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Multimodal, noninvasive seizure network mapping software: A novel tool for preoperative epilepsy evaluation

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ABSTRACT

Background: Despite rigorous preoperative evaluation, epilepsy surgery achieves seizure freedom in only two-thirds of cases. Current preoperative evaluation does not include a detailed network analysis despite the association of network-level changes with epilepsy.
Objective: We sought to create a software algorithm to map individualized epilepsy networks by combining non-invasive electroencephalography (EEG) source localization and nonconcurrent resting state functional magnetic resonance imaging (rsfMRI).
Methods: Scalp EEG and rsfMRI data were acquired for three sample cases: one healthy control case, one case of right temporal lobe epilepsy, and one case of bitemporal seizure onset. Data from rsfMRI were preprocessed, and a time-series function was extracted. Connection coefficients were used to threshold out spurious connections and model global functional networks in a 3D map. Epileptic discharges were localized using a forward model of cortical mesh dipoles followed by an empirical Bayesian approach of inverse source reconstruction and co-registered with rsfMRI. Co-activating brain regions were mapped.
Results: Three illustrative sample cases are presented. In the healthy control case, the software showed symmetrical global connectivity. In the right temporal lobe epilepsy case, asymmetry was found in the global connectivity metrics with a paucity of connectivity ipsilateral to the epileptogenic cortex. The superior longitudinal fasciculus, uncinate fasciculus, and commissural fibers connecting disparate and discontinuous cortical regions involved in the epilepsy network were visualized. In the case with bitemporal lobe epilepsy, global connectivity was symmetric. It showed a network of correlating cortical activity local to epileptogenic tissue in both temporal lobes. The network involved white matter tracks in a similar pattern to those seen in the right temporal case.
Conclusions: This modeling algorithm allows better definition of the global brain network and potentially demonstrates differences in connectivity between an epileptic and a non-epileptic brain. This finding may be useful for mapping cortico-cortical connections representing the putative epilepsy networks. With this methodology, we localized the epileptogenic brain and showed network asymmetry and long-distance cortical co-activation. This software tool is the first to use a multimodal, nonconcurrent, and noninvasive approach to model and visualize the epilepsy network.

1. Introduction

1.1. Preoperative analysis in epilepsy surgery

Epilepsy is one of the most common neurologic disorders with a prevalence of 0.5–1% [1]. Current data show that epilepsy in 20–30% of patients is refractory to medical therapy, and these patients are therefore possible candidates for resective neurosurgery [2]. Surgical candidates are evaluated using magnetic resonance imaging (MRI) to evaluate brain structure and electroencephalography (EEG) to identify and localize ictal and interictal activity. These two techniques are the most common ways to identify epileptic foci for targeted resection. Wada testing, functional MRI (fMRI), and neuropsychological evaluation are used to determine laterality of speech and memory function to minimize morbidity. Despite rigorous presurgical evaluation, resective surgery achieves seizure freedom in only two-thirds of cases [2]. Increasing the effectiveness of surgery will most likely either come from more accurate and precise surgical target mapping or more specific identification of candidates who will be responsive to surgery.

Abbreviations: MRI, magnetic resonance imaging; rsfMRI, resting state functional MRI; EEG, electroencephalography; SEEG, stereoencephalography; CSF, cerebrospinal fluid; BOLD, blood oxygen level dependent; ROI, region of interest; DTI, diffusion tensor imaging.

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1.2. Epilepsy as a network disorder

Recently, epilepsy has been reimagined as a network-level disorder. Alteration of global brain networks, mapped using graph theory techniques, has been shown in patients with epilepsy. Network-level alterations are characterized by decreased connectivity globally, decreased connection to the default-mode network, and increased small-world network segregation in the region of epileptogenic tissue [3–13]. Recent studies have demonstrated the value of resting state functional MRI (rsfMRI) in mapping brain networks [8,14–19]. The epileptogenic cortex can be identified by applying EEG source-localization algorithms [12,20–23]. Nonetheless, no generally available software is capable of mapping that network using conventional hardware, which includes MRI and scalp EEG. The field of individualized network analysis is still in its infancy, and potential uses for this technology can be categorized into three broad categories: diagnosis of epilepsy, identification of surgical candidates, and localization of surgical resection targets. Supporting evidence for the first category includes studies showing connectivity parameters from rsfMRI and EEG synchronicity used to create "biomarkers" for diagnosis of epilepsy and measure the progression of seizure-related atrophy [24,25]. For the second category, network asynchrony local to the epileptogenic focus and network correlation similarities with a retrospective cohort of patients with Engel class III–IV outcomes postsurgery have been used to prospectively identify ideal candidates who will have the best outcomes after surgery [26–28]. Finally, surgical targeting and resection of functional hubs, or network relay points, have been correlated with better surgical outcomes [29,30].

1.3. Network mapping techniques

Network mapping is made possible by taking measurements of brain activity over time and interpreting the data using a combination of correlation analysis, causality analysis, and graph-theory mapping techniques that implement correlation and/or causation to create a directed or non-directed graph [31]. Noninvasive scalp EEG is a sensitive modality to detect epileptiform discharges and has unmatched temporal resolution. However, it is characteristically limited in spatial accuracy because of the dampening effects of the brain, cerebrospinal fluid (CSF), bone, and skin. Comparatively, rsfMRI has better spatial resolution but lacks the temporal resolution needed to localize propagation patterns of ictal or interictal discharges. An algorithm that combines the two datasets would maximize the benefits and minimize the drawbacks of both technologies. Concurrently measured EEG and rsfMRI have been used to map brain connectivity [32], but the specialized hardware required is not commonly available. Stereoencephalography (SEEG) has been used in connectivity studies to dramatically improve the spatial accuracy of EEG measurements [31]. However, SEEG is necessarily an invasive measurement tool and is therefore not appropriate for all patients with epilepsy.

1.4. Objective

We developed a software algorithm that co-registers nonconcurrent scalp EEG and rsfMRI to create a 3D network map of each patient with epilepsy. The data used are purposefully nonconcurrent so that the algorithm could be optimized for analysis of data collected on commonly available scalp EEG and diagnostic MRI machines. This software algorithm is the first to map the epilepsy network noninvasively and with nonconcurrent EEG and rsfMRI data.

2. Materials and methods

2.1. Patient demographics

The algorithm was applied in three illustrative sample cases. These cases were selected because they present with disparate preoperative diagnoses that most likely represent situations with variable neural network characteristics. The first sample case is a healthy control, the second patient is a typical case of mesial temporal lobe epilepsy (MTLE), and the last one is a patient with bitemporal seizure onset.

First, a 27-year-old male with no history of neurological disorders was analyzed as a healthy control. The second sample case was a 33-year-old female patient with left temporal lobe epilepsy with an eight-year history of intractable epilepsy. Long-term EEG monitoring (LTM) revealed slow, sharply contoured rhythmic 1- to 2-Hz delta activity evolving to spike–wave and polyspike–wave 2-Hz morphology, which disseminated to the left frontocentral and contralateral temporal regions and generalizes within 3 s. Wada testing showed that expressive language lateralized to the right hemisphere and that memory was supported primarily in the right hemisphere. Positron emission tomography showed mild left mesial temporal hypometabolism. The third sample case was a 25-year-old male patient with bitemporal seizure onset with a history of seizures for five years. Long-term EEG monitoring showed frequent interictal sharp waves in the right temporal region and rare, less well-formed sharp waves in the left temporal region. Seven of eight seizures had left hemispheric onset with a burst of rhythmic 7- to 8-Hz theta/alpha activity over the left frontotemporal region with evolution to rhythmic 3- to 4-Hz delta/theta activity and at times followed by periodic sharp waves at 0.5–1 Hz lasting 30–90 s. The only seizure with a right-sided onset showed a burst of rhythmic 11- to 12-Hz alpha activity in the right frontotemporal region with evolution to rhythmic 3- to 4-Hz theta/delta activity and followed by periodic sharp waves at 0.5 Hz lasting 90 s. Wada testing showed that language expression and memory were supported bilaterally.

2.2. Data acquisition

Electroencephalography and rsfMRI were obtained as part of a standard epilepsy workup. Electroencephalography was acquired with twenty-four scalp electrodes in a standard International 10–20 configuration using an off-the-shelf Natus Neurology Long-Term-Monitoring EEG system (Natus Medical Inc., Pleasanton, CA). Resting state functional MRI was conducted in a 3-Tesla MRI scanner (Siemens, Munich, Germany) with a blood oxygenation level-dependent (BOLD) MRI sequence. Resting state functional MRI was acquired for a single run of 5 min with a repetition time (TR) of 3000 ms with the patient lying supine with eyes closed. Axial, noncontrast T1-weighted MRI with 1-mm slice thickness was acquired for accurate and precise co-registration with MNI brain models. Diffusion tensor MRI (DTI-MRI) was acquired to map white matter pathways. All MRI sequences were acquired in one single session, and the patient's head was stabilized to avoid any movement between scans so that the images would be preregistered.

2.3. Preprocessing

Magnetic resonance imaging and EEG preprocessing steps were performed using SPM12 (Wellcome Department of Imaging Neuroscience, University College London, UK). Electroencephalography data were cropped to include representative ictal and interictal waveforms (MATLAB 2016b, Natick, MA). For the right temporal sample case, one ictal event 10 s in duration at a 256-Hz acquisition rate was analyzed. For the bitemporal case, 5 ictal events were analyzed lasting 8, 8, 22, 30, and 38 s. Electroencephalography data were band-pass filtered between 0.1 and 100 Hz to remove nonphysiologic signals and notch filtered between 59 and 61 Hz to remove background electronic noise. T1-weighted MRI was transformed into Montreal Neurological Institute (MNI) space using the six-parameter rigid body spatial transformation algorithm built into the SPM12 fMRI toolbox. Twenty-four scalp electrodes in the standardized 24-electrode International 10–20 configuration were co-registered with a patient-specific brain mesh model generated from the thin-slice T1 MRI sequence using the SPM12 EEG source localization toolbox. The mesh was generated using a