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ASSESSMENT OF DEEP BRAIN STIMULATION ON GAIT IN PARKINSON DISEASE PATIENTS USING PRINCIPAL COMPONENT ANALYSIS

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Abstract: – **Principal component analysis (PCA) was applied to the vertical ground reaction force (GRF) for evaluating the effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on gait in Parkinson disease (PD). Thirty normal subjects (CG) and 15 PD subjects who underwent STN DBS were evaluated under four test conditions: stimulation alone, medication alone, stimulation with medication and without treatment. PCA was applied on the GRF, and six components were used for calculating a standard distance (SD). The treatment conditions moved SD from PD towards to CG values. PCA allowed quantifying the improvement on GRF in PD patients due to STN DBS, mainly when adopted in association with medications.**

Key-words**: Principal component analysis, Ground reaction force, Parkinson' disease, Deep brain stimulation**

Introduction

Parkinson disease (PD) is a neurodegenerative disorder characterized by bradykinesia, rigidity, tremor and postural instability. Gait hypokinesia is among the primary movement disorders associated with PD. The characteristic slow, short stepped, shuffling walking pattern results from a combination of constraints on locomotor control imposed by neurotransmitter imbalance [1].

Deep brain stimulation (DBS) of the subthalamic nucleus (STN), once considered an experimental treatment, is nowadays widely performed in advanced stages of PD. Many studies have showed the short-term effects [2-5]. More recently, four to five years follow-up studies were reported [6-8]. These reports found improvement on motor activities including gait and posture. However, the effectiveness of the STN DBS in PD patients has been limited to clinical motor scores, and few studies have employed quantitative analysis of the gait pattern [9-10]. Quantitative measurements can provide a reliable and objective alternative for assessing the effects of STN DBS. Additionally, multivariate statistical techniques reducing data complexity may increase the effectiveness of gait analysis, extracting useful information [11].

Principal components analysis (PCA) is a multivariate technique applied to reduce the dimensionality of a data set. This method provides a reduced set of uncorrelated variables by a linear transformation, retaining maximally the variances from the original data [12]. In gait analysis, this method is applied to classify normal and pathologic gait [13-16], as well as to obtain a quantitative index for measuring how closely an individual gait pattern approaches to normal [17-18].

The present study aims at testing the application of PCA in the vertical component of the ground reaction force (GRF) to evaluate the effects of STN DBS on PD patients with and without medication.

Method

A total of 15 PD patients (3 women and 12 men) with averaged age of 55.57 ± (8.25) participated in the study. All subjects had undergone bilateral STN DBS and were stable when the study was conducted. Average time since surgery was 15.06 (± 9.56) months and duration of the disease was 12.13 (± 4.31) years. A control group (CG) of 30 subjects (20 women and 10 men), without history of neurological illness, degenerative conditions, any general disease or medication that might interfere with normal balance and/or gait, with a averaged age of 50.1 ± 7.8 years was also evaluated. The study was approved by the Institutional Review Board of the University of Kansas Medical Center and each subject signed an informed consent.

For each PD subject quantitative gait measurement was obtained in two different days. In the first session, the subject had taken his/her usual doses of PD medications and stimulators were turned "on". The gait assessment was first conducted under medication and stimulation (mon-son). After the test, the stimulator was turned off for 30 minutes, and the measurements were repeated (mon-sof). In the second session, the subjects came to the laboratory without having taken any PD medication for at least 12 hours. Gait analysis was firstly conducted under stimulation (mof-son), and repeated after 30 minutes without stimulation (mof-sof).

Due to some problems in data collection, some subjects did not have GRF evaluated under all conditions. Then, it was evaluated 13 subjects on mof-sof (baseline), 12 on mof-son, 14 on mon-sof and 11 on mon-son conditions. Subjects from control group came to the laboratory just once and the gait test was performed.

Two AMTI force platforms (Advanced Mechanical Technology, USA) were used to measure the GRF. The sampled frequency was of 100 Hz. In this report, only vertical component of GRF was used in the analysis. The subjects practiced the walking trial at least five times before the experiment on an elevated walkway 12 cm above the floor. The force platforms were mounted in series at the middle of the walkway. The subjects walked at their self-selected speed and repeated the walking for five trials during the evaluation. The average of these trials was considered in analysis.

To minimize the effect of random noise, measured GRF was filtered using a digital, low pass, second order, Butterworth filter with 30 Hz cut-off frequency, as proposed by [19]. To prevent non-linear phase shifting a cascade forward-backward technique was performed. For each subject, the GRF was normalized by his/her body weight. The data was interpolated by cubic splines and resampled with 101 sample points per step, to normalize data according to the stance phase duration of the respective limb. Thus, each GRF from a complete stride (right and left side) was represented by 202 samples.

PCA method as described in [12] was applied to the covariance matrix of GRF from CG and PD subjects in baseline (mof-sof) condition. A broken stick test criterion was used for choosing the relevant principal components (PCs) for the analysis [12]. Similarly, the PC scores were obtained for the PD subjects in the treatment conditions (mon-sof, mof-son and mon-son). The first two PCs scores were considered to delimit an elliptical boundary with a 95% confidence interval for the CG. The two axes of the ellipse were obtained by PCA as proposed by Oliveira *et al*. [20]. This approach was used to allow visual interpretation of the data [12].

To obtain a measure of how far the PD subjects' gait was from CG, the standard distance proposed by Flury and Riedwyl [21] was calculated using all PC scores selected by the broken stick test. This parameter represents the distance between each observation and the center of the CG scores, normalized by the variance of each PC score. For classifying normal or abnormal GRF pattern, the cut-off point between the standard distance values from CG and PD group in mof-sof condition was obtained by logistic regression [22-23].

Non-parametric ANOVA for repeated measures (Friedman test) with missing data was applied to verify differences in the standard distance. Post hoc analysis was performed with the Dunn test. The significance level was set to $\alpha = 0.05$.

All signal processing procedures and statistical tests were implemented in Matlab 6.5 (The Mathworks, USA). The ANOVA and post hoc test were analyzed using SPSS software (SPSS, USA).

Results

The boundary generated by the first two PC scores by the elliptical contour of 95% confidence interval of CG showed a reasonable separation between CG and PD (Figure 1). This separation was mainly carried out by the first PC, which represented 53.9% of the total variance. The second PC accounted for 15.3% of the remaining variability.

The effect of treatments was assessed by the localization of the PD scores in each condition. In the no treatment (mof-sof) condition (Figure 1a) almost all subjects were located outside normal boundary. All subjects' data in the mof-son, mon-sof and mon-mon conditions (Figure 1b, 1c and 1d, respectively) moved towards to normal elliptical area, mostly with stimulation on. These results are evidences that STN DBS improves the GRF pattern of PD patients

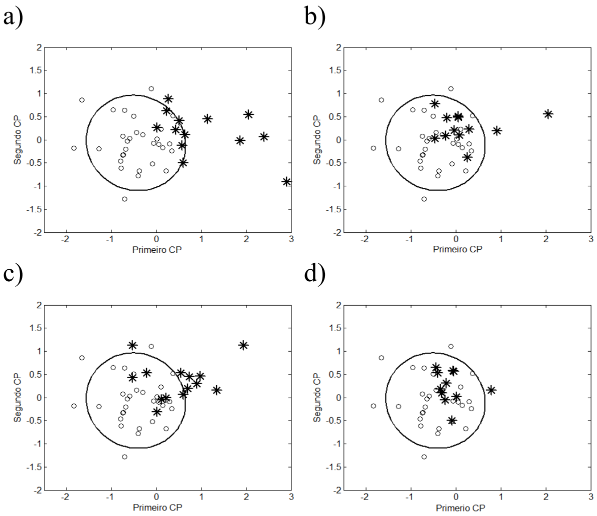

Figure 1 - Scatter plot of the first two PC scores of subjects from CG (○) and PD patients (*) in the four conditions: a) mof-sof, b) mof-son, c)mon-sof and d) mon-son. The elliptical boundaries correspond to 95% confidence interval of CG.

The broken stick test indicated that six PCs should be used, explaining 91.1% of the original data variance.

The normalcy threshold for standard distance values given by logistic regression was 3.57. Thus, distances higher than this value fell outside normal range (Table 1). In stimulation conditions, mof-son and mon-son, the standard distance showed smaller values with more subjects being classified as normals (Table 1). In the mof-sof condition, four subjects presented normal distances, while this number increased to six subjects in the mof-son condition, and eight in the mon-son condition. The Friedman's test showed a significant difference among conditions (p = 0.015), while the post hoc test showed a significant difference between mof-sof and mon-son conditions (Table 1).

Table 1 – Standard distance of PD in the four different conditions

Subjects	mof-sof	mof-son	mon-sof	mon-son
1	NA	5,58	6,50	NA
2	NA	NA	**3,34**	**2,68**
3	**3,31**	**1,94**	3,76	**2,88**
4	**2,57**	**2,41**	**3,13**	**3,50**
5	8,11	4,96	5,48	5,08
6	7,49	NA	5,80	NA
7	8,17	5,72	NA	NA
8	6,40	NA	6,55	NA
9	4,65	**2,62**	3,80	**2,83**
10	5,92	4,14	4,40	3,81
11	**2,20**	**2,78**	**2,98**	**2,69**
12	4,69	4,47	5,64	**3,42**
13	4,66	4,65	4,21	**2,11**
14	**3,16**	**2,77**	**2,55**	**1,85**
15	3,68	**2,71**	**3,22**	3,68
Mean ± SD*	5,00 ± 2,06	3,73 ± 1,33	4,38 ± 1,36	**3,14** ± 0,9

*Significant difference among conditions (ANOVA Friedman test, p = 0.015), mainly between mof-sof and mon-son conditions (Dunn post hoc test, p < 0.05). The cut-off point given by logistic regression was 3.57. Bold numbers are distances inside normalcy threshold. NA is not available.

Discussion

The quantitative evaluation of the GRF pattern between PD patients under four test conditions and CG was performed with the application of PCA. The plane produced by the first two PC scores allowed the visualization of each subject, as well as the effect of the treatments (Figure 1). PCA takes into account the complete time-series from GRF, maximizing the representation of original data variance, instead of focusing on only isolated measures, as performed in traditional parametric gait analysis.

The elliptical boundary of CG with 95% confidence interval allowed the visualization of the effects of treatments applied in the PD patients. This method also provided a reasonable separation between the CG and PD patients (Figure 2). The use of just two coefficients allowed easily describing the individual characteristics of each patient's GRF pattern, comprising 71.3% of original data variance. Additionally, it shows the parsimonious capability of the method [12]. Deluzio and Astephen [16], using two PC scores to classify 63 normal subjects and 50 patients with osteoarthritis, verified that PCA is a robust method to separate groups with different gait pattern. In early investigation using PCA, Yamamoto *et al.* [24] could also identify the characteristics of patients gait with the first two PCs.

Past studies have reported a higher gait speed and improved gait performance with stimulation alone and further improvement when combined with medication [9,25]. Similarly, the present results show a marked improvement in walking pattern with STN BDS. The PC scores from PD moved towards to the CG ones with the stimulation, both with and without medication. In this study, additional information was provided in mon-son condition by showing the PD scores inside the CG boundary (Figure 1d). According to Yamamoto *et al.* [24] the patients in a similar position on the gait evaluation plane should have similar gait ability.

The standard distance calculated by the first six PC scores represents an objective index to describe how far a PD patient's gait deviated from normal. This index also allowed the quantitative assessment of the results from different treatments. The STN DBS reduced the standard distance in both medication (mof-son and mon-son) conditions, increasing the number of patient who reached the normal distance (Table 1). Normalcy indexes were also proposed by others investigators [17-18] for quantifying the amount of deviation in a subject's gait from a normative data set. According to those authors, such indexes were sensitive enough to distinguish unimpaired subjects from patients with different involvements. Moreover, a normalcy index is clinically applicable, reliable and easy to use. Therefore, the standard distance is a valuable element in the quantitative evaluation of gait pathology. In the current study, such score showed adequate statistical discrimination when assumed as a single index for classifying the GRF from between CG and PD, evaluating the effect of the STN DBS.

Conclusion

Deep brain stimulation of the subthalamic nucleus showed effective improvement on vertical ground reaction force in patients with Parkinson disease, mainly when adopted in association with the regular daily dose of medication. Principal component analysis and the elliptical area given by the 95% confidence interval of a control group allowed delimiting a normalcy boundary, as well as an evaluation of gait improvements due to different treatments. Furthermore, the standard distance may be employed as a quantitative index for assessing the effects of treatments.

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