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Towards real-time detection of seizures in awake rats with GPU-accelerated diffuse optical tomography

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HIGHLIGHTS

- Diffuse optical tomography can image hemodynamics in awake rats during evoked acute seizures.
- Massive parallelization with graphic processing units allows real-time DOT image reconstruction.
- Hemodynamic changes induced by generalized seizure onset precede EEG spikes.

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ABSTRACT

Background: Advancement in clinically relevant studies like seizure interruption using functional neuro imaging tools has shown that specific changes in hemodynamics precede and accompany seizure onset and propagation. However, preclinical seizure experiments need to be conducted in awake animals with images reconstructed and displayed in real-time.
Methods: This article describes an approach that can be utilized to tackle these challenges. A subject specific head interface and restraining method was designed to allow for DOT to imaging of hemodynamic changes in unanesthetized rats during evoked acute seizures. Using CUDA programming model, the finite-element based nonlinear iterative algorithm for image reconstruction was parallelized.
Results: Early hemodynamic changes were monitored in real time and observed tens of seconds prior to seizure onset. Utilizing the massive parallelization offered by graphic processing units (GPU), DOT was extended to online image reconstruction within 1 s.
Comparison with existing methods: Pre-seizure state related hemodynamic changes were detected in awake rats. 3D monitoring of hemodynamic changes was performed in real time with our parallelized image reconstruction procedure.
Conclusion: Diffuse optical tomography (DOT) is a promising neuroimaging tool for the investigation of seizures in awake animals.

1. Introduction

Diffuse optical tomography (DOT) is an emerging imaging modality based on the scattering and absorption properties of non-ionizing near-infrared light in biological tissue (Paulsen and Jiang, 1995; Boas et al., 2001). As an extension of the established functional brain imaging tool near infrared spectroscopy (NIRS), DOT not only shares the merits of providing continuous readings of cerebral oxygenation, but also has the ability to provide spatial resolution in the millimeter scale (Habermehl et al., 2012). DOT has been successfully applied in the imaging of breast tumors (Dehghani et al., 2003), osteoarthritis (Zhang and Jiang, 2005) and cortex activations (Zeff et al., 2007). Recently DOT has been introduced in more dynamic neuroimaging studies of cerebral perfusion (Habermehl et al., 2011) and brain network analyses (White et al., 2012).

Despite pharmacological, surgical, and neuromodulation advances in the treatment of chronic epilepsy, seizures are often not controlled in as many as 25% of patients. A growing body of research indicates that preventing seizures may be possible if the

Abbreviations: DOT, diffuse optical tomography; GPU, graphic processing units; PTZ, pentylenetetrazol; IEEG, intracranial electroencephalogram.

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earliest stages of seizure initiation could be reliably identified by some means (Fisher, 2012; Berényi et al., 2012). To this end, DOT, which is capable of detecting hemodynamic responses spatially equivalent to fMRI (Eggebrecht et al., 2014) with high sampling rate (>1 Hz), may provide the necessary spatial and temporal resolution to identify impending seizures (Obrig, 2013). It is known that activity evoked optical spectroscopic changes measured in the brain are most likely generated by early changes in cerebral hemodynamics (Grinvald, 2005). Therefore, such optical property changes are also the hallmarks of seizure initiation and propagation. A deeper understanding of hemodynamic changes at the beginning and throughout the evolution of epileptic seizures can help identify the most susceptible brain regions (Zaveri et al., 2010). With such knowledge, preventative techniques could be developed and then coupled with treatment strategies in order to interrupt the process before seizure onset.

In our previous study with simultaneous DOT and IEEG in anesthetized rats, the pre-seizure state was investigated and uniformly identified (Zhang et al., 2014). We found that the onset of generalized seizures originates locally and early hemodynamic responses occur for several minutes before seizure onset. However, when introduced to the study of seizure prevention, the same challenge to immobilize the subject that affects other traditional neuroimaging tools like SPECT (Hong et al., 2008) and fMRI (Federico et al., 2005) arose. This brings the requirement to anesthetize animal subjects in order to achieve relatively long time stable recordings. Studies have demonstrated that hemodynamic responses elicited by seizure-induced drugs may differ between anesthetized and unanesthetized animals. This is due to the fact that anesthetics may act on various neurotransmitters and sensory feedback from the whole body contributes to the seizure threshold (Sicard et al., 2003). Ideally, experiments in non-paralyzed and fully conscious animals could overcome the profound impact of anesthetics on cerebral hemodynamics and better reflect neural activity in realistic situations.

Another challenge to applying DOT for early seizure detection is the requirement of having a timely response which refers to the real-time availability of the reconstructed images derived from hemodynamic changes. Finite-element based nonlinear iterative algorithm has been a powerful reconstruction method for obtaining high quality DOT Images (Jiang, 2010). However, it is computationally demanding especially in three-dimensional (3D) cases with high density optode arrays. The calculation for one reconstruction requires several to tens of minutes depending on the imaging domain size, making it an unrealistic task in real-time applications and therefore limited to retrospective analysis.

The primary goals of this study were to confirm that pre-seizure state related hemodynamic changes can be detected in awake rats with DOT, and to perform real-time 3D monitoring with our reconstruction procedure. To this end, first we developed methods to conduct seizure experiments in fully awake rats using a subject-specific helmet built with 3D scanning and printing, and a restraining mechanism based on hanging wraps. Second, graphic processing units (GPU) based parallel code was implemented using a CUDA programming model (NVIDIA), which allows, in principle, for online reconstructions. As these proof-of-concept methods and results are extended, we expect that DOT can become an important tool in the study for the prevention of epileptic disorders.

2. Methods

2.1. Animals

Five adult male Sprague-Dawley rats (Harlan Labs, Indianapolis) weighing ~400 g were used for the *in vivo* experiments. Animals were housed in pairs in a controlled environment (12:12-h light/dark cycle; food and water *ad lib*). All the experimental protocols and procedures involving animal care were conducted in conformity with the standards of the NIH and IACUC committee at the University of Florida.

Prior to imaging, rats were anaesthetized under inhalational anesthesia maintained at 2% isoflurane mixed with 0.4 L/min oxygen during the experiment preparation, which included shaving the heads of the rats with hair removing lotion, placing them on the hammock, strapping on the helmet, and plugging in all the fiber bundles. Then the rats rested for 1 h without anesthesia, allowing recovery to a fully conscious state.

The generalized tonic–clonic seizures were induced by an IP injection of 50 mg/kg of the GABA-antagonist pro-convulsant pentylenetetrazol (PTZ) (Sigma–Aldrich, Inc.) (André et al., 1998). Time-locked EEG/DOT were performed continuously for 30 min surrounding each PTZ or saline (control experiments) injection, 5 min before injection for the resting state recording, and then 25 min after injection for the seizure recording. A total of three rats received PTZ, while two rats were used as age-matched sham controls.

2.2. Restraining mechanism and training procedure

We implemented a restraining mechanism that allowed for the highest level of comfort possible (Topchiy et al., 2009), since the rat stayed awake during the relatively long time recording in the seizure experiment. For restraint, we used both hammocks and straight-jacket type wraps to better fit our needs. The jacket can kept the animals warm and with some Velcro on it, allowed for a tight fit and improved immobility. The use of a hanging wrap (hammock) provided rats with more comfortable and relaxed conditions (Fig. 1d). The hammock, consisting of a sheet bottom with leg holes and a laced top, created a tight fit around the rats, keeping them from wiggling extensively. To further lessen the weight on the rat head, the helmet was tied to the supporting bars on both sides.

Rats were habituated to immobilized conditions in hammocks 2 weeks before the experiments. The aim of the training was to achieve long term immobilization while reducing the stress of the rats. By observing the behavioral responses and gradually increasing the restraint time (starting at 15 min and continuing up to 2 h daily) as rats exhibited positive behaviors, long restraint times were achieved in order to evaluate how calm the animals remained. Only the best-behaved rats after training were selected for our experiments.

2.3. Head modeling and mesh generation

A handheld laser scanner (ZScanner 700) was used to acquire the accurate structural information of the shaved rat head. This 3D scanner has a high resolution of 0.1 mm in *xyz* directions, and stores the surface information in STL format. Rhino 3D was used to load this STL file and design the 3D helmet model. First, raw surface mesh (Fig. 1a) was repaired by removing overlapped surfaces, filling up holes, and smoothing (Fig. 1b). Then additional cylindrical holders for optical fiber bundles, holes for EEG electrodes, and fixing edge structures were added in the model (Fig. 1c). As shown in Fig. 1c, the helmet consists of two parts. The upper part has 16 holders and the lower part has eight holders. The distance between two holders is ~9 mm. The two parts are connected by four screws on each side of the helmet. An anchoring screw is placed in the upper part of the helmet to prevent any sliding between the scalp and helmet. It also serves as a stereotaxic marker and EEG reference electrode. A half-cylindrical shaped slot is added in the lower part to relieve pressure on the vagus nerve. Otherwise the helmet wall would suppress breathing when placed on the rat. To ensure the