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

DR BAZLI BIN MD YUSOFF

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (RADIOLOGY)

UNIVERSITI SAINS MALAYSIA

2021

ACKNOWLEDGEMENT

The completion of this undertaking could not have been possible without the participation, cooperation and assistance from so many people whose names may not all be enumerated. Their contributions are sincerely appreciated and gratefully acknowledged. I would like to thank the director of Hospital Universiti Sains Malaysia for granting the permission to use patient's data, medical record, space and assets belonging to the hospital during the process of conducting the research. I would like to express deep and utmost appreciation particularly to the following:

1. Prof Madya Dr Mohd Ezane Aziz as main supervisor and Dr Aini Ismafairus Abd Hamid as co-supervisor for this dissertation.

2. Dr Husbani binti Mohd Amin Rebuan as co-supervisor and the head of 'Delineating Mechanism of Brain Connectivity as Part of Multimodality treatment of Seizure' study which allow me to explore more on the previous data.

3. Prof Madya Dr Mohd Shafie Abdullah, Prof Madya Dr Juhara Haron, Dr Khairil Amir Sayuti, Dr Chandran Nadarajan, Dr Wan Aireene Wan Ahmed, Dr Ahmad Hadif Zaidin Samsudin and Dr Ahmad Tarmizi Musa, Dr Nur Asma, lecturers/radiologists all of whom directly or indirectly contributed their ideas and comments to the success of this study.

4. Colleagues and all the staff in the Department of Radiology, Hospital Universiti Sains Malaysia.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

DCM	Dynamic causal modelling
fMRI	Functional magnetic resonance imaging
SPM	Statistical parametric mapping
TLE	Temporal lobe epilepsy

ABSTRAK

Latar Belakang: Lobus temporal adalah tempat asal serangan sawan separa. Pesakit dengan Epilepsi Lobus Temporal (TLE) mewakili kira-kira dua pertiga daripada populasi sawan yang tidak dapat diatasi.

Objektif: Kajian ini bertujuan untuk membandingkan kawasan pengaktifan antara subjek sihat dan pesakit TLE akibat peningkatan tahap oksigen darah di bahagian otak yang berlainan semasa mengetuk jari secara sebelah dan kedua belah tangan. Di samping itu, kajian ini juga bertujuan untuk membandingkan kesambungan efektif antara dua kawasan yang ditentukan di dalam subjek sihat dan pesakit TLE semasa mengetuk jari secara sebelah dan kedua belah tangan.

Metodologi: Kajian ini melibatkan 12 subjek sihat dan 12 pesakit TLE. Kesemua mereka menjalani pengimejan resonans magnetik fungsional (fMRI) di mana mereka mengetuk jari secara sebelah dan kedua belah tangan secara sendiri. Gambar-gambar tersebut kemudian diproses dan menjalani analisis tahap pertama menggunakan Statistical Parametric Mapping (SPM). Analisis tahap kedua kemudian dilakukan untuk membandingkan kawasan pengaktifan pada subjek sihat dan pesakit TLE. Untuk kesambungan efektif, dua kawasan dipilih yang mewakili kawasan visual dan motor. Tiga model diuji di antara dua kawasan tersebut, iaitu dua arah, visual ke motor dan motor ke visual. Ujian ini dilakukan di setiap hemisfera otak kedua-dua subjek sihat dan pesakit TLE.

Keputusan: Pada kedua-dua subjek yang sihat dan pesakit TLE, analisis tahap pertama menunjukkan pengaktifan yang kuat di kawasan visual. Analisis tahap kedua dilakukan membandingkan dua kumpulan sampel, menggunakan dua sampel ujian-t, FWE $p < 0,05$, subjek sihat menunjukkan lebih banyak kawasan pengaktifan yang signifikan. Untuk

kesambungan yang berkesan, dua kawasan diuji, kawasan visual dan kawasan motor. Tiga model diuji, dua arah, visual ke motor, dan motor ke visual. Pada subjek yang sihat, visual ke motor adalah model yang dominan dengan nilai rata 0.03Hz di kedua-dua belah hemisfera. Dalam subjek TLE, di hemisfera kanan, hasil yang bertentangan diperhatikan di mana motor ke kawasan visual adalah model yang dominan. Di hemisfera kiri, model yang sama dengan subjek yang sihat adalah model yang dominan, visual ke motor, tetapi dengan nilai purata lebih tinggi 0.1Hz.

Kesimpulan: Kajian ini mendapati bahawa terdapat sedikit kawasan otak yang mempunyai pengaktifan yang signifikan pada pesakit TLE semasa aktiviti motor. Otak TLE juga menunjukkan kesambungan efektif yang berbeza di mana di hemisfera kanan, kawasan motor lebih banyak mempengaruhi kawasan visual dan di hemisfera kiri, kawasan visual lebih banyak mempengaruhi kawasan motor. Penemuan ini menunjukkan bahawa terdapat perubahan rangkaian motor pada pesakit TLE.

Kata kunci: Sawan lobus temporal, pengimejan resonans magnetik fungsi, pergerakan jari

ABSTRACT

Background: 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.

Objectives: This study aims to compare the area of activation in between Healthy subjects and Temporal Lobe Epilepsy (TLE) patients as a result of increase in blood oxygen level in different parts of the brain during self-paced unilateral and bilateral finger tapping. In addition, this study also aims to compare the effective connectivity in between region of interest in Healthy subjects and TLE patients during self-paced unilateral and bilateral finger tapping.

Methodology: This study involves 12 healthy subjects and 12 TLE patients. All of them undergone functional magnetic resonance imaging (fMRI) where they performed self-paced unilateral and bilateral finger tapping. The images were then pre-processed and undergone first level analysis using Statistical Parametric Mapping (SPM). Second level analysis were then performed to compare the area of activation in Healthy subjects and TLE patients. For effective connectivity, two regions of interest chosen which representing visual and motor region. Three models tested in between each region of interest which are bidirectional, visual to motor and motor to visual. These tests were conducted in each brain hemispheres of both Healthy subjects and TLE patients.

Results: In both Healthy subjects and TLE patients, first level analysis showed intense activation at the visual area. Second level analysis was performed comparing the two group of samples, using two samples t-test, FWE $p < 0.05$, Healthy subjects showed more areas of significant activation. For effective connectivity, two regions of interest were tested, visual area and motor area. Three models were tested, bidirectional, visual to motor, and motor to

visual. In healthy subjects, visual to motor was the dominant model with average value of 0.03Hz bilaterally. In TLE subjects, on the right hemisphere, a contrary result was observed whereby motor to visual area was the dominant model. On the left hemisphere, the same model as healthy subjects was the dominant model, visual to motor, but with higher average value of 0.1Hz.

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 whereby in the right hemisphere, motor area exerts more influence on the visual area and in the left hemisphere, visual area exerts significantly more influence on the motor area. These findings suggest that there is alteration of the motor networks in TLE patients.

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

CHAPTER 1: BACKGROUND

1.1 Introduction

Epilepsy is a disorder of the central nervous system that is characterized by recurrent seizures unprovoked by acute systemic or neurological insult. Seizures is a clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. It is a condition where sequence of events turn a normal neuronal network into a hyperexcitable network (Bromfield EB et al., 2006).

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 end up with surgical management (Blair, 2012). A comprehensive understanding of seizures mechanism at every level including cellular, clinical and brain networks is a must in order to integrate robust and effective treatment for the benefit of patients.

1.2 Problem Statement

Traditionally, TLE has been known to cause memory and language impairment (Sidhu et al., 2013). However, a few studies have shown that there was clinical evidence of motor dysfunctional as well in patients with focal epilepsy (Hermann et al., 1991; Horner et al., 1996; M.Drake et al., 2002; Labudda et al., 2009). With the development of neuroimaging, it is possible to study nervous system diseases at the network level. Therefore, this study aims to explore more on motor and executive function network of the brain in patients with TLE. This study will enhance the understanding on the effect of TLE on motor and executive function network and help other parties in multimodality treatment of TLE.

1.3 Objectives

1.3.1 General objective

To evaluate brain connectivity differences in patients with Temporal Lobe Epilepsy (TLE) and Healthy subjects.

1.3.2 Specific objectives

1. To compare the mean difference of brain activation signal changes in TLE patients and Healthy subjects during self-paced finger tapping.
2. To compare the difference of effective connectivity between regions of interest in TLE patients and Healthy subjects during self-paced finger tapping.

1.4 Research Questions

1. What are the brain activation signal differences in TLE patients and Healthy subjects during self-paced finger tapping?
2. What are the effective connectivity differences between regions of interest in TLE patients and Healthy subjects during self-paced finger tapping?

CHAPTER 2: LITERATURE REVIEW

2.1 Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) was defined in 1985 by the International League Against Epilepsy (ILAE) as a condition characterized by recurrent, unprovoked seizures originating from the medial or lateral temporal lobe. The seizures associated with this condition consist of simple partial seizures without loss of awareness and complex partial seizures (Berg et al., 2009). The temporal lobe is the most epileptogenic region of the brain (Blair, 2012). TLE is commonly associated with significant cognitive impairment. The pathological damage to medial temporal lobe structures will cause patients with TLE having difficulties in forming and storing long-term episodic memory (Stretton et al., 2012). Previously it is believed that frontal lobe function is spared in patients with TLE (Cave et al., 1992), but this assumption has been challenged with recent evidence for temporal lobe involvement in frontal lobe processes (Ranganath et al., 2005).

2.2 Motor function in patients with TLE

Temporal lobes primarily support higher-level cognitive process, comprising executive skills and working memory (Hanna-Pladdy, 2007). Executive skills deficits have been associated with poor outcomes on cognitive rehabilitation process (Ehlhardt et al., 2008). Researchers have been carrying out many studies to observe the clinical effect of executive motor function deficit in patients with TLE in order to further understand the ramification of TLE. They are interested in studying the possibilities of functional abnormalities that my exist outside the bounds of temporal lobe. More than 3 decades ago Herman et al. (1991) observed sixty-four patients over 16 years of age with TLE performing Wisconsin Card Sorting Test (WCST). The result shows 44% of the subjects exhibited clinically relevant executive dysfunction (Hermann et al., 1991). Similar study by Horner et al. (1996), involving 38 patients

with TLE using WCST shows 50% TLE patients showed clinical executive dysfunction as measured by perseverative responses (Horner et al., 1996). M.Drake et al. (1999) added Trail Making Test (TMT) in addition to WCST. The study involved 50 subjects which showed reduced executive performance across all tasks in subjects with TLE particularly with Hippocampal Sclerosis(M.Drake et al., 2002). A more recent study performed by Labudda et al. (2009) involving 20 subjects with TLE, using Iowa gambling test (IGT) and game of dice (GOD). In this study, subjects with TLE show reduced performance during the task (Labudda et al., 2009).

2.3 Multimodality neuroimaging study of executive function network in TLE

Researchers have understood that there are other functional alteration outside the known boundary of temporal lobe function. Brain is a structure with vast networks with each other. A wide variety of neuroimaging technologies such as MRI, fMRI, FDG-PET, MEG, or invasive intracranial EEG recording are available to explore our brain networks. A latest study by Yanping R et al. (2020) explored the functional brain network mechanism of executive control dysfunction in TLE. This study involves 20 TLE patients with 20 matched healthy control. Subjects performed the executive control task by attention network test while the scalp electroencephalogram (EEG) data were recorded. The results found that significant control impairment in the TLE group compared with healthy group. TLE group showed significantly weaker functional connectivity among EEGs in executive motor network(Ren et al., 2020). Oyegbile TO et al. (2018) study executive control network in 17 subjects with TLE and 18 healthy control using functional MRI (fMRI). In this study subjects performed N-back task in order to assess activation of the executive control network. The result showed subjects with TLE exhibit executive dysfunction and they concluded subjects with TLE have network alteration in non-temporal brain regions (Oyegbile et al., 2018). Zhang et al. (2017) utilised

resting-state functional MRI instead of task-based MRI to understand the executive control function network. In this study, 44 TLE subjects and 23 healthy volunteers were recruited. TLE subjects underwent extensive screening and divided in TLE's group with normal executive function and decreased executive function. The result revealed that TLE group with decrease executive function exhibits decrease functional connectivity between the executive motor network and resting state network (Zhang et al., 2017).

Diffusion Tensor Imaging (DTI) is also widely used as a tool to assess the brain network especially in TLE patient. DTI assess the fibre tract that connecting the vast brain network using DTI-derived metrics, typically fractional anisotropy (FA) or mean diffusivity (MD) to correlate with impairment on neuropsychological measures. Unlike memory and language networks, there is less consensus as to which fibre networks underlie executive dysfunction in TLE (Leyden et al., 2015). Widjaja et al. (2013) analysed lobar diffusion in a mixed sample of 40 children with predominantly frontal, temporal and frontotemporal epilepsy in conjunction with an extensive neuropsychological battery. In this study, Fractional Anisotropy (FA) decreases in right temporal region were associated with executive function impairment. In addition, there were correlations between FA and executive function in bilateral frontal, left temporal, right parietal, and the body of the Corpus Callosum (Widjaja et al., 2013). Riley et al. (2011) studied 9 patients with TLE and analysed rule learning, switching, and inhibition/switching performance together with less conventional DTI metrics. They found that reduced microstructural connections between left caudate and the dorsal prefrontal cortex were associated with slower inhibition/switching performance (Riley et al., 2011). Table 1 summarised the multimodality neuroimaging study of executive function network.

Table 1 Multimodality neuroimaging study of executive function network

Author	n. (group)	Assessment	Results
Yanping R et al. (2020)	20 TLE 20 healthy	EEG	TLE group showed significantly weaker functional connectivity
Oyegbile TO et al. (2018)	17 TLE 18 Healthy	Task based fMRI	Subjects with TLE exhibit executive dysfunction
Chao Zang et al. (2017)	44 TLE 23 Healthy	Resting state fMRI	TLE group with decrease executive function exhibits decrease functional connectivity
Widjaja et al. (2013)	40 Mixed epilepsy type	MRI – DTI	FA decreases in right temporal region were associated with executive function impairment.
Riley et al (2011)	11 TLE	MRI - DTI	Reduced microstructural connections between left caudate and the dorsal prefrontal cortex were associated with slower inhibition/switching performance

2.4 Landmark and functionality within the brain

2.4.1 Coordinate system in neuroimaging

MRI image are related to physical object and to relate the data points in the image to spatial locations in the physical object, a coordinate system is needed. The data matrix is three dimensional, therefore these dimensions (or axes) are called X, Y, and Z. This coordinate system provides a common space in which different individuals can be aligned and helps to facilitate many of the neuroimaging studies. The most famous coordinate system is developed by Jean Talairach (Talairach, 1967). However, a recently developed stereotactic coordinate space developed at the Montreal Neurological Institute (MNI) has become a standard in the neuroimaging field (Poldrack et al., 2011). In fMRI study, the activated coordinate is being localized in specific Brodmann areas, referring to Brodmann's divisions of the human cortex (Rasser et al., 2004).

2.4.2 Primary motor cortex

Broadmann area 4 is the primary motor cortex that located at the posterior part of the frontal lobe. Fundamental function of primary motor cortex is to control voluntary movements (Sanes et al., 2000). Kiviniemi et al. (2003) proposed the MNI coordinate for right sided primary motor cortex in between x 52 y -4 z 54 and x 62 y -14 z 30. Figure 1 shows the example for primary motor cortex as a coordinate inserted in between the proposed coordinate (https://bioimagesuiteweb.github.io/webapp/mni2tal.html). Central gyrus is part of the primary motor cortex, which is responsible for controlling voluntary motor movement on the body's contralateral side (Schott et al. 1993)

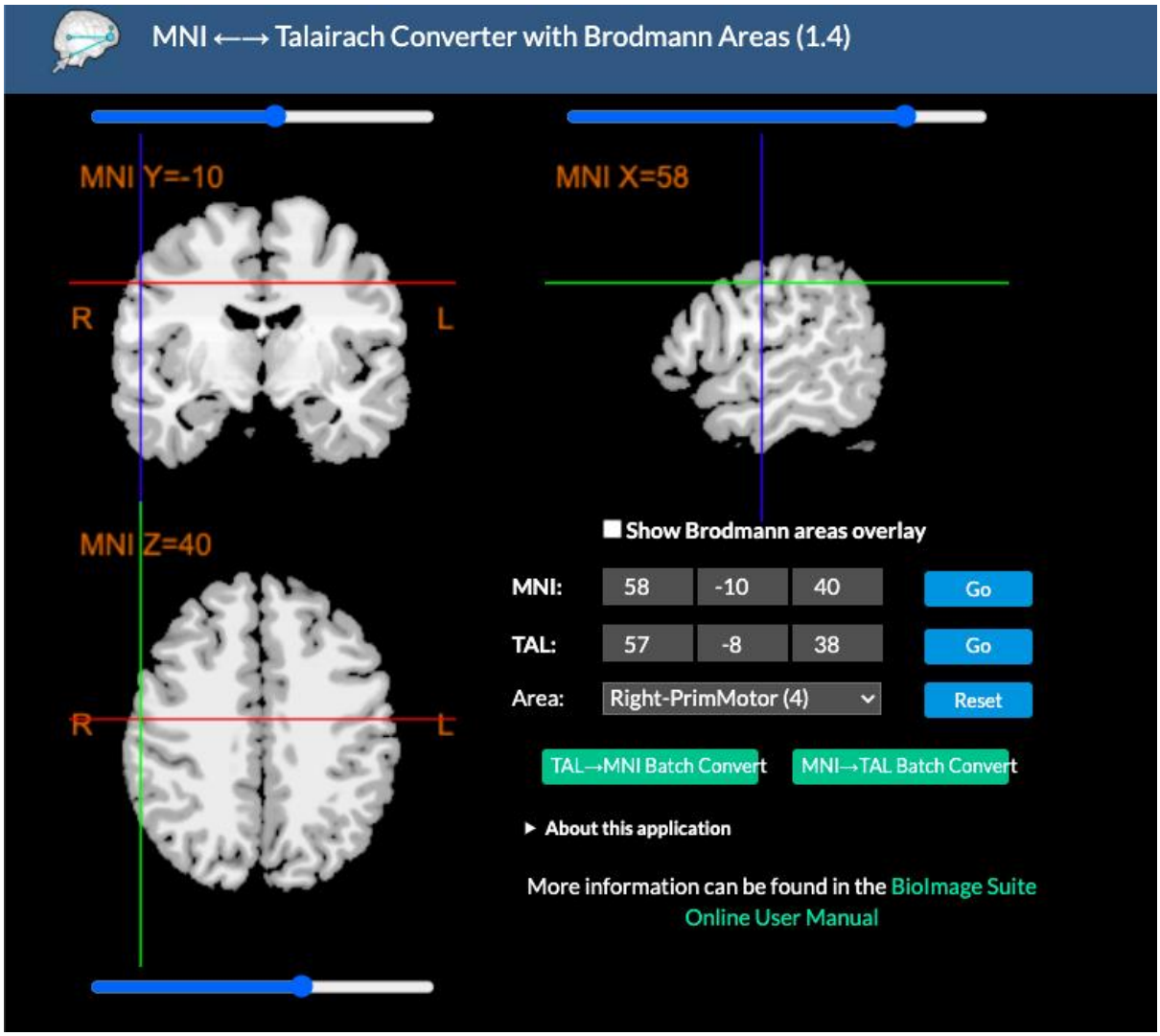


Figure 1: Primary motor cortex as a coordinate inserted in between the proposed coordinate.

2.4.3 Primary Visual Cortex

Broadmann area 17 (or V1, primary, calcarine, or striate cortex) is the end organ of the afferent visual system and is situated in the occipital lobe (Goetz et al., 2007). Kiviniemi et al. (2003) proposed the coordinate for right sided primary visual cortex as x 28 y -96 z -6. Figure 2 shows the example for primary visual cortex as the coordinate inserted (https://bioimagesuiteweb.github.io/webapp/mni2tal.html). Part of the primary motor cortex is Cuneus which receives input from the contralateral retina. The information is processed

through both ventral and dorsal pathways. The dorsal pathway is particularly important for higher spatial analysis and visual integration (Cohen et al. 2011)

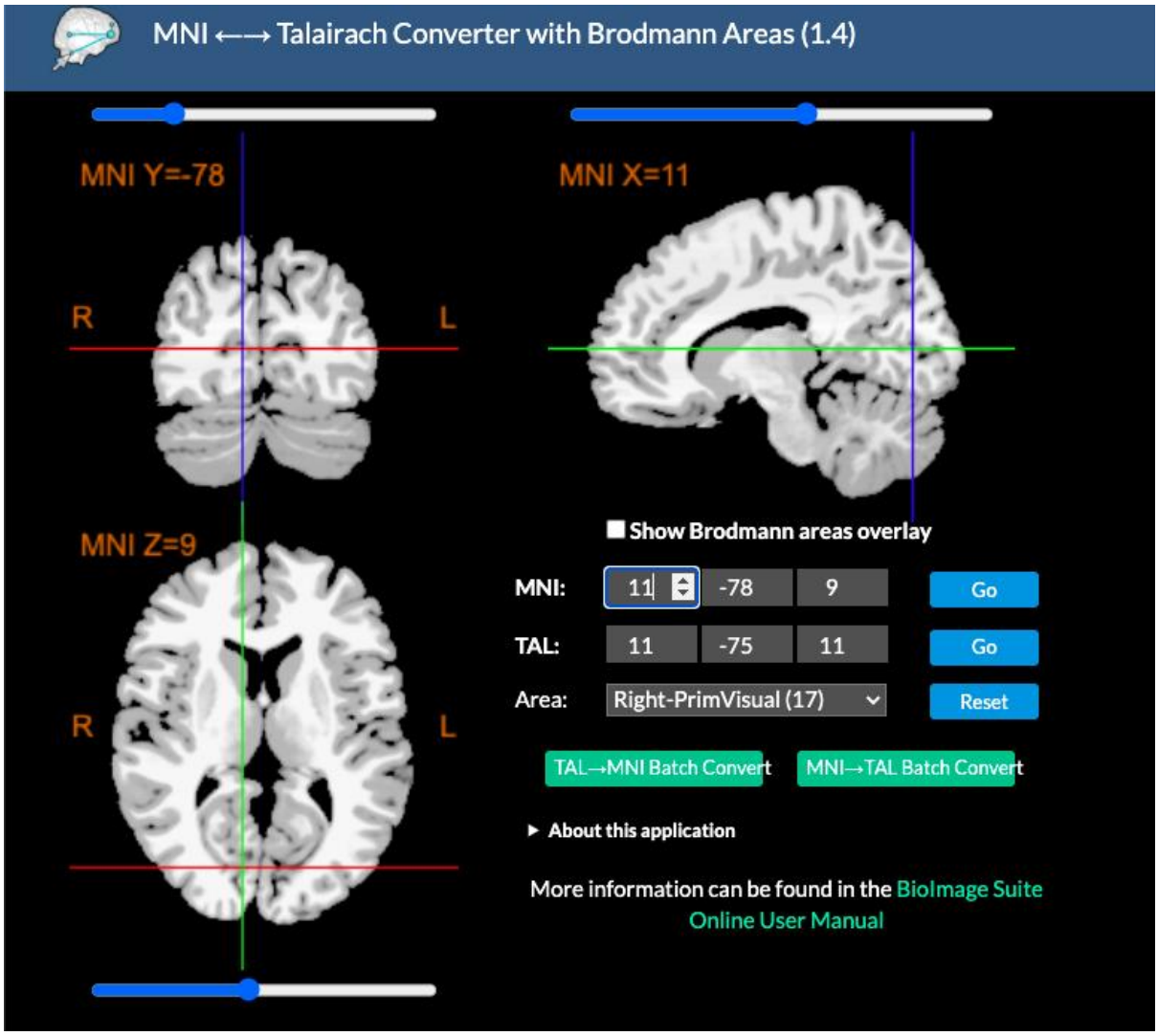


Figure 2: Primary visual cortex as a coordinate inserted.

2.5 Functional Magnetic Resonance Imaging (fMRI) as a tool for neuroimaging

2.5.1 Basis for fMRI

Functional Magnetic Resonance Imaging (fMRI) measures the blood oxygen level changes as a response to task performed or spontaneous modulation of neural metabolism. It helps to map neural activity in the brain of humans by imaging the change in blood flow. It takes advantage of the fact that when neurons in the brain become active, the amount of blood flowing through that area is increased. The amount of blood that is sent to the area is more than

is needed to replenish the oxygen that is used by the activity of the cells. Thus, the activity-related increase in blood flow caused by neuronal activity leads to a relative surplus in local blood oxygen. The signal measured in fMRI depends on this change in oxygenation and is referred to as the blood oxygenation level dependent, or BOLD, signal (Poldrack et al., 2011).

2.5.2 Brain activation

The activated brain regions in fMRI are represented in voxels. Activated voxels will be clustered together in space and the signals in fMRI will be spatially extended and often much larger than the size of a single voxel. fMRI data are often spatially smoothed and then oversampled to small voxels during spatial normalization, which results in a spreading of the signal across many voxels in the image. Functional neuroanatomy by Turesky et al. (2018) for the motor system in children showed that Primary Motor Area (SM1), Supplementary Motor Area (SMA), occipital cortex, and anterior cerebellum were activated during visually paced, left and right hand finger- tapping (Turesky et al., 2018). Figure 3 shows the activation maps for thumb movements in children and adults.

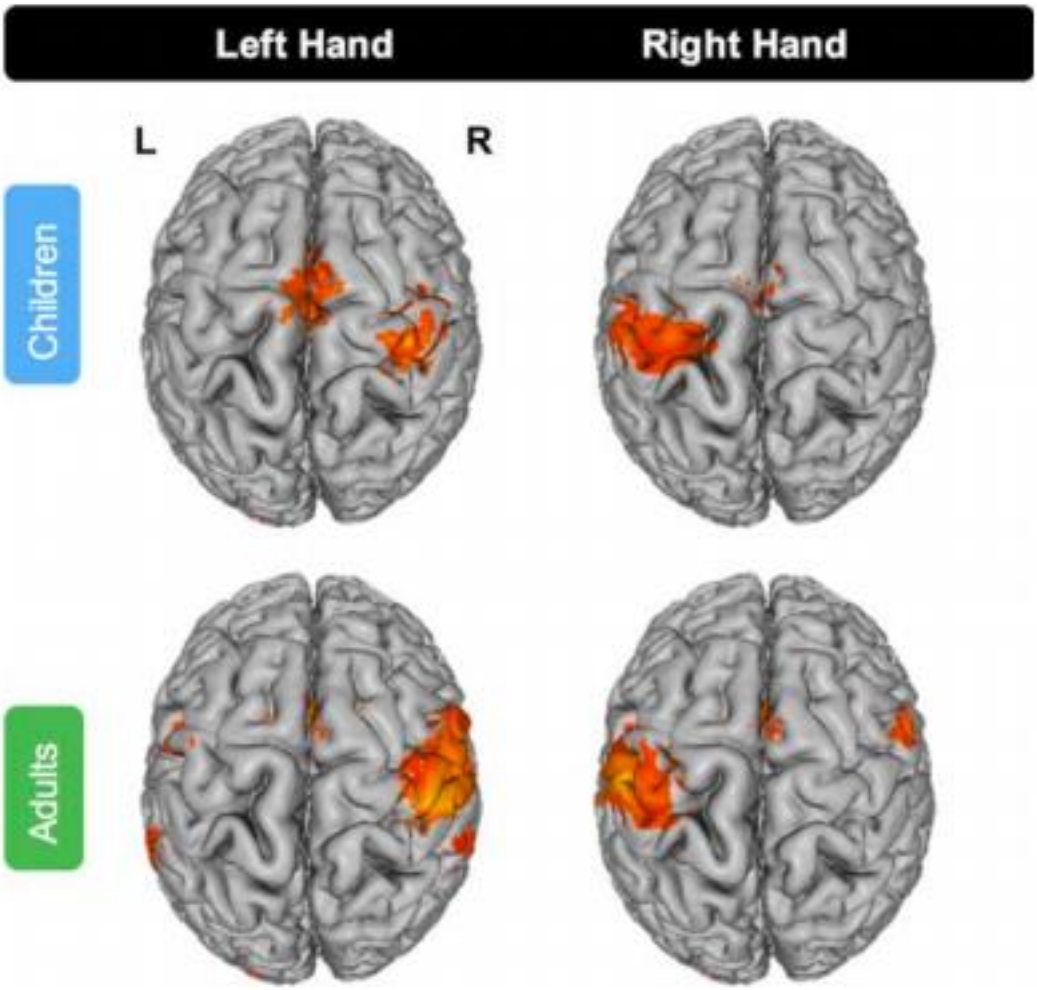


Figure 3: Whole-brain activation maps for thumb movements in children and adults.

2.5.3 Effective connectivity

Effective connectivity described 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. The presence of a correlation between region of interest implies that there is a causal relation between the them (Poldrack et al., 2011). Yun et al. (2019) evaluate the effective connectivity with the model in Figure 4. Three regions of interest (ROI) were included in the model, involving the left motor cortex and the early visual regions in both hemispheres. Reciprocal connections between both visual regions were constant in all models. Models 1 and

2 had bi-directional connections between the motor and visual regions. Models 3 and 4 only involved forward connections from the visual to the motor cortex. Task related modulations of connections between the visual and the motor areas were included in Models 1 and 3. From this exercise, model 1 as the dominant model (Yun et al., 2019).

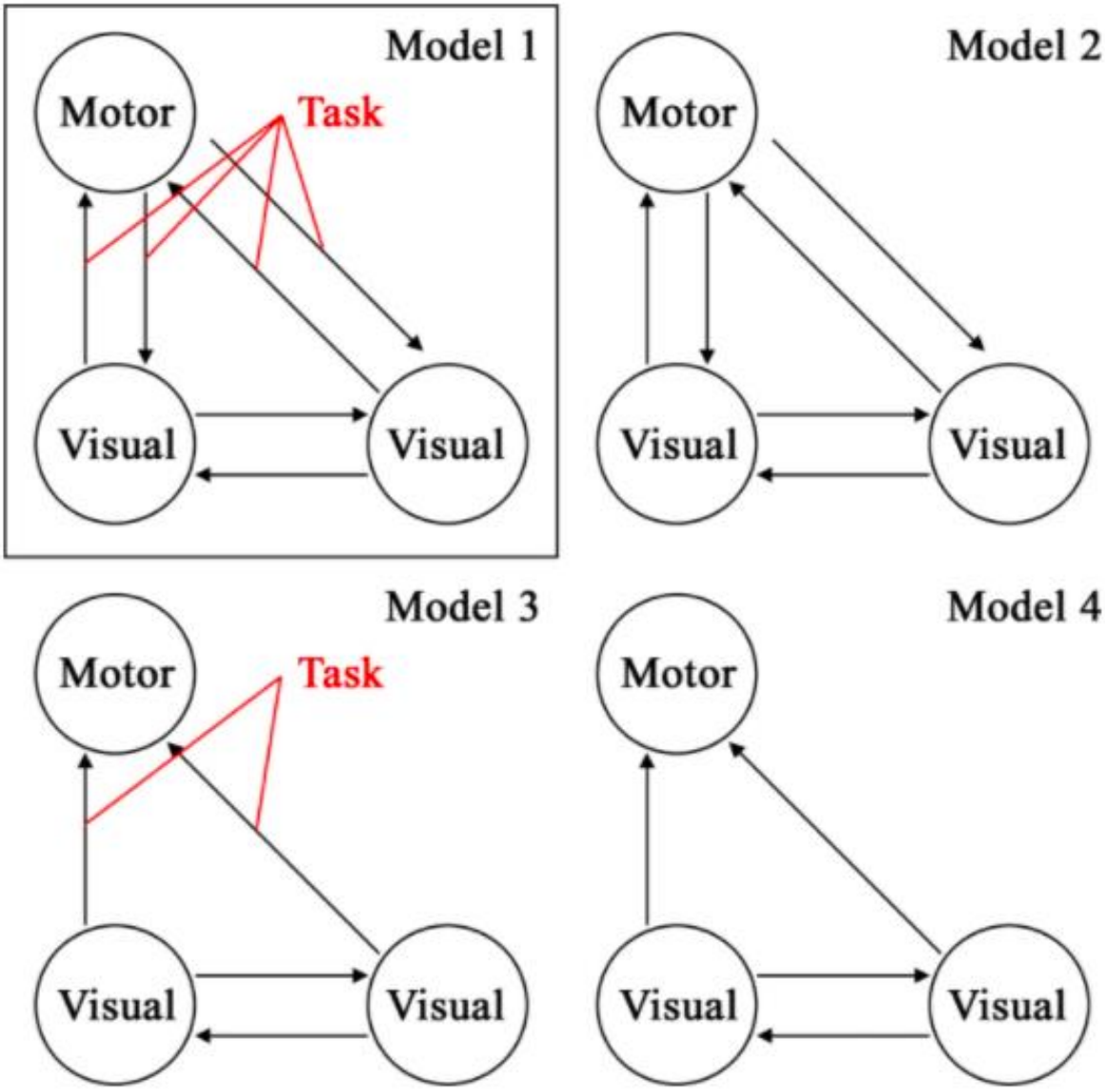
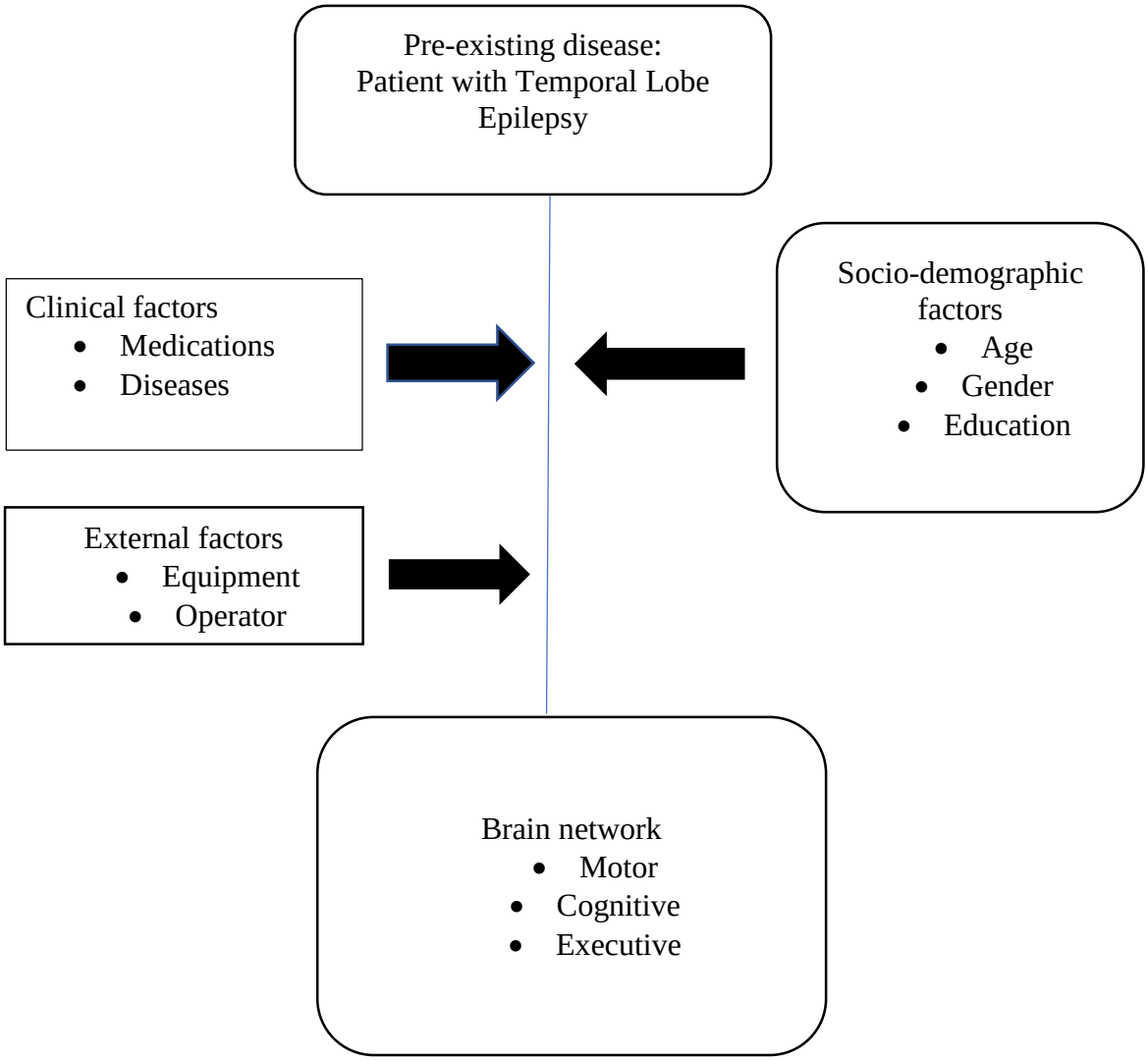


Figure 4: Effective connectivity modelling during finger tapping.

2.6 Conceptual framework



CHAPTER 3: METHODOLOGY

3.1 Study Design

Retrospective cross-sectional study

3.2 Study Location and Duration

Hospital Universiti Sains Malaysia

Jan 2020 until May 2021

3.3 Study Population and Sample

Patients with established diagnosis of Temporal Lobe Epilepsy (TLE) and Healthy subjects in Hospital Universiti Sains Malaysia.

3.4 Sampling Technique

This study used non-probability sampling method. All the data available from previous study 'Delineating Mechanism of Brain Connectivity as Part of Multimodality treatment of Seizure' (USM/JEPeM/16050175 – 5th October 2016 - 4th October 2017) were retrieved and analysed. Informed consent taken from previous study includes the data for this study.

3.5 Inclusion Criteria

1. Inclusion criteria for Temporal Lobe Epilepsy

    - 18 years old and above.
    - Clinically diagnosed as Temporal Lobe Epilepsy
    - Patients are seizure free for at least 24 hours.

2. Inclusion criteria for Healthy subjects

    - 18 years old and above.
    - No systemic disease or neurological symptoms e.g., weakness, tremor, etc.

3.6 Exclusion Criteria

1. Exclusion criteria for Temporal Lobe Epilepsy

- Brain structural abnormalities (except for hippocampal sclerosis), intracranial infection, tumor etc.
- Long-term abuse of alcohol and drug except for antiepileptic.
- Patients with severe cognitive impairment or mental disorder that they could not cooperate well.
- Post temporal lobe resection surgery.

2. Exclusion criteria for Healthy subjects

- Post brain trauma/ surgery

3.7 Sample Size Calculation

Objective 1

Two means hypothesis testing formula was used for sample size calculation. The expected difference of the mean between the normal and patients was 0.5 and of the standard deviation (σ) was 0.5(Horenstein et al., 2009). By using the Power and Sample Size program, total sample size is 18 with 10% dropout.

Objective 2

Two means hypothesis testing formula was used for sample size calculation. The expected difference of the mean between the normal and patients was 0.1 and of the standard deviation (σ) was 0.1 (Ahmad et al., 2011). By using the Power and Sample Size program, total sample size is 18 with 10% dropout.

3.8 Research Tools

1. MRI machine – Phillips 3 Tesla Achieva MR scanner, Best, The Netherland

2. MR Sequences

(a) Brain axial T1- weighted imaging sequence

(b) Blood oxygen level dependent (BOLD) fMRI (T2-weighted gradient echo planar imaging (EPI) sequence)

3. Matlab R2018b - Platform software to run Statistical Parametric Mapping (SPM) to analyse activation and Dynamic Causal Modelling (DCM) to analyse effective connectivity.

3.9 Variable Definition

1. Clinical diagnosis – Patient diagnosed as temporal lobe epilepsy by neurophysician based on clinical history, physical examination and EEG.
2. Variable 1 - Spatial activation

   Conceptual definition - cortical brain regions which are found to be significantly activated during the finger tapping task (Ahmad et al., 2011)

   Value – T-value (only voxels with statistically significant T-value)

   Programme used – Statistical Parametric Mapping (SPM)
3. Variable 2 – Effective connectivity

   Conceptual definition - the influence that a node exerts over another under a network model of causal dynamics and is inferred from a model of neuronal integration, which defines the mechanisms of neuronal coupling (Friston, 2011).

   Region of interest – Visual and Motor region

   Models – (1) Bidirectional (2) Visual to motor (3) Motor to Visual in both brain hemispheres.

   Value – Hertz (Hz)

   Programme used – Dynamic Causal Modelling (DCM)
4. Self-paced finger tapping - tap all four fingers against the thumb beginning with the thumb-index finger contact and proceeding to the other fingers in sequence which would then begin anew with contact between thumb and index finger. This study used a robust self-paced finger movement. The tapping of the fingers would approximately be two times in one second (using an intermediate force between too soft and too hard)(Ahmad et al., 2011).

5. Functional Magnetic Resonance Imaging (fMRI) - a class of imaging methods developed in order to demonstrate regional, time-varying changes in brain metabolism (Glover, 2011)
6. Matlab - is a proprietary multi-paradigm programming language and numerical computing environment developed by MathWorks. Platform software to run statistical parametric mapping to analyse activation and dynamic causal modelling to analyse effective connectivity.
7. Statistical Parametric Mapping refers to the construction and assessment of spatially extended statistical processes used to test hypotheses about functional imaging data.
8. Dynamic causal modelling (DCM) - is a Bayesian scheme for constructing and comparing generative models of measured blood oxygen level-dependent (BOLD) signals. In this framework, the dynamics of interacting neuronal populations is modelled by differential equations that represent synaptic coupling and its plasticity under experimentally controlled perturbations (e.g., task demands or learning).

3.10 Data Collection

1. This study analysed the archived data collected from previous study protocol (Protocol title: Delineating Mechanism of Brain Connectivity as Part of Multimodality Treatment of Seizure. JePeM Code: USM/JEPeM/16050175). The access for the data has been granted by previous principal investigator and head of department of radiology.
2. Informed consent taken during previous research includes the data in this study.
3. Approval taken from the hospital's director to use the previous data in this study.
4. The data was retrieved from the MRI workstation and it was anonymised.
5. Data was stored in the personal computer in the MATLAB software.
6. The data was only accessible to the researchers and involved personnel only.

Data collection procedure from previous study

1. Subjects lie down on the couch in MRI machine.
2. T1 weighted imaging for brain structural screening
3. Stimulus (picture of right hand, left hand or bilateral hands) was back-projected onto a computer screen that could be viewed through a mirror attached above the scanner's head coil.
4. Blood oxygen level dependent (BOLD) fMRI: Patients will start self-paced finger tapping (right/left/bilateral) when stimulus was projected accordingly in front of them.
5. The protocol for finger tapping is according to the paradigm protocol as shown in Figure 5.

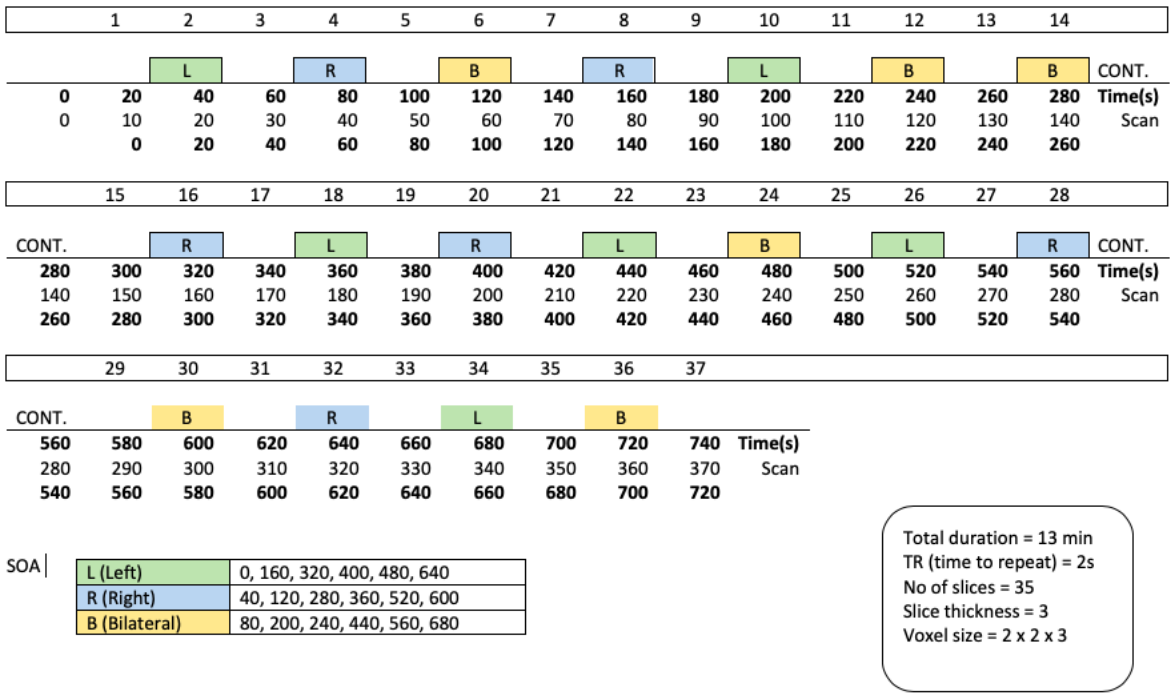


Figure 5: Paradigm for finger tapping

3.11 Image Analysis

1. Data were collected in DICOM (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 centre for Neuroimaging
2. Statistical Parametric Mapping (SPM12) (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London) software packages in the platform of MATLAB 7.4 – R2018b (Mathworks Inc., Natick, MA, USA) was used for pre-processing i.e., smoothing, realign and normalize the images so that all the images are standardized. For first objective, first level analysis was performed to observe the area of activation in each group. Activated region were localised using Montreal Neurological Institute (MNI) coordinates. The coordinates were assigned using neuromorphometrics atlas in SPM. Then we proceed with second level analysis to compare the difference of brain activation across individuals in TLE and Healthy subjects.
3. For second objective, to explore on the effective connectivity, dynamic causal modelling (DCM) function was used in statistical parametric mapping (SPM12) software. This study explored the effective connectivity between visual and motor area of right and left brain in both groups. Region were decided based from the first level analysis. In this study Cuneus was taken as region of interest as the coordinate is part of the primary visual cortex. For motor region, post central was taken as region of interest as the coordinate is part of the primary motor cortex. There models were tested, bidirectional, from visual to motor, and from motor to visual.

3.12 Statistical Analysis & Hypothesis

Statistical analysis

1. Descriptive statistic to analyse objective 1 and 2.
2. For brain activation, maps of activation are compared between groups by means (two samples 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 $p < 0.05$ FWE corrected being shown.
3. Effective connectivity was analysed using the novel method of Bayesian Model Selection (BMS): fixed function analysis (ffx) for group studies as implemented in Dynamic Causal Modelling (DCM).

Null hypothesis

1. There will be no difference in brain activation during self-paced finger-tapping in TLE patients and Healthy subjects.
2. There will be no difference in effective connectivity during self-paced finger-tapping in TLE patients and Healthy subjects.