

Lihong Wang  
Yoshiyuki Kuroiwa  
Toshiaki Kamitani  
Mei Li  
Tatsuya Takahashi  
Yume Suzuki  
Megumi Shimamura  
Osamu Hasegawa

## Visual event-related potentials in progressive supranuclear palsy, corticobasal degeneration, striatonigral degeneration, and Parkinson's disease

Received: 6 April 1999  
Received in revised form: 5 August 1999  
Accepted: 12 January 2000

L. Wang · Y. Kuroiwa (✉) · T. Kamitani ·  
M. Li · T. Takahashi · Y. Suzuki ·  
M. Shimamura · O. Hasegawa  
Department of Neurology, Yokohama City  
University School of Medicine, 3–9,  
Fukuura, Kanazawa-ku, Yokohama,  
236–0004, Japan  
Tel.: 81–45–7872800,  
Fax: 81–45–7886041

**Abstract** To determine whether there are characteristic changes in event-related potentials (ERPs) in parkinsonian syndromes we studied 8 patients with progressive supranuclear palsy (PSP), 10 patients with corticobasal degeneration (CBD), 9 patients with striatonigral degeneration (SND), and 16 patients with idiopathic Parkinson's disease (PD) with a mean duration of illness shorter than 5 years in each group. A visual oddball paradigm was employed to elicit P300. P300 to the rare target and rare nontarget stimuli and reaction time (RT) to rare target stimuli in each group were compared with those in the corresponding age-matched normal control group and to each other after age correction. The correlation of P300 and RT to motor disability score was also studied. In

PSP P300 amplitude was markedly reduced while in CBD P300 latency was prolonged. P300 amplitude to rare nontargets in SND and PD was attenuated. The mean RT in the PSP and the CBD group was significantly longer than in the other two groups. The mean RT in PD and P300 amplitude to rare nontargets in both CBD and PD showed significant correlation with the severity of motor disability. Simultaneous measurement of P300 and RT may yield useful supplementary information in facilitating diagnosis of parkinsonian syndromes in addition to clinical criteria.

**Key words** P300 · Progressive supranuclear palsy · Corticobasal degeneration · Striatonigral degeneration · Parkinson's disease

### Introduction

Reports have demonstrated that cognitive impairments are not rare in parkinsonian syndromes such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), striatonigral degeneration (SND), and idiopathic Parkinson's disease (PD) [1, 3, 5, 26, 28, 32]. PSP and PD often share clinical features, such as memory, linguistic, subcortical frontal conceptual, and behavioral disorders [22]. A comparison of the neuropsychological profile of CBD with PSP and Alzheimer's disease has revealed that CBD has a dysexecutive syndrome similar to that of patients with PSP [27]. A study in 16 patients with multiple system atrophy, most of the SND type, showed that the pa-

tients had impairment in attentional set shifting test, a frontal lobe-like dysfunction [32]. Pillon et al. [28] reported that the dysexecutive syndrome of SND is similar to that of PD but less severe than that in PSP. However, motor disabilities in these parkinsonian syndromes have limited the quantitative evaluation of cognitive impairments by neuropsychological assessments alone.

Event-related potentials (ERPs) which index cognitive processing quantitatively by neurophysiological methods might reveal differences among these diseases. P300 in response to rare events among frequent stimuli is the best studied ERP component. P300 latency is prolonged in diseases with dementia such as Alzheimer's disease [30] and advanced PD [8]. P300 findings in nondemented PD are still controversial [11–13, 33]. In contrast to extensive stud-

ies on ERPs in PD, only a few reports have described P300 in PSP [17, 25, 35]. Reports on P300 in CBD [42] and SND are few. Reports comparing ERPs between PSP, CBD, SND, and PD are completely lacking.

The purposes of our study were to investigate and compare P300 changes in PSP, CBD, SND, and PD and to clarify whether there are characteristic changes in ERPs in these parkinsonian syndromes. We recorded P300 in patients with mean duration of illness shorter than 5 years. P300 was elicited by a visual oddball task.

## Subjects and methods

### Subjects

We studied 8 patients with PSP, 10 with CBD, 9 with SND, 16 with PD, and 25 normal control volunteers. The clinical features of the patient groups and their normal controls are summarized in Table 1. All normal control subjects showed normal neurological findings without any history of neurological or psychiatric disorders. None of the control subjects exhibited any abnormal magnetic resonance imaging (MRI) findings. For exact age-matched comparison between patient groups and normal controls, normal subjects were selected as follows: 13 normal subjects for the PSP group (mean age 68.8±5.1 years), 10 normal subjects for the CBD group (70.5±4.8 years), 14 normal subjects for the SND group (60.5±7.8 years), and 22 normal subjects for the PD group (63.0±10.9 years). Some of the normal subjects overlapped between the groups.

Seven men and one right-handed woman (aged 61–79 years, 67.0±4.3) were diagnosed as having PSP. The diagnosis was based on the following clinical criteria [4, 20, 34]: progressive parkinsonism, vertical supranuclear palsy with downward gaze abnormalities, and postural instability with frequent falls. None exhibited encephalitis, hallucination, early or prominent cerebellar sign, dysautonomia, alien hand syndrome, unilateral dystonia, aphasia, apraxia, or agnosia. All patients responded poorly to levodopa and dopamine agonists. None of the patients had apparent focal lesions on computed tomography (CT) or MRI. Six patients were given the revised

Wechsler Adult Intelligence Scale (WAIS-R) test. The mean score of overall IQ was 89.0±20.5, verbal IQ, 91.8±20.2, and performance IQ, 86.5±18.8. The mean duration of illness was 4.0±1.3 years.

The CBD group consisted of three men and seven women (aged 64–77 years, 70.5±4.8). The diagnosis of CBD was made clinically on the basis of the following criteria [19, 21, 31, 36]: (a) insidious onset, (b) progression of asymmetrical akinetic-rigid syndrome, and (c) cerebral cortical signs such as apraxia (or clumsiness), cortical sensory loss, alien limb phenomena, limb dystonia, and focal reflex myoclonus. None exhibited encephalitis, hallucination, or limb ataxia. Dopaminergic therapy was ineffective in these patients. Focal lesions were excluded by CT or MRI in all patients. Five patients were given the WAIS-R test. The mean score of overall IQ was 78.4±13.9, verbal IQ, 83.0±14.5, and performance IQ, 76.2±15.7. The mean duration of illness was 3.1±1.4 years.

Five men and four women (aged 49–71 years old, 60.0±6.8) were diagnosed as having striatonigral degeneration based on the following criteria [6, 10, 43]: (a) progressive parkinsonian syndrome as the main feature, (b) poorly or not responsive to adequate treatment with levodopa, (c) autonomic failure suggested by genital, sphincter, or cardiovascular dysfunction, and (d) absence of family history, dementia, apraxia, supranuclear ophthalmoplegia, and detectable focal lesions on CT or MRI. Five patients were given the WAIS-R test. The mean score of overall IQ was 91.0±9.8, verbal IQ, 96.0±8.0, and performance IQ, 87.8±12.7. The mean duration of illness was 2.6±1.7 years.

Five male and 11 female patients (aged 41–75 years, 62.5±9.5) were diagnosed as having PD. All PD patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria for definite PD [15]. Patients with secondary parkinsonism or with evidence of focal cerebral lesions were excluded from the study. All patients showed good response to antiparkinsonian medication. Thirteen patients were given the WAIS-R test. The mean score of overall IQ was 96.7±11.6, verbal IQ, 98.5±14.3, and performance IQ, 95.9±10.5. The mean duration of illness was 2.3±1.1 years.

We evaluated the severity of major motor disabilities (akinesia, tremor, rigidity, retropulsion, and gait disturbance) of the four parkinsonian groups. The severity for each item was scored from 0 to 4 (Table 2). The Hoehn and Yahr stage was also determined for each patient (Table 2). No patients in the PSP, CBD, or SND group were on an anticholinergic or levodopa medication during the study because of ineffectiveness of the drugs. All the PD patients were on levodopa medication (308.3±156.4 mg/day) and two patients were also on anticholinergic medication.

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.

**Table 1** Patient groups and their corresponding normal control groups

	<i>n</i>	Sex (M/F)	Age (years)	Duration of illness (years)	Therapeutic effectiveness of L-dopa <sup>a</sup>
<b>PSP</b>					
Patients	8	7/1	67.0±4.3	4.0±1.3	0/8
Normals	13	7/6	68.8±5.1	–	–
<b>CBD</b>					
Patients	10	3/7	70.5±4.8	3.1±1.4	0/3
Normals	10	5/5	70.5±4.8	–	–
<b>SND</b>					
Patients	9	5/4	60.0±6.8	2.6±1.7	0/9
Normals	14	7/7	60.5±7.8	–	–
<b>PD</b>					
Patients	16	5/11	62.5±9.5	2.3±1.1	16/16
Normals	22	10/12	63.0±10.9	–	–

<sup>a</sup>Number of patients with levodopa effectiveness for motor deficits/number of patients treated with levodopa

### ERP tasks

A modified visual oddball paradigm was used to elicit ERPs. The modified oddball paradigm was previously employed by Tachibana et al. [40]. 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 ms. Subjects were instructed to press the button for rare target stimuli as correctly and rapidly as possible. Data of the experiment were recorded only after the subjects understood the tasks completely through a training period of about 5 min. Two sessions were performed for the experiment. Each session of the task consisted of three blocks with breaks of 2 min between blocks. Each block included four rare target stimuli.

**Table 2** Numbers of patients at each motor disability level in the four groups

	PSP	CBD	SND	PD
<b>Akinesia</b>				
Score 0	0	0	0	0
Score 1	1	0	0	9
Score 2	2	3	4	4
Score 3	5	3	5	3
Score 4	0	4	0	0
<b>Tremor</b>				
Score 0	6	8	8	0
Score 1	1	1	0	9
Score 2	1	1	1	4
Score 3	0	0	0	3
Score 4	0	0	0	0
<b>Rigidity</b>				
Score 0	0	2	0	0
Score 1	3	2	2	5
Score 2	1	2	1	9
Score 3	4	4	6	2
Score 4	0	0	0	0
<b>Retropulsion</b>				
Score 0	0	2	2	0
Score 1	1	2	1	11
Score 2	4	2	4	5
Score 3	3	4	2	0
Score 4	0	0	0	0
<b>Gait disturbance</b>				
Score 0	0	0	0	3
Score 1	2	2	1	10
Score 2	4	2	3	3
Score 3	1	4	4	0
Score 4	1	2	1	0
<b>Hoehn and Yahr</b>				
Stage I	0	1	0	3
Stage II	1	2	1	9
Stage III	2	1	4	3
Stage IV	4	1	3	1
Stage V	1	5	1	0

#### ERP recordings

ERPs were recorded with Ag/AgCl electrodes from Cz, Pz, and Oz referred to linked earlobes. The electro-oculography was monitored using a forehead-temple montage with a rejection level of  $\pm 100 \mu\text{V}$ . Electrode impedance was maintained below 5 K $\Omega$ . The bandwidth of the preamplifiers ranged from 0.1 to 50 Hz. The EEG activity was analyzed 100 ms preceding and 900 ms after each visual presentation. P300 latency and P300 amplitude were measured for rare targets and rare nontargets. P300 was identified as the largest positive wave at Cz and Pz between 300–700 ms following the onset of the stimulus. P300 amplitude was defined as the voltage difference between the P300 peak and prestimulus baseline (average voltage during 100 ms before the stimulus). P300 latency was measured as the interval between each peak and stimulus onset. Reaction time (RT) was defined as the interval between the appearance of the rare target and the onset of the button press.

#### Statistical data analysis

Each ERP value (P300 latency and P300 amplitude) and RT in each patient group were compared with the corresponding normal control group by the Mann-Whitney *U* test. As the mean ages of the PSP and CBD groups were nearly the same, ERP values and RT in the PSP and the CBD group were compared by the Mann-Whitney *U* test. Since the mean ages of SND and PD groups were nearly the same, ERP values and RT in the SND group and PD group were also compared by the Mann-Whitney *U* test. To reduce the aging effect we used linear age regression of normative samples to adjust P300 and RT values of the four groups to a standard age of 60 years [16, 24]. The age-corrected P300 and RT values were further Z-transformed [16]. Z scores of the age-corrected P300 and RT values were compared among the four groups using one-way analysis of variance (diagnosis as between subjects factor). When the analysis of variance yielded significant differences among data sets, a Fisher's PLSD test was performed as a post hoc test. The correlation of age-corrected P300 and RT values to motor disability scores was computed by Spearman's rank correlation ( $r_s$ ).

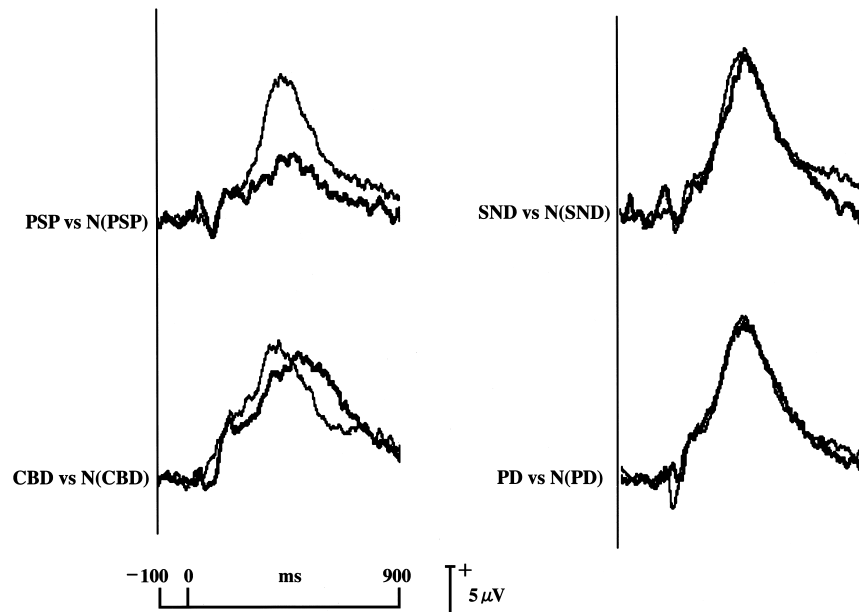
#### Results

In spite of neurological deficits all the patients had retained both mental and motor abilities sufficient to perform the maneuver for the oddball task. All the patients and normal subjects performed the tasks at an error rate not exceeding 5% following the training period.

Comparison of P300 and RT between each patient group and its corresponding normal control group

As shown in Fig. 1, low P300 amplitude was found in PSP during the task. In CBD P300 latency was delayed. No apparent P300 abnormality to rare targets was found during the oddball task in SND and PD groups. These ERP characteristics were further confirmed by statistical analysis (Table 3). In PSP, compared with its normal control group, P300 amplitude was significantly decreased to both rare targets and rare nontargets during the oddball task (rare targets, Cz,  $Z=3.114$ ,  $P<0.01$ ; Pz,  $Z=3.476$ ,  $P<0.001$ ; rare nontargets, Cz,  $Z=2.973$ ,  $P<0.01$ ; Pz,  $Z=3.127$ ,  $P<0.01$ ). RT in PSP group was significantly prolonged ( $Z=3.092$ ,  $P<0.01$ ). In CBD, compared with its normal control group, P300 latency to rare targets was significantly prolonged (Cz,  $Z=2.045$ ,  $P<0.05$ ; Pz,  $Z=2.532$ ,  $P<0.05$ ). RT in CBD was also significantly prolonged ( $Z=3.311$ ,  $P<0.001$ ). In SND none of P300 or the RT value to rare targets was found to differ significantly from normal values. However, P300 amplitude to rare nontargets was significantly declined (Cz,  $Z=2.116$ ,  $P<0.05$ , Pz,  $Z=2.873$ ,  $P<0.01$ ). In PD, as with the results in SND, none of P300 or the RT value to rare targets was found to differ significantly from normal values. P300 amplitude to rare nontargets was significantly reduced (Cz,  $Z=2.320$ ,  $P<0.05$ ).

**Fig. 1** Averaged ERP waveforms to rare targets during the oddball task recorded from Pz in patient groups (*thick line*) and their corresponding normal control groups (*thin line*)



The comparison of ERPs and RT between PSP and CBD, and between SND and PD

The P300 amplitude in the PSP group was significantly lower than that in the CBD group (rare targets, Cz,  $Z=2.598$ ,  $P<0.01$ ; Pz,  $Z=2.502$ ,  $P<0.05$ ; rare nontargets, Pz,  $Z=2.276$ ,  $P<0.05$ ). Compared with the PSP group the CBD group showed significantly prolonged P300 latency to rare target stimuli (Pz,  $Z=2.406$ ,  $P<0.05$ ). There was no significant difference of RT between the two patient groups. Neither P300 nor RT in the SND group showed any significant difference from those in the PD group.

The comparison of ERPs and RT among the four patient groups

To control statistically for the effect of age and thus to focus on P300 and RT between the four groups, an age regression procedure was used based on the age-ERP regression of the normative samples. Age-corrected P300 latency, amplitude, and RT were also Z-transformed to standardize the data of the four groups. One-way analysis of variance was computed to investigate the diagnosis effect on Z scores of age-corrected P300 and RT values. The result showed that the Z scores of age-corrected P300 latency to

**Table 3** Comparison of ERPs and RT in patient groups and their corresponding normal control groups

	P300 to rare target latency (ms)		P300 to rare target amplitude ( $\mu$ V)		P300 to rare nontarget latency (ms)		P300 to rare nontarget amplitude ( $\mu$ V)		RT to rare target (ms)
	Cz	Pz	Cz	Pz	Cz	Pz	Cz	Pz	
<b>PSP</b>									
Patients	435.3 $\pm$ 20.0	440.8 $\pm$ 32.4	6.7 $\pm$ 2.6**	7.0 $\pm$ 3.7***	465.1 $\pm$ 39.7	453.4 $\pm$ 48.2	5.33 $\pm$ 3.81**	5.30 $\pm$ 2.53**	712 $\pm$ 256**
Normals	420.5 $\pm$ 40.1	427.6 $\pm$ 34.6	15.1 $\pm$ 6.0	16.8 $\pm$ 4.5	431.8 $\pm$ 39.2	406.9 $\pm$ 57.4	12.14 $\pm$ 5.12	11.32 $\pm$ 3.02	446 $\pm$ 45
<b>CBD</b>									
Patients	473.8 $\pm$ 55.6*	501.6 $\pm$ 59.3*	13.1 $\pm$ 6.1	14.8 $\pm$ 6.4	444.8 $\pm$ 45.0	455.0 $\pm$ 78.8	10.1 $\pm$ 4.8	9.6 $\pm$ 4.1	725 $\pm$ 155***
Normals	420.0 $\pm$ 44.8	428.6 $\pm$ 43.6	14.4 $\pm$ 5.6	16.7 $\pm$ 5.0	428.0 $\pm$ 43.2	390.0 $\pm$ 53.7	11.5 $\pm$ 3.7	11.2 $\pm$ 3.1	453 $\pm$ 50
<b>SND</b>									
Patients	423.3 $\pm$ 19.3	413.8 $\pm$ 19.0	16.3 $\pm$ 5.5	19.0 $\pm$ 5.6	442.3 $\pm$ 45.8	437.7 $\pm$ 35.0	8.7 $\pm$ 4.0*	7.2 $\pm$ 3.3**	470 $\pm$ 70
Normals	408.9 $\pm$ 28.2	407.6 $\pm$ 29.1	18.2 $\pm$ 6.5	19.0 $\pm$ 4.9	412.6 $\pm$ 46.4	401.0 $\pm$ 45.0	14.1 $\pm$ 6.6	13.2 $\pm$ 3.7	426 $\pm$ 75
<b>PD</b>									
Patients	423.8 $\pm$ 44.8	430.4 $\pm$ 47.7	16.5 $\pm$ 7.5	17.7 $\pm$ 7.3	423.2 $\pm$ 48.9	412.7 $\pm$ 66.8	8.3 $\pm$ 7.7*	9.1 $\pm$ 6.4	459 $\pm$ 103
Normals	414.6 $\pm$ 37.6	418.2 $\pm$ 39.7	17.3 $\pm$ 5.6	18.9 $\pm$ 4.7	419.2 $\pm$ 40.0	409.1 $\pm$ 48.0	12.7 $\pm$ 6.2	12.2 $\pm$ 4.2	434 $\pm$ 68

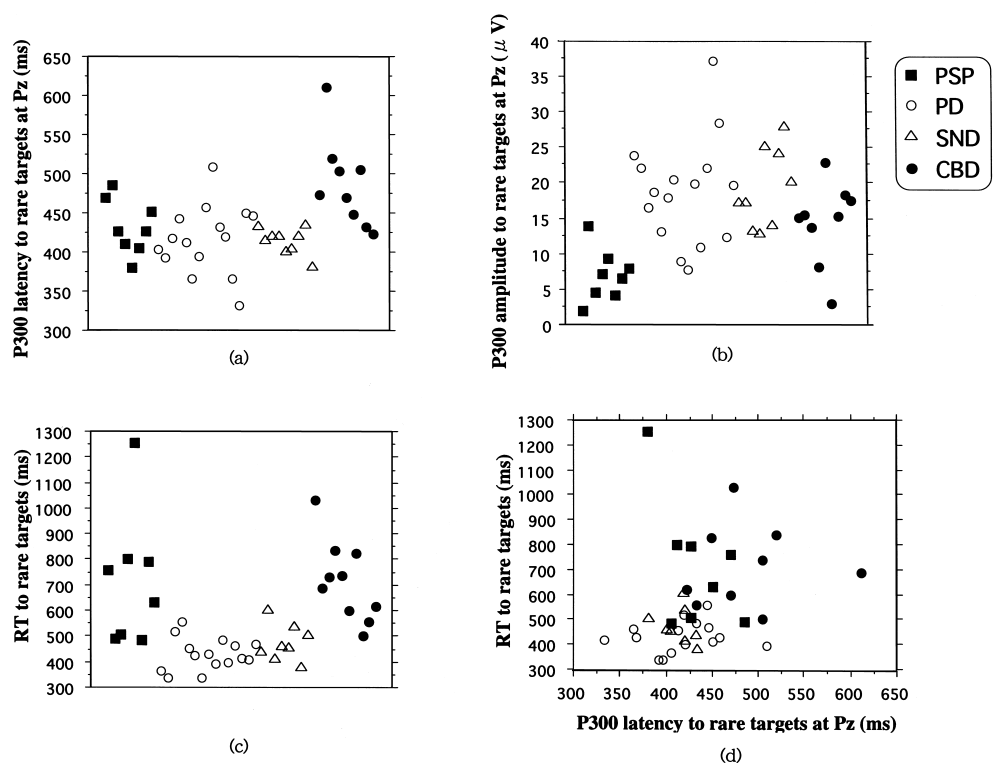
\* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$

rare targets differed significantly between the four groups (Cz,  $F=5.432$ ,  $P<0.01$ ; Pz,  $F=9.499$ ,  $P<0.0001$ ). Fisher's PLSD post hoc test showed that Z score of age-corrected P300 latency to rare targets in CBD was significantly higher than that in PSP (Cz,  $P<0.05$ ; Pz,  $P<0.01$ ), SND (Cz,  $P<0.001$ ; Pz,  $P<0.001$ ), and PD (Cz,  $P<0.001$ ; Pz,  $P<0.001$ ). The Z scores of age-corrected P300 amplitude to rare targets also differed significantly among the four groups (Cz,  $F=6.943$ ,  $P<0.001$ ; Pz,  $F=7.563$ ,  $P<0.001$ ). Fisher's PLSD post hoc test revealed that the Z score of age-corrected P300 amplitude to rare targets in PSP was significantly smaller than that in CBD (Cz,  $P<0.05$ ; Pz,  $P<0.05$ ), SND (Cz,  $P<0.01$ ; Pz,  $P<0.001$ ), and PD (Cz,  $P<0.0001$ ; Pz,  $P<0.0001$ ). The Z scores of age-corrected RT differed significantly between the four groups ( $F=12.216$ ,  $P<0.001$ ). Fisher's PLSD post hoc test showed that the Z score of age-corrected RT in PSP was significantly larger than that in SND ( $P<0.01$ ) and PD ( $P<0.0001$ ). The Z score of age-corrected RT in CBD was also significantly greater than that in SND ( $P<0.01$ ) and PD ( $P<0.0001$ ). From the scattergrams of age-corrected P300 latency, P300 amplitude, and RT in Fig. 2 (panels a, b, c) and the P300 to RT relationship graph in Fig. 2 (panel d), we found that to some extent we can separate PSP and CBD from the other two groups. However, PD and SND were mostly overlapping.

Correlation between age-corrected P300 and RT to motor disability scores

In PSP and SND, none of age-corrected P300 values or RT was correlated with motor disability scores. In CBD age-corrected P300 latency to rare nontargets was found to be significantly correlated with the scores of akinesia (Cz,  $r_s=0.882$ ,  $P<0.05$ ; Pz,  $r_s=0.819$ ,  $P<0.05$ ); retropulsion (Pz,  $r_s=0.778$ ,  $P<0.05$ ); and gait disturbance (Pz,  $r_s=0.815$ ,  $P<0.05$ ). Age-corrected P300 amplitude to rare nontargets was significantly correlated with retropulsion (Cz,  $r_s=-0.840$ ,  $P<0.05$ ; Pz,  $r_s=-0.927$ ,  $P<0.01$ ) and gait disturbance (Cz,  $r_s=-0.799$ ,  $P<0.05$ ). In PD P300 amplitude to rare nontargets was found to be significantly correlated with akinesia score (Cz,  $r_s=-0.765$ ,  $P<0.01$ ; Pz,  $r_s=-0.730$ ,  $P<0.05$ ). RT to rare targets was correlated with gait disturbance ( $r_s=0.812$ ,  $P<0.01$ ). In summary, our results showed characteristic ERP changes in PSP, CBD, SND, and PD. In the PSP group P300 amplitude was reduced and RT was prolonged, even though the patients could understand and perform the tasks well. In the CBD group we found prolonged P300 latency and RT to rare targets. In the SND and PD groups nearly normal P300 and RT to rare targets and declined P300 amplitude to rare nontargets were found. In the comparison of PSP and CBD, delayed P300 to the rare targets in CBD and attenuated P300 to rare targets in PSP separated the two diseases. In the comparison of PD and PSP, markedly reduced P300 amplitude to rare targets and

**Fig. 2** Age-corrected P300 latency (a), P300 amplitude (b), and RT (c) scattergrams of PSP (■), CBD (●), SND (△), and PD (▲) patients and the relationship of age-corrected P300 latency and RT (d) in the four patient groups.



prolonged RT in PSP differentiated the two diseases. In the comparison of PD and CBD, prolongation of P300 latency and RT to rare targets in CBD distinguished CBD from PD. P300 and RT in the PD and SND patients were overlapping. RT in PD and P300 to rare nontargets in CBD and PD were significantly correlated with some motor disability scores.

## Discussion

For the first time, we confirmed characteristic P300 and RT patterns among the parkinsonian syndromes: PSP, CBD, SND, and PD. Simultaneous evaluation of ERPs and RT may provide a hint for differentiating these diseases.

In the comparison of PD at an early stage with PSP, we found that RT and P300 amplitude are important for discrimination of the two diseases. Reduced P300 amplitude and prolonged RT especially to rare target stimuli with the duration of disease shorter than 5 years suggests PSP. It has been known that using P300 amplitude for detecting an abnormality is problematic because of marked variability in P300 amplitude due to many confounding factors [9]. However, ours and some other studies [7, 18, 29, 37, 38] confirm that the P300 amplitude measurement can be useful on some occasions. Although there is some individual amplitude variability, we found a strong tendency for low amplitude P300 in PSP. All of our PSP patients were enthusiastic to accomplish the task with an error rate of less than 5%. In addition, the reduction in P300 amplitude in PSP was not correlated with the severity of motor disability. Therefore we believe that attenuated P300 independent of motor disabilities is a characteristic neurophysiological feature in PSP. Both PD and PSP have been reported to have dysfunction of cholinergic system, which is thought to be due partially to cognitive impairments in the two diseases. A recent positron-emission tomography study revealed that the acetylcholine esterase activity is significantly reduced in cerebral cortex in PD whereas it was significantly reduced in the thalamus in PSP [39]. As the thalamus is thought to be one of the P300 generators [23, 44], the reduction in acetylcholine esterase activity in the thalamus might play a role in the attenuated P300 in PSP which could be differentiated from PD in the early stage.

In comparison of PD with CBD, prolonged P300 and RT to rare targets in parkinsonian patients with duration of illness shorter than 5 years suggests CBD. Prolonged P300 latency in CBD was in agreement with the other two reports [14, 42]. Although some reports show prolonged P300 in PD, most of those PD patients had had the illness for more than 5 years [2, 12, 13, 41]. Other studies on P300 in PD at an early stage agree with ours in that P300 latency was within normal range [11, 33]. Reaction time in PD was significantly influenced by the severity of motor disability (akinesia or gait disturbance) whereas reaction time in CBD was not. As P300 latency was also significantly de-

layed in CBD, it is very possible that the prolonged reaction time in CBD was due to the cognitive impairment instead of motor impairments.

PD is difficult to separate from SND clinically. To our knowledge, ours is the first report on ERPs comparison between PD and SND. However, we found no characteristic ERP changes that can help to differentiate PD from SND by ERP results.

Our results showed that obviously attenuated P300 in PSP and delayed P300 to the rare targets in CBD may help to separate the two diseases. The result is in contrast with two reports, which showed prolonged P300 latency in PSP [17, 42]. In the study of Takeda et al. [42] three of four patients with PSP were found to have prolonged P300 latency; P300 amplitude data were not reported. In the study of Johnson et al. [17] P300 latency was delayed, and amplitude was reduced in PSP. In our study two patients with PSP also showed relatively prolonged P300 latency. However, compared with the change in P300 latency, P300 amplitude reduction was more obvious and more consistent [17, 25, 35] and can be considered as a characteristic change in PSP. Our scattergrams also showed that three CBD patients had attenuated P300. Therefore ERP results give only some supplementary information for the diagnosis. Some individual variations in P300 measurements may cause overlapping P300 abnormalities in PSP and CBD. It remains to be elucidated why in CBD P300 to rare nontargets was correlated with motor disability scores whereas P300 to rare targets was not.

P300 results in SND were similar to those in PD and different from those in PSP and CBD. The only change in SND was attenuated P300 to rare nontargets. This was not correlated with the severity of motor disability. P300 to rare nontargets was thought to reflect an automatic cognitive processing [40]. To our knowledge, there have been no reports showing the impairment in automatic cognitive processing in SND, and further studies on this issue are necessary.

None of the ERP changes is specific to parkinsonian syndromes, as they are also observed in Alzheimer's disease and other neurological diseases with cognitive changes. However, we wish to emphasize the distinct characteristics of ERPs among the heterogeneous spectrum of parkinsonian syndromes.

In summary, we found distinct patterns of visual ERP changes in PSP, CBD, SND, and PD. A combined evaluation of P300 and RT seems useful in showing the differences among PD or SND vs. PSP, PD or SND vs. CBD, and PSP vs. CBD. We also found it difficult to separate PD from SND by ERP method. Although the diagnostic value of applying ERPs to an individual patient is of limited value, ERPs could potentially be useful as a supplementary tool in the differential diagnosis of the heterogeneous parkinsonian syndromes, which is based principally on the neurological symptoms and signs and neuroradiological findings.

**Acknowledgements** We are grateful to Professor of Statistics, Masaaki Sibuya, Keio University, Tokyo, for helpful assistance and comments concerning statistical analysis.

## References

- Albert ML, Feldman Rg, Willis AL (1974) The subcortical dementia of progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 37:121–130
- Aotsuka A, Weate SJ, Drake ME Jr, Paulson GW (1996) Event-related potentials in Parkinson's disease. *Electromyogr Clin Neurophysiol* 36:215–220
- Brown RG, Marsden CD (1990) Cognitive function in Parkinson's disease: from description to theory. *Trends Neurosci* 13:21–29
- Collins SJ, Ahlskog JE, Parisi JE, Maraganore DM (1995) Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria. *J Neurol Neurosurg Psychiatry* 58:167–173
- Dubois B, Pillon B (1996) Cognitive deficits in Parkinson's disease. *Arch Neurol* 244:2–8
- Fearnley JM, Lee AJ (1990) Striatonigral degeneration. A clinicopathological study. *Brain* 113:1823–1842
- Fukushima T, Ikeda T, Uyama E, Uchino M, Okabe H, Ando M (1994) Cognitive event-related potentials and brain magnetic resonance imaging in HTLV-1 associated myelopathy (HAM). *J Neurol Sci* 126:30–39
- Goodin DS, Aminoff MJ (1987) Electrophysiological differences between demented and nondemented patients with Parkinson's disease. *Ann Neurol* 21:90–94
- Goodin D, Desmedt J, Mauer K, Nuwer MR (1994) IFCN recommended standards for long-latency auditory event-related potentials. Report of an IFCN committee. International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol* 91:18–20
- Gouider-Khouja N, Vidailhet M, Bonnet AM, Pichon J, Agid Y (1995) "Pure" striatonigral degeneration and Parkinson's disease: a comparative clinical study. *Mov Disord* 10:288–294
- Green J, Woodard JL, Sirockman BE, Zakers GO, Maier CL, Green RC, Watts RL (1996) Event-related potential P3 change in mild Parkinson's disease. *Mov Disord* 11:32–42
- Hansch EC, Syndulko K, Cohen SN, Goldberg ZI, Potvin AR, Tourtellotte WW (1982) Cognition in Parkinson disease: an event-related potential perspective. *Ann Neurol* 11:599–607
- Hayashi R, Hanyu N, Shindo M, Tamaru F, Yanagisawa N (1993) Event-related potentials, reaction time, and cognitive state in patients with Parkinson's disease. *Adv Neurol* 60:429–433
- Homma A, Harayama H, Kondo H, Sato M, Saito Y, Hayashi T, Soma Y, Tsuji S (1996) P300 findings in patients with corticobasal degeneration. *No To Shikei* 48:925–929
- Hughes AJ, Daniel SE, Kilford L, Lee AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 55:181–184
- John ER, Easton P, Prichep L, Friedman J (1993) Standardized varimax descriptors of event related potentials: basic considerations. *Brain Topogr* 6:143–162
- Johnson R, Litvan I, Grafman J (1991) Progressive supranuclear palsy: altered sensory processing leads to degraded cognition. *Neurology* 41:1257–1262
- Kawasaki Y, Maeda Y, Higashima M, Nagasawa T, Koshino Y, Suzuki M, Ide Y (1997) Reduced auditory P300 amplitude, medial temporal volume reduction and psychopathology in schizophrenia. *Schizophr Res* 26:107–115
- Kompoliti K, Goetz CG, Boeve BF, Maraganore DM, Ahlskog JE, Marsden CD, Bhatia KP, Greene PE, Przedborski S, Seal EC, Burns RS, Hauser RA, Gauger LL, Factor SA, Molho ES, Riley DE (1998) Clinical presentation and pharmacological therapy in corticobasal degeneration. *Arch Neurol* 55:957–961
- Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 47:1–9
- Litvan I, Agid Y, Goetz C, Jankovic J, Wenning GK, Brandel JP, Lai EC, Verny M, Ray-Chaudhuri K, McKee A, Jellinger K, Pearce RKB, Bartko JJ (1997) Accuracy of the clinical diagnosis of corticobasal degeneration: a clinicopathologic study. *Neurology* 48:119–125
- Mayeux R, Stern Y, Rosen J, Benson D (1983) Is "subcortical dementia" a recognizable clinical entity? *Ann Neurol* 14:278–283
- Mecklinger A, Maess B, Opitz B, Pfeifer E, Cheyne D, Weinberg H (1998) A MEG analysis of the P300 in visual discrimination tasks. *Electroencephalogr Clin Neurophysiol* 108:45–56
- Naganuma Y, Konishi T, Hongou K, Tohyama J, Uchiyama M (1997) Epileptic seizures and event-related potentials (P300) in childhood partial epilepsies. *Clin Electroencephalogr* 28:106–111
- Onofrij MC, Ghilardi MF, Fulgente T, Nobilio D, Bazzano S, Ferracci F, Malatesta G (1990) Mapping of event-related potentials to auditory and visual odd-ball paradigms. *Electroencephalogr Clin Neurophysiol Suppl* 41:183–201
- Pillon B, Dubois B, Ploska A, Agid Y (1991) Severity and specificity of cognitive impairment in Alzheimer's, Huntington's, and Parkinson's diseases and progressive supranuclear palsy. *Neurology* 41:634–643
- Pillon B, Blin J, Vidailhet M, Deweer B, Sirigu A, Dubois B, Agid Y (1995) The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. *Neurology* 45:1477–1483
- Pillon B, Gouider-Khouja N, Deweer B, Vidailhet M, Malapani C, Dubois B, Agid Y (1995) Neuropsychological pattern of striatonigral degeneration: comparison with Parkinson's disease and progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 58:174–179
- Polich J (1997) On the relationship between EEG and P300: individual differences, aging, and ultradian rhythms. *Int J Psychophysiol* 26:299–317
- Polich J, Ehlers CL, Otis S, Mandell AJ, Bloom FE (1986) P300 latency reflects the degree of cognitive decline in dementing illness. *Electroencephalogr Clin Neurophysiol* 63:138–144
- Rinne JO, Lee MS, Thompson PD, Marsden CD (1994) Corticobasal degeneration. A clinical study of 36 cases. *Brain* 117:1183–1196
- Robbins TW, James M, Lange KW, Owen AM, Quinn NP, Marsden CD (1992) Cognitive performance in multiple system atrophy. *Brain* 115:271–291
- Rumbach L, Tranchant C, Viel JF, Warter JM (1993) Event-related potentials in Parkinson's disease: a 12-month follow-up study. *J Neurol Sci* 116:148–151

- 
34. Santacruz P, Uttl B, Litvan I, Grafman J (1998) Progressive supranuclear palsy: a survey of the disease course. *Neurology* 50:1637–1647
  35. Sato K, Takeuchi H, Kamoda M, Touge T, Yamada A, Nishioka M (1993) Event-related potentials in progressive supranuclear palsy. *Rinsho Shinkeigaku* 33:382–388
  36. Schneider JA, Watts RL, Gearing M, Brewer RP, Mirra SS (1997) Corticobasal degeneration: neuropathologic and clinical heterogeneity. *Neurology* 48:959–969
  37. Segalowitz SJ, Barnes KL (1993) The reliability of ERP components in the auditory oddball paradigm. *Psychophysiology* 30:451–459
  38. Shajahan PM, Glabus MF, Blackwood DH, Ebmeier KP (1997) Brain activation during an auditory ‘oddball task’ in schizophrenia measured by single photon emission tomography. *Psychol Med* 27:587–594
  39. Shinotoh H, Namba H, Yamaguchi M, Fukushi K, Nagatsuka S, Iyo M, Asahina M, Hattori T, Tanada S, Irie T (1999) Positron emission tomographic measurement of acetylcholinesterase activity reveals differential loss of ascending cholinergic systems in Parkinson’s disease and progressive supranuclear palsy. *Ann Neurol* 46:62–69
  40. Tachibana H, Toda K, Sugita M (1992) Age-related changes in attended and unattended P3 latency in normal subjects. *Int J Neurosci* 66:277–284
  41. Tachibana H, Aragane K, Kawabata K, Sugita M (1997) P3 latency change in aging and Parkinson’s disease. *Arch Neurol* 54:296–302
  42. Takeda M, Tachibana H, Okuda B, Kawabata K, Sugita M (1998) Electrophysiological comparison between corticobasal degeneration and progressive supranuclear palsy. *Clin Neurol Neurosurg* 100:94–98
  43. Wenning GK, Ben Shlomo Y, Magalhães M, Daniel SE, Quinn NP (1994) Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain* 117:835–845
  44. Yingling CD, Hosobuchi Y (1984) A subcortical correlate of P300 in man. *Electroencephalogr Clin Neurophysiol* 59:72–76