

Relationship between the Auditory P300 and the Procedural Memory Function in Drug-naive Patients with Parkinson's Disease

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We evaluated and compared procedural memory and auditory P300 event-related potential in age-matched normal controls (n=15) and drug-naive patients with Parkinson's disease (n=16). We used Gollin's incomplete picture test for visual procedural memory function and Tower of Hanoi puzzle for visuomotor procedural memory function. The mean latency of P300 was significantly prolonged in the Parkinsonian group than in the controls. In the neuropsychology test, the patients group revealed selective impairment of visuomotor procedural memory against preserved visual procedural memory. In the patients group, the latency of P300 was inversely correlated with performance of visuomotor procedural memory. These results suggest that prolonged auditory P300 event-related potential show the dysfunction of visuomotor procedural memory in the basal ganglia, which appears to be more selectively impaired than visual procedural memory in drug-naive patients with parkinson's disease.

Key Words: Auditory P300 event-related potential, visuomotor procedural memory, Parkinson's disease

In the human central nervous system, the presence of two functionally and anatomically different memory system have been recently proved. While the declarative memory system which conventionally regarded as memory requires conscious recall or recognition of previous events, the procedural memory system which results in acquisition of skills represents unconscious changes in performance as a result of prior experience (Cohen *et al.* 1980; Squire, 1980).

A current study propose that procedural memory is selectively impaired in Parkinson's disease (Phillips and Carr, 1987; Saint *et al.* 1988). Procedural memory function may be

consist of visuomotor and visual procedural memory. Parkinson's disease shows impaired visuomotor procedural memory but show intact visual procedural memory (Harrington *et al.* 1990; Pascual-Leone *et al.* 1993). These procedural memory function appears to be dependent on the neocortex such as the basal ganglia (Marsden, 1982; Butters *et al.* 1985; Saint *et al.* 1988).

The present study utilized P300 event related potential as an objective electrophysiological index of cognitive function in Parkinson's disease (Hansch *et al.* 1982). As a results of many clinical studies, it is generally assumed that the abnormal latency increase of P300 reflects generalized cognitive decline in Parkinson's disease (Hansch *et al.* 1982; Goodin and Aminoff, 1987; Polich *et al.* 1986; O'Donnell *et al.* 1987). However, whether or not specific rather than global cognitive deficits may be correlated with an abnormal P300 was not examined in most studies of Parkinson's disease (Pang *et al.* 1990).

The neuronal site of P300 generation is ex-

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plained as a multiple generator such as the hippocampus, basal ganglia and various subcortical sites, but the exact neuronal sites generating P300 is still unknown (Kropotov and Ponomarev, 1990). Studies with a monkey with Parkinsonian syndrome, induced by MPTP, suggests that MPTP also disrupts auditory P300 generation (Glover *et al.* 1988). These results suggested dopaminergic system in the basal ganglia could be a generator of P300. If this is true, the lesion for abnormal P300 in parkinson's disease might be responsible for impaired procedural memory function as a specific cognitive deficit.

To address this question, we investigate the relationship between the degrees of procedural memory dysfunction and the delay of P300 event-related potential in patients with Parkinson's disease. We select the patients who have never had antiparkinson treatment in order to exclude any possible influence from those medications.

SUBJECTS AND METHODS

Subjects

We studied 16 consecutive patients initially diagnosed with idiopathic Parkinson's disease (8 men, 8 women; mean age 62.6 years old; Mean symptom duration 2.3 (0.4 years; Hoehn & Yahr stage I:5, II:7, III-IV:4) and 15 age and sex matched normal healthy controls (7 men, 8 women; mean age 61.0 years old). All patients had never received any antiparkinson medications when recruited for this study. Exclusion criteria included any history of antipsychotics treatment, structural lesion on CT or MRI of brain, and less than 25 points on the minimental status exam.

Assessment of procedural memory function

We used Gollin's incomplete picture test (GIP) for assessing the visual procedural memory function (Gollin, 1960; Heindel *et al.* 1990; Mack and Patterson, 1993) and the Tower of Hanoi puzzle for visuomotor procedural memory function (Cohen *et al.* 1985; Grafman *et al.* 1992). Subjects were asked to perform both

tests as fast as they could. Gollin's incomplete picture test was repeated 3 times and the total number of pictures and the time spent for accomplishing the test were measured. Tower of Hanoi puzzle (THP) was repeated 6 times and the number of moves and the time spent were recorded.

The auditory P300 event related potential

Chlorided silver cup electrodes were affixed via collodion to midline sites Fz, Cz, and Pz and were referenced to comparable electrodes on linked mastoids for recording of the electroencephalogram. The EEG band pass was 1Hz, an "oddball stimulus" paradigm was employed in which subjects kept a running mental count of low-probability target tone pipes (2000 Hz) interspersed against a background of more common non target tone pipes (1000 Hz). The auditory stimulus with alternating phase had a rise-fall time 10 msec, a plateau time of 40 msec, and an intensity of 75db. The event related potential epochs consisted of 50 averaged trials. Trials with excessive eye movement were automatically excluded from the averages. Two consecutive averages of the first 50 artifact-free trials were obtained. An additional average with identical subject-task demands, in which evoked electrical activity following the common tone was averaged, served to contrast ERPs in response to target and nontarget stimuli. Verbal reports of rare tone counts were obtained after each session in order to assess task vigilance. Latency values of components P300 was defined as the intersection point of "best fit" slope lines on adjacent sides of component peaks.

Data analysis

The mean number of pictures to recognize in GIP (each 3 test) and the mean number of moves (sum of 1-2nd test, 3-4th test, 5-6th test) in the THP were obtained at each parkinson's disease and the normal control group and the differences between the two groups were analyzed. Also, correlation with auditory P300 latency and the number of moves (sum of 5-6th test) in THP was evaluated. Statistical analysis was performed with unpaired t-

test and regression analysis.

RESULTS

The mean latency of P300 event-related potential was significantly prolonged in the Parkinsonian group (354 ± 18) than in the controls (307 ± 23) ($p < 0.001$) (Fig. 1). In GIP, each tested 3-results revealed no significant differences between the two groups. The mean number of moves of THP in the 1-2nd test was 35.6 in the patients group and 26.3 in the control group, in the 3-4th test the results were 36.8 in patients group, 23.5 in control

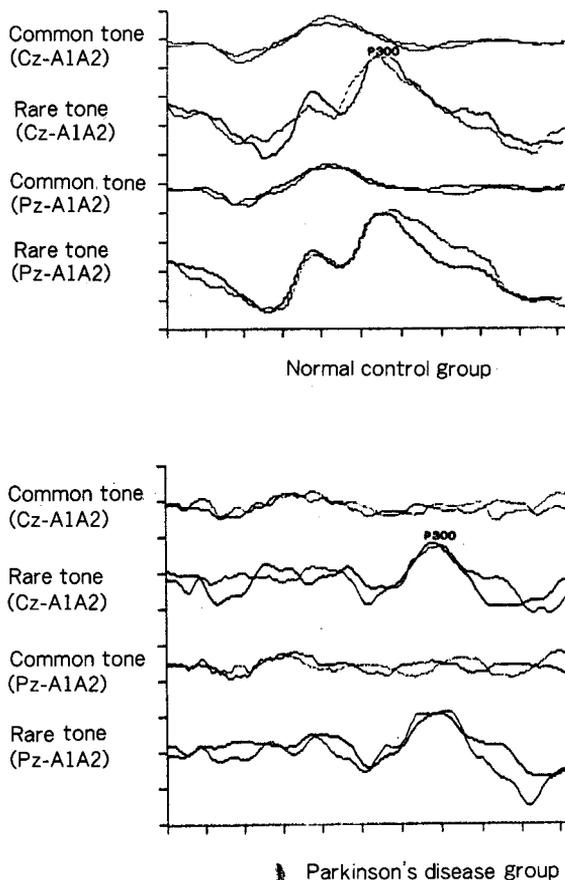


Fig. 1. The latency of P300 event-related evoked potential waveforms in normal and Parkinson's disease group.

group, in the 5-6th test the results were 25.7 in patients group, 16.5 in control group. The patients group revealed significant impairment of performance than the normal control in THP (1-2nd, 3-4th test; $p < 0.05$, 5-6th test; $p < 0.01$). In the patients group, the latency of P300 was inversely correlated with the mean number of moves of the 5-6th test of THP ($r = 0.54$, $p < 0.05$) (Fig. 2). However, each results of GIP were not correlated with P300 latency.

DISCUSSION

Both Gollin's incomplete picture test and the Tower of Hanoi puzzle are well-recognized test for evaluating procedural memory function (Gollin, 1960; Cohen *et al.* 1985; Heindel *et al.* 1990; Grafman *et al.* 1992; Mack and Patterson, 1993). The latter represents visuomotor, while the former mainly represents visual perceptual procedural memory function. The present results showing selective involvement of THP with preserved GIP in patients indicate that the main dysfunction of procedural memory in Parkinson's disease is visuomotor, not visual perceptual. This confirms previous reports showing abnormal rotatory pursuit task with preserved mirror reading in 20 parkinsonian patients (harrington *et al.* 1990).

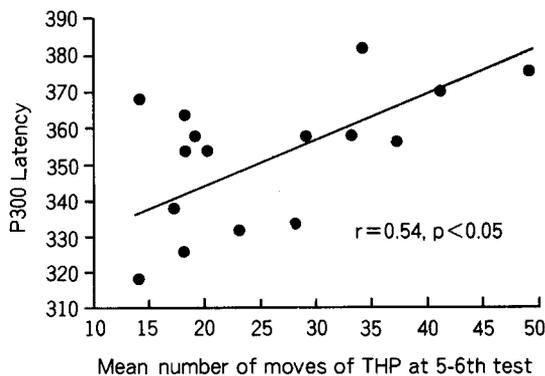


Fig. 2. In Patients group, the P300 was inversely correlated with mean number of moves at 5-6th test of Tower of Hanoi puzzle.

Antiparkinsonian Medication such as dopamine replacement therapy may influence its cognitive function (Loranger *et al.* 1973; Mohr *et al.* 1987; Gotham *et al.* 1988). Therefore, P300 may be influenced by antiparkinsonian medication. Latency of auditory P300 event related potential was significantly prolonged in our patients group. Its findings was no different with previous studies under treated situation (Ebmeier, 1992). However in this study, minimal states exam has been used as a test for screening the presence of dementia. And more than 24 points employed in this study usually means the subject's not having clinically significant dementia. The delayed P300 latency in the patients with early stage, non-demented Parkinson's disease revealed in the present results appears to be incompatible with prior report showing no significant differences in P300 of Parkinsonian patients if they are selectively non-demented or in an early stage (Goodin and Aminoff, 1987). The reason for, such an incompatibility is uncertain, but dopaminergic therapy in patients with other studies which are reported to improve P300 event related potential abnormalities observed in MPTP-treated monkeys, possibly make their results insignificant (Glover *et al.* 1988). In our study, patients have never been treated therefore, any parkinsonian medication effects were avoided. We suggest our results may provide one aspect of the natural course in cognitive dysfunction of Parkinson's disease. Therefore, the present results may indicate the P300 latency in drug-naive patients with Parkinson's disease is prolonged.

The correlation between the visuomotor procedural memory dysfunction and the prolonged P300 latency was observed in our study and this result might indicate the main lesion responsible for abnormal P300 in untreated and non-demented Parkinson's disease might be associated with the basal ganglia pathology, the main lesion in Parkinson's disease.

In summary, our results suggest that auditory P300 event related potential reflect the integrity of visuomotor procedural memory in the basal ganglia, which appears to be more selectively impaired than the visual procedural memory in drug-naive patients with Parkin-

son's disease.

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