



## Structural and effective connectivity in focal epilepsy

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### ABSTRACT

Patients with medically-refractory focal epilepsy may be candidates for neurosurgery and some may require placement of intracranial EEG electrodes to localise seizure onset. Assessing cerebral responses to single pulse electrical stimulation (SPES) may give diagnostically useful data. SPES produces cortico-cortical evoked potentials (CCEPs), which infer effective brain connectivity. Diffusion-weighted images and tractography may be used to estimate structural brain connectivity. This combination provides the opportunity to observe seizure onset and its propagation throughout the brain, spreading contiguously along the cortex explored with electrodes, or non-contiguously. We analysed CCEPs and diffusion tractography in seven focal epilepsy patients and reconstructed the effective and structural brain networks. We aimed to assess the inter-modal similarity of the networks at a large scale across the cortex, the effective and structural connectivity of the ictal-onset zone, and investigate potential mechanisms of non-contiguous seizure spread. We found a significant overlap between structural and effective networks. Effective network CCEP amplitude, baseline variation, and outward connectivity was higher at ictal-onset zones, while structural connection strength within the ictal-onset zone tended to be higher. These findings support the concept of hyperexcitable cortex being associated with seizure generation. The high prevalence of structural and effective connections from the ictal-onset zone to sites of non-contiguous spread suggests that macroscopic structural and effective connections are plausible routes for non-contiguous seizure spread.

### 1. Introduction

Focal epileptic seizures comprise localised areas of abnormal electrical activity which can subsequently spread to contiguous and non-contiguous brain areas. Approximately 30% of focal epilepsy patients are resistant to anti-epileptic drugs and in these cases resective surgery may be an option (Guerrini et al., 2003).

Pre-surgical evaluation aims to identify the area of seizure onset (the ictal-onset zone) and immediate spread to the brain regions which need to be resected to give the patient a good chance to become seizure free. In addition, identification of eloquent brain regions required for essential tasks, such as language, is important to understand the risks and benefits of surgery.

It may be challenging to localise the ictal-onset zone in focal epilepsy, particularly extra-temporal lobe epilepsies such as frontal lobe epilepsy (FLE). In FLE, there is incomplete understanding of how frontal lobe functional anatomy affects seizure semiology. Seizure freedom

rates are 60–70% in temporal lobe epilepsies and less after extra-temporal resections (Téllez-Zenteno et al., 2005). Little is known about mechanisms of seizure propagation. Contiguous seizure spread, which is more commonly observed than non-contiguous seizure spread, is thought to occur through cortical layer V (Telfeian and Connors, 1998). However, intracranial EEG recordings may also demonstrate spread of seizure activity between non-contiguous areas (Duchowny et al., 2000; Turkdogan et al., 2005), ipsilateral or contralateral to the ictal-onset zone (Blume et al., 2001; Baumgartner et al., 1996; Lieb et al., 1987). It is unknown whether non-contiguous seizure spread may occur via direct cortico-cortical connection or indirectly via other cortical or sub-cortical sites.

Diffusion-weighted images and cortico-cortical evoked potentials (CCEPs) provide complementary information regarding connectivity of the presumed ictal-onset zone. Tractography, derived from diffusion imaging, estimates the paths of macroscopic white matter tracts, allowing reconstruction of the structural connectivity of cortical regions

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underlying intracranial electrodes. CCEPs, recorded on the intracranial EEG following single pulse electrical stimulation (SPES), indicate the presence of a functional tract from the stimulation to recording site, and therefore measure effective connectivity. Combining data from intracranial EEG, CCEPs and diffusion tractography may help characterise the connectivity of the ictal-onset zone and elucidate the mechanisms of non-contiguous seizure spread, improving understanding of epileptogenic networks and possibly leading to higher rates of seizure freedom following surgery.

Tractography studies in FLE have shown disturbances in structural connectivity of regions involved in epileptogenesis (Guye et al., 2003; Campos et al., 2015; Kovac et al., 2009). Ipsilateral and contralateral changes in microstructural indices of tracts closely related to suspected epilepsy pathology have been reported (Guye et al., 2003; Campos et al., 2015). Changes in functional but not structural global topology and a decoupling between global structural and functional connectivity has been found in childhood FLE (Vaessen et al., 2014).

Many studies have examined effective connectivity of epileptogenic networks using responses to SPES (Valentín et al., 2002; Valentín et al., 2005b; Valentín et al., 2005a; Flanagan et al., 2009; Iwasaki et al., 2010; Kokkinos et al., 2013; Boido et al., 2014). Delayed responses have been reported in seizure onset regions (Valentín et al., 2002; Valentín et al., 2005b; Flanagan et al., 2009). Higher amplitudes of the N1 CCEP component at ictal-onset electrode contacts compared to surrounding contacts (Iwasaki et al., 2010) was more pronounced in contacts showing repetitive spiking compared to paroxysmal fast patterns of seizure onset (Enatsu et al., 2012). Some SPES studies have demonstrated favourable surgical outcome in patients who had brain regions with abnormal responses to SPES resected (Valentín et al., 2005b; Flanagan et al., 2009).

Two studies have combined CCEPs and diffusion tractography (Conner et al., 2011; Swann et al., 2012), but did not examine connectivity of the ictal-onset zone or seizure spread.

In the current study, we reconstruct large-scale structural and effective connectivity networks by analysing all implanted electrodes, with three primary aims: (i) to assess the inter-modal similarity between structural and effective networks at a large scale across the cortex; (ii) to assess the potential for diffusion tractography and CCEPs to identify structural and effective connectivity markers of the ictal-onset zone and (iii) to examine the mechanisms of non-contiguous seizure spread using structural and effective networks.

## 2. Methods

### 2.1. Patients

Seven patients (4 male, mean age 34.6 years old, range 26–49 years old) were retrospectively selected from a large cohort of drug-resistant epilepsy patients who had undergone invasive intracranial monitoring at the National Hospital for Neurology and Neurosurgery (NHNN). These patients were the only individuals from the cohort who fitted the selection criteria. The criteria for patient selection were the availability of pre-implantation T1-weighted and diffusion-weighted MRI, post-implantation CT and T1-weighted MRI, and SPES. The study was approved by the local ethics committee and written informed consent was obtained. Five patients had frontal lobe epilepsy, two had parietal lobe epilepsy. Four had evidence of cortical dysplasia on MRI (patient details in Table S1).

### 2.2. Reconstructing structural and effective networks

Networks were reconstructed using the pipelines described in Supplementary Methods.

In brief, structural networks were reconstructed by recording the tractography streamline density between electrode ROIs. ROIs were propagated from CT to diffusion space via the post-implantation and

pre-implantation structural MRI using linear and non-linear registration.

Effective connectivity networks were reconstructed by recording the absolute amplitude of significant CCEPs occurring between 12 ms and 250 ms post-stimulus, following SPES. This involved epoching, stimulation artefact reduction, visual exclusion of other artefacts, and identifying peaks in the CCEP. Inter-electrode effective connectivity was calculated as an average of the connectivity values from each stimulating electrode to the recording electrode. This conversion of data representations from the original format (stimulation electrode pair to recording electrode) to network format (stimulation electrode to recording electrode) allowed an analysis of CCEP connections with the native diffusion tractography network.

Networks were reconstructed for multiple connection features. Weighted effective networks were reconstructed for peak amplitude, latency and baseline standard deviation of the CCEP. Structural networks were reconstructed for streamline density. Both weighted and binary versions of the networks were analysed. Binary networks were produced by thresholding the weighted networks (see Supplementary Methods). As effective network weights were derived from the same set of significant CCEPs, the binary networks of different effective connectivity features are identical. For simplicity, the term effective networks will hereafter refer to the peak amplitude property of CCEPs, unless stated otherwise. Streamline density networks will be referred to as structural networks.

A summary of methods used to generate structural and effective networks is shown in Fig. 1. Reconstruction of structural connectivity networks required the pre-implantation diffusion-weighted and T1-weighted images in addition to the post-implantation T1-weighted and CT images. Reconstruction of effective connectivity networks required the original SPES data. Detailed methods for reconstructing structural and effective networks can be found in Supplementary Methods.

### 2.3. Graph theory analysis

Graph theoretical analysis was applied to binarised structural and effective networks, in order to compare the nodal connection topography between ictal-onset and non-ictal-onset contacts. Nodal graph theoretical measures calculated were indegree, outdegree, normalised indegree, normalised outdegree, clustering coefficient (Newman, 2003), centrality (Brandes, 2001) and reciprocity. Indegree and outdegree refer to the number of incoming and outgoing connections of a node, respectively. Normalised indegree and outdegree refer to the indegree and outdegree of each node normalised by the maximum given the number of nodes in the network. Reciprocity was calculated as the number of bidirectional connections as a fraction of the outdegree. Indegree, outdegree, clustering coefficient and centrality were calculated using the *igraph* package in R (Csardi and Nepusz, 2006). Reciprocity was calculated in R (R. C. Team, 2012).

### 2.4. Inter-modal agreement

Two comparison metrics were calculated:- the Jaccard Index, which measures the overlap in the binary structural and effective networks; and the Pearson correlation between structural and effective networks, which measures the correlation in the connection weights. The Jaccard Index was calculated on a patient-wise basis as the size of the set of intersecting connections divided by the size of the set of union connections.

### 2.5. Ictal-onset zone connectivity

During pre-surgical evaluation, each patient underwent video-EEG telemetry, recording multiple seizures. A set of typical seizures was identified for each patient by an experienced neurophysiologist (B.D).

Intracranial electrode contacts were classified by an experienced

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