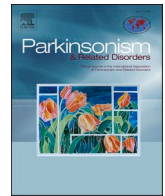




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Low frequency subthalamic stimulation and event-related potentials in Parkinson disease

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ABSTRACT

Background: High frequency (130 Hz) subthalamic Deep-Brain-Stimulation (STN-DBS) optimally improves cardinal motor symptoms in Parkinson disease (PD). Low stimulation frequencies (60–80 Hz) improve axial symptoms in some patients and, according to preliminary evidences, may also have a beneficial effect on the cognitive component of motor planning.

Objective: To analyze the configuration of the P300 component of cortical event-related auditory potentials (ERPs), a reliable index of attentive cognitive functions, at different stimulation frequencies in STN-DBS in PD patients.

Methods: 12 PD patients underwent ERPs recordings using a standard oddball auditory paradigm with STN-DBS at 60 Hz, 80 Hz, 130 Hz, and OFF-stimulation, applied in a randomized double-blind sequence. ERPs analysis considered the peak amplitude and latency of the P300 components at midline electrode positions (Fz, Cz, Pz).

Results: P300 latency over Cz and Pz electrodes significantly increased with STN-DBS at 130 Hz compared to OFF-stimulation. P300 latency was also significantly increased, though to a lesser degree, over Pz electrode with stimulation at 80 Hz. No significant P300 latency modifications were detected at 60 Hz stimulation compared to OFF-stimulation condition. P300 amplitude did not change significantly for any of the stimulation conditions tested.

Conclusions: Low frequency STN-DBS is associated with minor modifications of P300 latency compared to conventional stimulation at 130 Hz, possibly suggesting that 60 and 80 Hz may have less interference with attentive and cognitive processes in PD patients.

1. Introduction

Subthalamic nucleus (STN) Deep Brain Stimulation (DBS) is an effective therapy to improve motor symptoms of Parkinson's disease (PD) [1]. Patients are usually treated with high frequency stimulation (HFS) above 100 Hz to provide optimal control of cardinal motor symptoms. However, there is evidence that lowering stimulation frequency below 100 Hz (low frequency stimulation - LFS) may provide benefit in patients who develop axial symptoms, such as freezing of gait (FoG) or speech impairment [2–6] and may be less harmful to verbal fluency [7,8]. Recent evidences also suggest that LFS is able to enhance, oppositely to HFS, compensatory mechanisms of

cortico-basal-thalamo-cortical circuits [9,10] involved in the top-down control of complex movements, where cognition plays a fundamental role [11].

The analysis of long-latency event-related potentials (ERPs), and in particular of the P300 component, is an electrophysiological measure used for the evaluation of cognitive functions, including selective attention and short-term memory [12]. Significant ERPs deconstruction are described in patients with Alzheimer's disease, with longer latency and smaller amplitude of the P300 component [13]. In PD patients, P300 alterations have been reported both in cognitively impaired patients [14] and in non-demented PD patients [15], and the meaning of P300 modifications in PD patients as a possible index of specific cognitive

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alterations still remains to be clarified [12].

The influence of STN-DBS on P300 has been evaluated only in few studies [16–19], with conflicting results; moreover, the effect of different DBS stimulation frequencies on long-latency ERP has never been investigated.

The aim of this pilot study was to assess whether different frequencies of STN-DBS may induce modifications of P300 latency and amplitude.

2. Methods

2.1. Patients

We enrolled consenting patients with idiopathic PD admitted to our outpatient clinic between October 2019 and December 2019, implanted for bilateral STN-DBS at the Department of Neuroscience, University of Turin. Inclusion criteria were at least 3 months of follow-up since surgery (to avoid bias due to the post-surgical microlesion effect), stable stimulation parameters, and stable doses of dopaminergic treatment for at least four weeks prior to enrollment. Exclusion criteria were mild cognitive impairment or dementia (defined by means of the Movement Disorder Society level II criteria [20,21]), presence of other neurological illnesses and previous psychotic episode. The Local Ethical Committee approved the study protocol and all patients provided written informed consent.

2.2. STN-DBS surgical procedure

DBS surgery comprised bilateral stereotactic STN implantation based on MRI/computed tomography (CT) image fusion for anatomical targeting, intraoperative electrophysiological recording and micro-stimulation. Quadripolar leads (electrode model 3389; Medtronic, Minneapolis, MN) were implanted following the selected trajectory, and postoperative CT/MRI was performed to confirm electrode positioning and to exclude surgical complications.

2.3. Cognitive ERP recording

The recording procedure was carried out following the guidelines of the International Federation of Clinical Neurophysiology [22]. In all subjects, ERPs were recorded in the morning, at the same hour of the day, after at least 12 h of dopaminergic therapy withdrawal, to avoid possible interference of medical treatment on ERPs parameters [23]. Patients were also asked to avoid non-dopaminergic therapy and alcohol intake during the 12 h prior to the trial, except for those drugs whose morning intake was necessary (anti-hypertensive drugs in two patients and levothyroxine in one patient). Regarding antidepressant drugs, a 24-h withdrawal was requested (duloxetine in two patients). The subjects were seated in a quiet room with dimmed lights and were requested to keep their eyes closed and try not to blink. In accordance with the international 10/20 system, silver/silver-chloride electrodes were applied (Fz, Cz, Pz) and the inter-electrode resistance was kept always below 5 kOhm. Each electrode was referenced to the common A1/A2; the ground electrode was placed over the forehead. Electrooculographic activity was also recorded to identify ocular movements and to avoid artifacts. The calibrated output of an EEG was digitalized at a sampling rate of 1000 Hz, using a dedicated workstation (Galileo NT, Torino, Italy). The time constant was 1 s, while the gain was set individually to capture the optimal EEG signals. Apart from an anti-alias (500 Hz low-pass) analog filter, no other hardware filtering was applied during the EEG recording; then, an off-line digital band pass filter was applied, changing its frequency depending on the ON-stimulation condition considered (60 Hz, 80 Hz, or 130 Hz).

ERPs were elicited by using a simple discrimination task, the ‘odd-ball’ paradigm in which subjects were asked to silently count rate tones differing from others in pitch (“target” stimulus; 2000 Hz; probability

0.2) and occurring randomly among “non-target” events (1000 Hz; probability 0.8). Binaural tones of 100 ms duration were played at constant intensity (80 dB hearing level). Thirty-two trials in each condition were recorded and subsequently averaged. The inter-stimulus interval varied randomly between 1.5 and 2.5 s to achieve a comfortable stimulus presentation rate.

After a learning period, two consecutive recordings containing at least 50–60 valid triggers were made. ERP recordings begun 100 ms before the onset of each stimulus and were continued for the next 900 ms. The P300 component was defined as the most positive peak occurring within a window of 250–480 ms. Amplitudes and latencies were determined offline. The P300 amplitude was measured relative to the pre-stimulus baseline.

Four different stimulation conditions were tested in a random sequence: DBS turned off (OFF-stimulation) and DBS turned on (ON-stimulation) at 130 Hz, 80 Hz, and 60 Hz; all patients had cathodic, monopolar, constant-voltage stimulation. In the three ON-stimulation conditions, the total electrical energy delivered (TEED) was maintained, changing the stimulation amplitude using a validated formula ($TEED = \text{voltage}^2 \times \text{pulse width} \times \text{frequency}/\text{impedance}$) [24]. A 20-min break for refreshing was allowed between the consecutive recordings.

2.4. Statistical analysis

Continuous data were summarized as mean \pm standard deviation or percentages, as appropriate. Differences on “target” stimuli detection accuracy, P300 latency and P300 amplitude in the four stimulation conditions were evaluated by means of the non-parametric Friedman’s test, followed by pairwise comparisons by means of the Mann-Whitney’s test. The Bonferroni’s correction for multiple comparisons was applied. All tests were two-tailed and a p-value <0.05 was considered as statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 25 for Mac, Chicago, IL).

3. Results

3.1. Study population

The cohort consisted of 12 PD patients (11 males) treated with bilateral STN-DBS. The main demographic and clinical characteristics are summarized in Table 1. The average time since surgery was 3.0 ± 2.1 years. None of the patients reported significant side effects during the four experimental conditions. The accuracy of “target” stimuli detection did not differ in the four experimental conditions (98%, 97%, 98%, and 97% for OFF-, and 130, 80, and 60 Hz stimulation condition, respectively; $p = 0.216$).

3.2. P300 latency

P300 latency demonstrated significantly different values during the four experimental conditions over Cz and Pz electrodes ($p = 0.026$ and $p = 0.002$, respectively; Table 2 and Fig. 1), with lower values in OFF-stimulation condition than in the three ON-stimulation conditions. A gradient in the P300 latency increase was observed, with 60 Hz stimulation showing lower values, 80 Hz stimulation intermediate values, and 130 Hz stimulation higher values. At pairwise comparisons, the OFF-stimulation condition showed significantly shorter latencies vs. both 80 Hz stimulation ($p = 0.027$) and 130 Hz stimulation ($p = 0.003$) over the Pz electrode, and vs. 130 Hz stimulation over the Cz electrode ($p = 0.016$). A trend toward higher P300 latencies in the three ON-stimulation conditions was also observed over the Fz electrode, without reaching the statistical threshold (Table 2).

Table 1
Demographic and clinical features of the sample.

Demographic data	
Age (years)	61.7 ± 9.3
Age at PD onset (years)	44.9 ± 8.1
Age at STN-DBS (years)	57.0 ± 9.1
Presurgical clinical data	
Disease duration at STN-DBS (years)	12.3 ± 3.2
Motor fluctuation duration at STN-DBS (years)	3.7 ± 1.5
MMSE	28.2 ± 1.1
UPDRS-II OFF score	22.7 ± 5.5
UPDRS-II ON score	9.4 ± 5.4
UPDRS-III OFF score	48.1 ± 12.2
UPDRS-III ON score	22.2 ± 5.1
UPDRS-IV score	9.2 ± 3.5
Hoehn and Yahr Off score	3.1 ± 0.3
Postsurgical clinical data	
STN-DBS duration (years)	3.0 ± 2.1
UPDRS-II Stim-ON/Med-OFF score	14.4 ± 5.4
UPDRS-II Stim-ON/Med-ON score	12.1 ± 9.2
UPDRS-III Stim-ON/Med-OFF score	30.5 ± 5.1
UPDRS-III Stim-ON/Med-ON score	17.8 ± 9.4
UPDRS-IV score	3.6 ± 0.3
Stimulation settings	
Amplitude (V)	3.1 ± 0.9
Pulse width (µsec)	60.5 ± 0.9
Frequency (Hz)	121.7 ± 19.5

Results are reported as mean ± standard deviation. Postsurgical clinical data were collected at the time of experimental evaluation, with Med-ON conditions scored after the four experimental recordings. The stimulation settings are reported as mean of the two sides. Med: Medication; MMSE: Mini Mental State Examination; Stim: Stimulation; STN-DBS: Subthalamic nucleus Deep Brain Stimulation; UPDRS: Unified Parkinson’s Disease Rating Scale.

Table 2
P300 latency values in the four stimulation conditions over the three electrodes.

		OFF-Stimulation Condition			ON-Stimulation Condition			P value
					60 Hz	80 Hz	130 Hz	
P300 latency (msec)	Fz	363.5 ± 14.2 (337–395)			375.7 ± 14.2 (357–401)			.139
	Cz	364.2 ± 27.4 (321–415)			374.0 ± 15.3 (339–402)			.026
	Pz	361.5 ± 23.4 (321–403)			370.5 ± 24.0 (315–407)			.002

Values are reported as mean ± standard deviations; minimum and maximum values are reported in brackets. P value: statistical differences among the four stimulation conditions; *: significant differences (p < 0.05) vs. OFF-Stimulation condition after Bonferroni’s correction.

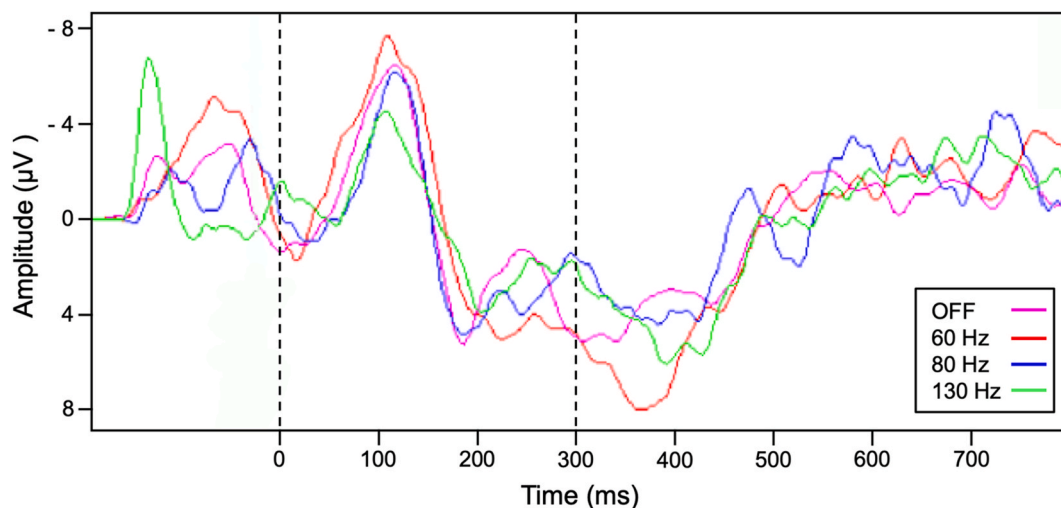


Fig. 1. P300 traces in the four different experimental conditions
The figure shows the different P300 recordings of a patient in the four experimental conditions. The traces refer to Pz electrode.

3.3. P300 amplitude

As for the P300 latency, a gradient in the P300 amplitude was observed in the four experimental conditions, in particular over Fz and Pz electrodes (Table 3). OFF-stimulation condition presented higher values, followed by 60 Hz and 80 Hz stimulation, while 130 Hz stimulation condition was associated with the lowest values. However, the extent of these differences was small, and the statistical threshold was not reached.

4. Discussion

In this pilot study we sought to analyze if P300, a possible neuro-physiological marker of cognitive decline in PD [12], was influenced by

Table 3
P300 amplitude values in the four stimulation conditions over the three electrodes.

		OFF-Stimulation Condition	ON-Stimulation Condition			P value
			60 Hz	80 Hz	130 Hz	
P300 amplitude (µV)	Fz	7.2 ± 4.3 (2–15)	6.9 ± 2.9 (3–12)	6.1 ± 2.7 (2–9)	5.8 ± 2.9 (1–10)	.487
	Cz	7.3 ± 4.5 (2–15)	5.7 ± 2.8 (2–10)	5.6 ± 2.1 (3–9)	5.7 ± 2.7 (1–9)	.582
	Pz	7.3 ± 4.3 (1–15)	6.4 ± 3.3 (1–11)	5.4 ± 2.0 (3–9)	4.9 ± 2.5 (1–8)	.623

Values are reported as mean ± standard deviations; minimum and maximum values are reported in brackets. P value: statistical differences among the four stimulation conditions.

STN-DBS at different frequencies. We showed that STN-DBS at lower frequencies is associated with less interference on the P300 latency compared to conventional stimulation at 130 Hz, suggesting that LFS may have a milder impact on neural circuits involved in the generation of P300.

The analysis of ERPs, and in particular of P300, is a reliable electrophysiological measurement of cognitive function in PD [12,14], but also in other neurodegenerative diseases [13]. To date, it is not clear if P300 modifications in PD patients represent a sensitive biomarker for global cognitive decline or for more specific alterations in fronto-striatal executive functions, such as selective attention, set-shifting, verbal fluency, working memory, and planning [12]. Moreover, the influence of dopaminergic treatment, as well as DBS on P300 characteristics has not been clarified yet [23,25]. Indeed, only few studies evaluated the influence of DBS on the ERPs characteristics [16–19], and the role of different stimulation frequencies has never been investigated. The study by Gerschlagler and colleagues [16] showed no significant differences of P300 latency between OFF- and ON-stimulation at 130 Hz, even if a trend towards a latency reduction ON-stimulation was described. The same observations were reported also in other three studies [17–19]. In all cases HFS was applied, and P300 latency in PD patients were longer than in non-PD patients. Regarding P300 amplitude, no significant differences were reported, even if one study [18] found a trend towards reduction in ON-stimulation condition, while another [17] found both reduction (in frontal regions) or increase (in midline and central regions) when the stimulation was turned on. On the contrary, our study found an inverse pattern of P300 modifications, with longer P300 latency and reduced amplitude in all three ON-stimulation conditions. This finding could be due to heterogeneity between our and the other studies, both in the clinical characteristics of patients and in the data acquisition (e.g. different sampling rate and intensity/duration of the auditory stimulus, “silent count” vs. “button-press” paradigm).

Moreover, we found a gradient of progressively increased P300 latency from OFF-stimulation condition to higher stimulation frequencies. In fact, shorter values of P300 latency were associated with OFF-stimulation condition, while 130 Hz stimulation significantly increased latency values. LFS, and in particular 60 Hz stimulation, was associated with lower values of P300 latency, not significantly different from the OFF-stimulation condition. Considering the P300 amplitude, we observed a gradient towards a progressive reduction with the increase of stimulation frequencies, in particular over Fz and Pz electrodes; however, these differences did not reach the statistical threshold, probably due to the small magnitude of the changes and the small sample size. On the other hand, it is conceivable that the amplitude of P300, that mainly reflect the degree of attention [26] rather than the evaluation speed and the cognitive performance, might not be affected by DBS, as indirectly suggested by the similar accuracy of “target” stimuli detection in the four experimental conditions.

HFS (>100 Hz) is the most commonly used stimulation paradigm, due to its well-known effect on parkinsonian cardinal symptoms [27]. However, in recent years, it has been shown that LFS may improve axial symptoms in PD patients treated with DBS, in particular FoG [2–5], dysphagia [5], and dysarthria [6]. In addition, subthalamic LFS seems to be less harmful than HFS on verbal fluency [7,8], a cognitive ability related to frontal cortex-basal ganglia circuits. There is also evidence that subthalamic LFS improves gait initiation during an interfering cognitive task [9], while a significant latency increase and amplitude reduction of P300 was reported during a cognitive dual task walking test, suggesting a specific recruitment of attentional networks during walking in PD patients [28]. Nonetheless, the worsening of appendicular symptoms, in particular tremor, after the switch from HFS to LFS, could limit the use of LFS in clinical practice [2,29].

Interestingly, it has been shown that STN-DBS at both HFS and LFS attenuate the pathological oscillations in the high beta-band (19–27 Hz) within the cortical-basal ganglia circuits, in particular within the hyperdirect pathway [10], leading to the relief of bradykinesia. On the

other hand, HFS and LFS have opposite effects on the alpha/low beta-band (11–15 Hz) oscillations, the former attenuating and the latter enhancing them, with a consequent improvement or worsening of tremor [10,30].

Alpha/low beta-band oscillations are also implicated in cortico-striato-pallidal-STN pathways relevant for the top-down control of movements [11,31,32]. These networks mainly involve the supplementary motor area (SMA), the anterior cingulate cortex (ACC) and the temporo-parietal cortex, implicated in the postural adjustment during movement initiation and in attentive processes for motor planning [11, 31,33]. Moreover, PD patients show a higher activation of prefrontal cortex than healthy subjects even during usual, non dual-task gait [34], suggesting a greater involvement of attentive processes during walking. Therefore, it has been suggested that LFS of STN, by enhancing the alpha/low beta-band oscillations, may have less interference, or even improve, the cognitive component of movement control [9,30]. Taking into account all these evidences, even though the cognitive network implicated in the top-down control of movement could differ from that involved in the P300 generation, our observation of a milder interference of LFS on P300 latencies might suggest a possible effect of LFS on the cognitive components of complex movement in PD patients.

Our findings are tempered by some limitations. First, the small number of patients limits the generalizability of our results. Second, the lack of a control group of healthy people and/or non-DBS PD patients does not allow for a reliable comparison of our P300 values in OFF-stimulation condition, even if they are similar to those reported by other authors using an analogous assessment [17]. Third, the lack of lead location evaluation does not allow us to hypothesize possible correlations between P300 variations and changes in volume of tissue activated due to LFS or HFS. Fourth, we did not assess motor or cognitive functions during the different experimental conditions; however, we maintained the same TEED in all ON-stimulation conditions. Finally, the absence of validated thresholds of P300 latency and/or amplitude changes associated with significant clinical variations, limits our conclusions on the clinical meaningfulness of the observed P300 modifications.

In conclusion, to the best of our knowledge, this is the first study showing significant differences of P300 characteristics between different stimulation frequencies in STN-DBS-treated PD patients. Lower stimulation frequencies seem to be associated with lower interference with P300 latency, suggesting that LFS may have a milder impact on neural circuits involved in attentive and cognitive processes related to the top-down control of movement. This hypothesis, along with the potential benefit of LFS on levodopa-resistant symptoms, could add evidences in favor of this modality of stimulation against HFS in those patients with higher impairment of axial symptoms and worse cognitive performances. However, future research endeavors, with larger sample size and possibly with dynamic measurements (i.e. during rest, standing, gait) will be needed to confirm our findings.

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Authors' roles

- 1) Research project: A. Conception; B. Organization; C. Execution
- 2) Statistical Analysis: A. Design; B. Execution; C. Review and Critique
- 3) Manuscript Preparation: A. Writing of the first draft; B. Review and Critique

Alberto Romagnolo: 1B, 1C, 2A, 2B, 3A.

Maurizio Zibetti: 1A, 1B, 1C, 2C, 3A.

Marco Lenzi: 1B, 1C, 2C, 3B.

Sergio Vighetti: 1B, 1C, 2C, 3B.

Chatkaew Pongmala: 1C, 2C, 3B.

Carlo Alberto Artusi: 1C, 2C, 3B.

Elisa Montanaro: 1C, 2C, 3B.

Gabriele Imbalzano: 1C, 2C, 3B.

Mario Giorgio Rizzone: 1C, 2C, 3B.

Leonardo Lopiano: 1A, 1B, 2A, 2C, 3B.

All the co-authors listed above gave their final approval of this manuscript version.

Data access and responsibility statement

A. Romagnolo and M. Zibetti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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