Brain Functional Connectivity in Parkinson's disease – EEG resting analysis

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Abstract— **Brain functional connectivity evaluates the statistical dependencies between spatially distributed brain regions. The patterns obtained from this analysis have been related to different cognitive processes and are altered by neurodegenerative diseases. Parkinson's disease (PD) is the second most frequent neurodegenerative disease and presents a combination of motor and cognitive disturbances. In this study the early changes in connectivity patterns in PD are evaluated. EEG was recorded at resting state with eyes closed in twenty-three patients with PD without cognitive decline (PD-CogNL) and twenty three healthy controls. Spectral coherence was estimated between electrode pairs in fronto-parietal and inter-hemispheric regions. Rhythms of interest were: delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz). Compared to controls, PD-CogNL had an increased coherence in frontal inter-hemispheric electrodes in delta and theta bands. In the fastest bands were found correlations between connectivity and executive function measured by INECO test. The results of this paper show early changes in frontal inter-hemispheric coupling in PD.**

Keywords—**Parkinson's disease, EEG, Functional Connectivity, Resting State, Coherence.**

I. Introduction

Normal cognitive functions are based on the integrated activity between distinct brain regions, and this is attained in essence by synchronization of distributed neuronal populations [1]. These events can be examined by studying interdependencies among signals from different brain regions [2], designated as functional connectivity [3]. Changes in brain connectivity patterns may be identified by different activation arrays within structural and functional networks linked to different cognitive processes [4]. Alterations in cortico-cortical synchronization, obtained by means of neurophysiological measures of functional connectivity, has been found in central nervous system diseases as Alzheimer's disease [5] multiple sclerosis [6], and schizophrenia [7].

Parkinson's disease (PD) is the second most frequent neurodegenerative disease and affects significantly life quality with a heterogeneous combination of motor and cognitive disturbances [8]–[10]. The physiopathological mechanisms in PD lead to a disruption in segregated cortico-thalamic circuits, which would be directly related to the various clinical features of the disease [11]. Changes in the activity of the cortical components of these circuits should alter the normal connectivity patterns with other cortical areas and might be expressed in modulation of cortico-cortical coupling indices. Although scarce, EEG studies in PD subjects show that resting state cortical synchronization measures can differentiate not demented PD individuals from healthy controls [12], and suggest that connectivity indices could be sensitive to different therapeutic interventions [13], [14]. Nevertheless, there is a lack of evidence about the early EEG connectivity changes in PD populations without objective cognition impairments, and it is unclear the association of the electrophysiological signature and the early cognitive dysfunction related to PD [15]. In this paper we analyze functional connectivity at rest in patients with PD classified as cognitively preserved and healthy controls. We sought to determine whether there are early changes in cortico-cortical coupling, and its relationship with executive function, which has been seen to be affected from the beginnings of the disease.

II. Methodology

A. Subjects

Twenty-three patients with PD without cognitive decline (PD-CogNL) and twenty three healthy controls matched for age, gender, and educational level were recruited. PD was diagnosed by an expert neurologist according to the criteria of the United Kingdom PD Society Brain Bank [16]. PD progression stage was determined with the Hoehn & Yahr scale (H&Y) [17], and motor disability was assessed with section III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) [18]. Moreover, all participants underwent an extense neuropsychological evaluation to appraise global cognitive efficiency and to exclude the coexistence of mild cognitive impairment (MCI) or dementia. The patient's cognitive screening was performed using the Montreal Cognitive Assessment (MoCA) [19], a reliable psychometric instrument which has shown to be capable to identify MCI in PD [20], [21], and that has been validated in the Colombian population [22]. The executive function was evaluated with the INECO frontal screening test [23]. Exclusion criteria were the presence of Parkinson-plus symptomatology, other neurological disorders, major psychiatric conditions or current use of psy-

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choactive drugs that could alter the EEG brain activity. Inclusion criteria for the PD-CogNL group were spared functional independence and a MoCA score of 23 or above. All PD patients were taking antiparkinsonian medication and were evaluated during the "on" phase of medication. Subject characteristics are listed in Table 1. Informed consent for participation was obtained from all subjects according to the protocol approved by the Human Subjects Committee of the Universidad de Antioquia.

Table 1 Subject characteristics (Mean ± Standard Deviation)

Item	PD-CogNL	Control	P-value
N	23	23	
Age (years)	60.74 ± 9.39	61.17 ± 7.93	0.4409
Gender (F/M)	8/15	8/15	
Education (years)	11.78 ± 5.05	12.35 ± 4.58	0.3490
Disease duration (years)	4.6 ± 2.84	N.A	
H&Y	2.1 ± 0.38	N.A	
UPDRS-III	28.3 ± 12.32	N.A	
MoCA	26.57 ± 1.56	27.26 ± 1.51	0.0686
INECO	20.89 ± 2.46	23.13 ± 2.78	0.0030

H&Y: Hoehn and Yahr rating scale. UPDRS-III: motor part of the Unified Parkinson's Disease Rating Scale. MoCA: Montreal Cognitive Assessment. INECO: Instituto de Neurología Cognitiva test. NA: not applicable.

B. EEG acquisition

EEG signals were recorded at awake resting (eyes closed, 5 minutes). The EEG was recorded with 58 tin electrodes (positioned according to the international 10-10 system) using the software and amplifiers Neuroscan (Scan 4.5, SynAmps2). The signal was digitized at a sampling rate of 1000 Hz and filtered online (bandpass filter: 0.05 to 200 Hz, and band reject filter 60 Hz to eliminate noise from the power supply). The reference acquisition consisted of an electrode located on the right earlobe, and an electrode located between Cz and Fz was used as ground.

C. EEG data pre-processing

It was implemented a semi-automated pre-processing pipeline using two MATLAB toolbox: EEGLAB [24] and the standardized early-stage EEG processing pipeline (PREP) [25], which includes a robust reference to average, where bad channels are excluded, and detection and interpolation of bad channels relative to this reference. The data were segmented into 2s epochs; and independent component analysis enhanced by wavelet was used to correct muscular and eye blinks artifacts [26]. Remaining bad epochs were rejected by a procedure based on linear trend, joint probability and kurtosis approach [27].

D. Functional connectivity analysis

Functional connectivity was estimated from spectral coherence function using the multi-taper spectral estimation method [28], available in Chronux MATLAB toolbox [29]. Despite coherence is affected by volume-conduction of remote EEG sources, and only captures the linear component of the functional coupling [30], we decided to use this analysis because EEG coherence is the most common methodological approach used in the study of several clinical applications [31]. The EEG coherence was calculated at all electrode pairs in six frequency bands: delta (1–4 Hz), theta (4–8Hz), alpha1 (8–10Hz), alpha2 (10–13Hz), beta1 (13–20Hz), and beta2 (20–30Hz), for 50 free artifacts epochs, which were randomly selected from each recording. Following previous studies [12], [15], we analyzed only the fronto-parietal functional coupling (intra-hemispheric) and callosal functional coupling (inter-hemispheric). The fronto-parietal electrode pairs of interest were F3–P3, Fz–Pz, and F4–P4, while the inter-hemispheric electrode pairs of interest were F3–F4, C3–C4, and P3–P4 (Fig. 1).

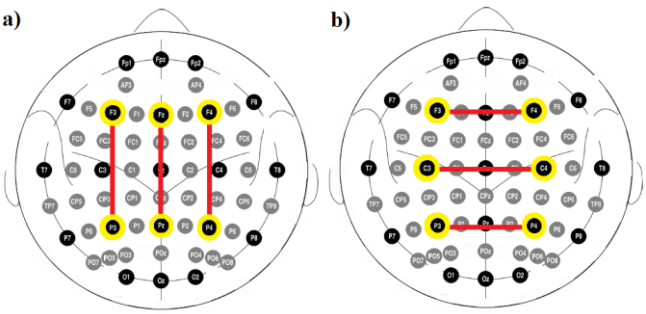

Fig. 1 a) Fronto-parietal (F3–P3, Fz–Pz, F4–P4), and b) Inter-hemispheric (F3–F4, C3–C4, P3–P4) pairs of electrodes. Electrodes positioned according to the International 10–10 System.

E. Statistical analysis

Differences between PD-CogNL and Control groups in connectivity measures for each frequency band were analyzed by means a non-parametric two-sample T-test, that uses permutations of group labels to estimate the null distribution [32]. Statistical significance used was $\alpha = 0.05$. P values were corrected for multiple comparisons using the false discovery rates method [33]. In order to complement P-values, we also estimated measures of effect size to calculate the magnitude of the difference between the groups [34], using the Hedges' g (standardized mean difference) [35]. In addition, we determined if there was any correlation between the functional connectivity and executive function using Spearman's rank correlation coefficient. All statistical analysis were implemented in MATLAB.

III. Results

There were no differences in demographic features (age, gender and education) or MoCA test, which indicates the good general cognitive state of the patients (Table 1). Difference in executive function between groups was found. PD-CogNL patients have a lower INECO scale compared to healthy controls ($p<0.01$). Regarding the connectivity analysis, no differences were found in fronto-parietal connectivity. In inter-hemispheric coupling there were significant differences in delta, theta and alpha2 bands (Table 2). Relative to the Control group, PD-CogNL had an increased coherence in frontal region in delta and theta bands, and a decreased coherence in parietal region in alpha2 band. Table 3 reports the Spearman's rank correlation coefficient between coherence and INECO score in all subjects considered as a whole group. There is a positive relationship with the fronto-parietal coupling for alpha1, alpha2 and beta1 bands. Conversely there is a negative relation between the inter-hemispheric coupling and INECO in parietal region for beta2 band.

Table 2 Control vs PD-CogNL - Inter-hemispheric connectivity

Band	Pair	P-value	Hedges	CI Bootstraped
Delta	F3-F4	0.0086	-0.8492	-1.5233 -0.2942
Theta	F3-F4	0.0135	-0.7844	-1.3805 -0.2501
Alpha2	P3-P4	0.0197*	0.6275	0.0529 1.3594

CI: confidence interval. *: P-value not corrected.

Table 3 Spearman's rank correlation coefficients

Connectivity	Band	Pair	P-value	r
Fronto-parietal	Alpha1	Fz-Pz	0.049	0.29
		F3-P3	0.024	0.33
	Alpha2	Fz-Pz	0.014	0.36
		F4-P4	0.011	0.37
	Beta1	F4-P4	0.048	0.29
Inter-hemispheric	Beta2	P3-P4	0.023	-0.33

r: correlation coefficient.

IV. Discussion

In this work we evaluated functional connectivity at rest in PD-CogNL patients and healthy controls. We found that PD-CogNL group showed mainly an increased inter-hemispheric coherence in frontal region in delta and theta rhythms. Also, a decrease is observed in parietal inter-hemispheric coherence in alpha2 band. In addition to these differences, we found relationship with executive function for the fronto-parietal and parietal inter-hemispheric connections. Previous studies have reported an increased coherence in non-demented PD patients (PD-ND) compared to controls mainly in theta and beta bands. Moazami et al [12], found enhanced coherence in PD-ND in frontal region in theta, high beta and gamma bands, and lower coherence in the parietal region around 10 Hz. Fonseca et al [15], only found an increase in inter and intra-hemispheric coherence in beta rhythm in demented PD patients (PDD) compared to PD-ND and controls. It has to be noted that the classification of PD-ND patients in previous studies included patients without cognitive impairment and patients with MCI. Our results confirm the increased coherence in theta band in frontal regions, which could be one of the first cortical locations disturbed in early stage of disease in patients, without the presence of cognitive impairment. Our work excludes patients with MCI and shows that neurophysiological changes occurs before cognitive impairment. It is possible that changes in higher rhythms are more related to cognitive decline with involvement of posterior components of cognitive large scale networks, as shown by decreased connectivity in inter-parietal alfa2 band and the correlations performed with executive function.

V. Conclusion

The results of this paper show early changes in frontal inter-hemispheric coupling in PD using EEG in resting state, a noninvasive methodology, easy to be carried out in clinical environment. This is a preliminary result of a broader analysis which involving the qEEG analysis in patients with PD with MCI, in order to search for markers to aid in the diagnosis, prognosis, and therapeutic control of PD patients.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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