Cognitive Impairment in Parkinson's Disease Assessed by Visuomotor Performance System and P300 Potential

ITARU KIMURA, AYUMU OHNUMA, HARUAKI SEKI, SHUN-ICHI SASO and KYUYA KOGURE*

Neurological Research Center, Miyagi National Hospital, Miyagi 989-22, and *Department of Neurology, Tohoku University School of Medicine, Sendai 980

KIMURA, I., OHNUMA, A., SEKI, H., SASO, S. and KOGURE, K. Cognitive Impairment in Parkinson's Disease Assessed by Visuomotor Performance System and P300 Potential. Tohoku J. Exp. Med., 1990, 161, Suppl., 155-165 — Motor impairment, clinically defined as bradycinesia has been considered as resulting only from motor system problems. Combined analysis of cognitive function and dynamic characteristics was studied in 20 patients with Parkinson's disease by a simple aiming task on visuomotor performance system. The dynamic characteristics in a Parkinson's disease patient was evaluated by two parameters: decreased amplitude of the voluntary movement (= low gain constant) and delayed initiation of voluntary movement (= long reaction time). The visual event-related potential elicited in a target detection paradigm (P300 component) was recorded in 12 patients with Parkinson's disease. P300 latency was significantly prolonged in the patient group than in the normal control group (p<0.05). P300 has been shown to be intimately related to the cognitive process in the human brain and might well serve as a tool to monitor and evaluate the cognitive state in a clinical situation. The main cause of cognitive involvement in Parkinson's disease may include coexisting dementia and defective motivation. This type of cognitive disturbance may also serve partly as a cause of bradycinesia. ——— Parkinson's disease; bradycinesia; event-related potential; cognition

Among the cardinal symptoms of Parkinson's disease, the most difficult one to treat successfully is the impairment of the voluntary movement, clinically described by bradycinesia. Several lines of argument suggest that disability of the voluntary movement is a "negative" symptom (Angel et al. 1970; Kimura et al. 1981). Tremor and rigidity, on the other hand, are considered as "positive" symptoms which are probably produced by abnormal discharges within the motor system and are readily estimated by the electromyographic techniques (Chan et al. 1979).

Address all correspondence to: Itaru Kimura, M.D., Neurological Research Center, Miyagi National Hospital, 100 Kassenhara, Takase, Watari, Yamanoto-cho, Miyagi 989-22, Japan.

This study is partly supported by Grants for Scientific Research on Prevention and Treatment for Senile Dementia and Normal Pressure Hydrocephalus from the Ministry of Health and Welfare, Japan.
In previous reports we have studied motor disability in patients with Parkinson's disease by their motor performance of a simple task, and found that motor disability could be defined by several dynamic parameters such as the amplitude of the voluntary movement (=gain constant), time necessary for the initiation of the voluntary movement (=reaction time), the accuracy of the movement (=coherency and correlation coefficient), error values in the aiming task and etc. (Kimura 1976; Kimura et al. 1977, 1981).

Recently some reports have been documented relating to cognitive changes in Parkinson's disease using standard psychometric tests. These clinical studies have shown that Parkinson's disease patients have some cognitive deficits particularly for those processes involving memory and learning (Boller 1980; Mortimer et al. 1982; Weingartner et al. 1984).

With modern techniques of the event-related potential (P300 component) quantitative assessment of the cognitive process in the human brain has become possible in several neuro-psychological disorders such as dementia, confusional states, depression, chronic alcoholics and uremic encephalopathy (Squires et al. 1980; Syndulko et al. 1982; Cohen et al. 1983; Goodin et al. 1983). Latency of P300 component has been shown to reflect the relative times to evaluate different stimuli, including process necessary for making a task-relevant decision (Kutas et al. 1977; Duncan-Johnson 1981).

The study reported here was designed to define the cognitive disturbance in patients with Parkinson's disease who showed characteristic motor impairment.

**Materials and Methods**

**Patients.** Twenty patients with clinically diagnosed Parkinson's disease, 12 men and 8 women, hospitalized in Miyagi National Hospital and Tohoku University Hospital for treatment, were examined. Their ages ranged from 27 to 75 (mean 52.8). All were alert and cooperative. Their then adopted medical regimens, which included anticholinergics, levodopa, amantadine and bromocriptine were not interrupted. All patients had frank signs of parkinsonism at the time of tests. Before their participation in the study standard psychometric tests including the Wechsler Adult Intelligence Scale (WAIS) and Mini-mental State by Folstein et al. (1975) were examined. Their WAIS results was above the normal range (mean of 126.0; and standard deviation of 14.5). Also Mini-mental State test showed normal range in all the subjects tested. No patients showed significant depression, sleep disturbance, sensory disturbance, speech disturbance or severe irritability.

**Control subjects.** Control group comprised 20 healthy volunteers, 14 men and 6 women, ranging in age from 25 to 82 (mean 51.9) who were hospital staffs and patients hospitalized for causes unrelated to the central nervous system. All were free of any disorder affecting movement or mental state.

**Apparatus.** Fig. 1 shows schematic representation of the experimental apparatus. A simplified block-diagram of the visuomotor performance system is shown in Fig. 2. The input signal, r(t), was unpredictable random noise produced by passing Gaussian noise through a filter transfer function of which was given by $1/(s+1)^2$. The frequency range of the input signal ranged from 0.01 to 3 Hz. A cathode ray oscilloscope was used for target display. A vertical target line, 40 mm in length, was displayed and driven horizontally
Fig. 1. A schematic representation of the experiment. Subject was requested to manipulate the handle of the potentiometer as fast as possible when he detected the target drift to the center. With the visuomotor performance system, dynamic characteristics evaluated by the reaction time and gain constant and the cognitive function measured by P300 potentials were studied, simultaneously.

Fig. 2. A simplified experimental block-diagram of a visuomotor performance system. Input, \( r(t) \)= unpredictable random noise; output, \( c(t) \); error, \( e(t) \)= displayed on an oscilloscope as a target movement; \( n(t) \)= the non-linear component of the human manipulation; the transfer function of the human operator \( G_h(s) \) and the transfer function of the system \( G_p(s) \).

across the screen within an 80 mm band. The subject manipulated the handle of the potentiometer to compensate for the movement of the target line from the center. The potentiometer's gain was set up so that a rotation of the handle 90 degrees to either side was virtually equal to a movement of 40 mm on either side of the target. The transfer function of the system was represented by the equation, \( G_p(s) = 1 \).

The gain constant between the input and output was measured with the open-loop and
closed-loop transfer function of the system. The dead time (reaction time in clinical basis) was calculated as a maximal lag time between the input and the output signals (Kimura 1976).

For recording of the event-related potential, a multimodality evoked potential analyzer (Pathfinder type II, Nicolet Com., Madison, WI, USA) was adopted in the visuomotor performance system. Electroencephalographic responses were recorded at the Pz in 10-20 international method, referred to linked mastoid electrode. Evoked responses to the rare sequence (attending to the target movement) and frequent stimuli (indifferent to the target movement) were filtered with a band-pass filter of 0.5-150 Hz (filter slope = 112 dB/octave) and averaged over an analysis time of 1000 msec. An impedance of each recording electrode was always maintained at 4 kило-ohms or less.

The subject was seated in a sound-attenuated, dimly lit room and affixed with Ag/AgCl standard electrodes placed on the midline of the scalp at Fpz and Pz. Additional electrodes was placed near the outer canthus of the left eye and in conjunction with the Fpz lead served as an eye movement/blink reflex monitor channel. The subject was requested to manipulate the handle of the potentiometer as fast as possible when he detected the target drift to the center line. The time of each experiment was set up 300 sec in consideration of the stability and fatigue of the patients. Control performance gradually improved with time; therefore, in this study, the data was analyzed only after the subject had learned how to use the manipulating handle.

**RESULTS**

With a simple aiming task using the visuomotor performance system, the dynamic parameters such as gain constant and dead time were obtained in all the patients with Parkinson’s disease and 20 normal subjects.

*Dynamic characteristics.* Gain constant was $8.34 \pm 9.6$ (mean ± S.D.) dB in patient group. This value was significantly decreased when compared to the

![Fig. 3. Relationship between gain constant and dead time in 20 patients with Parkinson’s disease (left) and 20 normal subjects (right). The regression line for both groups are identical and they are given by the equation $Y = -29.1X + 31.9$. The open circle mark indicates the mean values of gain constant and dead time for the control subjects (26.5 dB and 0.19 sec, respectively).](image-url)
values obtained in control group of 25.6±2.1 dB ($p < 0.01$). Dead time was 0.79±0.3 (mean ± S.D.) in patient group and was significantly prolonged than in normal subjects of 0.19±0.05 sec ($p < 0.01$). Relationship between gain constant and dead time was shown in Fig. 3. The regression line, as determined by the method of least squares, was the same for both the Parkinson’s disease patients and the control subjects. It could be represented by the equation:

$$Y = -29.1X + 31.9$$

Moreover, the correlation coefficient between the gain constant and the dead time for the Parkinson’s disease was 0.70. For the control group both parameters fell within a very small with a small deviation.

**P300 latency.** Visually evoked P300 component was recorded in 12 patients with Parkinson’s disease and 20 normal controls. Fig. 4 shows the visual event-related potentials recorded in a 42 year-old normal subject. Positive polarity is shown upward. Only in the rare (attending) sequence, prominent positive component with the peak latency of 360 msec (P300 component) is demonstrated. Results on three different trials are superimposed in each line. In Fig. 5 the event-related potentials obtained in a 50 year-old normal subject (upper traces) and in a 58 year-old patient with Parkinson’s disease (lower traces) were shown. P300 latency was prominently prolonged in the patient when compared to the age-matched normal subject.

Relationship between P300 latency and age of each subject is shown in Fig. 6.

![Fig. 4. Visually evoked event-related potentials recorded in a 42 year-old normal subject. In the rare sequence, a positive component with peak latency of 360 msec (P300 component) was noted.](image)
Fig. 5. The event-related potentials recorded in a 50-year-old normal subject (upper traces) and a 58-year-old patient with Parkinson's disease who showed typical motor disability (lower traces). P300 latency was prolonged in a patient when compared to a normal subject.

Fig. 6. Relationship between P300 latency and age of each subject. The regression line could be represented by the equation $Y = 1.88X + 275$. Out of 15 parkinsonian patients, 11 patients (●●●) showed prolonged P300 latency with the values beyond the mean + S.D. of normal controls (○○○).
In normal controls the regression line, as determined by the method of least squares, could be represented by the equation:

\[ Y = 1.88X + 275 \]

Moreover, the correlation coefficient between the P300 latency and the age was 0.65. The averaged P300 latency was \( 437 \pm 48.6 \) (mean \( \pm \) s.d.) msec in Parkinson’s disease patients and was significantly prolonged than the value in normal subjects of \( 368 \pm 78.4 \) msec (\( p < 0.05 \)). Out of 12, 8 patients showed prolonged P300 latency with the value beyond mean \( \pm \) s.d. for their age. There was no significant correlation between the degree of prolongation in P300 latency and decreased gain constant or prolonged dead time in patient group.

The amplitude of P300 component was calculated from the baseline to the peak of the component. No significant difference was obtained between Parkinson’s disease patient and normal subjects.

**DISCUSSION**

In a Parkinson’s patient, whether the motion is slow or rapid, quantitative analysis of the voluntary movement indicates that the accuracy of matching the target movement is considerably worse than it is in the normal subject. This parkinsonian motor disturbance has been defined by two characteristic parameters: (1) decreased gain constant which indicates the amplitude of the voluntary movement was prominently decreased and (2) prolonged reaction time which is assessed by the dead time on visuomotor performance system and it indicates initiation of the voluntary movement was delayed and movement itself was slow.

On the other hand, recent reports documented some cognitive dysfunction using standard psychometric tests (Mortimer et al. 1982; Weingartner et al. 1984) motivates our present study. The objective assessment of the cognitive function presents a special problem for the neurologist. Traditionally clinical examinations and specialized neuropsychological tests have been the only method used in clinical practice to assess mental and intellectual states. However, these methods frequently depend on subjective interpretation, and the examination procedures themselves can be so time-consuming that they are sometimes impractical as serial measures of the cognitive function.

In this study we have obtained significant prolongation of P300 latency in patients with Parkinson’s disease who showed typical motor disability, bradykinesia but with normal IQ scales in standard psychometric tests. Although clinical interpretation of P300 component has not been clarified yet, P300 latency has been shown to reflect the “relative” time necessary for making data analysis, differentiation and decision in the human brain. We all realize that P300 latency itself does not indicate the absolute time for the cognitive procedure in the brain, because P300 component was recorded as a far-field potential from the scalp electrodes. Little is known about exact neuronal gener-
ator responsible for the production of P300 component, however, P300 latency may indicate not only the absolute time for the cognitive processes from the stimulus input, through sensory perception at the primary sensory cortex and finally to the association area, but also the obscure time necessary for volume conduction from the P300 neural generator to the recording site. This hypothesis can explain the discrepancy that P300 latency is always longer than the dead time in the normal subject. On the assumption that P300 latency reflects the "relative" time necessary for the cognitive procedures in the human brain, we conclude that P300 latency is the only tool as a quantitative measure for the evaluation of the cognitive function at this moment.

The latency of P300 component increased regularly with the increasing of age at a rate of 1.88 msec per year in our study. This value conforms with those initially reported by Squires et al. (1980), Syndulko et al. (1982), Lawson et al. (1984) and Picton et al. (1984). The maximal slope of the regression line was somewhat less than a rate of 2.22 msec per year by Lawson et al. (1984), but slightly higher than the data of 1.36 and 1.07 msec per year by Picton et al. (1984) and Syndulko et al. (1982), respectively. Goodin et al. (1978) and Beck et al. (1980), on the other hand, described these relations with nonlinear, more complicated equations. In younger subjects aged below 15 year-old, Goodin et al. (1978) reported P300 latency decreased with the increasing of age. Recent report by Finley et al. (1985) confirmed this inverse relationship in younger ages. Mullis et al. (1985) obtained quadratic relationship between these two parameters. Concerning adult subjects with ages above 15 year-old, all data indicates P300 latency increases with the increasing of age at a rate of 1.0–2.2 msec per year. The difference of these rates of each reporter may mainly depend on variations of the subjects sampled and may also be due to technical differences in requiring target modality. Therefore, it is essential that P300 latency in each patient should be compared to the normal value of exactly age-matched controls.

This is the first report describing that P300 latency is significantly prolonged in patients with Parkinson's disease and there is no linear correlation between the prolongation of P300 latency and motor disability. P300 latency has been prolonged in several neuro-psychiatric disorders including dementia, depression, confusional states, chronic renal failure and chronic alcoholism (Pfefferbaum et al. 1980; Squires et al. 1980; Syndulko et al. 1982; Cohen et al. 1983; Goodin et al. 1983). Although the numbers of patients examined in this study was not enough to reach a conclusion, we suggest that main causes of the cognitive impairment in patients with Parkinson's disease are coexisting of dementia, whether it may be clinical or subclinical, and defective motivation just as it was observed in patients with depression and confusional states. Because we failed to obtain the relationship between the prolongation of P300 latency and the severity of the motor disability, we cannot conclude that cognitive failure is due to intrinsic deficit in Parkinson's disease. It will be essential to examine whether
P300 in Parkinson's Disease

Fig. 7. Idealistic schema explaining the relationship between the times for afferent sensory pathways and motor performance obtained in normal subjects, patients with Parkinson's disease and dementia utilizing the visuomotor performance system.

The cognitive impairment improves or not following the medical treatment.

Considering the results in other reports described in patients with dementia and our unpublished data examined in patients with cerebrovascular dementia, we represent a schema explaining the time relationship between the afferent sensory and motor performance components examined by the visuomotor performance system in normal subjects and patients with Parkinson's disease and dementia in Fig. 7. The time necessary for the afferent sensory perception is about the same in normal subjects, as in patients with dementia and Parkinson's disease, but the time necessary for the cognitive process is prolonged in patients, more prominent in patients with dementia than in patients with Parkinson's disease. On the other hand, the time necessary for the motor performance is significantly prolonged in patients with Parkinson's disease than in normal subjects or patients with dementia. Therefore, bradykinesia has been proved to be caused by impairments mainly in the motor side, however, the cognitive impairment has also been proved as another cause of this characteristic disability, although it plays very small parts.

References
