

Bereitschaftspotential preceding eyelid blinks in Parkinson's disease

Potencial de Bereitschafts precedendo o piscamento ocular na doença de Parkinson

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ABSTRACT

The Bereitschaftspotential (BP) is a negative wave observed in EEG retrograde averaging, preceding a motor act. The objective was to study the BP preceding voluntary eyelid blinks in Parkinson's disease (PD) patients during *off* and *on* phases of levodopa. **Methods:** Ten PD patients in stages 1 and 2 of the Hoehn & Yahr classification were compared to 18 healthy controls. Artifact-free EEG segments of two seconds preceding the onset of the blink potential were averaged and analyzed, and the statistical significance of the measured amplitudes were evaluated by analysis of variance models. **Results:** The presence of a BP in the PD patients was demonstrated. The mean amplitudes at 0 ms were respectively 0.6 μV and 3.3 μV for the BP patients and the normal controls, respectively. **Conclusions:** The BP amplitudes were significantly smaller in PD patients than normal participants. The amplitudes of the BP were not modified by levodopa.

Keywords: contingent negative variation; Parkinson disease; levodopa

RESUMO

O Potencial de Bereitschafts (PB) é uma onda negativa observada retrogradamente no EEG precedendo um ato motor. **Objetivo:** Estudar o PB precedendo o piscamento palpebral voluntário em pacientes com doença de Parkinson (DP) durante as fases *off* e *on* da levodopa. Foram comparados dez pacientes com DP nos estágios 1 e 2 de Hoehn & Yahr com 18 controles saudáveis. Os segmentos de EEG livres de artefatos 2 segundos antes do início do potencial foram calculados e analisados e a significância estatística das amplitudes foi medida por modelos de análise de variância. **Resultados:** A presença de PB nos pacientes com DP foi demonstrada. As amplitudes médias a 0 ms foram respectivamente 0,6 μV e 3,3 μV para os pacientes com DP e controles respectivamente. **Conclusões:** As amplitudes do PB foram significativamente menores nos pacientes com DP do que controles. As amplitudes do PB não foram modificadas pela levodopa.

Palavras-chave: variação contingente negativa; doença de Parkinson; levodopa

The increasing prevalence and incidence of Parkinson's disease (PD), along with the increase in the population's life expectancy, has made it the second most frequent neurodegenerative disorder. This has a significant socio-economic impact on the quality of life of PD patients and caregivers due to progressive physical dependence in activities of daily living, in addition to subsequent cognitive impairment.

Hypomimia, or masked facies, in PD is characterized by reduced automatic and voluntary facial muscle expressiveness from the early stages, progressing with advancing disease¹ and generating social implications due to the expressionless, apathetic, depressed and introspective appearance². Among the hypomimia findings, there is a decrease of the frequency of eyelid blink by different pathways related to the planning and execution of this

motor act. This signal is one component of the extensive bradykinesia presentation.

Bradykinesia results from neuronal damage to pathways related to motor planning³. Voids in the dopaminergic and nondopaminergic circuits have been involved in this pathophysiology, generating an imbalance between inhibition and excitation, deficits and compensation^{4,5,6}. Changes in the dopaminergic pathways explain, at least in part, disturbances in the kinematics of spontaneous eyelid blink^{7,8,9}, and the voluntary one¹⁰ and in the blink reflex habituation of PD¹¹.

Pharmacological treatment with dopaminergic medications, considered the gold standard^{12,13}, results in partial problem-solving of bradykinesia as it improves the speed of movement^{7,8,10}, but not its rhythm and amplitude¹⁴, although the damage regarding the amplitude is very evident¹.

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Bereitschaftspotential (BP), or readiness potential, described by Kornhuber and Deecke in 1964 corresponds to the negative gradient starting one-and-a-half to two seconds before the motor potential, seen in electroencephalogram (EEG) retrograde averaging. This potential is divided into an early component related to planning and a late potential related to motor execution^{15,16,17}. This study aimed to evaluate the ocular blink in patients with PD in the *off* (without levodopa) and *on* phases (with levodopa) by measuring the BP.

METHODS

Subjects

The study was approved by the University Human Research Ethics Committee (statement 90208). All participants signed an informed consent form.

Ten PD patients (nine males) aged 43 to 78 years were randomly recruited in the Parkinsonian Patient Care Service (Pro-Parkinson) at the Clinic Hospital of the Federal University of Pernambuco, Brazil. All patients were diagnosed by a neurologist trained in movement disorders. Eighteen normal individuals (eight males) aged 17 to 60 years served as a comparison group. The analysis of this normal data was recently accepted for publication¹⁸.

Procedures

The participants sat comfortably on a chair and were instructed to relax, restrain moving the muscles of the neck, head or face and fix their gaze on a spot placed two meters away at eye level, blinking as naturally as possible, once every ten seconds. There were no auditory or visual clues for the time of blinking and the rhythm was rehearsed before starting the recordings.

The PD patients who met the inclusion criteria were invited to return the next morning. The patients were instructed not to take their morning anti-Parkinson's medication, before coming to the laboratory. They were also advised to avoid the intake of protein foods.

The PD patients were initially recorded at least 12 hours after the last anti-Parkinson's medication (*off* phase). Then levodopa/benserazide 100/25 mg was offered and, after 40 minutes, a second recording section (*on* phase) was made. The normal controls were recorded only once.

The EEG was recorded from 11 EEG electrodes placed in positions F3, FZ, F4, C3, Cz, C4, P3, Pz, P4, O1, O2 of the international 10-20 system of electrode placement, referenced to two electrodes placed on the mastoids and linked together. The vertical electrooculogram was recorded from two electrodes placed one centimeter above and below the right eye. The ground electrode was placed on the skin over the right clavicle.

The recordings were made using a Neuron-Spectrum NET polygraph (Neurosoft). The bandpass of the filters were 0.1 Hz to 35 Hz. Inter-electrode impedances (10 Hz) were kept below 3kΩ.

Data analysis

Blinks were visually identified as large positive deflections on the vertical electrooculogram channel and the beginning of the blink potential was marked. The two-second EEG segments preceding the mark were back-averaged together. Blinks that presented artifacts during or close to this period were eliminated from the analysis.

The averages were saved in text files and analyzed in a specific program written in Matlab software. Initially, the waves obtained by the general averaging of each group of participants were observed. The measurement points were established at -1800 ms (at the beginning of the BP), -500 ms (at the start of the late component of the BP) and 0ms (at the onset of the blink potential). To compensate for background noise, the amplitudes were averaged in a 100 ms segment centered on the latency to be measured.

Statistical analysis of the BP amplitudes was performed on the C3, C4 and Cz electrodes, using the STATISTICA version 10 statistical package (StatSoft). The statistical analysis was performed using analysis of variance (ANOVA) models. A three-way repeated measures ANOVA model, condition (*off* and *on*), time (-1800 ms, -500 ms, 0s) and electrodes (C3, Cz, C4) was used to compare the PD group during the *off* phase and the *on* phase. A mixed-model ANOVA, group (PD and controls) and two repeated-measures, time (-1800 ms, -500 ms and 0 ms) and electrode (C3, Cz and C4), was used to compare the PD patients with the normal controls. The Geisser-Greenhouse correction was applied for violation of sphericity. The Newman-Keuls test was used for *post hoc* analysis, when necessary. The critical p-value was 0.05.

RESULTS

Table 1 lists some demographic and clinical characteristics of the studied PD patients.

Table 1. Some characteristics of the studied Parkinson's disease patients.

Initials	Sex	Age	TD	H&Y	UPDRS II	UPDRS III	UPDRS T	MMSE
AC	M	43	8	3	9	14	23	29
EL	M	44	3	1	10	29	39	25
DA	M	48	6	1	10	15	25	30
SF	F	52	2	1	10	24	34	26
JF	M	58	4	1	12	30	42	27
CE	M	53	5	2	19	90	109	30
MA	M	61	3	1	11	29	40	30
AJ	M	61	5	1	5	20	25	30
EV	M	68	1	2	8	35	43	24
JQ	M	78	4	1	5	7	12	30

M: male; F: female; TD: time of disease; HY: Hoehn and Yahr scale; UPDRS: unified Parkinson's disease rating scale; MMSE: mini-mental state examination. Age and TD in years.

A total of 230 blinks during the *off* phase and 250 blinks during the *on* phase were averaged from the 10 PD patients, giving a mean of 23 blinks per patient during the *off* phase and 25 blinks per patient during the *on* phase.

Figure 1 shows the grand average of the EEG recorded at all electrodes from the PD patients in the *off* (dashed line) and *on* (solid line) phases.

In both conditions, a negative potential of increasing amplitude was observed starting around -1,500 ms before the blink onset. This potential had a broad scalp distribution, but was most evident at the central regions. Around -500ms before the blink potential, a change in the wave configuration was observed. No obvious differences were seen between the potentials obtained during the *off* phase and the *on* phase.

Figure 2 shows the analysis of the amplitudes of the potentials at C3, Cz and C4 electrodes measured -1800 ms, -500 ms and 0 ms before the onset of the blink potential. The waveforms and measurement times are shown at the top of the figure. Amplitudes were averaged in a segment of 100ms centered on the latency to be measured (vertical gray shadows). The means and standard deviations of the amplitudes at each electrode, condition and time-point are illustrated at the bottom of the figure. Table 2 shows the ANOVA of the data.

The ANOVA showed a significant effect for time. No interactions were significant. The *post hoc* analysis (Newman-Keuls) showed that the amplitudes at -500ms (onset of the late component) and 0ms (end of the BP) were both significantly larger than the amplitude at -1800 ms (just before

the onset of the early BP component). The amplitudes at -500 and 0ms were not different. This is consistent with the presence of a BP preceding the voluntary blink of PD patients, during both *off* and *on* phases. No significant differences between the amplitudes during the *off* phase and the *on* phase were observed.

A total of 900 blinks were averaged from the 18 normal controls, giving a mean of 50 blinks per individual. As there were no significant differences between the measured amplitudes of the BP during *off* and *on* phases, all 580 blinks from the 10 PD patients were averaged, giving a mean of 58 blinks per participant.

Figure 3 shows the analysis of the amplitudes of the potentials at C3, Cz and C4 measured -1800, -500 and 0 ms before the onset of the blink potentials from the PD patients (solid line) and the normal controls (dashed line). The waveforms and measurement times are shown at the top of the figure. The means and standard deviations of the amplitudes at each electrode, condition and time-point are illustrated at the bottom of the figure. Different scales were used for the PD patients (right side) and for the control group (left side). Table 3 shows the ANOVA of the data.

The ANOVA showed a significant interaction between the time and the group. The *post hoc* analysis showed that the amplitudes at -500 ms and 0ms were both significantly larger in the control group than in the PD group. At -1800 ms the amplitudes were not different between groups. Therefore, the amplitude of the BP of PD patients is significantly smaller than the BP of normal controls at all analyzed electrode positions.

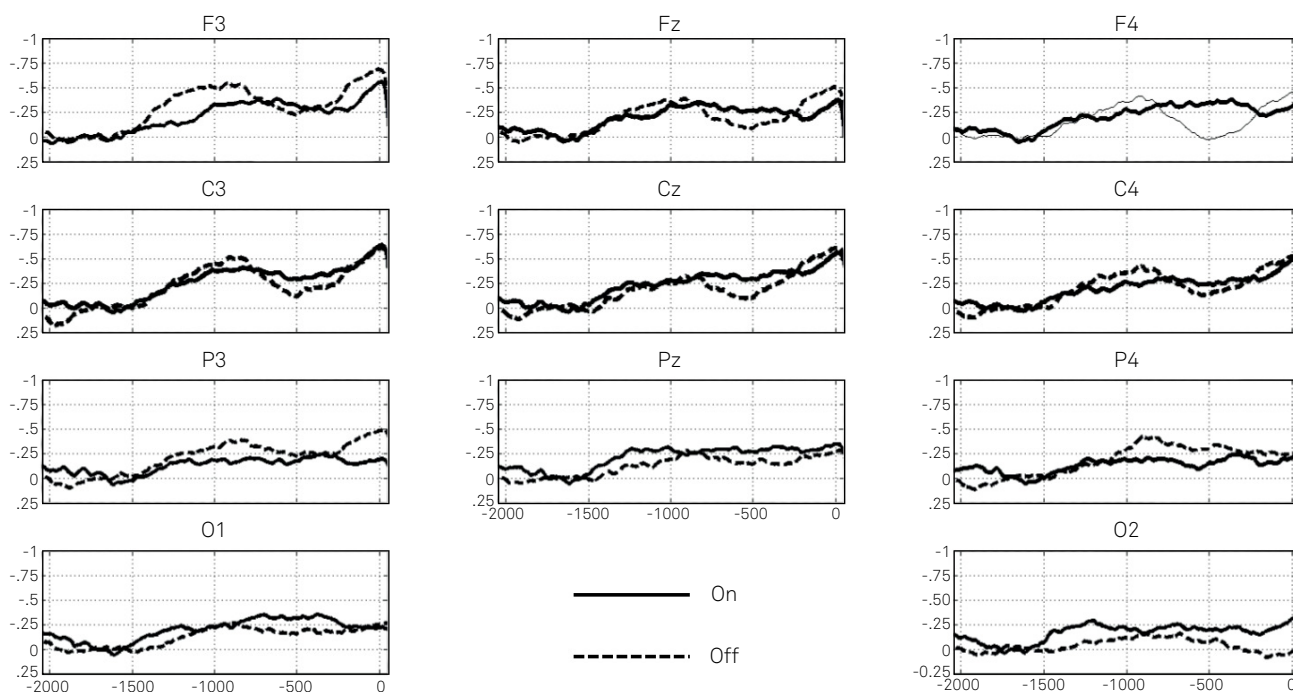


Figure 1. Grand average of the Bereitschaftspotential of the Parkinson's disease patients during the *off* phase (dashed line) and *on* phase (solid line) of medication at all electrode positions.

Table 2. Factorial repeated-measurement analysis of variance of the amplitudes of the Bereitschaftspotential of the Parkinson's disease patients, with three repeated measurements: condition (*off* and *on* medication), time (-1800, -500 and 0ms, relative to the onset of the blink potential) and electrode (C3, Cz and C4).

Variable	SS	df	MS	F	p
Intercept	11.706	1	11.706	12.145	0.007
Error	8.675	9	0.964		
Condition	0.212	1	0.212	0.284	0.607
Error	6.716	9	0.746		
Time	9.552	2	4.776	7.072	0.005*
Error	12.157	18	0.676		
Electrode	0.063	2	0.032	0.099	0.906
Error	5.730	18	0.318		
Condition × time	0.260	2	0.130	0.275	0.762
Error	8.494	18	0.472		
Condition × electrode	0.021	2	0.010	0.207	0.815
Error	0.8900	18	0.049		
Time × electrode	0.064	4	0.016	0.176	0.950
Error	3.293	36	0.092		
Condition × time × electrode	0.018	4	0.005	0.063	0.992
Error	2.534	36	0.070		
Newman-Keuls test of the main effect TIME					
-1800 ms × 0 ms					0.005*
-1800 ms × -500 ms					0.024*
-500 ms × 0 ms					0.233

SS: Sum of squares; Df: Degrees of freedom; MS: mean squares; F: ANOVA Statistic * P<0.05

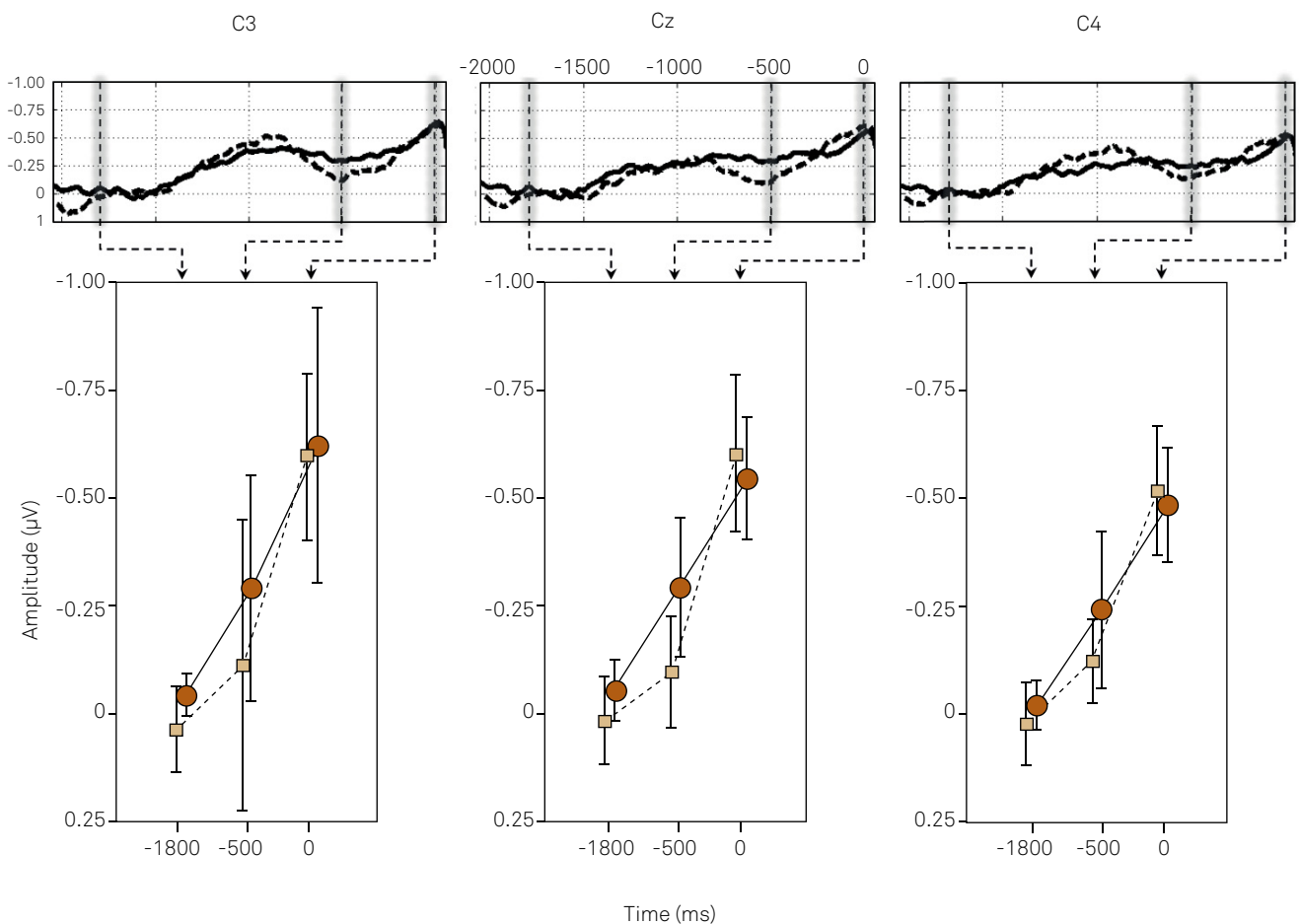


Figure 2. Analysis of the amplitudes of the Bereitschaftspotential of the Parkinson's disease patients at C3, Cz and C4 electrodes measured -1800, -500 and 0 ms before the onset of the blink potentials. The waveforms and measurement times are shown on the top of the figure. Amplitudes were averaged within a segment of 100 ms centered on the latency to be measured (vertical gray shadows). The means and standard deviations of the amplitudes at each electrode, condition and time-point are illustrated at the bottom of the figure.

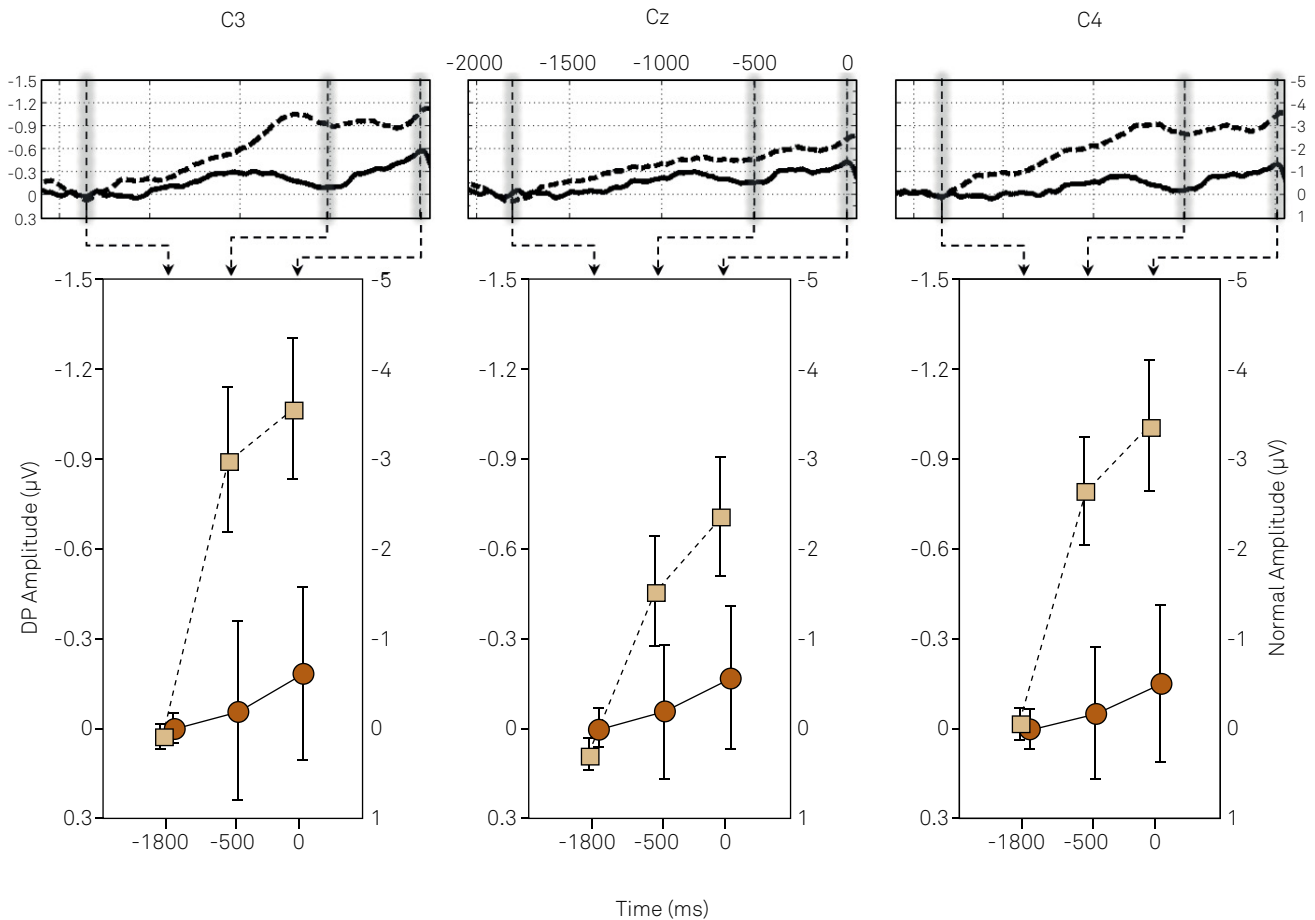


Figure 3. Analysis of the amplitudes of the Bereitschaftspotential of the Parkinson's disease patients (grand average of all recordings during the *off* phase and the *on* phase) and the normal controls at C3, Cz and C4 electrodes measured -1800, -500 and 0 ms before the onset of the blink potentials. The waveforms and measurement times are shown on the top of the figure. Amplitudes were averaged within a segment of 100ms centered on the latency to be measured (vertical gray shadows). The means and standard deviations of the amplitudes at each electrode, condition and time-point are illustrated at the bottom of the figure. Different scales were used for the PD patients (right side) and the normal controls (left side).

Table 3. Factorial mixed-model analysis of variance of the amplitudes of the Bereitschaftspotential of the Parkinson's disease patients and normal controls: Group (PD patients and normal controls) and two repeated measures: time (-1800, -500 e 0 ms, relative to the onset of the blink potential) and electrode (C3, Cz and C4).

Variable	SS	Df	MS	F	p*
Intercept	227.770	1	227.770	10.379	0.004*
Group	128.687	1	128.687	5.864	0.024*
Error	504.716	23	21.944		
Time	134.349	2	67.175	7.847	0.001*
Time × group	74.475	2	37.238	4.350	0.019*
Error	393.785	46	8.561		
Electrode	9.394	2	4.697	2.296	0.112*
Electrode × group	9.731	2	4.866	2.379	0.104*
Error	94.087	46	2.045		
Time × electrode	2.860	4	0.715	1.244	0.298*
Time × electrode × group	2.665	4	0.666	1.159	0.334*
Error	52.878	92	0.5748		
Newman-Keuls test of the interaction time × group					
Parkinson × Control at -1800 ms					0.902
Parkinson × Control at -500 ms					0.033*
Parkinson × Control at 0 ms					0.012*

SS: Sum of squares; Df: Degrees of freedom; MS: mean squares; F: ANOVA Statistic* P<0.05

DISCUSSION

This study demonstrated that there is a BP preceding voluntary blinks in PD patients. This BP does not differ significantly during the *off* phase and the *on* phase of medication. To our knowledge, there have been no studies on BP preceding blinks in PD patients. In a previous recently-accepted study¹⁸, we reported the presence of a BP preceding voluntary (but not spontaneous blinks) in normal participants.

The BP of PD patients had a broad scalp distribution, most clearly identified at the central regions, similar to the BP of normal controls and to the BP preceding other movements in PD and normal controls^{19,20,21}.

The amplitude of the BP of the PD patients was much smaller than the BP of the control group, even though the PD patients were at a relatively mild stage of the disease. At its largest negativity (just preceding the blink) the mean amplitudes of the BP of the PD patients and the normal controls were respectively 0.6 μ V and 3.3 μ V. This suggests a significant dysfunction of the motor neural networks, even in patients with few symptoms. This finding is consistent with previous descriptions of reduced amplitude of BP preceding other movements in PD patients, even in the early stages^{12,22,23,24,25,26}. It is also in accordance with the early clinical finding of paucity of facial expression and reduced blink rate in PD patients, suggesting that neural systems related to motor planning, especially those related to facial expression and blinks, are affected early in PD¹.

Most PD patients were at stage 1 of the H&Y scale and showed low scores on the motor and daily living activities of the Unified Parkinson's Disease Rating Scale. Although the disease has a progressive symptomatology, it is known that damage to neuronal pathways begins 8–17 years before the appearance of the first symptoms, with different progression characteristics depending on the compensatory mechanisms and the age of onset. Therefore, even patients who are diagnosed early may present with significant neural dysfunction.

Although most studies have reported smaller BP amplitudes in PD patients compared to normal controls, some studies have reported no differences^{21,24,26} or even larger amplitudes^{27,28}. The reasons for these discrepancies are not clear.

In our study, the dopaminergic drug did not significantly affect the BP. A larger amplitude during the *on* phase has been described in BP preceding the movement of the fingers^{22,23}.

The absence of an influence by levodopa on the BP preceding the eye blink may result from an earlier, and more severe, dysfunction of the dopaminergic networks involved in the planning of eye blinks, than finger movements.

Although levodopa is considered the gold standard drug for PD therapy, it does not appear to act on all the mechanisms that cause bradykinesia¹⁴. Nondopaminergic pathways play a role in the clinical improvement of motor planning and BP amplitude in PD patients, as observed after unilateral posteroventral pallidotomy²⁸ and after neurofeedback techniques²⁵. These studies corroborate the presence and importance of nondopaminergic or dopaminergic pathways resistant to modulation mechanisms of the motor planning in PD⁶.

The amplitudes at C3, Cz and C4 were not significantly different in PD patients. In our previous study with normal controls¹⁸, we found larger amplitudes at C3 and C4 in relation with Cz. This was also observed by Yamamoto²⁹, but not Shimizu and Okiyama²⁰, in their study with saccadic movements. A lateral component of the BP source complex, perhaps the face motor cortex, is less active in PD patients than in normal subjects. A source analysis study may shed some light on this issue.

The main objective of this study was to determine if a BP preceding voluntary blinks could be demonstrated in PD patients. We believe this was accomplished. The potentials we obtained had very low amplitudes in comparison with the potentials obtained from normal participants. Although the normal participants we used were not perfectly age-matched with the PD patients, we believe the differences in amplitudes are obvious. Furthermore, it has been shown that there is no significant change in BP amplitudes with increasing age, within certain limits³⁰.

In conclusion, this is the first study demonstrating a BP preceding eyelid blinks in PD patients. The BP of the PD patients had much smaller amplitudes than the BP of normal subjects, even though the PD patients were in the early stages of the disease. These potentials could be used in the future as early diagnostic and evolutionary markers of Parkinson's disease. Further investigations should be conducted. Currently considered the gold standard drug in Parkinson's disease, levodopa did not obviously modify the BP preceding blinks, suggesting that the resistant nondopaminergic or dopaminergic accessory pathways related to motor planning should be investigated in search of more effective medications.

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