APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

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1. Title.

Novel Network Analysis of Intracranial EEG to Identify the Epileptogenic Zone

2. Portfolio summary.

Aims: To establish whether neural network approaches to intracranial EEG data improves surgical decision making in children with medically intractable epilepsy.

Background: Epilepsy is one of the commonest chronic neurological conditions affecting children. Medical treatment is effective in many, but a significant number have seizures which are drug resistant. These children may be candidates for epilepsy surgery. Standard may not identify a surgical focus and some children therefore require intracranial recording of EEG (Jayakar et al 2016). Surgical resection is typically offered in 80% of these children, of whom 40-60% will become seizure free. This suggests that current approaches do not reliably identify the area of the brain responsible for generating seizures. Novel diagnostic approaches are thus required. Stereoecephalography (sEEG) is a technique for recording intracranial EEG in which multiple depth electrodes are placed within the brain to precisely identify seizure onset. The standard approach is to monitor electrical activity until at least 2 habitual, clinical, epileptic seizures are recorded and relate the clinical features to the area of the brain showing seizure activity in the EEG. Implicit in this approach is the idea that the inter-ictal EEG provides limited information about the epileptogenic zone (Singh et al 2015). There is, increasing evidence that neural network dynamics within epileptogenic regions remain abnormal in epileptic brain between seizures and analysis of interictal epileptic activity within the conceptual construct of an epileptogenic network can help pinpoint the epileptogenic zone (Serletis et al 2014).

The proposed study aims to use sEEG data to study the dynamics of neural networks both at the level of EEG and at the level of multiple simultaneously recorded single neurons in children with focal epilepsy. The main use of single neuron recordings is to understand system-level mechanisms of cognition. The rate at which a neuron fires with respect to sensory input (rate coding), the relationship of firing to ongoing oscillatory activity (temporal coding) and the correlation of firing activity between neurons (population coding) all contribute to normal cognition. Abnormalities in timing and population coding have been identified in the epileptic region of animal models of epilepsy supporting the idea that neurons are more predisposed to fire together in epileptic tissue, consistent with hyperexcitability (Tyler et al, 2012). Seizures during single unit recordings have been recorded in adults with epilepsy, showing marked variability in how neurons behave; some fire excessively, some stop firing and some continue as pre-seizure (Truccollo et al 2011). No monitoring of single unit firing activities have been carried out in children with epilepsy and no attempts have been made to identify an epileptogenic circuit in interictal data.
Proposed methodology to be adopted: We propose to study 12-16 children undergoing sEEG at Great Ormond Street Hospital (GOSH). GOSH is the leading paediatric epilepsy surgery centre in Europe and performs approximately 24 sEEG examinations per year. The children will be selected using our established clinical criteria and surgical planning will not be influenced by the proposed research. Electrodes containing macroelectrodes with interspersed microelectrodes will be implanted. The macroelectrodes are used for recording EEG and will be used for clinical purposes. The microelectrodes will be used to record single neuron firing activity and the data will be used for research purposes. There will be no additional burden on the patient and presurgical evaluation will proceed as clinically dictated. Once the data has been collected, it will be anonymized and stored for further analysis. Single neuron data will be extracted for each of the microelectrodes. We will use tools developed in the Scott laboratory to identify abnormalities in temporal and population coding interictally. We hypothesize that the brain region in which a seizure starts will be the same region that shows excessively correlated neuronal firing. Distant areas will have less correlated firing. Data will be co-localised with pre and post-operative imaging. We expect that patients in whom not all excessively correlated areas are removed will be less likely to become seizure free. If our hypothesis is correct then this could lead to a major improvement in presurgical evaluation and will ultimately improve the seizure burden and the quality of life of patients with severe focal epilepsy. The ability to identify the epileptogenic zone from interictal data offers the potential to decrease the length of intracranial recording by alleviating the need to collect data during seizures.

Skills to be achieved by the PhD trainee: The trainee will receive training in both clinical and research domains. Surgical training will include developing skills in planning implantation of sEEG electrodes, standard analysis of EEG data, defining the surgical resection strategy and operative training. The analysis of the electrophysiological data will require training in signal processing which will include the extraction of single units from the background EEG activity and decomposition of EEG signals into separate frequencies for coherence analyses. The use of mathematical tools for characterizing the neural networks will require training in Matlab, including some coding. The statistical tools for identifying relationships between the novel analyses, traditional EEG, the nature of the surgery and outcome are complex and will require training in appropriate biomedical statistics.

Relevance to the area of paediatric surgery: Epilepsy surgery is a core component of paediatric neurosurgery. A significant subset of children with drug resistant epilepsy who are candidates for surgery require invasive sEEG either because MRI scanning does not show a lesion or because pre-operative data are discordant. This PhD aims to develop techniques which will improve the efficiency and quality of sEEG investigations by allowing accurate delineation of the epileptogenic zone from interictal data. This has the potential to improve rates of seizure freedom in children undergoing resective neurosurgery for epilepsy and therefore lead to improved cognitive outcome and quality of life.

References: