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Graphic patterns of cortical functional connectivity of depressed patients on the basis of EEG measurements

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***Abstract*—Considerable evidences have shown a decrease of neuronal activity in the left frontal lobe of depressed patients, but the underlying cortical network is still unclear. The present study intends to investigate the conscious-state brain network patterns in depressed patients compared with control individuals. Cortical functional connectivity is quantified by the partial directed coherence (PDC) analysis of multichannel EEG signals from 12 depressed patients and 12 healthy volunteers. The corresponding PDC matrices are first converted into unweighted graphs by applying a threshold to obtain the topographic property in-degree (K_{in}). A significantly larger K_{in} in the left hemisphere is identified in depressed patients, while a symmetric pattern is found in the control group. Another two topographic measures, i.e., clustering coefficients (C) and characteristic path length (L), are obtained from the original weighted PDC digraphs. Compared with control individuals, significantly smaller C and L are revealed in the depression group, indicating a random network-like architecture due to affective disorder. This study thereby provides further support for the presence of a hemispheric asymmetry syndrome in the depressed patients. More importantly, we present evidence that depression is characterized by a loss of optimal small-world network characteristics in conscious state.**

***Index Terms*—Depression, electroencephalogram, partial directed coherence, α-waves, small-world network.**

I. Introduction

Over the last decade, the development of non-invasive methods based upon hemodynamic or electro-magnetic measurements improved our understanding of the activation of cerebral areas underlying different cognitive and/or psychotic states. According to [1], increased left frontal alpha power, suggesting a left-hemispheric hypo-activation, is believed to be a stable trait-like marker of depression. Since then, several studies have confirmed that depressed patients show an asymmetric pattern of cortical activation [2], [3]. The default asymmetric mode of depressed patients is mainly based upon the finding of a relative decrease in neural activity. Nevertheless, direct evidence for temporal correlation of resting-state neural activity between different cortical regions is lacking. Moreover, a number of key questions still remain, chief among them is whether the hypo-activation in the left frontal cortex shows an abnormally organized or disrupted cortical connectivity pattern in depressed patients. One possible way to address this question is to study the correlation between signals of brain activity collected from different cortical regions. In this regard, functional connectivity which describes the interactions between different cortical regions with both the direction and the strength of the information flow, is viewed as central for comprehending the organized behavior of cortical regions beyond the simple mapping of their activity [4].

A number of approaches have been proposed to estimate the functional connectivity which have led to a new insight into understanding inter- and intra-hemispheric interactions under various physiological or psychopathologic conditions [5]. Among these estimators, partial directed coherence (PDC) analysis, which is a representation of Granger causality [6] in the frequency domain, is of particular interest because of its ability to distinguish direct and indirect causal influence regardless of any common disturbing influences or sources [7]. PDC analysis thereby offers an opportunity for quantitatively analyzing and comparing the straightforward functional connectivity of the depressed patients. In our previous study, a lower frontal cortical interdependence within the beta band (13-30 Hz) was demonstrated in depressed patients in a resting state as well as a mental arithmetic task [8]. Indeed, considerable evidence has reported the loss of functional connectivity in depression [9]; however, it is still unclear how the decrease of functional connectivity is associated with a change in the global organization of the cortical network. Therefore, to extend the previous study, the graph theoretic analysis is employed in the present study to evaluate the PDC networks, when the participants are in an eye-closed wakeful resting state.

In graph theory, networks can be represented with interconnected nodes/vertices (Fig.1). Hence, graph theoretical metrics such as in-degree (K_{in}), clustering coefficient (C) and characteristic path length (L) could be employed to quantify the functional connectivity networks [10], [11]. According to [12], a graph with many relatively short connections and few random long distance connections is designated as a "small-world" network, which is often associated with the presence of clustering, denoted by high values of C and a short L [11], [12]. There have been indications that such a network pattern, may be more efficient in exchanging information on both a local and a global scale [13]. Over the last decade, a variety of biological and technological networks have been shown with small-world

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features [10], [11]. Most recently, Stam and colleagues evidenced a loss of the optimal small-world features in the functional connectivity networks of Alzheimer's patients [14]. Therefore, in this study we are going to address the following questions by means of PDC analysis and graphic indexes: is the functional connectivity abnormally organized in depressed patients under conscious state? If so, what is the "architecture" of functional connectivity networks in depressed patients?

II. Methods & Materials

A. Subjects

A total of 24 subjects participated in this study: 12 right-handed patients experiencing their first reported episode of depression (male/female=7/5, age: 37.2 ± 11.8 years) referred to the Shanghai Mental Health Center and 12 right-handed age- and gender-matched control subjects (male/female=6/6, age: 37.5 ± 11.7 years) without history of depression or any other psychopathology. All depressed subjects fulfilled CCMD-3 (F32: depressive episode, Chinese Psychiatric Association, 2001) and ICD-10 (the 10^{th} revision of International Classification of Diseases) diagnostic criteria and were not on any medication for 10 days before the experiments. Informed consent was obtained from each subject, which was approved by the local ethics committee in compliance with the Declaration of Helsinki.

B. EEG recording

Continuous EEG was acquired with Ag-AgCl electrodes at Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, and T6 (Fig.1(a)), complying with the international 10-20 system with the reference to linked earlobes using a 16-channel EEG system (Model: Sunray, LQWY-N, Guangzhou, China). EEGs were recorded in an acoustically and electrically shielded room while participants remaining seated in a resting state with their eyes closed for 5 min. The raw EEG recordings for each subject were digitized at 100 Hz with a 12-bit A/D converter and filtered into 0.5-30 Hz. Data containing eye blinks, excessive muscle activity, and movements of electrodes in the recordings were manually removed in an offline visual analysis. For computational simplicity, we created a data set containing reliable artifact-free 2048 samples of 16 channel EEG activity and only one recording per subject was selected for the further analysis in this study.

C. Functional connectivity estimation and graph theoretic analysis

The functional connectivity was estimated with PDC between all pair-wise combinations of EEG channels [7]. PDC quantifies the directed interdependence of Granger causality between any two signals in a multivariate set at each frequency. Mathematical details of PDC have been described in previous paper [8]. Given the relative temporal stability of alpha asymmetry and its potential relation to deficits in depression [1]–[3], rhythmic patterns of activity in the (8-13 Hz) range seemed to be an appropriate physiological signal for investigating functional connectivity patterns of depressed patients. Hence, the mean values within the alpha band, referred as αPDC hereafter, were

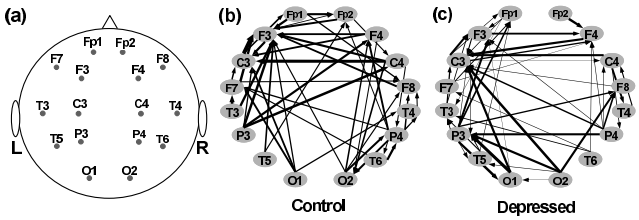

Fig. 1. Average connectivity networks for control subjects (b) and depressed patients (c) obtained from PDC in the alpha frequency band under conscious resting conditions. They show the 20% of the greatest connections in each group. Here only edges shared by at least four experimental subjects are shown. Flows direction is represented by an arrow, while intensity is coded by its width. Schematic image of the international 10-20 system, indicating the positions of the electrodes investigated in the present study is also demonstrated (a).

first compared with the threshold in the same frequency band following the procedure described in [20]. Then, significant greater ($p < 0.05$) causal interdependence formed an $M \times M$ (M=16 in this study) matrix B, where each element B_{ij} contains the value of the αPDC from the channel j to i. Based upon the αPDC matrix of all pair-wise combinations of electrodes, three graph theoretical measures, e.g., K_{in}, C, and L were derived to investigate cortical connectivity patterns of depressed patients.

1) In-degree and asymmetry pattern: Since there have been several reports [1]–[3] of hypo-activation of the left frontal lobe of depressed patients, we intend to demonstrate that decreased activity in the left cortex represents abnormal communication to other brain areas. To this end, the mean K_{in} in two hemispheres, i.e., ($K_{in-left}$, $K_{in-right}$), were employed to test asymmetry in cortical networks. The K_{in} of a specific vertex i (K_{in_i}) is the total number of afferent connections towards the node i, and the arithmetical average of K_{in} of all nodes within a region of interest (ROI) is denoted as the mean K_{in}: $K_{in} = \Sigma_i K_{in\_i}/N_{nod}$, where N_{nod} is the total number of vertexes in the ROI. K_{in} has a clear functional interpretations, i.e., a high K_{in} indicates that a neural region is influenced by a large number of other areas [11], [16]. To obtain K_{in}, the weighted digraph is converted into a binary one by applying a threshold. For example, when B_{ij} exceeds a threshold value, an edge is considered to exist from the node j to node i. A wide range of threshold, between 0.14 and 0.30 with step increment of 0.02, was initially employed to obtain the asymmetric hemisphere K_{in} pattern.

2) Clustering coefficient and characteristic path length for a weighted digraph: The clustering coefficient is an index of the local inter-connectedness of the graph whereas the characteristic path length is an indicator of its overall connectedness [11]. Optimal brain functioning requires a balance between local specialization and global integration [10]–[12]. Most graph theory studies to date have used symmetrical measures to construct undirected binary graphs, however, neglect the important weight and direction information [10]. Hence, the weighted directed networks from the αPDC matrix were derived to compute the weighted clustering coefficients (C_w) [17] and characteristic path length (L_w) [11]. Briefly, the binary clustering coefficient for a vertex i is the ratio between the number of triangles in the graph with i as one vertex and the number of all possible triangles that

it could have formed. The C_w of node i, in addition, incorporates the weights of edges into the calculation:

$$C_{w\_i} = \frac{\sum_{j\neq i}\sum_{h\neq i;h\neq j}(B_{ij}^{1/3}+B_{ji}^{1/3})(B_{ih}^{1/3}+B_{hi}^{1/3})(B_{jh}^{1/3}+B_{hj}^{1/3})}{2[(A^T+A)_i((A^T+A)_i-1)-2A_{ii}^2]} \quad (1)$$

where $B_{ij}^{1/3}$ is the cubic root of each elements from the asymmetric weighted αPDC matrix and A is the adjacency matrix ($A_{ij(i\neq j)}$=1 for $B_{ij(i\neq j)} \neq 0$). Then the weighted clustering coefficients of the graph could be obtained by averaging C_{w_i} over the M vertices: $C_w = \Sigma_i C_{w\_i}/M$.

For a weighted digraph, the path with the minimum number of edges may not be the the optimal one. Hence, the definition of the characteristic path length of a weighted graph could be extended as the smallest sum of the edge lengths throughout all the possible paths from i to j [11]. In this study, the length of an edge is defined as the reciprocal of the edge weight, i.e., $1/B_{ij}$, which thereby could be employed to obtain the distance matrix (D) and L_w:

$$L_w = \frac{\sum_{i\neq j} D_{ij}}{M(M-1)} \quad (2)$$

According to their definition, both C_w and L_w depend not only upon network structure but also on network size and edge weights. Specifically, a lower level of mean αPDC could influence the calculation of C_w and L_w, regardless of structure changes in networks. To obtain the salient feature of the network structure in depressed patients, which is free from the effect of the network size and different mean level of edge weights, C_w and L_w are normalized with those of a weighted-edge preserved random network, C_w/C_w^{random} and L_w/L_w^{random}.

D. Statistical analysis

Statistical analysis is done with SPSS15 for MS-Windows. Significant difference between the K_{in} calculated in the two populations is tested with ANOVA. Specifically, a one-way ANOVA is initially employed to obtain the statistical difference of K_{in} in both groups. The factor is GROUP (depressed *vs*. control). Moreover, two separate ANOVAs with the factor HEMISPHERE (left *vs*. right) are conducted to investigate the asymmetric pattern for both groups. A student paired t-test is also performed to test the difference of clustering coefficients and characteristic path length for both groups. All analysis were performed with the significance level set at 0.05.

III. Results

As an example of the estimated networks for the two groups, Fig.1 demonstrates the average functional connectivity calculated in the α frequency band. The figure shows the average intensity of 20% of the greater connections for each group. Compared with the depressed patients who present an asymmetric pattern (Fig.1(c)), the control group shows a trend of stronger cortical connectivity and a symmetric pattern of functional connectivity among various cortical regions (Fig.1(b)). However, the "architecture" difference between both groups is hard to obtain through examining the original graphs. Therefore, a graph theoretical approach was employed to quantitatively characterize the topographical properties. Here, the graphs in Fig.1 only represent group average results and serve primarily for display purpose.

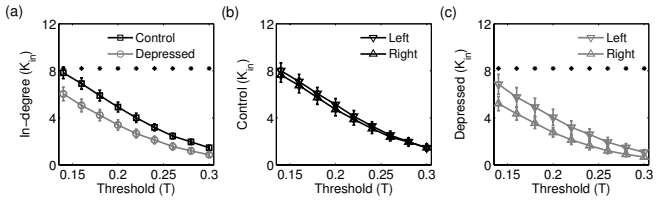

Fig. 2. (a) Average in-degree (K_{in}) for the depressed patients (gray circles) and the control subjects (black squares) as a function of threshold values $T(0.14 \leq T \leq 0.30)$. Error bars correspond to standard error of the mean (SEM). Asterisk indicates the threshold values at which the difference between the two groups is significant ($p < 0.01$). Compared to depressed patients, K_{in} is statistically higher in the control group. To evaluate the asymmetry of different hemispheric functional connectivity, K_{in} is divided into two parts: $K_{in-left}$ (down-triangle)and $K_{in-right}$ (up-triangle) for control (b) and depressed (c) subjects. An asymmetric pattern is identified in depressed patients, while no statistical difference is detected between $K_{in-left}$ and $K_{in-right}$ in control group.

The mean K_{in} as a function of threshold for the two groups and two hemispheres is presented in Fig.2. ANOVA performed on the parameter K_{in} from two groups shows significant difference for the factor GROUP (F=28.37, $p < 0.001$). Post-hoc tests reveal a consistently smaller ($p < 0.01$) K_{in} of depressed patients for the whole threshold range (Fig.2(a)), indicating a significantly lower level of functional connectivity in depressed patients. According to [18], the decreases of cortical thickness, neuronal sizes and neuronal and glial densities mainly in the frontal cortex of the depressed patients could result in the reduced cortical functional connectivity. This result later had also been confirmed by functional imaging (PET) studies [19]. More importantly, statistical analysis of asymmetric pattern for both groups reveals distinct results. For instance, significant difference for the factor HEMISPHERE (F=10.33, $p = 0.003$) is disclosed in depressed group. Moreover, post-hoc tests reveal a significantly ($p < 0.01$) greater $K_{in-left}$ for the whole threshold range (Fig.2(c)), while no statistical difference between $K_{in-left}$ and $K_{in-right}$ is uncovered in the control group (Fig.2(b)). These findings point in the direction similar to the previous electrophysiological studies which report a left hemispheric hypo-activation in depression [1]–[3]. More importantly, the asymmetry of $K_{in-left} > K_{in-right}$ suggests that the left hemisphere should be significantly influenced by its right counterpart in depressed patients, which is in agreement with the theory of hemispheric lateralization in the expression and the experience of emotion [21].

TABLE I

The ratios between real graph theoretical attributes (C_w, L_w) and those derived from weighted-edge preserved random networks (C_w^{random}, L_w^{random}). 100 surrogate random networks are generated to obtain the average C_w^{random} and L_w^{random} for each subject.

		C_w/C_w^{random}	L_w/L_w^{random}
Present study † (8-13 Hz)	Control	1.09	1.10
	Depressed	1.05*	1.07*
Stam and others (2009) (8-10 Hz)	Control	1.07	1.19
	Alzheimer	1.04	1.08

† Numbers are group average values.
Significant difference is shown with: * for $p < 0.05$.

It has been suggested that a small-world network represents an optimal pattern of complex systems in terms of low "wiring costs", local independence, global integration, and resilience to error [10], [11]. The implication is that a high level of clustering and short characteristic path length could deliver high-speed communication channels between distant parts of the system, thereby facilitating any dynamical process that requires global coordination and information flow [13]. Table I represents the ratios between real graph theoretical attributes (C_w, L_w) and those derived from weighted-edge preserved random networks (C_w^{random}, L_w^{random}). Compared with control subjects, significantly smaller values of C_w/C_w^{random} and L_w/L_w^{random} (Student paired $t-$test, $p < 0.05$) were evidenced in the depressed patients, indicating a loss of the optimal small-world network features. These results are comparable to a recent work by Stam and colleagues on the graph theoretical analysis of functional connectivity in Alzheimer's disease [14]. It was proposed that the depression could be a disorder with a distributed property of large scale functionally connected (sub-)cortical systems [19]. This view is well agreed with the modern concept that affective disorder is an anomaly in autonomic and functional connectivity [22] such as Parkinson's disease [23], schizophrenia [24], and Alzheimer's disease [14].

IV. Conclusion

This electro-neurophysiological study employed the PDC analysis to investigate the straightforward cortical functional connectivity patterns of depressed patients under conscious resting conditions. By characterizing this topography into a few summary graphic statistics, we found that depression was characterized by a hemispheric asymmetry syndrome and a randomized neural network feature. These findings thereby extend a previous study which reported a loss of small-world network properties of sleep neuronal functional networks in depressed patients [9]. Although EEG signals have poor spatial resolution in the present study, the depression related cortical regions investigated are consistent with previously reported functional neuroimaging results [19]. Nevertheless, utilization of high resolution EEG recording is encouraged for future attempts to replicate these discrimination effects. The emerging field of complex brain networks provides some of the first quantitative insights into general topological principles of cortical organization. Graph theory offers a nascent opportunity in the proper interpretation of functional connectivity between cortical regions in cognition or affective disorders, providing a potentially useful tool for diagnosis and therapeutic assessment in affective disorders.

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