Effect of Unilateral Pallidotomy on Auditory Long-latency Event-related Potentials in Parkinson’s Disease.

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Abstract.

**Background:** P300 component from event-related potentials (ERPs) is considered a general index of information processing as a reliable measure of cognitive function and is related to attention and working memory operations involved during the oddball task. Reduced P300 amplitude and increased latency have been reported previously in patients with Parkinson’s disease (PD). The purpose of the present study was to detect changes in the P300 component in patients with PD that underwent unilateral pallidotomy.

**Methods:** A standard oddball paradigm was employed to elicit ERPs in 10 PD patients before and six months after surgery. Recordings were performed when patients were off medication to avoid motor and pharmacological complications. Patients were instructed to press a button only to target stimuli. Peak amplitudes and/or latencies of N100, N200, P300 components at scalp positions Fz, Cz, and Pz and reaction times were compared.

**Results:** Accordingly to data analysis latency of components N100, N200 and reaction times showed any statistical difference (p>0.05). Furthermore, a slight increase in amplitude and latency of P300 at Pz electrode was found although neither of both parameters reached the level of statistical significance.

**Conclusion:** These results suggest apparent stability of cognitive operations assessed through the oddball paradigm. However, contribution from multiple sources participating also in the P300 generation may obscure the effect of pallidotomy.

Keywords: Event-related potentials, P300, Pallidotomy.
Background

Unilateral posteroventral pallidotomy is a safe and effective neurosurgical procedure for the treatment of motor symptoms in advanced stages of Parkinson’s disease (PD). Ablative procedures namely lesion, remain at the present time a readily available option when elevated cost or health care services restrict access to deep brain stimulation (DBS) [1]. The primary outcome following surgery is improvement in the motor function mainly in the contralateral side of the lesion and assessment may be performed with or without antiparkinsonian medication [2].

Neuropsychological evaluation by contrast, is carried out mostly under the effect of drug therapy to prevent poor performance due to diminished movement execution [3]. To evaluate motor and cognitive changes after pallidotomy, an independent measurement of medication status and motor response is desirable. The P300 component of the event-related potentials (ERP) has demonstrated to be a useful tool for the measure of certain fundamental cognitive function under in PD patients [4]. Its parameters (amplitude and latency) are considered a global index of information processing and are related to basic processes namely update context, memory and selective attention. Moreover, P300 is also sensitive to neurological and cognitive changes [5, 6].

In PD, studies of modifications in the configuration of P300 after DBS have been reported before, but no reports after unilateral pallidotomy are found in the literature.

The aim of the present study was to evaluate the impact of unilateral posteroventral pallidotomy on the amplitude and latency of the N100, N200 and P300 components of the ERPs using a standard auditory oddball paradigm.
Methods

Patients

Ten right-handed patients (age: 57.7 ± 10.0, years, 5 females, disease duration 6.6 ± 2.3 years) with idiopathic PD were selected to participate in the study. All patients exhibited rigidity and bradykinesia as predominant symptoms with little tremor. They also exhibited significant motor fluctuation with severe disabling medication-related dyskinesias, showed one side more affected than the other, according to the Unified Parkinson’s Disease Rating Scale (UPDRS III) scores (30.9 ± 8.7 ) and staged in the Hoehn and Yahr scale III and IV when off medication. Patients with previous lesions in the brain (as observed with MRI), neurological or psychiatric disorders not related to PD and significant cognitive impairment or dementia according to de MMSE (score ≥ 28 ±2) were not considered candidates for surgical procedure. Integrity of the auditory pathway was assessed with auditory brainstem evoked potentials. Absence of waves I, III and V were criteria for exclusion of the study. All patients signed the written informed consent form approved by the Scientific and Ethical Committees of the General Hospital of Mexico City. In all cases stereotactic unilateral pallidotomy were performed contralateral to the most affected side using a N50 radiofrequency equipment (Inomed, Germany) by standard procedure [7]. In order to confirm the correct site of lesion, three months after surgery MRIs were performed. Lesions were on the right side in 6 cases and on the left side in 4 cases.

In the present study patients acted as their own control. Electrophysiological recordings were performed one or two weeks before and after six months of surgery in the off medication phase.
**ERPs Recording**

Patients were tested in the morning without dopaminergic therapy following a minimum of twelve hours of drug withdrawal. Electroencephalographic activity was recorded with Ag/AgCl electrodes at 19 sites (FP1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz, and Pz) according to the 10/20 international system. All electrodes were referenced to linked earlobes with a forehead ground and impedance below 10 KΩ. Two additional electrodes were placed at the outer cantus and above the left eye to recording electro-ocular activity (EOG). Synamps amplifiers and Neuroscan acquisition software was used to record the EEG/EOG activity (Neuroscan Inc., El Paso, USA). The sample rate was set at 1 KHz Hz and bandpass filters were at 0.1-30 Hz.

**Stimuli and Procedure**

ERPs were elicited with an auditory standard oddball paradigm. 400 computer-generated pure tones of standard 1000 and target 2000 Hz were presented binaurally at 60 dB SPL (10 ms rise and fall; 80 ms plateau), in a random sequence (80% standard and 20% target) with a variable inter-stimulus period between 800-1300 ms to avoid habituation. Subjects were seated in a comfortable chair located in an isolated dimly lighted room at one meter away from the computer screen were a fixation point were displayed. A brief practice series of stimuli were presented before the task. Subjects were instructed to watch the fixation point and to respond only to the target stimuli by pressing a button in an adapted pad located at the edge of the right arm of the chair and to ignore and refrain from responding to the standard tones.
Data Analysis

EEG analysis was performed offline with the same software used for acquisition. Epochs with amplitude exceeded ± 110 µV, excessive EOG or muscular activity were rejected from averaging automatically using a rejection algorithm. The EEG was divided into epochs consisted of 100 ms prestimulus baseline and 900 ms poststimulus. Average was performed in channels Fz, Cz and Pz only in target trials with correct response. Selection of scalp sites and latency windows for identification and measuring of components were according to correlational strength reported by [8] P300 were defined as the most positive peak within 250 and 500 ms poststimulus at Fz, Cz and Pz and N200 between 160 and 300 ms at Cz and Pz as the most negative peak from difference waveforms subtracting standard from target stimuli. N100 was considered as the most negative peak between 60-170 ms at Fz.

Statistical Analysis

SPSS version 17.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analysis. Alpha level of significance test was set at 0.5. Paired t-test and Wilcoxon signed ranks were performed.

Results

Following surgery none of the patients developed further postoperative complications.
In two patients, P300 was not detected. Hence, statistical analysis was performed with the other 8 patients.

**Reaction Times**

Table 1 summarizes the task performance. The mean reaction time was practically unaffected and number of hits and errors were almost identical. No statistical differences were found in reaction times before and after surgery.

**P300 Amplitude and Latency**

The grand average waveforms of patients before and after surgery for midline scalp sites Fz, Cz and Pz are compared in Fig.1 Target stimuli elicited ERPs similar in morphology for the component P300. Both P300 amplitude and latency at Fz, Cz and Pz increase after surgery. However, analyses of amplitudes and latencies before and after pallidotomy failed to reach statistical difference. Results of N100, N200 and P300 latencies are summarized in table 2 and P300 amplitude in table 3.

**N100 and N200 Latencies**

Sensory component N100 at Fz electrode displayed little variation after surgery. The results did not show any statistical difference for N200 at Cz or Pz sites.

**Discussion**

The objective of the present study was to assess the changes in the configuration of cognitive ERPs in PD patients following pallidotomy. Neither the amplitude nor the latency
of any of the components elicited through the oddball paradigm showed statistical
differences. The same result was true also for its behavioral counterpart assessed with the
reaction times. Nevertheless, we found a clear tendency on P300 latency increasing after
six months of surgery.

Similar variations in P300 latency as well as in other components of ERPs can be found
regarding the effects of surgical treatment for PD. Literature about this topic is limited to a
few studies [9-11], even though the surgical technique and target differ from ours, the
results are comparable not only on paradigms employed and electrophysiological
measurements but also on their empirical significance according to the ERPs theory.

Firstly, the N100 is a component reflecting sensory characteristics of stimuli which elicit
them. It is the first component appearing after both standard and target stimuli presentation.
Changes on its latency suggest difficulties on perception as were found by Naskar et al., [9]
when bilateral deep brain stimulation (DBS) was switched from Off to On in patients with
PD implanted bilaterally with electrodes on the subthalamic nucleus (STN). The second
component, the N200 (N2b), is usually associated to P300 in discrimination tas
ks as a
constituent of the N2-P3 complex; since both components independently reflect
information processing stages regarding attention, context update and memory storage in
oddball tasks [12]. Prolongation of N200 latency and decreasing in amplitude have been
associated to a general decay in attentional processes with ageing when compared with
young participants [13], furthermore, this component has been reported delayed in PD [14].
Gerschlager et al., [11] measured not only the P300 but also the N100, N200 and P200
components using different frequency target and standard stimuli. When DBS in the STN
was turned Off, their patients showed delayed RTs compared to the On-DBS phase.
However, no electrophysiological differences were reported. Our results are not different from theirs but interpretations must be done in another direction. DBS and pallidotomy are not equivalent techniques and postoperative outcomes within a short and long term as well as underlying mechanisms are very dissimilar. In first place, our intention was to assess the effect of pallidotomy by comparing ERPs before and after surgical procedure without antiparkinsonian medication. The studies mentioned above, were intended to assess the effects of DBS phases On-Off. Thus, the previous state of patients was unknown. Stability of electrophysiological measurements mainly P300 is our primary concern.

In short, P300 is a component which is considered as a general index of attentional and working memory processes elicited under certain experimental circumstances like those employed in the oddball paradigm [15]. For instance, in the P300 model, amplitude is believed to reflect the amount of neural resources related to the target detection and discrimination, while latency is related to the timing of such processes. ERPs waveforms elicited by PD patients in response to target stimuli (Figure 1), showed a slight increment in amplitude and latency after six months of pallidotomy. Hence, these changes in amplitude and latency suggest an enhancement of discrimination processes and a cognitive slowing respectively. However, as mentioned before these differences did not reach the level of statistical significance and points to the opposite direction of tendencies reported by Kovacs et al. [10]. Increase of latency may change over time as a result of pallidotomy, which is why a follow up for a minimum period of two years is pertinent.

The effect of pallidotomy concerning P300 generation may be local since ERPs recorded at the scalp are mainly the result of multiple generators broadly distributed all over the brain, including both cortical and subcortical areas. Some of the proposed generators for P300 are
structures located in the basal ganglia (BG), including the internal segment of *Globus pallidus* (GPI) [16]. Still, particular contributions of individual generators have probed not to be unequivocal, since specific damaged or surgically removed brain areas did not demonstrate reliable differences [17]. Thus, it is unlikely that contributions of either GPI or areas influenced by DBS on STN could be assessed without conventional noninvasive techniques like the employed to record the P300 on scalp. In accordance to our results, participation of GPI in generation of the P300 after pallidotomy could be obscured by other generators including those not belonging to the cortico-subcortico-cortical loops. Nevertheless, utility of P300 is not intended to be an electrophysiological method of source localization rather to assess cognitive status and information processing, as in this case followed by pallidotomy.

Our expectation about P300 after pallidotomy was to enhance its parameters both amplitude and latency as result of the improvement in motor functions, considering that BG are involved in motor and cognitive functions [18-21]. Discrepancy in our results may be caused by the absence of dopamine in structures within the nigro-striatal loops and to some extent in structures outside the circuitry contributing also in P300 generation. This possibility leads P300 as a measurement partially reflecting the effects of pallidotomy. Moreover, considerations must be done regarding the patient history and experimental parameters like the years of disease evolution and the period after electrophysiological assessment.
Conclusion

The use of long-latency P300 ERPs is a valuable tool for estimation of several cognitive functions without pharmacological or motor complications in PD. Pallidotomy may affect the speed of information processing in patients with induced hipodopaminergic condition after withdrawal of their medication as revealed by the apparent increasing of P300 latency. The P300 is a sensitive component to changes in cognitive functioning but is not specific for detection of the local effect caused by GPi lesions after surgery.

Competing interest

The authors declare that they have no competing interests.

Authors’ contributions

DS participated in the conceptualization, data analysis and drafted the manuscript. LS and FJ participated in the clinical and surgical procedures. LS, GG, RH and YR carried out clinical evaluations. FJ participated in data analysis and design of the study. All authors have read and approved the final manuscript.

Acknowledgements

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References


[7] Ref liz


Tables and figures captions.

Table 1. Comparison of the behavioral data.

Responses to target stimuli in the oddball paradigm before and after six months of pallidotomy.

Table 2. Comparison of N100, N200 and P300 latency

Mean and standard deviations of components 100, N200 and P300 latency at the three midline electrodes Fz, Cz, and Pz before and after six months of pallidotomy.

Table 3. P300 amplitude.

Mean and standard deviations of P300 amplitude at the three midline electrodes Fz, Cz, and Pz before and after six months of pallidotomy.

Figure 1. Event-related potentials grand averages of eight patients to target stimuli at electrode positions (A) Fz, (B) Cz and, (C) Pz.

Solid line represents the mean of ERPs before pallidotomy and dashed line represents the mean of ERPs after six months of pallidotomy.
Table 1.

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<th>Postsurgery</th>
<th>P value</th>
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<td>Target Hits (%)</td>
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<td>False Positives (%)</td>
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Table 2

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