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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.

Contents

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.

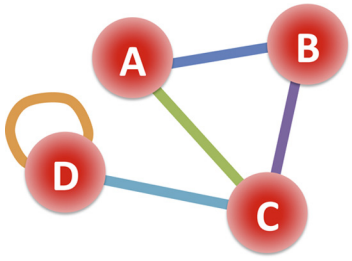
2. Structural brain connectivity alterations in epilepsy

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.

(or characteristic path length) than a randomly organised network. The characteristic path length measures how many connections have to be crossed on average to go from one node to another node in the network. Global efficiency is an alternative measure which uses the inverse of the shortest path lengths (Latora and Marchiori, 2001) so that shorter paths result in higher global efficiency. Excellent reviews of these graph metrics can be found in (Rubinov and Sporns, 2010) and (Kaiser, 2011).

In patients with temporal lobe epilepsy (TLE) who experience *focal* seizures several differences have been shown using graph theoretic measures. Specifically, in the limbic subnetwork there was a decreased fiber density, but an increased clustering coefficient in the superior temporal and thalamic structures, amongst others (Bonilha et al., 2012). This was accompanied by decreased a clustering coefficient in the ipsilateral hippocampus. In a further study by the same group, similar techniques were applied to TLE patients categorised according to the success of their surgery (Bonilha et al., 2013). For patients who were not seizure free after surgery, the temporal lobe subnetwork exhibited a decrease in small worldness, compared to those who become seizure-free. A separate study incorporated whole-brain connectivity (as opposed to only limbic structures in the aforementioned studies) and found that global network efficiency was decreased in patients with left TLE (de Salvo et al., 2014). Other studies, using cortical thickness correlation, as opposed to tractography, have shown alterations in the entorhinal cortex (Bernhardt et al., 2008) and an increase in global clustering (Bernhardt et al., 2011) in patients with TLE. In patients with *generalised* seizures there are somewhat fewer studies. For childhood absence epilepsy, a decrease in global efficiency was found, relative to control subjects (Xue et al., 2014). Abnormal subnetworks involving the thalamus were also identified in that study. Furthermore Zhang et al. (2011) showed a decrease in small-worldness in patients with idiopathic generalised epilepsy (IGE).

In addition to considering structural brain networks, one can also consider functional networks. Functional connectivity is perhaps an unfortunate term as an anatomical connection is not necessarily present (Rubinov and Sporns, 2010). Rather, the term refers to correlations in *time variant* properties (i.e. variables), such as blood oxygen level dependent (BOLD) signals measured by fMRI. Nonetheless, findings are, to some extent, in agreement with those for structural networks. For example, Moeller et al. (2010) demonstrated increased thalamic activity during childhood absence seizures.

Whilst the results of Moeller et al. (2010) and Xue et al. (2014) are compatible and show converging functional and structural evidence towards thalamic involvement, the interpretation of findings from other studies is more difficult. McGill et al. (2012) showed abnormalities in resting state functional connectivity in patients with IGE. The extent of change was correlated with the duration for which the patient has had epilepsy. Another study of patients with IGE showed that the structural connectivity and resting state functional connectivity became less similar with the duration that the patient has had epilepsy (Zhang et al., 2011). The authors termed this a 'decoupling' of the resting state functional connectivity from the structural connectivity. The reasons for the structure-function decoupling are not known however.

Although several differences have been reported in patient structural connectivity in the above studies there are some key issues with these results. First and foremost, it is not understood how these changes actually relate to the epileptic condition. Whether they are a cause or an effect of seizures remains largely unknown. Longitudinal studies that yield connectivity measures before disease onset, for at-risk subjects or for large cohorts of yet healthy subjects, could help to clarify this question. Secondly, it is not fully understood how the changes in structural connectivity give rise to changes in functional connectivity (if at all). For example, some features that affect structural connectivity, such as changes in the degree of myelination or fiber tract curvature, might not affect the synaptic organisation that affects functional coupling between brain regions. Third, many of the alterations that have been found were already known to be abnormal in patients. For example, it has long been known that patients with TLE have damage to the thalamus and hippocampus (Pitkänen et al., 1998; Bernasconi et al., 2004; Meade et al., 2008; DeCarli et al., 1998; Keller and Roberts, 2008). Thus it is reasonable to suggest the findings of Bonilha et al. (2012) and de Salvo et al. (2014) are related to such damage. Another example of this is the findings of (Xue et al., 2014) who found abnormal thalamic subnetworks. This is not necessarily surprising considering the wealth of experimental work implicating thalamic involvement in generalised seizures (Gloor, 1968; Meeren et al., 2002). In this light the usefulness of applying solely graph theoretic metrics has yet to be fully realised. However, we note that while population-level connectivity results agree with previous studies, connectivity information might be more informative for the assessment of diagnosis and treatment in *individual* patients.

How (ab)normal brain structure impacts brain function both during resting state and during the seizure state is poorly understood. While graph theoretic measures may have helped to discover specific network changes, it is still not known why and how these changes are related to the epileptic condition. Computational modelling could serve to bridge this gap by providing mechanistic insight linking network structure with brain activity patterns.

3. Computational modelling

One method of investigating the link between brain structure and function is through the use of computational models (Migliore et al., 2003; Leon et al., 2013; Woodman et al., 2014). Computer models in this context take the form of differential equations (see e.g. Deco et al. (2008) for review). These equations describe some property which changes over time, for example the firing rate of a population of neurons (Wilson and Cowan, 1972), the blood oxygenation level (Friston et al., 2003), or the phase in an oscillation (Breakspear et al., 2010). Often a simple set of equations with only two variables is used to describe the temporal evolution at a specific brain region (node) with other pairs of variables connected according to a DW-MRI inferred connectivity matrix. This matrix is therefore directly incorporated into the equations and consequently influences the dynamics. Essentially there is a pair of variables at each node and nodes are connected according to the connectivity matrix. This is summarised in Fig. 2. By simulating time-varying properties, computer models can therefore be used to predict functional aspects of the brain such as functional connectivity and time-series.

By incorporating DW-MRI data in a nonlinear computer model, Honey et al. (2009) demonstrated a prediction of resting state functional connectivity emerging from the network level effect of indirect connections. This was done by simulating the model and taking the correlations between the model variables to obtain a simulated functional connectivity. Indeed, various papers have showed similar findings that the functional network can be predicted from the structural network through the use of a computational model. Ghosh et al. (2008) and Deco et al. (2009) highlighted the importance of noise and time delays in the model at this large spatial scale in predicting functional correlations at low frequencies. The relationship between structural and functional connectivity is strong at ultraslow timescales (e.g. 0.1 Hz) for long sampling periods such as the default mode resting state network (RSN) measured by fMRI. For example, Honey et al. (2009) showed a correlation of up to 0.82 between structural connections

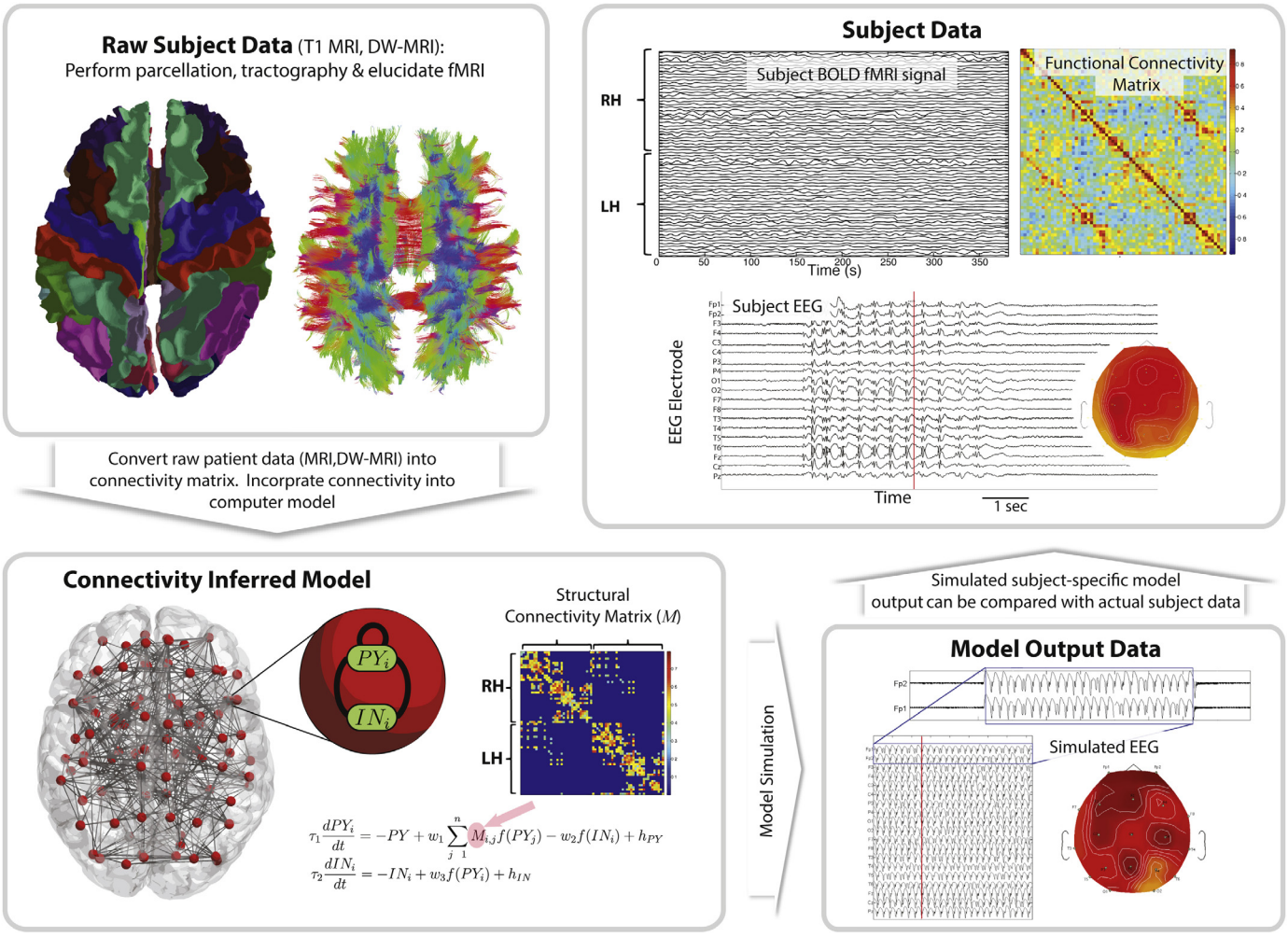


Fig. 2. Typical workflow for connectome based model simulations. The raw subject data obtained from MRI (upper left panel) is processed to form a structural connectivity network matrix which is then incorporated into a set of differential equations (lower left panel) which represent brain dynamics in multiple brain areas including the left and right hemispheres (LH, RH). These equations are then solved numerically, producing model output (lower right panel) which can be compared directly with patient data (upper right panel).

Image modified from Daducci et al. (2012) and Taylor et al. (2013a,b).

and functional correlations between ROI. In addition to oscillations at ultraslow frequencies however, computational models which have been used as predictors of the RSN have also shown faster fluctuations on shorter timescales (Ghosh et al., 2008). The relationship between structural connectivity and functional correlation at any timescale is highly nontrivial. However, computer models offer an exciting opportunity to explore this.

The approach of incorporating anatomical brain connectivity into a computer model is a relatively recent one, however it could see rapid growth in coming years (Kaiser, 2013). Indeed, research questions have already been addressed in the context of brain lesions (Alstott et al., 2009; Cabral et al., 2012), schizophrenia (Cabral et al., 2012; Raj et al., 2012), dementia (Raj et al., 2012), and epilepsy (Yan and Li, 2013; Taylor et al., 2013b).

Epilepsy modelling is one field which could see the most growth in coming years when one considers the known anatomical differences (e.g. (Xue et al., 2014; Zhang et al., 2011)) and the observed functional differences (e.g. (McGill et al., 2012; Moeller et al., 2010)) in patients (see section 2 for further information). Computational modelling could be the key to advancing our understanding of the link between the abnormalities in structure and function. A particularly interesting case is that of absence seizures. Absence seizures have a distinct electrographic manifestation (the spike and wave discharge, usually more prominent in frontal areas) and sudden onset & offset (see, e.g., Fig. 2 and Baier et al. (2012) for examples). Importantly the patient is often not moving whilst seizing so high quality recordings can be obtained. The seizure recordings have been described as stereotypic (i.e. patient-specific), with a dominance in frontal areas. By incorporating DW-MRI data, two recent large scale models of absence seizures have suggested that these factors can be explained by the patient connectivity (Yan and Li, 2013; Taylor et al., 2013b). Specifically, Yan and Li (2013) showed that the nodes with the highest degree of centrality ('frontal hubs') correspond with global synchronisation with frontal origin as is reported clinically (Pavone and Niedermeyer, 2000).

There are many other models of epilepsy into which the connectivity data can be 'plugged-in'. For example, the model of Terry et al. (2012) and Benjamin et al. (2012), which is based on a bistable system (Kalitzin et al., 2010; Lopes Da Silva et al., 2003), was used to demonstrate how patient-derived network structure can influence the time it takes to transit from one (healthy) state to another (seizing) state. In that model, Benjamin et al. (2012) showed that when using patient derived connectivity in the model, simulated seizures occur more often than when nonepileptic control connectivity is used. The full reasons for this remain to be elucidated however. Alternatively, rule-based models have been shown to exhibit varied

spreading dynamics which strongly depend on network connectivity (Kaiser et al., 2007; Goodfellow et al., 2012). Indeed, there is also a plethora of other models of epileptic activity which could be chosen specific to the patient's disorder (Suffczynski et al., 2004; Wendling et al., 2002; Breakspear et al., 2006; Taylor and Baier, 2011; Goodfellow et al., 2011; Wang et al., 2012; Taylor et al., 2013a; Jirsa et al., 2014). The key difference is that the connectivity of these models should be derived from human epileptic subjects.

One potential difficulty for this approach, certainly in the context of epilepsy is the intrinsic differences between nodes which cannot be captured by MRI alone. For example, it is widely accepted that the thalamus plays a key role in absence epilepsy (Avoli, 2012). Indeed, it has been suggested that the thalamocortical loop acts as a 'system' which, in the case of absence seizure patients, is abnormal and leads to seizures (Avanzini et al., 2012). The thalamus is inherently different to the cortex in terms of its intrinsic properties (e.g. neuron types, local connectivity) and a major challenge for a computational model is to capture this successfully. There is however, a large body of experimental work detailing these aspects, particularly in the thalamus (Pinault and O'Brien, 2005) and computational models of thalamocortical interactions in agreement have already been developed (Robinson et al., 2002). The next step would be to extend this using heterogeneous patient derived connectivity instead of using homogeneous connectivity as in (Robinson et al., 2002). This approach should also be used for other 'system' epilepsies (Avanzini et al., 2012).

4. Applications

In addition to attempting to elucidate the link between pathological brain structure and function (rather than the link in the healthy case as explored by Honey et al., 2009), there are many other reasons to develop such a large-scale model of epilepsy incorporating patient data. For example, brain stimulation has been hypothesised as a possible treatment for many patients with epilepsy (Rajna and Lona, 1989; Osorio and Frei, 2009; Saillet et al., 2012; Berényi et al., 2012). However, the application of brain stimulation in epilepsy is far from a solved problem. This is despite the recent FDA approval for the first cortical stimulation treatment (NeuroPace, Mountain View, CA). Computational modelling studies at the macroscopic scale have begun to offer suggestions for optimal stimulation protocols (Tass, 2003; Kramer et al., 2006). However, none thus far have investigated this in a spatially extended model incorporating human derived connectivity. A major research direction could be to elucidate not only the optimal timing of seizure abating stimuli, but also the optimal location to stimulate. This could be done using inspiration from modern techniques in network control theory (Liu et al., 2011; Ching et al., 2012; Bakouie et al., 2013; Ruths and Ruths, 2014; Ruths et al., 2014).

A second possible application of patient derived models may be to elucidate optimal brain areas for surgery. It has already been suggested at the mesoscopic spatial scale that so-called 'micro-incisions' could potentially limit the spread of seizures and thus stop their presence at the large scale (Wang et al., 2013, 2014). However, the connectivity in that model was not patient derived. The earlier findings of (Bonilha et al., 2013) which showed differences in the small world-ness of post-surgical seizure-free and not-seizure-free patients could serve as an excellent biomarker for identifying optimal surgical candidates. However, in those not-seizure-free patients the optimal area to operate is still not known. Model simulations could be used to predict this, or even predict the likelihood of success. Initial work in this direction has already shown some promising findings (Sinha et al., 2014). Incorporating the patient's own connectivity into the model would enable the prediction of such factors in a patient-specific manner through the simulation of either node resection or edge incision (removal). Indeed, it has already been shown clinically in patients that incisions to disconnect brain areas can limit spreading and consequently the likelihood of recurrent seizures (Ng and Valiante, 2010; Bower et al., 2013).

5. Summary

Computational models, when combined with physiological data, can improve the understanding of brain function and dysfunction, particularly in the case of epilepsy. The relatively recent advancements in brain imaging techniques allow this on an unprecedented scale. Nonetheless, a crucial element to understanding many aspects of the brain will be to consider dynamic brain processes in addition to static connectivity maps. It is crucial to combine efforts from neuroimaging experts, theoreticians and clinicians to do this in the context of disease. Computer models can bridge the gap in understanding the relationship between brain structure and brain (dys)function. It can also provide important and clinically relevant predictions regarding stimulation regimes and surgical interventions to treat brain disorders such as epilepsy.

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