic tool. *Hum Brain Mapp* 34:2402–2417, 2013. © 2012 Wiley Periodicals, Inc.

Key words: neonates; MRI; realistic head model; EEG; source localization; asphyxia; HIE

INTRODUCTION

Seizures are a common manifestation of neurological dysfunction in neonates [Volpe, 2008] and require early detection to enable prompt treatment with the aim to prevent further brain injury. Perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE) are the most common causes of seizures in newborns. Confirmation by video electroencephalography (EEG) is considered the gold standard in the diagnosis of neonatal seizures, whereas magnetic resonance imaging (MRI) is mainly used to diagnose structural brain damage. The majority of seizures occurring in sick neonates are subtle or subclinical and can be detected only by continuous EEG (cEEG) monitoring [Murray et al., 2008]. Electrographic neonatal seizures are claimed to be independently associated with poor outcome [McBride et al., 2000]. It is also known that the majority of newborns with neonatal seizures have acute brain lesions visible on MRI [Cowan, et al., 2003] and that certain MRI patterns of brain injury like thalamus and basal ganglia injury are strongly predictive of poor outcome in HIE [Barkovich et al., 1998]. Though few studies have tried to relate brain lesions seen on MRI and specific EEG patterns [Biagioni et al., 2001; Leijser et al., 2007; Scher et al., 1993], an objective study of the relationship between the localization of neonatal seizures and associated MRI patterns of brain injury, using quantitative techniques, has not yet been done. The combination of these modalities by means of three-dimensional (3D) source localization might provide further insight into the pathophysiology of neonatal seizure phenomena and will be explored in this article.

EEG source localization estimates the active anatomical zones of the brain using EEG signals measured on the scalp. Two problems are involved: (1) the forward problem, which calculates the electrode potentials in a head model for a given source (usually a current dipole) and (2) the inverse problem, which finds the dipole parameters that best represent the measured potentials at the scalp electrodes. The accuracy of source estimates highly depends on the selection of a volume-conductor head model, including the selection of head tissue conductivities. The earliest head models, used for adult source localization, consider a head as a set of concentric spheres representing different conductive layers like scalp, skull, and brain, to simplify the calculation of the forward and inverse problems. However, the human head is not a sphere and using a spherical instead of a realistic head model results in a dipole location error [Cuffin, 1996; Roth

et al., 1993; Silva et al., 1999; Yvert et al., 1997]. This is particularly important when studied sources are located in the temporal or occipital lobes [Vatta et al., 2010].

To perform EEG source localization and compare the results directly with MRI lesions, accurate electrode placement and coregistration of EEG and MRI data are required. The most common methods for placing the electrodes on the scalp are using EEG head caps or using the standard 10–20 International System that requires manual electrode placement based on anatomical landmarks and relative distances. In adults, standard EEG head caps with fixed electrode positions are often used, but using the same caps for neonates is challenging because of differences in head size and greater variation in head geometry among neonates. Although there are some promising solutions for this problem available in the market, like specially designed EEG head caps for neonates [Vanhatalo et al., 2008], which might have a great potential for clinical use in the near future, the standard 10–20 system is still the most commonly used method in clinical practice in neonates. In source localization studies that use realistic head model, the exact electrode positions on the scalp need to be projected on the surface of the head model. This can be solved by using a 3D digitizer, which transforms coordinates of electrode locations to the MRI coordinates. However, this method is not available in most EEG laboratories. Therefore, a common solution is to place the electrodes on the scalp using the standard 10–20 positions and anatomical landmarks (like theinion and nasion points). As a consequence, such an approximation can introduce errors in the source modeling procedure [Khosla et al., 1999; Wang and Gotman, 2001].

Although EEG dipole source analysis is widely used in adults to localize epileptic sources [Michel et al., 2004], it is still not well explored in neonates because of the unknown conductivity values of the neonatal head. Additional challenges in neonatal source localization using a realistic head model are due to significant anatomical differences between newborn and adult heads. For instance, head tissue segmentation in newborns is more complex than in adults because of the lower MRI resolution (due to the short scanning period and small size of the newborn brain), lower contrast-to-noise ratio (due to the higher water content and ongoing myelination of the white matter) and imaging artifacts (like ghosting effects, ringing, and noise). The most difficult structure to segment

TABLE I. Clinical, EEG, and radiological characteristics and outcome of the 10 neonates

No.	Sex	GA (wk)	Birth wt. (g)	Start cEEG (h, PP)	Duration (h)	EEG grade	Total sz. no.	Select sz. no.	Sz. onset	Spread	MRI (d,PP)	Outcome (year)
1	M	40	2900	24	25	1	53	4	O-R	PTO-R	9	Normal (3)
2	F	41.4	3525	21.5	45	2	57	5	C,O-R	PT-R	4	L-inattention (2)
3	F	38	2910	64.5	41	2	18	5	C-bil	P-bil	4	Dev. delay (3)
4	M	37	2700	8.5	58.5	4	50	5	CP-bil	TO-bil	5	Normal (3)
5	F	41.3	3025	20.5	68	1	46	5	C-bil, F-L	T-bil	7	Epilepsy, language dev. delay (4)
6	F	39.1	2780	26	46.5	4	26	4	O-L	O-R	4	Died (day 7)
7	F	41.2	3540	37.5	47	2	32	5	C-bil	PT-bil	3	West syndrome, severe PMR (4)
8	F	41	3250	17.5	77	1	63	5	CP-R	O-R	2	L-hemiparesis (1)
9	M	41	3390	47	69	2	24	5	CT-bil, O-R	F-L	4	Normal (2)
10	M	37.6	3280	21.5	77.5	1	3	2	C-L	T-L	5	Normal (3)

GA: gestational age in weeks; Birth wt.: weight in grams; Start cEEG: time of start EEG monitoring; PP: post partum; Duration: duration of cEEG; EEG grade: background activity classified as eight grades (see Methods); Total sz. no.: number of seizures recorded during cEEG; Select sz. no.: number of selected seizures; Sz. onset and spread: seizure location as visually scored; MRI: day (d) of MRI scan PP; Outcome: clinical outcome and the year of follow-up; PMR: psychomotor retardation; Dev. delay: mild motor and cognitive developmental delay; F: frontal; C: central; P: parietal; T: temporal; O: occipital; R: right; L: left; bil: bilateral.

is the skull, because it is hardly visible on MRI scans. Also, the skull is thinner in neonates and contains more inhomogeneities due to the fontanelles. Initial results on neonatal EEG source localization were reported recently [Roche-Labarbe et al., 2008].

The aim of this pilot study is to explore the utility of neonatal ictal EEG source imaging and study its relationship to anatomical lesions, visible on MRI. For this purpose, we developed an integrated method for ictal EEG dipole source localization in neonates based on a realistic head model. We applied this method on 45 electrographic seizures recorded by cEEG from 10 neonates with presumed perinatal asphyxia and HIE, and we attempt to verify the identified ictal sources by relating them to acute perinatal MRI lesions. We segmented MRI scans from each patient to construct personalized 3D realistic head models with four compartments: scalp, skull, cerebrospinal fluid (CSF), and brain tissue. Using personalized MRI in this study is important to directly relate 3D localization of the active sources in the brain with MRI lesions and to minimize the dipole position errors due to different head shapes in neonates and distinctive anatomical features. For each neonate, we built five personalized 3D realistic head models to experimentally evaluate the sensitivity of the method to variations in skull conductivity and skull geometry (including skull thickness and the presence of the anterior fontanelle). Also, we experimentally evaluated the sensitivity of the method to electrode mislocalization. After constructing the head model, the spatial distribution of seizures over scalp electrodes is extracted with previously developed algorithms [Deburghraeve et al., 2008, 2009] and the optimal dipole position is estimated with a finite difference method [Hallez et al., 2005]. We used the equivalent current dipole as a representative model for a group of synchronously active neurons. For all patients, we ana-

lyzed only seizures with an unequivocal focal onset as determined by visual inspection of cEEG data.

MATERIALS

Ten full-term newborns (six females and four males) with gestational ages between 37–41 weeks, admitted to the neonatal intensive care unit (NICU), were included in this study. All 10 neonates displayed features of perinatal asphyxia and HIE. The selection of these patients was based on both the presence of recorded electrographic seizures on cEEG and acute perinatal brain lesions [Cowan et al., 2003] on MRI. They are part of an ongoing study of utility of long-term cEEG monitoring in neonates with presumed perinatal asphyxia and encephalopathy. The selection for cEEG was based on criteria for asphyxia and/or a high degree of suspicion of seizures [Cherian et al., 2011]. The medical ethics committee of Erasmus University Medical Center Rotterdam approved this study.

In all patients, we selected and studied focal electrographic seizure discharges with clear focal onsets. All patients had brain lesions visible on MRI. Half of the patients had predominantly unilateral, focal brain injury (like a stroke), while the other half had bilateral brain lesions (due to HIE). The details about the patients and their lesions detected on MRI are shown in Tables I and IV. All EEG and MRI data were recorded at the Sophia Children's Hospital (part of the Erasmus University Medical Center Rotterdam, the Netherlands). cEEG registrations were started mostly within the first 24 h after birth and MRI scans were done within the first 10 days. This time difference in acquiring EEG and MRI data is important for a reliable diagnosis because EEG changes after asphyxia are best studied in the acute phase and the rate of

recovery gives an indication of the severity and duration of the presumed hypoxic insult, while the pattern of brain injury is most easily seen in MRI few days after birth, when brain swelling is lower [Biagioni et al., 2001], and helps to better predict the outcome [Rutherford et al., 1998].

cEEG registrations were made using a NervusTM monitor (Taugagreining hf, Reykjavik, Iceland). We used silver-silver chloride electrodes applied on the scalp according to the 10–20 International System (17 electrodes: $F_{p1,2}$, $F_{3,4}$, $C_{3,4}$, C_z , $P_{3,4}$, $F_{7,8}$, $T_{3,4}$, $T_{5,6}$, $O_{1,2}$) using conductive paste and fixed with collodion. F_z electrode was used as the reference. The impedances were kept below 5 k Ω . Polygraphy included ECG, respiration, electrooculogram (EOG), chin EMG, and limb movements. EEG sampling frequency was 256 Hz. Band-pass filter was 0.3–70 Hz. EEGs were reviewed in their entirety by an experienced clinical neurophysiologist and the background activity was classified according to an in-house developed eight-grade classification system, emphasizing the severity and evolution of discontinuity and recovery of sleep-wake cycles [Cherian et al., 2011]. We defined seizures as ictal-appearing electrographic discharges that showed a clear variation from background activity, displaying a repetitive pattern of sinusoidal oscillations or sharp waves, or a mixture of both, lasting 10 s, with evolution in amplitude and frequency over time [Bye and Flanagan, 1995; Cherian et al., 2011; Lombroso, 1993] whether they had clinical correlates or not. Seizures were visually scored for their onset location, frequency, amplitude, duration, morphology, and spread (see Table I).

MRI scans, including T_1 -weighted (T_1 -W) and T_2 -weighted (T_2 -W) spin echo sequences, 3D spoiled gradient recalled (SPGR) sequence and diffusion-weighted imaging (DWI), were acquired on a 1.5 T MRI scanner (Siemens, Germany), $256 \times 256 \times 20$ – 25 voxel matrix with a resolution of $0.7 \times 0.7 \times 4.2$ mm. All MRI scans were scored by a pediatric neuroradiologist according to well-described patterns of neonatal brain injury [Swarte et al., 2009].

METHODS

Our method for neonatal EEG ictal dipole source localization consists of three key components: (1) 3D realistic head modeling; (2) automatic extraction of the spatial distribution of the selected seizure over electrodes; and (3) solving the forward and inverse problems for source localization.

Head Modeling

Modeling a realistic head model as a volume conductor is not a trivial task because it requires three equally important steps: (1) segmentation of the various head structures (such as scalp, skull, and brain tissue), (2) selection of the correct tissue conductivities, and (3) appropriate electrode placement.

As brain MRI segmentation techniques have been mainly developed for adults and are not applicable for neonates, the segmentation of neonatal brain MRI has become a research focus in recent years. State-of-the-art methods [Prastawa et al., 2005; Shi et al., 2010, 2011; Weisenfeld and Warfield, 2009; Xue et al., 2007] are mainly focused on the problem of neonatal brain tissue segmentation such as cortical and subcortical gray matter, unmyelinated and myelinated white matter and CSF, but they are not developed to segment neonatal head structures such as skin, skull, and cranial cavity. Also, these methods generally rely on probabilistic atlases that present the spatial variability of the neonatal brain tissue structure. However, since the atlas-generation is based on a population of healthy babies and relies on subjective ground-truth manual segmentation, an atlas-based segmentation can be difficult and prone to errors. For instance, in patients with brain lesions or a brain-anatomy that significantly differs from the atlas template, the atlas alignment and the corresponding segmentation of the brain will fail or give inaccurate results.

Thus, in this study, we used an atlas-free segmentation algorithm based on T_1 -W and T_2 -W MRI scans that is able to segment four head structures: scalp, skull, CSF, and brain tissue. Before segmentation, we used cubic spline interpolation to interpolate low-resolution MRI scans and obtain the interslice resolution of 0.7 mm. Then, we did bias field (intensity inhomogeneity) correction [Sled et al., 1998] and multimodal T_1 -W and T_2 -W MRI registration [Mattes et al., 2001; Thevenaz and Unser, 2000]. After pre-processing, to identify and segment different head structures (scalp, CSF, and brain), we used a brain extraction algorithm [Despotovic et al., 2010b] and an algorithm that combines multimodal fuzzy c-means clustering [Despotovic et al., 2010a] and mathematical morphology. The most challenging head structure to segment was the neonatal skull because it is not easily visualized on MRI scans, contains structural inhomogeneities and partial volume voxels. For the skull reconstruction, we used the voxels between the brain and the scalp, which resulted in a skull layer that completely surrounds the brain. The anterior fontanelle was modeled as a part of the skull, where the skull layer is eroded (using mathematical morphology) to reach the maximum possible thickness (one voxel size). The fontanelle was diamond-shaped, ~ 2 – 3 cm wide and 3 – 4 cm long. Finally, all segmented structures are used to generate a cubic grid with a cube side equal 0.7 mm. The segmented skull, based on individual MRI, was 1.4 – 2.1 mm thick (two to three voxels), but sometimes also reaching 2.8 mm in the occipital lobe. The fontanelle thickness was set to 0.7 mm. These values fitted well in the realistic skull thickness range of 1.1 – 2.9 mm, which was determined by an expert pediatric radiologist, based on manual skull thickness measurements using all patients in this study.

When different compartments of the brain are obtained, the appropriate conductivities have to be attached to them. Since head conductivities, to our knowledge, have never

TABLE II. Head tissue conductivities

Components	Adult (S/m)	Neonate (S/m)
Brain	0.2–0.48	0.33
CSF	1.79	1.79
Skull	0.0067–0.015	0.033–0.2
Scalp	0.43	0.43

been measured for neonates, in this work, we estimated the conductivity values based on available studies for adults and small animals [Thuarai et al., 1984; Akhtari et al., 2002; Baumann et al., 1997; Geddes and Baker, 1967; Gibson et al., 2000; Goncalves et al., 2003; Lai et al., 2005; Oostendorp et al., 2000; Roche-Labarbe et al., 2008]. The neonatal scalp and CSF conductivities were assumed to be the same as in adults with the values 0.43 and 1.79 S/m, respectively [Baumann et al., 1997; Geddes and Baker, 1967], while the neonatal brain conductivity is set to 0.33 S/m [Gibson et al., 2000; Roche-Labarbe et al., 2008]. To estimate the conductivity of the neonatal skull, we used the previous study of Murray [Murray, 1981] where it was reported that the conductivity of the neonatal skull should be between 0.033 and 0.2 S/m (the adult skull conductivity is in the range from 0.0067 to 0.015 S/m [Akhtari et al., 2002; Lai et al., 2005; Oostendorp et al., 2000]). As the conductivity of the brain and the scalp is considerably higher than the conductivity of the skull, we used 0.033 S/m as the “normal” conductivity value of the neonatal skull, where the brain-to-skull conductivity ratio is 10. Furthermore, as wrong estimation of the skull conductivity can lead to source mislocalization, in this study, we estimated different source localizations based on different plausible values of human skull conductivities as given in Table II.

Finally, 17 electrodes were placed on the scalp using the standard 10–20 International System [Wang and Gotman, 2001]. The nasion and inion points were manually defined on each segmented head volume and were used as anatomical markers for electrode placement. For each patient, electrode positions were adapted regarding the shape of the head and the segmented scalp, which led to subject-dependent electrode placement. The coordinates of the electrodes were described using two parameters: the azimuth θ (angle with the vertical z -axis where $0^\circ \leq \theta < 180^\circ$) and the latitude φ (contra-clockwise angle with the x -axis in the horizontal x - y plane where $0^\circ \leq \varphi < 360^\circ$). All steps for the realistic head modeling are summarized in Figure 1a. An example of the 3D realistic head model with 17 electrodes projected on the scalp is illustrated in Figure 1b,c.

EEG Event Detection

Two to five seizures, which were considered to be representative of the expressed seizure patterns in each neonate, were visually selected by a clinical neurophysiologist. All analyzed seizures in this study were spike trains or mixed patterns with a large spiky component. The selected seiz-

ures were then reviewed by two experienced clinical neurophysiologists, and a consensus was reached about the identified seizure characteristics.

To automatically and objectively extract the spatial topography of the seizures, we applied a two-step method. The first step is the application of the recently developed automated spike train detector [De Vos et al., 2011; Deburchgraeve et al., 2008] which detects highly similar, high energetic spikes in a seizure. These detected spikes are aligned and grouped into a tensor, which is modeled with a trilinear structure using parallel factor analysis (PARAFAC) [De Vos et al., 2007; Deburchgraeve et al., 2009]. Note that in this study, we consider stationary seizures, but for an extension of the method that takes into account the evolution of the seizure, we refer to [Deburchgraeve et al., 2010]. As a result, the spatial distribution vector of the spikes over the EEG channels is obtained and is used as an input for source localization (Fig. 2). The advantage of this preprocessing step is that the signal-to-noise ratio of the input for source localization is increased compared to raw topographies of single spikes. We have also shown previously that the PARAFAC localization is more robust and less sensitive to added noise as compared to simple spike averaging [Deburchgraeve et al., 2009]. The automated detections and localizations of all the 45 seizures were subsequently checked by the clinical neurophysiologist to ensure that they corresponded to the visual interpretation.

EEG Source Localization

Using a topographic plot as a graphical representation of the spatial distribution of the spikes over the EEG electrodes is suboptimal to relate EEG spatial information with 3D brain anatomy. However, the combination of EEG and MRI data for 3D source localization can provide a representation of electrical generators inside the 3D anatomical space of the brain and enable exploring their relationship with underlying lesions. To achieve this goal, three input elements are required: the electrical fields modeled with an equivalent current dipole, a realistic head model (Head Modeling section), and the spatial distribution of the seizure over the EEG electrodes (EEG Event Detection section). As all events in this study were assumed to be focal activities, we used a single rotating dipole for the dipole fit.

The dipole source localization consists of solving forward and inverse problems. By solving the forward problem, we obtain the electrode potentials caused by a dipole source. The forward problem can be solved by an analytical expression for spherical head models, while numerical solutions are needed for realistic inhomogeneous head models. In this study, we used a finite difference method [Hallez et al., 2005], where a cubic computational grid is defined to the vertices at the edges of the labeled voxels in the realistic head model. To solve the system of equations in the forward problem, we used successive overrelaxation. Furthermore,

Figure 1.

Realistic head modeling: (a) the algorithm steps; (b) and (c) a 3D head model with 17 electrodes, placed on the scalp using standard 10–20 system. Nasion and inion points together with T_3 , T_4 electrodes form the equatorial plane and the electrode C_z represents the north pole. The x-axis points to the right side of the

head (through T_4), the y-axis points to the front of the head (through the nasion point), and z-axis passes through C_z . The coordinates θ (the azimuth) and φ (the latitude) are used to describe the electrode positions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

reciprocity was used to speed up the forward calculation in the inverse problem [Vanrumste et al., 2001].

Solving the inverse problem consists of finding the parameters of the dipole source that best explain the set of measured potentials consisted of the preprocessed EEG-spike trains. We find the optimal dipole position $\mathbf{r}_{\text{opt}}$ and components $\mathbf{d}_{\text{opt}}$ for the input potentials V_{in} at 17 scalp electrodes. This was done by minimizing the relative residual energy (RRE):

$$\text{RRE} = \frac{\|V_{\text{in}} - V_{\text{model}}(\mathbf{r}, \mathbf{d})\|_2^2}{\|V_{\text{in}}\|_2^2} + C(\mathbf{r}), \quad (1)$$

where V_{in} are the preprocessed spike trains and V_{model} are the electrode potentials obtained by solving the forward problem with a dipole source position $\mathbf{r}$ and components $\mathbf{d}$. $\|\cdot\|_2$ indicates the L_2 -norm. $C(\mathbf{r})$ is zero for dipole posi-

tions in the brain compartment (brain tissue) and is set to a high value elsewhere. This additional term will constrain the solution of the inverse solver to the brain compartment. The Nelder–Mead simplex method was used to find the minimum of the RRE, which is a measure of the goodness of fit (GOF). A reasonable GOF was assumed if the RRE was ≤ 0.20 .

To examine the relationship between EEG seizures and MRI brain lesions, for each patient, we performed source localization for each selected event (seizure) using personalized head model obtained from patient's MRI data. The source reconstruction solutions (equivalent dipoles) were projected onto the original T_1 -W, T_2 -W, and DWI MRI volumes. To delineate the lesions on MRI, we used MRI sequences where the lesion was best visualized (like DWI or SPGR) and the distance between the dipole and the nearest lesion margin was measured using 3D Euclidean

Figure 2.

EEG seizure localization. An example of the spike train detection is shown on the left. All marked segments (gray-shaded and delineated by rectangle) are detected by the segmentation step. After applying the spikiness operator and correlation analysis, only the shaded segments remain as being part of a spike train type seizure, localized over the right temporal and central regions. All seg-

mented spikes are used as an input for a PARAFAC decomposition where we calculate the spatial distribution of the spikes over the EEG channels, which can be plotted as a topographic plot (shown on the right). Positive and negative brain regions are indicated with red and blue color, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

distance. The manual delineation of the lesions was checked and approved by a pediatric neuroradiologist.

EXPERIMENTAL SETUP

Although the main goal of this study was to explore the relationship of acute perinatal brain lesions visible on MRI to estimated EEG sources of neonatal seizures, we also needed to explore the influence of different parameters on these estimates. As EEG source localization results may be affected by the skull reconstruction errors (including skull thickness and the presence of the fontanelle), the wrong estimation of the skull conductivity and the errors in electrode placement, we performed experimental studies to better understand the influence of these elements on ictal EEG source localization in neonates.

Conductivity and Geometry of the Skull

For the experimental study, for each patient, we built five head models: “normal,” “maxcond,” “mincond,” “no fontanelle,” and “thick,” to test the sensitivity of the source localization to variations in skull conductivity and geometry. The “normal” head model is the first head model obtained after the MRI segmentation and the initial head conductivity estimation, where the skull conductivity is set to 0.033 S/m and the segmented skull thickness is 1.4–2.1 mm, containing the anterior fontanelle (0.7 mm thick). This head model was used as the reference (true) head model in this study.

The second and the third head models, “maxcond” and “mincond,” were used to test the influence of differences in estimation of the skull conductivity. In comparison to

the “normal” head model, in the “maxcond” and “mincond” head models, we only changed the skull conductivity to 0.2 and 0.0067 S/m, respectively, which correspond to the maximal and minimal head conductance estimated in adults. For instance, the conductivity of most soft tissues is around 0.2 S/m (white matter in the adult brain) [Geddes and Baker, 1967], whereas the lowest value reported for the adult skull conductivity is 0.0067 S/m [Lai et al., 2005; Saha and Williams, 1992] (see Table II).

The last two head models, “no fontanelle” and “thick,” were used to test the influence of the anterior fontanelle and skull reconstruction errors on dipole localization. In comparison to the “normal” head model, the “no fontanelle” head model does not contain the anterior fontanelle and the “thick” head model has voxel-size (0.7 mm) thicker skull with the values between 2.1 and 2.8 mm (in some cases reaching 3.5 mm in occipital regions). The “no fontanelle” head model was used to explore whether the fontanelles, as thin cartilage structures, create paths of low conductivity for the volume currents in the brain and tend to concentrate dipoles around the current leakage [Benar and Gotman, 2002]. The “thick” head model was used to examine how the errors in the skull thickness, caused by partial volume effects and MRI segmentation, influence the source estimates. The summary of the five head models is given in Table III. To calculate the dipole shifts (distances) caused by using different head models of the same patient, we used 3D Euclidean distance.

Electrode Mislocalization

As incorrect assumptions of electrode positions on a realistic head model can also introduce source localizations errors, we performed the experimental study to investigate

TABLE III. Five head models used for the experimental study

Head model	Skull cond. (S/m)	Skull thick. (mm)	Fontanelle yes/no	Font. thick. (mm)
"Normal"	0.033	1.4–2.1	Yes	0.7
"Maxcond"	0.2	1.4–2.1	Yes	0.7
"Mincond"	0.0067	1.4–2.1	Yes	0.7
"Thick"	0.033	2.1–2.8	Yes	0.7
"No fontanelle"	0.033	1.4–2.8	No	–

Skull cond.: skull conductivity; Skull thick.: skull thickness; Font. thick.: fontanelle thickness.

how spatial electrode misplacements from the standard 10–20 system influence dipole localization results (using 17 electrodes). To estimate these errors, we used five patients, each with five focal seizures and median GOF <0.20 , and we displaced the electrodes from their initial 10–20 position. This is achieved by angular displacement of the parameters θ and ϕ (see Fig. 1b), where it is assumed that these displacements were zero-mean Gaussian with the same standard deviation for all electrodes [Khosla et al., 1999]. We did four experiments where different standard deviation values (2° , 5° , 10° , and 12°) were chosen. For each standard deviation and for each patient, we generated eight different electrode position sets by adding Gaussian displacements to original electrode positions using the "normal" head model (see Table III). This resulted in 200 inverse problem calculations for each experiment. To calculate the dipole shifts (distances) caused by electrode mislocalization, we used 3D Euclidean distance.

The results of this experimental study should help in understanding how important is to know the exact electrode positions in solving the inverse problems and whether the electrode mislocalization errors are big enough to justify the additional cost of digitizing electrode positions.

RESULTS

Relationship of Seizure Foci to Brain Lesions Detected by MRI

To compare 3D EEG source localization results with well-defined brain lesions seen on MRI, for all 10 patients we used the "normal" head models as they provided the best GOF. The dipole source localization results together with delineated MRI lesions (marked with red color) with axial, coronal, and sagittal views are shown in Figure 3 (Patients 7 and 8) and Figure 4 (Patients 1–6, 9, and 10). Different EEG events (seizures) are illustrated with different color and a corresponding topological plot, and for each seizure dipole, GOF and the distance from the closest lesion border are displayed.

As we hypothesized that the location of the seizure would be on the lesion border [Hartings et al., 2003], we

classified localized dipoles in three categories: dipoles very close or on the edge of the lesion (≤ 5 mm), dipoles in the vicinity of the lesion (≤ 15 mm), and dipoles far from the lesion (>15 mm) [Ding et al., 2007]. For each patient, good relationship between the estimated dipoles and MRI lesions was accepted only if the following conditions were simultaneously satisfied: (1) lesions and dipoles are located at the same side and in the same lobe of the brain (colocalization is positive "+"), (2) majority of dipoles are located ≤ 5 mm from the edge of the lesion, (3) majority of the remaining dipoles are in the vicinity of the lesion (≤ 15 mm) and (4) median GOF is ≤ 0.20 . If the majority of dipoles are located far from the lesion >15 mm, good relationship is rejected (Fig. 4 and Table IV, Patient 5). These relationship results are summarized in Table IV, which shows that in 9 of 10 patients, we found good relationship between localized dipoles and visible MRI lesions. In all 9 cases, the majority of dipoles were located at the edge or very close to the edge of the lesion, and no single dipole is located far from the lesion, >15 mm (see Figs. 3 and 4).

Patients 7 and 8 are good examples where dipole locations relate very well with the lesions, and they are shown separately in Figure 3. These two patients had clinical features of severe HIE. Patient 7 had bilateral white matter hemorrhages (in posterior frontal, parietal and occipital lobes) and dipole locations were bilaterally located at the border of the lesions. Patient 8 had infarcts in right parietal, posterior, and anterior frontal lobes, and all dipole locations corresponded to these regions. However, in Patient 5 (Fig. 4), who had a small left basofrontal hemorrhage, we found that the dipole locations were situated much higher in the left frontal region. The reason for this is that we have no EEG electrode near the putative seizure focus close to the lesion, located very deep in the brain. It is possible that the seizures in this patient spread vertically [Caveness et al., 1973] leading to secondary sources, resulting in the GOF values for the ictal dipoles of >0.20 . This patient also illustrates the limitation of volume conductor models of EEG source localization, which do not take into account factors like anisotropies or the presence of various corticocortical networks [Plummer et al., 2008], in localizing certain types of seizure foci. Moreover, distinguishing the primary EEG source that initiates ictal activity from secondary sources, which are due to propagation, can often be difficult [Ding et al., 2007], as could have happened in this patient. It is also well known that some frontal lobe seizures are difficult to localize using noninvasive methods [Salanova et al., 1994; Quesney, 1991]. Our overall results are in agreement with animal experiments that show that majority of the seizures after perinatal hypoxic ischemic brain injury originate from the periarfarc regions [Hartings et al., 2003; Kadam et al., 2010].

Similar to what has been reported [Bye and Flanagan, 1995; Patrizi et al., 2003], we found that majority of our seizure foci tend to cluster near the central parasagittal regions. The majority of the brain lesions in our patients also colocalized to these areas. Vulnerability of the perirolandic regions

Figure 3.

Dipole localizations results of Patient 7 (with bilateral white matter hemorrhages) and Patient 8 (with infarct lesions). For both patients, we plotted 3D dipole fit results onto the patients' T_1 -W, T_2 -W, or DWI MRI using projections on three planes: axial, coronal and sagittal. Color of the dipole represents different EEG events (seizures), which are also illustrated with a cor-

responding two-dimensional (2D) topological plot (derived from PARAFAC analysis that represents the spatial distribution of the seizure discharges over the EEG channels). For each seizure dipole, GOF and the distance from the closest lesion border are given next to the topological plot.

to brain injury may be due to regional metabolic differences [Chugani and Phelps, 1986]. The parasagittal watershed regions are also vulnerable in perinatal HIE [Volpe and Pasternak, 1977].

Dipole Position Errors due to Volume Conductor Model Errors

Sensitivity results due to variations in skull geometry and conductivity are shown in Table V. For each patient, we show the mean dipole shift value of all patient-specific

dipoles calculated between two head models indicated in each column. The variability in mean dipole shifts between patients (visible in Table V) is most probably due to differences in the modeled spikes (source topography) and anatomical variability of the lesions. This variation is small and always below 5 mm. In the last row, we show the total mean dipole shift for all 10 patients with the standard error of the mean. The mean dipole shift of dipole locations between "normal" and "thick" head models was 1.42 mm, between "normal" and "no fontanelle" head models was 0.65 mm, between "normal" and "mincond" head models was 1.55 mm, and between "normal" and "maxcond" was

Figure 4.

Dipole localizations results of patients 1–6, 9, and 10. Estimated dipoles are plotted onto the patients' T_1 -W, T_2 -W or DWI MRI using projections on three planes: axial, coronal and sagittal. Color of the dipole represents different EEG events (seizures), which are also illustrated with a corresponding 2D topological

plot (derived from PARAFAC analysis that represents the spatial distribution of the seizure discharges over the EEG channels). For each seizure dipole, GOF and the distance from the closest lesion border are given next to the topological plot. Detailed description of the lesions and localized dipoles is in Table IV.

TABLE IV. Relationship between MRI lesions and dipole localization results of the 10 neonates

No.	MRI lesions (clinical diagnoses)	Dipole positions (localization results)	Coloc.	GOF	No. of dipoles with dist. (mm)			Relationship
					≤5	≤15	>15	
1	Bilateral (right > left) watershed (sub)cortical lesion in occipital lobe	Right occipital lobe	+	0.16	3	1	0	Good
2	Watershed (sub)cortical lesion in right post. frontal and parietal lobes	Right posterior frontal and parietal lobes	+	0.12	4	1	0	Good
3	Bilateral (sub) cortical injury, mainly in frontal and occipital lobes	Bilateral posterior frontal and parietal lobes	+	0.12	4	1	0	Good
4	Bilateral infarction in temporal and parietal (postrolandic) lobes	Bilateral posterior frontal, temporal, and parietal lobes	+	0.10	3	2	0	Good
5	Ischemia and hemorrhage left basofrontal and frontal periventricular	Four dipoles (left frontal lobe) One dipole (right posterior frontal)	–	0.22	0	0	5	Not good
6	Subdural and subarachnoid hematoma in the left occipital region	Left occipital lobe	+	0.09	4	0	0	Good
7	Bilateral white matter hemorrhages in post. frontal, parietal, and occipital lobes	Bilateral posterior frontal and parietal lobes	+	0.09	5	0	0	Good
8	Infarction, in right parietal, posterior, and anterior frontal lobes	Right anterior and posterior frontal and parietal lobes	+	0.12	4	1	0	Good
9	Bilateral (right > left) white matter and (sub)cortical injuries in frontal, occipital and temporal lobes and basal ganglia	Bilateral (three right and two left) posterior frontal and temporal lobe	+	0.14	5	0	0	Good
10	Bilateral white matter injury in frontal lobe	Left posterior frontal	+	0.09	2	0	0	Good

The second column of the table describes the lesions seen on MRI including their location (the side and the lobe of the brain). The third column describes the dipole localization results (the side and the lobe of the brain). The fourth column shows the colocalization results between dipoles and lesions where “+” and “–” indicate positive and negative colocalization. Median goodness of fit is shown in the fifth column, while the qualitative results from the measured dipole-lesion distances are summarized in the sixth column. The dipoles are classified into three groups: very close or at the edge of the lesion (≤ 5 mm), in the vicinity of the lesion (≤ 15 mm) and far from the lesion >15 mm. The last column shows the final relationship results (good/not good) between MRI lesions and dipole locations. Coloc.: colocalization, dist.: distance of the dipole from the edge of the nearest lesion.

2.34 mm. From these results, we can say that the influence of the anterior fontanelle to dipole localization is almost negligible (~ 0.7 mm), but increasing the skull thickness for 0.7 mm (from the range of 1.4–2.1 mm to the range of 2.1–2.8 mm) caused mean dipole shift of ~ 1.5 mm. In a previous study [Roche-Labarbe et al., 2008], it was reported that the main source of uncertainty for dipole localization is the skull conductivity. They estimated that the mean dipole shift between head models with skull conductivities of 0.33 and 0.0042 S/m is ~ 11.6 mm. However, selecting 0.033 S/m as a “normal” neonatal skull conductivity, which is six times smaller than 0.2 S/m (“maxcond”) and five times bigger than 0.00067 (“mincond”), we got smaller mean dipole shifts of ~ 2.5 and ~ 1.6 mm, respectively.

We also calculated the mean dipole shift caused by inaccurate electrode positioning. By increasing the angular mis-

localization of the electrode positions by 2° , 5° , 10° , and 12° , we obtained mean dipole position shift of 2.80, 6.41, 11.72, and 14.79 mm, respectively. These shift results are slightly higher comparing with the adult study with a realistic head model [Wang and Gotman, 2001], where they used 29 electrodes for EEG recording. As we used only 17 electrodes, we expect that increasing the number of electrodes can cause reduction in the localization error. However, for the purpose of this study, we think that this error is acceptable.

DISCUSSION

Comparisons with Previous Studies

To our knowledge, there has been only one previously published study about neonatal EEG source localization

TABLE V. Sensitivity results to variations in skull geometry and conductivity

Patient	Mean dipole shift			
	Skull geometry		Skull conductivity	
	"normal"– "thick"	"normal"–"no fontanelle"	"normal"– "mincond"	"normal"– "maxcond"
1	3.00	0.40	2.55	2.71
2	1.25	0.56	1.82	4.32
3	3.60	0.81	1.35	1.05
4	0.39	1.61	1.03	1.65
5	1.62	0.62	1.80	1.85
6	1.28	0.10	2.67	2.81
7	0.71	1.23	0.96	4.91
8	0.96	0.92	1.57	1.50
9	0.65	0.40	0.90	1.85
10	0.77	0.86	0.81	0.79
	1.42 ± 1.06	0.65 ± 0.32	1.55 ± 0.67	2.34 ± 1.36

Mean dipole shift in a table represents mean distance (measured in mm) of all dipoles located in one patient between different head models indicated in columns. The last row in a table shows the total mean dipole shift ± the standard error of the mean between different head models for all patients.

[Roche-Labarbe et al., 2008] where sensitivity of different parameters on source estimates was evaluated. From a clinical point of view and methodology, our study is different from theirs and is based on a larger number of patients. The main contribution of our study is to show the first clinical results in regard to the feasibility of localizing neonatal ictal EEG activity and its good relationship to acute perinatal brain lesions visible on MRI.

Our method is based on automatic extraction of the seizure topography and more sophisticated MRI segmentation for 3D volumetric modeling of the neonatal head. We localize the pathological seizures (ictal phenomena that are associated with acute, serious brain injury), while Roche-Labarbe et al. localize transients in neonatal EEG. Our head models consist of four compartments: scalp, skull, CSF, and brain tissue, while they used a three-layer boundary element method (BEM) (which uses surfaces tessellations) to model the scalp, skull, and brain tissue. A difference of our approach is that, together with CSF, we model the ventricular system, giving the head model more realistic structure with an additional conductive layer. This is important because the electrode potentials are dependent on the total electrical field generated in the head caused by a current dipole. Also, CSF and the ventricles can be used to constrain the dipole location. Current dipoles cannot be placed in the ventricles or CSF and this can be added in the EEG source localization procedure. In adults, it has been shown in a previous study [Vanrumste et al., 2000] that not incorporating the ventricles in the head model causes a dipole location error of about 7 mm in the vicinity of the ventricles (deep gray matter) and about 3 mm in the brain cortex. However, as neonates

have lower volume conduction than adults, we believe that this error could be smaller in babies.

Another difference between our studies is that Roche-Labarbe et al. used a patented cap for electrode placement and a magnetic digitizer for 3D digitization of the spatial positions of the electrodes, whereas we used the standard 10–20 International System to manually place the electrodes on the scalp in a relation to the anatomical markers. However, none of these methods is error free. Electrode caps can move slightly in position [Atcherson et al., 2007] and may have fixed interelectrode distances, but less accurate relationship to anatomical landmarks of the skull. In the case of applying individual electrodes, one relies on an experienced EEG technician who should have less margin of error. On the other hand, digitized electrode positions, which were not available for this study, describe the true electrode positions on the scalp more precisely than the standard 10–20 positions. In the study of Khosla et al. [Khosla et al., 1999.], it was shown that on average, the digitized electrode locations deviated from the standard 10–20 positions by about 4° in adults. This misallocation has not yet been measured in neonates, but it might be very similar if the fine adjustments based on the anatomical markers and head shape are made during electrode positioning. For studying the relationship of seizures to brain lesion in this pilot study, this mismatch is tolerable. However, if higher precision source localization is desired (e.g., for surgical planning in epilepsy patients), the digitization of electrode positions is recommended.

Finally, our study is the first to evaluate the influence of electrode mislocalizations on source localization in neonates. Our experimental results indicated that the electrode mislocalization is the most critical component for the accurate source localization. As we used a clinical setup of only 17 electrodes, we believe that using a higher number of electrodes would give more accurate source estimation. This had been already shown in adult studies [Vanrumste et al., 2000]. While highly accurate dipole localization is needed for presurgical evaluation of patients with refractory epilepsy, our primary aim in neonates is to study the relationship of seizures to brain lesions and eventually their pathophysiology. Hence, we think that the obtained error is acceptable. The reality in most NICUs doing cEEG is that eight to nine scalp electrodes are used for this purpose. Thus, the 17 electrodes that we use may be a reasonable compromise between the need to obtain high accuracy (more electrodes) and practical applicability in a NICU setting (less number of electrodes).

Estimation of the Skull Conductivity

As the skull conductivity has never been measured for human neonates, one of the challenges in this study was to estimate the neonatal skull conductivity using available studies for adults and animals. In adults, the conductivity of the skull was measured both in vitro and in vivo

[Akhtari et al., 2002; Geddes and Baker, 1967; Lai et al., 2005; Oostendorp et al., 2000], but still there is little consensus on the absolute skull conductivity value or the brain-to-skull conductivity ratio. Also, the skull conductivity is electrically anisotropic and depends on the skull thickness, skull composition, test frequencies, and temperature. The adult skull conductivity reported in the literature ranges from 0.0067 to 0.015 S/m. It has recently been suggested that the human brain-to-skull conductivity ratio is 15 [Oostendorp et al., 2000] and 25 [Lai et al., 2005] instead of the widely used value of 80 [Rush and Driscoll, 1986]. In the study of Akhtari et al. [Akhtari et al., 2002], the conductivity of the three-layer live human skull was measured (top compact bone, middle spongiform layer and lower compact bone). They reported that the skull conductivity is frequency dependent in the range from 10 to 90 Hz by as much as $\sim 10\%$ in compact bone and $\sim 13\%$ in spongiform (percent increase in conductivity). Also, they indicated that there may be a weak relationship between the thickness and conductivity in different skull layers.

In the recent study of Pant et al. [Pant et al., 2011], the first measured conductivity values for neonatal and preterm mammalian skull were reported. They used fresh neonatal piglet skull samples with the average thickness about 1.3 mm and found the average neonatal/preterm piglet skull conductivity in the range 0.025–0.035 S/m (average 0.030 S/m) at 1 kHz. They also found that the skull conductivity increased linearly with the skull thickness. Note that although the piglet brain is a well-accepted preclinical model for neurodevelopmental research in humans (due to its anatomic and physiologic similarities to humans, like similar patterns in brain growth and development), the similarity between the piglet neonatal/preterm skull and the human neonatal skull is still controversial.

In this study, we used three different values for the neonatal skull conductivity (0.2, 0.033, and 0.0067 S/m) and tested their influence on source mislocalization. In these experiments, we used 0.033 S/m as the “normal” neonatal skull conductivity value. Taking into account the incomplete development of the neonatal bone, it is reasonable to assume that the neonatal skull has higher conductivity than the adult skull. Also, comparing with the adult studies, the brain-to-skull ratio of 10 seems reasonable. Our results also indicate that the mean dipole mislocalization using conductivities 0.2 or 0.0067 S/m is less than 5 mm. Like in the most EEG source localization studies in adults, we assumed the skull conductivity to be isotropic. It is an open question how this assumption affects the accuracy of EEG dipole source localization in neonates and it should be handled in a separate study.

Strengths and Limitations

Strengths of our study include the use of continuous multichannel EEG monitoring for more complete sampling of seizure data, automated seizure localization, as well as

the use of a realistic head model. The expertise needed to interpret neonatal EEGs is not available around the clock in the NICU. Also, EEG monitoring is highly labor intensive as it generates large amounts of data. Because of these reasons, automated analysis methods are needed in the context of cEEG monitoring in the NICU. We also attempted to place our ictal source localization in the clinical context by relating them to the acute brain lesions seen on MRI.

Limitations of our study are the small number of patients, as well as the deliberate selection of patients with discrete lesions visible on MRI and clear-cut focal seizures recorded on EEG. This may be justified as our aim was to explore the relationship of neonatal seizures to brain injury patterns visible on MRI. These type of studies are useful for hypothesis generation and cannot be generalized to all neonates with HIE and seizures. As compared to interictal spike localization studies, ictal source localization studies are more challenging. By the time the seizure is expressed in the scalp electrodes, a large volume of intracranial tissue is involved by the ictal discharge, and the model may be showing the spread and not the origin [Merlet and Gotman, 2001]. Wide-spread regional propagations of the seizures are expected to be less of a problem in the neonate as compared to older children and adults due to the immature corticocortical connections that have been shown by anatomic [Caveness et al., 1973] and metabolic [Kato et al., 1980] studies. We also took care in each patient to select seizure patterns that were reproducible.

Future Directions

The near-term clinical application of dipole localization of neonatal seizures is still limited in the NICU, and the studies like ours are needed to close our present gaps in the knowledge about pathophysiology of neonatal seizures. We feel that with further validation, this type of multimodal approaches could improve therapy (for example, by using more targeted neuroprotective therapies for particular type of seizures) as well as outcome predictions in the future. Large, multicenter cEEG studies are needed to study the pathophysiology of neonatal seizures, their relationship to acute brain lesions as well as the effect of their treatment with antiepileptic drugs. Studying large amounts of cEEG data is highly labor intensive and will be simplified by the use of automated methods like the one we used. Although evolution of EEG background activity in the first few days after perinatal asphyxia is known to be a robust predictor of clinical outcome [Murray et al., 2009; Watanabe et al., 1980], prediction of outcome in neonates with moderately severe EEG background abnormality is very difficult. In this selected group, multimodal evaluations, such as estimation of MRI lesion location and volume, electrographic seizure burden as well as ictal source localization may help to improve prognostication. A recent study showing that watershed brain injuries are related to impaired language ability

[Steinman et al., 2009] in survivors of HIE, is a step in this direction.

Long-term follow-up is needed in our patients to look for neurocognitive deficits and epilepsy. This is further emphasized by the fact that patient nos. 5 and 7 in this study developed epileptic seizures on follow-up. A recent study using an animal model of neonatal hypoxic ischemic brain injury has shown that development of epilepsy in later life is strongly related to the presence of pathological brain lesions [Kadam et al., 2010]. Similar studies in neonates with HIE will help to refine our prognostication in patients with particular combinations of seizures and brain injury patterns on MRI.

CONCLUSIONS

This pilot study evaluated the utility of 3D localization of neonatal seizures using a realistic head model and relationship of seizure foci to brain lesions detected by MRI. Despite many difficulties, we have shown that EEG ictal source localization is feasible in newborns and can lead to important new insights into the properties of cerebral neural networks and 3D comparison with brain lesions.

The results have shown that the majority of calculated 3D sources were at the edge or ≤ 5 mm from the nearest MRI lesions. Also, using approximate head tissue conductivities (which were found in literature) with an accurate geometrical description of the head (i.e., based on a subject's MRI), yielded reasonable results for both cortical and deep EEG sources. Considering that the 3D sources were computed using only 17 electrodes and the standard 10–20 system of electrode placement, our results are very promising for further research on the relationship between EEG source localization and brain injury visible on MRI.

REFERENCES

- Akhtari M, Bryant HC, Mamelak AN, Flynn ER, Heller L, Shih JJ, Mandelkern M, Matlachov A, Ranken DM, Best ED, DiMauro MA, Lee RR, Sutherling, WW (2002): Conductivities of three-layer live human skull. *Brain Topogr* 14:151–167.
- Atcherson SR, Gould HJ, Pousson MA, Prout TM (2007): Variability of electrode positions using electrode caps. *Brain Topogr* 20:105–111.
- Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F, Ferriero DM (1998): Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. *AJNR Am J Neuroradiol* 19:143–149.
- Baumann SB, Wozny DR, Kelly SK, Meno FM (1997): The electrical conductivity of human cerebrospinal fluid at body temperature. *IEEE Trans Biomed Eng* 44:220–223.
- Benar CG, Gotman J (2002): Modeling of post-surgical brain and skull defects in the EEG inverse problem with the boundary element method. *Clin Neurophysiol* 113:48–56.
- Biagioni E, Mercuri E, Rutherford M, Cowan F, Azzopardi D, Frisone MF, Cioni G, Dubowitz L (2001): Combined use of electroencephalogram and magnetic resonance imaging in full-term neonates with acute encephalopathy. *Pediatrics* 107:461–468.
- Bye AM, Flanagan D (1995): Spatial and temporal characteristics of neonatal seizures. *Epilepsia* 36:1009–1016.
- Caveness WF, Echlin FA, Kemper TL, Kato M (1973): The propagation of focal paroxysmal activity in the Macaca mulatta at birth and at 24 months. *Brain* 96:757–764.
- Cherian PJ, Deburchgraeve W, Swarte RM, De Vos M, Govaert P, Van Huffel S, Visser GH (2011): Validation of a new automated neonatal seizure detection system: A clinician's perspective. *Clin Neurophysiol* 122:1490–1499.
- Chugani HT, Phelps ME (1986): Maturation changes in cerebral function in infants determined by 18FDG positron emission tomography. *Science* 231:840–843.
- Cowan F, Rutherford M, Groenendaal F, Eken P, Mercuri E, Bydder GM, Meiners LC, Dubowitz LM, de Vries LS (2003): Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 361:736–742.
- Cuffin BN (1996): EEG localization accuracy improvements using realistically shaped head models. *IEEE Trans Biomed Eng* 43:299–303.
- De Vos M, Vergult A, De Lathauwer L, De Clercq W, Van Huffel S, Dupont P, Palmmini A, Van Paesschen W (2007): Canonical decomposition of ictal scalp EEG reliably detects the seizure onset zone. *NeuroImage* 37:844–854.
- De Vos M, Deburchgraeve W, Cherian PJ, Matic V, Swarte RM, Govaert P, Visser GH, Van Huffel S (2011): Automated artifact removal as preprocessing refines neonatal seizure detection. *Clin Neurophysiol* 122:2345–2354.
- Deburchgraeve W, Cherian PJ, De Vos M, Swarte RM, Blok JH, Visser GH, Govaert P, Van Huffel S (2008): Automated neonatal seizure detection mimicking a human observer reading EEG. *Clin Neurophysiol* 119:2447–2454.
- Deburchgraeve W, Cherian PJ, De Vos M, Swarte RM, Blok JH, Visser GH, Govaert P, Van Huffel S (2009): Neonatal seizure localization using PARAFAC decomposition. *Clin Neurophysiol* 120:1787–1796.
- Deburchgraeve W, Cherian PJ, De Vos M, Swarte RM, Blok JH, Visser GH, Govaert P, Van Huffel S (2010): Time varying neonatal seizure localization. *Methods Info Med* 5:473–478.
- Despotovic I, Goossens B, Vansteenkiste E, Philips W (2010a): T_1 - and T_2 -weighted spatially constrained fuzzy c-means clustering for brain MRI segmentation. *SPIE Med Imaging* 76231V–76231V-9.
- Despotovic I, Vansteenkiste E, Philips W (2010b): Brain volume segmentation in newborn infants using multi-modal MRI with a low inter-slice resolution. *Proc IEEE EMBC* 5038–5041.
- Ding L, Worrell GA, Lagerlund TD, He B (2007): Ictal source analysis: localization and imaging of causal interactions in humans. *NeuroImage* 34:575–586.
- Geddes LA, Baker LE (1967): The specific resistance of biological material a compendium of data for the biomedical engineer and physiologist. *Med Biol Eng* 5:271–293.
- Gibson A, Bayford RH, Holder DS (2000): Two-dimensional finite element modelling of the neonatal head. *Physiol Meas* 21: 45–52.
- Goncalves SI, de Munck JC, Verbunt JPA, Bijma F, Heethaar RM, Lopes da Silva F (2003): In vivo measurement of the brain and skull resistivities using an EIT-based method and realistic models for the head. *IEEE Trans Biomed Eng* 50:754–767.
- Hallez H, Vanrumste B, Van Hese P, D'Asseler Y, Lemahieu I, Van de Walle R (2005): A finite difference method with reciprocity used to incorporate anisotropy in electroencephalogram dipole source localization. *Phys Med Biol* 50:3787–3806.

- Hartings JA, Williams AJ, Tortella FC (2003): Occurrence of non-convulsive seizures, periodic epileptiform discharges, and intermittent rhythmic delta activity in rat focal ischemia. *Exp Neurol* 179:139–149.
- Kadam SD, White AM, Staley KJ, Dudek FE (2010): Continuous electroencephalographic monitoring with radio-telemetry in a rat model of perinatal hypoxia-ischemia reveals progressive post-stroke epilepsy. *J Neurosci* 30:404–415.
- Kaiser J (1990): On a simple algorithm to calculate the energy of a signal. *Proc IEEE ICASSP* 1:381–384.
- Kato M, Malamut BL, Caveness WF, Hosokawa S, Wakisaka S, O'Neill RR (1980): Local cerebral glucose utilization in newborn and pubescent monkeys during focal motor seizures. *Ann Neurol* 7:204–212, 230–232.
- Khosla D, Don M, Kwong B (1999): Spatial mislocalization of EEG electrodes—effects on accuracy of dipole estimation. *Clin Neurophysiol* 110:261–271.
- Lai Y, van Drongelen W, Ding L, Hecox KE, Towle VL, Frim DM, He B (2005): Estimation of in vivo human brain-to skull conductivity ratio from simultaneous extra- and intra-cranial electrical potential recordings. *Clin Neurophysiol* 116:456–465.
- Leijser LM, Vein AA, Liauw L, Strauss T, Veen S, Wezel-Meijler G (2007): Prediction of short-term neurological outcome in full-term neonates with hypoxic-ischaemic encephalopathy based on combined use of electroencephalogram and neuro-imaging. *Neuropediatrics* 38:219–227.
- Lombroso CT (1993): Neonatal EEG polygraphy in normal and abnormal newborns. In: Niedermeyer E, Lopes da Silva F, editors. *Electroencephalography, Basic Principles, Clinical Applications, and Related Fields*. Baltimore: Williams & Wilkins. pp803–875.
- Mattes D, Haynor DR, Vesselle H, Lewellen T, Eubank W (2001): Nonrigid multimodality image registration. *SPIE Med Imaging* 1609–1620.
- McBride MC, Laroia N, Guillet R (2000): Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology* 55:506–513.
- Merlet I, Gotman J (2001): Dipole modeling of scalp electroencephalogram epileptic discharges: correlation with intracerebral fields. *Clin Neurophysiol* 112:414–430.
- Michel CM, Murray MM, Lantz G, Gonzales S, Spinelli L, Grave de Peralta R (2004): EEG source imaging. *Clin Neurophysiol* 115:2195–2222.
- Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S (2008): Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal* Ed 93:F187–F191.
- Murray DM, Boylan GB, Ryan CA, Connolly S (2009): Early EEG Findings in Hypoxic-Ischemic Encephalopathy Predict Outcomes at 2 Years. *Pediatrics* 124:e459–e467.
- Murray PW (1981): Field calculations in the head of a newborn infant and their application to the interpretation of transcephalic impedance measurements. *Med Biol Eng Comput* 19:538–546.
- Oostendorp TF, Delbeke J, Stegeman DF (2000): The conductivity of the human skull: results of in vivo and in vitro measurements. *IEEE Trans Biomed Eng* 47:1487–1492.
- Pant S, Te T, Tucker A, Sadleir RJ (2011): The conductivity of neonatal piglet skull. *Physiol Meas* 32:1275–1283.
- Patrizi S, Holmes GL, Orzalesi M, Allemand F (2003): Neonatal seizures: characteristics of EEG ictal activity in preterm and fullterm infants. *Brain Dev* 25:427–437.
- Plummer C, Harvey AS, Cook M (2008): EEG source localization in focal epilepsy: where are we now? *Epilepsia* 49:201–218.
- Prastawa M, Gilmore JH, Lin W, Gerig G (2005): Automatic segmentation of MR images of the developing newborn brain. *Med Image Anal* 9:457–466.
- Quesney LF (1991): Preoperative electroencephalographic investigation in frontal lobe epilepsy: electroencephalographic and electrocorticographic recordings. *Can J Neurol Sci* 18(4 Suppl):559–563.
- Roche-Labarbe N, Aarabi A, Kongolo G, Gondry-Jouet C, Dümpelmann M, Grebe R, Wallois F (2008): High-resolution electroencephalography and source localization in neonates. *Hum Brain Mapp* 29:167–176.
- Roth B, Gorbach A, Sato S (1993): How well does a three-shell model predict positions of dipoles in a realistically shaped head? *Electroencephalogr Clin Neurophysiol* 87:175–184.
- Rush S, Driscoll DA (1986): Current distribution in the brain from surface electrodes. *Anesth Analgesia* 47:717–723.
- Rutherford MA, Pennock JM, Counsell SJ, Mercuri E, Cowan FM, Dubowitz LM, Edwards AD (1998): Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxicischaemic encephalopathy. *Pediatrics* 102:323–328.
- Saha S, Williams PA (1992): Electric and dielectric properties of wet human cortical bone as a function of frequency. *IEEE Trans Biomed Eng* 39:1298–1304.
- Salanova V, Quesney LF, Rasmussen T, Andermann F, Olivier A (1994): Reevaluation of surgical failures and the role of reoperation in 39 patients with frontal lobe epilepsy. *Epilepsia* 35:70–80.
- Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ (1993): Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. *Pediatrics* 91:128–134.
- Shi F, Fan Y, Tang S, Gilmore JH, Lin W, Shen D (2010): Neonatal brain image segmentation in longitudinal MRI studies. *Neuroimage* 49:391–400.
- Shi F, Shen D, Yap PT, Fan Y, Cheng JZ, An H, Wald LL, Gerig G, Gilmore JH, Lin W (2011): CENTS: Cortical enhanced neonatal tissue segmentation. *Hum Brain Mapp* 32:382–396.
- Silva C, Almeida R, Oostendorp T, Ducla-Soares E, Foreid JP, Pimentel T (1999): Interictal spike localization using a standard realistic head model: simulations and analysis of clinical data. *Clin Neurophysiol* 110:846–855.
- Sled JG, Zijdenbos AP, Evans AC (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imag* 17:87–97.
- Steinman KJ, Gorno-Tempini ML, Glidden DV, Kramer JH, Miller SP, Barkovich AJ, Ferriero DM (2009): Neonatal watershed brain injury on magnetic resonance imaging correlates with verbal IQ at 4 years. *Pediatrics* 123:1025–1030.
- Swarte R, Lequin M, Cherian P, Zecic A, van Goudoever J, Govaert P (2009): Imaging patterns of brain injury in term-birth asphyxia. *Acta Paediatr* 98:586–592.
- Thevenaz P, Unser M (2000): Optimization of mutual information for multi resolution image registration. *IEEE Trans Image Processing* 9:2083–2099.
- Thurairai M, Goodridge VD, Sheppard RJ, Grant EH (1984): Variation with age of the dielectric properties of mouse brain cerebrum. *Phys Med Biol* 29:1133–1136.
- Van Hoey G, Vanrumste B, D'Have M, Van de Walle R, Lemahieu I, Boon P (2000): Influence of measurement noise and electrode

- mislocalization on EEG dipole source localization. *Med Biol Eng Comput* 38:287–296.
- Vanhatalo S, Metsäranta M, Andersson S (2008): High fidelity recording of brain activity in the extremely preterm babies: Feasibility study in the incubator. *Clin Neurophysiol* 119:439–445.
- Vanrumste B, Van Hoey G, Van de Walle R, D’Have M, Lemahieu I, Boon P (2000): Dipole location errors in electroencephalogram source analysis due to volume conductor model errors. *Med Biol Eng Comput* 38, 528–534.
- Vanrumste B, Van Hoey G, Van de Walle R, D’Have M, Lemahieu I, Boon P (2001): The validation of the finite difference method and reciprocity for solving the inverse problem in EEG dipole source analysis. *Brain Topogr* 14, 83–92.
- Vatta F, Meneghini F, Esposito F, Mininell S, Di Salle F (2010): Realistic and spherical head modeling for EEG forward problem solution: a comparative cortex-based analysis. *Comput Intell Neurosci* 972060.
- Volpe JJ. 2008. *Neurology of the Newborn*, 5th ed. Philadelphia: WB Saunders.
- Volpe JJ, Pasternak JF (1977): Parasagittal cerebral injury in neonatal hypoxic-ischemic encephalopathy: clinical and neuroradiologic features. *J Pediatr* 91:472–476.
- Wang Y, Gotman J (2001): The influence of electrode location errors on EEG dipole source localization with a realistic head model. *Clin Neurophysiol* 112:1777–1780.
- Watanabe K, Miyazaki S, Hara K, Hakamada S (1980): Behavioral state cycles, background EEGs and prognosis of newborns with perinatal hypoxia. *Electroencephalogr Clin Neurophysiol* 49:618–625.
- Weisenfeld NI, Warfield SK (2009): Automatic segmentation of newborn brain MRI. *NeuroImage* 47:564–572.
- Xue H, Srinivasan L, Jiang S, Rutherford M, Edwards AD, Rueckert D, Hajnal JV (2007): Automatic segmentation and reconstruction of the cortex from neonatal MRI. *NeuroImage* 38:461–477.
- Yvert B, Bertrand O, Thevenet M, Echallier JF, Pernier J (1997): A systematic evaluation of the spherical model accuracy in EEG dipole localization. *Electroencephalogr Clin Neurophysiol* 102:452–459.