Combining EEG and Diffuse Optical Imaging: A New Approach to Monitoring Neonatal Seizures?

Seizures in the newborn infant brain represent a major unsolved problem in neonatal medicine. Neonatal seizures are poorly classified, frequently under-diagnosed, and are difficult to treat. Estimates of incidence vary; a recent review placed the figure at between 1.8 and 3 per 1000 live births, however, the risk for babies with a very low birthweight (< 1.5 Kg) is thought to be higher, between 10-11 per 1000. In the term infant, hypoxic-ischaemic brain injury is the most common cause of seizures, although perinatal stroke is an increasingly recognised cause in the population group. In the preterm infant, haemorrhagic and ischaemic lesions as well as infection account for the majority of seizures. Neonatal seizures have been associated with adverse neurodevelopmental outcome, but there is continuing debate about the extent to which seizures can cause or aggravate brain injury themselves.

Traditionally, neonatal seizure has been diagnosed on the basis of clinical observation of changes in behavioural state, motor and autonomic function. It is now known that diagnosis by clinical observation alone dramatically underestimates the prevalence of neonatal seizures. This is because the majority of seizures, as diagnosed by EEG, do not manifest themselves clinically.

Video-EEG is rightly considered to be the gold standard for seizure detection, but even with EEG diagnosis can remain difficult because of the high-amplitude, discontinuous nature of neonatal EEG activity. It is also important to consider the case where classic clinical manifestations of seizure are apparent whilst the EEG remains seizure negative. Many of these events can be explained by paroxysmal ‘nonepileptic’ behaviours, but as EEG is known to have limited sensitivity to sub-cortical neurons there remains an important question: do neonates who exhibit clinical manifestations of seizure have a sub-cortical seizure focus, which EEG cannot detect?

Diffuse Optical Imaging

Diffuse optical imaging (DOI) uses the relative absorption of two or more wavelengths of near-infrared light to measure changes in the concentration of oxyhaemoglobin and deoxyhaemoglobin in tissue. If enough light sources and detectors are arranged at the scalp, it is possible to produce three-dimensional images of changes in blood volume and oxygen saturation in both cortical and sub-cortical regions of the brain. Indeed, three-dimensional, whole-head diffuse optical imaging has been performed in both healthy and brain-injured neonates.

The application of DOI techniques has become increasingly common in the last 15 years in both clinical and research environments. Diffuse optical imaging is often used to investigate brain function in response to a particular external stimulus. The increase in metabolic demand of activated groups of neurons usually results in an over-compensation in localised cerebral blood flow. This haemodynamic response to stimulation gives rise to the blood-oxygen level dependant (BOLD) signal observed in functional magnetic resonance imaging (fMRI) and is also what allows DOI to localise and quantify functional activation in the brain. However, DOI has several important advantages over fMRI. Diffuse optical imaging can be performed at the bedside, which makes it particularly suited to studies of vulnerable infants, it is silent, does not affect neonatal developmental care procedures and it is relatively inexpensive.

Diffuse optical imaging techniques have been used to study healthy neonatal brain function in response to a variety of visual, auditory and somatosensory stimuli. However, an external stimulus is by no means necessary; DOI has been used to monitor continuous changes in blood volume and oxygen saturation including studies in neonates with hypoxic-ischaemic encephalopathy.

Combining EEG and DOI

Electroencephalography is the oldest method of non-invasively interrogating brain function, and has survived as a technique because it can provide a vast amount of clinical information whilst being easy to perform at the bedside. It has, however, had its clinical usefulness limited by the advent of structural imaging techniques, particularly x-ray CT and MRI. This is because despite having far superior temporal resolution (sample rates routinely reach 2 KHz) the nature of scalp EEG severely limits its spatial resolution. Where once EEG was used to investigate all manner of cerebral disease, it now has one dominant clinical purpose: the study and diagnosis of epileptic disorders.
Combining EEG and DOI has several advantages because the two systems are complementary in nature. Whilst EEG measures the overall electrical activity of groups of neurons, DOI measures the haemodynamic response to this activity. A combined system will therefore allow the relationship between these two signals (broadly referred to as neuro-vascular coupling) to be studied directly. A better understanding of neuro-vascular coupling in the neonate, particularly under conditions of encephalopathy may well have clinical applications. The spatial resolution of DOI is good, comparable to that of fMRI. Given the excellent temporal resolution of EEG, a combined EEG-DOI system has the advantage of good spatio-temporal resolution, a characteristic which is rare in non-invasive functional imaging techniques. Unlike EEG and fMRI, EEG and DOI do not interfere with one another, making it less technically challenging to obtain simultaneous measurements. Both EEG and DOI are totally non-invasive, can be performed at the bedside and are not overly sensitive to movement artifacts. It is for these reasons that a combined system is well suited to the study of vulnerable patient groups, particularly neonates in intensive care. The importance of a combined electrophysiological and optical approach to the future of neonatal neuromonitoring was recently highlighted in a review by Toet and Lemmers. In order to facilitate simultaneous EEG and DOI, an integrated optical-electrical probe has recently been developed at the Biomedical Optics Research Laboratory at UCL. This probe combines a modified EEG cup electrode and an optical fibre bundle, as shown in Figure 1a. The probe design maximises the number of optodes and electrodes which can be placed on a given area of the scalp (which is vital in neonatal studies) whilst maintaining the standard clinical electrode application method. This probe design has allowed full neonatal EEG to be performed simultaneously with diffuse optical imaging of the temporal lobes for the first time (Figure 1b).

DOI and EEG to study seizures

There are several reasons why EEG-DOI has great potential in the clinical monitoring of neonatal seizures. First, as each system measures a different neurophysiological response, an additional indication of seizure onset and measure of seizure burden will be provided beyond that of EEG alone. Second, a combined system will significantly improve localisation of a partial seizure focus. Third, seizure-induced failures in cerebrovascular function can be directly observed in real time, and fourth, the addition of DOI will allow regions of the brain to be interrogated which, because of their depth or orientation, are essentially invisible to EEG. Given that sub-cortical seizure foci have been observed which do not manifest themselves electrographically, we believe a combined system could be of great clinical benefit.

Combined EEG and DOI methods have already been used to study functional activation and neuro-vascular coupling in adults, but the use of such systems in the study of epilepsies is also becoming increasingly common. Between 1997 and 2000, Watanabe et al. successfully employed EEG DOI techniques in a study of 28 adult patients exhibiting partial seizures. In 2008 the haemodynamic response to absence seizures in children was characterised and EEG DOI methods were used to detect seizure focus in a child prior to surgery. The haemodynamic response to non-epileptic discontinuous neonatal EEG activity has been studied using EEG and simplified diffuse optical techniques and last year similar methods were used to produce the first ever study of a seizing neonate. This study was the first to show that a haemodynamic response can be observed in response to neonatal seizures.

While both techniques are independently well established, there remain several important questions which must be answered before a combined EEG DOI system can begin to be clinically implemented. It has to be determined whether neonatal seizures produce a truly robust and identifiable haemodynamic response, and that response must be carefully characterised. It will then be necessary to examine whether a combined EEG DOI system can more reliably identify seizure events than EEG alone, or indeed whether it is possible for EEG DOI to identify seizure events which EEG misses altogether. Nevertheless this integrated approach to seizure detection and classification may yield important and novel information on brain activity in this high risk population.
REFERENCES


