Altered structural connectivity and network organization in mesial temporal lobe epilepsy

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Purpose: Epilepsy is one of the most common neurological disorders with mesial temporal lobe epilepsy (mTLE) accounting for about half of all patients with epilepsy. Although classically mTLE has been theorized to relate to isolated injury of mesiotemporal structures, more recent studies have revealed widespread cortical atrophy involving both temporal and extratemporal areas, leading to the concept of mTLE as a "network disease[1]." The default mode network (DMN) has been consistently found to be among the extratemporal areas affected by TLE in studies of structural and functional connectivity, which may explain certain cognitive and psychiatric symptoms of patients with mTLE[234]. Graph theory has proven to be a powerful new method to quantify properties of complex connectivity networks created using structural and functional neuroimaging techniques[5]. To our knowledge, this study is the first to use a graph theoretical approach to compare high resolution whole brain structural connectivity networks between patients with mTLE and healthy controls using diffusion tensor imaging (DTI) without selecting *a priori* seed regions or visually inspecting the results of independent component analysis (ICA) to study specific networks.

Methods: Data was reviewed and analyzed from 23 patients with left mTLE and 23 healthy controls. High resolution T1-weighted images were segmented into 83 regions of interest (ROIs) using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) after registration to b_0 DTI images. Cortical surfaces were further parcellated into 1000 ROIs using the Connectome Mapper (www.connectomics.org). Deterministic streamline tractography (angle threshold=60^0) was performed on DTI data (b=700, 60 gradient directions) after voxel-wise tensor calculation. Whole brain structural connectivity matrices were generated using the density of connecting fibers per unit surface area between each pair of cortical ROIs (Fig. 1). Graph theoretical measures of structural connectivity networks were calculated using the Brain Connectivity Toolkit (www.brain-connectivity-toolbox.net). Graph measures and connectivity were statistically compared across subjects using two-sample unpaired Student's t-tests.

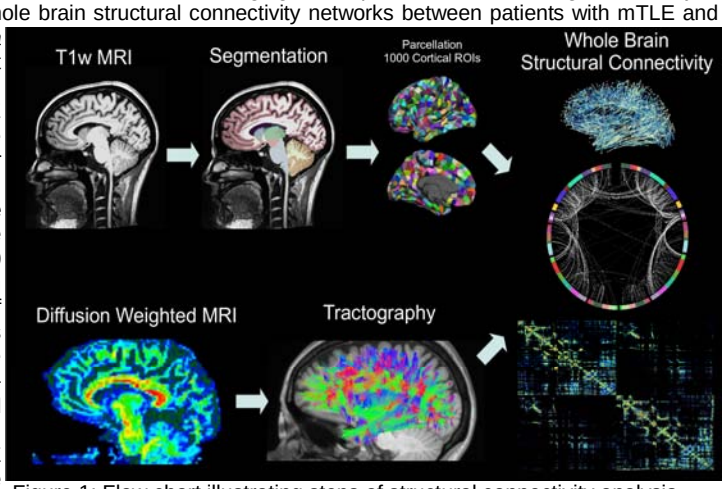

Figure 1: Flow chart illustrating steps of structural connectivity analysis

Results: Increased connection density was observed in patients with mTLE involving ipsilateral temporal and bilateral precuneus and posterior cingulate cortices while decreased connectivity was observed among ipsilateral frontal areas (Fig. 2). Although network modularity was not statistically significant between groups, global efficiency was increased in the setting of mTLE ($p<0.001$). Local clustering coefficient and efficiency were also increased in ipsilateral temporoparietal and cingulate cortices ($p<0.05$). Modularity analysis generated five anatomical modules: bilateral lateral frontal cortices, medial frontal/cingulate cortex/precuneus and bilateral temporoparietooccipital cortices. The precuneus had a lower within-module z-score of degree ($p<0.05$) but higher participation coefficient ($p<0.05$) in the setting of mTLE.

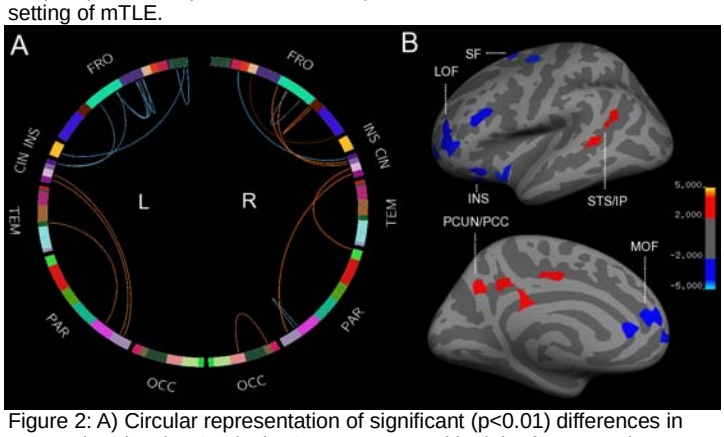

Figure 2: A) Circular representation of significant ($p<0.01$) differences in connection density. Cortical ROIs are arranged by lobe from anterior to posterior. B) Cortical surface of left hemisphere highlighting ROIs with significant ($p<0.01$) differences in connection density. PCUN=precuneus; PCC=posterior cingulate cortex; INS=insula; SF=superior frontal; INS=insula; STS=superior temporal sulcus; IP=inferior parietal; MOF=medial orbitofrontal; LOF=lateral orbitofrontal; Dark gray=sulci; Light gray=gyri

Discussion: Networks of both patients with mTLE and healthy controls exhibited small world properties and modular community structure, yet the mTLE group had important global and local alterations in structural network properties. Increased clustering and efficiency within the ipsilateral temporal lobe suggests increased local interconnectedness likely related to aberrant self-reinforcing connectivity due to epileptic activity. In contrast to prior studies that employed seed-based or ICA approaches to study the DMN, our data-driven analysis showed increased (rather than decreased) structural connectivity between bilateral precuneus and posterior cingulate cortices, which are important hub areas within the DMN. However, because the precuneus had decreased within-module z-score of degree and increased participation coefficient in the setting of mTLE, it is likely that the role of posterior DMN areas is altered in mTLE such that they are less densely connected within the DMN while simultaneously more connected to other modules. Similar to prior studies, we found decreased structural connectivity in ipsilateral frontal areas including medial orbitofrontal cortex, an anterior DMN area, which we hypothesize may relate to disrupted connectivity through posterior DMN areas. This altered pattern of long-range connectivity and structural subnetworks may underlie the pathophysiology of epileptiform activity propagation that may reinforce an altered mTLE network. This may also lead to distant effects such as cortical thinning in the DMN[6].

Conclusion: These results suggest that left mTLE is associated with increased structural connectivity within left temporal and bilateral DMN areas as well as altered global and local network properties. These findings reinforce the hypothesis that mTLE involves distant alterations in structure and function far beyond the medial temporal lobe, especially in the DMN, and that may provide a non-invasive biomarker for diagnosis, prognosis and therapy monitoring in patients with mTLE and related seizure disorders.

References

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