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Analysis of Brain Activation and Effective Connectivity During Self-paced Unilateral and Bilateral Finger Tapping Using Functional Magnetic Resonance Imaging in Patients with Temporal Lobe Epilepsy

Temporal Lob Epilepsisi Hastalarında Fonksiyonel Manyetik Rezonans Görüntüleme Kullanarak Öznel Zamanlı Tek Taraflı ve Çift Taraflı Parmak Tıklama Sırasında Beyin Aktivasyonu ve Etkin Bağlantılılığın Analizi

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ABSTRACT

Objective: The temporal lobes are the most frequent sites of origin of partial seizures. Patients with temporal lobe epilepsy (TLE) represent approximately two thirds of the intractable seizure population. This study aims to explore motor networks in TLE patients.

Methods: This study involves 12 healthy subjects and 12 TLE patients who have undergone functional magnetic resonance imaging performing self-paced unilateral and bilateral finger tapping. The images were then preprocessed and analyzed using statistical parametric mapping. The activated areas were compared between healthy subjects and TLE patients. The effective connectivity for visual and motor nodes was performed using dynamic causal modelling.

Results: Comparing the two groups, using two samples t-test, familywise error rate $p<0.05$. Healthy subjects showed more areas of significant activation. For effective connectivity, in healthy subjects, visual to motor was the dominant model with average value of 0.03 Hz, bilaterally. In TLE patients, on the right hemisphere, a contrary result was observed whereby the motor to visual area was the dominant

ÖZ

Amaç: Temporal lob, kısmi nöbetlerin en sık başlangıç noktasıdır. Temporal lob epilepsisi (TLE) olan hastalar, kontrol edilemeyen nöbet popülasyonunun yaklaşık üçte ikisini temsil eder. Bu çalışma, TLE hastalarında motor ağları incelemeyi amaçlamaktadır.

Yöntemler: Bu çalışma, kendi hızında tek taraflı ve çift taraflı parmak tıklama gerçekleştiren fonksiyonel manyetik rezonans görüntüleme uygulanan 12 sağlıklı denek ve 12 TLE hastasını içermektedir. Görüntüler daha sonra ön işlemden geçirilmiş ve istatistiksel parametrik Haritalama kullanılarak analiz edilmiştir. Aktive olan alanlar sağlıklı deneklerle TLE hastaları arasında karşılaştırılmıştır. Görsel ve motor düğümleri arasındaki etkin bağlantı dinamik nedensel modelle kullanılarak analiz edilmiştir.

Bulgular: İki grubun karşılaştırılması sonucunda, iki örnek t-testi, aile düzeyinde hata oranı $p<0,05$ ile sağlıklı deneklerde daha fazla anlamlı aktivasyon alanı gözlemlenmiştir. Etkin bağlantıda, sağlıklı deneklerde görselden motor alana doğru model baskındı ve çift taraflı olarak ortalama değer 0,03 Hz idi. TLE hastalarında, sağ yarımkürede motor alandan görsel alana doğru ters bir sonuç gözlemlenmiştir, yani bu

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pattern. On the left hemisphere, the model was the same as in healthy subjects, visual to motor, but with a higher average value of 0.1 Hz.

Conclusion: This study found that there were fewer areas of the brain with significant activation in TLE patients during motor activity. TLE brains also exhibit alteration in effective connectivity between visual and motor regions.

Keywords: Temporal lobe epilepsy, functional magnetic resonance imaging, finger tapping

ÖZ

model baskındı. Sol yarımkürede, sağlıklı deneklerde olduğu gibi görselden motor alana doğru model baskındı, ancak ortalama değer 0,1 Hz ile daha yüksekti.

Sonuç: Bu çalışma, TLE hastalarında motor aktivite sırasında anlamlı aktivasyon gösteren beyin alanlarının daha az olduğunu bulmuştur. TLE beyinleri ayrıca görsel ve motor bölgeler arasındaki etkin bağlantıda değişiklikler göstermektedir.

Anahtar Sözcükler: Temporal lob epilepsisi, fonksiyonel manyetik rezonans görüntüleme, parmak vurma

INTRODUCTION

Epilepsy is a disorder of the central nervous system that is characterized by recurrent seizures unprovoked by acute systemic or neurological insult. Seizures are a clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. It is a condition where a sequence of events turns a normal neuronal network into a hyperexcitable network (1). Temporal lobe is the most frequent site of origin of partial seizures. Patients with temporal lobe epilepsy (TLE) represent approximately two thirds of the intractable seizure population, which may require surgical management (2).

TLE can be conceptualized as a network disease. The network can be characterized by inter-regional functional connectivity, i.e., correlations between any two regions (3). Traditionally, TLE has been known to cause memory and language impairment (4). However, studies have also shown that there was clinical evidence of motor dysfunction as well in patients with focal epilepsy (5-8), which necessitates further study on the motor network. With the development of neuroimaging, it is possible to study nervous system diseases at the network level. The in-depth study of brain networks can lead to a better understanding of network diseases such as TLE. Functional magnetic resonance imaging (fMRI) measures the blood oxygen level changes as a response to tasks performed, shown as activated areas in cortical brain regions (9). The neural signal network refers to the study of the interconnection and functional integration of neural signals when the brain is in a certain functional state, including effective connectivity (10,11). Effective connectivity describes whether activity in one region has a causal influence on activity in another region. It provides the ability to test causal models regarding the interactions between regions (9). This study aims to analyse brain activation and effective connectivity in TLE patients and healthy subjects during self-paced finger tapping using functional fMRI. Different cortical brain regions will be significantly activated during the finger tapping task.

MATERIALS AND METHODS

Procedures approved by the Human Research Ethics Committee of Universiti Sains Malaysia (approval number: USM/JEPeM/20060340, date: 03.01.2021) which complies with the Declaration of Helsinki. Consent for MRI and publications were obtained from subjects.

Subjects and Patients

A cross-study conducted at the radiology department of Hospital Universiti Sains Malaysia from 5th October 2016 until 4th October 2017 involved 12 healthy subjects and 12 TLE patients. Patients with TLE were above 18 years old, were clinically diagnosed with TLE, and were seizure free for at least 24 hours. Patients with brain lesions, history of alcohol and drug abuse, severe cognitive impairment or mental disorder, and post temporal lobe resection surgery were excluded from this study. Healthy subjects were 18 years old and above with no systemic disease or neurological symptoms. Patients with post brain trauma or surgery were excluded.

fMRI Acquisition

Each healthy subject and patient lay supine in the gantry of the MRI machine (Phillips 3 Tesla Achieva MR scanner, Best, The Netherlands). T1-weighted imaging sequence for brain structure was performed. The stimulus (picture of the right hand, left hand, or bilateral hands) was back-projected onto a computer screen that could be viewed through a mirror attached to the scanner's head coil above. Blood oxygen level-dependent (BOLD) fMRI, using a T2-weighted gradient echo planar imaging sequence, was acquired when the patients started self-paced finger tapping (right/left/bilateral) according to the stimulus projected in front of them. The protocol for finger tapping followed the paradigm protocol [total duration: 13 minutes, time to repeat (TR): 2 seconds, number of slices: 35, slice thickness: 3, voxel size: 2x2x3].

Image Analysis

Data were collected in Digital Imaging and Communications in Medicine format. Data were converted to NIfTI format using MRIConvert version 2.1.0 build 440, 2013, University of Oregon, Lewis Center for Neuroimaging. Statistical Parametric Mapping (SPM12) (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London) software packages on the platform MATLAB 7.4-R2018b (Mathworks Inc., Natick, MA, USA) were used for pre-processing, i.e., smoothing, realigning, and normalizing the images so that all the images are standardized. First-level analysis was performed to observe the area of activation in each group. Activated regions were localized using Montreal Neurological Institute coordinates and assigned with the Neuromorphometrics Atlas in SPM. Second level analysis was performed to compare the difference in brain activation between TLE patients and healthy subjects across individuals.

For effective connectivity, the dynamic causal modelling (DCM) function was used in the SPM12 software. Bayesian Model Selection (BMS) in DCM was used to analyze the interaction between the visual and motor areas of the right and left brain in both groups. Three models were tested: bidirectional; from visual to motor; and from motor to visual.

Statistical Analysis

Descriptive statistic to analyse demographic data. Maps of activation are compared between groups by means of two-sample t-tests as implemented in the SPM12 software. All maps are reported at a level of p<0.001 uncorrected, with only clusters passing a threshold of p<0.05 familywise error rate (FEW) corrected are shown.

Effective connectivity was analysed using the novel method of BMS, fixed function analysis (FFX) for group studies as implemented in DCM.

RESULTS

Demographic Findings

The mean age for healthy subjects was 36 years, while for TLE patients, it was 35 years. The youngest healthy subjects were 21 years and the oldest were 51 years with a standard deviation of 9.8. The youngest TLE patient was 25, and the oldest was 52 years, with a standard deviation of 8.3. The majority of the participants were female, 75% for healthy subjects and 92% for TLE patients. Demographic findings are summarised in Table 1.

Table 1. Demographic data of participant according to healthy and TLE

Variable	Study group	
	Healthy	TLE
Age, year		
Mean	36.2	35.3
Standard deviation	9.8	8.3
Minimum	21	25
Maximum	51	52
Gender, n (%)		
Female	9 (75)	10 (91.7)
Male	3 (25)	1 (8.3)

TLE: Temporal lobe epilepsy

Brain Activation

The areas within the brain cortex that were significantly activated were at the occipital region, as shown in Figure 1. This was the same for healthy individuals, and TLE patients. For first level analysis, more areas within the brain cortex were significantly activated in healthy subjects as compared to TLE subjects (all maps were reported at a level of p<0.001 uncorrected with only clusters passing a threshold of p<0.05 FWE corrected were shown). Table 2 and Table 3 show all the areas that have significant activation in healthy subjects and TLE patients, respectively. Regarding specific areas of activation, in healthy subjects, the right and left cuneus were the most active brain areas in the brain with peak values (T-values) of 13.27 and

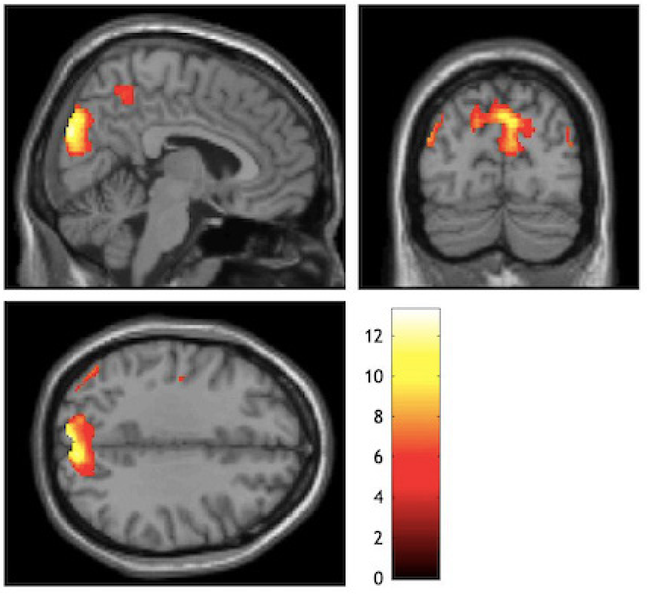

Figure 1. Rendered image for healthy subjects during bilateral finger tapping. This image shows intense activation at the bilateral occipital lobe, where the primary visual cortices are located [the higher the value, the higher the peak value (T-value) for activation as represented by colour coding].

Table 2. Activation in healthy subjects during bilateral finger tapping

Anatomical landmark	Coordinate			Peak level (T)
	x	y	z	
Left cuneus	-6	-88	32	13.27
Right cuneus	6	-84	26	12.36
Left middle occipital lobe	-47	-74	26	8.05
Left precuneus	-1	-49	53	7.92
Right angular gyrus	47	-69	38	7.00
Left lateral ventricle	-27	-57	8	6.66
Right precuneus	18	-59	14	6.63
Right middle occipital lobe	45	-78	20	6.52
Right lingual gyrus	16	-42	-7	5.86
Left cerebral white matter	-35	-43	-13	5.77
Right post central gyrus	45	-11	32	5.76
Left post central gyrus	-42	-13	35	5.21

Table 3. Activation in TLE patients during bilateral finger tapping

Anatomical landmark	Coordinate			Peak level (T)
	x	y	z	
Right cuneus	6	-81	26	6.53
Left precuneus	-11	-69	26	6.05
Right middle occipital lobe	49	-71	29	5.45
Right superior frontal medial segment	1	56	14	5.16
Right cerebral white matter	16	-79	26	5.07
Right angular gyrus	57	-61	26	4.98
Right precuneus	9	-52	11	4.94

TLE: Temporal lobe epilepsy

Table 4. Areas that are significantly more activated in healthy subjects compared to the TLE patients in unilateral and bilateral finger tapping

Anatomical landmark	Coordinate			Peak level (T)	p
	x	y	z		
Left inferior occipital lobe	-42	-69	8	131.92	0.001
Right lingual gyrus	20	-40	-7	108.21	0.002
Left postcentral medial segment	-9	-38	-9	65.74	0.018
Right cerebral white matter	21	-73	-4	63.05	0.021
Left lingual gyrus	-3	-79	-1	62.46	0.022

TLE: Temporal lobe epilepsy

12.36, respectively. In TLE subjects, the most active areas during finger tapping were the right cuneus and the left pre-cuneus, with peak values (T-values) of 6.53 and 6.05, respectively. In healthy subjects, there was significant activation in bilateral motor areas (the right and left post central gyrus) with peak value of 5.76 and 5.21. However, no significant activation of the motor areas can be observed in TLE subjects. Second level analysis compared both groups using the means of two-sample t-tests as implemented in the SPM12 software. In the condition where the healthy state is more activated than TLE (Healthy > TLE), a few areas were shown to be significantly activated, as displayed in Table 4. The areas were left inferior occipital, right lingual gyrus, left medial segment of the postcentral gyrus, right cerebral white matter, and left lingual gyrus. For condition TLE is more activated than healthy (TLE > Healthy), no suprathreshold clusters was found.

Effective Connectivity

The influence between visual and motor nodes was tested using effective connectivity. For the visual node, cuneus (coordinate; right brain hemisphere x 6 y -84 z 26, left brain hemisphere x -7 y -86 z 31) was set as the coordinate of interest. Meanwhile, for the motor node, post central gyrus (coordinate; right brain hemispherex 45 y -11 z 32, left brain hemisphere x -42 y -14 z 35). The representative diagram shown in Figure 2. Three models were tested using DCM for BMS: fixed effect analysis. The models were bidirectional, visual to motor, and motor to visual, indicating whether motor and visual are influencing each other. In the bilateral hemispheres of healthy subjects, visual input has more influence on motor function, with the second model being the dominant one, as shown in Figure 3. The average value, 0.03 Hz, was equal bilaterally, 0.03 Hz. In right brain hemisphere of TLE subjects, the motor area exerts more influence on the visual area, as the third model was dominant as shown in Figure 4. The average value was 0.06 Hz. On the left-brain hemisphere, the dominant model was the same as in healthy subjects; the visual influences the motor processes more significantly. However, the average value was higher: 0.1 Hz. The effective connectivity between postcentral gyrus and cuneus in TLE patients is represented in Figure 5.

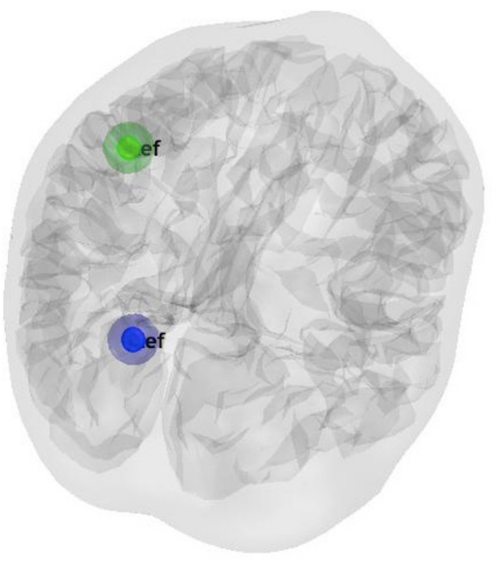

Figure 2. Nodes selected for effective connectivity (ef), left brain cuneus (blue circle) and post central gyrus (green). The same nodes were selected for the right brain hemisphere.

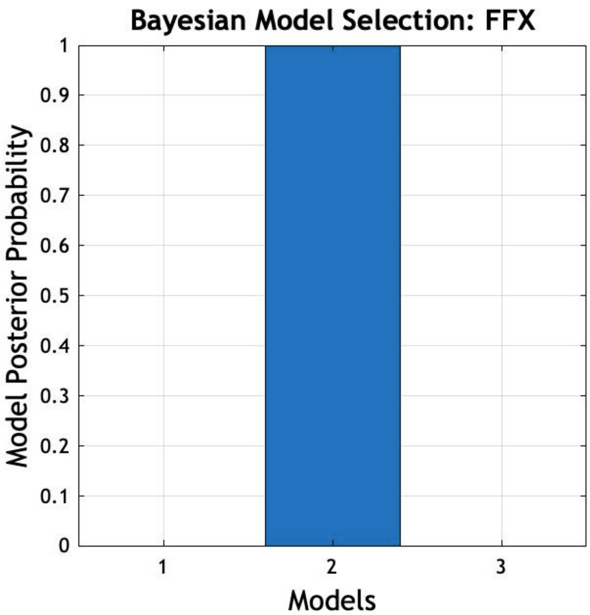

Figure 3. Bayesian model selection: fixed function analysis (FFX) bar chart for dominant model in bilateral brain's hemisphere for healthy subjects and left brain's hemisphere for TLE patients. Model 1: Bidirectional, Model 2: from cuneus to postcentral gyrus, Model 3: From Postcentral gyrus to cuneus.

TLE: Temporal lobe epilepsy

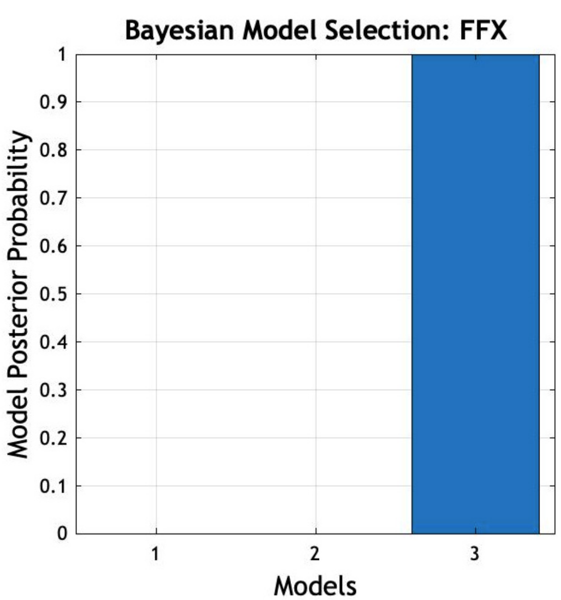

Figure 4. Bayesian model selection: fixed function analysis (FFX) bar chart for winning model in right brain's hemisphere for TLE patients. Model 1: Bidirectional, Model 2: From cuneus to Postcentral gyrus, Model 3: From Postcentral gyrus to cuneus.

TLE: Temporal lobe epilepsy

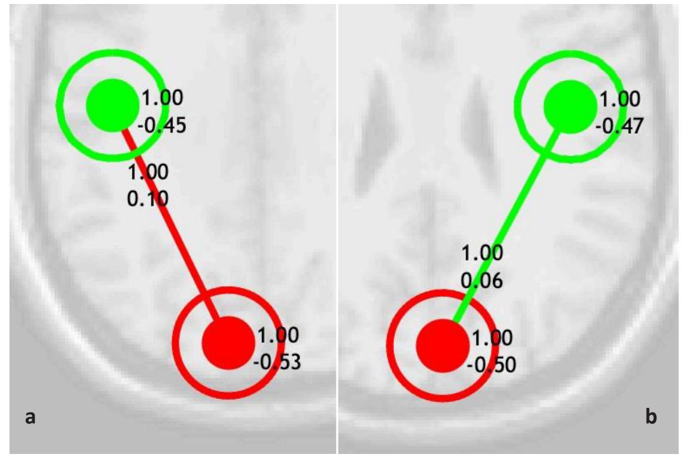

Figure 5 (a,b). Right and Left cerebral effective connectivity in TLE patients (green circle: postcentral gyrus, red circle: cuneus, numbers within the green and red circle represent effective connectivity within the region itself while the numbers at the green and red line represent the effective connectivity in between regions).

TLE: Temporal lobe epilepsy

DISCUSSION

The electrical activity of neurons and neuron clusters is the basis of cortical excitability, which is closely related to the tasks performed (12). The blood oxygen level is also changing in response to those tasks. In this study, the most activated region in the brain during visual cued self-paced finger tapping was in the occipital region, which is the visual area (13). This phenomenon was observed in both healthy and TLE subjects. The cue for finger tapping was a back-projected picture to the patients in the MRI. When the subjects saw the picture, they started the finger tapping task. We postulated that the intense activation in the visual region was due to the significant focus on the visual activity in order to perform the task fluently. Theoretically, during a motor task such as finger tapping in normal subjects, previous studies have shown that Primary Sensorimotor Cortex (SM1), Supplementary Motor Area (SMA), Basal Ganglia (BG), and Cerebellum were activated (14-16). From the first level analysis, there was not much activation seen in the motor areas as described in previous studies except for the group of healthy subjects, where significant activation was seen in bilateral primary motor areas. However, there were no significantly activated areas in the expected motor region observed in the subjects with TLE. This is the observation when the significance level was set to 0.05 FWE. Only if the significance level was set to 0.001 (uncorrected) did the motor areas become activated. The most common measure of Type I error over multiple tests is the "familywise error rate", abbreviated FWE. FWE is the chance of one or more false positives anywhere in the image. With a valid FWE =0.05 threshold, there is 95% confidence that there are no false positive voxels (or clusters) in the threshold map (9). Since there are activations in the motor areas when p=0.001, but not at p=0.05, the changes might not be strong enough to be significant.

In general, there are more areas with significant activation observed in healthy subjects than in TLE patients. The value for peak activation was also noted to be higher in healthy subjects. The second level analysis was performed to compare means between the groups to prove the observation that there are more areas of activation in healthy subjects than in TLE subjects during the finger-tapping task, or vice versa. In the condition where healthy subjects are more activated than TLE (healthy > TLE), a few areas in healthy subjects were activated more significantly than in TLE patients. The areas are left inferior occipital gyrus, right lingual gyrus, left medial segment postcentral gyrus, right cerebral white matter, and left lingual gyrus, as shown in Table 4. In the condition where TLE is more activated than healthy (TLE > Healthy): TLE patients do not show any suprathreshold clusters. Reduced activation observed in TLE patients may be due to detrimental effects of seizure propagation from the seizure focus, causing patients to rely less on the epileptic hemisphere. Seizure propagation paths formed strong neuronal networks due to synchronous and repetitive activity during the ictal process, causing disruption in normal motor networks in the brain (17). In addition, although patients were taking a variety of anticonvulsant medications, previous studies have shown that these drugs can also decrease BOLD activity during task-based fMRI studies (18,19).

TLE is a network disease. The network can be characterized by inter-regional functional connectivity, i.e., BOLD signal correlations between any two regions (3). The interconnection and functional integration of neural signals in a particular functional state can be studied by neural network analysis, including effective connectivity (10,11). Effective connectivity describes whether activity in one region has a causal influence on activity in another region (9). In this study, self-paced finger tapping was cued by visual images. The flow of signals is thought to be from visual to motor as information is processed and relayed in the brain. Thus, the interest was to study the interconnection between the visual and motor areas. Yun et al. (20) found that there is a bidirectional influence between visual and motor functions in their controlled subjects. In this study, the cuneus was chosen as the visual node and the Postcentral Gyrus as the nearest motor node. Three models were analysed using BMS, with fixed function analysis applied in DCM. The models are bidirectional: visual to motor and motor to visual. In both brain hemispheres of healthy subjects, the dominant model involved visual to motor pathways, as shown in Figure 3. This suggests that in healthy subjects, the visual regions exert more influence on the motor area. The value is similar in both sides of the brain hemispheres. Interestingly, the contrary was seen within the right brain hemisphere of TLE subjects whereby the motor to visual was the dominant model, which means that the motor node exerts more influence on the visual node. In the left hemisphere, the dominant model was the same as in healthy subjects. The visual node exerts more influence on the motor node with a higher influence value. The majority of the TLE patients are right-handed, and the dominant area is the left hemisphere. Dominant hemisphere connections are generally stronger because of increased use. Therefore, they may be less susceptible to detrimental seizure activity. If non-dominant hemisphere connections were impacted by seizure activity, this might cause patients to rely more on the dominant hemisphere during motor task performance (17).

Hermann et al. (21) suggest that epilepsy affects the brain both during seizures and interictally due to progressive structural and functional changes in the brain related to syndrome-specific network variations. Previous studies using rat models of epilepsy have suggested that disinhibition may underlie seizure-induced changes in cortical motor map representations (22). Both decreases in GABAergic transmission and increases in glutamatergic transmission, which occur in humans with epilepsy, have been shown to influence the recruitment of additional motor regions through pre-existing cortico-cortical connections (23).

Study Limitations

This study includes small numbers of participants and is very specific to finger tapping as main stimulant to assess the areas of activation and connectivity. A further study which may involves larger sample size and multiple stimulants would be helpful to further characterise areas of activation activation and connectivity in the brain.

CONCLUSION

This study found that there was less area of brain that has significant activation in TLE patients during motor activity. TLE brains also exhibit different effective connectivity, in which, in the right hemisphere, the motor area exerts more influence on the visual area, and in the left hemisphere, the visual area exerts more influence on the motor area. These findings suggest that there is an alteration of the motor networks in TLE patients. Since there are changes in cortical activation which may contribute to motor deficits observed in TLE patients, this study suggests that longer periods of seizure freedom may reduce motor deficits.

Ethics

Ethics Committee Approval: Procedures approved by the Human Research Ethics Committee of Universiti Sains Malaysia (approval number: USM/JEPeM/20060340, date: 03.01.2021) which complies with the Declaration of Helsinki.

Informed Consent: Consent for MRI and publications were obtained from subjects.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.M.Y., M.E.A., H.M.A.R., Concept: B.M.Y., M.E.A., A.I.A.H., H.M.A.R., Design: B.M.Y., A.I.A.H., H.M.A.R., M.R.A.R., Data Collection or Processing: H.M.A.R., M.R.A.R., Analysis or Interpretation: M.R.A.R., A.I.A.H., M.R.A.R., Literature Search: B.M.Y., Writing: B.M.Y.

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