

Visual event-related potential changes at two different tasks in nondemented Parkinson's disease

L. Wang, Y. Kuroiwa*, T. Kamitani

Department of Neurology, Yokohama City University School of Medicine, Yokohama, 236-0004, Japan

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Abstract

A visual oddball paradigm and an S1–S2 paradigm were employed to evoke event-related potentials (ERPs) in 38 nondemented Parkinson's disease (PD) patients and 24 healthy elderly subjects. Delayed N200 and reduced P300 amplitude in the whole PD sample were only found in the S1–S2 paradigm. Delayed N200 and reaction time in PD with short duration of illness were found only after the S1–S2 paradigm, which might be an early sign of cognitive changes in PD. This is the first study to apply an S1–S2 paradigm for a visual P300 test in PD and proved the value of this paradigm for detecting minor cognitive abnormalities. ERP changes were correlated with clinical features. Reduced P300 amplitude for the S1–S2 paradigm was significantly correlated with WAIS-R scores and gait disturbance. The correlation between P300 amplitude and clinical scores has rarely been discussed before. P300 latency during the oddball paradigm in PD was influenced by age at test, age at onset, and duration of illness. This may explain why P300 results in nondemented PD have varied among previous authors. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: P300; N200; Parkinson's disease; WAIS-R; Oddball paradigm; S1–S2 paradigm; Motor disability; Event-related potential

1. Introduction

Cognitive impairment in Parkinson's disease (PD) has been observed in a large body of studies over the past three decades. About 10–15% PD patients may have dementia [1], but cognitive deficits including subtle and subclinical changes are observed very frequently in nondemented PD [2]. The existence of cognitive impairment or not in PD has become a critical point for clinical treatment [3]. Therefore, a sensitive test is essential to detect minor cognitive changes in an early stage of PD. The so-called P300 test, which is thought to be an electrophysiological index of cognitive function independent of motor influence [4], is often used to study cognitive changes in PD.

Delayed P300 is found in demented PD. However, results of P300 changes in nondemented PD vary largely among authors. Some authors have reported prolonged

P300 latency in nondemented PD [5–10], whereas others have not found it [11–14]. Most studies failed to verify P300 amplitude abnormality in PD, whereas Green et al. [14] found enlarged P300 amplitude in an early stage of nonmedicated PD. The inconsistencies of ERP changes in nondemented PD may be due to different modalities of the oddball paradigm employed to evoke the P300. The clinical status of patients may also be an important factor. Age at onset, for example, is known to be responsible for the wide diversity of mental status in PD [15]. Stanzione et al. [16] reported that age and stage were important for P300 latency changes in PD patients.

The first purpose of the present study was to find a clinically useful task that would be sensitive enough to detect minor cognitive changes in PD. In addition to using the conventional oddball paradigm, we also designed a more complicated paradigm which we called the S1–S2 paradigm. We studied how ERPs in PD changed during the two tasks. The second purpose was to find the cause of the inconsistent P300 results among the various authors. We

*Corresponding author. Tel.: +81-45-787-2800; fax: +81-45-788-6041.

analyzed how clinical features such as age at test, age at onset, and duration of illness influenced ERPs in non-demented PD.

2. Subjects and methods

2.1. Subjects

The subjects consisted of 24 elderly healthy volunteers (11 men, 13 women) and 38 non-demented patients (14 men, 24 women) with the clinical diagnosis of idiopathic Parkinson's disease. The normal subjects had no history of neurological or ophthalmological disorders with a visual acuity score of 20/25 or better with or without correction. The PD patients had a visual acuity score of 20/40 or better with or without correction. All patients fulfilled UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [17] for definite Parkinson's disease. Patients with secondary Parkinsonism or with evidence of focal cerebral lesions were excluded from the study. All patients diagnosed as demented according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, were excluded from the study.

2.1.1. PD group

The age of the whole PD group ranged from 41 to 77 years, with a mean±SD of 65.8±8.8 years. All patients were being treated with antiparkinsonian medication. The data were analyzed according to several subdivisions. One was age at test: PD(younger) [age at test<62 years old] and PD(older) [age at test≥62 years old]. Another subdivision concerned age at onset: PD(early) [age at onset<62 years old] and PD(late) [age at onset≥62 years old]. The third subdivision concerned duration of illness: PD(short) [duration of illness<5 years] and PD(long) [duration of illness≥5 years].

Motor disability was graded on a modified motor

disability rating scale used in Japan [18]. This scale rates mask-like face, postural changes, bradykinesia, finger tapping, tremor, rigidity, propulsion, retropulsion, gait disturbance, start hesitation, and ADL (activities of daily living). There are five scores (0, 1, 2, 3, 4) for each item. Wechsler Adult Intelligence Scale-Revised (WAIS-R) was also evaluated in PD patients. The details of PD patients are presented in Table 1.

2.1.2. Normal control group

The whole normal control group was age matched for the whole PD group; ranging in age from 42 to 79 years old, with mean±SD of 62.3±10.4 years. Age-matched normal control subgroups for each PD subgroup were referred to as follows: group N1 (10 cases, 52.4±6.9 years) matched for PD(younger), group N2 (14 cases, 69.2±6.1 years) matched for PD(older), group N3 (23 cases, 62.8±10.8 years) matched for PD(early) and PD(short), group N4 (16 cases, 68.3±5.9 years) matched for PD(late) and PD(long). Some of the normal subjects were overlapped between group N3 and N4.

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.

2.2. ERPs

2.2.1. Stimuli and tasks

A modified visual oddball paradigm and a delayed matching S1–S2 paradigm were used to elicit ERPs (Fig. 1). The modified oddball paradigm was previously employed by Tachibana et al. [19]. Three kinds of visual stimuli: rare target (20%), rare nontarget (20%), and frequent nontarget (60%) were presented randomly on an electronic tachistoscope screen (Iwasaki Tsushin, Tokyo). The duration of each stimulus was 68 ms. The interval between the onset of each sequential stimulus was 1600

Table 1
PD patient backgrounds

		Number of cases	Age at test (years) Mean±SD	Age at onset (years) Mean±SD	Duration of illness (years) Mean±SD	L-dopa dosage (mg/day) Mean±SD	F-IQ ^a ±SD	V-IQ ^b ±SD	P-IQ ^c ±SD
Age at test	PD(younger)	9	52.8±6.7	42.2±6.4	4.6±4.3	300±200	98.2±10.9	97.0±11.8	100.7±10.1
	PD(older)	29	69.8±4.2	61.5±8.5	8.3±8.5	390±140	94.3±11.8	100.2±13.9	89.1±9.9 ^d
Age at onset	PD(early)	19	61.0±9.7	50.2±6.9	10.8±9.6	385±171	99.6±9.6	104.1±11.5	94.7±10.6
	PD(late)	19	70.5±4.1	66.5±3.2	4.1±3.0	347±146	90.8±11.9 ^d	95.6±14.0	88.1±10.3
Duration of illness	PD(short)	21	63.2±9.6	60.7±9.6	2.5±1.1	294±148	95.6±12.9	98.3±15.0	94.1±11.1
	PD(long)	17	68.9±6.5	55.4±9.6	13.5±8.2	441±136 ^c	94.5±10.7	101.0±11.7	88.4±10.0

^a F-IQ=full-scale IQ.

^b V-IQ=verbal IQ.

^c P-IQ=performance IQ.

^d $P<0.05$

^e $P<0.01$ [the comparison of PD(younger) vs. PD(older), PD(early) vs. PD(late), and PD(short) vs. PD(long)].

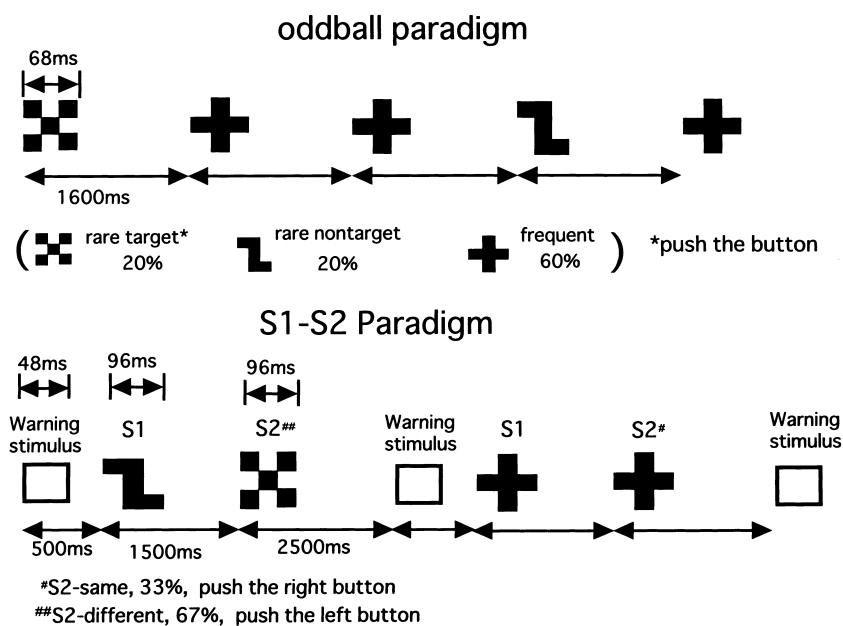


Fig. 1. A sketch representing the time course and the task for the oddball and S1–S2 paradigms. For further explanation see text.

ms. Subjects were instructed to press the button for rare target stimuli as rapidly and correctly as possible.

The S1–S2 task employs a delayed matching paradigm consisting of an empty frame warning stimulus (48 ms); the first stimulus, S1 (96 ms); and the second stimulus, S2 (96 ms). The duration of the warning stimulus was 48 ms. S2 was presented 1500 ms after the onset of S1. The interval between the onset of S2 and that of the next warning frame was 2500 ms. Subjects were instructed to compare the figures of S1 and S2. When S2 was the same as S1, we called it S2–same stimulus (33%), for which the subjects were asked to press the right button. When S2 was different from S1, we called it S2–different stimulus (67%) for which the left button was to be pressed. Data of both experiments were recorded only after the subjects understood the tasks completely through a training period.

2.2.2. Recordings

ERPs were recorded with Ag/AgCl electrodes from Cz, Pz, and Oz referred to linked earlobes. The EOG was monitored using a forehead-temple montage with a rejection level of $\pm 100 \mu\text{V}$. Electrode impedance was maintained below $5 \text{ K}\Omega$. The bandwidth of the preamplifiers ranged from 0.1 to 50 Hz. Two trials of 10–20 summations to rare target or S2–same stimuli were performed for each session, to confirm the reliability of recording. The EEG activity was analyzed 100 ms preceding and 900 ms following each visual presentation.

2.2.3. Measurement of latency and amplitude

N200 latency, P300 latency and P300 amplitude were measured after rare target stimuli of the oddball paradigm and S2–same stimuli of the S1–S2 paradigm. N200 was

identified as a negative component (peak or notch) at Cz and Pz occurring 200–400 ms after the onset of the stimulus. P300 was identified as the largest positive wave at Cz and Pz 300–700 ms after the onset of the stimulus. N200 latency and P300 latency were measured as the interval between each peak (or notch) and the onset of stimulus. Reaction time (RT) was defined as the interval between the onset of the rare target or the S2–same stimulus and the onset of the button press.

When the P300 peak was identified at Cz and Pz, P300 amplitude was defined as the voltage difference between the P300 peak and the prestimulus baseline (averaging voltage of 100 ms before the stimulus). When the P300 peak could not be identified in the patient group, we arbitrarily defined P300 amplitude at Cz and Pz as the maximum upward deflection in μV from the prestimulus baseline between 300–700 ms after the onset of the stimulus.

2.3. Statistical data analysis

A two-tailed Student's *t*-test or Mann-Whitney U test was used to compare the ERP difference between the two groups.

Since 'age at test', 'age at onset' and 'duration of illness' were closely related to each other, the effect of these factors on ERPs and RT could not be computed by three-way ANOVA. Therefore, two-way ANOVA was computed for ERPs and RT using the factors 'age at test' and 'duration of illness' as covariates. Two-way ANOVA was also computed separately using the factors 'age at onset' and 'duration of illness'. The post hoc test was

performed by means of Fisher's PLSD (Fisher's Protected Least Significant Difference).

Pearson product-moment correlation coefficients (r) were computed while evaluating the relationships of WAIS-R scores to ERP components and RT. When r was 0.5 or more, the correlation was thought to be significant. The Spearman rank correlation (r_s) test was used for evaluation of relationships of modified motor disability rating scores to ERP components and RT.

3. Results

The patients' performance error rate did not exceed 5% on either task. While N200 and P300 peaks could be clearly identified at Cz and Pz in each session in the normal control group, they were sometimes difficult to identify in PD patients (3 cases in oddball paradigm and 7 cases in S1–S2 paradigm). Those subjects with unrecognizable P300 response were found to have had a longer duration of illness.

3.1. ERP and RT abnormalities in PD compared with the normal control group

3.1.1. Comparisons of ERPs and RT between the whole PD group and the whole normal control group

The whole PD group showed significantly prolonged N200 latency and reduced P300 amplitude during S1–S2 paradigm. However, none of ERP components during oddball paradigm showed significant difference between the whole PD group and the normal control group (Table 2).

RT to both paradigms was significantly prolonged in PD group.

3.1.2. Comparisons of ERPs and RT between PD subgroups and their normal control subgroups

Fig. 2 is a comparison of grand averaging waveforms

between PD subgroups and their normal control subgroups using the classification of duration of illness.

Tables 3 and 4 show the comparisons of ERPs at Cz and RT, between PD subgroups and their age-matched normal control subgroups. The following statistical ERP changes in PD subgroups were found in both oddball and S1–S2 paradigms: significantly delayed N200 in PD(older) and PD(late) as well as reduced P300 amplitude and prolonged RT in PD(long).

However, on some occasions, significant difference between PD subgroups and normal controls was found only in the S1–S2 paradigm: delayed N200 in PD(early), PD(short), and PD(long); reduced P300 amplitude in PD(older), PD(early), PD(late); delayed P300 in PD(long) and prolonged RT in PD(older), PD(early), PD(late) and PD(short).

3.2. The effect of age at test, age at onset, and duration of illness on ERPs and RT in the whole PD group

None of the ERP components or RT were linearly correlated with age at test, age at onset, or duration of illness. However, significant effect of these factors was found after statistical analysis using ANOVA.

3.2.1. The effect of age at test and duration of illness

ERP components and RT were analyzed by two-way ANOVA using 'age at test' [PD(younger), PD(older)] and 'duration of illness' [PD(short), PD(long)] as covariates. P300 latency for the oddball paradigm showed significant variation as a function of the factor 'age at test' (Cz, $F=10.706$, $P<0.01$; Pz, $F=8.282$, $P<0.01$). Significantly prolonged P300 latency was found in PD(older) compared with that in PD(younger) (Fisher's PLSD, Cz, $P<0.01$; Pz, $P<0.01$). P300 amplitude for the oddball paradigm showed significant variation as a function of the factor 'duration of illness' (Cz, $F=8.889$, $P<0.01$). Significantly reduced P300 amplitude was found in PD(long) compared with that in PD(short) (Fisher's PLSD, Cz, $P<0.01$).

For the S1–S2 paradigm, N200 latency showed signifi-

Table 2

Mean and standard deviation of ERPs and RT to the oddball and S1–S2 paradigms in the whole PD group and the whole normal control group^a

		Oddball paradigm		S1–S2 paradigm	
		Cz	Pz	Cz	Pz
N200	PD	271.4±38.1	265.4±35.4	269.2±38.1**	273.3±42.3*
Latency (ms)	Normal control	251.4±40.3	260.3±31.1	239.0±37.6	247.7±32.3
P300	PD	432.1±59.0	437.3±61.8	432.3±76.4	437.9±76.8
Latency (ms)	Normal control	418.4±38.5	425.3±42.9	409.4±33.2	423.9±38.2
P300	PD	13.9±7.5	15.8±8.0	12.3±7.8*	12.8±8.3*
Amplitude (μV)	Normal control	16.9±5.6	18.6±4.6	16.2±5.5	16.7±5.9
RT	PD	515.6±161.4*		889.5±360.6**	
(ms)	Normal control	439.5±68.6		624.3±148.3	

^a Significant differences of ERPs or RT between the whole PD group and the whole normal control group by Student's t -test.

* $P<0.05$; ** $P<0.01$.

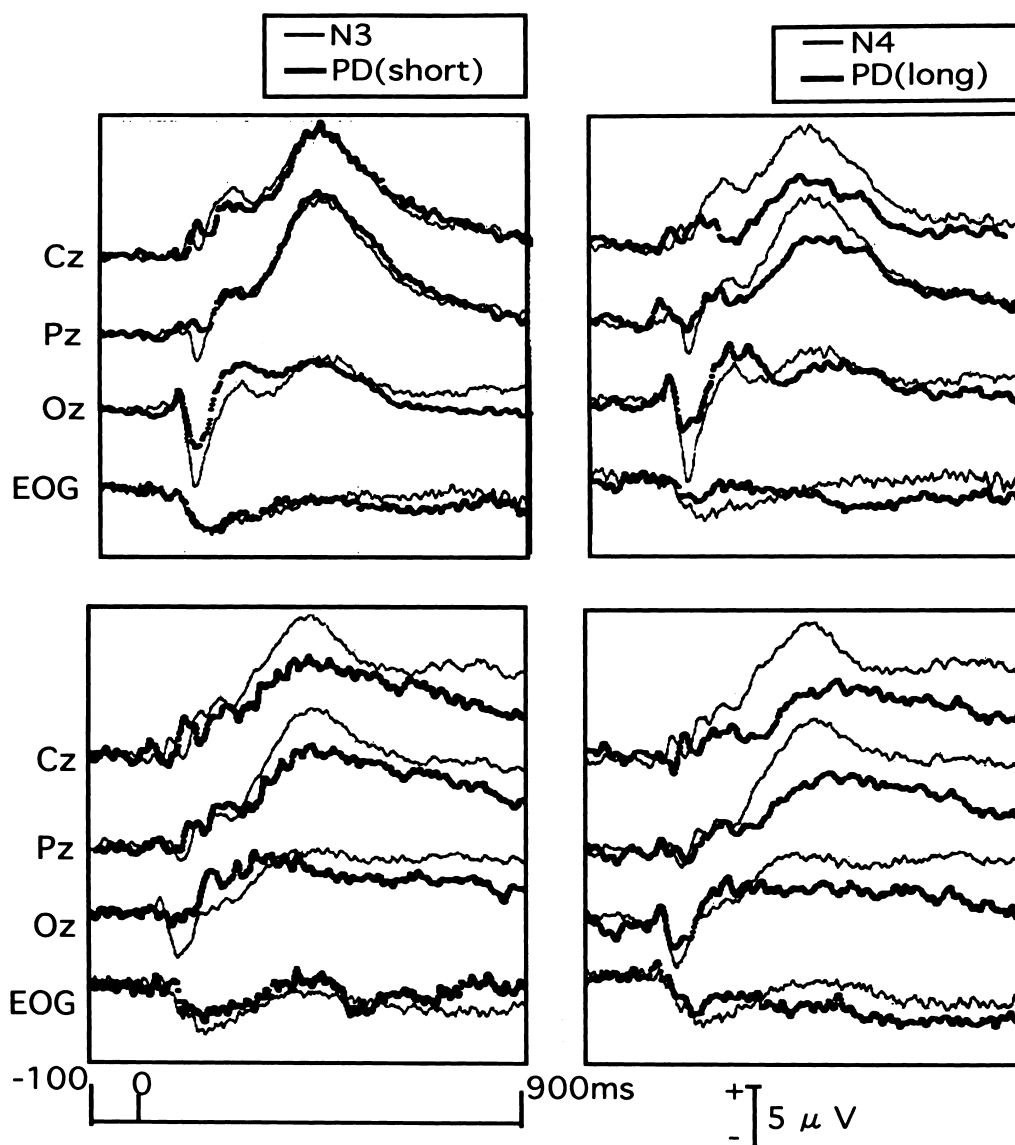


Fig. 2. Average ERPs in patients (upper panel: oddball paradigm; lower panel: S1–S2 paradigm). Left: PD(short) and its normal control group, N3; Right: PD(long) and its normal control group, N4. Obviously prolonged P300 latency and reduced P300 amplitude were found in the PD(long) group during the S1–S2 paradigm.

cant variation as a function of the factor ‘age at test’ (Cz, $F=7.322$, $P<0.05$; Pz, $F=4.664$, $P<0.05$). Significantly prolonged N200 latency was found in PD(older) compared with that in PD(younger) (Fisher’s PLSD, Cz, $P<0.01$; Pz, $P<0.05$).

RT varied as a function of the factor ‘duration of illness’ during both paradigms (oddball, $F=33.106$, $P<0.0001$; S1–S2, $F=4.339$, $P<0.05$). Significantly prolonged RT was found in PD(long) compared with RT in PD(short) (Fisher’s PLSD, oddball, $P<0.001$; S1–S2, $P<0.05$).

3.2.2. The effect of age at onset and duration of illness

Using ‘age at onset’ [PD(early), PD(late)] and ‘duration of illness’ [PD(short), PD(long)] as covariates, two-way ANOVA was also computed for ERP components and RT.

N200 latency for the oddball paradigm showed significant variation as a function of the factor ‘age at onset’ (Pz, $F=4.286$, $P<0.05$). Significantly prolonged N200 latency was found in PD(late) compared with that in PD(early) (Fisher’s PLSD, Pz, $P<0.05$). P300 latency for the oddball paradigm showed significant variation as a function of both the factor ‘age at onset’ (Pz, $F=5.862$, $P<0.05$) and the factor ‘duration of illness’ (Cz, $F=4.438$, $P<0.05$). Significantly prolonged P300 latency in PD(late) and in PD(long) was found. P300 amplitude for the oddball paradigm showed significant variation as a function of the factor ‘duration of illness’ (Cz, $F=9.088$, $P<0.05$; Pz, $F=6.048$, $P<0.05$). Significantly reduced P300 amplitude was found in PD(long) compared with those in PD(short) (Fisher’s PLSD, Cz, $P<0.01$; Pz, $P<0.05$).

Table 3

Comparison of ERPs at Cz and RT to the oddball paradigm between PD subgroups and their corresponding normal control subgroups (numbers are mean±standard deviation)

		N200 latency (ms)	P300 latency (ms)	P300 amplitude (μV)	RT (ms)
Age at test	PD(younger)	253.8±37.8	384.9±31.6	15.8±9.0	569.5±239.5
	N1	263.6±43.0	409.0±33.2	18.9±3.2	428.4±86.6
	PD(older)	276.6±37.2*	447.8±57.9	13.3±7.0	497.6±127.7
	N2	245.4±41.0	426.3±42.4	15.8±6.5	451.2±58.5
Age at onset	PD(early)	265.3±38.0	419.7±53.6	13.7±8.3	519.1±194.3
	N3	252.5±41.8	419.1±39.0	17.1±5.5	437.2±68.6
	PD(late)	277.8±38.2*	444.4±63.1	14.2±6.9	512.8±136.4
	N4	245.6±36.0	419.9±41.4	16.3±6.6	438.9±55.0
Duration of illness	PD(short)	272.1±37.2	419.0±48.7	16.8±7.4	456.9±100.5
	N3	252.5±41.8	419.1±39.0	17.1±5.5	437.2±68.6
	PD(long)	270.6±40.1	448.4±68.0	10.1±5.9**	613.3±198.2**
	N4	245.6±36.0	419.9±41.4	16.3±6.6	438.9±55.0

* $P<0.05$; ** $P<0.01$ (Student's *t*-test or Mann-Whitney U test).

N1, N2, N3, N4; normal control subgroup age-matched to each PD subgroup.

Table 4

Comparison of ERPs at Cz and RT to the S1–S2 paradigm between PD subgroups and their corresponding normal control subgroups (numbers are means±standard deviation)

		N200 latency (ms)	P300 latency (ms)	P300 amplitude (μV)	RT (ms)
Age at test	PD(younger)	239.0±33.1	390.0±74.6	13.7±7.4	732.9±312.6
	N1	245.8±43.5	407.6±46.4	11.9±8.0	630.3±147.9
	PD(older)	278.9±34.9****	444.7±73.8	11.9±8.0*	935.2±366.7**
	N2	227.0±35.3	412.0±23.0	17.4±6.0	622.4±169.2
Age at onset	PD(early)	267.8±42.4*	419.5±67.0	12.6±7.0*	811.2±335.6*
	N3	234.3±38.9	410.3±33.2	16.7±5.1	613.8±152.2
	PD(late)	270.8±34.3**	444.4±84.6	12.0±8.6*	946.1±376.6**
	N4	232.0±34.6	409.9±22.5	16.6±6.4	609.3±153.6
Duration of illness	PD(short)	263.1±38.1*	404.4±56.9	13.6±8.4	810.3±325.3*
	N3	234.3±38.9	410.3±33.2	16.7±5.1	613.8±152.2
	PD(long)	277.6±38.0**	476.5±84.8**	10.5±6.8*	1033.5±391.8**
	N4	232.0±34.6	409.9±22.5	16.6±6.4	609.3±153.6

* $P<0.05$; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$ (Student's *t*-test or Mann-Whitney U test).

N1, N2, N3, N4; normal control subgroup age-matched to each PD subgroup.

For the S1–S2 paradigm, P300 latency showed significant variation as a function of the factor 'duration of illness' (Cz, $F=11.569$, $P<0.01$; Pz, $F=4.472$, $P<0.05$). Significantly prolonged P300 latency was found in PD(long) compared with that in PD(short) (Fisher's PLSD, Cz, $P<0.01$; Pz, $P<0.05$).

RT varied as a function of the factor 'duration of illness' during both paradigms (oddball, $F=8.679$, $P<0.01$; S1–S2, $F=4.226$, $P<0.05$). Significantly prolonged RT was found in PD(long) compared with RT in PD(short) (Fisher's PLSD, oddball, $P<0.01$; S1–S2, $P<0.05$).

Table 5 is a summary of the effect of age at test, age at

Table 5

Summary of effects of age at test, age at onset, and duration of illness on ERPs and RT during the oddball and S1–S2 paradigms

	N200 latency	P300 latency	P300 amplitude	RT
Oddball paradigm	Age at onset	Age at test Age at onset Duration of illness	Duration of illness	Duration of illness
S1–S2 paradigm	Age at test	Duration of illness	Not influenced by any of the three factors	Duration of illness

onset, and duration of illness. P300 amplitude during the S1–S2 paradigm was not influenced by any of the three factors.

3.3. The correlation of ERPs and RT to WAIS-R scores and motor disability scores in the whole PD group

3.3.1. The relationships of ERPs and RT to WAIS-R scores

P300 amplitude was found to be correlated with full-scale IQ (oddball, Pz, $r=0.540$, $P<0.01$; S1–S2, Cz, $r=0.655$, $P<0.0001$, Pz, $r=0.544$, $P<0.01$), performance IQ (oddball, Cz, $r=0.530$, $P<0.01$; Pz, $r=0.545$, $P<0.01$; S1–S2, Cz, $r=0.703$, $P<0.0001$; Pz, $r=0.575$, $P<0.001$) and digital symbol, a subset of performance IQ (oddball, Pz, $r=0.587$, $P<0.01$; S1–S2, Cz, $r=0.772$, $P<0.0001$; Pz, $r=0.602$, $P<0.001$). P300 latency showed significant correlation to digital symbol (oddball, Pz, $r=-0.501$, $P<0.01$; S1–S2, Cz, $r=-0.577$, $P<0.01$; Pz, $r=-0.634$, $P<0.001$). N200 latency showed significant correlation with digital symbol (S1–S2, Pz, $r=-0.521$, $P<0.01$). No other subsets of WAIS-R were found to be significantly correlated with any ERP components.

RT was found to be correlated with full-scale IQ (oddball, $r=-0.621$, $P<0.0001$; S1–S2, $r=-0.632$, $P<0.0001$), verbal IQ (oddball, $r=-0.649$, $P<0.0001$), and performance IQ (oddball, $r=-0.720$, $P<0.0001$; S1–S2, $r=-0.675$, $P<0.0001$). RT was correlated to digital symbol (oddball, $r=-0.505$, $P<0.0001$; S1–S2, $r=-0.675$, $P<0.0001$), object arrangement (oddball, $r=-0.635$, $P<0.0001$; S1–S2, $r=-0.626$, $P<0.0001$), and block design (oddball, $r=-0.660$, $P<0.0001$; S1–S2, $r=-0.506$, $P<0.0001$) in performance IQ subsets, and to similarities (oddball, $r=-0.576$, $P<0.0001$), comprehension (S1–S2, $r=-0.643$, $P<0.0001$) and digital span (oddball, $r=-0.583$, $P<0.0001$) in verbal IQ subsets.

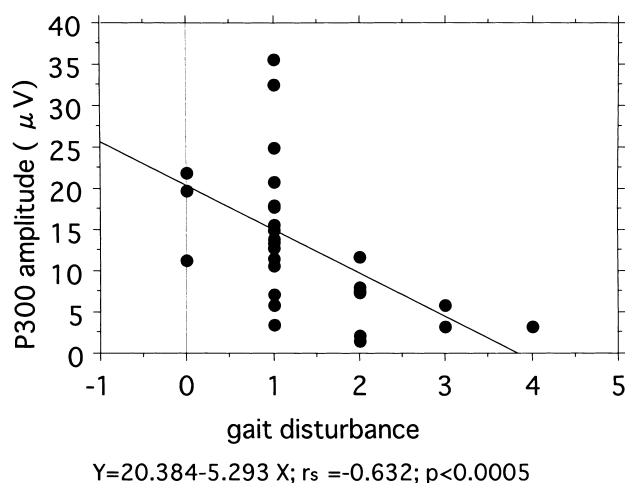


Fig. 3. The correlation of P300 amplitude at Pz with gait disturbance score in patients during the S1–S2 paradigm.

3.3.2. The relationships of ERPs and RT to motor disability scores

With regards to relationships between ERP components and various motor disability scores, significant correlation was found only between P300 amplitude during the S1–S2 paradigm and gait disturbance (Cz, $r_s=-0.617$, $P<0.001$; Pz, $r_s=-0.632$, $P<0.001$, Fig. 3). RT was found to be correlated with akinesia (oddball, $r_s=0.605$, $P<0.005$; S1–S2, $r_s=0.517$, $P<0.01$), start hesitation (oddball, $r_s=0.689$, $P<0.005$; S1–S2, $r_s=0.590$, $P<0.01$), gait disturbance (oddball, $r_s=0.624$, $P<0.005$; S1–S2, $r_s=0.624$, $P<0.005$) and total motor disability score (oddball, $r=0.640$, $P<0.0001$; S1–S2, $r=0.547$, $P<0.0001$).

4. Discussion

The present study revealed a great discrepancy of ERP changes in PD according to the different tasks. Abnormalities of ERPs in the whole patient group were only found during the S1–S2 paradigm, but not during the oddball paradigm. P300 delay was found only in the PD(long) subgroup after the S1–S2 paradigm. In the early stage of PD, PD(short), delayed N200 was also only found in the S1–S2 paradigm, and not in the oddball paradigm. Thus, ERP abnormalities were more often found in the S1–S2 paradigm than in the oddball paradigm. Cognitive processes involved in the oddball paradigm may include acquisition, identification, and determination of button press, whereas cognitive processes involved in the S1–S2 paradigm are more complicated, including acquisition, encoding of stimuli, retrieval and comparison of stimuli, and determination of the left or right button [20]. To accomplish the S1–S2 task, secondly short-term memory is crucial since the subject has to remember the first stimulus, S1. Only then the subject can compare whether stimulus S2 is the same as S1 or not. To continue the next pair, the previous pair has to be forgotten and be replaced by the new S1 stimulus. Therefore, normal working memory and executive function are necessary for the accomplishment of the task. ERP abnormalities found during the S1–S2 paradigm might be evidence of working memory and executive function impairments in PD. Our data suggest that the S1–S2 paradigm is more useful than the oddball paradigm in detecting cognitive abnormalities in the early stage of PD. This is the first study in which the S1–S2 paradigm was applied as a visual P300 test in PD and proved to be of value for detecting minor cognitive abnormalities.

Instead of prolonged P300 latency, the main abnormal ERP findings in PD of this study were delayed N200 and reduced P300 amplitude. Similar results were reported only recently [21–23]. Many earlier ERP studies in PD paid attention only to changes in P300 latency. However, in our study, significantly prolonged P300 latency was found only in the PD(long) subgroup, and not in the

PD(short) group. P300 latency does not seem to be a sensitive parameter in identifying the existence of early cognitive impairment in PD. Delayed N200 after the S1–S2 paradigm was found in the early stage of PD, PD(short). Therefore, we suggest that N200 latency prolongation might be an early sign of ERP abnormalities in PD. Although only a few studies evoked N200 by visual paradigm, they agreed that visual negativity (N200) processing is similar to what is called N2b in an auditory paradigm [24,22]. N2b is thought to reflect the processing of task discrimination and classification [25]. Therefore, the prolongation of N200 latency in an early stage of PD indicates some impairment in such cognitive processing. It has been a long-debated question whether or not there is slowness of thought in PD. The prolongation of N200 latency in our study suggests that there may be some kind of slowness of thinking.

We subdivided the PD patients according to three different criteria: age at test, age at onset, and duration of illness. With the oddball paradigm, our data showed that delayed N200 and P300 latency as well as reduced P300 amplitude were more prominent in PD in older people with later onset or longer duration of illness. A very recent report revealed age and stage dependency of auditory P300 latency alteration in nondemented PD [16]. Our ANOVA study further proved that not only age at test and duration of illness, but also age at onset was important for P300 latency prolongation in PD. A previous psychological study showed a more marked frontal lobe dysfunction in the late onset PD group than in the early onset PD group [26]. Other studies also showed that cognitive dysfunction was more often found in the PD group with late onset [27,28]. However, to our knowledge, our study is the first to demonstrate the importance of age at onset for cognition in PD by visual P300 methodology.

The ANOVA analysis using age at onset and duration of illness as covariates revealed that duration of illness was also important for P300 delay in PD. This result may explain the discrepancy among the reports of P300 changes in nondemented PD patients [5,11,14]. The relatively short duration of illness in the studies of Goodin et al. and Green et al. seems to be responsible for the normal P300 latency they found.

In contrast to the P300 latency during the oddball paradigm which was influenced by age at test, age at onset, and duration of illness, P300 latency during the S1–S2 paradigm only showed change related to duration of illness. P300 amplitude during the S1–S2 paradigm did not show significant change in relation to variation in any of the three factors. This again proved that the S1–S2 paradigm is more useful clinically, since P300 evoked by the S1–S2 paradigm is less affected by clinical factors than the P300 evoked by the oddball paradigm.

In our study, P300 amplitude in PD showed significant correlation with full-scale IQ, performance IQ, and digital symbol. Many studies reported the correlation of P300

latency to various psychological tests including digital symbol of WAIS-R test [5,21,29]. However, P300 amplitude and clinical scores have rarely been discussed before.

P300 amplitude was also found to be correlated with the severity of gait disturbance instead of the cardinal symptoms of PD: tremor, rigidity, and bradykinesia. This suggests that the alteration of P300 amplitude is unlikely to be related to dopaminergic dysfunction. Neuropathological evidence also suggests that cognitive impairment in PD is a result of the involvement of neurons other than the dopaminergic nigro-striatal system [30,31]. There is quite a body of evidence that nondopaminergic systems are responsible for cognitive impairment in PD [32–36].

In summary, ERP results in PD were task dependent and correlated with the clinical status of the patients. An S1–S2 task rather than the routine oddball paradigm is necessary to detect early cognitive changes in PD quantitatively. P300 amplitude in PD showed significant correlation with clinical status, which has rarely been reported before. ERP abnormalities were more often found in patients with older age, late onset, and long duration of illness. P300 latency during the oddball paradigm was most influenced by these factors. The effect of age at test, age at onset, and duration of illness should be considered when interpreting the changes of P300 latency in PD.

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