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Structural connectivity based whole brain modelling in epilepsy

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HIGHLIGHTS

- Advances in neuroimaging pipelines now allow us to infer subject-specific large-scale brain networks.
- Sophisticated computer models allow the prediction of brain dynamics based on these networks.
- Here we review the use of neuroimaging informed computer models in the context of epilepsy.
- We suggest that computational models can be used as a tool to predict optimal strategies for stimulation and surgical intervention patient-specifically.

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ABSTRACT

Epilepsy is a neurological condition characterised by the recurrence of seizures. During seizures multiple brain areas can behave abnormally. Rather than considering each abnormal area in isolation, one can consider them as an interconnected functional 'network'. Recently, there has been a shift in emphasis to consider epilepsy as a disorder involving more widespread functional brain networks than perhaps was previously thought. The basis for these functional networks is proposed to be the static structural brain network established through the connectivity of the white matter. Additionally, it has also been argued that time varying aspects of epilepsy are of crucial importance and as such computational models of these dynamical properties have recently advanced. We describe how dynamic computer models can be combined with static human *in vivo* connectivity obtained through diffusion weighted magnetic resonance imaging. We predict that in future the use of these two methods in concert will lead to predictions for optimal surgery and brain stimulation sites for epilepsy and other neurological disorders.

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1. Introduction

It has long been known that alterations to brain structures can be strongly associated with abnormal brain function such as epileptic seizures. What is less well understood however is the relationship of why this association exists and how we can use it to aid treatment. Advances in diffusion weighted magnetic resonance imaging (DW-MRI) allow us to now infer subject specific brain connectivity *in vivo*. Meanwhile, advances in computer modelling allow us to make predictions of brain function which are constrained by the aforementioned connectivity. In this article we review existing studies which use human brain connectivity to constrain a model of predictive

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value. We suggest likely research avenues in the context of epilepsy.

Using DW-MRI it has been shown that in patients with epilepsy there are differences in anatomical brain connectivity when compared to nonepileptic controls (Bonilha et al., 2012). One key assumption of these measured brain networks is that large scale anatomical brain connections do not change rapidly over time (on the order of seconds/milliseconds), but rather over the course of several years (Lim et al., 2013).

Although large scale anatomical brain connectivity is not thought to vary much at rapid timescales of around a second, neural activity certainly does. Electroencephalographic (EEG) recordings of brain activity show oscillations which are clearly associated with certain normal and abnormal brain states. For example, delta oscillations of around 2 Hz are present during sleep and 3 Hz spike-wave oscillations are detectable during many types of epileptic seizures. Another way of measuring brain activity, which varies on the order of seconds, is to use functional magnetic resonance imaging (fMRI). fMRI measures the blood oxygenation level in the brain which is thought to be related, to some extent, to neural activity (Logothetis et al., 2001). This has also been shown to be associated with specific types of human activity such as eyes closed resting state (Fox et al., 2005) and epileptic seizures (Moeller et al., 2010).

At rapid timescales, sophisticated nonlinear computational models of oscillatory brain activity (as seen in healthy subjects as well as patients) have been developed (Lytton, 2008). These models have suggested possible mechanisms to explain transitions to seizure states, through the incorporation of macroscopic level excitatory & inhibitory variables (Baier et al., 2012). Variables and parameters are the key components of a computational model and a notable advance is our ability to now use subject-specific connectivity data to constrain model parameters. An important distinction should be made between parameters (which do not change – or change very slowly, e.g. over hours, days, years) and variables (which vary rapidly, e.g. seconds, milliseconds) in these models.

Computational models enable the prediction of time varying activity, given sets of parameters, and are an ideal tool to investigate how brain connectivity relates to brain dynamics (and ultimately brain function) (Deco et al., 2013; Honey et al., 2010, 2007). However, several questions remain to be addressed in the context of epilepsy. Specifically, how do the changes in epileptic patient's connectivity relate to their likelihood of transiting to seizure oscillations? How does surgical outcome depend on the network? What is the best spatial location to place a stimulating electrode for seizure abatement? The answers to these questions are likely not a direct consequence of the connectivity parameters, but rather a combination of connectivity and inherent nonlinear brain processes. In this article we review the current state of DW-MRI informed models of human brain activity and suggest how they could be used to make better predictions for epilepsy treatment. We limit ourselves to macroscopic level connectivity as obtained by DW-MRI due to the high availability of data at this spatial scale and the difficulties in obtaining data with more detailed higher resolutions *in vivo*. Nonetheless, it should be noted that many of the principles described here can be applied at the meso- and microscopic scale.

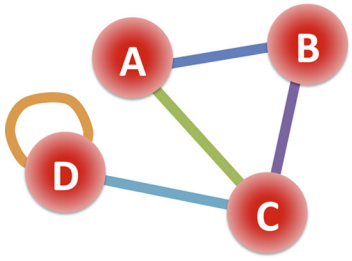
2. Structural brain connectivity alterations in epilepsy

If epilepsy is to be considered a disorder of abnormal brain network(s) then one should carefully consider what constitutes the network components, specifically the nodes and the edges which connect them (Kramer and Cash, 2012; Richardson, 2012; Engel et al., 2013). Brain networks can be observed at the local level of connections between neurons or populations of neurons – the micro-connectome – or at the level of connections between brain regions – the macro-connectome (Van Essen, 2013). However, biological mechanisms at the macro-level are less well understood (Stanley et al., 2013).

One technique for network definition is by utilising magnetic resonance imaging (MRI) and Diffusion-Weighted MRI (DW-MRI) data. In this technique the static image of the subject's brain is divided into parcellated regions of interest (ROI) corresponding to a predefined atlas. Several pre-defined atlases exist at various levels of detail. For example the AAL atlas (Tzourio-Mazoyer et al., 2002) has 90 regions of interest, whilst the atlas described by Hagmann et al. (2008) has multiple levels of resolution including up to around 1000 ROI. An example parcellation scheme is shown in the upper left of Fig. 2 (adapted from Daducci et al. (2012)). Regions of interest assigned using the atlas matching algorithm are typically defined as the 'nodes' in the network.

To assess structural connections between each ROI, a tractography algorithm infers macroscopic tracts which pass through multiple continuous voxels (Parker et al., 2003; Wedeen et al., 2008). When the parcellated cortical and subcortical structures are combined with the inferred tracts one can infer the presence of a connection between two ROIs if there is a tract beginning/terminating in the voxels contained in the corresponding ROI. This approach gives a macroscopic large-scale whole brain network – a 'connectome' – which is essentially a static, time invariant representation of the subject's brain connectivity. A popular example of this workflow/pipeline is summarised by Daducci et al. (2012). The output of this workflow is a subject-specific brain connectivity network. In more formal terms, this network can be defined as a graph represented by an adjacency matrix, whereby nodes (ROI) are represented in each axis and the connection between them is specified as entries in the matrix. Since the ordering of the nodes is the same on both axes, self-connections are therefore represented on the diagonal. An example abstract network to demonstrate this is shown in Fig. 1. Notice how the matrix is symmetric since the connections in the graph are undirected. This is also the case when inferring connections using DW-MRI since it is not possible to infer the directionality of the tracts and is therefore a drawback of this approach (Jbabdi and Johansen-Berg, 2011) in contrast to, for example, tract tracing through injected dyes in *post mortem* studies (Felleman and Van Essen, 1991; Stephan et al., 2001).

Various studies have applied graph theory analysis to these brain networks, both in controls and in patients with epilepsy (Chiang and Haneef, 2014). Graph theory is a formal way of investigating networks (graphs) and can elucidate various properties of the graph. For example, the clustering coefficient measures how well neighbours of a node, that means nodes that are directly connected to that node, are connected to each other (Rubinov and Sporns, 2010; Kaiser, 2011). Furthermore, a small-world network (Watts and Strogatz, 1998) can be defined having a higher clustering coefficient but a comparable all-pairs shortest path length



	A	B	C	D
A	0	1	1	0
B	1	0	1	0
C	1	1	0	1
D	0	0	1	1

Fig. 1. Example of a network (left) and its corresponding adjacency matrix (right). The network is undirected, meaning all connections are bidirectional and unweighted, meaning connections are indicated in binary form representing the presence or absence of a connection.