

Event based and time based prospective memory in Parkinson's disease

S Katai, T Maruyama, T Hashimoto, S Ikeda

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See end of article for authors' affiliations

Correspondence to:
Dr S Katai, Department of Neurology, Kakeyu Rehabilitation Centre and Clinic, 1308 Nishiuchi, Maruko-machi, Chiisagata-gun, Nagano 386-0396, Japan; skatai@valley.ne.jp

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Background: Patients with Parkinson's disease have been reported to have retrospective memory impairment, while prospective memory, which is memory for actions to be performed in the future, has not yet been investigated.

Objective: To investigate the prospective memory of patients with Parkinson's disease.

Methods: Twenty Parkinson's disease patients and 20 age matched normal controls were given event based and time based prospective memory tasks. In the event based prospective memory task, the subject was asked to perform an action whenever particular words were presented. In the time based prospective memory task, the subject was asked to perform an action at certain times.

Results: The Parkinson's disease patients were impaired on the event based prospective memory task but not on the time based prospective memory task. The impairment of the Parkinson's disease patients on the event based prospective memory task was not the result of their forgetting the content of the prospective memory instructions, but the result of their failure to retrieve it spontaneously when the target words appeared.

Conclusions: These results suggest that event based prospective memory is impaired in patients with Parkinson's disease, presumably relating to frontal lobe dysfunction.

Memory impairment has been well investigated in patients with Parkinson's disease.^{1–3} However, most studies on the memory impairment of Parkinson's disease patients have focused on retrospective memory, and prospective memory has not yet been reported. Retrospective memory is memory for past events, such as remembering what you did yesterday or remembering the words from a list learned in an experiment.⁴ On the other hand, prospective memory is memory for actions to be performed in the future, such as remembering to post a letter as you pass the postbox or remembering an appointment at 5 pm.⁴ We have to perform many activities using prospective memory in everyday life, and its decline may lead to substantial disability.

Knight described that prospective memory involves both the "what" knowledge of declarative memory and the planning abilities of executive functions.³ Executive functions refer to the mental processes needed for the elaboration of adaptive behaviour in response to new challenging environmental situations, which include the processing of relevant information, the generation of new concepts or mental sets, problem solving, and planning abilities.³ Some of these processes have been reported to be disturbed in patients with Parkinson's disease,³ while planning ability to realise delayed intention, which is necessary for successful prospective memory, has not yet been investigated.

Einstein and McDaniel proposed an important distinction between event based and time based prospective memory.^{4,6} Event based prospective memory is remembering to perform an action when some external event occurs, such as remembering to give a message to a friend when you meet the friend. Time based prospective memory is remembering to perform an action at a certain time, such as remembering to attend a meeting at 10 am.

Einstein and McDaniel also pointed out that prospective memory contains two components: a retrospective component and a prospective component.^{4,6} The retrospective component is remembering what action has to be performed and when it has to be performed, and the prospective component is remembering to perform the action when the appropriate

event or time occurs. For example, in remembering to give a message to a friend, the retrospective component is remembering the message and the friend to whom it is to be given. The prospective component is remembering to perform this action when we see the friend. Einstein and McDaniel have argued that this second component, which seems not to be present in most laboratory tests of retrospective memory, is typically accomplished through spontaneous remembering.⁶ That is, successful prospective memory requires that the occurrence of the appropriate event or time activates the memory without the benefit of a specific external prompt to initiate a controlled search of memory at the time of remembering.

In this study, we investigated event based and time based prospective memory in patients with Parkinson's disease, using prospective memory tasks analogous to those of Einstein *et al.*^{4,7}

METHODS

Subjects

Twenty patients with Parkinson's disease and 20 normal control subjects gave informed consent and were included in this study. The 20 patients with Parkinson's disease were all outpatients at the Kakeyu Rehabilitation Centre and Clinic. Parkinson's disease had been diagnosed in each patient by a neurologist, and there was no history of other neurological illness or injury in any patient. The Mini-Mental State Examination (MMSE)⁸ was administered to all patients and only those who scored 24 of 30 or above were included in this study. The Parkinson's disease group included seven men and 13 women. The average age was 64.6 years, ranging from 52 to 73 years. The mean duration of Parkinson's disease was 5.5 years, ranging from 2 to 12 years. Six patients were classified at Hoehn and Yahr stage I, five at stage II, and nine at stage III. The mean (SD) score on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS)⁹ in the "on" medication state was 27.3 (12.4). Eighteen patients were treated with levodopa (mean dose 336 (195) mg/day) in conjunction

Table 1 Demographics, clinical characteristics, and neuropsychological test results of the control group and the Parkinson's disease group

	Control group mean (SD)	Parkinson group mean (SD)	p Value*
Age (y)	63.1 (5.6)	64.6 (5.2)	NS
Education (y)	11.2 (2.0)	10.0 (2.1)	NS
Duration of disease (y)	--	5.5 (3.0)	
Hoehn and Yahr stage	--	2.2 (0.9)	
UPDRS motor	--	27.3 (12.4)	
MMSE	28.8 (1.3)	28.0 (1.4)	NS
RAVLT			
Total recall	48.3 (8.3)	37.7 (8.2)	<0.01
Delayed recall	10.1 (2.5)	7.8 (2.9)	<0.01
Delayed recognition	13.5 (1.2)	13.5 (1.6)	NS
WCST			
Categories	5.9 (0.3)	5.4 (0.9)	<0.05
Total errors	10.2 (1.7)	12.3 (3.0)	<0.05
PEN	0.8 (1.1)	1.3 (1.5)	NS
PEM	1.0 (1.4)	1.4 (2.0)	NS
VFT			
Category task	31.2 (8.3)	22.0 (6.0)	<0.01
Letter task	21.1 (6.8)	13.2 (5.9)	<0.01
ZSDS	36.9 (8.4)	52.5 (10.8)	<0.01

*Mann-Whitney U test. NS, not significant; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; WCST, Wisconsin Card Sorting Test; PEN, Perseverative errors of Nelson; PEM, Perseverative errors of Milner; VFT, Verbal Fluency Test; ZSDS, Zung's Self-rating Depression Scale.

with a dopa-decarboxylase inhibitor. Eleven patients were treated with trihexyphenidyl, six patients with bromocriptine, four with pergolide, eight with amantadine, six with droxidopa and one with carbergoline. All medicated patients were tested in the "on" state.

The control group included seven men and 13 women, with no history of neurological or psychiatric disorder. The average age of the control group was 63.1 years, ranging from 54 to 70 years. The two groups were matched for age, sex, and education (table 1).

Neuropsychological evaluation

A comprehensive battery of tests was administered to assess general cognitive and memory functions: the MMSE⁸ to measure global cognitive function, the Rey Auditory Verbal Learning Test (RAVLT)¹⁰ to evaluate retrospective memory, the Wisconsin Card Sorting Test (WCST),¹¹ and the Verbal Fluency Test (VFT)¹² to measure frontal lobe functions, and Zung's Self-rating Depression Scale (ZSDS)¹³ to evaluate depression. The VFT consisted of two subtests: the category task, in which the subject was asked to generate as many words as possible belonging to animals and vehicles in one minute; and the letter task, in which the subject was asked to generate as many words as possible beginning with the designated Japanese letters "Shi" and "I" in one minute.

Event based prospective memory task

The subject was initially instructed that they should tap the desk whenever the Japanese word "ushi (cow)" or "mikan (orange)" (target events) appeared during the subsequent tasks. Next, the subject was given a number selection task using 20 question cards. On each card, 12 two digit numbers were printed. The subject was told to select the smallest number in the first 10 cards and the largest number in the next 10 cards. After the number selection task, the subject was given a word selection task in which the target events for the prospective task were embedded. The task consisted of 30 question cards. On each card, 12 common Japanese words were printed. Ten of the 12 words belonged to one category, and the remaining two words belonged to another category. The subject was told to select the two words that belonged to a category that differed from the other 10 words. The experimenter presented each card to the subjects, who were then

instructed to answer verbally at their own pace. The target events for the prospective memory task occurred on the 15th (ushi), 20th (mikan), 24th (mikan), and 29th (ushi) cards of the word selection task. After the word selection task, the subject was asked to recall the instructions of the prospective memory task.

A prospective memory score, a retrospective memory score and the subject's performance on the number selection task and the word selection task were recorded. The prospective memory score refers to the subject's performance on the prospective memory task. A score of 1 was given for each correct response to a target event, and a score of 0 was given for an incorrect response (maximum score 4). The retrospective memory score refers to the subject's performance on recalling the instructions of the prospective memory task after the word selection task. The instructions were separated as follows: tap the desk whenever "ushi" appears; and tap the desk whenever "mikan" appears. Each phrase that was correctly recalled was worth two points (maximum score 4).

Time based prospective memory task

The subject was initially given the instructions for the prospective memory task, which were to tap the desk after 10 minutes had elapsed, and to do it again after 15 minutes had elapsed from the start time. We showed the subject a digital clock (which displayed hours, minutes, and seconds), which was situated about one metre away behind their right shoulder, and told the subject to use this clock to check the time. The position of the clock required the subject to turn their head to check the clock. This ensured that an external cue was not visible, and it allowed the experimenter to record the number of times the subject checked the clock. At the end of the instructions, the clock was set to display 0 hour 0 min 0 s. After the clock was started, the subject was given the number selection task, which consisted of 20 cards and, subsequently, the word selection task, which consisted of 100 cards. These tasks were identical to those described in the event based prospective memory task. The word selection task was stopped when the digital clock indicated 17 minutes. The number of times the subject checked the clock was recorded at one minute intervals. After the word selection task, the subject was asked to recall the instructions of the prospective memory task.

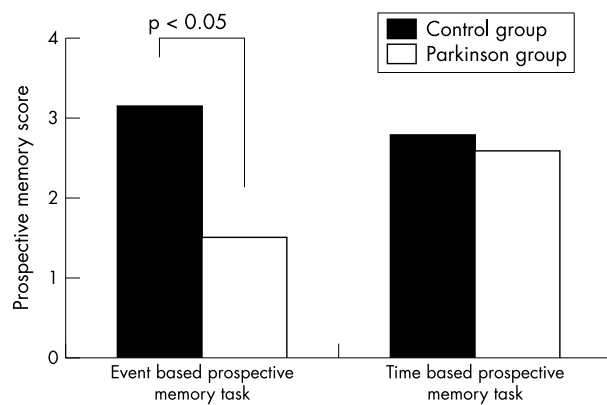


Figure 1 Mean prospective memory scores of the control group and the Parkinson's disease group on the event based and time based prospective memory tasks.

A prospective memory score, a retrospective memory score, the number of times that the subject checked the clock, and the subject's performance on the number selection task and the word selection task were recorded. The prospective memory score refers to the subject's performance on the prospective memory task. Subjects who responded from 10 seconds before to 10 seconds after the target time were given a score of 2, and all other subjects were given a score of 0 (maximum score 4). The retrospective memory score refers to the subject's performance on recalling the instructions of the prospective memory task after the word selection task. The instructions were separated as follows: tap the desk in 10 minutes; and tap the desk in 15 minutes. Each phrase that was correctly recalled was worth two points (maximum score 4).

For both groups, 10 subjects performed the event based prospective memory task first and the other 10 subjects performed the time based prospective memory task first.

Statistical analysis

Performance on the event based and time based prospective memory tasks in the Parkinson's disease and control groups, and the number of time monitoring responses in the two groups, were compared by analysis of variance. Simple comparisons between the two groups were achieved using the Mann-Whitney U test. Correlations were determined with Spearman rank correlation coefficient. Results were considered significant if $p < 0.05$.

RESULTS

Neuropsychological evaluation

Table 1 summarises the results of the neuropsychological evaluation. The scores on the MMSE obtained by the Parkinson's disease and control subjects did not differ significantly. The performance of the Parkinson's disease group was significantly poorer than that of the control group on the following tests: the total number of words recalled ($p < 0.01$) and

number of words recalled after a delay ($p < 0.01$) on the RAVLT; the number of categories achieved ($p < 0.05$) and the number of total errors ($p < 0.05$) on the WCST; and both subitems (category task and letter task; $p < 0.01$, $p < 0.01$) of the VFT. The depression score on ZSDS of the Parkinson's disease group was significantly higher than that of the control group ($p < 0.01$).

Prospective memory tasks

Figure 1 shows the mean prospective memory scores of the Parkinson's disease and control groups on the event based and time based prospective memory tasks. These data were subjected to analysis of variance with group (control versus Parkinson's disease) as the between subjects variable and type of prospective memory task (event based versus time based) as the within subjects variable. This analysis showed a main effect of group, reflecting the Parkinson's disease group's poorer performance relative to the control group ($F(1, 38) = 9.11$, $p < 0.01$). The main effect of the type of prospective memory task was not significant; however, there was a significant interaction between these two variables ($F(1, 38) = 5.54$, $p < 0.05$). Analysis of the simple main effects of this interaction confirmed that the Parkinson's disease group had lower prospective memory scores than the control group in the event based task ($F(1, 76) = 14.41$, $p < 0.01$), while there was no significant difference between the two groups in prospective memory performance on the time based task.

Event based prospective memory task

Table 2 summarises the performance of the Parkinson's disease and control groups on the subitems of the event based prospective memory task. There was no significant difference between the two groups in the total number of correct responses on either the number selection task or the word selection task. The prospective memory score of the Parkinson's disease group (1.5 (1.6)) was significantly lower than that of the control group (3.2 (1.0)) ($p < 0.01$), indicating that event based prospective memory was impaired in the Parkinson's disease group. There was no significant difference in the retrospective memory score of the two groups.

Correlation analyses were performed between the event based prospective memory score and motor and neuropsychological parameters, listed in table 1, among the Parkinson's disease subjects, but no significant correlations were obtained.

Time based prospective memory task

Table 3 summarises the performance of the Parkinson's disease and control groups on the subitems of the time based prospective memory task. There was no significant difference between the control and Parkinson's disease groups in the total number correct on either the number selection task or the word selection task. The prospective memory score of the two groups did not differ significantly. According to the procedure of Park *et al.*,¹⁴ we calculated additional measures of time based prospective memory performance. A group of six scores, with different windows for responding, was calculated for

Table 2 Performance of the control group and the Parkinson's disease group on subitems of the event based prospective memory task

	Control group mean (SD)	Parkinson group mean (SD)	p Value*
Background task			
Number selection task	19.7 (0.7)	19.5 (0.8)	NS
Word selection task	59.4 (1.1)	58.6 (2.1)	NS
Prospective memory score	3.2 (1.0)	1.5 (1.6)	<0.01
Retrospective memory score	3.8 (0.6)	3.4 (1.0)	NS
Time for administration (s)	529.7 (127.5)	641.9 (179.2)	NS

*Mann-Whitney U test. NS, not significant.

Table 3 Performance of the control group and the Parkinson's disease group on subitems of the time based prospective memory task

	Control group mean (SD)	Parkinson group mean (SD)	p Value*
Background task			
Number selection task	19.8 (0.6)	19.5 (0.8)	NS
Word selection task	67.4 (19.7)	60.3 (26.4)	NS
Prospective memory score	2.8 (1.2)	2.6 (1.6)	NS
Retrospective memory score	4.0 (0.2)	4.0 (0.0)	NS
Number of clock checking responses	32.3 (14.9)	29.3 (12.8)	NS

*Mann-Whitney U test. NS, not significant.

each subject. The most stringent window was a three second interval in which subjects who responded from one second before and one second after the target time were given a score of 2 for each correct response. Additional scores were calculated for intervals of $\pm 1, 2, 3, 5, 30, 60$ s, resulting in windows of 3, 5, 7, 11, 61, 121 s, respectively. Six separate Mann-Whitney U tests were conducted on these results, and none of these analyses showed significant differences between groups. Another accuracy measure was calculated by determining—for all responses that occurred within a 121 second window—the absolute difference in seconds from the time a subject made a prospective response relative to the time when the response should have occurred. There was no significant difference between the two groups (control group, 13.6 (12.4) seconds; Parkinson's disease group, 17.1 (16.3) seconds). There was also no significant difference in the retrospective memory score of the two groups.

There was no significant difference between the two groups in the number of total clock checking responses over the 17 minute period. Figure 2 shows the mean number of clock checking responses per one minute over 17 minutes in the two groups. Both groups checked the clock most frequently right before the target times. These data was subjected to analysis of variance with group (control versus Parkinson's disease) as the between subjects variable and with one minute periods as the within subject variable. There was a significant effect of one minute periods ($F(16, 608)=13.48, p<0.01$). Neither the effect of group, nor the group times one minute periods interaction, was significant. These analyses indicate that the frequency and pattern of clock checking did not differ significantly between the two groups.

Correlation analyses were performed for the time based prospective memory score and motor and neuropsychological parameters, listed in table 1, among the Parkinson's disease subjects. Only delayed recognition performance of the RAVLT was significantly correlated with the time based prospective memory score ($r=0.57, p<0.05$). No other correlations were significant.

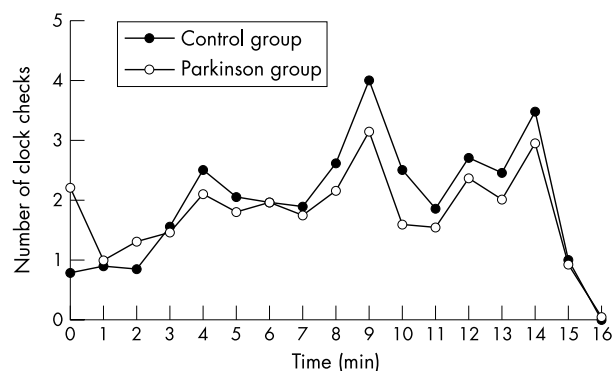


Figure 2 Mean number of clock checking responses in the control group and the Parkinson's disease group in each one minute period during the time based prospective memory task.

As anticholinergic drugs are known to affect cognitive function in Parkinson's disease,¹⁵ patients receiving anticholinergic drugs were compared with those not taking anticholinergic drugs. There was no significant difference between the two groups in the prospective memory score of either the event based task or the time based task.

DISCUSSION

These results show that the Parkinson's disease group performed poorly on the event based prospective memory task, but performed normally on the time based prospective memory task. It seems unlikely that these results are attributable to depression or anticholinergic medication, because severity of depression did not associate significantly with the prospective memory scores of either task, and patients receiving anticholinergics did not differ from the remainder of the Parkinson's disease group on the prospective memory scores of either task.

Event based prospective memory

On the event based prospective memory task, the prospective memory score of the Parkinson's disease group was significantly lower than that of the control group. On the other hand, the retrospective memory score of the Parkinson's disease and control groups did not differ significantly. Therefore, the impairment of event based prospective memory in the Parkinson's disease subjects did not result from their forgetting the content of the prospective memory instructions, but from their failure to retrieve it when the target events occurred. Thus, the impairment of event based prospective memory in the Parkinson's disease subjects was attributable mainly to impairment of the prospective component.

Einstein and McDaniel pointed out that the retrospective component of prospective memory tasks seemed to be identical to the ability that is evaluated by retrospective memory tasks.^{4,6} The retrospective memory of patients with Parkinson's disease has been reported to be impaired.^{1,3} However, the deficit in retrospective memory in Parkinson's disease is generally mild,^{1,3} and the retrospective component of the task was quite simple in our study. These may be the reasons why the Parkinson's disease group did not show significant impairment on the retrospective component.

The prospective component is an essential part of prospective memory.^{4,6} Several authors¹⁶⁻²⁰ have mentioned that the frontal lobe plays a critical part in the prospective component of prospective memory. Hécaen and Albert reported "forgetting to remember" in patients with frontal lobe lesions, meaning that an intended act or memory is forgotten, although it may be retrieved later.¹⁷ Lezak mentioned that the retrospective memory of patients with frontal lobe damage may be comparatively intact, but that they are unable to carry out previously decided upon activities at designated times or places.¹⁶ Shimamura *et al* described that the frontal lobe plays an important part in self initiated retrieval of information in prospective memory.¹⁹ A recent study on local brain activation

using positron emission tomography demonstrated activations relating to prospective memory in the prefrontal cortices.²¹ Impaired frontal lobe functions in patients with Parkinson's disease have been revealed by neuropsychological studies^{1,3} and by metabolic studies.^{22,23} Taken together, it is possible that the impaired prospective component of prospective memory found in this study arises from frontal lobe dysfunction in the Parkinson's disease patients.

However, the event based prospective memory score did not correlate with either frontal measure (WCST or VFT) among the Parkinson's disease subjects in this study. The pattern of results can be reconciled if one views possible dissociations within frontal lobe functions, as has been suggested by Baddeley *et al*,²⁴ in which 24 patients with defined frontal lobe lesions were assigned to one of two groups (dysexecutive group and non-dysexecutive group) based on whether or not they had a behaviourally assessed dysexecutive syndrome. All participants were tested on a dual task (working memory task) and two traditional frontal tasks, the WCST and the VFT. The dysexecutive group showed significantly impaired capacity for dual task coordination as compared with the non-dysexecutive group, but there were no significant differences on the WCST and the VFT. Also, the correlations among the three frontal tasks were not statistically significant. Thus, the lack of correlation between the event based prospective memory score and the WCST or the VFT in Parkinson's disease patients in this study suggests that these tests reflect different processes in frontal lobe functions.

The event based prospective memory task in this study might seem to be similar to the dual task paradigm, which was used by Baddeley *et al*^{24,25} to study the central executive functioning of working memory, in that the prospective task and the background task are performed simultaneously. There are, however, substantial differences in these two tasks. The dual task paradigm of Baddeley *et al*^{24,25} requires continuous sustained attention for both the visuospatial tracking task and the auditory digit span task, while the event based prospective memory task requires continuous attention for the background task but does not require it for the prospective task. The Simple Activation model, which was developed by Einstein and McDaniel⁶ to account for the mental process in event based prospective memory tasks, expresses this characteristic well. According to the Simple Activation framework, when a subject is given a prospective memory task, they form an associative encoding of the cue-action pairing. When a subject then begins to perform other intervening activities (background task), the activation of the cue-action coding subsides to levels below conscious awareness. As activation decreases, the probability of reactivating the prospective memory into awareness when the target event seems also to decrease. Activities that raise activation levels (such as rehearsal of the cue-action association) make it more probable that subsequent exposure to the target cue at the time of intended remembering will raise activation above threshold, and in so doing, elicit prospective remembering. Thus, the dual task paradigm of Baddeley *et al*^{24,25} assesses the coordinating operations of the central executive of working memory, while the event based prospective memory task assesses the self initiated retrieval of information from long term memory, rather than coordinating function of the central executive.

Time based prospective memory

On the time based prospective memory task, neither the prospective memory score, nor the retrospective memory score of the Parkinson's disease and control groups differed significantly. This indicates that the prospective component, as well as the retrospective component, of the time based prospective memory task in the Parkinson's disease group was preserved. The retrospective component of the time based prospective memory task was as simple as that of the event based

prospective memory task. Therefore, the lack of a significant difference in performance on the retrospective component of the time based task between the two groups is attributable to the same reason as that underlying the event based task.

On the other hand, the nature of the prospective component of the time based prospective memory task was essentially different from that of the event based prospective memory task.^{6,7} In the time based prospective memory task, there was no obvious external cue, and the subjects had to remember on their own to monitor the passage of time and to initiate the action. Harris and Wilkins developed a specific model of the processes that are necessary to successfully perform a time based prospective memory task.²⁶ Their model, called the Test-Wait-Test-Exit model, proposes that subjects initially encode a prospective memory task and then wait for a period of time until a check or test of memory seems appropriate. They then wait for another period of time until another check seems appropriate. They continue looping through the test-wait cycles until a test is made during a critical period (that is, a period in which it is appropriate to respond). At this point, they exit the loop and perform the action. According to this model, successful remembering is critically dependent on monitoring or checking the time during a critical period. To test this view, Einstein *et al* investigated the relations between clock checking frequency and time based prospective memory performance.⁷ They found that clock checking frequency, especially clock checking close to the target time, highly correlated with time based prospective memory performance, with higher clock checking associated with faster responding (that is, more punctual prospective memory). Thus, the prospective component of the time based prospective memory task was heavily dependent on clock checking or time monitoring behaviour,⁷ but there was no significant difference in either the frequency or the pattern of clock checking between the two groups in this study.

Harris and Wilkins²⁶ pointed out that the accuracy of time monitoring is related to time estimation, and it has been reported that patients with Parkinson's disease not treated with dopaminergic medication underestimate the length of time intervals (that is, the "internal clock" is abnormally slow).^{27,28} Based on this finding, it is predicted that the Parkinson's disease group might show impairment on the time based prospective memory task. However, it has also been reported that the administration of levodopa to the Parkinson's disease patients led to time judgments that were similar to those of normal control subjects.²⁸ In this study most of the Parkinson's disease patients (18 of 20 patients) were receiving stable levodopa medication and were tested in the "on" state. Taken together, these observations suggest that time estimation of the Parkinson's disease group was not significantly impaired in this study, and that if the Parkinson's disease group were tested in the "off" state, they might show impairment on the time based prospective memory task.

Finally, why was the Parkinson's disease group impaired on the event based prospective memory task, but not on the time based prospective memory task? Okuda *et al* investigated localised brain activations in relation to an event based prospective memory task using positron emission tomography and concluded that retaining the intention of future behaviour in the event based prospective memory tasks was mediated by the right ventrolateral prefrontal region and the left frontal pole.²¹ On the other hand, Harrington *et al* suggested that a neural network composed of the right inferior parietal cortex to the right middle and superior frontal gyri plays a crucial part in the temporal monitoring process in time perception tasks.²⁹ These findings suggest that prospective memory components of event based and time based prospective memory tasks may be mediated by different neural networks, and dissociation in prospective memory impairment in Parkinson's disease may be attributable to selective impairment of these neural networks. In contrast

with our results, Maylor *et al* observed that patients with Alzheimer's disease performed poorly on both event based and time based prospective memory tasks as compared with age matched normal controls despite having ensured that all participants had successfully retained the prospective memory task instructions.³⁰ The impaired cortical areas relating to prospective memory may be broader in patients with Alzheimer's disease than in those with Parkinson's disease.

Authors' affiliations

S Katai, T Maruyama, Department of Neurology, Kakeyu Rehabilitation Centre and Clinic, Nagano, Japan
T Hashimoto, S Ikeda, The Third Department of Medicine, Shinshu University School of Medicine, Nagano, Japan

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