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Do P1 and N1 evoked by the ERP task reflect primary visual processing in Parkinson's disease?

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Abstract. *Objectives:* To evaluate whether P1 and N1 evoked by ERP tasks could appropriately reflect primary visual processing in Parkinson's disease (PD). *Methods:* We recorded ERPs in 13 PD patients with duration of illness less than 5 years and 18 age-matched normal control subjects. P1 and N1 from Oz were evoked by a visual oddball and a delayed matching S1-S2 task. The effect of different events on P1 and N1 was studied. All patients were given an ECD-SPECT examination, and the SPECT images were overlaid on the 3D-MRI. The correlation of P1 or N1 to the regional cerebral blood flow (rCBF) was studied. *Results:* P1 was not influenced by different events. There was no significant P1 differences between the PD and the normal group. N1 was significantly shorter and smaller in the patients than that in the normal group. N1 amplitude after the waveform subtraction (target-frequent) in the PD group did not show significant difference with that in the normal controls, nor with the N1 before the subtraction. Nd, the subcomponent of N1 after the subtraction in the patients was significantly earlier and smaller than that in the normal controls. P1 only weakly correlated with the rCBF in the occipital lobe. N1 was correlated with the rCBF in a global region. *Conclusions:* The results provided some evidence that P1 might reflect the primary visual processing, and N1 might be involved in both primary and cognitive visual processing. The altered N1 in the PD patients might be due to the deformed Nd.

Key words: event-related potentials, N1, P1, Parkinson's disease, SPECT, visual cortex

Abbreviations: ERPs – event-related potentials; PD – Parkinson's disease; SPECT – single photon emission computed tomography; [^{99m}Tc]-ECD – technetium-99mN,N′-1,2-ethylene-diylbis-L-cy steine diethylester

Introduction

Recording event-related potentials (ERPs) provides an effective electrophysiological method for studying stages of information processing. A basic assumption of this approach is that stimulus input is processed in a number of parallel or hierarchical stages including pattern encoding, pattern recognition,

stimulus classification, task evaluation, response selection, and execution of the response. A visual oddball paradigm may yield a large P3 component to target stimuli, which was thought as an endogenous potential and may reflect the time of task evaluation and/or decision making. As P3 latency is independent of motor reaction, it is thought to be a useful parameter in evaluating the cognitive impairments in patients with motor disorders such as Parkinson's disease (PD). On the other hand, the early components P1 and N1, which could also be evoked after a visual oddball task, are usually considered representing the primary visual response. It would be very useful clinically if we could evaluate both the primary and high visual processing simultaneously by only one task such as visual oddball paradigm. However, the properties of the P1 and N1 components are not clear yet. Some authors regard them as exogenous components reflecting pure sensory processing [1], whereas the others believe that they are endogenous components and could be enhanced with attention [2]. There are also many reports showing an endogenous N1 overlapped with a negative difference, Nd component [3]. Up to now, the problem of whether the early Nd reflects a N1 modulation or an endogenous processing negativity (PN) are unsolved [4, 5]. Therefore, it is very necessary to clarify the properties of these early components. In order to clarify the properties of these early components, in this study, we investigated: (1) whether P1 and N1 are influenced by different events in different tasks, such as a rare target stimulus in oddball task and a S2-same stimulus in a delayed matching S1-S2 task, (2) how P1 and N1 change after the waveform subtraction (rare target- frequent, Figure 1), (3) whether there are any differences of these components between the PD patients and normal controls, (4) how these components correlate with the regional cerebral blood flow (rCBF). Due to the variability and uncertainty of early components at Fz and Cz, we focused our interest on these early components at Oz. We studied these early components in PD patients, since PD was reported to be involved in both the primary and high visual function [6]. Using grating pattern stimuli, Bodis-Wollner et al. found delayed VEP in PD patients [7]. Later studies of the same authors [8] and others reported the delayed [9, 10] and/or attenuated P300 [11] using an oddball paradigm. However, none of them tried to evaluate both the primary and the high order function in PD using the same paradigm.

We compared the P1 and N1 after a visual oddball and a visual S1-S2 task to study the different stimuli effects. The correlation of P1 or N1 to rCBF was also studied in order to clarify their possible function. To get relatively accurate rCBF in each cerebral region, SPECT results were overlaid on the 3D-MRI. The interest region was determined by the MRI image.

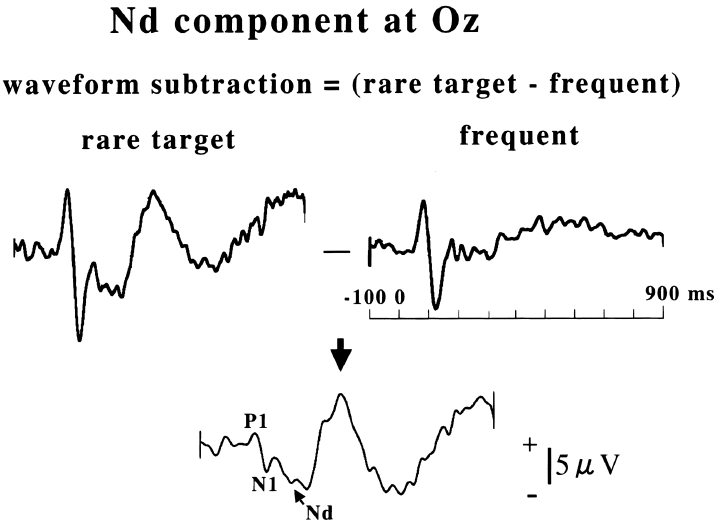

Figure 1. The waveform subtraction to isolate N1 and Nd subcomponents of N1 complex.

Materials and methods

Subjects

The subjects were 13 PD patients with duration of illness less than 5 years (mean age, 63.1±9.5 years, 3 men, 10 women) and 18 age-matched healthy volunteers (mean age, 65.2±10.3 years, 8 men, 10 women). All PD patients fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for definite Parkinson's Disease [12]. Patients with secondary parkinsonism or with evidence of focal cerebral lesions were excluded from the study. All patients showed good response to antiparkinsonian medication. The mean duration of illness was 2.3±1.1 years. All normal control subjects showed normal neurological findings without any history of neurological or psychiatric disorders. None of the control subjects exhibited any abnormal MRI findings. All subjects had the visual acuity score of 20/25 or better with or without correction. All the subjects gave signed informed consent after the purpose of the study and the protocol had been explained to them, and before any procedures were performed.

ERP tasks

A modified visual oddball paradigm and a visual S1-S2 paradigm were performed as described previously [13]. The modified visual oddball paradigm had three kinds of visual stimuli: rare target (田, 20%), rare nontarget (乙, 20%), and frequent nontarget (口, 60%). The three kinds of stimuli had the

same size (15×15 cm^2) and contrast (0.7). The duration of each stimulus was 68 ms. The interval between the onset of each sequential stimulus was 1600 ms. The view distance for subjects was 70 cm. The subjects were instructed to press the button with the right thumb for the rare target stimuli.

The S1-S2 task employed a delayed matching paradigm consisting of a warning stimulus, i.e. a frame figure (duration, 48 ms); a first stimulus, S1(duration, 96 ms); and a second stimulus, S2 (duration, 96 ms). The figures of the S1 and S2 stimuli were random pairs of the three kinds of figures used in the oddball paradigm. S2 followed S1 by 1500 ms. The interval between the start of S2 and that of the next warning frame was 2500 ms. Subjects were instructed to compare the figures of S1 and S2. Two sessions were performed for each experiment condition. The subjects were instructed to compare the two figures. When S2 was the same as S1 (S2-same, 33%), the right button was to be pressed by the right thumb or middle finger. When S2 was different from the S1 (S2-different, 67%), the left button was to be pressed by the left thumb or middle finger.

Each session of the oddball task consisted of 3 blocks with breaks of 2 minutes between blocks. Each block included four rare target stimuli. Each trial of the S1-S2 task consisted of 2 blocks with breaks of 2 min between blocks. Each block included 6 S2-same stimuli.

P1 and N1 were recorded from Oz referred to linked earlobes. In order to confirm the reliability of the results, P300 from the Cz and Pz was also recorded simultaneously. The EOG was monitored using a forehead-temple montage with a rejection level of± 100 μV. The advantage of using the forehead-temple montage is that we could monitor both the vertical and horizontal eye movement as well as blinking. The bandwidth of preamplifiers ranged from 0.1 to 50 Hz. EEG was analyzed 100 ms before and 900 ms after each visual presentation. The Nd component was obtained by subtracting the waveforms to the frequent from waveforms to the rare target (Figure 1). We measured the latency and amplitude of P1, N1 and Nd to the rare targets in the oddball task, and P1 and N1 to the S2-same in the S1-S2 task.

SPECT measurement

SPECT was performed using [^{99m}Tc]1,1-ECD (Neurolite) as a tracer. Transaxial SPECT images were taken parallel to the orbitomeatal line at three levels [14]. The three SPECT images were reconstructed and overlaid on 3D-MRI display, separately. The rCBF in each region of the frontal, parietal, temporal, and occipital lobes was identified based on the MRI images. The rCBF was measured according to the rCBF pixel analysis. We calculated the mean rCBF pixel value in each of the above region as the rCBF value in each cerebral lobe [14].

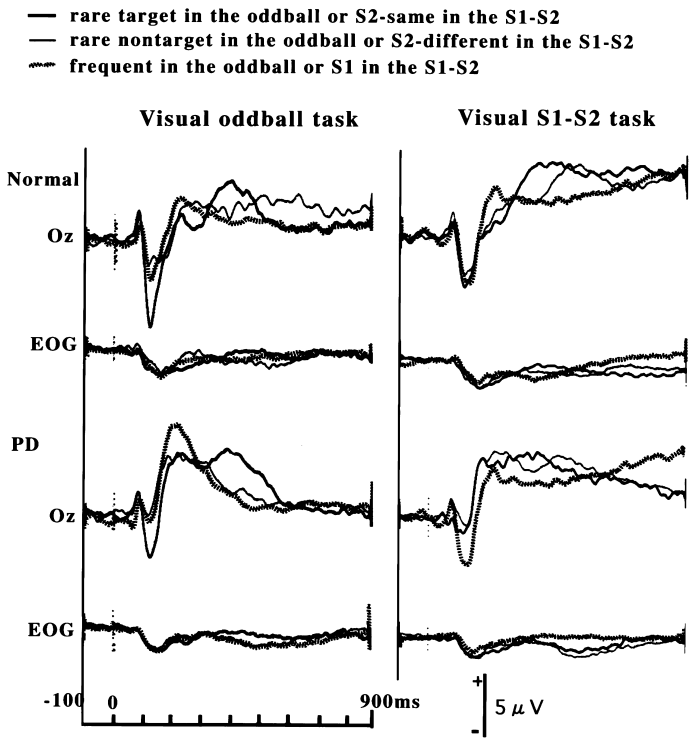

Figure 2. Comparison of P1, N1 to different events in the normal control group (the upper part) and the PD group (the lower part). N1 amplitude was largest to the rare target stimuli.

Results

As shown in Figure 2, we recorded clear P1 and N1 at Oz to the rare target, rare nontarget, and frequent stimuli of the oddball task, and to the S2-same, S2-different, and S1 of the S1-S2 task. Clear P300 from Cz and Pz was also obtained, which implied that the subjects attended the task actively (Figure 3). Similar responses were also evoked in PD patients (Figures 2 and 3).

The comparison of P1 and N1 among different stimuli in normal controls and PD patients

The mean±SD latency and amplitude values in both the normal controls and the PD patients were summarized in Table 1. Two-way ANOVA was computed to study the effects of the diagnosis (Normal, PD) and the stimuli (rare target, rare nontarget, frequent, S2-same, S2-different, and S1) on P1 and N1. Neither the diagnosis nor the stimuli were found to influence P1 latency or amplitude significantly. Diagnosis showed significant effects on N1 latency ($F=26.609$, $p<0.0001$) and N1 amplitude ($F=18.357$, $p<0.0001$). N1 latency

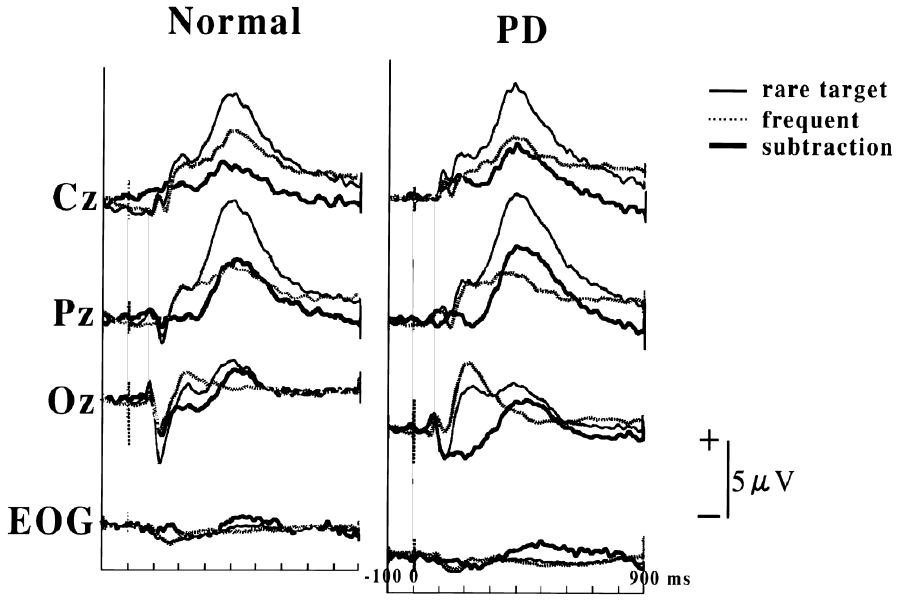

Figure 3. P1 and N1 before and after the waveform subtraction in the normal control group (left) and the PD group (right). P1 was not changed before and after the waveform subtraction, whereas, N1 amplitude was significantly reduced after the waveform subtraction in both the normal and the PD group. The N1 amplitude in the PD group was smaller than that in the normal group.

in the PD group was significantly shorter than the N1 latency in the normal controls to the following stimuli: frequent (t=2.424, p<0.05), S2-same stimuli (t=2.547, p<0.05), S2-different (t=2.816, p<0.05). N1 amplitude in the PD group was significantly attenuated compared with that in the normal controls to the following stimuli: rare nontarget (t=2.592, p<0.05), frequent (t=2.145, p<0.05), and S2-different (t=2.241, p<0.05).

A significant stimulus effect was found in N1 amplitude (F=3.182, p<0.01). The N1 amplitude to the rare target was significantly larger compared with that to the rare nontargets (t=3.752, p<0.005), frequent (t=2.252, p<0.005), S2-same (t=3.093, p<0.01), and S2-different (t=3.093, p<0.005).

The comparison of P1 or N1 before and after the waveform subtraction in the normal and the PD group

Two-way ANOVA was computed to study the diagnosis (Normal, PD) and the subtraction effect (before and after the waveform subtraction) on P1 and N1. P1 latency did not change significantly before and after the waveform subtraction, neither in the normal, nor in the PD group (Figure 3). There was no P1 or N1 latency difference between the normal and the PD group, either. N1

Table 1. The mean ± SD latency and amplitude of P1, N1 at Oz before the subtraction and Nd after the subtraction in the normal subjects and the PD patients

			Latency (ms)		Amplitude (μV)	
			Normal	PD	Normal	PD
Oddball task	P1	Rare target	95.8±9.7	90.6±17.1	4.2±2.6	4.9±4.0
		Rare nontarget	93.3±19.7	94.8±16.3	3.9±2.3	3.9±3.0
		frequent	91.5±17.1	89±6.2	3.4±2.6	4.4±3.4
	N1	Rare target	135.1±15.3	120.5±19.9	−8.4±5.5	−5.6±3.6
		Rare nontarget	136.5±28.8	115.5±30.3	−5.1±3.5	−1.4±3.4*
		frequent	138.0±15.2	117.0±17.1*	−5.5±4.5	−1.3±4.6*
	Nd	(raretarget-frequent)	181.0±29.6	170.5±27.8*	−2.6±3.5	–
S1-S2 task	P1	S2-same	92.6±20.9	89.4±25.8	3.4±2.9	3.7±3.9
		S2-different	91.0±14.0	90.7±11.4	4.7±3.4	5.1±4.1
		S1	90.3±4.4	83.5±17.8	3.5±2.4	2.8±2.3
	N1	S2-same	139.4±16.3	119.5±19.8*	−5.7±4.2	−2.0±4.7
		S2-different	140.1±15.1	120.5±16.7*	−5.0±2.8	−1.5±4.4*
		S1	139.1±13.1	126.7±12.6	−6.9±2.9	−5.1±2.8

*$p<0.05$ significant difference of P1 or N1 between the PD subjects and the normal controls by student t test.

amplitude was significantly different between the normal and the PD group (F=5.633, $p<0.005$), also different between before and after the waveform subtraction (F=4.081, $p<0.01$). N1 amplitude was significantly reduced in the PD group compared with that in the normal group (t=2.745, $p<0.001$). N1 amplitude after the waveform subtraction was significantly smaller than that before the subtraction to the rare target (t=2.748, $p<0.05$) (Figure 3).

The comparison of Nd between the normal and the PD group

Nd latency was earlier in the PD group compared with that in the normal group (Table 1). Nd waveform was deformed and overlapped with the late component N200 in the PD group (Figure 4). Therefore, it was difficult to evaluate the Nd amplitude difference between the normal and the PD group (Figure 4).

The correlation of P1, N1, or Nd to the rCBF in the PD group

Table 2 showed the significant correlation of P1, N1, or Nd to the rCBF of each cerebral cortex in the PD patients. R>0.5 and $p<0.05$ was defined as significant. However, due to this multiple linear regression test and a small number of subjects, spurious correlation might be produced. In order to avoid

Table 2. The significant correlation of the rCBF values with the P1, N1, or Nd (r>0.5; p<0.05)

		the rCBF of each cerebral cortex	*r* value	*p* value
	P1 latency			
	Rare target	vs. left occipital cortex	−0.532	0.042
	S2-different	vs. left occipital cortex	−0.554	0.047
P1	S1	vs. left occipital cortex	−0.570	0.031
		right occipital cortex	−0.604	0.012
	P1 amplitude			
	Frequent	vs. right occipital cortex	0.500	0.033
	N1 latency			
	S2-same	vs. left temporal cortex	−0.500	0.049
		left parietal cortex	−0.502	0.050
		left occipital cortex	−0.639	0.009*
	S2-different	vs. left temporal cortex	−0.564	0.010*
		right occipital cortex	−0.693	0.008*
	N1 amplitude			
	Rare target	vs. right parietal cortex	0.661	0.0001*
	Rare nontarget	vs. right parietal cortex	0.844	0.005*
		right occipital cortex	0.7000	0.011
N1		left occipital cortex	0.823	0.001*
	Frequent	vs. right parietal cortex 0.781	0.019	
		left occipital cortex	0.851	0.011
	S2-same	vs. right temporal cortex	0.615	0.010*
		left occipital cortex	0.810	0.004*
	S2-different	vs. right parietal cortex	0.957	<0.0001*
		left temporal cortex	0.730	0.009*
		left parietal cortex	0.697	0.003*
		left occipital cortex	0.924	0.001*
		right occipital cortex	0.733	0.002*
	S1	vs. left temporal cortex	0.696	0.038
	Nd latency	vs. left parietal cortex	−0.579	0.043
Nd	(rare target-frequent)	left occipital cortex	−0.799	0.006*
		rare occipital cortex	−0.703	0.032

*p<0.01 significant correlation after the correction.

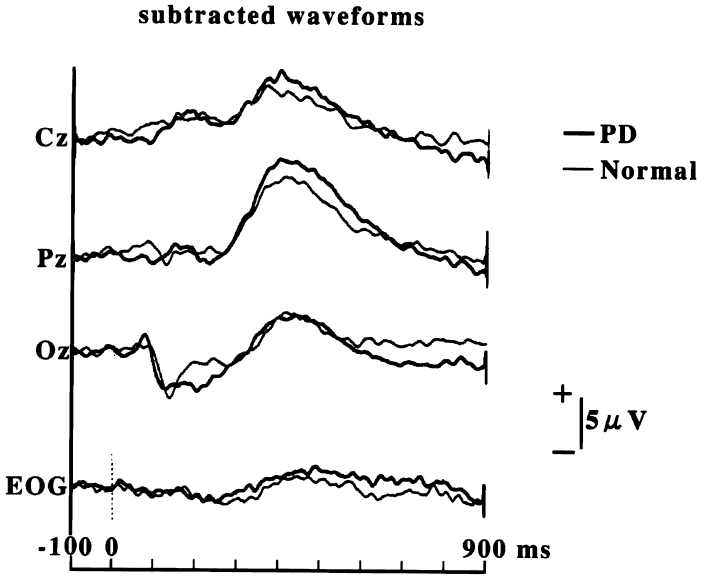

Figure 4. Comparison of Nd subcomponent between the normal control group and the PD group. Nd was smaller and earlier in the PD group than in the normal group.

this false leading result, we corrected the significant criteria to $r<0.5, p<0.01$. With this correction, we found that the significance of the correlation between the P1 and the rCBF value in the left or/and right occipital cortex vanished. The significant correlation found were: N1 latency to the S2-same vs. the rCBF value in the left occipital cortex; N1 latency to the S2-differenct vs. the rCBF value in the left temporal and the right occipital cortex; N1 amplitude to S2-different vs. the rCBF value in bilateral parietal, left temporal, and bilateral occipital lobe; N1 amplitude to other stimuli (rare target, rare nontarget, frequent, and S2-same) vs the rCBF value in the right parietal, the left occipital, and temporal cortex. Nd latency was significantly correlated with the rCBF value in the left occipital cortex.

Discussion

P1 was not influenced by different events either in the oddball nor the S1-S2 tasks. P1 latency and amplitude in PD showed weak correlation only with the rCBF in the occipital lobe. This result indicates that P1 might be an exogenous component reflecting the primary visual processing. However, the correlation of P1 with the rCBF in the occipital lobe disappeared after we used the correction. Therefore, further studies should be done to confirm this matter. Unlike the VEP studies [7], we did not find any P1 difference between

the PD and the normal group. This might be due to the fact that our patients were in the early stage of the disease and had good responses to the levodopa therapy [15].

N1 latency did not show any difference among different events. However, N1 amplitude was significantly larger to the rare targets compared to the other stimuli. N1 latency showed significant correlation with the rCBF values in the occipital cortex, whereas N1 amplitude showed significantly correlation with the rCBF value in a global cortical area. Therefore, N1 might be both an exogenous and an endogenous component related to early selective attention.

The N1 latency was earlier and amplitude was smaller in the PD group compared with that in the normal control group. However, the N1 subcomponent after the waveform subtraction in the PD group did not show significant difference with that in the normal control group. The N1 subcomponent after the waveform subtraction in the PD group did not show significant difference with the N1 before the waveform subtraction, either. Therefore the N1 subcomponent does not seem to be important for the difference of N1 between the PD and the normal group before the waveform subtraction. Nd latency in the PD group was significantly earlier and deformed, therefore, the deformed Nd in the PD group might be one of the explanations for the N1 difference between the PD and the normal group before the waveform subtraction.

Due to the small number of the subjects and the lack of rCBF correlation evidence from the normal subjects in the present study, it might be difficult to give a conclusion that P1 evoked by ERP tasks at Oz is an exogenous component whereas N1 is a complex exogenous and endogenous component. Nevertheless, our results provide some important information on this matter, and cast light on further pursing the nature of these early components. Large scale of normal studies are very necessary before the application of simultaneous evaluation of P1 and P3 components clinically.

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