

## The MemTrax memory test for detecting and assessing cognitive impairment in Parkinson's disease

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### ABSTRACT

**Introduction:** A valid, reliable, accessible measurement for the early detection of cognitive decline in patients with Parkinson's disease (PD) is in urgent demand. The objective of the study is to assess the clinical utility of the MemTrax Memory Test in detecting cognitive impairment in patients with PD.

**Methods:** The MemTrax, a fast on-line cognitive screening tool based on continuous recognition task, and Montreal Cognitive Assessment (MoCA) were administered to 61 healthy controls (HC), 102 PD patients with normal cognition (PD-N), 74 PD patients with mild cognitive impairment (PD-MCI) and 52 PD patients with dementia (PD-D). The total percent correct (MTx-%C), average response time (MTx-RT), composite score (MTx-Cp) of MemTrax and the MoCA scores were comparatively analyzed.

**Results:** The MoCA scores were similar between HC and PD-N, however, MTx-%C and MTx-Cp were lower in PD-N than HC ( $p < 0.05$ ). MTx-%C, MTx-Cp and the MoCA scores were significantly lower in PD-MCI versus PD-N and in PD-D versus PD-MCI ( $p \leq 0.001$ ), while MTx-RT was statistically longer in PD-D versus PD-MCI ( $p \leq 0.001$ ). For PD groups, the MemTrax performance correlated with the MoCA scores. To detect PD-MCI, the optimal MTx-%C and MTx-Cp cutoff were 75% and 50.0, respectively. To detect PD-D, the optimal MTx-%C, MTx-RT and MTx-Cp cutoff were 69%, 1.341s and 40.6, respectively.

**Conclusion:** The MemTrax provides rapid, valid and reliable metrics for assessing cognition in PD patients which could be useful for identifying PD-MCI at early stage and monitoring cognitive function decline during the progression of disease.

### 1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer disease (AD). Patients with PD have an almost six-fold higher risk of developing dementia than people without PD of similar age and education [1]. Cognitive decline can occur at any

stage of PD, even preceding motor manifestations [2]. Once a patient with PD develops mild cognitive impairment (MCI), the risk for dementia is markedly increased [3], which could seriously affect the quality of life and social activity. As a result, early detection of cognitive decline in patients with PD has been recognized as extremely important.

To date, assessing cognitive status regularly to identify PD-MCI at

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early stage is not an easy task in clinical practice. The Montreal Cognitive Assessment (MoCA), which is most widely used in cognitive evaluation, is the least time consuming instrument for global cognition assessment recommended by Movement Disorder Society (MDS) for the diagnosis of PD-MCI [4]. Even so, it takes at least 10–15 min to complete and requires a healthcare professional to administer the MoCA to the patients. Conversely, the MemTrax memory test, based on the computerized continuous recognition task (CCRT), is a 2-min on-line assessment to evaluate episodic memory (EM), attention and other cognitive domains [5]. MemTrax has been proved effective in detecting MCI in Alzheimer's Disease (AD) [6] with better or comparable accuracy compared with the MoCA [7] and has been successfully implemented and utilized in different languages and countries, such as the United States [8], France [9], Netherlands [6] and China [7,10].

Whether MemTrax can be used in detecting early cognition decline in patients with PD is unknown although a difference in MTx-RT between self-reported PD and non-PD patients in the Brain Health Registry cohort was reported [11]. Here we report the clinical utility of MemTrax as a digital cognitive assessment in a Chinese cohort to detect cognitive impairment associated with PD-MCI and Parkinson's Disease dementia (PD-D). We focused on the cross-validation of MemTrax with the MoCA in PD in order to determine whether MemTrax could be utilized effectively as a cognitive screen in clinical practice.

## 2. Materials and methods

### 2.1. Study design and participants

Between January 2020 and May 2023, 61 healthy subjects and 228 individuals with PD were recruited in this cross-sectional study. Healthy controls excluding neurodegenerative disease, cerebrovascular disease, or cognition decline were recruited from the community. All patients were diagnosed with PD according to the MDS criteria by movement disorders specialists in the First Affiliated Hospital of Sun Yat-sen University [12]. Participants with depression (the total score of Beck Depression Inventory BDI more than 16 [13]), anxiety (the total score of Beck Anxiety Inventory more than 12 [14]), severe visual or hearing impairment or other PD-associated comorbid conditions (e.g., severe motor impairment, or excessive daytime sleepiness, or psychosis which could hinder their completion of the assessment) were excluded. After enrollment in the study, demographic factors, such as gender, age, years of education, disease duration since PD symptoms began, Body Mass Index (BMI), occupation, smoking status, exercise status, marriage, family history, and medical history were collected. Hoehn & Yahr (H-Y) Stage and Movement Disorders Society Unified PD Rating Scale Part III (MDS-UPDRSIII) were determined by the movement disorders specialist in charge of the patients. Cognition status was evaluated by Mini-Mental State Examination (MMSE), Beijing Version of Montreal Cognitive Assessment (BJ-MoCA) and Memtrax. Functional independence of the patients was evaluated by the movement disorders specialist based on the medical history and the MMSE and MoCA score. Patients were evaluated with medication-on.

All participants signed an informed consent after receiving a detailed explanation of the study, and the study protocol was reviewed and approved by Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University ([2017]318-1).

### 2.2. Classification of PD-N, PD-MCI and PD-D

Patients were divided into three groups according to the cognitive status, PD patients with normal cognition (PD-N), PD patients with mild cognitive impairment (PD-MCI) and PD patients with dementia (PD-D). The inclusion criteria of PD-N were PD patients without cognitive impairment (a total MoCA score  $\geq 26$ ). PD-MCI was diagnosed according to MDS level 1 criteria [4], including the following elements: (1) Gradual cognition decline reported by either the PD patient or

informant, or observed by the clinician. (2) Objective cognitive impairment on a scale of global cognitive abilities (a total MoCA score  $< 26$ ). (3) Cognitive deficits were not sufficient to interfere significantly with functional independence. (4) No dementia (a total MoCA score  $\geq 21$ ). The diagnosis of PD-D was based on the MDS probable PD-D criteria [15] and China diagnostic criteria for Parkinson's disease dementia [16] as follows: (1) A dementia syndrome with insidious onset and slow progression. (2) Cognitive deficits severe enough to impair daily life (a total MMSE score  $< 26$ , or a total MoCA score  $\leq 20$ ) [17,18]. (3) Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (attention, executive functions, visuo-spatial functions and memory tested by MoCA). All the patients with PD-MCI and PD-D have no other primary explanations for cognitive impairment.

### 2.3. MemTrax memory test

Detailed description of the theory and design of MemTrax has been published previously [8]. Briefly, with each MemTrax test, a series of 50 images are shown – 25 new images and 25 repeated images. Each picture is presented on the screen for 3 s or until a behavioral response, at which time the next picture is shown immediately. The participants are instructed to respond by either pressing the space-bar when performing the test on a computer or touching the screen when a smart phone is used only when presented with a repeated picture as quickly as possible. The program automatically calculates the total percent correct (MTx- %C) and the average response time (MTx-RT, s). The MemTrax composite score (MTx-Cp) is calculated according to the above two measurements. The calculation formula is:  $MTx-Cp = (MTx- \%C) \times 100 \times (1/MTx-RT)$  [8]. MemTrax can be administered on the Chinese social media platform WeChat on a phone or web on a computer in China (<http://www.memtrax.com.cn>) [19]. All the participants in our study completed the MemTrax on WeChat on a phone at the Parkinsonism Center, the outpatient clinic of the First Affiliated Hospital of Sun Yat-sen University.

### 2.4. Montreal cognitive assessment and scoring

All the participants in our study completed the Beijing version of the MoCA (MoCA- BJ) [20]. The assessment was administered and scored by trained researchers. MoCA scores, ranging from 0 to 30, were adjusted to account for education influences. Administration of a single MoCA test took about 10–15 min depending on the participant's cognition and movement symptoms.

### 2.5. Statistics

Statistical analyses were carried out using SPSS 26.0. Normality was checked for all variables by the Shapiro-Wilk test and homogeneity of variance was checked by Levene Test. T-test or Mann-Whitney *U* test (when non-parametric required) examined differences between 2 groups and effect size power analysis was calculated using Hedges'g measure. One-way ANOVA or Kruskal-Wallis tests (when non-parametric required) examined differences among 3 groups on demographic and clinical variables. One-Way ANCOVA with Bonferroni examined the differences among PD groups while controlling for the education and disease duration of the patients, Mann-Whitney *U* test examined differences between HC and PD-N on MoCA and Memtrax variables. Chi-squared tests for categorical variables were performed. Spearman correlation tests were calculated to assess the relation between MemTrax test results (e.g. MTx- %C, MTx-RT and MTx-Cp) and MoCA in patients with PD. To determine the cutoff values of the MTX test for PD-MCI or PD-D measured by MoCA, and the corresponding sensitivity and specificity values, a Receiver Operator Characteristic (ROC) analysis was performed. For all statistical analyses, *p*-value  $< 0.05$  was considered as threshold for statistical significance.

### 3. Results

#### 3.1. Participant characteristics

A total of 289 participants were enrolled in this study, 61 HC, 102 with PD-N, 74 with PD-MCI, and 52 with PD-D. Demographic and clinical characteristics of the participants are shown in [Supplementary Table 1](#). The mean education year was  $12.44 \pm 2.99$  years in HC and  $12.20 \pm 3.50$  years in PD-N ( $Z = 0.641, p = 0.552$ ). The mean education year among PD-N, PD-MCI ( $10.23 \pm 3.88$  years) and PD-D ( $8.47 \pm 4.14$  years) was significant different ( $H = 26.762, p < 0.001$ ). The disease duration was  $5.55 \pm 3.82$  years in PD-N,  $6.17 \pm 3.92$  years in PD-MCI and  $7.53 \pm 4.40$  years in PD-D, respectively ( $H = 7.662, p = 0.022$ ). [Supplementary Table 1](#) listed the results for the other characteristics including sex, age, BMI, H-Y stage, and MDS-UPDRSIII.

#### 3.2. Cognition assessment

As shown in [Table 1](#) and [Fig. 1](#), MTx- %C and MTx-Cp were significantly lower in PD-N than HC ( $Z = -4.716, p < 0.001; t = 3.211, p = 0.002$ ), MTx- %C and MTx-Cp was significantly lower in the PD-MCI group as compared to the PD-N group ( $p = 0.002, p = 0.003$ ) and in the PD-D group as compared to the PD-MCI group ( $p = 0.007, p = 0.002$ ). MTx- RT was not significantly different between PD-N and PD-MCI groups ( $p = 0.628$ ), but it was significantly longer in the PD-D group as compared to the PD-MCI ( $p = 0.008$ ) or PD-N group ( $p < 0.001$ ). The MoCA score was different between PD-N and PD-MCI groups ( $Z = -1.500, p < 0.001$ ), as well as between PD-MCI and PD-D groups ( $p < 0.001$ ), where each of the former groups had higher scores than the latter groups, respectively. The difference in MoCA scores is expected owing to this score being used to create the groups.

#### 3.3. Correlation of MoCA and MemTrax

To explore the relationship between MoCA and MemTrax performance, the Spearman correlation tests were calculated between them as shown in [Supplementary Fig. 1](#). MTx- %C and MoCA showed a moderate correlation ( $r = 0.555, p < 0.001$ ), and also moderate correlations were found between MTx-RT and MoCA ( $r = -0.333, p < 0.001$ ), MTx-Cp and MoCA ( $r = -0.541, p < 0.001$ ).

**Table 1**  
MoCA and MemTrax results of PD-N, PD-MCI, and PD-D groups.

Cognition assessment	Group	Mean $\pm$ SD	HC vs PD-N*			Among PD-N, PD-MCI and PD-D**	
			Statistic values	Effect size Hedges' g	p-value	Statistic values	p-value
MoCA	HC(n = 61)	27.46 $\pm$ 1.19	Z = -1.500	0.268	0.134	F = 71.598	< 0.001
	PD-N (n = 102,44.7 %)	27.80 $\pm$ 1.31 <sup>bc</sup>					
	PD-MCI (n = 74,32.5 %)	23.30 $\pm$ 1.69 <sup>ac</sup>					
	PD-D (n = 52,22.8 %)	17.17 $\pm$ 3.76 <sup>ab</sup>					
MTx- %C ( %)	HC	84.92 $\pm$ 5.42	Z = -4.716	0.813	< 0.001	F = 19.732	< 0.001
	PD-N	78.16 $\pm$ 9.63 <sup>bc</sup>					
	PD-MCI	70.86 $\pm$ 9.42 <sup>ac</sup>					
	PD-D	64.08 $\pm$ 9.72 <sup>ab</sup>					
MTx-RT (s)	HC	1.36 $\pm$ 0.23	t = -1.411	0.206	0.160	F = 8.974	< 0.001
	PD-N	1.41 $\pm$ 0.25 <sup>c</sup>					
	PD-MCI	1.47 $\pm$ 0.26 <sup>c</sup>					
	PD-D	1.64 $\pm$ 0.27 <sup>ab</sup>					
MTx-Cp	HC	64.18 $\pm$ 11.27	t = -3.211	0.485	0.002	F = 16.770	< 0.001
	PD-N	57.57 $\pm$ 14.83 <sup>bc</sup>					
	PD-MCI	50.17 $\pm$ 13.03 <sup>ac</sup>					
	PD-D	40.17 $\pm$ 9.27 <sup>ab</sup>					

Abbreviations: HC, healthy controls; PD-N, PD patients with normal cognition; PD-MCI, PD patients with mild cognitive impairment; PD-D, PD patients with dementia. \* Compared between HC and PD-N by T-test or Mann-Whitney U test, \*\* compared among PD-N, PD-MCI and PD-D by One-Way ANCOVA; <sup>abc</sup> by Bonferroni, <sup>a</sup> Values compared with PD-N,  $p < 0.05$ ; <sup>b</sup> values compared with PD-MCI,  $p < 0.05$ ; <sup>c</sup> values compared with PD-D,  $p < 0.05$ .

#### 3.4. ROC curve analyses

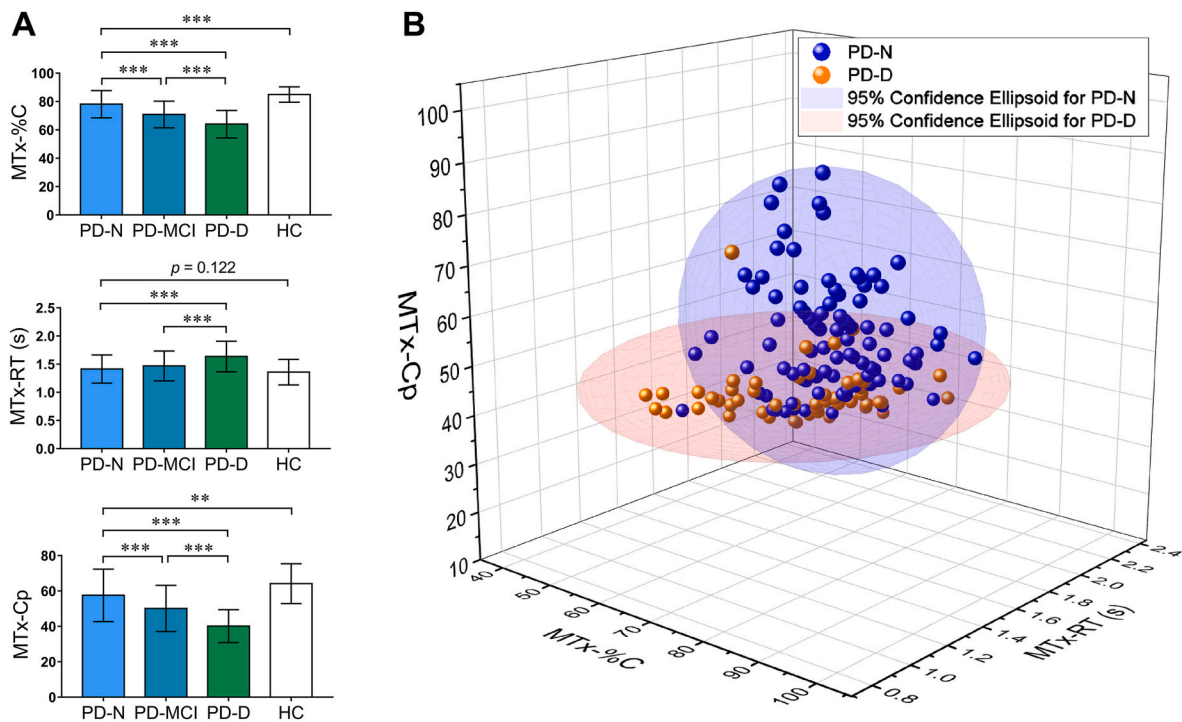
To determine the diagnostic accuracy of the MemTrax, ROC curve analyses were conducted ([Fig. 2](#)). The AUCs of MTx- %C and MTx-Cp to diagnose PD-MCI when comparing PD-N to PD-MCI were 71.6 % (95 % CI: 63.9–79.4,  $p < 0.001$ ) and 64.8 % (95 % CI:56.6–73.0,  $p = 0.001$ ). The optimal MTx- %C and MTx-Cp cut-off scores, which maximized true positives while minimizing false positives according to the maximum Youden index, were 75 % (sensitivity = 70.3 %; specificity = 68.6 %) and 50.0 (sensitivity = 58.1 %; specificity = 66.7 %), respectively ([Table 2](#)). The AUCs of MTx-RT to diagnose PD-MCI was 55.1 % (95 % CI: 46.5–63.7  $p = 0.249$ ).

The AUCs of MTx- %C, MTx-RT and MTx-Cp to diagnose PD-D when comparing PD-MCI to PD-D were 77.9 % (95 % CI: 71.0–84.8,  $p < 0.001$ ), 70.6 % (95 %CI: 62.6–78.7,  $p < 0.001$ ) and 80.6 % (95 % CI:74.3–86.9,  $p < 0.001$ ), respectively. The optimal MTx- %C, MTx-RT and MTx-Cp cut-off scores based on the maximum Youden index, were 69 % (sensitivity = 69.2 %; specificity = 72.7 %), 1.341 (sensitivity = 90.4 %; specificity = 39.2 %) and 40.6 (sensitivity = 63.5 %; specificity = 83.0 %), respectively.

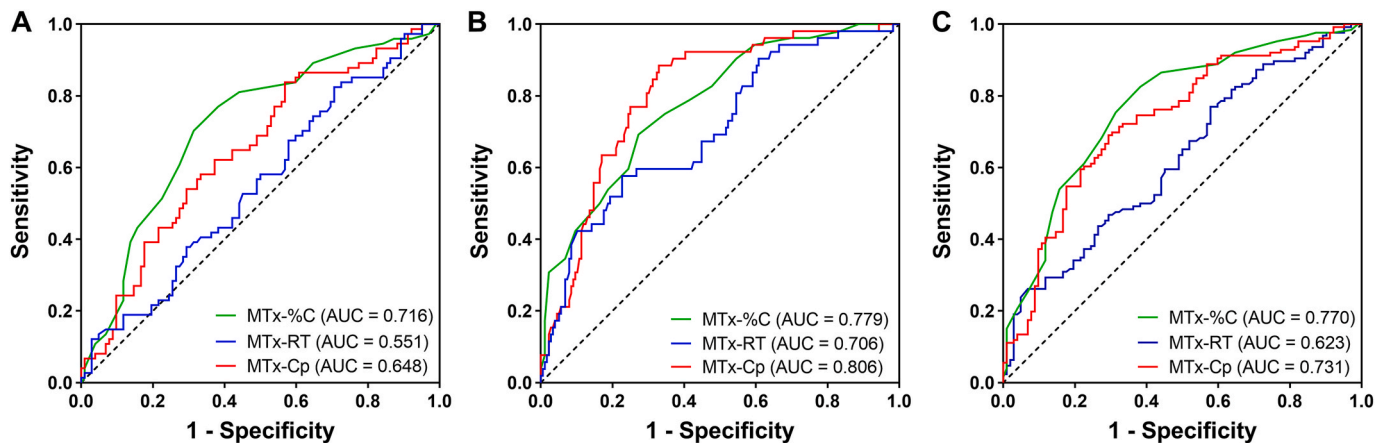
The AUCs of MTx- %C, MTx-RT and MTx-Cp to diagnose cognitive impairment in PD (PD-CI, combined PD-MCI and PD-D) when comparing PD-N to PD-CI were 77.0 % (95 % CI: 70.8–83.2  $p < 0.001$ ), 62.3 % (95 % CI: 55.1–69.5  $p = 0.001$ ) and 73.1 % (95 % CI: 66.5–79.7  $p < 0.001$ ), respectively. The optimal MTx- %C, MTx-RT and MTx-Cp cut-off scores based on the maximum Youden index were 77 % (sensitivity = 82.5 %; specificity = 61.8 %), 1.333 (sensitivity = 77.0 %; specificity = 42.2 %) and 48.4 (sensitivity = 69.0 %; specificity = 70.6 %), respectively. In order to avoid missing potential cognitive decline patients and to identify cognitive impairment in PD during screening, we adjusted the sensitivity to 88.9 % and then cut-off were 81 % for MTx- %C, 1.232s for MTx-RT and 61.4 for MTx-Cp.

### 4. Discussion

This study investigated the MemTrax memory test, an on-line CRRT cognitive screen instrument, for estimating cognitive impairment in patients with PD in a Chinese cohort using the MoCA as a reference. Our findings support MemTrax's clinical utility in detecting cognitive impairment associated with PD patients. To our knowledge, it was the first time to use the MemTrax to assess the cognitive function of PD patients to distinguish between PD-MCI and PD-D to PD-N. Our study



**Fig. 1.** MemTrax results of HC, PD-N, PD-MCI, and PD-D groups. **A.** The MTx-%C, MTx-RT and MTx-Cp scores were shown through a bar chart for the HC, PD-N, PD-MCI and PD-D. MTx-%C and MTx-Cp scores were statistically different in all comparisons: HC versus PD-N, PD-N versus PD-MCI, PD-MCI versus PD-D and PD-N versus PD-D. MTx-RT can only distinguish PD-D from PD-N and PD-MCI. **B.** 3D analysis graphics. As MTx-%C, MTx-RT and MTx-Cp were all significantly different between PD-N and PD-D, a 3D analysis graphics for PD-N vs PD-D were shown.



**Fig. 2.** MTx-%C, MTx-RT, and MTx-Cp scores to predict PD-MCI, PD-D, and PD-CI in ROC analyses. **A.** PD-N vs PD-MCI, **B.** PD-MCI vs PD-D, **C.** PD-N vs PD-CI. PD-CI, cognitive impairment in PD, combined PD-MCI and PD-D. ROC analyses with AUCs were carried out using the MTx-%C, MTx-RT, and MTx-Cp scores from clinically diagnose PD-N, PD-MCI, and PD-D for the prediction of PD-MCI from PD-N, PD-D and PD-CI from PD-MCI as indicated in A, B and C.

reconfirmed the correlation between MoCA and MemTrax metrics, consisting of MTx-%C, MTx-RT and MTx-Cp. We observed MTx-%C and MTx-Cp were more suitable for the early cognitive assessment in PD patients, while MTx-RT was more useful for monitoring cognitive function in PD patients with cognitive decline. The optimal cut-off values were 75 % for MTx-%C and 50.0 for MTx-Cp for the detection of PD-MCI. The optimal MTx-%C, MTx-RT and MTx-Cp cut-off scores to detect PD-D were 69 %, 1.341s and 40.6, respectively. The optimal cut-off scores to predict cognitive impairment in PD were 81 % for MTx-%C, 1.232s for MTx-RT and 61.4 for MTx-Cp with a higher sensitivity, 88.9 %.

The MoCA was used as a comparator because it is currently widely used and recommended by MDS as an abbreviated cognitive assessing

instrument for PD-MCI [4]. The sensitivity and specificity of MoCA to diagnose PD-MCI based on MDS PD-MCI Level I diagnostic criteria were 57.1 % and 75.9 % [21], which is similar to the MemTrax in our study. However, there are some limitations of MoCA such as requiring trained evaluators, face-to-face administration, and the test is influenced by language, culture, education and motor symptoms. In comparison, the MemTrax is an on-line CRRT, which is less time consuming and more engaging. It can be self-administered or guided by either informant or clinician without the need of trained personnel. Moreover, the MemTrax is based on recognition of pictures that is unique for each test, therefore, it can be tested repeatedly with minimal learning effect and is less influenced by language, culture and education. In addition, the scoring is automatically carried out and immediately provided to the user. In

**Table 2**  
Sensitivity and specificity analyses for different cut-off values of MemTrax metrics.

PD-MCI			PD-D			PD-CI		
Cut-off	Sensitivity (%)	Specificity (%)	Cut-off	Sensitivity (%)	Specificity (%)	Cut-off	Sensitivity (%)	Specificity (%)
MTx- %C						MTx- %C		
<73	60.8	72.5	<67	59.6	75.6	< 77	<b>82.5</b>	<b>61.8</b>
<b>&lt;75</b>	<b>70.3</b>	<b>68.6</b>	<b>&lt;69</b>	<b>69.2</b>	<b>72.7</b>	< 79	86.5	55.9
<77	77.0	61.8	<71	75.0	65.3	< 81	88.9	40.2
MTx-RT						MTx-RT		
>1.244	82.4	28.4	>1.337	90.4	38.6	>1.232	88.9	27.5
<b>&gt;1.249</b>	<b>82.4</b>	<b>29.4</b>	<b>&gt;1.341</b>	<b>90.4</b>	<b>39.2</b>	>1.288	81.7	36.3
>1.253	81.1	29.4	>1.343	88.5	39.2	<b>&gt;1.333</b>	<b>77.0</b>	<b>42.2</b>
MTx-Cp						MTx-Cp		
<49.9	56.8	66.7	<40.5	61.5	83.0	<b>&lt;48.4</b>	<b>69.0</b>	<b>70.6</b>
<b>&lt;50.0</b>	<b>58.1</b>	<b>66.7</b>	<b>&lt;40.6</b>	<b>63.5</b>	<b>83.0</b>	<52.1	74.6	62.7
<50.1	58.1	65.7	<40.7	63.5	82.4	<61.4	88.9	43.1

Bold values are the recommended optimized cut-off values of MTx- %C, MTx-RT and MTx-Cp, while sum of sensitivity and specificity reached maximum.

In this study, the cognition in both HC and PD-N group was normal with no obvious difference in MoCA. However, the MTx- %C and MTx-Cp were significantly higher in HC than in PD-N group, illustrating MemTrax may be more sensitive in estimating subtle cognitive changes compared with MoCA. MoCA has a low sensitivity of 57.1 % and may miss many cases of PD-MCI [21], while MTx- %C of MemTrax can identify more PD-MCI with the sensitivity of 70.3 %. Furthermore, by adjusting the cut-off of MTx- %C to 81 %, sensitivity of identifying cognitive impairment in PD could be improved to 88.9 %. As the MemTrax is a simple and quick screening tool, more cases detected by MemTrax can be further evaluated by comprehensive assessment according to the MDS PD-MCI Level II diagnostic criteria. Although the MoCA has several sub-scores partially reflecting specific cognitive domains, these values are not often used in clinical situations, where only the total score is used for assessing global cognitive performance. The outcomes of MemTrax memory test have been reported to be correlated with multiple cognitive domains [6] and is a superior cognitive screening instrument compared to the MoCA for broad, frequent and periodical use in clinical practice.

MemTrax requires complex picture information encoding and storage into short-term memory (STM), recognition and retrieval during the test. The MemTrax, based on the CRRT, is a useful measurement for episodic memory (EM) and has proven efficiency [8]. EM impairment is a hallmark of AD for which was MemTrax originally designed [9]. Interestingly, EM impairment is also common in patients with PD and related to hippocampal function [22]. In the Parkinson's Progression Markers Initiative (PPMI) cohort, a multi-site study of early and untreated PD patients, memory was the most affected cognitive domain (9 %–17 % impaired on the four Hopkins Verbal Learning Test- Revised (HVLT-R) subtests) [23]. Similarly, a meta-analysis of 1346 patients from eight different cohorts of PD-MCI found memory impairment was the most common deficit (13.3 %), followed by visuospatial impairment (11.0 %) and then attention/executive function impairment (10.1 %) [24]. Memory impairment in PD is related to encoding and retrieval deficits [25], and may be secondary to impaired attention and executive function. The MemTrax, a computerized continuous recognition task, also requires executive abilities to encode and retrieve the information. Consistent with these findings, our results demonstrated that the MemTrax memory test is efficient for assessing recognition memory through MTx- %C and attention/executive function through MTx-RT, and is a useful tool for memory and cognitive assessment in PD patients.

The MemTrax outcome measures contained two specific metrics, the degree of correctness of recognition memory (MTx- %C) and the latency to respond, response time (RT). In our study, the median MTx-RT was 1.47s in PD patients (1.41s in PD-N, 1.46s in PD-MCI, and 1.67s in PD-D), which were longer than that of HC, 1.31s ( $p = 0.01$ ). In a recent Ashford et al. study, the distribution of RT was skewed with 1 % faster than 0.62 s, a median at 0.890 s, and 1 % slower than 1.57 s from 322,996 valid first tests [5]. RT is a readout of two processes operating in succession: the central decision component for information processes

and the transduction component related to the initiation and completion of the physical response to the stimuli [26]. The movement disorders of PD patients, such as tremor and bradykinesia, are not completely normal even during the medication-on period, which will cause physical response delay and result in prolonged RT. As well as movement time, reaction time, which could not be improved by medication, was also prolonged in Parkinson's disease independently [27].

In addition, we found MTx-RT in PD-D was longer than that in PD-MCI or PD-N while there was no statistical difference between PD-MCI and PD-N group, which was consistent with previous studies in AD [7, 10]. It was reported RT distribution followed a reverse-exponential (RevEx) model, which can be interpreted as a requirement for doubling the processing power for every 100 ms of decrease in RT. As a result, the nervous system must double the resources expended to analyze and respond to the complex information in order to reduce the RT by 100 ms, while increasing the RT by 100 ms may reflect reduction of neuronal resources by half [5]. When MTx-RT was shorter than a certain range, the faster RT was at the expense of accuracy [28]. In other words, it was not that the shorter the RT, the higher the correct response, which could explain the minor differences of MTx-RT between PD-MCI and PD-N group. The prolonged RT in PD-D could be due to the failure to either encode or recognize repeated images and taking exponentially longer to process the visual information, thus, the loss of synaptic connections in neurodegeneration or the damage to motor neuron function may be the key contributor [29]. MTx-RT, as an important indicator for evaluating neurodegenerative diseases, is suitable for monitoring cognitive function in progressive Parkinson's disease with cognition decline.

There are some limitations in the present study. Previous studies have shown the effects of age and education on MemTrax metrics [8,30]. The education years and disease duration among the three groups of PD in our study were different. But the differences were adjusted in statistical comparison. The age and sex of participants between HC and PD-N groups were different. Cognitive changes in PD are heterogeneous leading a portion of individuals with PD to have memory difficulties while others do not but to have difficulties in other cognitive domains. This limitation makes it difficult for the MemTrax to identify all PD patients with cognitive decline, but it does not hinder its use as a rapid and effective screening tool for cognitive impairments in PD. In the study, we did not evaluate other function of cognitive domains in patients of PD, and we will further refine this in future studies. Our study was a cross-sectional retrospective study and a longitudinal study based on the results of present study for prediction of the progression from PD-N to PD-D is needed in the future.

## 5. Conclusion

In conclusion, the MemTrax Memory Test can be utilized as an effective brief cognitive assessment instrument to detect cognitive

impairments associated with PD-MCI and PD-D in a Chinese cohort compared to the MoCA. The MemTrax Memory Test is a simple, accessible and effective cognitive assessment tool that can be widely applied throughout the entire process of Parkinson's disease in clinical practice. It can not only identify MCI in PD in the early stage, but also potentially monitor cognitive function in the moderate and late stages in PD.

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## CRediT authorship contribution statement

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2024.106016>.

## References

- [1] D. Aarsland, K. Andersen, J.P. Larsen, A. Lolk, H. Nielsen, P. Kragh-Sorensen, Risk of dementia in Parkinson's disease: a community-based, prospective study, *Neurology* 56 (6) (2001) 730–736.
- [2] S. Fengler, I. Liepelt-Scarfone, K. Brockmann, E. Schaffer, D. Berg, E. Kalbe, Cognitive changes in prodromal Parkinson's disease: a review, *Mov. Disord.* 32 (12) (2017) 1655–1666.
- [3] K.F. Pedersen, J.P. Larsen, O.B. Tysnes, G. Alves, Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study, *Neurology* 88 (8) (2017) 767–774.
- [4] I. Litvan, J.G. Goldman, A.I. Troster, B.A. Schmand, D. Weintraub, R.C. Petersen, B. Mollenhauer, C.H. Adler, K. Marder, C.H. Williams-Gray, D. Aarsland, J. Kulisevsky, M.C. Rodriguez-Oroz, D.J. Burn, R.A. Barker, M. Emre, Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement Disorder Society Task Force guidelines, *Mov. Disord.* 27 (3) (2012) 349–356.
- [5] J.W. Ashford, J.O. Clifford, S. Anand, M.F. Bergeron, C.B. Ashford, P.J. Bayley, Correctness and response time distributions in the MemTrax continuous recognition task: analysis of strategies and a reverse-exponential model, *Front. Aging Neurosci.* 14 (2022) 1005298.
- [6] M.D. van der Hoeek, A. Nieuwenhuizen, J. Keijer, J.W. Ashford, The MemTrax test compared to the Montreal cognitive assessment estimation of mild cognitive impairment, *J Alzheimers Dis* 67 (3) (2019) 1045–1054.
- [7] X. Liu, X. Chen, X. Zhou, Y. Shang, F. Xu, J. Zhang, J. He, F. Zhao, B. Du, X. Wang, Q. Zhang, W. Zhang, M.F. Bergeron, T. Ding, J.W. Ashford, L. Zhong, Validity of the MemTrax memory test compared to the Montreal cognitive assessment in the detection of mild cognitive impairment and dementia due to Alzheimer's disease in a Chinese cohort, *J Alzheimers Dis* 80 (3) (2021) 1257–1267.
- [8] J.W. Ashford, F. Tarpin-Bernard, C.B. Ashford, M.T. Ashford, A computerized continuous-recognition task for measurement of episodic memory, *J Alzheimers Dis* 69 (2) (2019) 385–399.
- [9] M.F. Bergeron, S. Landset, F. Tarpin-Bernard, C.B. Ashford, T.M. Khoshgoftaar, J. W. Ashford, Episodic-memory performance in machine learning modeling for predicting cognitive health status classification, *J Alzheimers Dis* 70 (1) (2019) 277–286.
- [10] W. Chen, C. Lin, F. Su, Y. Fang, G. Liu, Y.C. Chen, X. Zhou, X. Yao, C.B. Ashford, F. Li, J.W. Ashford, Q. Fu, Z. Pei, Early diagnosis of mild cognitive impairment due to Alzheimer's disease using a composite of MemTrax and blood biomarkers, *J Alzheimers Dis* 94 (3) (2023) 1093–1103.
- [11] B. Cholerton, M.W. Weiner, R.L. Nosheny, K.L. Poston, R.S. Mackin, L. Tian, J. W. Ashford, T.J. Montine, Cognitive performance in Parkinson's disease in the Brain Health Registry, *J Alzheimers Dis* 68 (3) (2019) 1029–1038.
- [12] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, *Mov. Disord.* 30 (12) (2015) 1591–1601.
- [13] A.F. Leentjens, F.R. Verhey, G.J. Luijckx, J. Troost, The validity of the Beck Depression Inventory as a screening and diagnostic instrument for depression in patients with Parkinson's disease, *Mov. Disord.* 15 (6) (2000) 1221–1224.
- [14] A.F. Leentjens, K. Dujardin, L. Marsh, I.H. Richard, S.E. Starkstein, P. Martinez-Martin, Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale, *Mov. Disord.* 26 (3) (2011) 407–415.
- [15] M. Emre, D. Aarsland, R. Brown, D.J. Burn, C. Duyckaerts, Y. Mizuno, G.A. Broe, J. Cummings, D.W. Dickson, S. Gauthier, J. Goldman, C. Goetz, A. Korczyn, A. Lees, R. Levy, I. Litvan, I. McKeith, W. Olanow, W. Poewe, N. Quinn, C. Sampaio, E. Tolosa, B. Dubois, Clinical diagnostic criteria for dementia associated with Parkinson's disease, *Mov. Disord.* 22 (12) (2007) 1689–1707; quiz 1837.
- [16] P.S.D.a.M.D.S.o.N.B.o.C.M.D.A, Chinese Society of Parkinson's Disease and Movement Disorders, Chinese Society of Neuropsychology and Behavioral Neurology, the diagnostic criteria and treatment guideline for Parkinson's disease dementia (second version), *Chin. J. Neurol.* 54 (No. 8) (2021) 762–771.
- [17] M. Skorvaneck, J.G. Goldman, M. Jahanshahi, C. Marras, I. Rektorova, B. Schmand, E. van Duijn, C.G. Goetz, D. Weintraub, G.T. Stebbins, P. Martinez-Martin, members of the MDS Rating Scales Review Committee, Global scales for cognitive screening in Parkinson's disease: critique and recommendations, *Mov. Disord.* 33 (2) (2018) 208–218.
- [18] J.C. Dalrymple-Alford, M.R. MacAskill, C.T. Nakas, L. Livingston, C. Graham, G. P. Crucian, T.R. Melzer, J. Kirwan, R. Keenan, S. Wells, R.J. Porter, R. Watts, T. J. Anderson, The MoCA: well-suited screen for cognitive impairment in Parkinson disease, *Neurology* 75 (19) (2010) 1717–1725.
- [19] M.F. Bergeron, S. Landset, X. Zhou, T. Ding, T.M. Khoshgoftaar, F. Zhao, B. Du, X. Chen, X. Wang, L. Zhong, X. Liu, J.W. Ashford, Utility of MemTrax and machine learning modeling in classification of mild cognitive impairment, *J Alzheimers Dis* 77 (4) (2020) 1545–1558.
- [20] J. Yu, J. Li, X. Huang, The Beijing version of the Montreal Cognitive Assessment as a brief screening tool for mild cognitive impairment: a community-based study, *BMC Psychiatr.* 12 (2012) 156.
- [21] J.A. Boel, R.M.A. de Bie, B.A. Schmand, J.C. Dalrymple-Alford, C. Marras, C. H. Adler, J.G. Goldman, A.I. Troster, D.J. Burn, I. Litvan, G.J. Geurtsen, MDS study group mild cognitive impairment in Parkinson's disease, level I PD-MCI using global cognitive tests and the risk for Parkinson's disease dementia, *Mov Disord Clin Pract* 9 (4) (2022) 479–483.
- [22] T. Das, J.J. Hwang, K.L. Poston, Episodic recognition memory and the hippocampus in Parkinson's disease: a review, *Cortex* 113 (2019) 191–209.

- [23] D. Weintraub, T. Simuni, C. Caspell-Garcia, C. Coffey, S. Lasch, A. Siderowf, D. Aarsland, P. Barone, D. Burn, L.M. Chahine, J. Eberling, A.J. Espay, E.D. Foster, J.B. Leverenz, I. Litvan, I. Richard, M.D. Troyer, K.A. Hawkins, I. Parkinson's Progression Markers, Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease, *Mov. Disord.* 30 (7) (2015) 919–927.
- [24] D. Aarsland, K. Bronnick, C. Williams-Gray, D. Weintraub, K. Marder, J. Kulisevsky, D. Burn, P. Barone, J. Pagonabarraga, L. Allcock, G. Santangelo, T. Foltynie, C. Janvin, J.P. Larsen, R.A. Barker, M. Emre, Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis, *Neurology* 75 (12) (2010) 1062–1069.
- [25] D. Weintraub, P.J. Moberg, W.C. Culbertson, J.E. Duda, M.B. Stern, Evidence for impaired encoding and retrieval memory profiles in Parkinson disease, *Cognit. Behav. Neurol.* 17 (4) (2004) 195–200.
- [26] F. Marmolejo-Ramos, D. Cousineau, L. Benites, R. Maehara, On the efficacy of procedures to normalize Ex-Gaussian distributions, *Front. Psychol.* 5 (2014) 1548.
- [27] E.V. Evarts, H. Teravainen, D.B. Calne, Reaction time in Parkinson's disease, *Brain* 104 (Pt 1) (1981) 167–186.
- [28] W. Liu, L. Yu, Q. Deng, Y. Li, P. Lu, J. Yang, F. Chen, F. Li, X. Zhou, M.F. Bergeron, J.W. Ashford, Q. Xu, Toward Digitally Screening and Profiling AD: A GAMLSS Approach of MemTrax in China, *Alzheimers Dement*, 2023.
- [29] R. Ratcliff, D.W. Scharre, G. McKoon, Discriminating memory disordered patients from controls using diffusion model parameters from recognition memory, *J. Exp. Psychol. Gen.* 151 (6) (2022) 1377–1393.
- [30] J.W. Ashford, E. Gere, P.J. Bayley, Measuring memory in large group settings using a continuous recognition test, *J Alzheimers Dis* 27 (4) (2011) 885–895.