# Principal Component Latent Variate Factorial Analysis of MER Signals of STN-DBS in Parkinson's Disease (Electrode Implantation)

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## Abstract

Although clinical benefits of deep brain stimulation (DBS) in subthalamic-nuclei (STN) neurons have been established, albeit, how its mechanisms improve the motor features of PD have not been fully established. DBS is effective in decreasing tremor and increasing motor-function of Parkinson's disease (PD). However, objective methods for quantifying its efficacy are lacking. Therefore, we present a principal component analysis (PCA) method to extract-features from microelectrode-recording(MER) signals of STN-DBS and to predict improvement of unified Parkinson's disease rating scale(UPDRS) following DBS (applied on 12 PD patients). Hypothesis of this study is that the developed-method is capable of quantifying the effects-of-DBS "on state" in PD-patients. We hypothesize that a data informed combination of features extracted from MER can predict the motor improvement of PD-patients undergoing-DBS-surgery. This shows the high-frequency-stimulation in diseased-brain did not damage subthalamic-nuclei (STN) neurons but protect. Further, it is safe to stimulate STN much earlier than it was accepted so far. At the experimental level, high-frequency-stimulation of the STN could protect neurons in the subsstantia-nigra (SN, an important element of the brain). Therefore, to test this hypothesis in humans, we need to perform STN stimulation at the very beginning of the disease so that we can predict the disease at an early-stage. The latent-variate-factorial is a statistical-mathematical technique PCA based tracking method for computing the effects of DBS in PD. Ten parameters capturing PD characteristic signal-features were extracted from MER-signals of STN. Using PCA, the original parameters were transformed into a smaller number of PCs. Finally, the effects-of-DBS were quantified by examining the PCs in a lower-dimensional-feature-space. This study showed that motor-symptoms of PD were effectively reduced with DBS.

## 1 Introduction

Parkinson's disease (PD) is a chronic disorder characterized by four primary cardinal symptoms, namely, resting tremor, bradykinesia, postural instability and rigidity. Currently, the diagnosis is based on the presence of clinical-features (i.e., symptoms and signs) and the response to antiparkinsonian medications [1–3].

The most established scale for assessing disability and impairment in PD-disease is the "Unified Parkinson's disease Rating Scale" (designated as UPDRS) [4] is based on subjective clinical evaluation of features. Hence, it is required to quantify PD characteristics objectively in order to enhance the prognosis, and prognostic diagnosis to identify disease sub forms, observe disease progression and explain healing treatment-curing efficacy [5, 6]. Deep brain stimulation (DBS) is a well established surgical technique for PD treatment that uses high frequency electrical pulses to stimulate the subthalamic nuclei(STN) and associated brain-regions. However, large outcome disparity exists

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**Fig. 1** The signal patterns of single and multi-unit subthalamic-nuclei neurons at range of depths
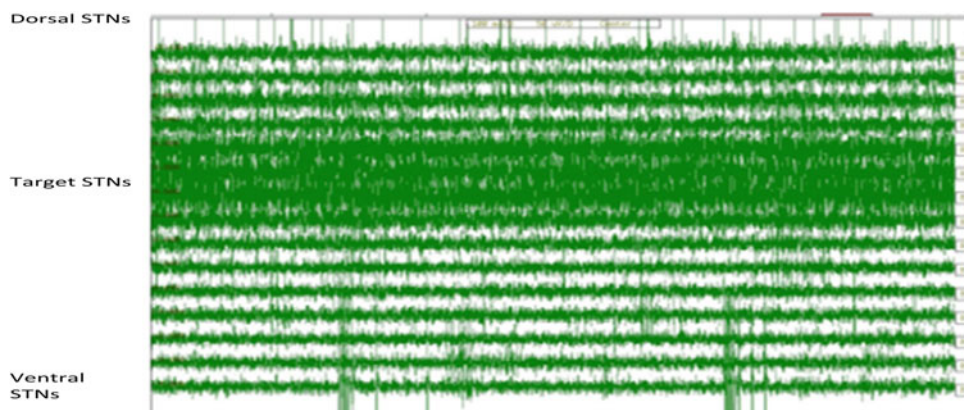


among recipients due to varied standards for postoperative management, particularly concerning DBS programming optimization [6, 7]. Though, mechanisms of DBS act are not clear properly and correct electrode placement, the effectiveness of lead-point position and stimulation might advance motor features and restore increase motor function and allows for a reduction in antiparkinsonian medication doses [1–8]. Further, DBS stimulation parameters are set by subjective evaluation of PD symptoms, and no physiological-based quantitative measures are used to optimize the efficacy of DBS in reducing motor disorders [8, 9]. Hence, a tracking method (PCA based) is worth or objective reasoning. The objective of this study is to quantify the efficacy of DBS.

## 2 Methods

12subjects with PD diagnosis having more than 6 years as per united kingdom (UK) PD society brain bank criteria with good response to a precursor to dopamine cells "Levodopa" and Hoehn and Yahr score of less than 4 with normal cognition were included in this study. The signal-acquisition—microelectrode recording was performed in all patients. To perform MER in STN-DBS, five MER/macrostimulation electrodes were placed in an array with a central, lateral, medial, posterior, and an anterior position placed 2 mm apart, to define the borders of the nucleus. Depending on the pre-operative magnetic resonance imaging (MRI), it was decided in some cases to acquire with three or four microelectrodes rather than five. Usually, 3–4 channel-recordings were performed in the central, medial, posterior, and lateral channel. The anterior channel was included rarely. Extracellular single and multi-unit MER was performed with small (10 μm-micron meters width) polyamide-coated tungsten microelectrodes (Medtronic maker; microelectrode 291; input impedance was $1.1 \pm 0.4$ Mega Ohm; measured

at 220 Hz, at the beginning of each trajectory) mounted on a sliding burrow/or cannula. Signals were recorded with the amplifiers (10,000 times amplification) of the Lead-Point system (Medtronic), using a bootstrapping principle and were filtered with analog Band-Pass filters between 0.5 and 5 kHz (−3 dB;12 dB/Oct). The signal was sampled at 12 kHz, by employing a 16 bit analog to digital (A∕D) converter (ADC). Later using Nyquist criteria sampled up to 24 kHz. Following a two seconds signal stabilization period after electrode movement cessation, multi-unit segments were recorded for five to twenty seconds. For STN, 8 and 12 mm above the MRI-based target, the microelectrodes were advanced in steps of 500 μm towards the target by a manual microdrive. When the needles were inside the STN, at each depth, the spiking activity of the neurons lying close to the needle (pick-up area up to 200 μm) could be recorded. Depending on the neuronal density not more than 3–5 units were acquired—recorded concurrently. More distant units could not be distinguished from the background level. The following Fig. 1 obtained with MER. The subthalamic-nuclei was detected by interfered noise with a bigger electrical zero line and asymmetrical discharge patterns of multiple-frequencies.

The STN was clearly distinguished from the dorsally located zona incerta and lenticular fasciculus ($H_2$-field) by an abrupt amplify (signal amplitudes) in background-noise level and augment in discharge-rate typically characterized by rhythmic bursts of activity with a burst frequency. All five microelectrodes were passed through STN and signal-recording was performed from dimensions ±10 mm, and STN calculated on MRI. The STN was detected by a high noise with a large electrical baseline and an irregular discharge patterns with multiple frequencies. Figure 2 shows the microelectrode recording which was obtained from the STN.

The STN MER signals features (Table 1). PCA is used to transform originally correlated variables into uncorrelated and to reduce number of variables.

Single unit (single channel) STN

Central Channel (11 mm) typical firing pattern with irregular firing and broad baseline (from -1.00 level)



**Fig. 2** MER-signal recording. At the posterior level, STN was encountered lower than expected at that location

**Table 1** Feature-values: Mean ± SD) for Parkinson's disease subjects with DBS "ON" and "OFF"

| Signal feature | PD patients with DBS on | PD patients with DBS off |
|---|---|---|
| $D_{2, r}$ | 6.1 ± 1.0 | 5.4 ± 1.6 |
| $D_{2, 1}$ | 5.7 ± 1.4 | 5.4 ± 2.1 |
| % $REC_r$ | 9.2 ± 5.1 | 14.9 ± 13.6 |
| % $REC_1$ | 12.7 ± 7.6 | 15.3 ± 14.9 |
| R M $S_r$ $10^3$ | 0.8 ± 0.4 | 2.5 ± 4.6 |
| R M $S_1$ $10^3$ | 1.0 ± 0.9 | 6.0 ± 12.4 |
| Samp $En_r$ | 0.9 ± 0.3 | 0.7 ± 0.3 |
| Samp $En_1$ | 1.0 ± 0.4 | 0.8 ± 0.4 |
| $Coherence_r$ | 1.3 ± 0.7 | 1.5 ± 1.4 |
| $Coherence_1$ | 1.4 ± 0.8 | 2.2 ± 1.5 |

The ten calculated signal parameters were sequentially placed and normalized (to zero mean and unit SD of subjects) to form feature vectors for all subjects. The dimension of the feature vectors was then reduced by applying the PC approach. In that approach, the feature vectors were decomposed into weighted sums of orthogonal basis vectors where the scalar weights were called the principal components. These PCs were the new uncorrelated features.

## 3 Results

In our results, the UPDRS motor score was lower with DBS "ON" comparing with DBS "OFF" in 12 subjects but the decrease rate was patient character. The clinical scores describing disabilities in hand movements decreased for all subjects in either side of the body. The principal components were computed (in Mat Lab tool) for 12 subjects using computed Eigen-vectors. We observed that the first three PC scores are sufficient to account the variance approximately 80% (in our scatter plot). These PCs are good enough to discriminate between the DBS "ON" and "OFF" states, and between the PD patients. The first Eigen vector is the best mean-square fit for the feature-vectors. Consequently, first highest magnitude value is the PC1, second highest magnitude is PC2, and third highest magnitude is PC3 in the order of decreasing. These magnitudes are amplitudes of 12 subjects MER signals of STN. By visually inspecting the morphology of the third Eigen-vector, we could recognize, that PC3 emphasizes differences between right and left side variables. Indeed, the unilateral onset continual and unrelenting asymmetries of symptoms support the diagnosis of PD in relation to other similar diseases. The distances between the DBS "ON" and "OFF" states in the feature

**Table 2** Characteristics' of Parkinson's diseased subjects

| P#. | Age | Gender | UPDRS off | UPDRS on | Medications | Co-morbidities |
|---|---|---|---|---|---|---|
| 1 | 70 | F | 56 | 43 | Clozapine, Diazepam, Fludrocortisone Acetate, Namenda, Senna Plus, Seroquel | None |
| 2 | 70 | F | 64 | 48 | Levodopa | Chronic obstructive pulmonary disease |
| 3 | 82 | F | 59 | 40 | Mirapex | none |
| 4 | 71 | M | 34 | 14 | Lipitor, Glipizide, Lisinopril, Aspirin | Diabetes, angioplasty in 2000 |
| 5 | 61 | M | 71 | 42 | Sinemet, Omeprazole, Aspirin | none |
| 6 | 61 | M | 38 | 31 | Sinemet | Hypertension |
| 7 | 66 | F | 47 | 28 | Azilect, Amitriptyline, Evista | None |
| 8 | 63 | M | 57 | 33 | Sinemet Tasmar, Pantprozol | None |
| 9 | 50 | M | 43 | 34 | Mirapex, Trazadone, Metformin, Glimepiride Advair, Metolazone | Diabetes |
| 10 | 59 | M | 43 | 24 | Levodopa, Detrol LA | Diabetes |
| 11 | 63 | M | 44 | 30 | Sinemet, Simvastatin | None |
| 12 | 64 | M | 62 | 38 | Carbidopa, Naproxen, Ropinirole | Hypertension |

space were highly individual. Similarly, the improvements in clinical scores were individual. However, strong changes in the total UPDRS motor score did not result in strong changes in the analyzed principal components. This could be the fact that the total UPDRS motor score [4] is a complicated score that consists of a large number of sub-scores. These sub-scores are defined for different areas of the body in different movement conditions (Table 2).

We presented a principal component analysis (PCA) based tracking method for quantifying the effects of DBS in. It was observed that the PC-based tracking method was more sensitive to PD with associated tremor.

## 4 Conclusions

In this study, we applied PCA-based latent variate-factorial tracking method. The hypothesis of the study was that the developed method is capable of quantifying the effects of DBS "ON" patients with PD objectively. Our findings suggest that electrophysiological STN signal characteristics are strongly correlated to the ex tent of motor behavior improvement observed in STN-DBS. In the future studies, multivariate PCA approach can be tested in serving the adjustment of DBS settings. In addition, the sensitivity of the presented method to different types of PD should be estimated more carefully in further experimental studies. The exciting systems approach and computational framework can be prepared performed in our future studies. The proposed approach can employ few signal features within the STN to compute prognostics, separately for each PD subject,

the performance and behavioral outcome of STN-DBS, justifying further investigation and, possibly, clinical-experimental applications. Lastly, only few neurophysiologically interpretable MER signal features are sufficient to account for predicting UPDRS improvement. Future study also involve applying nonlinear time domain analysis of average amount of mutual information (AAMI) technique with controls for better prediction and understanding of Parkinson's disease through MER with STN-DBS.

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