Epilepsy Research (2014) xxx, xxx—xxx

ELSEVIER

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

Differences in graph theory functional connectivity in left and right temporal lobe epilepsy

Sharon Chiang[a,1], John M. Stern[b], Jerome Engel Jr.[b,c,d,e], Harvey S. Levin[f,g], Zulfi Haneef[h,i,*,1]

[a] Department of Statistics, Rice University, Houston, TX, USA
[b] Department of Neurology, University of California, Los Angeles, CA, USA
[c] Department of Neurobiology, University of California, Los Angeles, CA, USA
[d] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA
[e] The Brain Research Institute, University of California, Los Angeles, CA, USA
[f] Department of Physical Medicine, Baylor College of Medicine, Houston, TX, USA
[g] Michael E. DeBakey VA Medical Center, Houston, TX, USA
[h] Department of Neurology, Baylor College of Medicine, Houston, TX, USA
[i] Neurology Care Line, VA Medical Center, Houston, TX, USA

Received 4 June 2014; received in revised form 7 September 2014; accepted 20 September 2014

KEYWORDS
Brain imaging;
Epilepsy;
Functional MRI;
Graph theory;
Functional reorganization

Summary
Purpose: To investigate lateralized differences in limbic system functional connectivity between left and right temporal lobe epilepsy (TLE) using graph theory.
Methods: Interictal resting state fMRI was performed in 14 left TLE patients, 11 right TLE patients, and 12 controls. Graph theory analysis of 10 bilateral limbic regions of interest was conducted. Changes in edgewise functional connectivity, network topology, and regional topology were quantified, and then left and right TLE were compared.
Results: Limbic edgewise functional connectivity was predominantly reduced in both left and right TLE. More regional connections were reduced in right TLE, most prominently involving reduced interhemispheric connectivity between the bilateral insula and bilateral hippocampi. A smaller number of limbic connections were increased in TLE, more so in left than in right TLE. Topologically, the most pronounced change was a reduction in average network betweenness centrality and concurrent increase in left hippocampal betweenness centrality in right TLE.

Abbreviations: TLE, temporal lobe epilepsy; fcMRI, functional connectivity MRI; DMN, default mode network; AAL, automated anatomical labeling; FWER, family wise error rate; AED, anti-epileptic drug; FDR, false discovery rate.

* Corresponding author at: Department of Neurology, Baylor College of Medicine, One Baylor Plaza, MS: NB302, Houston, TX 77030, USA. Tel.: +1 832 355 4044; fax: +1 713 798 7561.
E-mail addresses: zulfi.haneef@bcm.edu, zulfihaneef@gmail.com (Z. Haneef).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.eplepsyres.2014.09.023
0920-1211/Published by Elsevier B.V.

In contrast, left TLE exhibited a weak trend toward increased right hippocampal betweenness centrality, with no change in average network betweenness centrality.
Conclusion: Limbic functional connectivity is predominantly reduced in both left and right TLE, with more pronounced reductions in right TLE. In contrast, left TLE exhibits both edgewise and topological changes that suggest a tendency toward reorganization. Network changes in TLE and lateralized differences thereof may have important diagnostic and prognostic implications.

Introduction

Temporal lobe epilepsy (TLE) is the most common epilepsy in adults and most common pharmaco-resistant epilepsy amenable to surgical treatment. However, surgery is not possible in about 30% of TLE patients, primarily due to a lack of clear localizing abnormality (Berg et al., 2003). In standard surgical evaluation protocols, high-resolution MRI and video-EEG play a central role (Duncan, 1997). Functional connectivity MRI (fcMRI) may provide an additionally potential useful technique to aid lateralization.

Structural and functional neuroimaging has shown that TLE is a disorder of altered brain networks involving both temporal and extratemporal changes (Chiang and Haneef, 2014; Engel et al., 2013; Spencer, 2002). In additional to temporal lobe structures (Bettus et al., 2010; Pittau et al., 2012), seizure-induced neuronal loss has been hypothesized to lead to reorganization of limbic connectivity (Spencer, 2002). Structural reorganization of the limbic system has been observed in TLE using diffusion tensor imaging, mostly involving the insula, superior temporal lobe, thalamus, and hippocampus (Bonilha et al., 2012).

Recent studies have found different patterns of functional connectivity between right and left TLE, including global functional impairment in right TLE and redistribution of functional activation in left TLE (Billingsley et al., 2001; Dupont et al., 2002; Vlooswijk et al., 2010). Other lateralized differences in subnetworks such as the default mode network (DMN) have also been identified (Haneef et al., 2012). A graph theoretic approach to investigating lateralized differences in TLE functional connectivity permits a network-level approach that can help elucidate pathophysiology (Chiang and Haneef, 2014). Additionally, characterization of the functional connectome using graph theoretic measures allows for quantification of connectomic differences which may potentially aid clinical lateralization.

In this study, we used a graph theoretic approach to analyze resting state fcMRI and characterize differences in limbic functional connectivity between left and right TLE compared to healthy controls. This consisted of three steps: (1) comparison of edgewise differences in functional connectivity, (2) comparison of whole-brain limbic network properties, and (3) comparison of network properties of limbic structures at a nodal level.

Materials and methods

Subjects

We studied 14 subjects with left TLE, 11 subjects with right TLE, and 12 controls. The study was approved by the Institutional Review Board for Baylor College of Medicine (BCM). Consenting patients were recruited from July 2011 to March 2014 from the BCM comprehensive epilepsy center following clinical evaluation, video-EEG monitoring, and high-resolution MR imaging. Patients with disabling cognitive impairment or other neurological co-morbidities were excluded. Control subjects were recruited through university advertisement and word-of-mouth, and were selected to match patient groups in age, gender, and educational background.

Image acquisition

Imaging was performed on a Philips Ingenia 3T MRI scanner (Philips Medical Systems, Best, Netherlands). Resting state fMRI was acquired axially for 10 min (TR = 6000 ms, TE = 30 ms, FOV = 228 mm, matrix = 100×100, slice thickness = 2.25 mm, 67 slices, 100 volumes). Subjects were instructed to lie still with eyes closed, and not asked to think about anything in particular during the functional sequence. Patients were requested not to fall asleep during imaging and were monitored by the imaging technician. T_1-weighted imaging was also performed as follows: TR = 2500 ms, TE = 4600 ms, FOV = 199 mm, matrix = 244×206, slice thickness = 1.4 mm, 284 slices.

fMRI preprocessing

Data pre-processing were performed using FSL (fMRIB Software Library) version 5.0.2 (Oxford, UK, www.fmrib.ox.ac.uk/fsl) (Forman et al., 1995; Woolrich et al., 2001). The first 12 s were discarded to attain magnetization equilibrium. Resting state functional images underwent non-brain tissue elimination (Smith, 2002); slice-timing correction; spatial smoothing using a Gaussian kernel (5 mm full-width half maximum); and co-registration to the T_1-weighted structural image. Common pre-processing steps for resting state fMRI were then applied, including temporal bandpass filtering ($0.01 < f < 0.1$ Hz) (Fox et al., 2005; Uddin et al., 2009) and removal of the following sources of spurious various using linear regression: six motion parameters and their temporal derivatives, ventricular signal, and white matter signal (Fox et al., 2005). Whole-brain signal regression was not performed, in order to increase test-retest reliability in graph theory analyses (Liang et al., 2012). Motion scrubbing was also performed (Power et al., 2012). Residuals were normalized prior to further analysis.

Please cite this article in press as: Chiang, S., et al., Differences in graph theory functional connectivity in left and right temporal lobe epilepsy. Epilepsy Res. (2014), http://dx.doi.org/10.1016/j.eplepsyres.2014.09.023