Graph-Theoretical Analysis in Schizophrenia Performing an Auditory Oddball Task

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Abstract—**The aim of this research was to study the organization of the brain functional network during an auditory oddball task in schizophrenia (SZ). Electroencephalographic (EEG) activity was recorded from 31 schizophrenic patients and 38 healthy controls. In a first step, coherence was used to estimate the similarity between the spectral content of each pair of electrodes. In a second step, a graph was generated from the similarity matrix and two network parameters were computed: the clustering coefficient and the path length. Our results indicate that SZ patients obtained lower clustering coefficient and longer path length variations between the baseline and the P300 response than controls. These findings suggest an abnormal organization of the brain functional network in SZ.**

Keywords—**Schizophrenia, coherence, graph network, clustering coefficient, path length.**

I. INTRODUCTION

Schizophrenia (SZ) is a psychiatric disorder of cognition, characterized by a cognitive processing dysfunction [1]. It is accompanied by hallucinations, delusions, loss of initiative and cognitive impairments. Recent formulations have defined SZ as a disconnection syndrome, associated to a reduced capacity to integrate information between different brain regions [2]. Some studies have addressed the interpretation of functional connectivity in SZ. Magnetic resonance imaging (MRI) studies have shown morphological abnormalities of regional gray matter structures [3].

Neural oscillations are the main mechanism for enabling coordinated activity during normal brain functioning [4]. Oscillations in high frequency ranges (beta and gamma) establish synchronization in local cortical networks, whereas lower frequency ranges (delta, theta and alpha) modulate long-range synchronization [4]. Coherence has been widely applied to electroencephalographic (EEG) signals to analyze the functional connectivity between brain regions [5]. A further approach to study the complex organization of the human brain network is the application of the "network theory" principles. A graph is a mathematical representation of a network, which is essentially reduced to nodes and connections between them. The use of a graph-theoretical approach has been considered potentially relevant and useful, as demonstrated on several sets of brain functional networks [6]. Graph network analysis offers information about integration, segregation, connectivity and overall organization of brain networks. For this regard, its application to study SZ revealed several neural network changes [3, 5–9]. Most of these studies have focused on resting state [8] or two-back working memory task [5–7]; however, the auditory oddball paradigm has been used in few researches [9].

In the present study, the coherence was used to generate connectivity/similarity patterns between the spectral content of EEG activity from different electrodes. The aim of this research was to characterize some neuropathological alterations associated with SZ, during an auditory oddball task, by means of graph network theory.

II. MATERIALS

A. Subjects

Sixty-nine subjects were enrolled in the study. Thirty-one were SZ patients, including 20 chronic stably treated patients (CP) (12 men and 8 women, age = 40.4 ± 10.4 years, mean ± standard deviation, SD) and 11 minimally treated patients (MTP) (7 men and 4 women, age = 33.5 ± 9.9 years, mean ± SD). MTP had not received any previous treatment prior to their inclusion (first episode patients) or they had dropped their medications for longer than 1 month. The diagnosis was made according to Diagnostic and statistical manual of mental disorders (DSM-IV) criteria and the patients' clinical status was scored using the Positive and Negative Syndrome (PANSS). The control group was formed by 38 healthy volunteers (23 men and 15 women, age = 33.7 ± 13.1 years, mean ± SD).

B. EEG Recording

EEG recordings were acquired while subjects were relaxed and with eyes closed. An oddball 3-stimulus paradigm was employed with a 500 Hz-tone target, a 1000 Hz-tone distracter and a 2000 Hz-tone standard stimulus.

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The experiment was composed by a random series of 600 tones with probabilities of 0.20, 0.20 and 0.60, respectively.

The EEG was recorded using a BrainVision® equipment (Brain Products GmbH; Munich; Germany) formed by 17 tin sensors mounted in an electrode cap according to the 10/20 International System. Recordings were re-referenced to the average activity of all active sensors and the sampling rate was 250 Hz. EEG signals were filtered between 1 and 70 Hz and a 50 Hz notch filter was applied to remove power line noise. Artifact rejection was conducted following a two-steps approach. Firstly, Independent Component Analysis was carried out to decompose the signal in 17 components. Components related to eyeblinks were discarded. Secondly, artifacts were automatically rejected using an adaptive thresholding method. To complete the preprocessing, each EEG recording was divided into 800 ms–length epochs from -250 ms to 550 ms with respect to the stimulus onset (200 samples per epoch).

III. METHODS

A. Coherence Measure

In order to quantify the differences in the spectral content between EEG sensors, the coherence was applied. Coherence is a measure to assess functional interplays between pairs of cortical regions [10]. It describes the strength of the correlation between two time series as a function of frequency [11]. The mean square coherence (MSC) between two signals corresponds to their cross–spectral density function normalized by their individual auto–spectral density functions [10].

$$MSC_{XY}(t,f) = \frac{\left|S_{XY}(t,f)^2\right|}{S_{XX}(t,f)\cdot S_{YY}(t,f)}. \quad (1)$$

Rappelsberger et al. [12] proposed a coherence estimation to retain temporal information, named event-related coherence (ERC). ERC is based on the assumption that the same patterns of physiological activity are repeated at the same latency trial to trial [12]. To obtain a time course of coherence, each EEG epoch (200 samples) was divided into temporal segments of 41 samples with a 90% overlapping. Then, 32 time intervals were obtained and coherence was calculated as described above. Finally, ERC values were averaged in the six conventional frequency bands: δ (1-4 Hz), θ (4-8 Hz), α (8-13 Hz), β_1 (13-19 Hz), β_2 (19-30 Hz) and γ (30-70 Hz).

B. Graph Theory

The brain can be assimilated to a complex anatomical and functional network. Hence, it can be represented by means of a graph. A graph is defined as a number of nodes or vertices and the corresponding edges between them [13]. The value of each edge depends on the importance of the relationship between the nodes [12, 13].

Coherence is limited from 0 to 1. The higher the coherence values, the higher the correlation between the spectral content. Hence, coherence values can be applied directly to the edges of a graph analysis. Then, a network with N=17 vertices (corresponding to the 17 electrodes) can be defined and ERC values between two electrodes be used to establish the edges weights (denoted as w^b_{ij}, where b denotes the frequency band). A graph can be characterized using several parameters [11]. In this research, the clustering coefficient and the average path length were used. These parameters measure the nature of structural building blocks and subnetworks, and the sensitivity to the level of integration in a network, respectively [11].

The clustering coefficient of a vertex i, C_i, reflects the presence of triangles (complete subgraphs of three vertices) in networks [11, 14]. It should be noted that symmetry is required ($w^b_{ij} = w^b_{ji}$) and $0 \le w^b_{ij} \le 1$ [14]. These constrains are fulfilled by ERC. Therefore, the clustering coefficient for the vertex i at each frequency band is defined as,

$$C_i^b = \frac{\sum_{k\neq i}\sum_{\substack{l\neq i\\ l\neq k}} w_{ik}^b \cdot w_{il}^b \cdot w_{kl}^b}{\sum_{k\neq i}\sum_{\substack{l\neq i\\ l\neq k}} w_{ik}^b \cdot w_{il}^b}, \quad b=\{\delta,\theta,\alpha,\beta_1,\beta_2,\gamma\}. \quad (2)$$

The average clustering coefficient, C_W, for the whole graph at each frequency band is defined as the average of the clustering coefficient in the 17 nodes.

The path length is defined as the average number of edges of the shortest path between pairs of edges. The length between two vertices i and j is defined as the inverse of the weight between them: $L_{ij}^b = 1/w_{ij}^b$ if $w_{ij}^b \neq 0$, and $L_{ij}^b = +\infty$ if $w^b_{ij} = 0$ [14]. The path length between two vertices is then defined as the sum of the lengths of the edges of this path. The shortest path L^b_{ij} between two vertices i and j is the path between i and j with the shortest length [14]. Equation (3) shows the average path length of the entire graph at each frequency band. It is calculated using the harmonic mean. Hence, it takes into account infinite path lengths between isolated nodes (i.e. $1/\infty \rightarrow 0$) [14].

$$L_W^b = \frac{1}{\frac{1}{N\cdot(N-1)}\cdot\sum_{i=1}^{N}\sum_{j\neq i}^{N}\frac{1}{L_{ij}^b}}, \quad b=\{\delta,\theta,\alpha,\beta_1,\beta_2,\gamma\} \quad (3)$$

C. Parameter Baseline Correction

In order to achieve a stimulus-independent characterization, a baseline correction process has been carried out. A pre-stimulus value was obtained by averaging the values in the interval (-250 0) ms. Likewise, a response value was obtained considering the (150 450) ms post–stimulus interval. The baseline correction was then carried out using the "percent change from baseline" method [15]. For that purpose, pre-stimulus mean value was subtracted from response value and the result was divided by the pre–stimulus value for each subject.

D. Statistical Analysis

Initially, the exploratory analysis revealed that data did not meet parametric test assumptions. Afterwards, a two level statistical analysis was made. Firstly, a Wilcoxon signed rank test (α=0.05) was used to analyze the evolution in each group. In a second step, statistical significance between groups was assessed by means of Mann-Whitney *U*–tests (α=0.05).

IV. RESULTS AND DISCUSSION

Mean values of clustering coefficient and path length were calculated from each graph, obtaining the temporal evolution of these parameters. In a first step, a Wilcoxon signed rank test was applied to analyze the differences between the baseline and the P300 response. As Table 1 shows, controls reached a statistically significant increase in C_W^{δ} (p<0.0001) and C_W^{θ} (p=0.0021), as well as a decrease in $C_W^{\beta_2}$ (p=0.0020), between the P300 response and the baseline. On the other hand, Table 2 shows the path length obtained at each frequency band. A significant decrease of L_W^{δ} (p=0.0032) between the P300 response and the baseline was obtained in CP group. In the control group, the P300 response showed higher values of L_W^{δ} (p<0.0001) and L_W^{θ}

Table 1 Clustering coefficient (mean ± SD) at baseline and P300 response for each group. Only the frequency bands with statistically significant results are displayed. Significant p-values are marked with asterisks (*, p<0.05; **, p<0.01; ***, p<0.0001).

Group	Segment	Frequency band δ	θ	β_2
CP	Baseline	0.32 ± 0.07	0.35 ± 0.08	0.30 ± 0.10
	P300	0.34 ± 0.08 *	0.35 ± 0.07	0.30 ± 0.09
MTP	Baseline	0.32 ± 0.09	0.37 ± 0.10	0.30 ± 0.08
	P300	0.34 ± 0.09	0.38 ± 0.08	0.28 ± 0.07 *
C	Baseline	0.33 ± 0.10	0.34 ± 0.10	0.31 ± 0.12
	P300	0.37 ± 0.09 ***	0.38 ± 0.08 **	0.30 ± 0.11 **

Table 2 Path length (mean ± SD) at baseline and P300 response for each group. Only the frequency bands with statistically significant results are displayed. Significant p-values are marked with asterisks (*, p<0.05; **, p<0.01; ***, p<0.0001).

Group	Segment	Frequency band δ	θ	β_2
CP	Baseline	3.45 ± 0.74	3.12 ± 0.59	3.78 ± 0.98
	P300	3.25 ± 0.73 **	3.12 ± 0.47	3.78 ± 0.94
MTP	Baseline	3.60 ± 0.96	3.12 ± 0.65	3.81 ± 0.77
	P300	03.35 ± 0.91	2.95 ± 0.51	3.92 ± 0.68
C	Baseline	3.54 ± 0.94	3.31 ± 0.69	3.71 ± 0.98
	P300	3.15 ± 0.75 ***	3.01 ± 0.51 ***	3.91 ± 1.06 ***

(p=0.0002), as well as lower values of $L_W^{\beta_2}$ (p=0.0009), than the baseline segment. These results suggest that the brain network features are altered during the auditory oddball task [9].

In a second step, baseline correction was calculated for each subject and results were statistically analyzed using Mann-Whitney *U*–tests. Figs. 1 and 2 summarize the mean clustering coefficient and path length at each frequency band for each group, respectively. They represented the relationship between the P300 response and baseline, expressed in percent of change. A positive value indicates that the P300 value is higher than the baseline value. On the contrary, a negative value indicates a lower P300 value than the baseline value. As Fig. 1 shows, a statistically significant higher ΔC_W^{θ} (p=0.0283) was obtained in controls in comparison with CP. On the other hand, Fig. 2 depicts that controls obtained statistically significant lower ΔL_W^{θ} (p=0.0049) than CP.

Previous studies have reported that statically significant lower C_W values in SZ imply relatively sparse local connectedness of the brain functional networks [5]. Interactions between interconnected brain regions are believed to be a basis of human cognitive processes [8]. Short absolute path lengths have been demonstrated to promote interactions between and across different cortical regions [8]. The higher ΔL_W^{θ} obtained by controls in comparison with CP, may indicate that information interactions between interconnected brain regions are slower and less efficient in SZ [8]. Thus, the lower clustering coefficients and the longer path length obtained by CP in comparison with controls support the SZ disconnection hypothesis and may indicate an abnormal organization of the brain functional network [5, 9].

Finally, some aspects of the present research merit further consideration. Additional work is required to compute other connectivity measures and to extract other network parameters, like centrality, efficiency or modularity. In addition, it could be interesting to examine the assessment of regional patterns.

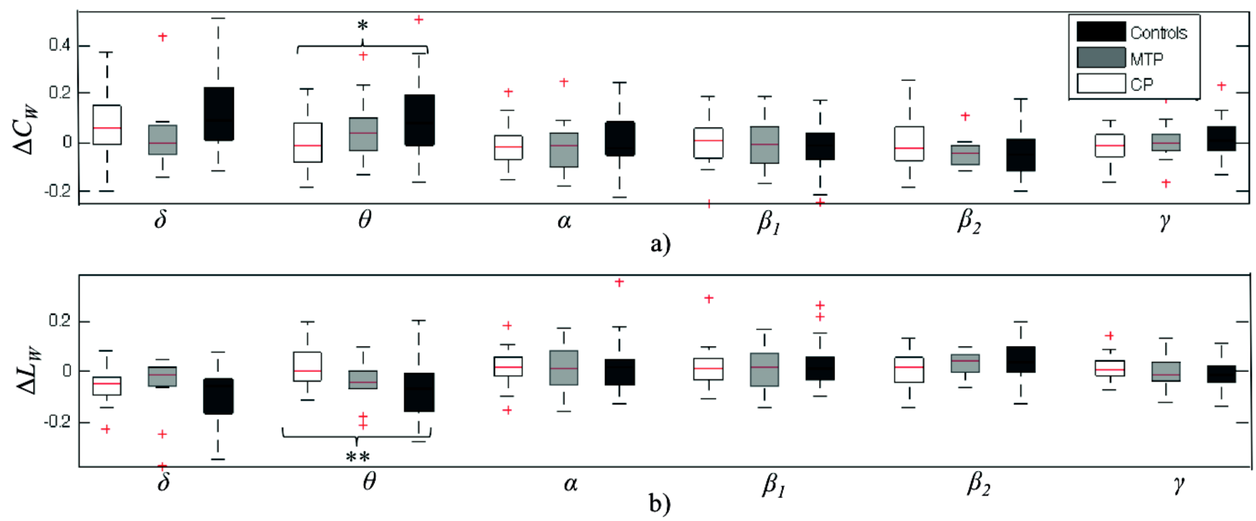

Fig. 1 Boxplot displaying the percent of change for the network parameters in CP, MTP and controls groups. a) Clustering coefficients (ΔC_W) for each frequency band. b) Path length (ΔL_W) for each frequency band. Statistically significant *p*-values are marked with asterisks (*, $p<0.05$; **, $p<0.01$)

V. Conclusions

Our research analyzes the application of ERC to generate a graph, useful for characterizing the organization of brain networks. Our findings support the notion that SZ is a disconnection syndrome, showing frequency-dependent neural network alterations.

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References

1. Weinberger DR, Egan MF, Bertolino A et al. (2001) Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 50:825–844
2. Friston KJ (1998) The disconnection hypothesis. Schizophr Res 30:115–125
3. van den Heuvel MP, Mandl RC, Stam CJ et al. (2010) Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. J Neurosci 30: 15915–15926
4. Uhlhaas PJ, Singer W (2010) Abnormal neural oscillations and synchrony in schizophrenia. Nat Neurosci 11:100–113
5. Fallani FDV, Maglione A, Babiloni F et al. (2010) Cortical network analysis in patients affected by schizophrenia. Brain Topogr 23: 214–220
6. Micheloyannis S, Pachou E, Stam CJ et al. (2006) Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr Res 87:60–66
7. Bassett DS, Bullmore ET, Meyer-Lindenberg A et al. (2009) Cognitive fitness of cost-efficient brain functional networks. Proc Natl Acad Sci 106:11747–11752
8. Liu Y, Liang M, Zhou Y et al. (2008) Disrupted small-world networks in schizophrenia. Brain 131:945–961
9. Yu Q, Sui J, Rachakonda S et al. (2011) Altered small-world brain networks in temporal lobe in patients with schizophrenia performing an auditory oddball task. Front Syst Neurosci 5:1–13
10. Nunez PL, Srinivasan R, Westdorp et al. (1997) EEG coherency: I: statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. Electroenceph Clin Neurophysiol 103:499–515
11. Stam CJ, van Straaten ECW (2012) The organization of physiological brain networks. Clin Neurophysiol 123:1067–1087
12. Rappelsberger P, Pfurtscheller G, Filz O (1994) Calculation of event-related coherence—a new method to study short-lasting coupling between brain areas. Brain Topogr 7:121–127
13. Boccaletti S, Latora V, Moreno Y et al. (2006) Complex networks: structure and dynamics. Phys Rep 424:175–308
14. Stam CJ, De Haan W, Daffertshofer et al. (2009) Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. Brain 132:213–224
15. Roach BJ, Mathalon DH (2008) Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. Schizophr Bull 34:907–926

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