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Low functional robustness in mesial temporal lobe epilepsy

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ABSTRACT

Objectives: Brain functional topology was investigated in patients with mesial temporal lobe epilepsy (mTLE) by means of graph theory measures in two differentially defined graphs. Measures of segregation, integration, and centrality were compared between subjects with mTLE and healthy controls (HC).
Methods: Eleven subjects with mTLE (age 36.5 ± 10.9 years) and 15 age-matched HC (age 36.8 ± 14.0 years) participated in this study. Both anatomically and functionally defined adjacency matrices were used to investigate the measures. Binary undirected graphs were constructed to study network segregation by calculating global clustering and modularity, and network integration by calculating local and global efficiency. Node degree and participation coefficient were also computed in order to investigate network hubs and their classification into provincial or connector hubs. Measures were investigated in a range of low to medium graph density.
Results: The group of patients presented lower global segregation than HC while showing higher global but lower local integration. They also failed to engage regions that comprise the default-mode network (DMN) as hubs such as bilateral medial frontal regions, PCC/precuneus complex, and right inferior parietal lobule, which were present in controls. Furthermore, the cerebellum in subjects with mTLE seemed to be playing a major role in the integration of their functional networks, which was evident through the engagement of cerebellar regions as connector hubs.
Conclusions: Functional networks in subjects with mTLE presented both global and local abnormalities compared to healthy subjects. Specifically, there was significant separation between groups, with lower global segregation and slightly higher global integration observed in patients. This could be indicative of a network that is working as a whole instead of in segregated or specialized communities, which could translate into a less robust network and more prone to disruption in the group with epilepsy. Furthermore, functional irregularities were also observed in the group of patients in terms of the engagement of cerebellar regions as hubs while failing to engage DMN-related areas as major hubs in the network. The use of two differentially defined graphs synergistically contributed to findings.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common localization-related epilepsy in the adult population (Engel et al., 1997). Disabling and medication resistant seizures, neurobehavioral comorbidities (cognitive and psychiatric complications), and reduced quality of life often accompany mTLE, making the surgical resection of the affected network a suitable option for this syndrome (Engel, 2003; Lachhwani and Lüders, 2003; Lin et al., 2012). Although seizures occur in mesial temporal regions, which are important for the integrity of both semantic and episodic memory (McAndrews and Cohn, 2012), there is evidence that anatomical irregularities extend to other regions both ipsilateral and contralateral to the side of temporal lobe seizure onset, including the left thalamus, right middle cingulate gyrus, right thalamus,

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right and left postcentral gyrus, left precuneus, and the right precentral gyrus for left-hemispheric mTLE in terms of gray matter concentration (Holmes et al., 2013), which could help to explain the diffuse cognitive impairment that is often observed in this population (Doucet et al., 2013a; Hermann et al., 1997; Lin et al., 2012). Such diffuse impairment contributes to comprises in executive functions, language, and other abilities aside from the well-known memory-related deficits (Bell et al., 2011). In addition to cognitive dysfunction, behavioral and psychiatric comorbidities such as anxiety and depression are common as well (Doucet et al., 2013b; Quiske et al., 2000). Altogether, these neuropsychological and psychiatric disturbances indicate that mTLE is a disorder impacting not only functional systems arising from the anatomically affected area (e.g., memory), but also adversely affecting more global brain function (Zhao et al., 2014).

Recently, graph theoretical analyses have been implemented in brain networks at both the structural and functional levels and in both healthy and patient populations (Buckner et al., 2009; He et al., 2009a; for reviews: Bassett and Bullmore, 2009; He et al., 2009b). This has been possible since brain structure and function has been found to present complex graph-like properties such as integration and segregation. Having an integrated brain topology represents the capacity for effective communication and transfer of information, while segregation in the brain denotes the ability for specialized processes to take place. Aside from general network properties such as integration and segregation, centrality measures can be investigated in brain networks. Centrality is a property that investigates the influence of a region inside a network, helping in the identification of the most crucial areas in the configuration of the network (Sporns et al., 2007).

Graph theory analyses have been implemented in mTLE patients at both the anatomical (Bernhardt et al., 2011; Bonilha et al., 2012; Liu et al., 2014) and functional (Doucet et al., 2015; Liao et al., 2010; Zhang et al., 2011) levels; however, for the functional studies, graph definitions have been mainly based on anatomical segmentation from structurally defined regions of interest (ROI) or nodes. The abstract nature of brain functional processes calls for a less strict network definition. Therefore in this study functional integrity in mTLE patients was studied with two differentially defined graphs: one using anatomically segmented nodes and the second one using nodes defined from putative functional networks. We believe that both forms would lead to a better understanding of brain function in a more complete manner by providing complementary information.

The main interest of this study is to investigate the resting-state functional networks in terms of integration and segregation in a sample of patients with mTLE. In addition, we wanted to investigate which functional regions were most important for functional communication by identifying the most central regions in the networks. Finally, we sought to determine how graph definition conveys differential information about functional brain topology.

2. Methods

2.1. Subjects

Eleven (age 36.5 ± 10.9 years) right-handed epilepsy patients with mesial temporal epilepsy were included in the study, along with fifteen (age 36.8 ± 14.0 years) age-matched healthy control subjects. Clinical characteristics for the patient group and summary of demographics for both groups can be found in Tables 1 and 2, respectively. Epilepsy participants were recruited from the University of Wisconsin (UW) clinical patient service while controls were recruited from the UW community. An MRI scan was acquired for each patient between August 2010 and August 2013 at the Health Emotions Research Institute (HERI) of the University of Wisconsin—Madison. Following the International League Against Epilepsy (Berg et al., 2010), diagnosis was based on clinical, EEG, and MRI characteristics. The University of Wisconsin Health Sciences Review Board approved all aspects of this study, and all participants provided voluntary written consent.

Table 1
Clinical and demographic characteristics of the patient group.

Patients	Age	Gender	SO (years)	H	No. AEDs
1	43	F	19	L	3
2	34	F	1	L	2
3	40	M	32	L	3
4	52	F	49	L	6
5	26	F	25	L	3
6	36	F	31	R	2
7	29	F	14	L	2
8	53	M	16	R	3
9	43	F	35	L	2
10	19	F	2	L	3
11	27	F	3	R	2

H: hemisphere; SO: syndrome onset; AED: antiepileptic drug.

Table 2
Summary of characteristics for patients and control subjects.

	mTLE ($n = 11$)	HC ($n = 15$)
Age (mean ± SD)	36.5 ± 10.9	36.8 ± 14.0
Gender (M/F)	2/9	7/8
Syndrome Onset (mean ± SD)	20.6 ± 15.4	–
Number of AED (mean ± SD)	2.8 ± 1.2	–
HS location (L/R)	8/3	–

HS: hippocampal sclerosis; AED: antiepileptic drugs.

The patients of this study met the following criteria during clinical evaluation: (i) displayed one or more typical symptoms of mTLE and experienced complex partial seizures alone or accompanied by simple partial seizures and/or secondary generalized tonic-clonic seizures; (ii) MRI manifestations of the hippocampal sclerosis (HS) through unilateral hippocampal atrophy on T_1 image with associated hyperintensity on T_2 fluid attenuated inverted recovery image; (iii) no other structural MRI abnormality identified in the brain other than the hippocampal sclerosis.

2.2. Data acquisition

During acquisition, all patients laid supine with their head securely held by straps and foam pads to minimize head motion. Participants were instructed to lie as still as possible with their eyes closed, not to think of anything specific and not to fall asleep. Five-minute eyes-closed resting-state images were acquired using a 3.0-T MRI scanner (GE MRI 750, Milwaukee, USA) at the UW—Madison.

The eyes-closed resting-state functional MRI data on patients was acquired using an echo-planar imaging sequence with the following parameters: 28 axial slices, TR = 2.0 s, TE = 30 ms, resolution/thickness = 3.5/5 mm, FOV = 24 × 24 cm, 150 volumes. A high resolution (1 mm × 1 mm × 1 mm) 3D T1-weighted BRAVO anatomical MRI was acquired in an axial orientation encompassing the entire brain. Functional data for healthy subjects was acquired from a research protocol with different acquisition parameters. The resting-state images were collected for 10 min with the following parameters: 42 slices, TR = 2.6 s, TE = 22 ms, isotropic 3.5 mm, FOV = 24 × 24 cm, 231 volumes. A high resolution (1 mm × 1 mm × 1 mm) 3D T1-weighted BRAVO anatomical MRI was acquired in an axial orientation encompassing the entire brain.

Differences in scanning parameters between groups are attributable to the different nature of recruitment from each group.