ORIGINAL ARTICLE

Effective connectivity between precuneus and supramarginal gyrus in healthy subjects and temporal lobe epileptic patients

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ABSTRACT

Introduction: The effective connectivity (EC) when the brain is resting and how a neuronal system exerts influence over other regions of the brain, in different groups of subjects are still being investigated. Limited information was seen about the relationship between precuneus (PRE) which is a well-known resting state hub with supramarginal gyrus (SMG) in healthy subjects (HS) and temporal lobe epilepsy (TLE) participants.

Materials and methods: Fourteen HS and 14 TLE patients with age and gender matched underwent resting state functional magnetic resonance imaging (rsfMRI) scanning using a 3-Tesla MRI machine to investigate the EC and percentage of amplitude fluctuation (PerAF) involving SMG and PRE. The rsfMRI data were analysed using Statistical Parametric Mapping (SPM12) and Spectral Dynamic Causal Modelling (spDCM) from which causal models were specified, estimated and inferred.

Results: Model with bidirectional connections between PRE and SMG was chosen as the winning model. The EC from PRE to SMG is positive but the EC from SMG to PRE is negative in both hemispheres and in HS and TLE. Based on the findings from the EC analysis, there is an excitatory effect shown by PRE to SMG connection indicating a dominant role of PRE over SMG in both groups.

Conclusion: There is important evidence showing that PRE might also have influence on areas outside resting state network and the influence changes in the presence of brain abnormality.

KEYWORDS:
Bayesian, effective connectivity, temporal lobe epilepsy, supramarginal gyrus, precuneus

INTRODUCTION

Temporal lobe epilepsy (TLE) is a condition characterized by recurrent, unprovoked seizures originating from either medial or lateral temporal lobe. Recent research shows that longstanding TLE is associated with extra-temporal damage. These findings relate to the importance and relevance of the study of the effective connectivity of other extra-temporal areas of the brain in TLE. Both precuneus (PRE) and supramarginal gyrus (SMG) is located in the extra-temporal area which is a major hub in default mode network (DMN).[1] Precuneus is located at the postero-medial region of parietal lobe while SMG is located in the lateral surface (Wernicke's area) at the inferior parietal lobule region.[2] Based on our preliminary analysis on the most active areas of the brain in both healthy and TLE participants during resting, it was found that the highest brain activity present in the PRE and SMG areas which was represented by the highest number of voxels. Precuneus (PRE), is an area in resting state network, has received attention due to its role as a resting-state hub while SMG in the parietal area is well known as a visual word recognition area. We proposed that PRE which has highly integrated function has a greater influence on SMG would have connectivity changes between two areas in the presence of TLE. Little attention has been given to the relationship between these two areas before especially in the presence of brain abnormality such as TLE. Based on a previous study, it was found that in brains of TLE patients, there is reduced connectivity at the region outside the temporal lobe particularly from the posterior to the anterior DMN during rest.[3]

Effective connectivity (EC) is a measurement on neuronal units in one part of the brain which communicate and influence other parts of the brain. It is causal in nature, that is, the influence one region to over another which is caused by some external stimulations generated within an experimental context.[3,4,5]

Initial study used stochastic DCM (sDCM) to model the observed BOLD time series of each node and to estimate the model parameters and any hyper-parameters that parameterize the random fluctuations.[6,7] Later, a DCM analysis of resting-state fMRI (rsfMRI) data, known as spectral DCM (spDCM) was introduced.[8,9] The spDCM uses a neuronally plausible power-law model of the coupled dynamics of neuronal populations to generate complex cross spectra among measured responses. It estimates the time-invariant parameters of their cross spectra and models the

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observed endogenous random fluctuations between nodes to obtain the cross spectra density which was then used in estimating the EC between the DMN nodes.

Given the fundamental cognitive functions of both regions when the brain is in an active state, it is important to obtain more information about their connectivity and the changes that could occur in the presence of brain abnormality such as TLE when their brain is at rest. To our knowledge, not many studies have focused on resting state connectivity in patients with TLE. Furthermore, there is no study available comparing the EC of specific extra-temporal areas in healthy subjects (HS) and TLE participants during resting state.

Thus, in our study we had investigated the forward and backward connections EC between PRE and SMG in both healthy subjects and temporal lobe epileptic patients. In this study, the causal models that show the best presentation of the EC between PRE and SMG in two groups of subjects (healthy and TLE patients) was developed. We hypothesised that PRE which is known as an area of highly integrated function has a greater influence on SMG and their connectivity changes in the presence of TLE.

Temporal lobe epilepsy is a disease with morbidity in which patient suffers from unpredictable seizure which reduce their quality of life. Thus, our study could give a valuable information on the neuronal electrical circuit that happens in the brain of TLE patient particularly involving PRE and SMG which may give insight to prediction of seizure for better management of this disease. The information gained is valuable in indicating the extent of spread of seizure to both sides of the brain from the focal onset and might be able to trigger a warning that another seizure will happen.

MATERIALS AND METHODS

Subjects

This was an experimental study in which two groups of subjects were involved.

One group consisted of 14 healthy subjects (11 females 3 males) (average age ± standard deviation = 36.93 ± 8.75 years) and another group also consisted of 14 patients (11 females 3 males) with TLE (average age ± standard deviation = 37.00 ± 8.79 years). The subjects from the two groups were matched by their age and gender. Clinical history of their temporal lobe of epilepsy in TLE participants is shown on Table I(a).

The healthy subjects in this study were recruited from persons who accompanied patients (relatives) who went for treatment at polyclinic Hospital Universiti Sains Malaysia (HUSM). HUSM staff were also among the healthy participants who were involved in this study. The inclusion criteria of the healthy subjects where that they were free from medical and/or surgical illness based on history taking done by the medical officer in-charged. Once patients consented to participate, they were screened for MRI compatibility. Then, they underwent preliminary scanning by MRI producing T1-weighted images (T1WI) and T2-weighted images (T2WI). A radiologist was present during the MRI scanning to interpret the MRI findings, and all patients who had normal T1 and T2-weighted images (which were one of the inclusion criteria) were included.

The 14 patients with TLE who were recruited were diagnosed to have TLE by the neurology team and under neurology clinic follow-up. The patients were diagnosed to have TLE based on clinical semiology features of the seizure and the EEG findings that fit the diagnosis. The EEG was also done with video monitoring. All subjects agreed to involve in this study by signing the consent form after being given full explanation about the study including the nature and risks of the research. This study was approved by the Institutional Ethics committee (IEC) of HUSM number USM/JEPeM/16050175. The exclusion criteria of the participants include patients with brain abnormality caused by surgery or injury, tumors, significant malformation of cortical development leading to distortion of brain anatomy, patients who had previous history of brain injuries and psychiatric disorders.

Resting State MRI Scanning

Patients underwent MRI scanning in the Department of Radiology, HUSM using a 3-T Phillips Achieva MRI scanner equipped with 32-channel head and neck system. Particular MRI protocol was executed to ensure that the images taken were in the resting state.

The first three scanned images from the patients 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) = 1700 ms, flip angle (α) = 75°, slice thickness = 4 mm, slice gap = 0 mm, field of view (FOV) = 192 × 192 mm, matrix size = 64 × 64, voxel size = 2 × 2 × 4 mm, number of scans = 250 and total imaging time = 425 s.[10]

Resting state

To ensure that the patients were in resting state, they were requested not to move their heads during the scan. They were required to be relaxed, empty their mind and passively focus on a fixation point "×" symbol on the screen throughout the session. Subjects were not to fall asleep during the scan because "sleeping brain" is very different from the "resting brain".[11]

Data analysis:

The analysis of the fMRI data involved a number of steps including spatial processing, signal extraction, correlation analysis, modelling and percentage of amplitude of fluctuation.

1. Spatial Processing

A total of 247 functional images were analyzed using Statistical Parametric Mapping (SPM12), Functional Imaging Laboratory (FIL), and Wellcome Trust Centre for NeuroImaging (WTCN), in the Institute of Neurology (ION) at the University College London (UCL), UK – which runs on MATLAB R2016b (The Mathworks, Inc. USA) platform.[12] The functional images of each measurement was first entered into a slice timing module for acquisition time correction. They were then realigned using the 6-parameter affine transformation in translational (x, y and z) and rotational

Table I(a): Clinical history of temporal lobe of epilepsy

Side and cause of TLE	Last seizure attack	Treatment
1) Not known	1 year before scan	Y
2) L	6 months before scan	Y
3) L	2 weeks before scan	Y
4) R temporal mesial sclerosis	3 years before scan	N
5) R temporal mesial sclerosis	4 days before scan	Y
6) Bilateral mesial temporal sclerosis	1 months before scan	Y
7) L	2 years before scan	Y
8) L mesial temporal sclerosis	3 months before scan	Y
9) R	1 month before scan	Y
10) Not known	11 days before scan	Y
11) L	1 year before scan	Y
12) R	1 year before scan	Y
13) R mesial temporal sclerosis	1 year before scan	Y
14) L	1 year before scan	Y

Y = Yes; N = No; R=Right; L=Left; TLE = Temporal lobe epilepsy

Table I(b): Healthy subjects' and TLE patients' percentage of amplitude fluctuation obtained from all regions

	PerAF/% ($p<0.05$)			
	LPRE	LSMG	RPRE	RSMG
Healthy subjects				
1	0.74	0.73	0.58	0.50
2	0.73	0.67	0.68	0.57
3	0.48	0.28	1.00	0.93
4	1.09	0.44	1.44	1.83
5	0.83	0.50	1.40	0.82
6	0.52	0.40	0.45	0.30
7	0.40	0.69	0.82	0.55
8	0.70	0.30	0.39	0.80
9	0.62	0.33	0.65	0.55
10	0.52	0.33	0.44	0.26
11	0.44	0.50	0.46	0.44
12	0.42	0.39	0.37	0.33
13	0.52	0.49	0.43	0.46
14	0.79	0.40	0.59	0.81
Average	**0.63**	**0.46**	**0.69**	**0.65**
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(pitch, roll and yaw) directions to reduce the effects on the overall signal intensity from movements of the participants. 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).[12] 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 high-passed filter.

2. Signal Extraction

A general linear model (GLM) containing the time corrected, realigned, normalized and smoothed images was chosen for each subject and a design matrix was constructed. This design matrix was then estimated and was used in extracting the time series signals from cerebrospinal fluid (CSF) and white matter (WM) centered at (0, -40, -5) and (0, -24, -33) of a 6-mm radius volume of interest (node) respectively. The extracted signals from the two regions were then used to construct a second design matrix. This new design matrix was then estimated.

The second design matrix was later used to extract signals from the 8-mm radius node of the four DMN nodes; left precuneus (PRE) centered at -9, -78, 36, right PRE centered at 10, -73, 39 [9], left supramarginal gyrus (SMG) centered at -52, -28, 23 and right SMG centered at 55, -28, 28.[10] The time series signal extracted from all the nodes were entered into a third design matrix, together with the extracted signals from CSF and WM, six realigned parameters and global. This newly constructed design matrix was used to generate activation for left and right PRE, left SMG and right SMG for each subject by means of t-contrast (t-test) looking for the effects these nodes would have during which the brain is at rest. Group activation was later produced using one-sample t-test at the second level, in the random-effects framework, corrected for multiple comparisons ($p < 0.05$), testing for the effects against no activation.

3. Correlation analysis

The EC between left PRE and left SMG as well as from right PRE and right SMG was also investigated by means of correlation analysis to determine the distribution of EC between the activated areas across all subjects. The EC obtained from PRE vs. SMG plot for both groups of subjects were averaged and were compared by means of independent t-test. Comparisons in the slopes were also made between the two hemispheres. Similar treatment was also done for SMG vs. PRE plot. Only intra hemispheric connectivity was considered in this study. All the results were reported based on significant level (α) of 0.05 with a 95% confidence interval.

4. Modelling

The time series signals for each node were then used in specifying and constructing the causal models in DCM analysis. Left hemisphere causal models comprising of left PRE and left SMG; and right hemisphere causal models comprising of right PRE and right SMG were constructed using dynamic causal modelling.[13] Based on Figure 1, model 1 has a one directional connection from PRE to SMG. Model 2 has a one directional connection from SMG to PRE and model 3 has a bidirectional connection between PRE and SMG. No input was specified as this study was motivated by resting state condition and all models are assumed to have self-connection on each region, shown by the curved arrows.

The causal models were then estimated using spectral DCM (spDCM) to obtain the coupling parameters, the effective connectivity (EC) between nodes. Their endogenous fluctuation of activity was recorded and analyzed to generate complex cross spectra. The time invariant covariance of the random fluctuations between nodes was then estimated to obtain the cross spectra density which was then used in estimating the EC between the DMN nodes. The EC among coupled neuronal responses was then estimated using a plausible power-law model.[14]

The inverted models were then compared by means of Bayesian model selection (BMS) for group studies under the FFX framework[15], to test the null hypothesis that no single model is better than any other competing models and to obtain a model that has the best balance between fit/accuracy and complexity.

Upon obtaining the most optimum model, the EC values among the DMN nodes were then averaged over the subjects using Bayesian parameter averaging. In Bayesian framework, a connection is considered significant if its posterior probability value is equal or larger than 0.9.[16]

Percentage of amplitude of fluctuation

The percentage of amplitude of fluctuation (PerAF)[17,18] for the left and right hemisphere PRE and SMG were computed for every healthy subject and TLE patient. This is done by first extracting the signal (random fluctuation) from the highest intensity voxel of the main cluster of activation for each region. The SPM maximum intensity projection (MIP) was used to locate the respective voxel. A series of time points (n) on the random fluctuation, denoted as Xi, was used to calculate the average of the fluctuation amplitude (μ) as given by equation (1).

$$\mu = \frac{1}{n}\sum_{i=1}^{n} X_i$$

The PerAF was then computed for each region using μ obtained from equation (1) by means of equation (2).

$$\mathrm{PerAF} = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{X_i - \mu}{\mu}\right| \times 100\%$$

RESULTS

Dynamic causal models and effective connectivity

Figure 2 shows the results of model comparisons obtained from Bayesian model selection (BMS) for left and right hemispheres in healthy subjects and TLE participants. The structure for Models 1, 2 and 3 are shown in Figure 1. From Figure 2, it can be seen that Model 3 is the winning model among the three competing models which has the highest

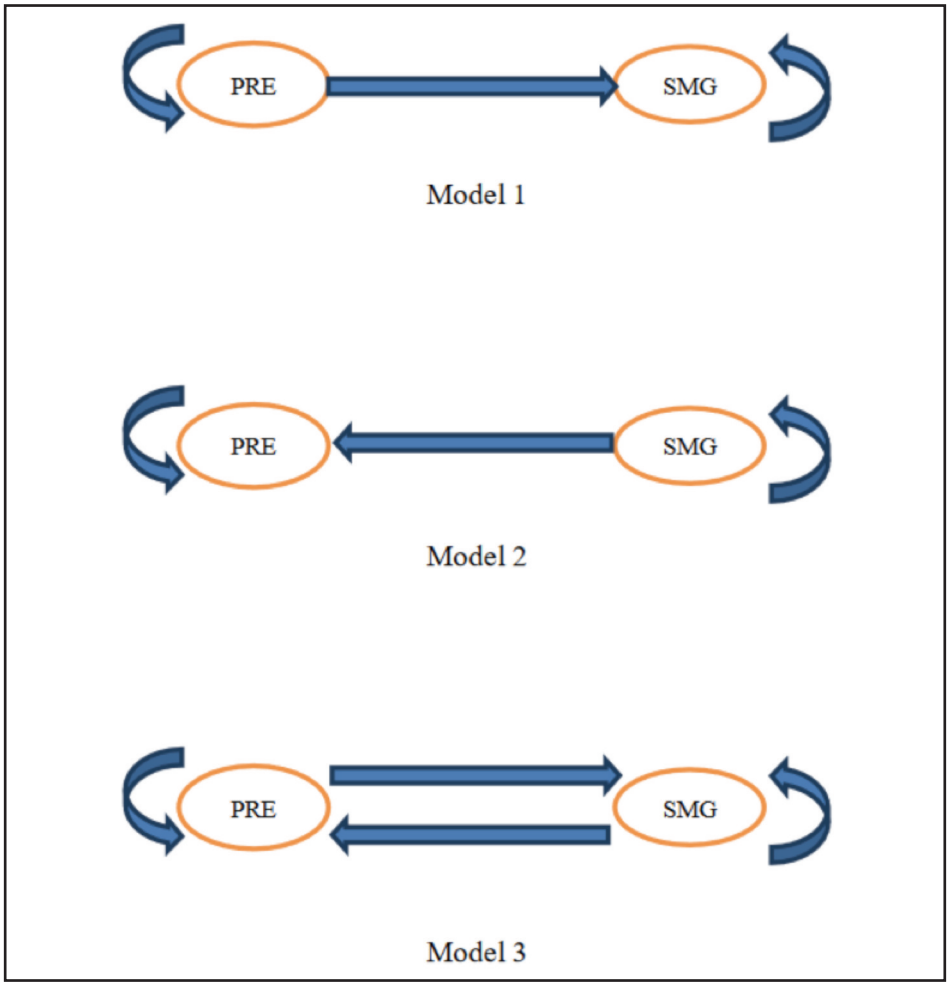

Fig. 1: Dynamic causal model specified to all subjects in this study. Straight arrows represent coupling while curved arrows indicate self-connection.

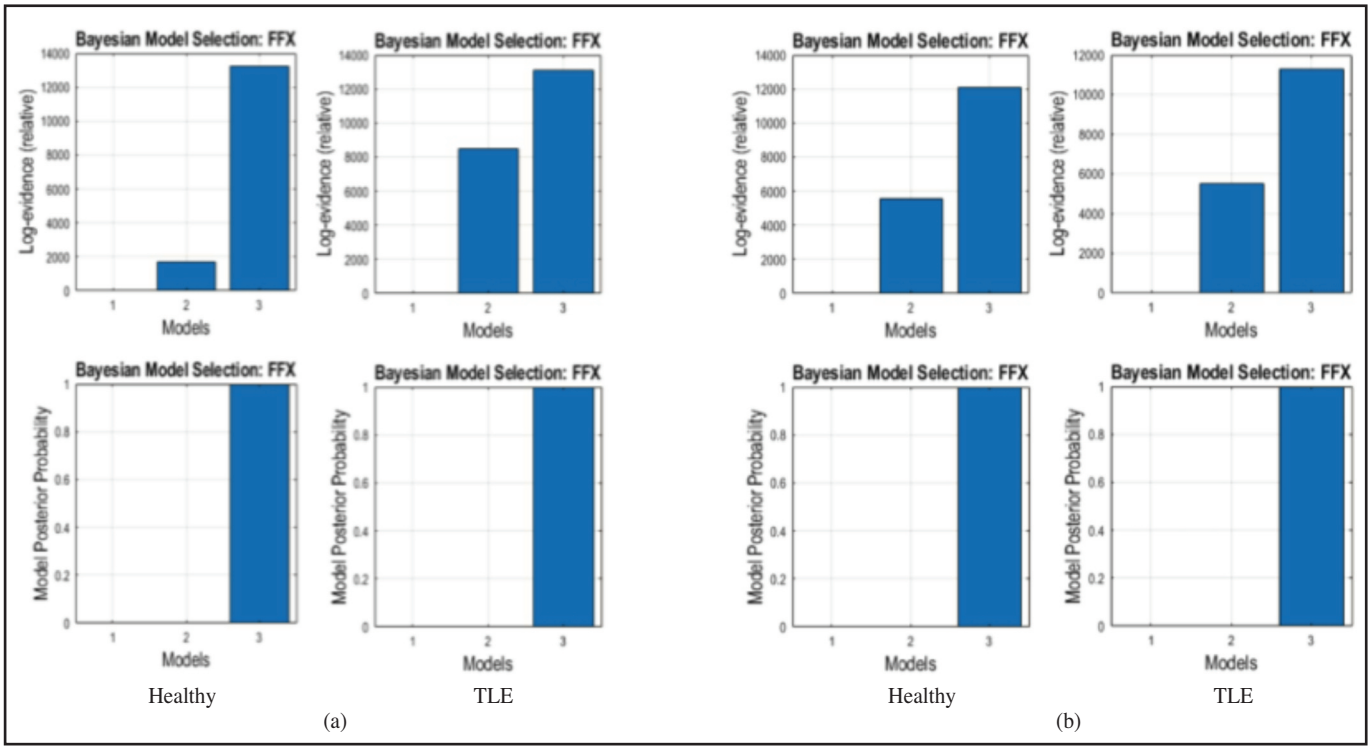

Fig. 2: Model comparison results using BMS for healthy subjects and TLE patients; (a) left hemisphere (b) right hemisphere.

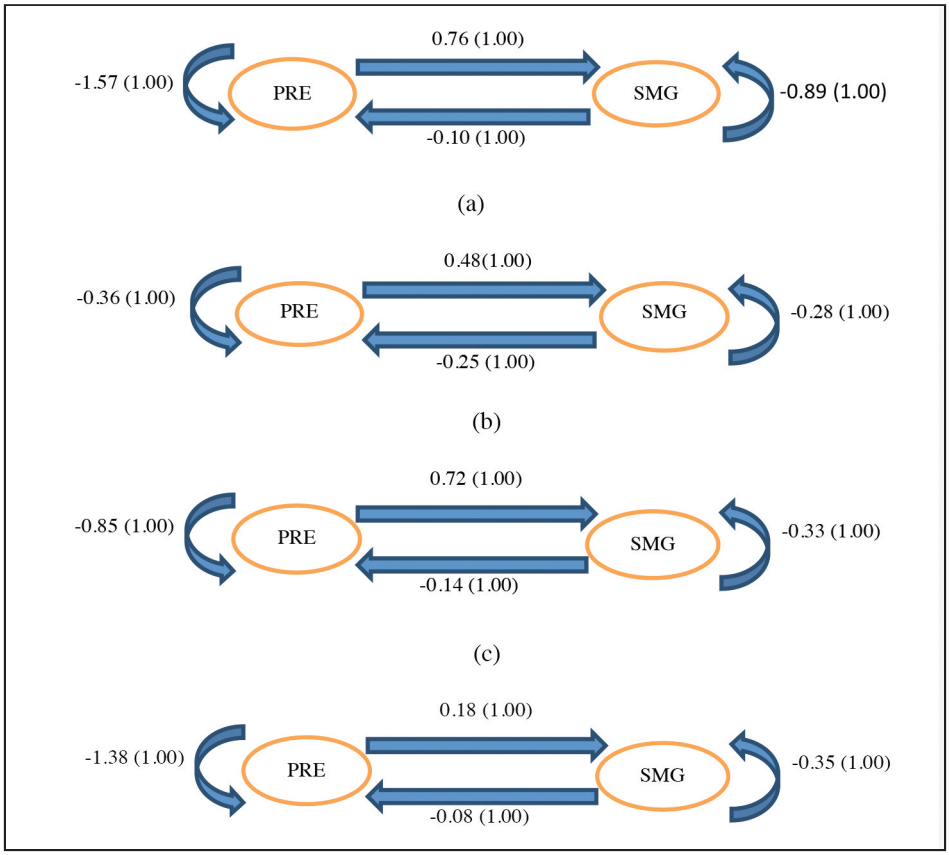

Fig. 3: The EC between PRE and SMG for (a) healthy subjects' left hemisphere, (b) TLE patients' left hemisphere, c) healthy subjects' right hemisphere and d) TLE patients' right hemisphere. Straight arrows represent coupling while curved arrows indicate self-connection. All connectivity values are in Hz. All values are significant (posterior probability > 0.9); ($p < 0.05$; 95% CI).

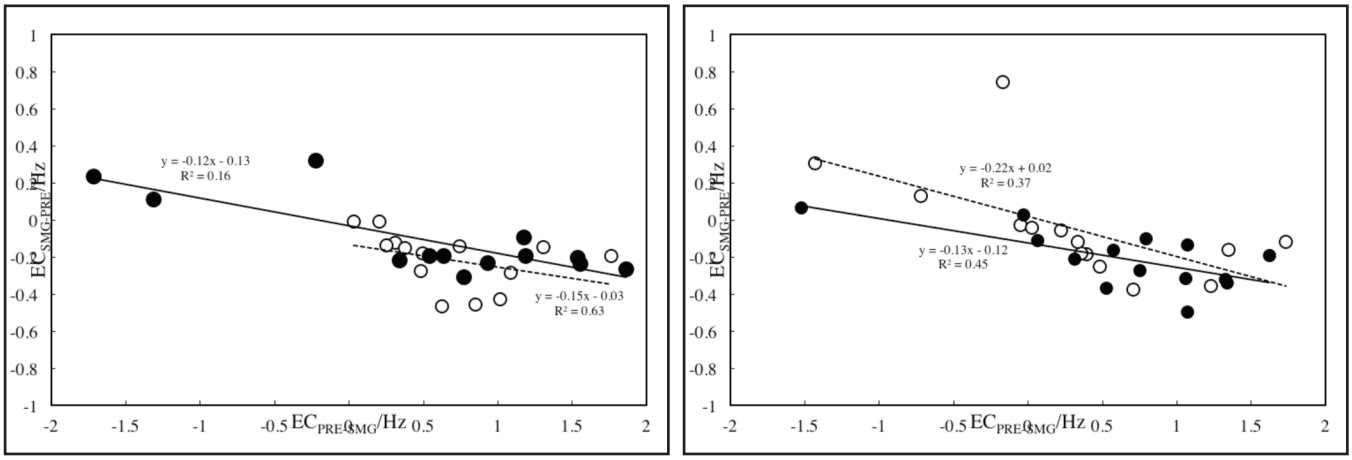

Fig. 4: The EC from SMG to PRE (ECSMG-PRE) plotted against the EC from PRE to SMG (ECPRE-SMG) for healthy subjects (open circle and broken line) and TLE patients (solid circle and solid line); left hemisphere (top) and right hemisphere (bottom).

model evidence and posterior probability. The results are consistent for both hemispheres in healthy subjects as well as in TLE participants. From the results, it can be said that the form of connectivity between PRE and SMG during resting state for both left and right hemispheres is the same in both groups of subjects with bidirectional connectivity between the two regions.

The average EC values and their posterior probabilities (in brackets) for Model 3 obtained from BPA for both groups and hemispheres are shown in Figure 3. Also shown in the figure is the self-connection for both regions. All values are significant (posterior probability > 0.9).

Based on Mann-Whitney U test, it was found that the PRE to SMG connection for HS is no different with that of TLEP ($p > 0.05$; 95% CI) in both the left and right hemispheres. Similar analyses conducted on SMG to PRE connections using similar tests also show insignificant difference ($p > 0.05$; 95% CI).

Based on Mann-Whitney U test, it was found that the PRE to SMG connection for the left hemisphere is no different with that of the right hemisphere ($p > 0.05$; 95% CI) in both the HS and TLEP. Similar analyses conducted on SMG to PRE connections using similar tests also show insignificant difference ($p > 0.05$; 95% CI).

Both the PRE and SMG have negative self-connectivity as can be seen in Figure 3. Statistical analysis conducted using the non-parametric Wilcoxon Signed Rank test revealed significant ($p < 0.05$; 95% CI) differences in the self-connectivity between both regions with PRE having a larger self-connection than SMG for all cases.

In Figure 3, the structures for model 1, 2 and 3 are shown. It shows the connectivity between PRE and SMG during resting state for both left and right hemispheres in both groups of subjects with bidirectional connectivity between the two regions. The average EC values and their posterior probabilities (in brackets) for Model 3 obtained from BPA for both groups and hemispheres are shown in Figure 3. Also shown in the figure is the self-connection for both regions. All values are significant (posterior probability > 0.9).

Figure 3 shows that the magnitude of EC for PRE→SMG connection is larger than for SMG→PRE connection for both hemispheres in healthy subjects and TLE patients. Based on Wilcoxon signed-rank test, the median of differences between PRE→SMG and SMG→PRE connections equals zero indicating a significant difference between the two values ($p < 0.05$; 95% CI) in all cases, rejecting the null hypothesis of no difference. The PRE→SMG connection is positive while the SMG→PRE connection is negative for all cases indicating non-reciprocal behavior of connectivity that could possibly be due to the inhibitory-excitatory interactions between the two regions.

Based on Mann-Whitney U test, it was found that the PRE→SMG connection for healthy subjects is no different from that of TLE patients ($p > 0.05$; 95% CI) in both the left and right hemispheres. Similar analyses conducted on SMG→PRE connections using similar tests also show insignificant different ($p > 0.05$; 95% CI).
Based on Mann-Whitney U test, it was found that the PRE→SMG connection for the left hemisphere is no different from that of the right hemisphere ($p > 0.05$; 95% CI) in both the healthy subjects and TLE patients. Similar analyses conducted on SMG→PRE connections using similar tests also show insignificant different ($p > 0.05$; 95% CI).

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Figure 4 is the distribution of PRE→SMG (and SMG→PRE) connections in the left (top) and right (bottom) hemispheres across healthy subjects and TLE patients. All graphs show a negative linear correlation between EC from PRE to SMG and from SMG to PRE from which it can be said that an increase in connectivity from PRE to SMG results in a decrease in connectivity from SMG to PRE. This non-reciprocal behaviour of connectivity is similar in both the left and right hemispheres and the correlation were found to be small to moderate but significant ($p < 0.05$; 95% CI) for all cases, as tested using Spearman correlation test.

Percentage of amplitude fluctuation (PerAF)
The PerAF computed for all regions for healthy subjects and TLE participants are tabulated in Table I(b). The average value for each region is shown in bold-face numbers at the bottom of the table. Statistical analyses conducted within healthy subjects by means of 2-way Friedman's ANOVA by ranks showed no significant difference ($p > 0.05$) in the median of PerAF among regions of interest. This concluded that the distribution of PerAF among left hemisphere PRE and SMG as well as right hemisphere PRE and SMG in both groups of subjects are the same. However, for TLE participants, Friedman's ANOVA indicated a significant difference ($p = 0.041$) in PerAF between one pair of regions; that is between left hemisphere SMG and right hemisphere PRE .

Between groups comparisons (matched region-to-region e.g. PRE for healthy participants vs. PRE for TLE participants conducted using Wilcoxon signed-rank test found no significant difference ($p > 0.05$) in the median of PerAF of all regions between healthy participants and TLE participants. The findings concluded that the fluctuation of signal amplitude is no difference between healthy participants and TLE participants for all regions of interest.

DISCUSSION

The spatial activations that were obtained at a stringent significant level corrected for family wise errors (FWE) for supramarginal gyrus (SMG) and precuneus (PRE) during resting state fMRI is an evidence of higher brain activity (as compared background) that took place in PRE and SMG when the brain is in its default mode.

From the results of our study, it was found that both healthy subjects and TLE patients activated SMG and PRE at rest and both regions were significantly connected in the respective hemisphere. Furthermore, the effective connectivity between SMG and PRE was similar in both the right and left hemispheres, from which the bidirectional model is the model of choice to explain the information exchange between SMG and PRE.

From the spDCM results obtained, it seemed that higher self-connection in PRE is accompanied by higher excitatory (positive EC) connectivity strength from PRE to SMG which in turn return a lower inhibitory (negative EC) connectivity value from SMG to PRE.

In DCM analysis, self-connection parameters are dimensionless and scale up or down the default self-

connection of -0.5 Hz.17 If the values of the self-connections are positive (or more positive), they indicate increased in self inhibition and if negative (or more negative), the values indicate self-disinhibition (or self-excitation).[18] For the between regions connection, positive values indicate excitation and negative values indicate inhibition. In view of the dynamic causal models shown in Figure 2, it can be said that PRE is more negative than SMG in all cases indicating self-excitation whereas SMG is more positive which means that it indicates self-inhibition. It is thought that this self-excitation of PRE drives positive excitatory connectivity from PRE to SMG. To achieve a balanced state of information transfer, the self-inhibitation of SMG then drives negative inhibitory connectivity from SMG to PRE.[16] At the neurophysiological level, this may be seen as non-reciprocal connectivity between two neuronal systems of a network.

The similarity in the model structure for the healthy subjects and TLE participants as well as for the left and right hemispheres for both groups of subjects was validated by the average PerAF values for the respective regions shown in Table I(b). There was significant difference in the median PerAF between left hemisphere SMG and right hemisphere PRE. However, there was an insignificant difference in PerAF values among the regions within both groups due to small differences in each node's activity. Therefore, the EC (that parameterized the model) was not much changed because it was derived from within one region neuronal activity. Furthermore, the abnormality within the TLE participants brain were mainly located at the temporal lobe which is situated outside the regions of interest in this study. Both PRE and SMG are located in the extra-temporal area which is grossly anatomically normal similar to healthy participants. In terms of distance, the epileptic center is at another part of brain which might not significantly affect the connectivity to the PRE and SMG area. Upon MRI screening during selection of the samples, both control and study subjects did not show significant structural abnormality in the brain. Perhaps, the medication taken by TLE participants might have reduced the effects of TLE in the brain. A firm conclusion regarding the relationship between EC and PerAF require confirmation with studies having a larger set of data.

The behaviour (or pattern) of the influence of the activity of one region on another in the form of EC in Figure 4 supports the above discussion. Left and right hemisphere PRE and SMG for both groups of subjects show similar negative correlation of effective connectivity influences. The relationship is non-reciprocal as can be seen from the negative slopes on the graphs. More importantly, the graphs represent the distribution of data from the whole subjects that comprise the group. Non-reciprocity in the EC between two regions has been observed in many previous studies.[16,17,18] Non-reciprocity could be caused by different responses or fluctuations in each region. The difference in brain activity fluctuation, such as delay and amplitude, can be attributed to different responses in particular brain region. This difference could impose influence on the information encoded in another region.

There were several limitations noted in this study. One was the number of participants in our study. However the preliminary results obtained is still meaningful. Larger sample size give more reliable results with greater precision and power, but they also cost more time and money which was limited in our study. The TLE patients recruited in this study were mainly from patients who had been treated with anti-epileptic drugs. This could affect the brain activity and thus EC. We would like to suggest that in future in order to get more findings, patients could stop the treatment 24-hours before the scanning time to see the brain activation without the effect of drug.

Non-homogenous sample size in which varieties of causes of TLE included in our study was due to limited number of cases obtained from in-patient data only. We suggest in future, a homogenous cause of TLE only were recruited in the study as it will create more specific findings related to the group.

CONCLUSION

The resting state fMRI technique via statistical parametric mapping and dynamic causal modeling is able to summarize the connectivity behavior between PRE and SMG in healthy subjects and TLE participants. The winning model in both groups is a bidirectional connection model in which the influence of PRE on SMG is excitatory while the influence of SMG on PRE is inhibitory. The connection strength from PRE to SMG is inversely correlated in which when there is an increase in unidirectional strength from PRE to SMG, there will be a decrease in the unidirectional strength from SMG to PRE, hence explaining the inhibitory nature of SMG to PRE connection. Even though SMG seldom being reported as the main area of DMN in the human brain as much as PRE, it's connectivity at rest to one prominent region of DMN in this study is very significant. Statistical analysis indicates the dominance of PRE as compared to SMG. In this study, even though unidirectional connection from PRE to SMG for HS seemed to be larger than that of TLEP in both the left and right hemispheres, the difference was not significant. TLEP differs significantly with HS only on the PerAF value of RPRE and LSMG.

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