Altered structural connectivity in patients with medial temporal lobe epilepsy: A Diffusion Spectrum Imaging and Graph Analysis study

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INTRODUCTION

Medial temporal lobe epilepsy (MTLE) is the most common type of refractory focal epilepsy, and hippocampal sclerosis (HS) is the most frequent underlying pathology. Imaging studies have shown alterations of functional and structural brain connections that extend beyond the affected temporal lobe in the ipsi-lateral and contra-lateral hemisphere. Diffusion Magnetic Resonance Imaging and fiber-tracking offer a noninvasive technique for mapping human brain connectivity and have been increasingly used to study patients with epilepsy. In this study we investigated the effects of medial temporal lobe epilepsy on the global characteristics of brain connectivity estimated by topological measures (graph theory) to reduce the complexity of its interpretation. We used Diffusion Spectrum Imaging (DSI) [1], a high angular resolution diffusion technique, to address the difficulty of Diffusion Tensor Imaging (DTI) to disentangle multiple fiber orientations in a single voxel.

MATERIAL and METHODS

33 healthy volunteers and 5 right-sided MTLE patients with HS underwent DSI (voxel size = 2.2x2.2x3 mm; 44 slices; 257 diffusion directions; max b-value = 6400 s/mm^2), T1-weighted MPRAGE (TR/TE = 2300/2.86 ms, voxel size = 1x1x1.2 mm, 160 slices) and T2-weighted (TR/TE = 3200/408 ms, voxel size = 1x1x1.2 mm, 160 slices) images on a 3T Trio a Tim System (Siemens, Erlangen, Germany) using a 32-channel head coil.
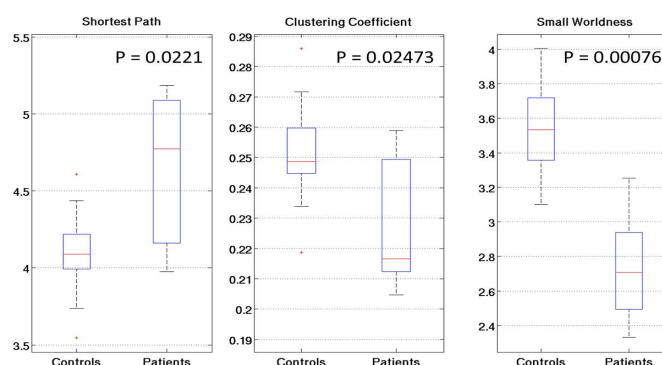
Analysis has been carried out using the Connectome mapper, freely available at [2]. In details, thirty-five cortical and eight subcortical regions of interest (ROI) with anatomical landmarks were mapped from individual T1 weighted images using Freesurfer 5.0 software [3] for each hemisphere. The ROIs were co-registered to the diffusion image space using a nonlinear registration between T1 to T2 , then T2 to the diffusion space [4]. The Diffusion Tool Kit [5] was used for the reconstruction of the diffusion Orientation Distribution Function (ODF) in each voxel. Fiber-tracking was then performed in the white matter areas using an in-house streamline-based algorithm adapted to work with DSI data. Two scalar maps, notably the Fractional Anisotropy (FA) and the Generalized Fractional Anisotropy (GFA) [6] were calculated. The FA was obtained by fitting a tensor from the full Cartesian data of DSI in each voxel from a shell interpolated at b-value = 1000 s/mm^2. For each subject a connectivity matrix (which represents the adjacency matrix of the corresponding network or graph) was computed to quantify the mean GFA and FA value along all fiber-bundles connecting any pair of ROIs. Finally, we estimated the following properties [7] of these networks: *Characteristic Path Length* or *Shortest Path* (L), *Clustering Coefficient* (C) and *Small Worldness* (S), where S = (C/C$_{rand}$)/(L/L$_{rand}$) with C$_{rand}$ and L$_{rand}$ being the previous features computed on a random network for reference. A Wilcoxon rank-sum test was used to assess the significant difference between the MTLE patients group and the healthy subjects group.

RESULTS

All the three global features of the connectivity networks showed a significant difference between patient and control groups. The figure reports the analysis conducted on the GFA scalar map; however results holds for FA, too. In the patients, we found a higher *Characteristic Path Length* (p=0.022), lower *Clustering Coefficient* (p=0.025) and lower *Small Worldness* (p<0.001). The connectivity alterations were bilateral, although with a clear predominance for the ipsi-lateral hemisphere. Temporal as well as extra-temporal structures were affected with a predilection for regions associated with the limbic network. These results suggest that the global interaction between the nodes is decreased and that there is a lack of specialized communities, meaning that the network of the patient group is less segregated compared to the control group.

CONCLUSIONS

These global measures of the structural connectivity as estimated with DSI suggest that the network organization of unilateral MTLE is less efficient compared to the control group, in relation to alteration of intra-temporal and extra-temporal connections in both hemispheres. The results of our white matter connectivity analysis are concordant with altered functional connectivity in TLE studied with fMRI and intracranial EEG [8] as well as with altered structural networks based on grey matter thickness using T1-volumetry [9]. Further studies are needed to establish the relevance of these findings for the propagation of epileptic activity, cognitive deficits in MTLE and outcome of epilepsy surgery.

References

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