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The correlation between P300 alterations and regional cerebral blood flow in non-demented Parkinson's disease

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Abstract

P300 was evoked by a visual oddball and an S1-S2 task in 22 non-demented Parkinson's disease (PD) patients (13 in the early stage, nine in the late stage) and 18 normal controls. Reaction time was also measured. All patients undertook the ^{99}Tc-ECD SPECT examination. Quantitative regional cerebral blood flow (rCBF) was obtained by overlying SPECT image on the 3D-magnetic resonance image. In the PD patients in the late stage, P300 latency to S2-same and reaction time were significantly prolonged, while rCBF at bilateral frontal, temporal, and the right parietal lobes was decreased. P300 latency to S2-same was significantly correlated with the rCBF at bilateral temporal lobes. Reaction time was significantly correlated with the rCBF at the right frontal and parietal lobes, as well as the temporal and occipital lobes. The results suggest that P300 changes in non-demented PD in the late stage could be related to the temporal lobe dysfunction.

Keywords: Regional cerebral blood flow; ^{99}Tc-ECD SPECT; P300; Reaction time; Parkinson's disease; Duration of illness

P300 component of event-related potentials is a useful electrophysiological parameter in studying cognitive processing in Parkinson's disease (PD) as it is independent of motor processing. Some reports provided evidence of cognitive slowing during oddball task by showing delayed P300 in PD. P300 latency is affected by the different tasks and also by the different clinical status in PD, especially by duration of illness [15]. Although the dysfunction of fronto-striatal dopamine transmission or cholinergic transmission has been proposed to explain P300 changes [5,14], the knowledge on pathophysiological mechanism for P300 alterations in different stages of PD is not sufficient. In the present study, we investigated the correlation between the alteration of P300 and regional cerebral blood flow (rCBF) to pursue the anatomical and pathophysiological basis for such P300 changes in PD.

Single photon emission computed tomography (SPECT) imaging which is adequate for in vivo representation of rCBF has been used to investigate cognitive disorders. In demented PD [7,11], low rCBF in frontal, parietal and temporal lobes was found. In non-demented PD, however, there is not a consistent pattern; normal cortical blood flow [11], significantly decreased blood flow in the frontal [9] or parietal region [3] were reported. The heterogeneous rCBF changes in non-demented PD might reflect the multifactorial pathophysiology of the disease. Little attention is paid on the rCBF changes at different stages in non-demented PD. Studies on the relationship between rCBF and P300 changes in non-demented PD are completely lacking. Therefore, we focused on studying the rCBF and P300 changes at different stages of the disease and their relationships.

The subjects were 22 patients (nine men, 13 women) with the definite clinical diagnosis of idiopathic PD and 18 age-matched healthy volunteers (eight men, ten women). The patients were divided into two subgroups according to the duration of illness: PD (short) group in the early stage with duration of illness <5 years (13 patients, mean age, 63.0 $\pm$ 9.5 years); PD (long) group in the late stage with duration of illness ≥ 5 years (nine patients, mean age, 66.0 $\pm$ 7.0 years). The mean age of the normal controls (NC) was 65.2 $\pm$ 10.3 years. All control subjects had no clinical signs of mental deterioration or abnormal neurological findings. Any patients diagnosed as having dementia, secondary parkinsonism were excluded from the study. All patients were treated with antiparkinsonian medication. No significant

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difference of global mental status between the two PD subgroups was found evaluated by Wechsler adult intelligence scale-revised test.

A modified visual oddball paradigm and a visual S1–S2 paradigm were performed as we described previously [15]. The modified visual oddball paradigm had three kinds of visual stimuli: rare target (20%), rare non-target (20%), and frequent non-target (60%). The subjects were instructed to press the button with the right thumb for the rare target stimuli. The S1–S2 paradigm had two stimuli, S1 and S2. The S2 was presented 1500 ms later after the onset of the S1. The subjects were instructed to compare the two figures. When S2 was the same as S1 (S2-same), the right button was to be pressed by the right thumb or middle finger. When S2 was different from the S1 (S2-different), the left button was to be pressed by the left thumb or middle finger. P300 was recorded from Cz and Pz referred to linked earlobes. The electrooculogram was monitored using a forehead-temple montage with a rejection level of $\pm$ 100 μV. Bandwidth of preamplifiers ranged from 0.1 to 50 Hz. Electroencephalogram was analyzed 100 ms before and 900 ms after each visual presentation. We measured P300 latency and amplitude to rare targets in the oddball task and to S2-same in the S1–S2 task. We also recorded reaction time to rare targets and to S2-same.

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 (Fig. 1). The three SPECT images were reconstructed and overlaid on 3D-magnetic resonance imaging (MRI) display separately. The rCBF in each area of the frontal, parietal, temporal, or occipital lobes was identified based on the MRI images. The rCBF was measured according to the rCBF pixel analysis. The interest region of each cerebral lobe was also determined on the basis of excluding the volume effect. We calculated the mean rCBF pixel value in each of the above region as the rCBF value in each cerebral lobe. The mean rCBF values of bilateral frontal, parietal, temporal, and occipital lobes and cerebellar hemisphere were named as RF, LF, RP, LP, RT, LT, RO, LO, RCH, and LCH (Fig. 1).

A two-tailed Student *t*-test was computed to compare the values of P300 or reaction time among the groups (Table 1). In the PD (short), neither P300 nor reaction time revealed

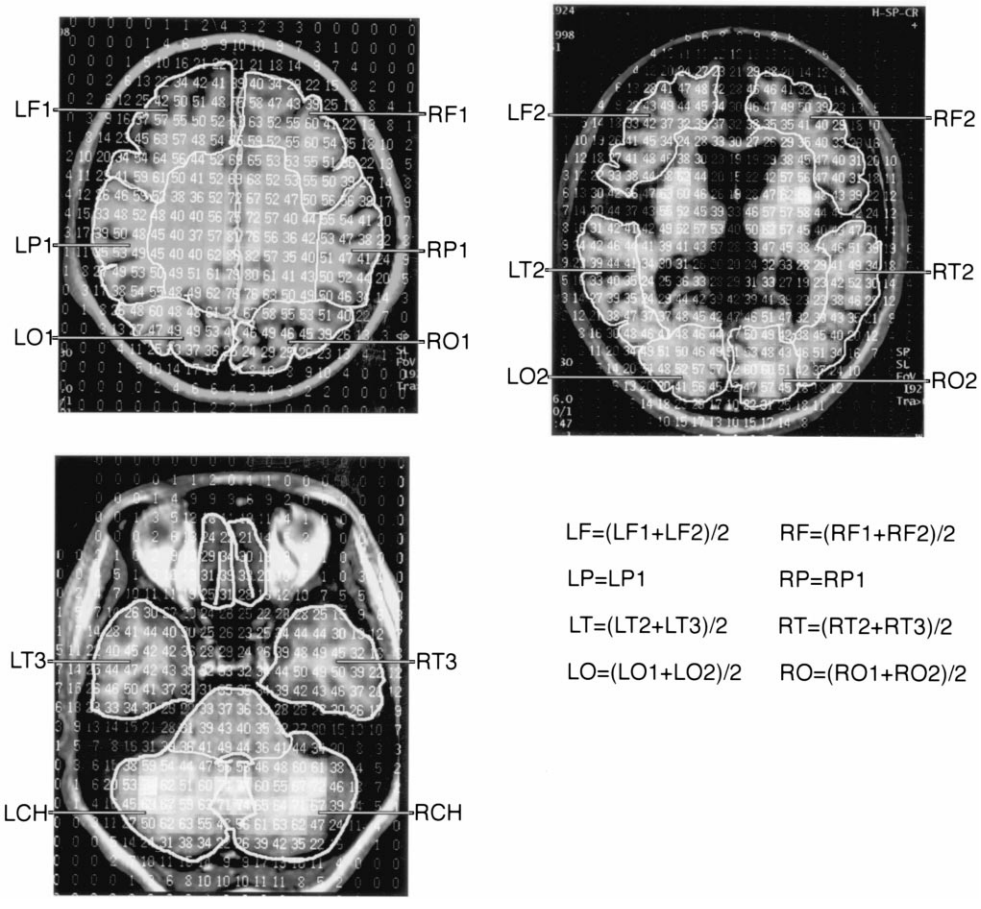

Fig. 1. Example of the SPECT and MRI overlay imaging in one patient. The numbers shown upon the MRI are the rCBF pixel values (ml/100 g/min). The rCBF value in the regions in each segment was calculated as the mean value of each region. The final rCBF value in each cerebral lobe was calculated as shown in the lower right side of the figure. L = left; R = right; F = frontal lobe; P = parietal lobe; T = temporal lobe; O = occipital lobe; CH = cerebellar hemisphere.

Table 1
The mean ± SD of P300 latency, P300 amplitude and reaction time in PD subgroups and normal controls during the two tasks

		PD (short)	PD (long)	Normal controls
Oddball task	P300 latency (ms)			
	Cz	421.4 ± 41.0	430.2 ± 56.3	423.4 ± 42.6
	Pz	427.7 ± 45.2	426.4 ± 57.1	431.3 ± 46.2
	P300 amplitude (μV)			
	Cz	18.4 ± 8.1	12.5 ± 5.6	16.2 ± 6.3
	Pz	19.3 ± 8.0	15.3 ± 6.1	17.8 ± 4.5
	Reaction time (ms)	412.4 ± 49.2	618.9 ± 237.6[a,b]	434.7 ± 50.1
S1-S2 task	P300 latency (ms)			
	Cz	401.2 ± 56.6	478.3 ± 116.2[c]	416.0 ± 28.0
	Pz	416.3 ± 50.8	476.0 ± 120.5	431.4 ± 34.1
	P300 amplitude (μV)			
	Cz	13.3 ± 6.6	12.5 ± 6.8	16.8 ± 6.0
	Pz	13.8 ± 7.2	13.2 ± 10.7	16.5 ± 6.2
	Reaction time (ms)	660.9 ± 165.5	853.7 ± 318.7[c]	589.6 ± 140.9

[a] $P < 0.01$ Student's t-test: the comparison between the PD (short) and the PD (long) groups, [b] $P < 0.01$ Student's t-test: the comparison between the PD (long) group and the normal controls; [c] $P < 0.05$.

significant difference compared with those in the NC. In the PD (long), P300 latency to S2-same tended to be longer than that in the PD (short) ($t = 1.926$, $P = 0.072$) and was significantly longer than that in the NC ($t = 2.126$, $P < 0.05$). P300 amplitude to rare targets tended to be reduced in the PD (long) compared with that in the PD (short) ($t = 1.9$, $P = 0.07$). Reaction time to rare targets in the PD (long) was significantly longer than that in the PD (short) ($t = 2.961$, $P < 0.01$) and the NC ($t = 2.944$, $P < 0.01$). Reaction time to S2-same in the PD (long) was also longer than that in the NC ($t = 2.623$, $P < 0.05$).

As shown in Table 2, compared with the PD (short), the mean rCBF values in the PD (long) was significantly reduced in the following regions: bilateral frontal (LF, $t = 2.959$, $P < 0.01$; RF, $t = 2.709$, $P < 0.05$), bilateral temporal (LT, $t = 3.702$, $P < 0.01$; RT, $t = 2.723$, $P < 0.05$), and the right parietal lobe ($t = 2.134$, $P < 0.05$).

The correlation between P300 and rCBF was computed by Pearson's correlation coefficients (r). P300 latency to rare targets did not show correlation with the rCBF changes in any of the regions measured. P300 latency to S2-same at Cz, however, showed significant correlation with the rCBF values in the bilateral temporal lobes (LT, $r = -0.539$, $P < 0.05$; RT, $r = -0.505$, $P < 0.05$) (Table 3). P300 amplitude to rare targets was correlated with the rCBF of the temporal (Cz, RT, $r = 0.582$, $P < 0.005$; Pz, LT, $r = 0.511$, $P < 0.05$; RT, $r = 0.540$, $P < 0.01$) and left occipital lobe (Cz, LO, $r = 0.654$, $P < 0.0005$). P300 amplitude to S2-same didn't show any correlation with the rCBF detected in this study.

Table 2
The mean ± SD of rCBF (ml/100 g/min) in the PD (short) and the PD (long)[a]

		PD (short)	PD (long)
Left	Frontal lobe	43.9 ± 3.3	39.6 ± 3.3**
	Parietal lobe	44.6 ± 4.7	40.5 ± 4.2
	Temporal lobe	41.0 ± 3.4	35.8 ± 3.1**
	Occipital lobe	46.5 ± 4.6	42.8 ± 6.5
	Cerebellar hemisphere	51.5 ± 16.7	48.8 ± 7.3
Right	Frontal lobe	44.3 ± 4.0	39.7 ± 4.1*
	Parietal lobe	44.7 ± 4.8	39.7 ± 6.2*
	Temporal lobe	41.2 ± 2.9	36.8 ± 4.7*
	Occipital lobe	48.8 ± 4.0	45.5 ± 5.4
	Cerebellar hemisphere	51.3 ± 3.8	49.0 ± 5.7

[a] *$P < 0.05$; **$P < 0.01$ Student's t-test, the comparison between the PD (short) and the PD (long) group.

Reaction time to both the rare targets and S2-same was correlated with the rCBF in the right frontal (rare targets, $r = -0.594$, $P < 0.01$; S2-same, $r = -0.557$, $P < 0.05$), and the right parietal lobe (rare targets, $r = -0.659$, $P < 0.005$; S2-same, $r = -0.521$, $P < 0.05$). In addition, reaction time to rare targets was correlated with the rCBF in the right temporal ($r = -0.715$, $P < 0.0005$), and the right occipital lobe ($r = -0.630$, $P < 0.005$), whereas, reaction time to S2-same was correlated with the rCBF in bilateral temporal (LT, $r = -0.547$, $P < 0.05$; RT, $r = -0.629$, $P < 0.005$) and the left occipital lobe ($r = -0.576$, $P < 0.05$).

In summary, our major findings were that P300 latency to S2-same and reaction time to both rare targets and S2-same were delayed in the PD (long). Compared with that in the PD (short), the rCBF of bilateral frontal, temporal, and the right parietal lobes in the PD (long) was significantly reduced. P300 latency to S2-same was correlated with the rCBF in bilateral temporal lobes. P300 amplitude to rare targets was correlated with the rCBF in bilateral temporal and the left occipital lobe. Reaction time was correlated with the right frontal and parietal lobe, as well as the temporal and occipital lobe.

P300 delay to S2-same in the PD (long) was in consistent

Table 3
Significant correlation found between P300 or reaction time and the rCBF in PD

	Rare targets		S2-same	
	P300 amplitude	Reaction time	P300 latency	Reaction time
Left hemisphere	LT, LO	–	LT	LT, LO
Right hemisphere	RT	RF, RP, RT, RO	RT	RF, RP, RT

with our previous report and Stanzione et al. [12] who showed age and stage dependency of P300 latency alterations. As our S1-S2 paradigm is a task that critically requires a preserved visual short-term memory [2], P300 delay to S2-same might reflect the deficits of visual short-term memory in PD (long). P300 was reported to be influenced by mesocortical dopaminergic, cholinergic, and serotonergic neuronal systems [1,4,13]. It is reasonable that P300 delay may reflect the derangement in these neurotransmitter systems with the progression of the disease.

Many reports showed SPECT alterations in PD using ^{133}Xenone and radiolabeled tracers such as [^{123}I]IMP and ^{99}Tc-HMPAO. Reports on ^{99}Tc-ECD SPECT are rare. L'eveillé at al. [8] found superior images of ^{99}Tc-ECD SPECT to images of ^{99}Tc-HMPAO SPECT. Instead of routine ROI measurement, we overlaid the SPECT images on the MRI and obtained more accurate rCBF in each cerebral region. Jagust et al. [6] reported that in non-demented PD patients with lowest rCBF ratios in left and right temporal lobes performed more poorly than controls in all cognitive domains of the neuropsychological test. They assumed that there is an association between reduced temporal lobe rCBF and global cognitive decline in non-demented PD.

To our knowledge, our study is the first report describing the relationship between rCBF and P300 changes in non-demented PD. Our result suggests that bilateral temporal blood flow reduction in PD might be related to decreased information processing speed on P300 production during the visual S1-S2 paradigm. This result is supported by the finding that failure of visual memory was related to the hippocampal atrophy in PD [10].

While the rCBF in the bilateral temporal lobes in PD was correlated with both P300 latency and reaction time, the rCBF in the right frontal and parietal lobes in PD was correlated only with reaction time during the S1-S2 task. This discrepancy between reaction time and P300 latency may be due to the fact that reaction time involved both cognitive and motor processing. We assumed that the right prefrontal and premotor cortex activities were related to the prolonged reaction time in PD.

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