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Deep brain stimulation of subthalamic nucleus helps in improving late phase motor planning in Parkinson's disease

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ABSTRACT

Objective: Deep brain stimulation of subthalamic nucleus (DBS-STN) is a well-accepted treatment for Parkinson's disease (PD) but its effect on motor planning in the disease is yet unclear. This study examines the effect of switching the stimulation ON and OFF on components of bereitschaftspotentials in PD.

Patients and methods: Scalp bereitschaftspotentials were recorded during self-paced right wrist extensions at Fz, Cz, Pz, C3 and C4 sites in patients on DBS-STN plus medications (DBS-STN group) as treatment modality or on medications only (Med group) and compared with age matched healthy controls. In DBS-STN group, the potentials were recorded in stimulation ON, stimulation OFF, and again after re-switching stimulation ON-2. Offline analysis of potentials was done to calculate peak amplitude, late slope (−500 to 0 ms) and early slope (−1500 to −500 ms).

Results: We observed that the two components of bereitschaftspotentials in stimulation ON state were comparable to those in age matched controls. The late slope was found to be significantly reduced during stimulation OFF as compared to stimulation ON at Cz ($p < 0.001$), C3 ($p < 0.001$) and C4 ($p < 0.01$) electrode sites. This parameter failed to improve on re-switching stimulation ON at Cz ($p < 0.01$). No significant change was observed in early part of bereitschaftspotentials among any of the conditions.

Conclusion: Our study shows that DBS-STN along with anti-parkinsonian medications helps in improving both components of bereitschaftspotentials in PD. Switching stimulation OFF for fifteen minutes principally affects the late component i.e. the execution part of motor planning; which cannot be reversed by re-switching ON. Thus the chronic and acute effects of switching DBS-STN ON are different and principally affect the later part of motor planning.

1. Introduction

Bereitschaftspotentials (BP) are negative cortical evoked potentials that begin 1000–1500 milliseconds (ms) prior to the onset of a self-paced movement [1]; they represent the cortical activity before the actual onset of the movement. Recording scalp BP has helped to study motor planning in health as well as in disease [2,3]. Two major components of BP can be distinguished associated with voluntary movement viz early and late BP. The early component is bilaterally symmetrical across the scalp with maximal amplitude recorded at the vertex and with a principal source in the bilateral supplementary motor area [4,5]. Late BP reflects premovement activity localized to the contralateral motor cortex and supplementary motor area [4,5]. Though some studies have observed near normal BP in PD compared to age match controls [6,7]; many other studies have found BP abnormalities in PD [8–14]. The duration and amplitude of BP recorded at the Cz (vertex) are reduced in Parkinsonism and levodopa treatment is associated with changes in these parameters of BP [11]. Based on this observation they suggested that these premovement readiness potentials are influenced by the basal ganglia output to supplementary motor area via dopaminergic control [11]. BP are even affected by lesions in basal ganglia circuitry; both early BP and late BP are flatter in patients with bilateral lesions in basal ganglia [8]. Further, it was shown that it is the early component of BP that is significantly reduced in PD during externally cued movements, implying defective activation of supplementary motor area [9].

Few electrophysiological studies have explored the properties of scalp BP during and after DBS as the treatment modality. They have demonstrated recordable BP over the scalp as well as at different sites in the basal ganglia [15–17]. These studies point towards the role of basal ganglia nuclei during motor preparation. Only one study has evaluated the effect of switching DBS ON and OFF on these potentials; Brown and

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his colleagues observed that after STN stimulation there were improvements in the time taken for movement and force of contraction while no prominent effect on time for initiating movement. However, as the BP amplitudes were small in some patients they could not study different components of BP during ON and OFF stimulation states [18]. Given that DBS-STN effectively modulates the whole basal ganglia circuitry, which plays an important role in motor planning, we postulate that switching stimulation OFF may differentially influence the components of BP and re-switching ON would revert the changes back to the initial ON condition. By studying the effect of switching stimulation ON and OFF on bereitschaftspotentials in Parkinson's disease, we aim to understand the mechanism behind motor improvement after deep brain stimulation of subthalamic nucleus.

1.1. Material and methods

This study was approved by institute ethical committee and in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All the participants were well informed about the nature and purpose of the study and written informed consent was obtained from each.

1.2. Participants

The participants in this study consisted of three groups viz. DBS-STN plus medications (DBS-STN group), patients on medications only (Med group), and healthy age matched controls (Control group). The DBS-STN group consisted of patients with age between 50 and 70 years affected by idiopathic Parkinson's disease and on bilateral DBS-STN. Only patients with post implant interval of > 4 weeks were included and had electrodes implanted in bilateral subthalamic nucleus with similar optimal stimulation settings (bipolar, 2.9 ± 0.35 V, 62.5 ± 8.6 ms, 139.1 ± 9 Hz). Furthermore to study the effect of stimulation on BP the DBS-STN group was divided into three conditions: DBS ON/DRUGS ON, DBS OFF/DRUGS ON and DBS ON-2/DRUGS ON (discussed in recording protocol). Med group also consisted of patients with age between 50 and 70 years affected by idiopathic Parkinson's disease but only on levodopa medications. Only right handed [19] participants with bilateral disease (right > left) and those who could perform the task with recordable BP were included in this study. Participants with any history of head trauma, stroke or any other neurological complications, or psychiatric disorders were excluded from the study. Based on DBS-STN group other groups were age and gender matched with each group having 8 males and 4 females participants. (DBS-STN group: mean age = 57.08 ± 5.62 years; Med group: mean age = 54.25 ± 4.14 years; and Control group: mean age = 54.50 ± 4.93 years). Clinical severity assessment of patients with PD was done using Unified Parkinson's Disease Rating Scale (UPDRS) [20]. Table 1 shows the details of the patients group.

Table 1
Clinical details of the patients in the study.

Groups → *Parameters ↓*	Med Group	DBS-STN group		
		DBS ON/ DRUGS ON	DBS OFF/ DRUGS ON	DBS ON-2/ DRUGS ON
Age (years)	54.25 ± 4.14	57.08 ± 5.62		
Duration of disease (years)	8.83 ± 4.73	9.42 ± 3.03		
UPDRS III Motor Score	37.08 ± 4.58	27.67 ± 2.61	39.83 ± 2.92	27.75 ± 2.30

DBS-STN group was divided into three conditions: DBS ON/DRUGS ON, DBS OFF/DRUGS ON and DBS ON-2/DRUGS ON. Values represented as mean ± SD.

1.3. Recording protocol

The potentials were recorded using Evoked Potential Recorder Neuropack 8 (Nihon Kohden, Japan). All the recordings were taken in medication ON state in both patient groups. Electroencephalography was recorded from the scalp using silver/silver chloride surface electrodes and International 10–20 system for electrode placement. Potentials were recorded at Fz, Cz, Pz, C3 and C4 electrode sites placed according to international 10–20 system with linked earlobes electrodes as reference and a forehead electrode (Fpz) used as ground. The EEG signal was amplified with a gain of 10,000 by the in-build amplifiers of Neuropack 8 through a filter band pass 0.05–45 Hz for scalp recordings; such a setting helps in reducing stimulation artifacts in the EEG data. The electromyogram from the extensor carpi radialis was used as a trigger for collection of bereitschaftspotentials. Filter band pass for EMG was 0.05–3 KHz with sensitivity set at 200 μV/div. Impedance was kept less than 5KΩ throughout the recording.

Participants were seated comfortably in an armchair with eyes open and fix on a screen during the recording. They were trained to perform precise right wrist extensions (50–60 degree from horizontal position) once every 5–10 s, for a duration not more than 0.5 s (Fig. 1). To ensure active participation during the task, the subjects were asked to keep the interval between the contractions random but always more than 5 s. They were given feedback to stop whenever the researcher observed that the contractions were rhythmic and averaging was paused. The onset of EMG signal was used as trigger for back averaging BP. Neuropack 8 was programmed to back average the EEG 3.0 s prior to and 0.5 s after the EMG onset. Sweeps of each of the trials were inspected for eye blinks (Fp1-A1 and Fp2–A2 electrode pairs) or other artifacts. Sweeps with EEG amplitudes of more than 60 μV or EMG signal lasting for more than 0.5 s were excluded from the averaging. Online artifact rejection was thus done. 100 such artifact free sweeps (trials) were averaged to obtain BP. Analysis of the waveform components was done offline.

An initial recording in DBS-STN group with the stimulation ON and medication ON state (the first day when the participant was enrolled and in whom stimulation was ON for more than 72 h without any interference) was considered as DBS ON/DRUGS ON i.e. a baseline BP record. To study the effect of switching DBS OFF or ON two addition sessions were recorded for DBS group on separate days. In another session, BP was recorded in medication ON but stimulation OFF state (waiting for a period of 15 min after switching OFF) this was considered as DBS OFF/DRUGS ON. In the third session, BP was recorded in medication ON but after re-switching stimulation ON (waiting for a period of 15 min after switching OFF and another 15 min after re-switching ON); this was considered as DBS ON-2/DRUGS ON. Apart from sweep rejection criteria mentioned before, only trials where the EMG amplitude was more than 60% of EMGmax (noted on day 1) were included for averaging in all the conditions for the given individual to reduce intra-individual variation. Offline analysis of BP parameters mentioned below was done for each participant separately.

1.4. Analysis and statistics

The BP morphology was analysed for following parameters: peak amplitude, early slope, and late slope. Baseline activity was calculated from −2500 ms to −2000 ms i.e. prior to the onset of BP in all recordings. The maximum amplitude of bereitschaftspotentials occurring near the time of movement (around −50 ms) was noted as peak amplitude. Early slope was calculated as an average slope over the period of −1500 to −500 ms prior to EMG onset using linear regression; this slope represents the activity associated with the early component of BP [10]. Similarly late slope was calculated as average slope over the period from −500 ms to peak BP. Cortical activity during the time period of −500 ms to peak BP represents the late component of these potentials. BP parameters were compared between controls vs Med