NeuroImage: Clinical 18 (2018) 202–214

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The impact of epilepsy surgery on the structural connectome and its relation to outcome

Peter N. Taylor[a,b,c,*], Nishant Sinha[a,b], Yujiang Wang[a,b,c], Sjoerd B. Vos[d,e], Jane de Tisi[c], Anna Miserocchi[c], Andrew W. McEvoy[c], Gavin P. Winston[c,e,1], John S. Duncan[c,e,1]

[a] Interdisciplinary Computing and Complex BioSystems Group, School of Computing Science, Newcastle University, UK
[b] Institute of Neuroscience, Faculty of Medical Science, Newcastle University, UK
[c] NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
[d] Translational Imaging Group, Centre for Medical Image Computing, University College London, UK
[e] Chalfont Centre for Epilepsy, Chalfont St Peter SL9 0LR, UK

ARTICLE INFO

Keywords:
Connectome
Network
Temporal lobe epilepsy
Surgery
Machine learning
Support vector machine (SVM)

ABSTRACT

Background: Temporal lobe surgical resection brings seizure remission in up to 80% of patients, with long-term complete seizure freedom in 41%. However, it is unclear how surgery impacts on the structural white matter network, and how the network changes relate to seizure outcome.

Methods: We used white matter fibre tractography on preoperative diffusion MRI to generate a structural white matter network, and postoperative T1-weighted MRI to retrospectively infer the impact of surgical resection on this network. We then applied graph theory and machine learning to investigate the properties of change between the preoperative and predicted postoperative networks.

Results: Temporal lobe surgery had a modest impact on global network efficiency, despite the disruption caused. This was due to alternative shortest paths in the network leading to widespread increases in betweenness centrality post-surgery. Measurements of network change could retrospectively predict seizure outcomes with 79% accuracy and 65% specificity, which is twice as high as the empirical distribution. Fifteen connections which changed due to surgery were identified as useful for prediction of outcome, eight of which connected to the ipsilateral temporal pole.

Conclusion: Our results suggest that the use of network change metrics may have clinical value for predicting seizure outcome. This approach could be used to prospectively predict outcomes given a suggested resection mask using preoperative data only.

1. Introduction

Epilepsy is a serious neurological disorder characterised by recurrent unprovoked seizures affecting 1% of the population. Neurosurgical resection can bring remission in up to 80% of those with refractory focal epilepsy, with 41% remaining entirely seizure free for years (De Tisi et al., 2011). The most common type of epilepsy surgery is anterior temporal lobe resection, in which the amygdala, anterior hippocampus, and anterior temporal neocortex are removed. The commonest neurological sequelae of temporal lobe surgery are memory impairment, visual field deficits and word-finding difficulties (Jutila et al., 2002; Gooneratne et al., 2017).

Recent studies have investigated surgical outcome by considering the brain as a network of connected regions. Such networks can then be subjected to quantitative analysis techniques, which measure local and global properties in networks (see Bernhardt et al. (2015) for review). Network measures that have been found to be altered in temporal lobe epilepsy (TLE) include the clustering coefficient of a region, which captures the connectedness of neighbours of a region (Bernhardt et al., 2011). Furthermore, the strength of a connection (e.g. the number of streamlines connecting two areas), or the strength of a region's connectivity (e.g. the number of streamlines connecting a region to all other regions) may also be altered in TLE (Besson et al., 2014a, 2014b; Taylor et al., 2015). Another measure of a network is its efficiency, which is a measure of network integration - i.e. how easy it is to travel between one region to another via direct and indirect paths, and has been shown to be altered in patients with TLE (Liu et al., 2014). Finally, regression analysis and machine learning approaches have also been

* Corresponding author at: Interdisciplinary Computing and Complex BioSystems Group, School of Computing Science, Newcastle University, UK.
E-mail address: peter.taylor@newcastle.ac.uk (P.N. Taylor).
[1] Equal contribution.

https://doi.org/10.1016/j.nicl.2018.01.028
Received 26 July 2017; Received in revised form 5 December 2017; Accepted 21 January 2018

applied to brain networks of TLE to relate them to surgical outcome (Bonilha et al., 2013; Munsell et al., 2015; Bonilha et al., 2015; Ji et al., 2015).

A challenge in comparing networks across subjects is the choice of an appropriate baseline or benchmark. There are two common approaches to this. One is to threshold the connectivity so that all subjects have the same number of connections. A range of thresholds are then checked, and the most significant results reported across thresholds (Zhang et al., 2011). This has the drawback of removing 'weak' but potentially important connections. A second approach is to compare the network to a random network with the same number of regions and connections. Typically this is done by either rewiring the existing network (Maslov and Sneppen, 2002), or by generating a new network according to predefined rules (Betzel et al., 2016; Bauer and Kaiser, 2017). Many different types of baseline networks can be used and this will therefore influence results.

Recently Kuceyeski et al. (2013) introduced the network modification (NeMo) tool in the context of stroke (Kuceyeski et al., 2015a, 2015b) and multiple sclerosis (Kuceyeski et al., 2015a, 2015b). The NeMo tool is a method to enable a direct comparison between networks that undergo change. For example, in their study of stroke, the authors drew masks over stroke affected areas and overlaid this mask with data from healthy subjects. Normal connectivity from the healthy subjects, and altered connectivity (i.e. tracts which pass through the stroke mask) were calculated. This approach allowed the authors to calculate a change in connectivity metric (ChaCo), which was shown to correlate with outcomes. Since the authors use the pre-stroke network as a baseline to investigate the implied post-stroke differences, the analysis is possible without the need to generate random networks or threshold the connectivities. This obviates the need for arbitrarily chosen surrogate networks by effectively using the patient's own network as the surrogate instead – a distinct advantage of the technique. A drawback of that study is that the tractography was derived from a cohort of healthy controls, rather than the stroke patients. Nonetheless, this framework is ideally suited to investigate *changes* in networks, given a well-defined alteration such as a stroke or surgery.

In this study we used a ChaCo-like approach in the context of epilepsy surgery and addressed the following questions: What is the impact of surgery on the patient's network? How does this impact graph theoretic properties such as region strength, network efficiency? Do these *changes* to patient networks correlate with surgical outcome?

Although the resection masks we use in this study are derived retrospectively from postoperative data, our methods could in future be applied preoperatively using a mask of the intended resection.

2. Materials and methods

2.1. Patients & MRI acquisition

We retrospectively studied 53 patients who underwent temporal lobe epilepsy surgery at the National Hospital for Neurology and Neurosurgery, London, United Kingdom. Full patient details can be found in Table S11, a summary is given in Table 1. Patient outcomes were defined at 12 months postoperatively, according to the ILAE classification of surgical outcomes (Wieser et al., 2001) and separated into two groups. Group 1 includes patients who were completely seizure free (ILAE 1), and group 2 incorporates all other possibilities (ILAE 2–6). No patient had any prior history of neurosurgery. We used a χ^2 test to check for differences between outcome groups in gender, side of surgery, and evidence of hippocampal sclerosis. We applied Kruskal-Wallis test to check for differences in age between outcome groups.

All patients underwent preoperative anatomical T1-weighted MRI and preoperative diffusion MRI. Postoperative T1-weighted MRI was obtained within 12 months of surgery with the exception of one patient, who was rescanned later.

MRI studies were performed on a 3T GE Signa HDx scanner (General Electric, Waukesha, Milwaukee, WI). Standard imaging gradients with a maximum strength of 40mT m^{-1} and slew rate 150 T m^{-1} s^{-1} were used. All data were acquired using a body coil for transmission, and 8-channel phased array coil for reception. Standard clinical sequences were performed including a coronal T1-weighted volumetric acquisition with 170 contiguous 1.1 mm-thick slices (matrix, 256 × 256; in-plane resolution, 0.9375 × 0.9375 mm).

Table 1
Patient demographics and relation to outcome group.

	ILAE 1	ILAE 2–6	Significance
N	36 (68%)	17 (32%)	
Male/female	16/20	4/13	p = 0.3597, χ^2 = 0.839
Left/right TLE	22/14	8/9	p = 0.3353, χ^2 = 0.923
Age (mean, S.D./median, I.Q.R.)	37, 11.6/ 39.6, 19.25	41.5, 10.6/ 42.3, 10.8	p = 0.2374
Hippocampal sclerosis	25 (69%)	10 (59%)	p = 0.4460, χ^2 = 0.5808

Diffusion MRI data were acquired using a cardiac-triggered single-shot spin-echo planar imaging sequence (Wheeler-Kingshott et al., 2002) with echo time = 73 ms. Sets of 60 contiguous 2.4 mm-thick axial slices were obtained covering the whole brain, with diffusion sensitizing gradients applied in each of 52 noncollinear directions (b value of 1,200mm^2 s^{-1} [δ = 21 ms, Δ = 29 ms, using full gradient strength of 40 mT m^{-1}]) along with 6 non-diffusion weighted scans. The gradient directions were calculated and ordered as described elsewhere (Cook et al., 2007). The field of view was 24 cm, and the acquisition matrix size was 96 × 96, zero filled to 128 × 128 during reconstruction, giving a reconstructed voxel size of 1.875 × 1.875 × 2.4 mm. The DTI acquisition time for a total of 3480 image slices was approximately 25 min (depending on subject heart rate).

2.2. Image processing

2.2.1. T1 processing

Preoperative anatomical MRI was used to generate parcellated regions of interest (network nodes: ROIs). We used two different approaches to do this, generating two different parcellation schemes. First, we used the FreeSurfer recon-all pipeline (https://surfer.nmr.mgh.harvard.edu/), which performs intensity normalization, skull stripping, subcortical volume generation, gray/white segmentation, and parcellation (Fischl, 2012). The default parcellation scheme from FreeSurfer (the Desikan-Killiany atlas (Fischl et al., 2002; Desikan et al., 2006)) contains 82 cortical ROIs and subcortical ROIs and is widely used in the literature (e.g. Munsell et al., 2015; Taylor et al., 2015). The method FreeSurfer uses to generate its ROIs uses anatomical priors based on a manually annotated dataset from healthy controls. However, this may be suboptimal in the case of disease and therefore, we use a second approach based on geodesic information flow (GIF) to generate ROIs which has the advantage of performing well even in the presence of neuropathology (Cardoso et al., 2015). Using the GIF approach, we generate 114 cortical and subcortical ROIs (Table 2). A drawback of using the GIF approach is comparison to previous studies is less straightforward since most previous work use alternative atlases. The results presented in the main manuscript use the GIF derived ROIs, while we include results using FreeSurfer derived ROIs in supplementary materials to aid comparison to previous studies.

2.2.2. DWI processing

Preoperative diffusion MRI data were first corrected for signal drift (Vos et al., 2016), then eddy current and movement artefacts were