

THE IMPACT OF BILATERAL SUBTHALAMIC DEEP BRAIN STIMULATION ON LONG-LATENCY EVENT-RELATED POTENTIALS

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ABSTRACT

The analysis of long-latency event-related potentials (ERPs) is of importance in the evaluation of certain cognitive functions and in following their subsequent changes. The aim of the present study was to investigate whether deep brain stimulation (DBS) itself can cause changes in the configuration of the ERPs.

Using a standard oddball auditory paradigm, we elicited auditory cognitive ERPs in 23 Parkinson's disease patients (in both DBS-ON and DBS-OFF conditions) and in 14 healthy controls. The P200 and P300 amplitudes and latencies, the motor reaction times and the accuracy of button pressing were compared between the DBS-ON and DBS-OFF states and subsequently correlated with the applied stimulation voltage and disease duration.

Comparison of the DBS-ON and DBS-OFF conditions revealed that neither the amplitude nor the latency of the examined ERP components changed significantly. However, the behavioral and attentional aspects (e.g. the accuracy of the button pressing responses to the target signal) definitely improved after the DBS was turned on. Positive correlations were demonstrated between the P300 amplitudes over the central and frontal regions and the optimal stimulation voltage and between the disease duration and P300 latencies over the Cz and Fz sites.

In conclusion, our data indicate that DBS may have different impacts on various electrophysiological parameters of the oddball paradigm.

Keywords: deep brain stimulation; P300; event-related potentials; subthalamic nucleus

Introduction

The analysis of long-latency event-related potentials (ERPs) is of importance in the evaluation of certain cognitive functions and in following their subsequent changes. Alternatively, various neuropsychological tests can be applied for a similar purpose, but severely affected Parkinson's disease (PD) patients (especially in an off-medication and off-stimulation state) may experience considerable difficulties in performing such tests. The advantages of applying ERPs rather than neuropsychological tests include the higher reproducibility, the shorter performance time and the lack of possibility of delusion by the subjects.

The aim of the present study was to evaluate whether the deep brain stimulation (DBS) itself can cause any changes in the configuration of the ERPs and in the accuracy of the performance during the oddball paradigm.

Methods

The patients

Twenty-three right-handed patients with idiopathic PD [1] participated in the study (age: 61.3 ± 5.7 years, 13 males, disease duration 8.9 ± 2.1 years). In all cases, subthalamic electrodes were implanted bilaterally with similar optimal stimulation settings (unipolar, 3.10 ± 0.42 V, 60 μ s, 130-135 Hz). None of the patients suffered from any other neurological illnesses or dementia, and had not experienced any psychotic episode previously.

The control group consisted of 14 subjects (62.3 ± 4.8 years, 8 males) who did not have any kind of neurological disorder or dementia. In accordance with the Regional Ethical Committee, all the participants gave their written informed consent to participate in the study; they all received scores of $>27/30$ points in the Hungarian version of the Mini-Mental State Examination [2] to exclude dementia.

Cognitive ERP recording

Cognitive ERP measurements were carried out at least 6 months (on average 11.1 ± 2.9 months) after implantation, by which time the micro-lesion effect had disappeared and the DBS had achieved constant, marked effects in relieving the PD symptoms.

The whole procedure was based on the current guidelines of the International Federation of Clinical Neurophysiology [3] and the technical review by Polich [4]. Briefly, the subjects were seated in a comfortable chair in a quiet room with their eyes open. In accordance with the international 10/20 system, silver/silver-chloride electrodes were applied (Fz, Cz, Pz, Oz; F3, C3, P3, F7, T3, T5, F4, C4, P4, F8, T4 and T6) and their resistance was kept below 5 kOhm. Each of the electrodes was referenced to the common A1/A2, and the ground electrode was placed over the forehead. Additionally, electrooculographic activity was recorded to identify eye movement artifacts during the offline analysis [5]. The calibrated output of an EEG16X (Medicor Inc., Budapest, Hungary) was digitalized at a sampling rate of 1000Hz, using a CED Power 1401 A/D converter (Cambridge Electronic Devices Inc, Cambridge, UK). The time constant was 1s, 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 performed during the recording.

ERPs were elicited by using a simple discrimination task, the oddball paradigm. Among the frequent (approximately 85%), 2000Hz, irrelevant (non-target) signals, randomly generated lower tone (1000Hz), relevant (target) stimuli were played at constant intensity (70 dB hearing level, 50 ms duration). The interstimulus interval varied randomly between 1.5 and 2.5s to achieve a comfortable stimulus presentation rate. Subjects were asked to press a button immediately after hearing the target signal. The speed and the accuracy of button pressing were equally emphasized; the patients were instructed to press the button as quickly as they could after hearing the target signal, and to avoid button pressing after non-target signals.

All measurements were carried out after at least 12h (usually overnight) drug withdrawal in order to eliminate the aliasing-effect of dopaminergic therapy on the P300 characteristics [6, 7]. The

DBS turned off (**DBS-OFF**) and DBS turned on (**DBS-ON**) states were evaluated in random sequence. Following a short learning period in each state, two recordings were made, each containing at least 50-60 valid relevant triggers (signals that were followed by button pressing). Recordings were accepted for further analysis only if the online ERP curves of both recordings were well-configured and reproducible [3]. Between the DBS-ON and DBS-OFF recordings, there was a 5-10-min break for refreshing, but the electrode positions remained unchanged and their resistance was re-checked.

Data analysis

All offline measurements and data modifications were carried out with Spike2 (version 6.03, Cambridge Electronic Devices Ltd, Cambridge, UK). Since all recordings were identified by a randomly generated alphanumeric ID, neither the identity of the subjects nor the nature of the measurements (DBS ON vs. OFF) was known to the investigator (NK).

Technical and eye-movement artifacts were first removed by using semi-automated methods under visual guidance. On the basis of current guidelines [3, 4], a bandpass infinite impulse response digital filter [8] was constructed and applied with a bandpass of 0.3-30Hz (Butterworth type, 4th order).

During ERP calculations (offset: 200 ms, epoch length: 1000 ms), only those target signals were included which were followed by button pressing. Subsequently, the **latencies and amplitudes of the P200 and P300 components** were determined. In cases of bifurcated P300, P3b was measured [3]. The **reaction time** (the interval between the target stimulus and the button pressing), the **button pressing time** (the interval between the starting and the ending point of button pressing), the **percentage of valid signals** (the number of target signals followed by button pressing divided by the number of target signals) and **occurrence of erroneous button presses** (the number of button presses after non-target signals divided by the number of non-

target signals) were also calculated. Finally, we **correlated** these parameters with the disease duration and stimulation amplitude.

Statistical analysis

All statistical analyses were carried out with an SPSS software package (version 15, SPSS Inc, Chicago, Illinois). The statistical significance level was set at 5%. Since none of the critical variables were distributed normally, nonparametric Wilcoxon signed ranks and Mann-Whitney U-tests were performed. For correlations, Kendall's tau was calculated.

Results

P300 and P200 latencies and amplitudes

Comparison of the results for the control group with those for the DBS-ON or DBS-OFF states demonstrated that the P300 latencies of Cz, Fz and Pz were significantly shorter ($p < 0.05$). Further, neither the amplitudes nor the latencies differed significantly over any other electrodes. Detailed information on the P300 latencies can be found in **Table 1**.

On comparison of the DBS-ON and the DBS-OFF recordings, none of the examined P200 and P300 latency and amplitude parameters was found to exhibit statistically significant differences. However, tendencies were observed to differences between these two states. After the stimulator was turned on, the P300 latencies became slightly shortened and the amplitude increased in some electrode positions (e.g. most midline electrodes: Cz, Pz and Oz, and the central region: C3 and C4), but these changes did not attain the level of statistical significance. Interestingly, in the frontal region (Fz, F8, F7, F3 and F4) the P300 latency was slightly prolonged and the amplitude was decreased after the stimulator was turned on, but likewise to statistically insignificant extents. The P200 amplitudes decreased minimally in the midline positions after the stimulation was initiated.

Reaction time

The reaction times were significantly longer in the DBS-OFF state than in the DBS-ON state ($p < 0.05$) or in the healthy group ($p < 0.05$, **Table 2**).

Button pressing time

In contrast with our expectations, the duration of button pressing was significantly shorter when the DBS was turned off than it was turned on ($p < 0.05$, **Table 2**).

Percentage of valid signals

In the DBS-OFF state, the patients missed the button pressing after the target signals more often ($p < 0.01$, **Table 2**) than during the stimulation.

Occurrence of erroneous button pressing

In the DBS-OFF condition, the patients erroneously pressed the button after the non-target signals ($p < 0.05$, **Table 2**) significantly more frequently than they did in the DBS-ON condition.

Correlation with the stimulation voltage

In the DBS-ON state, the P300 amplitudes over the Cz, F4, C4, F7, F3, T3, C3 and P3 electrodes exhibited a moderate, but statistically significant positive correlation with the stimulation voltage applied (coefficients: 0.41-0.51, $p < 0.05$); the strongest correlation demonstrated in the case of F7 (coefficient: 0.51, $p = 0.009$).

Correlation with the disease duration

The P300 latencies over Fz, Cz, F8 and P3 during stimulation and over F2 and F3 with the DBS turned off displayed a significant positive correlation with the disease duration. Moreover, the button pressing time in both the DBS-ON and the DBS-OFF condition correlated with the disease duration (coefficients: 0.43-0.58, $p < 0.01$).

Discussion

Bilateral subthalamic DBS is a technique widely used to treat drug-resistant, advanced idiopathic PD. However, some contradictory data have been reported on the impact of DBS on the cognitive process [9-11].

By making use of long-latency ERPs, we set out to test various cognitive factors including attention, memory and speed of stimulus evaluation time [4]. We hypothesized that if any impact of DBS on the cognitive processes would result in P300 and P200 amplitude and latency alterations.

The inter-group analysis between the PD patients (either DBS-ON or DBS-OFF) and the control subjects confirmed the previously published data, demonstrating significantly increased P300 latencies in the midline channels. The difference in P300 latency prolongations between non-demented, advanced PD patients and age-matched control subjects is a well-established phenomenon [12, 13], that is unrelated to the DBS itself.

Our comparison of the ERPs elicited during the DBS-ON and DBS-OFF conditions did not demonstrate uniform, statistically well-established alterations. Neither the amplitude nor the latency of the examined ERP components changed significantly over any electrode position. However, even though statistical significance was not attained, the topographic analysis revealed definitive tendencies: Over most of the midline positions, the P300 latencies slightly shortened, while over the frontal electrodes they became mildly prolonged in the DBS-ON state.

In contrast, the measurements of the behavioral and attentional changes, such as the time of button pressing or the percentage of missed button pressing and erroneous pressings clearly indicated the positive effects of bilateral subthalamic stimulation: the accuracy and the latency of the button pressing responses to the target signal affected significantly after the DBS was turned on, the stimulation resulting in fewer erroneous button presses after non-target signals and a shorter reaction time.

Interestingly we observed a moderate positive correlation between the P300 amplitudes (mostly over central and frontal regions) and the optimal stimulation voltage. As previous studies have demonstrated a relation between the P300 amplitudes and performance IQ and the motor items of the Functional Independence Measure [14], it may be assumed that the higher stimulation voltage affects not only the motor performance, but also the P300 amplitudes.

On the other hand, we also detected a moderate correlation between the disease duration and the P300 latencies. A longer disease duration resulted in longer P300 latencies among others in some midline positions (Cz and Fz) when the DBS was turned on, which may be associated with the more pronounced subclinical cognitive changes produced by the PD neurodegeneration.

Few studies have been reported on DBS and cognitive ERPs. Gerschlager et al. [15] demonstrated that after the DBS was turned on, the reaction time decreased significantly; but the reaction times they observed were much longer than ours (DBS-ON: 599 ± 93 ms; DBS-OFF: 671 ± 98 ms). Similarly to our results, they could not identify significant P300 latency changes after the DS was turned on; but again the latencies that they reported were much longer than ours (DBS-ON 429 ± 36 ms; DBS-OFF 440 ± 45 ms). These differences may be explained by several factors: we included considerably more patients (23 vs. 8), whose disease duration (7.1-12.3 vs. 8-22 years) and stimulation settings (3.10 ± 0.42 Volt, $60 \pm 0 \mu\text{s}$ vs. 2.4 ± 0.76 V, $84.4 \pm 12.1 \mu\text{s}$) were more homogeneous. Further, the stimulation mode (unipolar vs. bipolar) and the time interval between the operation and the examination were not mentioned in their manuscript. Furthermore, they compared only the latency of P300 over Cz between the DBS-ON and DBS-OFF conditions by applying a sampling frequency rate of 250 Hz with a 100 Hz digital low-pass filter, and a constant interstimulus interval (2 s), which may also have had an impact on the ERP configuration [3, 16].

As far as we are aware, our study is the first attempt to compare the topographic distribution of both the latencies and amplitudes of the P200 and P300 components [16-21] between DBS-ON and DBS-OFF conditions. Unexpectedly, we could not discern a clear-cut, uniform effect of

bilateral subthalamic stimulation on the configuration of the cognitive ERPs by comparing the latencies and amplitudes. However, the topographic distribution of the P300 components and the attentional and motor performance aspects seem to be changed in response to DBS. Similar to the neuropsychological tests, these results may indicate that deep brain stimulation possibly exerts different effects on different electrophysiological parameters and presumably on different aspects of mental functions, as well. Since the time interval between the operation and the ERP examination was rather short in our case (approximately 1 year), we intend to repeat this investigation on the same subjects with the same protocol, but at 5 years postoperatively.

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Legends

Table 1. P300 latency data in the PD group (both DBS-ON and DBS-OFF) and the control group. All values are given in ms.

Electrode position	DBS-OFF			DBS-ON			Control group		
	Median	25 th percentile	75 th percentile	Median	25 th percentile	75 th percentile	Median	25 th percentile	75 th percentile
Fz	355.61	342.519	404.576	364.429	324.589	401.638	315.634	309.864	379.857
F8	375.2	348.762	420.243	398.869	346.314	429.301	367.545	324.325	412.353
T4	371.283	341.907	402.618	366.387	328.198	405.272	339.864	301.244	378.973
T6	379.117	341.907	407.514	370.304	327.219	397.722	352.348	298.654	378.96
Cz	380.096	341.907	406.534	355.616	325.87	386.95	329.874	297.684	368.965
F4	378.138	341.907	411.43	379.794	327.22	420.033	350.134	312.342	399.863
C4	369.369	343.621	405.066	361.002	343.11	399.19	340.632	323.146	375.678
P4	367.366	341.418	402.618	372.752	344.845	404.576	345.674	323.464	380.463
Pz	374.906	348.517	403.842	369.325	344.845	400.659	334.975	306.785	371.864
F7	403.597	335.053	431.994	413.597	349.731	434.599	382.14	315.863	413.453
T3	369.52	332.795	409.227	371.773	342.152	406.304	346.231	316.435	379.865
T5	375.2	342.397	398.946	377.158	331.136	401.638	350.134	303.846	379.783
Oz	385.482	353.168	429.301	368.346	354.357	397.722	342.357	325.675	386.532
F3	361.491	339.085	404.086	384.963	341.908	406.779	353.562	315.749	382.462
C3	369.325	342.513	401.149	358.554	338.236	398.864	332.134	309.853	375.443
P3	368.239	338.48	400.17	360.512	318.896	404.087	339.874	302.453	379.563

Table 2. Comparison of reaction time, duration of button pressing, percentage of valid signals and the occurrence of erroneous button pressings in both the PD and the control group.

Studied task	Median	DBS-OFF		Median	DBS-ON		Median	Control group	
		25 th percentile	75 th percentile		25 th percentile	75 th percentile		25 th percentile	75 th percentile
Reaction time	486 ms	398ms	710 ms	439ms	378ms	527ms	418ms	328ms	489ms
Duration of button press	272ms	243ms	332ms	324ms	293ms	397ms	305ms	285ms	368ms
Percentage of valid signals	95.7%	92.7%	97.1%	98.3%	95.2%	98.6%	98.9%	96.9%	99.2%
Occurrence of mistakenly pressed buttons	1.34%	0.62%	3.48%	0.47%	0.22%	0.70%	0.38%	0.13%	0.68%

Figure 1. Event-related potential over the Cz electrode of a PD patient with bilateral subthalamic deep brain stimulation turned on (A) and turned off (B). Time is presented in s, the voltage in μs . The latency and the amplitude of the P300 and P200 components are marked with cursors showing the exact values.

