Evaluation of default mode network in temporal lobe epilepsy patients and healthy subjects: a preliminary result

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Abstract. The default mode network (DMN) is thought to be impaired in epileptic patients, where the functional integrity of its core regions compromised. Fourteen healthy participants and fourteen aged and gender-matched patients with temporal lobe epilepsy (TLE) took part in this study. The resting-state fMRI (rsfMRI) imaging protocol was executed using a 3-T Phillips Achieva MRI scanner at the Department of Radiology, HUSM. The TLE patient displays decreased activation clusters in precuneus and supramarginal gyrus compared to the healthy group. However increased activation clusters were found on middle frontal gyrus, superior temporal gyrus, and angular gyrus compared to healthy subjects. The result from random effects (RFX) on healthy TLE revealed that the left middle frontal gyrus, bilateral superior temporal gyrus, bilateral precuneus, and right supramarginal gyrus were significantly activated but the NOV survive was so small. The findings suggested that TLE patients suffer from impairment in some DMN region, which may cause certain neuropsychological and cognitive degradation. Keywords: TLE=Temporal lobe epilepsy; DMN=default mode network.

1. Introduction

1.1. Epilepsy

Epilepsy is characterized by the occurrence of abnormal neuro-electrical activity in the brain. In focal seizures and epilepsy, the epileptic activity arises primarily within networks limited to one hemisphere. The origin of focal seizures may be associated with the localization of radiologically visible brain lesions or electrophysiological abnormalities. However, there is growing evidence from neuroimaging studies that focal epilepsies involve abnormal functional networks rather than a single epileptogenic region \cite{1}.

In resection treatment for epilepsy, vascular lesions, and tumors, it is important to preserve healthy functional tissue. Pre-surgical mapping involves identifying healthy functional tissue that should be preserved during resection. For example, damage to the default-mode network may affect cognitive functions such as planning for the future, navigation of social interactions and memory retrieval \cite{2}. Furthermore, any damage to the
motor network may lead to deficits in motor function [3].

1.2. Default Mode Network (DMN)

The DMN is a brain network of interacting brain regions known to have activity highly correlated with each other [2] with major hubs being located in the posterior cingulate cortex and precuneus, the medial prefrontal cortex, and the angular gyrus [4]. In neuroscience, the default network, also known as the default mode network (DMN), is a large scale brain network of interacting brain regions known to have activities that are highly correlated with each other and distinct from other networks in the brain [5].

1.3. Functional Magnetic Resonance Imaging (fMRI)

fMRI has the potential to predict possible deficits in language, visual, motor and sensory functions that would arise from surgical intervention or post-operation [6]. This would be of great help to the treating physician or the surgeon in explaining the relative risk of intervention against non-intervention so that a decision about treatment options can be made after considering their costs and benefits. In many cases, the decision making requires a judgment to be made regarding the balance between reduction of seizures and maintenance of function, to ensure minimal effects on the quality of life (QOL).

It is well known that fMRI is a noninvasive technique that has demonstrated great promises for pre-surgical planning [7] especially when used preoperatively to localize areas of the eloquent cortex [8]. Connectivity study using resting-state fMRI in neurosurgery has also become a promising tool that can be used in diagnosing functional abilities and abnormalities [9]. It can also make functional mapping more interactive by allowing ongoing paradigms to be adjusted if the need arises, making fMRI a more flexible tool for neurological investigations [10].

The aim of the study was to determine whether there was a significant activation present in the resting brain. Thus, in this study, we explore the location of the brain activation area in patients with temporal lobe epilepsy (TLE) and healthy subject. It might be useful for providing complementary information to other clinical diagnostic measures.

2. Methodology

2.1. Subjects

Fourteen healthy participants (3 males,11 females) (average age ± standard deviation = 36.93 ± 8.75 years) and fourteen patients (3 males,11 females) with TLE (average age ± standard deviation = 37.00 ± 8.79 years) took part in this study. The participants from the two groups were matched by age and gender. The healthy participants were purposely recruited from those who accompanied their relatives at the polyclinic and also among staff from Hospital Universiti Sains Malaysia (HUSM). The TLE patients were screened by a neurologist based on reported clinical semiology of the seizures and were confirmed by video-EEG monitoring. The TLE patients were reported to be on drug treatment. The participants agreed to participate in the study by signing the informed consent form after being given full explanation and understand the nature and risks of the research. All participants were screened for MRI compatibility. This study has been approved by the institutional ethics committee (IEC) USM/JEPeM/16050175. All participants with major brain abnormalities caused by surgery or injury, tumors, significant malformation of cortical development leading to distortion of brain anatomy, had a previous history of brain injury and psychiatric disorders were excluded.

2.2. Data acquisition for Resting-state fMRI

The rsfMRI blood oxygen level-dependent (BOLD) imaging protocol was executed using a
3-T Phillips Achieva MRI scanner equipped with a 32-channel head and neck system at the Department of Radiology, HUSM. The first three scans were discarded by the BOLD imaging protocol to eliminate the magnetic saturation effect. The echo-planar imaging (EPI) parameters for acquiring functional T2* weighted images are echo time (TE) = 33 ms, repetition time (TR) = 1.7 s, flip angle = 75°, slice thickness = 4 mm, slice gap = 0 mm, field of view (FOV) = 192 x 192 mm, matrix size = 64 x 64, voxel size = 2 x 2 x 4 mm, number of scans = 250 and total imaging time = 425 s.

The participants were instructed not to move their head during the scan. They were required to be in a state of relaxation, empty their mind and passively focus on a fixation point “×” symbol on the screen throughout the session. Participants must not fall asleep during the scan because “sleeping brain” is very much different from “resting brain” [11]. A demographic and clinical data from both patients and control subjects were obtained prior to the study. We studied a continuous response variable from both groups using t-test statistical analysis.

2.3. Pre-processing and data analysis
A total of 247 functional images were analyzed using Statistical Parametric Mapping (SPM12) obtained from the Functional Imaging Laboratory, Wellcome Trust Centre for Neuroimaging, in the Institute of Neurology at the University College London (www.fil.ion.ucl.ac.uk/spm/) which runs on MATLAB R2016b (The Mathworks, Inc. USA) platform. The functional images in each measurement were first entered into a slice timing module for time correction. They were then realigned using the 6-parameter affine transformation in translational (x, y, and z) and rotational (pitch, roll, and yaw) directions to reduce the effects on the overall signal intensity from participant’s movements. After realigning the data, a mean image of the series was used to estimate some warping parameters that mapped it onto a template that already conforms to standard anatomical space (EPI template provided by the Montreal Neurological Institute – MNI). The normalization procedure used a 12-parameter affine transformation. The images were then smoothed using a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel. Low-frequency responses caused by aliased biorhythms, cardiac effects, and other oscillatory signal variations were removed using a high-passed filter.

The human brain has been found to exhibit low-frequency fluctuations signal (LFF) when it is at rest. This LFF ranges from 0.01 to 0.08 Hz [12]. The LFF detected during resting state is associated with internally and externally oriented consciousness [13]. Thus, to model the LFF, a combination of mathematical functions such as sine and cosine functions of different frequencies that show a resemblance of LFF, can be used. This Fourier basis set is thought to be suitable to model brain responses during the resting state which is assumed to oscillate between 0.01 – 0.08 Hz [14].

The functional T2* weighted images were also separately entered into a group analysis design matrix (GLM) to search for voxels that survived the uncorrected significant level of 0.001. This was done for both groups by means of fixed effects analysis (FFX) due to the constraint in the number of subjects for each group. Random (RFX) effects analyses and inferences based on the group responses were made onto the whole subject.

3. Results and discussion
3.1. Study sample
We collected data from 14 healthy participants (mean age: 36.93) and 14 TLE patients (mean age 37). The healthy participants were matched to the patients on their gender, age, race, and education level. Table 1 shows the mean age of the fourteen healthy subjects (average age ± standard deviation = 36.93 ± 8.75 years) and fourteen TLE patients (average
age ± standard deviation = 37.00 ± 8.79 years).

Table 1. Mean Age and gender

| GROUP      | Number of subjects (n) | Mean    | Std. Deviation |
|------------|------------------------|---------|---------------|
| AGE HEALTHY| 14                     | 36.93   | 8.748         |
|            | 14                     | 37.00   | 8.788         |
| TLE        |                        |         |               |

3.2 Activations
There was a difference between cluster size of the activation in bilateral middle frontal gyrus (MFG), superior temporal gyrus (STG), precuneus (PRE) and supramarginal gyrus (SMG) between healthy and TLE, where healthy subjects display higher activation in PRE and SMG compared to TLE subjects. The TLE patient displays higher activation clusters in MFG, STG, and angular gyrus compared to healthy subjects. Table 2 showed the clusters of activation between subjects in the same group using a one-sample t-test in SPM12 (thresholded at p= 0.001), while Figure 1 shows the activations overlaid onto standard brain space.

The present study found that there was a significant difference between cluster size of the activation in bilateral MFG, STG, PRE and SMG between healthy and TLE, where healthy subjects display higher activation in PRE and SMG compared to TLE subjects. Similar results were found in the previous study on TLE with bilateral hippocampal sclerosis shows decreased activation in posterior cingulate cortex/ PRE [15]. However, in this study the TLE patient displays higher activation clusters in MFG, STG and angular gyrus (ANG) compared to healthy subjects but contrary with the findings from Zhang (2008) which the TLE subjects display decreased activation in MFG and STG as well as other structures such as dorsal lateral prefrontal cortices, superior temporal gyri, caudate heads, dorsal brain stem and the posterior cerebellum [15]. By comparison, rsfMRI study of the brain's network of TLE and TLE with depression, they found more strong active brain areas including thalamus and the default-mode network which involved in prefrontal cortex, PRE, ventral anterior cingulate and hippocampus. They found that the extra-temporal activation in DMN is increased in TLE with depression compared to non-depression group [16]. No SMG activation mentioned in these two journals. This is probably due to the different conditions of the disease or types of TLE.
Table 2. The number of voxels (NOV) of the region of interest (ROIs) on FFX in healthy and TLE.

| REGION                                    | HEALTHY | Coordinates | NOV | Coordinates |
|-------------------------------------------|---------|-------------|-----|-------------|
| Left Middle Frontal Gyrus (L MFG)         | 5       | -30 58 22   | 50  | 44 32 46    |
| Right Middle Frontal Gyrus (R MFG)        | 63      | 30 60 6    | 97  | -28 38 34   |
| Left Superior Temporal Gyrus (L STG)      | 0       | 0          | 187 | -62 -30 14  |
| Right Superior Temporal Gyrus (R STG)     | 2       | 56 -14 6   | 53  | 56 -20 6    |
| Left Angular (L ANG)                      | 0       | 0          | 35  | -46 -66 48  |
| Right Angular (R ANG)                     | 50      | 30 -68 46  | 57  | 46 -62 38   |
| Left Precuneus (L PRE)                    | 145     | -6 -62 14  | 98  | -2 -52 54   |
| Right Precuneus (R PRE)                   | 208     | 8 -66 62   | 33  | 2 -38 54    |
| Left Supramarginal Gyrus (L SMG)          | 82      | -50 -46 30 | 33  | -64 -28 30  |
| Right Supramarginal Gyrus (R SMG)         | 157     | 62 -34 42  | 34  | 58 -24 30   |

Figure 1. (a) ROI on FFX in TLE and (b) healthy brain.

The result from random effects (RFX) analysis (2-sample t-test thresholded at $p = 0.001$) on healthy < TLE revealed that the left MFG, bilateral STG, bilateral precuneus, and right SMG were significantly activated (shown in Table 3) but the NOV survive was so small. This may be attributed to small activation clusters or may be influenced by the fact that all the TLE patients were already stabilized with epileptic medication. These results were compared with the activation from both groups across within and between subjects. The fixed effect analysis is a more sensitive analysis than the random effect method [17]. A robust random-effect analysis needs a large number of subjects to achieve high confidence in
parameter estimation. A small number of subjects lead to low degrees of freedom in variance estimation.

### Table 3. NOV of ROIs on RFX analysis in healthy and TLE at $p = 0.001$ uncorrected.

| Region                              | NOV $H<TLE$ | $H>TLE$ |
|-------------------------------------|------------|--------|
| Left Middle Frontal Gyrus (L MFG)   | 7          | 0      |
| Right Middle Frontal Gyrus (R MFG)  | 0          | 0      |
| Left Superior Temporal Gyrus (L STG)| 3          | 0      |
| Right Superior Temporal Gyrus (R STG)| 2         | 0      |
| Left Angular (L ANG)                | 0          | 0      |
| Right Angular (R ANG)               | 0          | 0      |
| LeftPrecuneus (L PRE)               | 2          | 0      |
| RightPrecuneus (R PRE)              | 1          | 0      |
| Left Supramarginal Gyrus (L SMG)    | 0          | 0      |
| Right Supramarginal Gyrus (R SMG)   | 9          | 0      |

### 4. Conclusion

These findings suggested that TLE patients suffer from impairment in some DMN regions, that may cause certain neuropsychological and cognitive degradation. Further studies should be conducted to investigate the impact of these impairments to the integrity of brain function in TLE patients. In spite of its limitations, the study certainly adds to our understanding of the activation in TLE patient is beyond the temporal area. This understanding is important to help the clinicians in order to support their decision making.

There are some limitations to this study. First, the number of TLE patients is small, which permitted meaningful results but shall be treated as preliminary at best. Second, the structural integrity of the DMN may be useful in analyzing any functional degradation in the network, to support the findings and further clarify its impairments.

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