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Electroencephalographic inverse localization of brain activity in acute traumatic brain injury as a guide to surgery, monitoring and treatment

Andrei Irimia[a], S.-Y. Matthew Goh[a], Carinna M. Torgerson[a], Nathan R. Stein[b], Micah C. Chambers[c], Paul M. Vespa[b], John D. Van Horn[a,*]

[a] The Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Los Angeles, USA
[b] Brain Injury Research Center, Department of Neurosurgery, University of California, Los Angeles, USA
[c] Department of Neurology, University of California, Los Angeles, USA

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ABSTRACT

Objective: To inverse-localize epileptiform cortical electrical activity recorded from severe traumatic brain injury (TBI) patients using electroencephalography (EEG).
Methods: Three acute TBI cases were imaged using computed tomography (CT) and multimodal magnetic resonance imaging (MRI). Semi-automatic segmentation was performed to partition the complete TBI head into 25 distinct tissue types, including 6 tissue types accounting for pathology. Segmentations were employed to generate a finite element method model of the head, and EEG activity generators were modeled as dipolar currents distributed over the cortical surface.
Results: We demonstrate anatomically faithful localization of EEG generators responsible for epileptiform discharges in severe TBI. By accounting for injury-related tissue conductivity changes, our work offers the most realistic implementation currently available for the inverse estimation of cortical activity in TBI.
Conclusion: Whereas standard localization techniques are available for electrical activity mapping in uninjured brains, they are rarely applied to acute TBI. Modern models of TBI-induced pathology can inform the localization of epileptogenic foci, improve surgical efficacy, contribute to the improvement of critical care monitoring and provide guidance for patient-tailored treatment. With approaches such as this, neurosurgeons and neurologists can study brain activity in acute TBI and obtain insights regarding injury effects upon brain metabolism and clinical outcome.

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1. Introduction

Electroencephalography (EEG) plays an important role in the treatment of critically ill patients [1,2], in the monitoring of acute traumatic brain injury (TBI) [3,4] and in the preoperative planning of epileptogenic focus removal [5–7]. The use of continuous EEG (cEEG) is particularly important in the neurointensive care treatment of patients with TBI and with status epilepticus, where cEEG can allow clinicians to determine treatment effectiveness in patients undergoing continuous infusion of antiseizure drugs [8]. The Neurocritical Care Society has suggested that cEEG, rather than serum drug levels, should guide therapy of refractory status epilepticus [8], which highlights the importance of this method in the acute care of patients with epileptic seizures.

Recent research on acute TBI pathophysiology has led to renewed interest in the potential use of cEEG to improve TBI outcomes [3,9,10]. When combined with physiologically driven decision making via multimodal brain monitoring, EEG can aid neurointensivists to determine when the brain is at risk for injury and whether clinical intervention is warranted to prevent permanent brain damage [11]. Unfortunately, though scalp EEG can provide much clinically useful information, its spatial resolution is too low for the task of resolving the detailed spatial patterns of electric activity in the hours and days following brain trauma. This makes it difficult to determine which specific brain locations exhibit TBI-related pathophysiology, which largely precludes the integration of EEG with structural neuroimaging methods such as magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) to improve clinical decision making.

In the context of the present article, inverse localization involves the process of computationally estimating the locations, orientations and strengths of the electric currents in the brain which generate EEG signals. As a consequence of being a noninvasive method for identifying the sources of brain activity, EEG inverse localization has been used extensively in the past to identify and

* Corresponding author at: The Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, 2001 North Soto Street, Room 102, MC 9232, Los Angeles CA 90089-9235, USA. Tel.: +1 323 442 7246; fax: +1 323 442 7246.
E-mail address: jvanhorn@usc.edu (J.D. Van Horn).

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to study the neurophysiological correlates of phenomena such as sleep, cognition and affect [12,13].

Given the past and present usefulness of EEG in the context of acute TBI clinical care, the absence of neurological and neurosurgical insights derived from EEG inverse localization may equate to missed opportunities to track acute injury evolution both spatially and temporally, with possibly negative consequences upon the formulation of treatment decisions for TBI patients. Thus far, the use of inverse localization methods in TBI has been extremely limited because standard source localization techniques can generate inaccurate results in the presence of pathology. The anatomy of the TBI head and the spatial variations in its conductivity have previously been challenging to take into account, and EEG inverse localization has been used very seldom in the TBI research community, let alone the neurointensive care setting.

In this paper, we demonstrate the use of anatomically precise models derived from multimodal MRI to localize epileptiform electrical activity recorded noninvasively from severe TBI patients using scalp EEG. Our contribution illustrates a realistic, patient-specific approach to TBI source localization and the investigation itself can be appropriately conceptualized as a proof-of-concept study to assess the feasibility of the implemented method.

2. Materials and methods

Participants included three males of ages 31, 25 and 45, respectively, from whom MRI volumes were acquired at 3.0 Tesla (1 mm^3 voxel size, Siemens Trio TIM Scanner, Erlangen, Germany) within 72 h after injury. Although the Glasgow coma scale (GCS) scores of the three patients upon admission to the neurointensive care unit (NICU) were 9, 14 and 14, respectively, their Glasgow outcome scale (GOS) score upon transfer from the NICU was 3 for all patients, reflecting the severity of their injuries as well as the decline of their clinical condition subsequent to hospital admission. The study was approved by the Institutional Review Board of the School of Medicine at the University of California, Los Angeles, and signed informed consent was obtained from the patients' legally authorized representatives prior to the performance of any procedure (UCLA IRB approval #10-000929 dated 11/8/2012). The three subjects are examples of TBI patients with progressive lesion loads and were selected for the study based on (1) the type, location and spatial extent of their lesions, as well as (2) the presence of epileptiform discharges in their cEEG recordings, as identified in the EEG recordings subsequent to their acquisition (see below).

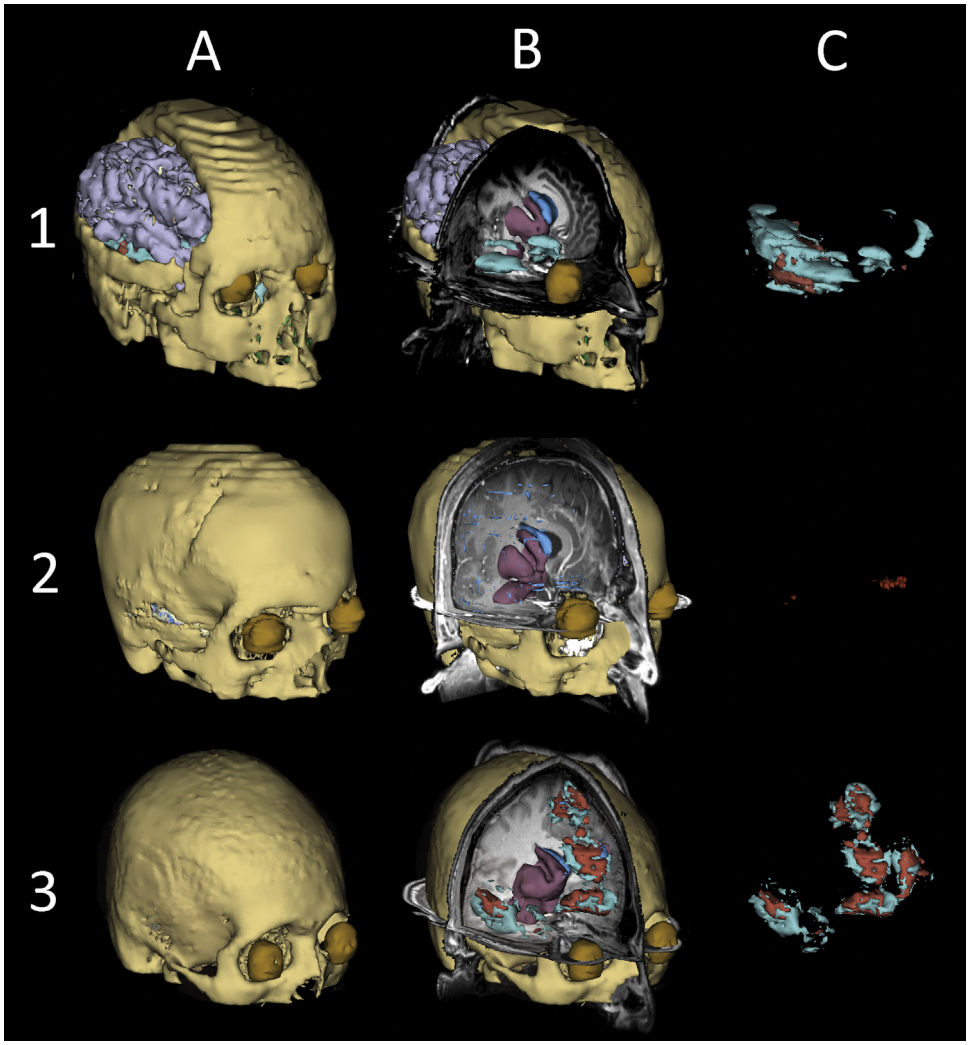

Fig. 1. Three-dimensional models of representative tissue types in three sample TBI patients. Models were generated in 3D Slicer [16] based on MRI volume segmentations. For each subject, the full model is shown in the first column (A), cross-sections through the head are shown in the second column (B), and TBI-related brain pathology is displayed in the third column (C). Each row corresponds to a patient. In (B), MRI T_1 images are superposed onto each FEM model, and 3D models of subcortical structures, CSF and pathology are also shown available. Skin is omitted for convenience. Bone is shown in light brown, eyes in dark brown, gray matter in lilac, subcortical structures in purple, CSF in blue, edema in cyan and hemorrhage in red.

The TBI neuroimaging protocol is described extensively elsewhere [14]. Briefly, acquired MRI sequences included magnetization prepared rapid acquisition gradient echo (MP-RAGE) T_1-weighted imaging, fluid attenuated inversion recovery (FLAIR), turbo spin echo (TSE) T_2-weighted imaging, gradient-recalled echo (GRE) T_2-weighted imaging, and susceptibility weighted imaging (SWI). Conventional computed tomography (CT) scans were also acquired. Image alignment, bias field correction and skull stripping were performed using the LONI (Laboratory of Neuro Imaging) Pipeline (http://pipeline.loni.ucla.edu/). White matter (WM), gray matter (GM), cerebrospinal fluid (CSF), cerebellar WM/GM and subcortical structures were segmented in FreeSurfer (FS) [15], and manual correction of tissue labeling errors was performed by three experienced users with training in neuroanatomy. TBI-related lesions were segmented from GRE/SWI/FLAIR volumes as detailed elsewhere [14], skin was segmented from T_1 MRI, and hard bone was segmented from CT. Eyes, muscle, cartilage, mucus, nerves, teeth, and ventriculostomy shunts were segmented from T_1/T_2 MRI. 3D models and visualizations were created using 3D Slicer (http://www.slicer.org/) [16].

Acquisition of cEEG recordings from each patient was performed in the NICU at 250 Hz over three consecutive days using a standard referential electrode montage. Because scalp EEG potentials are due to electrical currents within the apical dendrites of cortical pyramidal neurons [17], EEG generators were modeled as dipolar currents oriented perpendicular with respect to the cortical surface. A total of 25 tissue types with distinct conductivity values were modeled, including healthy-appearing and edematous skin, fat, hard and soft bone, cerebrospinal fluid (CSF), healthy-appearing and edematous GM, healthy-appearing and edematous WM, cerebellum, spinal cord, subcortical structures, epidural hemorrhages, connective tissue, muscle, eyes, cartilages, mucus, nerves, teeth, silicone polyurethane (the manufacturing material of the ventriculostomy shunts), and sinus air. After co-registering the head and all sensor locations, each head volume was discretized into volume elements from which finite element method (FEM) models were generated [18,19]. For each subject, a regular grid-based mesh (~400,000 nodes, ~450,000 linear elements, ~2 mm average edge length) was created and the so-called forward matrix (the values of the electric potential at each sensor due to every cortical source) was computed [18].

The inverse localization technique employed has been widely used for the study of epilepsy [20–22] and its technical details have been comprehensively explored elsewhere [23,24], particularly in our previous publication [25]. Briefly, source localization is performed using a minimum-norm inverse linear operator [26] which seeks to minimize the expected difference between the estimated and the true inverse solution. The localization accuracy of each model can be quantified using the localization error (LE) measure, defined as the distance from the estimated source location to the true source location [27]. Previous results on our TBI-specific implementation [25] indicate that the latter can localize cortical sources in the presence of brain injury with an approximate LE in the range of ~0.5–1.5 cm for relatively superficial sources (i.e. most gyri and sulci), and ~1.5–2.5 cm for deep sources (e.g. insula and cingulate cortex). To visualize the results of the source localization process, the inverse estimate of the cortical activity can be mapped onto the surface of a reference brain using t scores, such that the magnitude of t associated with some cortical location indicates the likelihood for that location to be electrically active. The locations most likely to be active have $|t| > 4$. The sign of t indicates whether the localized electric current is oriented out of ($t > 0$) or into ($t < 0$) the cortex (see Figs. 2 and 3 for details and examples).

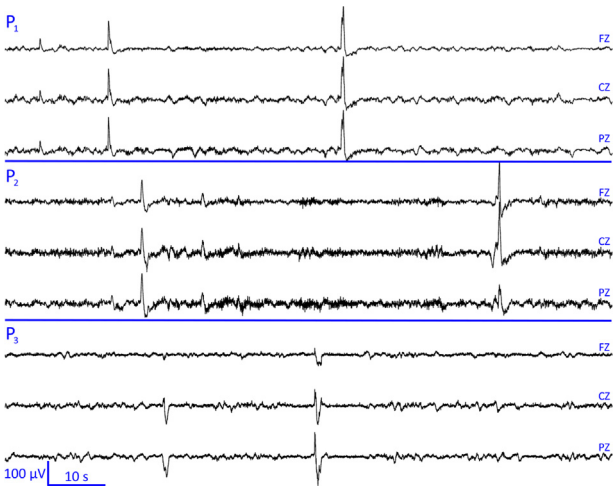

Fig. 2. Sample 60-s EEG recordings for three representative sensors (FZ, CZ and PZ) in each of the three patients denoted as P_1, P_2, and P_3, respectively. Note, in each case, the aperiodic epileptiform spikes and their large magnitudes compared to the rest of the recording.

3. Results

For each subject, each row of Fig. 1 displays anatomical 3D models of the appropriate subject included in the study. The first column (A) displays the full model (except skin), while the second column (B) shows cross-sections through the head with MRI T_1 superposed onto each FEM model. Also included in (B) are 3D models of subcortical structures, CSF and pathology where available. The third column (C) only displays brain pathology visible in the MR scans (edematous and hemorrhagic GM/WM, as segmented from GRE T_2 and SWI imaging, see Methods section). As Fig. 1 shows, each selected patient exhibits variable lesion loads and types of pathology; whereas fronto-temporal lesions and a large craniotomy are both visible in the right hemisphere of Patient 1, Patient 2 exhibits a comparably low lesion load. Patient 3, by contrast, has large lesions over both frontal and temporal cortices.

Fig. 2 illustrates 60 s of EEG recordings from each patient, containing aperiodic epileptiform spikes, and Fig. 3 shows examples of inverse localization for the three selected patients. Each subject's illustration demonstrates the localization of the cortical source responsible for the generation of an interictal epileptiform discharge. In each patient, the EEG signal (i.e. sensor-space) waveform associated with the localized activity is shown, and the EEG potentials recorded at the time of the discharge are mapped over the scalp using the interpolated values of the potentials measured at each sensor (see figure caption for details). The inverse estimate of the cortical activity responsible for the epileptiform activity is mapped onto the surface of a reference brain as Student's t scores, such that the magnitude of t associated with some cortical location indicates the likelihood for that location to be electrically active at the time of the spike. Thus, the locations most likely to be active have $|t| > 4$. The sign of t indicates whether the electric current at the location in question is oriented out of ($t > 0$) or into ($t < 0$) the cortex.

Comparing EEG topographic maps to cortical localization plots reveals that, for every patient, the epileptiform discharge was localized to the same cortical region below the scalp where the negative deflection in electric potential had been identified in the topographic map. Additionally, however, epileptiform activity generators were localized to specific gyri or sulci at previously unavailable resolution. In the first subject, the epileptiform generator is localized to the left middle temporal gyrus, whereas in the second subject it is localized to the precentral sulcus of the

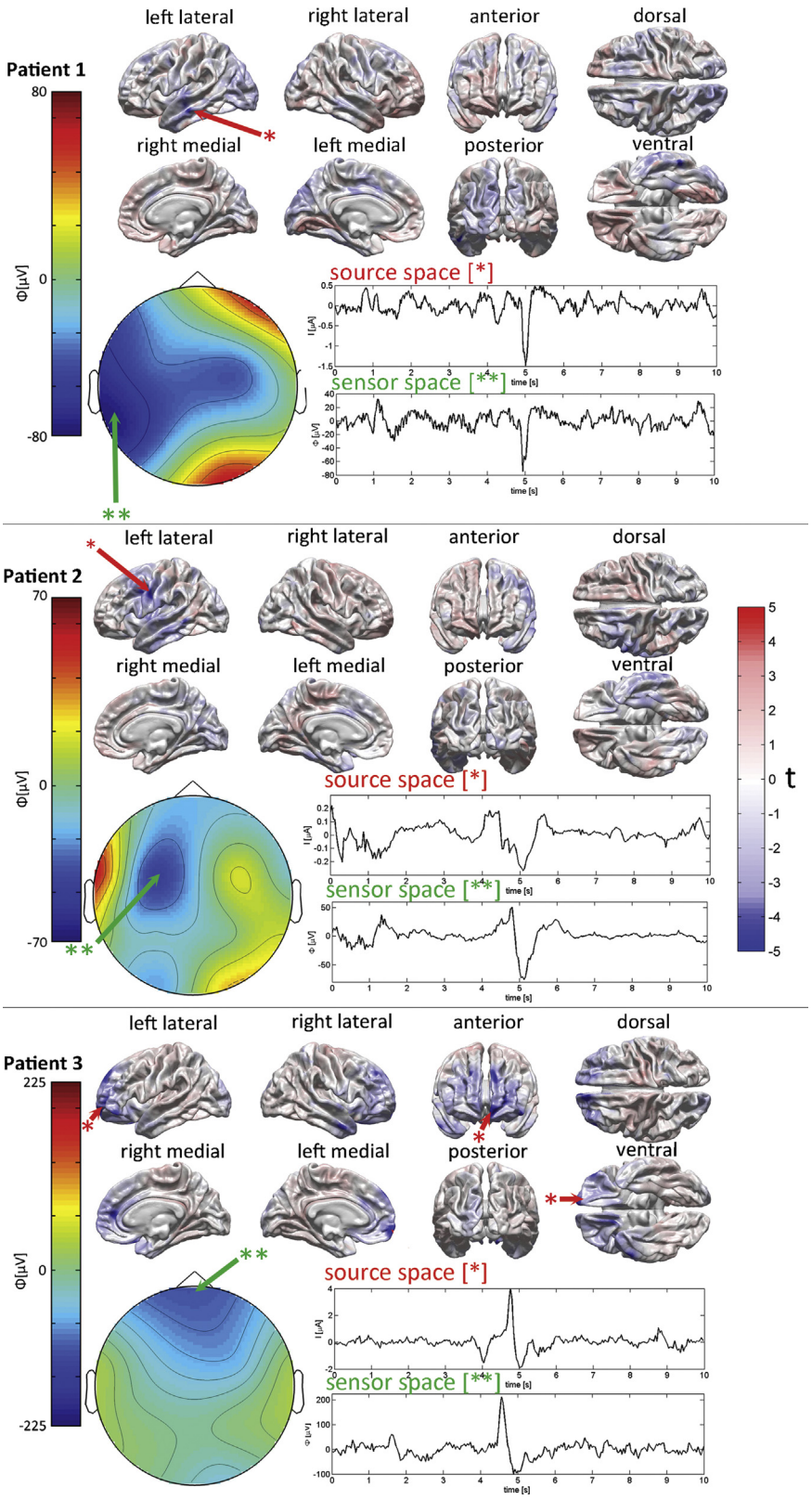

Fig. 3. Examples of inverse localization in three acute TBI patients. The localization technique is used to identify the cortical source responsible for the generation of an EEG waveform containing a large-magnitude deflection (often referred to as a "graphoelement" in the EEG literature). For each subject, the waveform of the EEG potential, Φ, being localized is shown for an interval of 10 s. Localization is illustrated at the time point with a latency of 5 s with respect to the beginning of the waveform. The EEG potentials recorded at this time point are mapped over the scalp using the interpolated values of the potentials measured at each sensor. The amplitudes of the potential Φ are measured in μV and different ranges are used for the topographic map of each subject to emphasize scalp differences in potential which are specific to each subject. The inverse estimate of the cortical activity responsible for the graphoelement is mapped onto the surface of a reference brain as t scores (see Methods section). The locations most likely to be active have $|t| > 4$. The sign of t indicates whether the localized electric current is oriented out of ($t > 0$, red hues) or into ($t < 0$, blue hues) the cortex. A single color map is used for t in all subjects, and color intensity indicates likelihood for the presence of electrical activity. In each subject, the scalp location which exhibits

left hemisphere. In the third subject, as one might expect based on the scalp potential map, the most likely source responsible for the activity is identified in the frontopolar region of the left hemisphere. The sensor-space (scalp potential, in μV) and source-space (cortical current, in μA) waveforms are similar but not identical due to the physical effect of superposition, whereby the total scalp potential is the sum of potentials due to all active sources (many of which do not contribute to the recorded discharge).

4. Discussion

EEG monitoring as practiced for the critical care of acute TBI has typically focused on seizure identification in contrast to source localization. Reasons for this are manifold, including the complexity of structural changes affecting the TBI brain and the computational difficulty of modeling them accurately. However, because many clinical centers routinely obtain high-resolution CT and MRI data of the brain following admission to the NICU, leveraging such data to identify skin, skull, intact and injured brain in addition to hemorrhagic and edematous lesions can be used to look beyond the simple presence or absence of seizures toward precise localization of electrical sources. Currently, the relationship between the spatial configuration of epileptiform activity generators and that of brain atrophy is insufficiently understood [4], as is the manner in which these two factors jointly contribute to brain tissue fate [28,29]. However, because epileptiform discharge frequency appears to be correlated with clinical outcome [10,30], inverse localization of brain locations which initiate such discharges may reveal the spatiotemporal relationships between these factors, permitting the use of EEG to identify brain locations which are likely to experience atrophy in the months and years following injury.

Evidence from multiple sources indicates that EEG-derived information on the spatial profile of neuronal activity after brain injury could provide insights on how acute pathophysiology influences clinical outcome. For example, acute EEG recordings from cerebral ischemia patients with poor outcome exhibit significantly more spreading depolarizations of gray matter cells than those of patients with good outcome [31]. Because the spatial pattern of neuronal activity in these patients correlates with both neurological deficits and with clinical symptoms [31], spatial information on such patterns obtained using EEG inverse localization could be clinically insightful. For example, studies on spreading depolarizations due to anoxia in the ischemic brain have led to some optimism that their detailed characterization could offer real-time insight and comprehensive indications of progressive ischemic injury when the latter phenomenon is known to occur [32–35]. It has even been suggested that acute therapeutic strategies might be tailored based on electrophysiological information provided by EEG to protect the ischemic penumbra from recruitment into the injury core [33]. Vespa et al. [36] have suggested that depolarization events could occur in perihematomal brain tissue and then lead to regional hyperglycolysis and metabolic crisis, and that ongoing injury occurring in metabolic penumbral tissue may be a new clinical target for pharmacological intervention to interrupt electric depolarization. In this context, it is plausible that inverse localization of EEG potentials could complement measures of metabolic dysfunction in the attempt to monitor and reduce the effects of brain ischemia. Because neuronal activity and cerebral blood flow are coupled, large decreases in the latter are associated with EEG frequency changes, and this is partly why intraoperative EEG monitoring has long been used in patients at high risk of cerebral ischemia [37]. Because cEEG can detect time windows in which surgical intervention can potentially prevent permanent brain damage [38,39], EEG inverse localization could be useful to neurosurgeons by identifying brain regions at risk of permanent ischemic brain injury in acute TBI patients, thereby possibly also improving surgical efficacy. Because spreading depolarizations have been detected in human TBI only invasively via electrocorticography (ECoG) [34,35], the prospects for deriving clinically useful information from such phenomena in routine TBI cases remain poor due to the need for invasive intervention. Consequently, the availability of inverse localization methods to detect and study TBI-related disruptions in brain function could ease ongoing translational efforts to use electrophysiological indicators as prognostic factors during acute TBI treatment.

Though anatomically faithful approaches have been used to model the TBI head in contexts ranging from transcranial current stimulation [40] to military blast simulations [41], brain source localization in the presence of brain lesions has been very infrequent. Even when it was performed [42], spherical head models were used most often despite being considerably less realistic than ours and therefore less likely to be appropriate for inverse localization. Given that increased forward model realism translates into improved accuracy when estimating the sources of electrical activity in the brain [43], the localization method applied here constitutes an appreciable improvement over existing methods for electric source localization in TBI patients.

While analysis techniques can be directly applied to recorded EEG signals without performing inverse localization, such methods are unlikely to provide accurate information regarding the spatial profile of cortical electrical activity during the hours and days following TBI. In addition, such methods do not take into account information pertaining either to the anatomy of the head or to spatial variations in its conductivity. Thus, the approach illustrated here has advantages over conventional analysis methods which are commonly used to study the uninjured brain, and anatomically constrained source modeling should be seen as a potentially valuable tool for the study of TBI-related pathophysiology in a clinical setting. For most cortical locations, the LEs to be expected from this approach are generally comparable to or lower than those of other methodologies which do not account for injury-related pathology [26,27]. Nevertheless, improvements in localization accuracy can be achieved in this context by various means, such as by applying inverse algorithms with superior spatial accuracy [44], obtaining EEG measurements with higher SNR [43,45], increasing the scalp density of EEG sensors [46], refining the forward model (e.g. by accounting for tissue anisotropies) [47,48], combining EEG with other modalities such as functional MRI [49] or magnetoencephalography (MEG) [27], etc. In the case of the latter technique, the use of combined EEG/MEG recordings is likely to improve localization accuracy, although multiple challenges are likely to exist from the standpoint of acquiring such simultaneous recordings. One reason for this is related to the logistical difficulty of acquiring MEG recordings in a magnetically shielded room while simultaneously carrying out clinical monitoring and intervention. In addition, localization of cortical sources in TBI can involve the challenge of accounting for the magnetic noise due to (large) accumulations of blood iron in hemorrhagic areas. Despite these and other considerations, however, the use of simultaneous EEG/MEG recordings in the context of this study is likely to be benefic [26] and should be considered in facilities which possess the required instrumentation.

the largest negative values at a latency of 5 s is indicated by a green arrow. Similarly, the cortical location with the most negative value of $|t|$ corresponding to the spike generator is indicated by a red arrow. The waveform of the electric current (measured in μA) at the most likely location of each generator is depicted in addition to the sensor space waveform of the scalp potential (measured in μV).

5. Conclusion

Inverse localization of electrical activity in acute TBI patients using anatomically faithful models derived from multimodal MRI/CT may be useful for the localization of epileptogenic foci, the improvement of surgical efficacy, the enhancement of critical care monitoring and for guiding patient-tailored treatment. Such approaches might allow neurosurgeons and neurologists to study brain activity in acute TBI and to obtain insights regarding injury and surgical effects upon patient recovery. This implementation for inverse localization could also facilitate experimental studies to investigate the relationship between brain metabolism and electric pathophysiology in acute TBI [32]. Thus, because severe brain injury is believed to give rise to metabolic crisis and can have major effects upon the potential for outcome and recovery, accurate spatial mapping of electrical brain activity is important. Aside from its relevance to the study of pathophysiology in acute TBI, this source localization approach may also be of interest to the study of stroke, where the occurrence of cortical spreading depolarization and peri-infarct depolarization early after brain injury have been identified using subdural ECoG [32]. Compared to the latter, however, inverse localization of EEG potentials in TBI patients holds the advantage of being non-invasive, thereby allowing neurointensive care professionals to study electrical activity with more ease in advance of, or as an adjunct to, a surgical course of treatment.

Our primary aim in the foregoing has been to demonstrate a methodological approach which could be used to inform patient treatment and to improve TBI outcome scores, rather than focus on the type of novel information regarding TBI pathophysiology which can be obtained using this method. Importantly, our use of a highly detailed anatomical model to perform inverse localization in TBI patients is crucial for the purpose of obtaining highly accurate estimates of brain activity locations. Future studies in our laboratory will aim to incorporate the method presented here with our previous use of EEG to prognosticate TBI outcome [3,4,50–52] and to evaluate the extent to which the proposed methodology can be used throughout the clinical management of TBI patients with acute epileptiform discharges in order to improve their clinical outcome.

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Industry affiliation and conflict of interest statement

The authors declare no potential conflicts of interest.

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