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Impairment of time-based prospective memory in patients with Wilson's disease

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Abstract. – OBJECTIVE: The aim of this study was to investigate the effect of basal ganglia lesion of Wilson's disease (WD) patients on event-based prospective memory (EBPM) and time-based prospective memory (TBPM).

PATIENTS AND METHODS: A total of 30 WD patients and 30 age and education level matched healthy controls were included. EBPM (an action whenever particular words were presented) and TBPM (an action at certain times) were performed to test the involvement of the prospective memory in WD.

RESULTS: A significant difference was found in the performance of TBPM (2.9±1.1 vs. 5.8±0.4, $p<0.05$), but not EBPM (5.4±0.7 vs. 5.5±0.7, $p>0.05$) in patients with WD compared with the healthy controls.

CONCLUSIONS: Our results demonstrated that basal ganglia are involved in the prospective memory in patients with WD.

Key Words:
Wilson's disease, Event-based prospective memory, Time-based prospective memory, Prospective memory.

Introduction

Wilson's disease (WD), a rare autosomal recessive disorder of copper metabolism, is characterized by copper accumulation in the liver, brain and kidney[1]. Typically, WD begins with a presymptomatic period, during which copper accumulation in the liver causes subclinical hepatitis, and progresses to liver cirrhosis and development of neuropsychiatricsymptoms[2,3]. With neuropsychiatric symptoms, WD patients often manifest behavior or emotional disorders (showing impulsive, instinctive behaviors, or depression), and mild cognitive deficit[4,5].

Memory, an important cognitive function, refers to the mental process in which individual experience is accumulated and preserved; it plays an important role in the entire mental activity. Currently, two main types – retrospective memory (RM) and prospective memory (PM) – are used to assess memory in a quantitative manner[6]. RM refers to the memory of things or actions that have occurred in the past, and PM refers to the memory of completing a certain activity at the appropriate time in the future, which can be further divided into time-based prospective memory (TBPM) and event-based prospective memory (EBPM)[7,8]. TBPM refers to the memory of the execution of an action at a target time, such as remembering to call a friend in 1 h. EBPM refers to the memory of performing an action when a specific target event occurs, such as remembering to buy some fruits when passing by a fruit stand. PM has important practical significance for the elderly for maintaining the normal activities of daily life, such as taking their medication at a specific time.

Recent studies suggested that EBPM and TBPM tasks may be mediated by different neural networks. By using positron emission tomography technology, Okuda et al[9] showed that the

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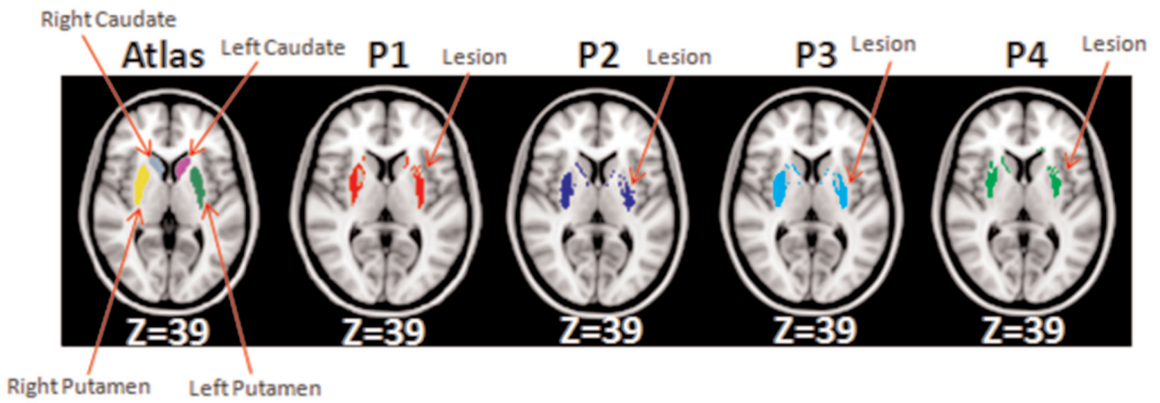

Figure 1. Lesion location in left and right brain of Wilson's disease patients. (Number of patients with basal ganglia locations that overlap increase from red to green).

right ventrolateral prefrontal region and the left frontal pole were activated by EBPM task. Moreover, several neuroimaging[10-12] further identify the involvement of the prefrontal region in EBPM. In addition, Cheng et al[13] proved in a neuropsychological study that the prefrontal region is involved in EBPM. Compared with EBPM, the neuromechanism of TBPM is rarely reported. It has been reported[14] that the thalamus was activated by TBPM tasks. It was documented[15] that patients with Parkinson's disease manifested a particular impairment of TBPM. However, activation of basal ganglia by TBPM tasks has not been reported yet.

Based on the above theoretical background, our neuropsychological findings seem to correspond to some of the previous neuroimaging evidence about PM, that is, the basal ganglia may be involved in PM[16,17]. Several studies[18-20] have investigated memory function in WD patients. However, the details of the involvement of the basal ganglia in EBPM or TBPM have not completely understood, and very few studies have hitherto investigated EBPM and TBPM in WD patients with basal ganglia lesions. In the present research, we investigated EBPM and TBPM tasks in 30 WD patients to test the hypothesis that the basal ganglia lesion is involved in EBPM or TBPM.

Patients and Methods

Patients

Thirty WD patients were recruited in the Neurology Department of The Affiliated First Hospital of the Anhui University of Chinese Medicine, including 14 men and 16 women; 6 with a lesion in right basal ganglia, 5 with a lesion in left, and 19 with bilateral lesions. The mean age was 17.5±1.3 years (range: 14-22 years), and the average education level was 8.2±1.6 years, ranging from 6 to 10 years.

The diagnosis of WD was based on clinical, Kayser-Fleischer (KF) ring on slit lamp examination, urinary copper >40 μg/day, and serum ceruloplasmin <20 mg/dl. Moreover, all the subjects had no history of psychiatric illness or other neurological lesions and were in stable neurological condition at the time of testing. The Mini- Mental State Examination (MMSE)[21] was administered to all patients, and only those who scored >24 were included in this study. None of the patients showed significant language impairment that would have interfered with task performance.

With cranial magnetic resonance imaging (MRI) scans proven, the sites of lesion restricted to the basal ganglia were identified and patients with lesions outside the basal ganglia were excluded. The locations of these lesions were shown in Figure 1.

Thirty (19 male and 11 female) age- and education-matched adults also participated in the study as control subjects.

The study was approved by the Research Ethics Committee of The First Affiliated Hospital of the Anhui University of Chinese Medicine, and written informed consent was obtained from all participants.

Neuropsychological Background Measurement

All the subjects recruited for this study were evaluated using a neuropsychological back-

ground test, which consisted of MMSE test, the verbal Fluency Test (VFT)[22], Digit Span test[23]. All of the assessments were performed by experienced psychologists and psychiatrists.

Event-based Prospective Memory Task

Before the testing, the subjects were informed that, in the following test, they were to select two words on each card that specifically belonged to a subclass. If the two words they selected belonged to the category of animals (target word), then the subjects were required to knock on the table or to provide their contact telephone number at the end of the experiment (no hints were provided at the end of the testing). The experimental stimuli were 32 cards, each containing 12 high-frequency Chinese substantives, of which 10 words belonged to one category (major category) and the other two belonged to another category (minor category). The subjects were asked to read out the two words belonging to the minor category on each card during the learning period. There were two cards for learning, and the first card contained no target word, while the second card did. As instructed before the testing, when the selected words represented animals, the subjects fulfilled the task by knocking on the table; when the card selection was complete, the subjects performed another task by providing their telephone number. The subjects' performance on the word selection task was recorded using a method similar to the report by Einstein et al[24]. The subjects were to perform a target action when the target words appeared, and the numbers of correct performances of a target action were recorded as the EBPM score. There was a total of six target cards (card numbers 6, 11, 16, 21, 25, and 31) in this test. The subjects received 1 point by making the correct response when the target card appeared, and they received 2 points by remembering to write down their phone number at the end of the test. The RM1 refers to the performance of subjects on recalling animal words after the word selection task; 1 was given for each correct recall of an animal word. The total score was 8 points for EBPM and the maximum score was 12 points for RM_1.

Time-Based PM Task

Before the test, the subjects were asked to knock once on the table at three-time points (5 min, 10 min, and 15 min after the test had begun), and the subjects were also required to pick out the maximum and minimum values on each card. A clock, which was set to 0:00:00 at the beginning of the testing, was placed right behind the subject for them to check the time on their own. The experimental stimuli were 100 cards with 12 two-digit numbers on each card, which were sequentially shown to the subjects after the clock started. The subjects were expected to complete the task by picking out the minimum and the maximum values on each card and to complete the other task at the specified target time points (5 min, 10 min, and 15 min after the start of the testing), which was to knock on the table. The test stopped at the 17-min time point. The subjects received 2 points if they knocked on the table within 10 s around the target time, and 1 point if within 30 s. The subjects were also asked to recall the exact time of tapping the desk after the test (recorded as RM2 score). The RM2 refers to the participants' performance on correct recalling exact time of each actually tapping the desk during the test. A score of 2 was given for each correct recalling. The maximum score of TBPM and RM_2 was 6 points.

Statistical Analysis

All the statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). The data were examined for normal distribution and homogeneity of variance with the Kolmogorov-Smirnov test and the Levene test, respectively. One-way analyses of variance (ANOVAs) and the Mann-Whitney U test was used for parametric tests for normal and abnormal distributed data, respectively. Pearson or Spearman correlations was respectively used examination of potential relations between variables $p<0.05$ was considered as statistical significance.

Results

Neuropsychological Evaluation

Neuropsychological tests were performed in both group patients and the results were shown in Table I. No significant difference was found on age, education level, Handedness and MMSE between WD patients and control patients, whereas a significant difference was found on VFT and DS.

Event-Based Prospective Memory Task

As shown in Figure 2 and Table II, no significant difference was found on a number of selec-

Table I. Demographic data and neuropsychological test scores of Wilson's disease patients.

Variables	Patients with Wilson's disease (n=30)	Normal controls (n=30)	*p*-value
Age	17.3 ± 2.4	17.5 ± 1.3	NS
Male/female	14/16	19/11	NS
Disease duration	2.7 ± 0.9	-	-
Education level (year)	8.5 ± 0.7	8.5 ± 0.5	NS
Handendness	30R/0L	30R/0L	NS
The Mini-Mental State Examination (MMSE)	27.5 ± 0.6	28.3 ± 0.7	NS
Verbal fluency test (VFT)	8.2 ± 1.1	8.8 ± 0.9	<0.05
Digital Span (DS)	6.6 ± 1.3	7.2 ± 0.8	<0.05

NS: not significant.

tion task, word selection task, and time to response. The RM_1 score of WD patients was significantly lower than that of the controls (t=-14.367, $p<0.001$), while no significant difference was found on EBPM score between WD patients and control subjects.

Time-Based Prospective Memory Task

As shown in Figure 2 and Table III, no significant difference was found on a number of selection task, word selection task, and number of clock checking responses. The TBPM score (t=-12.814, $p<0.001$) and RM_2 score (t=-17.514, $p<0.001$) of WD patients were significantly lower than that of the controls.

Correlation Between Wilson's Disease Lesion Volume and PM, RM, VFT, DS, MMSE, and Age

Furthermore, we also performed Pearson correlations analyses between Wilson's disease patients and control subjects. Significant positive correlation was found between DS and VFT (r=0.649, $p<0.05$), EBPM and MMSE (r=0.495, $p<0.05$), TBPM and DS (r=0.511, $p<0.05$), and RM and VFT (r=0.771, $p<0.05$), DS (r=0.749, $p<0.05$) and TBPM (r=0.663, $p<0.05$) (Table IV).

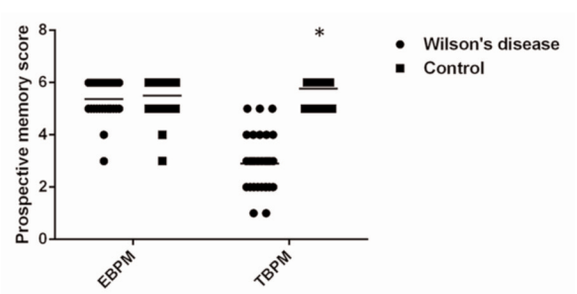

Figure 2. Mean prospective memory (PM) scores in the patients with Wilson's disease. The score was conducted according to the results of event-based prospective memory (EBPM) and time-based prospective memory (TBPM) tasks. $^{*}p<0.01$ compared to normal control.

Discussion

In the present study, we demonstrated that a significant difference was found on the performance of TBPM, but not EBPM in patients with WD compared with the healthy controls. To the best our acknowledgement, this is the first study to verify the involvement of TBPM in WD patients.

In the setting of WD, different parts of the central nervous system (including cerebellum, brainstem, thalamus, and subcortical white matter) can be affected, but the greatest damage usually occurs in the basal ganglia[25-27]. Studies[28-30] have shown that lesion of the basal ganglia may result in impairment of memory. However, the exact contribution of basal ganglia to EBPM or TBPM remained unclear.

However, the main finding of this work was that the WD patients were significantly impaired in the TBPM, but not in the EBPM. As far as we know, this is the first neuroanatomical data from WD patients which provide evidence that the basal ganglia is associated with TBPM. The single dissociation between impaired performance of TBPM and normal performance of EBPM implies that TBPM and EBPM may be mediated differently by basal ganglia, and basal ganglia may be particularly involved in the TBPM.

TBPM is heavily dependent on time-monitoring behaviors (such as clock checking), which is

Table II. Performance of Event-Based Prospective Memory (EBPM) and Retrospective Memory (RM) tasks in patients with Wilson's disease.

Variables	Patients with Wilson's disease (n=30)	Normal controls (n=30)	*p*-value
Age	17.3 ± 2.4	17.5 ± 1.3	NS
Male/female	14/16	19/11	NS
Disease duration	2.7 ± 0.9	-	-
Education level (year)	8.5 ± 0.7	8.5 ± 0.5	NS
Handendness	30R/0L	30R/0L	NS
The Mini-Mental State Examination (MMSE)	27.5 ± 0.6	28.3 ± 0.7	NS
Verbal fluency test (VFT)	8.2 ± 1.1	8.8 ± 0.9	<0.05
Digital Span (DS)	6.6 ± 1.3	7.2 ± 0.8	<0.05

NS: not significant.

Table III. Performance of Time-Based Prospective Memory (TBPM) and Retrospective Memory (RM) tasks in patients with Wilson's disease.

Variables	Patients with Wilson's disease (n=30)	Normal controls (n=30)	*p*-value
Number selection task	56.3±1.6	56.4±1.5	NS
Word selection task	75.8±1.4	76.6±1.2	NS
Number of clock checking responses	26.5±2.3	26.6±1.6	NS
TBPM	2.9±1.1	5.8±0.4	<0.05
RM_2	3.4±0.6	5.4±0.8	<0.05

NS: not significant.

Table IV. Correlations between Wilson's Disease Volume (WDV) and Prospective Memory (PM), Retrospective Memory (RM), Verbal Fluency Test (VFT), Digit Span (DS), Mini-Mental State Examination (MMSE), and age.

Age	WDV	MMSE	VFT	DS	EBPM	TBPM	RM	
Age	-							
WDV	-0.159							
MMSE	0.049	0.009						
VFT	-0.023	-0.020	-0.051					
DS	0.174	-0.190	0.064	0.649**				
EBPM	0.001	0.153	0.495**	0.036	0.141			
TBPM	0.138	-0.107	-0.025	0.255	0.511**	0.224		
RM	0.159	-0.167	-0.150	0.771**	0.749**	0.059	0.663**	-

** $p<0.05$

related to time perception[31]. Time perception is believed to be dependent upon basal ganglia[32]. It is also suggested that the neural network for time perception is composed of the right inferior parietal cortex and the right middle and superior frontal gyrus[33]. The results of this study, TBPM impairment of basal ganglia, provided neuropsychological evidence that basal ganglia may be involved in TBPM.

There was also a significant difference between RM performance of WD patients and that of controls. Einstein et al[8] pointed out that EBPM and TBPM contain two components: a retrospective component and a prospective component. 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. In the current results, interaction effect among the performance of EBPM, TBPM and RM were also examined by analysis of variance. There were no significant interaction effects in EBPM and RM or EBPM and TBPM, but a significant interaction between TBPM and RM. Although both of TBPM and the accompanying RM were impaired, the TBPM impairment of WD patients could not be explained by RM deficit, and may be attributable mainly to impairment of the prospective component relative to TBPM.

There are also some limitations in the present study. First, the number of WD patients is relative small. Further investigation with more patients should be performed to examine the difference between subregions. Moreover, comparison with the brain-damaged controls also needed to confirm that deficiency of TBPM is a consequence of basal ganglia rather than a more general result of brain damage. Second, the difficulty of excluding confounds to the present results such as the multiple etiological factors and duration of the WD. The primary objective of the investigation, however, was to determine if WD persons have changes in PM. Although the limitations of the present research, the data here indicate that TBPM impairment is a feature of diencephalic amnesia.

Conclusions

The current results showed that WD patients were impaired in TBPM but not in EBPM. The present neuropsychological evidence supported the hypothesis that the basal ganglia is involved in PM and particularly in TBPM, which in turn increased our understanding of the relationship between basal ganglia and PM. Further investigation of basal ganglia involvement in TBPM in larger samples of patients with basal ganglia lesion appears warranted. In future researches of patients with Wilson's disease, special attention needs to be paid to TBPM that might influence their cognitive outcome.

Author Contribution

Conceived and designed the experiments: Ting Dong, Kai Wang, Wenming Yang
Performed the experiments: Peng Huang, Wenwen Dong, Ting Dong
Analyzed the data: Huaidong Cheng, Ju Qiu, Ting Dong
Contributed reagents/materials/analysis tools: Ju Qiu, Ting Dong Wrote the paper: Ting Dong

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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