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Mapping cortical haemodynamics during neonatal seizures using diffuse optical tomography: A case study

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ABSTRACT

Seizures in the newborn brain represent a major challenge to neonatal medicine. Neonatal seizures are poorly classified, under-diagnosed, difficult to treat and are associated with poor neurodevelopmental outcome. Video-EEG is the current gold-standard approach for seizure detection and monitoring. Interpreting neonatal EEG requires expertise and the impact of seizures on the developing brain remains poorly understood. In this case study we present the first ever images of the haemodynamic impact of seizures on the human infant brain, obtained using simultaneous diffuse optical tomography (DOT) and video-EEG with whole-scalp coverage. Seven discrete periods of ictal electrographic activity were observed during a 60 minute recording of an infant with hypoxic–ischaemic encephalopathy. The resulting DOT images show a remarkably consistent, high-amplitude, biphasic pattern of changes in cortical blood volume and oxygenation in response to each electrographic event. While there is spatial variation across the cortex, the dominant haemodynamic response to seizure activity consists of an initial increase in cortical blood volume prior to a large and extended decrease typically lasting several minutes. This case study demonstrates the wealth of physiologically and clinically relevant information that DOT–EEG techniques can yield. The consistency and scale of the haemodynamic responses observed here also suggest that DOT–EEG has the potential to provide improved detection of neonatal seizures.

1. Introduction

Neonatal brain injury is a significant cause of lifelong disability. Seizures are a common symptom of brain injury in the newborn infant, but they are poorly classified, frequently under-diagnosed, and are difficult to treat (Rennie and Boylan, 2007; van Rooij et al., 2013a,b). They are also independently associated with poor neurodevelopmental outcome (Payne et al., 2014; van Rooij et al., 2013a). Monitoring with video-synchronized electroencephalography (video-EEG) has become the clinical gold standard for identifying seizures (Connell et al., 1987, 1989; Hahn and Riviello, 2004; Smith, 2005; Shellhaas et al., 2011). However, application and interpretation of neonatal EEG are challenging and require expertise. It is therefore rarely used for continuous monitoring. As a result, seizures are commonly identified through clinical observation, despite the fact that clinical manifestations can be extremely subtle or absent in the newborn (Pinto and Giliberti, 2001; Weiner et al., 1991). In some cases clinical manifestations of seizures are apparent despite the EEG being seizure-negative (van Rooij et al., 2010); frontal seizures, for example, often present no scalp EEG correlate. This observation is unsurprising given the complex relationship between neuronal hyperactivity, neuronal synchrony and the EEG signal that is observed at the scalp. Direct comparisons between intracranial and scalp EEG approaches have shown that epileptiform discharges occurring in the cortex are not always apparent on the scalp (Ray et al., 2007; Tao et al., 2005).

Localized changes in haemodynamic parameters such as the concentration of oxy- and deoxy-haemoglobin (HbO and HbR respectively) have long been used as proxy measures for changes in neuronal activity (Boas et al., 2014; Obrig and Villringer, 2003). In the healthy brain, the changes in local haemodynamic parameters are tightly coupled to the

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metabolic demand of surrounding neurons. Whether this relationship is maintained during seizures is still a matter of debate, and has been investigated extensively in adults, in children and in animal models using functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and optical approaches (Avery et al., 2000; Suh et al., 2005; Zhao et al., 2007; Zimmermann et al., 2008; Chaudhary et al., 2013; Zhao et al., 2011). Infant studies are more challenging due to the unpredictable nature of seizures and the vulnerability of the cohort, but there is growing evidence that seizures in the infant are not just a symptom of brain injury, but can cause injury themselves (Legido et al., 1991; McBride et al., 2000; van Rooij et al., 2010; West et al., 2011).

Near-infrared spectroscopy (NIRS) has been used to investigate the infant brain for over 25 years (Lloyd-Fox et al., 2010; Boas et al., 2014). This technique is non-invasive, low-cost and can be readily employed at the cot-side in the intensive care environment without interfering with other physiological recording systems (including EEG, which may be recorded simultaneously). Recent advances in near-infrared hardware and image reconstruction methods have made it possible to produce three-dimensional images of changes in haemodynamic parameters in the brain. Such techniques, which use multiple sources and detectors of near-infrared light, are commonly referred to as diffuse optical tomography (DOT) (Joseph et al., 2006; Arridge, 2011; Zeff et al., 2007; Eggebrecht et al., 2012).

Wallois et al. (2009, 2010) were the first to observe the haemodynamic response to neonatal seizures in humans. Haemodynamic features were isolated using single-channel NIRS during the onset of 'seizure-like' EEG discharges in an infant. This response consisted of an increase in HbO and HbR, followed by an undershoot of HbR only, and a slow return to baseline. A previous study by our group (Cooper et al., 2012) used DOT–EEG to reveal the existence of transient haemodynamic events in neonates who had previously experienced electrographic seizures. These events consisted of an increase in HbO and HbR followed by a rapid decrease in the concentration of both parameters with slow recovery back to baseline. These biphasic features were of untypically high amplitude and lasted up to 2 min. The EEG traces recorded simultaneously did not exhibit any distinct abnormality during the observed haemodynamic events. It was therefore not possible to associate these events with electrographic seizures, but they were not observed in a large number of healthy, age-matched controls.

Intrinsic optical imaging with simultaneous EEG has been used in adult studies to investigate seizures in the exposed cortex intra-operatively (Zhao et al., 2007). A focal increase in both blood volume and HbR was observed during seizure activity, indicating that perfusion was not adequate to meet localized metabolic demand. Remarkably, the observed haemodynamic changes preceded the onset of the electrographic seizures by approximately 20 s, a phenomenon that has been observed repeatedly (Zhao et al., 2011; Ma et al., 2013).

Because the spatial and temporal relationship between ictal electrical activity and cerebral haemodynamics remains unclear, particularly in the newborn, we have begun a series of studies of neonatal seizures using diffuse optical tomography and EEG with whole-scalp coverage. These studies aim to improve our understanding of the haemodynamic variations associated with neonatal seizures and neonatal neuropathology in general. Specifically, we seek to determine a) whether neonatal seizures produce a measurable and consistent DOT signal, b) whether this DOT signal can provide a clearer indication of seizure events than EEG alone and c) whether seizure-induced haemodynamic changes provide a mechanism to exacerbate brain injury.

In this paper, we present images which are, to our knowledge, the first ever DOT images recorded in an infant with seizures. The simultaneously recorded video-EEG allows us to investigate the temporal and spatial relationship between electrographic seizures and the haemodynamic signal across the cortex.

2. Materials and methods

2.1. Patient history

The patient was a female infant born by spontaneous vaginal delivery at 40 weeks and 4 d postmenstrual age. The infant had an abnormal cardiotocography (CTG) and at birth presented without heart rate or respiratory effort. Full resuscitation was commenced and the infant was admitted with severe hypoxic–ischaemic encephalopathy to the neonatal intensive care unit of the Rosie Hospital. A 72-hour period of therapeutic hypothermia (with a target core temperature of 33.5 °C) was initiated shortly after birth, followed by a re-warming period where the core temperature was increased at the rate of 0.5 °C per hour until the infant reached a normal temperature. Therapeutic hypothermia provides a neuroprotective effect and is standard clinical practice in term infants who have suffered a hypoxic–ischaemic insult.

Amplitude-integrated EEG via a cerebral function monitor (CFM) (Olympic CFM™ 6000, Natus Medical Inc., California) recorded seizures during both the cooling and re-warming phases with evidence of clinical manifestation despite treatment with anticonvulsants including phenobarbital, clonazepam and phenytoin. A structural magnetic resonance imaging (MRI) scan on day 7 showed abnormal signal intensity in the basal ganglia, brainstem and corpus callosum. It also indicated thromboses in major sinuses and dilation of medullary intra-cerebral veins and internal cerebral veins. Informed written parental consent was obtained for a simultaneous DOT–EEG recording, approved by the National Research Ethics Service Committee East of England (REC reference 09/H0308/125).

2.2. Data acquisition

Simultaneous DOT–EEG was performed over a 60 minute period after the re-warming phase, during which the infant showed no signs of consciousness and exhibited little motion. DOT data were acquired using the UCL Diffuse Optical Tomography System (Everdell et al., 2005), a continuous-wave system consisting of 16 dual wavelength laser diode sources illuminating at 780 and 850 nm and 16 avalanche photodiode detectors (APDs). Frequency multiplexing allows all sources to be illuminated simultaneously. The system has a sampling rate of 10 Hz. The sources and detectors were coupled to the infant's head using optical fibre bundles attached to a soft, flexible head cap (EasyCap, Germany). The cap has a circumference of 34 cm, matched to the age and size of the infant. The optical fibres were positioned within the cap at a subset of locations taken from the 10–5 system (Oostenveld and Praamstra, 2001). These locations were chosen to maximize the density of DOT source–detector pairs (channels) with optimal separations between 20 and 40 mm while also covering the whole scalp. The array design, which provides a total of 58 dual-wavelength DOT channels, is shown in Fig. 1.

Eleven annular Ag/AgCl electrodes (EasyCap Gmbh, Germany) were also coupled directly to the cap in a standard neonatal EEG montage (Fp1, Fp2, Fz, T3, T4, C3, Cz, C4, Pz, O1, O2) with reference and ground electrodes at AFpz and FC1 respectively. Video-EEG recordings were performed using a Micromed SystemPlus clinical EEG system (Micromed S.p.A., Italy) with a sampling frequency of 256 Hz. The EEG data were band-pass filtered (0.3–70 Hz) and notch filtered at 50 Hz to eliminate main interference. A single channel electrocardiogram (ECG) was recorded using the auxiliary channels of the EEG system.

In order to synchronize the DOT and EEG data, a custom-built external pulse generator was programmed to send a predetermined pattern of electrical pulses to both systems during recording. The pulse events within the two datasets could then be aligned during data processing and analysis.