iMEDiTEC 2017

ORIGINAL PAPER

Estimating Brain Connectivity in Schizophrenia Patients Using Electroencephalography Signals

H. Husni A. Halim[a], S. Balqis Samdin[b], Chee-Ming Ting[a,b,*], Sh-Hussain Salleh[a,b], Yin Fen Low[c], Alias Mohd Noor[b]

[a] Faculty of Biosciences and Medical Engineering, Universiti Teknologi Malaysia, 81310 Skudai, Johor, Malaysia
[b] Center for Biomedical Engineering, Universiti Teknologi Malaysia, 81310 Skudai, Johor, Malaysia
[c] Faculty of Electronic and Computer Engineering, Universiti Teknikal Malaysia Melaka, 76100 Durian Tunggal, Melaka, Malaysia

* Corresponding author: cmting@utm.my

ABSTRACT

Schizophrenia has been shown to be associated with a disorder of connectivity in brain networks. In this paper, electroencephalography (EEG) is used to investigate the brain connectivity in Schizophrenia (SCZ). The brain regions investigated are the frontal lobe and temporal lobe involving 12-channel EEG. The covariance matrix of EEGs is used to quantify the functional brain connectivity and vector autoregressive (VAR) model the effective connectivity. We also analyze the time-evolution of the connectivity over repetitive trials, and frequency-specific connectivity using the partial directed coherence (PDC). Visualization of brain connectivity was performed using the e-connectome tool. Results on an EEG data set with auditory selective attention show difference in the brain connectivity patterns across trials at different important frequency bands between the healthy subjects (HS) and SCZ patients. The findings can be potentially used in developing a biomarker to differentiate HS and SCZ.

INTRODUCTION

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels and behaves. There are three types of Schizophrenia's symptoms which are positive symptoms – hallucinations, delusions, thought disorder and movement disorder –, negative symptoms – reduced feelings of pleasure, reduced speaking and difficulty in beginning and sustaining activities – and cognitive symptoms – trouble in paying attention, problem with working memory and poor executive function – [1]. It was proposed by 19th-century pioneers that psychotic disorders might be arise from abnormal axonal connectivity between anatomically dissected cortical regions which this has been generalized to the concept of

dysconnectivity (an abnormal relationship between neurons)[2]. Brain connectivity itself is divided into three types which are structural or anatomical connectivity, functional connectivity, and effective connectivity. Structural connectivity refers to the brain structure called white matter which it is principally composed of axons that covered by myelin sheath and functioned to transmit information from one part of the brain to another[3] whereas functional connectivity refers to the temporal correlation among the different neuronal activities in different brain regions[4]. For the effective connectivity, it involves in the direct or indirect influence that one neuronal system exerts over another[4].

Currently, the diagnosis of Schizophrenia is only based on subjective method. Doctors or psychiatrist are only referring to the manual that has been published by the American Psychiatric Mental Disorder which is the Diagnostic and Statistical Manual of Mental Disorder where according to this manual, they just need to conduct a clinical interview with questionnaires given to the patients and also having some observation on the physical behaviors[5]. This method of diagnosing Schizophrenia patients shows a lack in objective approach which is more reliable compared to the interview session as the symptoms of the illness are hardly can be recognized through observations and only the person who suffers from this kind of disease knows the best on their own condition. Apart from that, the current studies on detecting Schizophrenia illness are only focused on the single channel approach where it ignores the interaction between brain regions [6]. There is actually a number of studies that involved in investigating the connectivity of the brain, but it only emphasizes on the functional connectivity.

In this paper, the aim of this study is to estimate the functional and effective brain connectivity based on the multichannel EEG on a healthy control subject and a Schizophrenia patient. We propose two types of connectivity assessment which are sample covariance and vector autoregressive (VAR) model for functional and effective connectivity estimation respectively. These methods are applied to assesses the connectivity patterns during auditory evoked potential response from both subjects. We also use partial directed coherence used to analyze the time-frequency directed interactions between channels of the EEG recording. The results from the effective brain connectivity estimation are used to differentiate between the Schizophrenia patient and the normal subject.

MATERIALS AND METHODS

Sample Covariance for Functional Connectivity Estimation

Sample covariance estimator is one of the traditional methods of estimating the correlation between two or more random variables [7]. In this study, sample covariance model is used to estimate the functional brain connectivity with the model equation is stated as below:

$$\hat{\Sigma} = \frac{1}{T}\sum_{t=1}^{T}(y_t - \bar{y})(y_t - \bar{y})' \qquad (1)$$

where y_t is the vector of t-th observation of the EEG signal with dimension $N \times 1$, and $\bar{y}$ is the sample mean. Here we assume N is the number of channels.

OPEN ACCESS Freely available online
eISBN 978-967-0194-93-6 FBME

VAR Model for Effective connectivity Estimation

VAR model is a multivariate time series analysis methods that is generalization of univariate autoregressive model. Let the measured EEG signals denote as, $y_t = [y_{1t}, \dots, y_{Nt}]'$, for time, $t = 1, \dots, T$ and N-dimensional vectors. The VAR model with model order, p, can be written as:

$$y_t = \sum_{k=1}^{p} A_k y_{t-i} + v_t \tag{2}$$

where $\{A_k\}_{k=1}^{p}$, is a set of $N \times N$ matrices of VAR coefficeints. v_t is $N \times 1$ vector of independent and identically distributed Gaussian noise with zero mean covariance, $\boldsymbol{R}$ matrix. VAR coefficients is mapping the linear relation of current observation with the given previous observation. This VAR cofficients can be estimated by using least square estimator (LSE) [8].

Partial Directed Coherence (PDC)

Partial directed coherence is a frequency-domain interpretation of Granger causality [7]. It measures the directed influence of one signal on another at a specific frequency. Let $\boldsymbol{A}(f) = \boldsymbol{I} - \sum_{k=1}^{p} \boldsymbol{A}_k e^{-i2\pi f_k}$ be the Fourier transform of the VAR coefficient matrices. Thus, the PDC is defined as:

$$\pi_{ij}(f) = \frac{|A_{ij}(f)|}{\sqrt{\sum_{n=1}^{N} |A_{nj}(f)|^2}} \tag{3}$$

where $|\pi_{ij}(f)|^2 \in (0,1)$ is quantifies the strength of directed influence from j to i at frequency, f [8].

Data set

We used an EEG dataset collected at the Universiti Kebangsaan Malaysia Medical Centre, Malaysia. Ethical clearance was granted by the Research Ethics Committee, with the approval number UKM 1.5.3.5/244/FF-2015-321. The dataset consists of 11 control (mean age: 26) and 11 schizophrenia patients (mean age: 32). Subjects were provided with the information sheet and the consent form was signed prior to the experiment. We assess the connectivity pattern 12-channels EEG (T6, T4, F8, FP2, FPz, FP1, F3, Fz, F4, T5, T3, and F7) with a sampling frequency of 512 Hz. The regions that mainly assessed for auditory evoked potential are the frontal and temporal regions. The experiment was conducted with the implementation of auditory stimuli by using the oddball paradigm method. This study is focused on the single subject analysis for both group and also to study the effective brain connectivity based on the frequency band of delta (0-4Hz), theta (4-7Hz), alpha (8-13Hz) and beta (14-30Hz).

RESULTS AND DISCUSSION

The results were being obtained based on the single subject analysis. In this article, the result for subject 4 for HS (HS-4) and subject 8 for SCZ (SCZ-8) are being discussed. In general, the connectivity changes across trials are different for both group and also there are certain trends that can be establish to differentiate between HS with SCZ.

For functional connectivity: the results show in Fig. 1 that, there are higher in brain connectivity in HS with the indication of red color (high connectivity with parameter 1) compared to the SCZ which has lower connectivity throughout the brain regions with the indication of yellow and orange color (lower connectivity with parameter 0.1 to 0.4). The frontal areas were the highly connected for both subject, especially between channel F3, Fz and F4.

Generally, the results for the functional connectivity clearly shown that HS-4 has higher connectivity throughout the brain regions

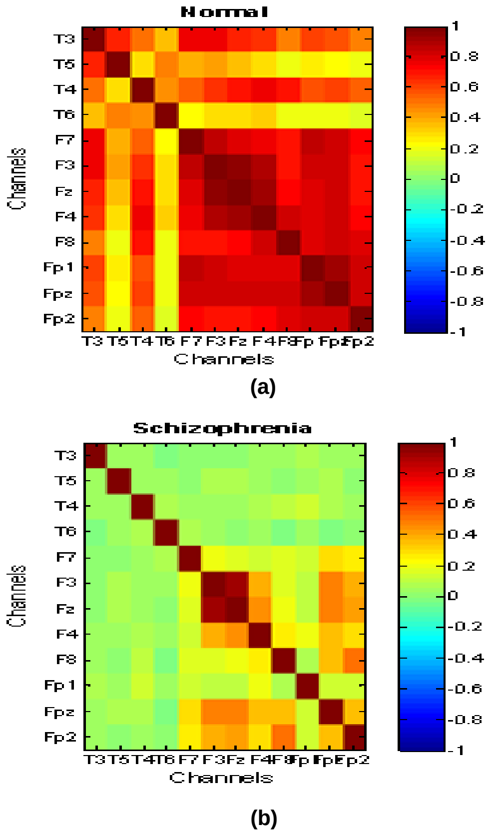


Fig 1. Functional connectivity between 12-channels EEG for HS-4 **(a)** and for SCZ-8 **(b)**.

as it has been indicated by the red color with the parameter of 0.6-1 that shows stronger connection compared to the SCZ-8 which averagely has lower connectivity strength. Studies have showed that the disordered brain connectivity at cortical level is generally defined as a failure of effective-functional integration within and between brain areas. This phenomenon has been proposed as a core deficit of Schizophrenia patients. Finding of this study is quite similar to the extensive investigation on the studies of functional connectivity using functional Magnetic Resonance Imaging (fMRI), EEG or Transcranial Magnetic Stimulation (TMS) where it showed an abnormal representation of functional connectivity in Schizophrenia patients [9].

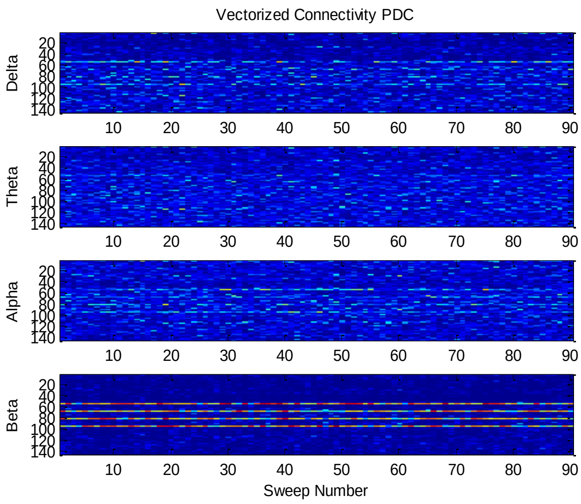
Efective Connectivity: We further assessed the trial-varying PDC of both subjects. Based on the result in Fig. 2, it shows that there is inconsistency of connectivity in the SCZ after one-third of the trial compared to normal subject which has a consistent connectivity along the trials.

The result in Fig. 3 show the e-connectome plot for each EEG frequency band. In delta band, SCZ-8 has a sparse connectivity compared to HS-4 which has dense connectivity. However, there are strong connectivity in the prefrontal region indicate by the red color of connection for the SCZ-8 compared to the HS-4. While in theta band, there are equally dense connectivity in both subject but with stronger connectivity in SCZ-8. In alpha band, sparse and lower connectivity in SCZ-8 whereas higher connectivity in HS-4.

The results on effective connectivity based on the frequency band of EEG generally shows that the brain networks in SCZ subject are abnormally organized especially after the middle of the trial shown by the trial-varying connectivity graph. The main findings can be summarized as:

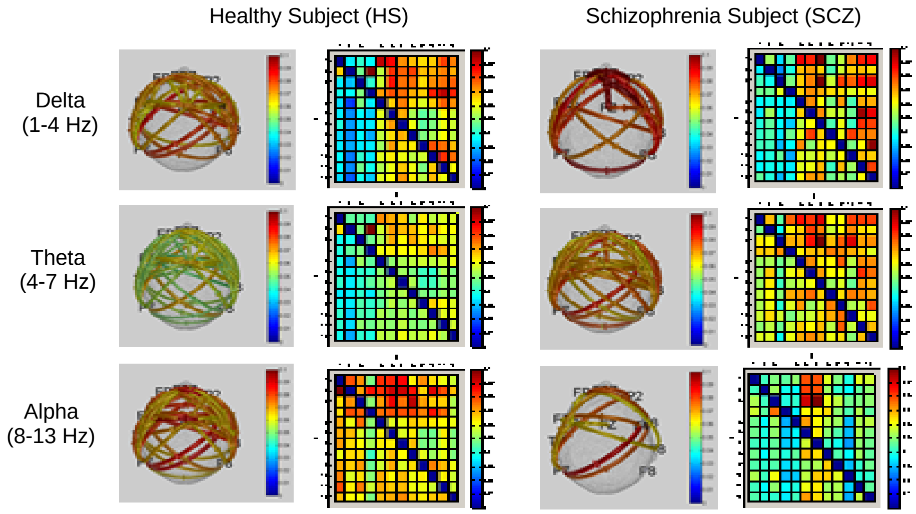
- In low frequencies (delta and theta), the SCZ-8 showed high brain connection (specifically in theta band) and stronger connectivity compared to HS-4.
- In the alpha band, again SCZ-8 has a sparse connectivity with a lower strength of connection compared to the HS-4.

OPEN ACCESS Freely available online
eISBN 978-967-0194-93-6 FBME



(a) (b)

Figure 2. Trial-varying connectivity for all frequency bands in 90 sweeps. Trial-varying PDC in HS-4 **(a)** and in SCZ-8 **(b)**.



(a) **(b)**

Figure 3. Visualization of the average effective brain connectivity for all frequency bands (delta, theta and alpha) in HS-4 **(a)** and in SCZ-8 **(b).**

Higher connectivity in low-frequency (delta and theta) is one of the most consistent findings in Schizophrenia patients [10]. Earlier studies have found an increased coherence in low frequencies. In delta, the strong connectivity are more focusing at the frontal region where it involved thinking in generating decision while in theta band, the connectivity are more spread through the brain regions. This shows efforts in the subject for making decision in response with the experiment activities. However, recent evidence of abnormal theta connectivity in subject has been reported suggesting that impairment in this frequency band could be a trait of Schizophrenia [11].

The reduced in connectivity for the alpha-band in this study has shown some parallel finding with the previous reports on Schizophrenia patients [12]. This result might represent a preliminary trait marker in diagnosing this illness. This reduction in alpha-band coherence which indicate the synchronization and connectivity of the brain has related to the psychopathological dimension of Schizophrenia.

CONCLUSION

We analyzed EEG based functional and effectivity connectivity in schizophrenia patients, quantified by covariance and VAR coefficient matrices. Experimental results on a 12-channel EEG data with a odd-ball paradigm auditory attention experiemtns show difference in the connectivity patterns between different brain regions in the schizophrenia patients compated to normal subjects, across different frequency bands and over trials of repeated stimulus.

ACKNOWLEDGEMENT

This work was financially supported by the Universiti Teknologi Malaysia and the Ministry of Higher Education, Malaysia under Grants R.J130000.7845.4L840, R.J130000.7809.4L841 and R.J130000.7809.4F668

REFERENCES

Health, N.I.o.M., *Schizophrenia.* http://www.nimh.nig.gov

Lynall, M.E., et al,. (2010). Functional Connectivity and Brain Networks in Schizophrenia. *The Journal of Neuroscience.*30(28):9477-9487.

Kirkwood, C. (2015). *Myelin : An Overview*

OPEN ACCESS Freely available online
eISBN 978-967-0194-93-6 FBME

Horwitz, B. (2003). The Elusive Concept of Brain Connectivity. *NeuroImage*. 19, 466-470

Azlan,W.A. (2016). *Objective Quantification of Selective Attention in Schizophrenia: A Hybrid TMS-EEG Approach*. Master Thesis Page 3, Universiti Teknikal Malaysia Melaka, Melaka.

Dvey-Aharon Z, Fogelson N, Peled A,Intrator N (2015) *Schizophrenia Detection and Classification by Advanced Analysis of EEG Recordings Using a Single Electrode Approach*.PLoS ONE 10(4): e0123033. doi:10.1371/journal.pone.0123033.

Omidvarnia, A., et al. (2011). Analysis of the Time-Varying Cortical Neural Connectivity in the Newborn EEG: A Time-Frequency Approach. *7th International Workshop on System, Signal Processing and their Application*. Australia, 978

S. B. Samdin, C. M. Ting, H. Ombao and S. H. Salleh, "A Unified Estimation Framework for State-Related Changes in Effective Brain Connectivity," in *IEEE Transactions on Biomedical Engineering*, vol. 64, no. 4, pp. 844-858, April 2017.

Lorenzo, G.D., et al,. (2015). Altered Resting-state EEG source functional connectivity in Schizophrenia: the effect of illness duration. *Frontier in Human Neuroscience*.9,234.

Moran, L.V., and Hong, L.E. (2011). High vs Low Frequency Neural Oscillations in Schizophrenia. *Schizophr. Bull.* 37,659-663.

Andreou, C., et al. (2015). Resting-state Theta-band Connectivity and Verbal Memory in Schizophrenia and in High-risk State. *Schizophr. Res.* 161,299-307.

Jetha, M.K., Schmidt, L.A., and Goldberg, J.O. (2009). Long-term stability of resting frontal EEG alpha asymmetry and power in a sample of stable community outpatients with schizophrenia. *Int. J. Psychophysiol*. 72,228-233.

OPEN ACCESS Freely available online
eISBN 978-967-0194-93-6 FBME