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A Study on Validity of Cortical Alpha Connectivity for Schizophrenia

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Abstract—**Abnormalities in schizophrenia are thought to be associated with functional disconnections between different brain regions. Most previous studies on schizophrenia have considered high-band connectivity in preference to the Alpha band, as there has been some uncertainty correlating the latter to the condition. In this paper we attempt to clarify this correlation using an Electroencephalogram (EEG) analysis of the Alpha band from schizophrenic patients. Global, regional Omega and dimensional complexity and local Omega complexity differentials (LCD) of single channel are calculated using 16 channels of resting EEG data from 31 adult patients with schizophrenia and 31 age/sex matched control subjects. It was found that, compared to the controls, anterior alpha Omega and dimensional complexity are higher in schizophrenia patients ($p<0.05$) with the single channel LCD also increasing at FP1, FP2, F7 and F8 electrodes. Furthermore, higher left hemisphere dimensional complexity and LCD at T3 point was also found. The results suggest there is lower connectivity in the prefrontal and left temporal regions with respect to the alpha band in schizophrenia patients.**

I. Introduction

Schizophrenia is a severe and chronic debilitating psychiatric disorder usually with the symptoms of delusions, auditory hallucinations, thought disorder [1]. The abnormal symptoms observed in schizophrenia are considered to be due to functional disconnections of neural networks or a disturbance in the coordination of information processing in the brain [2-3]. Researches on functional abnormalities in schizophrenia have suggested that specific brain regions might be related to the disorder. Therefore, functional disconnection between specific brain regions has attracted considerable attention. Most EEG based researches on disconnection have mainly focused on beta (13-30Hz) [4] and gamma (30-50Hz) bands [5], while the alpha (8-13Hz) band usually has been neglected.

However, alpha activity is a basic rhythm of the human brain, associated with attention, emotion, levelheadedness and cognition, so studying the connectivity with respect to this band may lead to important insights into Schizophrenia. Also, there are some studies indicate that alpha band has long-term stability in schizophrenics. Michelle K. Jetha et al. recorded EEG in schizophrenia [6] and they found that their resting frontal alpha asymmetry remained stable during two years. Edward L Merrin et al. also studied schizophrenics using alpha asymmetry and found that when under taking a task, patients had an overactive left hemisphere [7]. The above results indicate that the alpha band may be a useful tool to analyze the physiological and psychological state of schizophrenia.

In general, EEG analysis methods on schizophrenia mainly include conventional time-frequency domain methods and nonlinear dynamics approaches. EEG coherency is a common traditional method. A number of studies have examined the coherency across scalp-recorded EEG from subjects with schizophrenia, but the results were inconsistent [8-9]. Compared to traditional time-frequency approaches, the coordination of brain information processing can be more accurately estimated by nonlinear dynamic methods. Dynamic methods such as correlation dimension [10], the first Lyapunov exponent [11] and Lempel-Ziv complexity [10], have been used to investigate the differences between schizophrenic patients and controls. These methods have been used to reflect the degree of coordination present, but the results only reflect the time information of the EEG series. Since the spatial information has not been considered, the connectivity of cortical information processing has not been fully reflected. Approaches based on multichannel EEG could compensate for this inadequacy, as they are able to show the connectivity from different perspectives.

In our study, in order to give a comprehensive description of schizophrenic cortical EEG connectivity, the alpha band is extracted to study the connectivity from global, regional and local points of view. Dimensional complexity and Omega complexity are employed as parameters. Dimensional complexity is an approach that acquires a single value from global or regional channels to estimate the independence of brain activity. Omega complexity [12] was proposed by Wakermann to estimate the spatial cooperativity state of brain activity. Additionally, the LCD [13] is used to quantify the contribution of each channel to global synchronization from a local point of view. The advantages of our methods are as follows: 1) instead of time information associated with a single channel EEG, our features reflect time and spatial information of multichannel EEG in the same time; 2) the connectivity or coordination of various regions can be obtained; 3) the results are obtained from global, regional and local aspects will be evidenced by each other.

The paper is organized as follows. In section 2 we describe the selection of subjects, the procedure of EEG recording and signal pre-processing. The algorithm of dimensional

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complexity, Omega complexity and LCD are also introduced in section 2. Section 3 presents the results of our study. In section 4 we discuss our results. Conclusion of this study will be given in section 5.

II. Materials and Methods

A. Subjects

31 outpatients with schizophrenia and 31 age/sex matched control subjects participated in this study. Schizophrenic patients ranged in age from 18 to 31 (25.3±4.5 year, mean±std) and control subjects ranged in age from 23 to 27 (25.9±4.2 year, mean±std). Schizophrenic patients were recruited from Lanzhou Psychiatry Hospital. All of them were diagnosed as paranoid schizophrenia according to the DSM-IV criteria and BPRS (Brief Psychiatric Rating Scale, Ventura, Green, Shaner & Liberman, 1993). Control subjects were healthy individuals with no history of psychiatric or neurological disease and no first degree relatives had been diagnosed with schizophrenia disorder. They were selected from 37 volunteers. All subjects were self-reported right-handers. Subjects with history of alcohol or drug abuse, head trauma, cerebral disorders or other homogeneous disease that might affect brain functions were excluded.

B. EEG Recording and Signal Pre-processing

For the alpha rhythm reaches its maximum during relaxed, wakefulness with closed eyes, the subjects sat on a comfortable sofa in a quiet recording room in a relaxed state with eyes closed. According to 10-20 international standard system, EEG signals were recorded with Ag/AgCl electrodes from 16 locations (FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6), referenced to earlobes. For each subject, their EEG signals were continuously collected for 3 minutes. The sampling frequency was 200Hz. All raw data we got were filtered with a band-pass of 0.2-35Hz by EEG recording equipment.

Raw EEG signals from subjects are generally contaminated with artifacts, such as baseline wander, power-line interference, failing electrode, eye movement, electromyography (EMG), electrocardiography (ECG) and electrooculography (EOG). In order to remove these artifacts, for each subject, the continuous 25 seconds (5000 points) EEG data with the least artifacts were selected from the raw EEG signals. Then, the selected continuous 25 seconds EEG signals were filtered by a FIR band pass filter with 2-35Hz cut off frequency, and then a wavelet transform was applied to remove eye movement and EOG [14].

C. Feature Extraction

After the EEG signals are recorded and denoised, the features are extracted. The features of three regions are calculated to compare the connectivity of the two groups. Specifically the regions are: (1) Global regions, including all recorded electrodes; (2) Regional regions, including left hemispheric (FP1, F3, F7, C3, T3, P3, T5, O1), right hemispheric (FP2, F4, F8, C4, T4, P4, T6, O2), anterior (FP1, FP2, F3, F4, F7, F8) and posterior (P3, P4, T5, T6, O1, O2) areas; (3) Local regions, every single electrode. For the global and regional areas, Omega and dimensional complexity are calculated. For the local areas, the LCD of every single channel is estimated. To examine the differences between the two groups, a two-tailed t-test was done based on the above features. After statistical analysis, a ROC curve is employed to test the ability of the features to differentiate schizophrenic patients from normal controls.

Dimensional complexity: The classic correlation dimension (D2) measures the dynamic characteristics of a single EEG channel. However, the EEG spatial dynamics are not taken into consideration by this metric. The Dimensional complexity is required to include the influence of spatial position, giving a more comprehensive measure of the dynamic characteristics of the EEG signals. According to Wackermann [15], the Dimensional complexity is calculated the same way as the classic correlation dimension, but without reconstructing the multidimensional state-space.

Omega complexity and LCD [12-13]: Wackermann proposed a method to calculate Omega complexity based on multichannel inputs. Omega complexity estimates the complexity of multichannel brain electric filed data to reflect the spatial synchronization with respect to global or regional brain regions. For computation of the Omega complexity, the K*K covariance matrix (namely C) between the signals (recorded from the K channels) is calculated firstly.

$$C = \frac{1}{N}\sum_{i=1}^{N} u_i * u_i^T \quad (1)$$

Here, N stands for sampling points, N=5000, u_i is voltage vectors of ith channel.Then the normalized eigenvalues ($\lambda_i^{'}$) are computed.

$$\lambda_i^{'} = \lambda_i / \sum \lambda_i \quad (2)$$

Here, i represents ith channel, and λ_i are the eigenvalues of covariance matrix C. Omega is then computed using the formula:

$$\Omega = \exp\{-\sum_{i=1}^{K} \lambda_i^{'} * \log(\lambda_i^{'})\} \quad (3)$$

Small values of Omega indicate a strength connectivity or synchronization, and vice versa. The value range of Omega is $1 \le \Omega \le K$.

To estimate local contributions to Omega complexity, LCD is calculated. The kth-channel LCD is defined as:

$$LCD_k = \log(\Omega) - \log(\Omega_k^-) \quad (4)$$

Here Ω is the Omega complexity calculated with all recorded channels (16), and Ω_k^- is the Omega complexity calculated by excluding kth-channel. $LCD_k < 0$ indicates that the kth-channel signal is well correlated with the other signals and therefore reduces the global complexity of the data, and vice versa.

III. Results

The results are analyzed statistically using SPSS 17.0.0. Differences between the two groups are analyzed using t-tests. A two-tailed P value of less than 0.05 is considered significant. Those features with significant variance are then evaluated as discriminators using ROC curves.

A. Global and Regional Regions

The global and regional results of Omega and dimensional complexity are shown in TABLE I. The schizophrenic patients show a significantly higher Omega value (p=0.000) in the anterior region. As to dimensional complexity, compared with controls, the global (p=0.047), anterior (p=0.037) and left (0.014) regions alpha dimensional complexity is significantly higher in schizophrenic patients.

B. Local Regions (LCD of Single Channel)

The 16 electrodes topography map of average local Omega complexity values in 8-13Hz for schizophrenia and controls are showed in Figure 1, and the corresponding P value of each channel is displayed in Figure 2. The two groups have a significant variation in frontal (Fp1, p=0.006; Fp2, p=0.001; F7, p=0.011; F8, p=0.049) and left temporal regions (T3, p=0.020). Compared with controls, schizophrenic patients have an increased LCD in the frontal and left temporal areas.

C. ROC Curve

The ROC (Receiver Operating Characteristic) curve is evaluated by means of a plot of sensitivity versus 1-specificity using a continuously varying decision threshold [16]. The Area under the ROC Curve (AUC) estimates the probability of a correct classification. The value of AUC ranges from 0.5 to 1. The precision of classification is considered to be poor with a value of AUC between 0.5 and 0.7, good between 0.7 and 0.9, and excellent when higher than 0.9. TABLE II summarizes the results with AUC larger than 0.7. The Omega complexity of the anterior region has the highest sensitivity (90.9%), the highest accuracy (77.90%) and the highest AUC (0.822). The highest specificity (96.8%) is obtained from the local complexity of FP1.

IV. Discussion

In this study, all results are based on the study of EEG alpha rhythms, for brain activities in the alpha band are functionally related to arousal, emotion, cognition and attention. As symptoms of schizophrenia are generally manifested as dysfunction in these same aspects, the study of abnormal alpha band patterns would be expected to be related in some way. In this paper, we explore the Omega and dimensional complexity of schizophrenia patients in alpha band, which describe the global and regional characteristic of brains electric field. Omega reflects the spatial synchronization of the brain, while dimensional complexity estimates the independence of brain activity. Both of the two features demonstrate the global and regional connectivity of schizophrenic EEG series. Thus, the results from Omega and dimensionality measurements should corroborate each other, giving a reliable benchmark to the results. Moreover, LCD is an approach which can decompose the global spatial complexity of brain activity into local/regional contributions while retaining the global context. Together, Omega, dimensional complexity and LCD provide a comprehensive set of measurements to study global, regional and local aspects of alpha band activity in the brain.

TABLE I. T-TEST RESULTS OF OMEGA AND DIMENSIONAL COMPLEXITY

Location	Omega complexity			dimensional complexity		
	CG	***SG***	***P***	***CG***	***SG***	***P***
Global	3.258	3.710	0.078	4.178	4.497	0.047*
Anterior	1.845	2.480	0.000*	3.215	3.443	0.037*
Posterior	2.631	2.586	0.722	3.279	3.388	0.296
Left	2.367	2.533	0.236	3.201	3.495	0.014*
Right	2.187	2.307	0.390	3.042	3.230	0.176

a. The mean and P values of global and regional Omega, together with dimensional complexity(P values ≤ 0.05 are marked by '*')

TABLE II. ROC RESULTS OF FEATURES

Features	Threshold	Sensitivity	Specificity	Accuracy	AUC
Anterior Omega	1.832	90.3%	65.5%	77.90%	0.822
Left Dimension	3.324	74.2%	67.7%	70.95%	0.703
FP1 of LCD	0.054	45.2%	96.8%	71.00%	0.720
FP2 of LCD	0.045	51.6%	93.5%	72.55%	0.750

b. The ROC values for features in different regions that have significant differences between the two groups and the AUC is larger than 0.7.

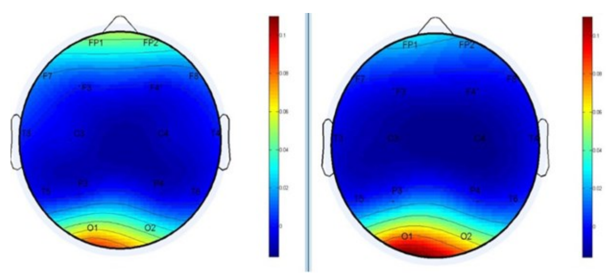

Figure 1. The topography map of schizophrenic patients' and normal controls' average LCD.

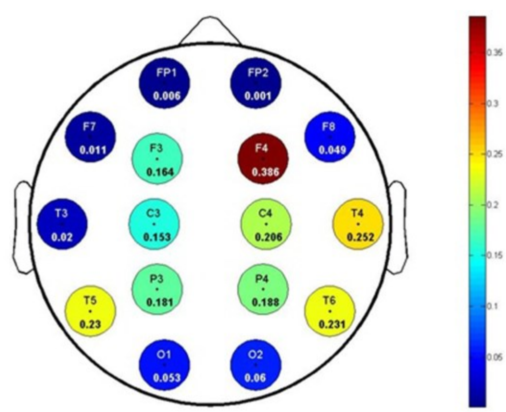

Figure 2. The P values of 16 single channels' LCD between two groups

According to TABLE I, our results from alpha Omega complexity are consistent with that from dimensional complexity, and both results show significantly higher value in schizophrenics than controls. A higher Omega complexity indicates that schizophrenics may have increased spatial complexity or a decreased spatial synchronization. A larger dimensional complexity reflects an increased independence of co-occurring processes. Both of these can be considered as a loosened coordination or decreased connectivity in anterior areas. So we may draw the conclusion that schizophrenics show functional disturbances in the anterior regions manifested as a loosened connectivity of brain information processes. Meanwhile, the increased frontal alpha LCD found in our results also gives strong evidence of aberrant anterior alpha connectivity in the schizophrenic brain. Higher frontal LCD indicates that the frontal EEG signals in schizophrenics have abnormal increased independence. The results from LCD highlight the aberrant alpha connectivity in schizophrenics, and indicate that the frontal channels (FP1, FP2, F7 and F8) are dominant channels which cause loosened coordination in the anterior area. The aberrant anterior alpha activity is in agreement with the studies of alpha asymmetry [6], decreased alpha EEG coherency [7].

We also found abnormalities in the left hemisphere regions. Both the alpha dimensional complexity and LCD in the left hemisphere are significantly higher. The higher dimensional complexity shows that schizophrenic patients have higher independence of brain information processes in the left hemispheric regions than normal controls. These results of LCD indicate that in comparison with other left channels, T3 has the least correlation with other channels, which demonstrates functional disturbance in the left temporal area and T3 is the main channel which causes this disturbance. Again, our results are consistent with earlier EEG studies that considered the complexity or connectivity of the schizophrenic left brain areas. Guenther [17] reported that the left hemisphere area was closely related to schizophrenic behavior. Breakspear [18], using nonlinear independence to analyze schizophrenic EEG, found that differences between schizophrenics and controls were obvious in the left intra-hemispheric regions. Our results are compatible with the above studies, and directly point to T3 as being the dominant location which contributes to the left regions' aberrant connectivity.

For global regions, the global complexity is significantly higher in schizophrenics, which may be caused by the aberrant regional (anterior and left regions) independence of brain activity.

In conjunction with the statistical analysis, a ROC curve was employed to distinguish the features with the greatest statistical differences with respect to sensitivity, specificity and accuracy. In this study, the highest accuracy (77.90%) and AUC (0.822) are obtained from the alpha Omega complexity of anterior regions. Thus, we conclude that the anterior Omega complexity is a superior feature to distinguish schizophrenics from normal controls.

V. CONCLUSION

Global and regional Omega dimensional complexity and single channel LCD have been used to analyze the coordination or connectivity of information processing of schizophrenics in the alpha band. Historically, schizophrenic information processing in higher bands such as the beta (13-30Hz) and gamma (30-50Hz) bands has been used to assess the connectivity among different cortical regions. In contrast we focus on the alpha band connectivity by calculating the Omega and dimensional complexity.

The results indicate that in the alpha band, compared with normal controls, patients with schizophrenia have abnormal connectivity or coordination in anterior and left hemisphere regions, and the dominating electrodes which lead to disordered functional connectivity in alpha band in patients are FP1, FP2, F7, F8 and T3. Therefore, we conclude that the dysfunctional connectivity associated with the information processing in the alpha band are mainly caused by the disconnections of prefrontal and left temporal regions.

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REFERENCES

[1] American Psychiatric Association (1994). American Psychiatric Association: diagnostic and statistical manual of mental disorders: DSM-IV: Washington, DC.

[2] Friston, K.J., Frith, C.D., "Schizophrenia: A disconnection syndrome?" *J.Sci. Clin.Neurosci,* Vol.3 (2) 89-97, 1995.

[3] Phillips, W.A., Silverstein, S.M., "Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia," *J.Sci. Behav. Brain Sci,* Vol.26, pp.65–82, 2003.

[4] Yeragani, V.K., Cashmere D., Miewald J., Tancer M., Keshavan M.S., "Decreased coherence in higher frequency ranges (beta and gamma) between central and frontal EEG in patients with schizophrenia: A preliminary report," *J.Sci. Psychiatry Res,* Vol.141, pp.53-60, 2006.

[5] Riečanský, I., Kašpárek, T., Řehulová, J., Katina, S., Přikryl, R., "Aberrant EEG responses to gamma-frequency visual stimulation in schizophrenia," *J.Sci. Schizophr Res,* Vol.124, pp.101–109, 2010.

[6] Jetha, M.K., Schmidt, L.A., Goldberg, J.O., "Long-term stability of resting frontal EEG alpha asymmetry and power in a sample of stable community outpatients with schizophrenia," *J.Sci. Int J Psychophysiol,* Vol.72, pp.228–233, 2009.

[7] Merrin, E.L., Floyd, T.C., "Negative symptoms and EEG alpha in schizophrenia: a replication," *J.Sci. Schizophr Res,* Vol.19, 151-161, 1996.

[8] Michelogiannis, S., Paritsis, N., Trikas, P., "EEG coherence during hemispheric activation in schizophrenics," *J.Sci. Eur Arch Psychiatry Clin Neurosci,* Vol.241, pp.31–34, 1991.

[9] Nagase, Y., Okubo, Y., Matsuura, M., Kojima, T., Toru, M., "EEG coherence in unmedicated schizophrenic patients: Topographical study of predominantly never medicated cases," *J.Sci. Biol Psychiatry,* Vol.32, pp.1028 –1034, 1992.

[10] R¨oschke, J., Fell, J., Beckman, P., "The calculation of the first positive Lyapunov exponent in sleep EEG data," *J.Sci. Electroencephalogr Clin Neurophysiol,* Vol.86, pp.348 -352, 1993

[11] Zhao, Q.L., Hu, B., Liu, L., Ratcliffe, M., Peng, H., Zhai, J.W., "An EEG based nonlinearity analysis method for schizophrenia diagnosis," *Biomedical Engineering,* pp.764-137, 2012.

[12] Wackermann, J., “Towards a quantitative characterisation of functional states of the brain: from the non-linear methodology to the global linear description,” *J.Sci. Int. J.Psychophysiol,* Vol.34, pp.65–80, 1999.

[13] Kikuchi, M., Hashimoto, T., Nagasawa, T., Hirosawa, T., Minabe, Y., Yoshimura, M., Strik, W., Dierks, T., Koenig, T., “Frontal areas contribute to reduced global coordination of resting-state gamma activities in drug-naïve patients with schizophrenia,” *J.Sci. Schizophr Res,* vol.130, pp.187-194, 2011.

[14] Hu, B., Majoe, D., Ratcliffe, M., Qi, Y.B., Zhao, Q.L, Peng, H., Fan, D.P., Zheng, F., Jackson, M., Moore, P., “EEG-Based Cognitive Interfaces for Ubiquitous Applications: Developments and Challenges,” *J.IEEE Xplore. Intelligent Systems,* Vol.26, no.5, pp.46 – 53, 2011.

[15] Wackermann, J., Lehmann, D., DvoraÂk, I., Michel, C.M., “Global dimensional complexity of multi-channel EEG indicates change of human brain functional state after a single dose of a nootropic drug,” *J.Sci. Electroencephalogr Clin Neurophysiol,* Vol.86, no.3, pp.193-198, 1993.

[16] Zweig, M.H., Campbell, G., “Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine,” *J. Clin Chem,* Vol.39, no.4, pp.561–577, 1993.

[17] Guenther, W., Breitling, D., “Predominant sensorimotor area left hemisphere dysfunction in schizophrenia measured by brain electrical activity mapping,” *J.Sci. Biol Psychiatry,* Vol.20, no.5, pp.515-532, 1985.

[18] Breakspear, M., Terry, J.R., Friston, K.J., Harris, A.W.F., Williams, L.M., Browm K., Brennan K., Gordon, E., “A disturbance of nonlinear interdependence in scalp EEG of subjects with first episode schizophrenia,” *J.Sci. Neuroimag,* Vol.20, no.1, pp.466–478, 2003.