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Intraoperative optical mapping of epileptogenic cortices during non-ictal periods in pediatric patients

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ABSTRACT

Complete removal of epileptogenic cortex while preserving eloquent areas is crucial in patients undergoing epilepsy surgery. In this manuscript, the feasibility was explored of developing a new methodology based on dynamic intrinsic optical signal imaging (DIOSI) to intraoperatively detect and differentiate epileptogenic from eloquent cortices in pediatric patients with focal epilepsy. From 11 pediatric patients undergoing epilepsy surgery, negatively-correlated hemodynamic low-frequency oscillations (LFOs, ~0.02–0.1 Hz) were observed from the exposed epileptogenic and eloquent cortical areas, as defined by electrocorticography (ECoG), using a DIOSI system. These LFOs were classified into multiple groups in accordance with their unique temporal profiles. Causal relationships within these groups were investigated using the Granger causality method, and 83% of the ECoG-defined epileptogenic cortical areas were found to have a directed influence on one or more cortical areas showing LFOs within the field of view of the imaging system. To understand the physiological origins of LFOs, blood vessel density was compared between epileptogenic and normal cortical areas and a statistically-significant difference ($p < 0.05$) was detected. The differences in blood-volume and blood-oxygenation dynamics between eloquent and epileptogenic cortices were also uncovered using a stochastic modeling approach. This, in turn, yielded a means by which to separate epileptogenic from eloquent cortex using hemodynamic LFOs. The proposed methodology detects epileptogenic cortices by exploiting the effective connectivity that exists within cortical regions displaying LFOs and the biophysical features contributed by the altered vessel networks within the epileptogenic cortex. It could be used in conjunction with existing technologies for epileptogenic/eloquent cortex localization and thereby facilitate clinical decision-making.

1. Introduction

Complete removal of epileptogenic brain areas in which seizures originate offers patients with refractory epilepsy the chance of being seizure free. However, this resection must be balanced against the preservation of eloquent cortical areas to reduce postoperative morbidity (Tharin and Golby, 2007). Many screening technologies based on the occurrence of both interictal and ictal abnormal activities have been used during the preoperative evaluation phase for epilepsy surgeries, including electroencephalograms (EEG), (functional) magnetic resonance imaging ((f)MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Together, they provide the general location but not the exact boundaries of seizure-inducing brain areas. In addition, the usefulness of information provided by these non-invasive techniques degrades during the course of surgery because of brain shifting and deformation that is invariably induced by the loss of cerebrospinal fluid (Gasser et al., 2005; Winston, 2013).

Electrocorticography (ECoG) has been demonstrated to be a valuable intraoperative tool, not only to precisely delineate such boundaries (Alarcon et al., 1997), but also to identify eloquent cortical areas (Pondal-Sordo et al., 2007). However, the technique requires prolonged recordings with electrodes implanted long-term, thereby elevating the risks of hemorrhage, infection and cerebral edema. Intraoperative MRI (iMRI) and fMRI (ifMRI) have recently started to play crucial roles in epilepsy surgery, as they enable the maximum extent of resection despite the lesion's proximity to eloquent brain cortex and fiber tracts which, in turn, leads to favorable seizure-reduction outcomes and acceptable neurological deficit rates (Sommer et al., 2013). Unfortunately, the use of iMRI or ifMRI demands an extremely high standard of infrastructure and maintenance. As a result, only a limited number of hospitals and research institutes have the financial and technical capabilities to offer

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these technologies for routine patient care. In addition, the functional mapping of ifMRI relies on the selection of hemodynamic response functions, which could compromise the accuracy of localization (Cannestra et al., 2001). Therefore, additional intraoperative evaluations are always needed to finalize the surgical plan and guide surgery.

Recently, dynamic intrinsic optical signal imaging (DIOSI) has been considered very useful as an alternative intraoperative technique to separate epileptic and tumorous cortices from eloquent brain areas (Haglund and Hochman, 2004; Sato et al., 2002; Sobottka et al., 2013). DIOSI is believed to hold great scientific potential that could both improve the interpretation of neuroimaging data and provide more detailed understanding about the cortical micro-environment. It has been suggested that DIOSI is capable of identifying epileptogenic cortex very well during ictal episodes, but it is impractical to implement such a localization technique in intraoperative settings, because seizure attacks are required. DIOSI can also be used for functional mapping, when external neuronal stimulation, like electrocortical stimulation (Cannestra et al., 2000; Suh et al., 2006) and/or peripheral stimulation (Sato et al., 2002; Sobottka et al., 2013) are applied. The dependence on external stimulation, however, requires delicate control of anesthetic administration to maintain the patient's consciousness, which could introduce additional risks to the surgery, especially in pediatric patients. Recently, Song et al. (2012) observed some unique hemodynamic low-frequency oscillations (LFOs, around 0.025 Hz) within very confined areas of the cortical surface of pediatric epilepsy patients undergoing epilepsy surgery. These areas were found to coincide with either epileptogenic or eloquent areas. However, methods to differentiate these two types of cortex using the observed LFOs were not explored. Therefore, improving the DIOSI technique's ability to delineate the epileptogenic cortices from the normal and eloquent areas using data recorded during non-ictal periods and without any stimulation would advance this modality as an intraoperative guidance tool.

In this study, a new methodology was developed to accurately delineate epileptogenic and eloquent cortices that requires only about 5 min of intraoperative DIOSI recording that occurs during spontaneous non-ictal periods. The proposed methodology focuses on functional and effective brain connectivity within cortical regions with LFOs, as well as on the anatomical and functional features of alterations in the vascular network of epileptogenic cortex. Its development is inspired by two past observations: 1) the existence of hemodynamic LFOs with possible neuronal sources in both epileptogenic and eloquent cortical areas during non-ictal periods (Song et al., 2012); and 2) seizure-induced reorganization of the vascular network in epileptogenic cortices (Rigau et al., 2007). There are three critical elements in this methodology. Specifically, a spontaneous DIOSI recording from the entire craniotomy is used to determine cortical regions with LFOs. To that end, we combine seed-based correlation, feature clustering and Granger causality analyses. Vessel densities in the superficial layers of the cortex are estimated using a static digital imaging modality for the entire craniotomy to uncover anatomical alterations in the vascular network of epileptogenic cortex. Finally, a stochastic modeling of vessel volume/oxygen dynamics based on the Balloon model (Buxton et al., 2004; Buxton, 2012) is combined with a machine learning method (i.e., a support vector machine, SVM) to differentiate areas with changes in vessel resistivity. Independent, routine ECoG analysis was performed by neurologists at Nicklaus Children's Hospital, and its results were used as the reference to confirm the localizations of epileptogenic and eloquent cortical areas and hence verify the accuracy of the proposed methodology.

2. Methods

2.1. Patient selection

This in vivo study was approved by the Western Institutional Review Board. Eleven patients (<18 years old) with lesional epilepsy undergoing one- or two-stage epilepsy surgery were chosen by their neurosurgeons (Dr. Bhatia and Dr. Ragheb) at Nicklaus Children's Hospital. Informed consent was obtained from each patient and their parents prior to surgery. Patients' demographic and clinical information are summarized in Table 1. The neurosurgeons were not aware of the results of this study at the time of surgery.

2.2. Optical data acquisition

Images at 500 nm and 700 nm were acquired simultaneously and continuously from the exposed cortical surface intraoperatively using a DOSIS system that had been developed in-house (Song et al., 2012). The exposed cortex was illuminated by the surgical light in the operating room and imaged through a Nikon dSLR lens (Nikon AF 28-80 mm f/3.5–5.6 D Lens with Aperture Ring). Images were recollimated and then split into two branches using a dichroic mirror (#49–471, Edmund Optics) with a transmission wavelength range of 400–595 nm and a reflection wavelength range of 640–750 nm. Two CCD cameras (DMK 21 AU04, The Imaging Source Europe GmbH) were attached to the holder of the dichroic mirror: one at the transmission port ($\mathrm{Cam_T}$) and the other at the reflection port ($\mathrm{Cam_R}$). The $\mathrm{Cam_T}$ recorded images through a 500 nm band-pass filter (#65–149, Edmund Optics) and the $\mathrm{Cam_R}$ through a 700 nm band-pass filter (#88–012, Edmund Optics). Both cameras were synchronized using external triggers provided by a function generator. In each single-image acquisition sequence, at least 1000 frames were acquired by each camera at a rate of five frames per second. The imaging system was controlled by a LabVIEW program via an IEEE 1394a interface.

During each DIOSI study, the patient was kept still and his/her physiological condition kept stable under normal anesthesia. A list of anesthetic agents and other surgery-related information are provided in Table 2.

2.3. Electrocorticography (ECoG) acquisition and analysis

The procedures described in this section are part of the routine protocol provided to epilepsy surgery candidates at Nicklaus Children's Hospital. For patients undergoing two-stage epilepsy surgery, the ECoG electrode arrays were placed on top of the cortical surface following the optical imaging acquisition procedure. Placement of the ECoG electrode arrays was determined by the results of the pre-operative evaluations using scalp EEG, MRI/fMRI, PET and/or SPECT, which were not influenced by the results of DIOSI data analysis. After the first-stage surgery, the electrical activities of the target cortex of these patients were monitored for at least one week to identify the brain areas producing the ictal/interictal spikes. The final decision on the area of resection was determined by the ECoG results, in conjunction with those from the neuro-imaging studies. Once the surgery plan was finalized, these patients underwent the second stage of surgery to remove the electrode array and all epileptogenic brain areas. For patients undergoing one-stage epilepsy surgery, optical imaging acquisition was also performed prior to the confirmatory ECoG study, which was performed to identify the resection margin.

Neurologists at Nicklaus Children's Hospital analyzed all ECoG data and provided information on the localization of eloquent and epileptic cortical areas based on all neuro-imaging results (Jayakar et al., 1994, Jayakar et al., 2008). Eloquent areas are defined as cortical areas consistently related to a given function; e.g., sensory or motor. Epileptogenic cortex is considered an area of cortex that is required for seizure onset. Areas generating interictal spikes and discharges are also generally considered epileptic. DIOSI data analyses in the previous section were conducted without any knowledge of the results of the ECoG study. Later, the ECoG study results and the actual area of surgical resection were used as gold standards to define the epileptogenic and eloquent cortical areas.