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Vestibular Spontaneous Response as a Potential Signature for Parkinson's Disease

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Abstract— **In this paper, we report on a new method for potential diagnosis of Parkinson's Disease (PD) based on the analysis of the spontaneous response of vestibular system recorded by Electrovestibulography (EVestG). EVestG data of 20 individuals with PD and 28 healthy controls were adopted from a previous study. The field potentials and their firing pattern in response to whole body tilt stimuli from both left and right ears were extracted. We investigated several statistical and fractal features of the field potentials and also their firing patterns. One-way analysis of variance (ANOVA) was used to select the features showing the most significant differences between individuals with PD and the age-matched controls. Linear Discriminant analysis classification was applied to every selected feature using a leave-one-out routine. The result of each feature's classifier was used in a heuristic weighted average voting system to diagnose PD patients. The weights of the voting system were the (posterior) probabilities calculated by the designed classifier to indicate a subject related to a specific class. The results show more than 97% accuracy for PD diagnosis. Given that the patients were at different stage of disease, the high accuracy of the results encourages the use of vestibular response for PD diagnosis as a plausible quick and non-invasive screening tool.**

I. Introduction

Idiopathic Parkinson's disease (PD) is the second largest neuro-degenerative disorder, and is estimated to afflict approximately 3% of the population over the age 65 [1]. It is not yet known how to prevent or cure PD but there are different treatments including medication, deep brain stimulation, and dopaminergic cell transplantation. Early diagnosis of PD would greatly assist its treatment by allowing administration of neuroprotective agents before the appearance of motor symptoms and while a higher percentage of dopamine nigral cells still remain [2].

Parkinson's disease belongs to a group of conditions called motor system disorders. It occurs as a result of a slow and progressive loss of dopaminergic neurons. The loss of dopaminergic neurons causes the reduction of dopamine neurotransmitters concentration in neural pathways and it weakens the motor cortex signals that coordinate muscle movement [2]. Currently, no early detection method exists for PD. Its diagnosis is based on the patient's medical history and neurological examination. A definite diagnosis of PD requires autopsy [2].

There is a link between dopamine and the vestibular system; dopamine receptors (D2) have been identified in medial vestibular nuclei and lateral vestibular nuclei [3]. Also, meaningful levels of dopamine have been detected in a region of the vestibular nuclei [4]. Abnormalities in the vestibular system have been previously documented in PD, in relation to an abnormal vestibular-ocular reflex [5].

Electrovestibulography (EVestG) [6, 7] is a non-invasive technique to record neural activity from the vestibular apparatus and vestibular nuclei. EVestG measures a vestibular driven response stimulated by passively whole body tilting the subject, who is seated in a special hydraulic chair located in an electrically and acoustically shielded chamber. The EVestG signal is recorded during dynamic and static phases via an electrode resting proximal to the tympanic membrane [6, 7]. The electrodes are simply and painlessly positioned and rested close to the left and right ear drums of the subject.

In previous studies on the use of EVestG for PD diagnosis the main width of the EVestG field potentials during the side tilt stimuli was found significant between the patients and controls [8], and also the correlation of this feature with the severity of PD was shown to be significant 9]. In our previous study [10], using the same data as in [8, 9], we found the Katz Fractal Dimension (KFD) of the timing intervals of the field potentials from the side tilt stimulus to be significant between the patients and controls. In our recent study [11], we used features extracted from both the field potentials and their time interval signals of the side tilt of the left and right ear data. Then, we applied linear discriminant analyses (LDA) classification for each of the statistically significant feature, followed by a heuristic voting classifier by averaging the vote of each of the single feature classifier. The results showed about 95% accuracy.

In this study, we followed the same steps as in [11] but with one main difference: we used a weighted average voting classifier, where the weighting coefficients were the posterior probabilities obtained for every subject in LDA classification algorithm. We treated every feature as a symptom with a weighting coefficient reflecting its diagnostic importance, and investigated whether this weighted average voting system would improve the overall accuracy.

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II. METHOD

A. Data

We used data from a previous study of ours [11], including data of 20 individuals with PD (65.8 ± 6.8 y, 10 males) and 28 healthy individuals (54.5 ± 7.7 y, 14 males). The PD patients' EVestG signals were recorded, while they had been off their medication (Levadopa preparations) for at least 4 hours and typically overnight. Among PD subjects, 6 were diagnosed to have PD's symptoms mostly on the right side, 5 on the left and 9 on both sides of their body. The severity of the disease was assessed using the Modified Hoehn and Yahr PD Staging Scale [12]. In this test, the tremor along with other initial signs (symptoms) was used to grade the severity of the disease. Future applications may look at separating other tremor syndromes. Based on this scale, one patient was severely affected (had the degree of severity of 5 out of 5), while the others were at mild to moderate stages (had the degree of severity of 1-3 out of 5). One of the PD subjects was excluded from the analysis because it was right affected and its left side data could not be used due to noise and artefact.

B. EVestG Experiment

The EVestG experiments [6, 7] include several tilting stimuli. We used the side tilt stimulus, in which almost the entire vestibular organ in the inner ear is stimulated. The side tilt stimulus has a duration of 120 s; it begins with a 20 s background recording, with the subject sitting in a still position without any inclination, followed by a 3 s tilt to the right (about 40 degrees), 17 s rest in the tilted position, 3 s moving back to center, 37 s rest at the center position, 3 s tilt to the left, 17 s rest at the left position, 3 s return to the center and 17 s rest at the center (Fig. 1). The periods of interest are 1.5 s before the movement, labeled as background (BGi), and the 3 s tilting stimuli. The first 1.5 s after the onset of the tilt is marked as OnAA and the next 1.5 s is marked as OnBB, representing acceleration and deceleration phases, respectively. Since the chair is tilting to both left and right sides while recording both right and left ears, there are both contralateral (CT) and ipsilateral (IP) stimuli in each tilt. The EVestG signal was recorded at the sampling rate of 41666 Hz. This high sampling rate was necessary as one of the components of EVestG signal (the Sp point) is only a few samples wide. The EVestG-evoked response field potentials were extracted using the Neural Event Extraction Routine (NEER) [13].

C. Signal Analysis

We used the EVestG field potential signals and their corresponding firing time interval signals of the BGi, OnAA, and OnBB segments of the tilts from center to either side. Given that signals of both ears were recorded, for every subject in each of the 3 segments, we had 4 signals: Contralateral left (CTL), contralateral right (CTR), ipsilateral left (IPL) and ipsilateral right (IPR); this resulted in 12 different shape and firing pattern signals for each subject. Figure 2 shows a typical EVestG field potential response signal of the OnBB segment for a CTL tilt of a control

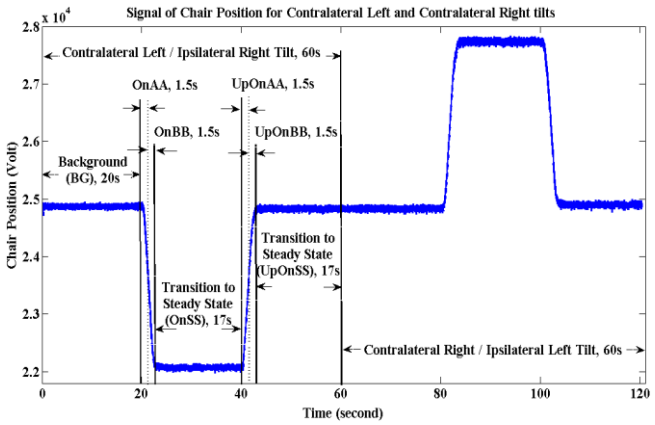

Figure 1. The pattern of the chair movement during the side tilt trial.

subject. The waveform's minimum point is called the action potential (AP) point, and the time duration of 3-6 ms before and after the AP can be assumed as the pre- and post-potential intervals (Fig 2.). The features were extracted from these two time regions in this study.

Moreover, we investigated the changes in the differences between BGi and either OnAA or OnBB segments to examine the effects of dynamic changes in response from resting to acceleration or deceleration, and also the differences between the two phases of movement. In addition, the difference between the right and left ears' signal were investigated to test for vestibular asymmetry. Given the two sides of recording, 6 segments in each recording and accounting for differences between dynamic and background segments in each type of tilt, overall we ended up with 48 signals to extract features for each subject. Since the NEER algorithm removes segments of the original signal that are corrupted by large artifact (due to hydraulic chair, muscle artifact, movements, etc.), not all the segments were of 1.5 s duration; we excluded the segments shorter than 1.36s. Therefore not every subject had all the extracted features; this was another reason to consider each feature as a symptom and develop a heuristic average voting classifier.

For PD subjects, who were unilaterally affected, only the EVestG signal of their opposite side was considered as the PD signal. Thus, we used left signals of the right affected PD subjects, right signals of left affected patients, and both right and left signals of bilateral PD patients. The following classes of features were calculated from every segment followed by a Statistical test of ANOVA [14]. In all statistical tests a *p-value* < 0.05 was considered significant.

1) Statistical Features

We calculated mean, mean of the absolute value and variance of the pre- and post-potential regions of every field potential signal. We also calculated the average power of the aforementioned intervals for the range of 100-11000 Hz. As for the firing time signals, we calculated the total number of firings and the variance of the histogram of the time intervals (Fig. 3).

2) Fractal Dimension

Katz Fractal dimension (KFD) is a geometrical measure of the signal's complexity representing the fractional

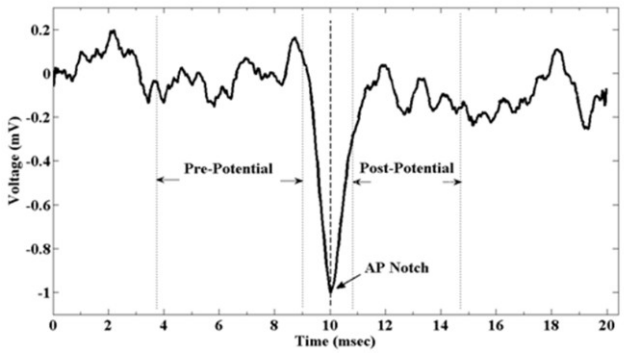

Figure 2. The EVestG field potential of OnBB segment for a CTL tilt of a control subject.

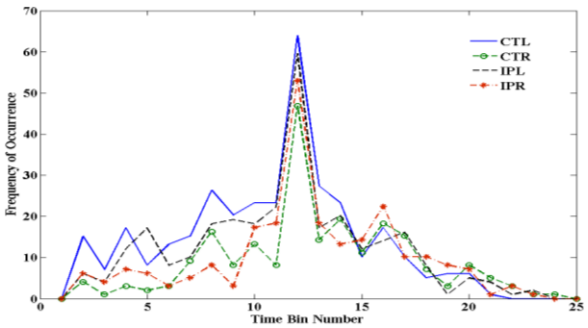

Figure 3. The histogram of the time interval signal for IPL, IPR, CTL, and CTR tilts for one control.

dimension of a self-similar (or self-affine) object [15]. We used Katz algorithm to calculate the FD values due to its robustness with respect to noise [16].

On the other hand, Entropy-based fractal dimensions, such as the Information dimension (DI) and the Correlation dimension (DC) are methods for characterizing the shape of self-affine objects/signals [17]. We used KFD, DI and DC fractal dimensions of the firing time and field potential signals of each segment for each subject.

3) Weighting Average Voting Classifier

Each feature was used in a single feature classifier using linear discriminant classification algorithm (LDA) [18]. Due to the small size of subjects and to remove any bias of over fitting problem, we used a leave-one-out routine [18] for training and testing the classifiers. As mentioned before, not all subjects had all the features (either due to artifacts or due to being unilaterally affected); therefore, we considered each feature as a symptom, and used a heuristic method of weighted average voting symptoms: each feature (symptom) was used with LDA classifier to assign the left-out subject (all other subjects were used as training dataset) as PD patient or healthy. LDA calculates two posterior probabilities (*pp*) (since we have only two groups of data), which shows the probability of the subject being as healthy or patient; these two *pp* values are normally used to classify the test subject to a class (the one with higher *pp* value). In our previous study [11] we assigned a vote of 0 or 1 for either healthy or PD patient groups and then averaged the votes across all the single classifiers. In this study, however, we averaged the *pp* values of all single feature classifiers and then classified the subjects as healthy or patient depending which of the average *pp* was higher. In another word, we used the *pp* values as the weighting coefficients for the votes and hence, the name of weighting average voting classifier was chosen. Our heuristic classification can be formulated as:

$$Ave\_pp^{H}(j)=\frac{\sum_{i=1}^{n} pp^{H}(i,j)}{n} \qquad (1)$$

$$Ave\_pp^{PD}(j)=\frac{\sum_{i=1}^{n} pp^{PD}(i,j)}{n},$$

where, j represent a subject, *pp(i,j)* is the posterior probability of feature *i* classifier for either healthy or PD groups. Obviously, $Ave\_pp^{H}(j)=1-Ave\_pp^{PD}(j)$. If $Ave\_pp^{H}(j)>Ave\_pp^{PD}(j)$, the subject is classified as healthy or vice versa. It should be noted that *n* is the number of available features/classifiers for each subject; therefore the value of *n* may differ between the subjects. In fact, one of the reasons to develop this heuristic method of classification was that not all subjects had all the characteristic features (due to noise or artefact in original signal).

III. Results

Table 1 shows the list of significant features and the original signals they were calculated from. It also shows the result of ANOVA for the selected features. The results of our heuristic classification showed 100%, 96.4% and 97.9% sensitivity, specificity and accuracy, respectively. This implies that all the PD patients (19 in total) were classified correctly. Only one control subject was misclassified. Further analysis such as Receiver-operator characteristic (ROC) with Area under the curve (AUC) might be suggested to validate the classifier [19].

We also tested the significance of the extracted features using a randomly selected 70% subset of the data. Nine out of the 18 features remained significant. However, we still used all the 18 features for classification since some subjects did not have all the features due to noise or because we had to use the signals of one side only (one side affected PD subjects). Also, due to small size of dataset there is no way to ensure which features are the final best characteristic features. Therefore, we used the ad hoc classification procedure as described. This extra test was performed to examine the plausible over-fitting of the selected features for the population of this study.

IV. Discussion

The extracted features are either calculated directly from the shape or time interval of the field potentials (group 1) or calculated from the differences between the segments or sides (group 2). Interpretation of the features of the first group is more straight forward; perhaps a larger population of data from a future study will provide a better interpretation for the 2nd group of features.

TABLE I. LIST OF SIGNIFICANT FATURES

Feature Name	Original Signal	p_value
Mean of Pre-Potential	BGi, CT(R)	0.023
Mean of Pre-Potential	BGi, CT(L-R)	0.013
Mean of Pre-Potential	BGi-OnBB, CT(L-R)	0.046
Mean of Post-Potential	BGi-OnAA, CT(L)	0.02
Mean of abs Pre-Potential	OnAA-OnBB, IP(L+R)	0.005
Mean of abs Pre-Potential	BGi-OnBB, IP(L-R)	0.03
Mean of abs Post-Potential	BGi, CT(R+L)	0.007
Variance of Post Potential	BGi-OnAA, IP(L)	0.0004
Variance of Post Potential	OnAA-OnBB, CT(L-R)	0.006
Average Power of Pre-Potential	OnAA-OnBB, IP(L-R)	0.03
Average Power of Post-Potential	OnAA, IP(L-R)	0.017
Number of Firings	OnBB, CT (R)	0.012
Variance of pdf of Time Interval signal	OnBB, IP(L-R)	0.025
Information Dimension of Pre-Potential	OnBB, IP(L-R)	0.03
Information Dimension of Post-Potential	BGi-OnAA, IP(L-R)	0.025
Correlation Dimension of Pre-Potential	BGi, IP(L-R)	0.018
Katz Dimension of Firing time signal	OnAA, IP(R)	0.02
Katz Dimension of Firing time signal	OnBB, IP(R)	0.03

Among the features related to the firing time signals, the FD values of the controls were higher than that of the PD patients, implying a higher complexity of the signals of the control group versus PD group. This observation was previously seen among the fractal dimension of pathological signals versus healthy signals [20, 21]. We may speculate that higher FD values in control subjects represent higher degree of self similarity implying a more synchronous firing among control subjects compared to PD subjects.

Another firing time feature, was the variance of pdf of the time interval signal that showed significantly larger values for PD subjects than controls. We assume that a neurological condition such as PD affects the neurons' firing pattern so that it may cause a different distribution compared to healthy neural firing.

Our heuristic classification method using the average posterior probabilities of the LDA signal feature classifiers showed high performance in terms of accuracy, sensitivity and specificity. For pathological signal diagnosis, we propose the use of such ad hoc voting classification as it is more reliable and logical; it is similar to the way a physician diagnoses a condition or disease. The main advantage of this method is that if a feature does not exist for a subject due to noise/artefacts, still that subject's data can be used and a diagnosis can be made. We had used a similar approach but using the average vote of the signal classifiers in our recent study [11]. However, the use of averaged posterior probabilities in this study instead of a vote of 0 or 1 used in [11] for final classification has increased the accuracy, and seems to be a more logical approach.

Overall, the results of this study shows a new potential of EVestG signals towards generating an adequate set of biofeatures for diagnosis, monitoring, and perhaps measuring the efficacy of drug treatment during early PD stages. The results may lead to a simple, objective, and non-invasive clinical assessment of Parkinson Disease.

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