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Lower Delayed but Comparable Working Memory Performance in Patients With Parkinson's Disease

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Lower Delayed but Comparable Working Memory Performance in Patients with Parkinson's Disease

Eun-Young Lee *

Department of Health Care and Science[1], Dong-A University, Busan, South-Korea; enyoungee@dau.ac.kr
* Correspondence: enyoungee@dau.ac.kr

Abstract: The present study examined mechanisms underlying memory deficits in patients with Parkinson disease (PD)and their associations with structural metrics. Nineteen PD and 22 matched controls underwent two memory experiments. In experiment 1 (delayed memory task), subjects were asked to remember an array of colored rectangles with varying memory set sizes [Low-Load (2 items), Low-Load with Distractor, & High-Load (5 items)]. After a 7s delay period, they reported whether the orientation of any relevant figures had changed (test period). In experiment 2 (working memory task), memory arrays were presented in varying set sizes (2 to 6 items) with no distractors that were followed by a 2s delay period and subsequent test period. Brain MRI data were acquired to assess structural differences (volumes and cortical thickness) in brain areas related to attention, working memory storage, and episodic memory. Compared to controls, PD patients had lower memory capacity scores in all memory load conditions for experiment 1 ($p < 0.021$) whereas there were no group differences in any memory load conditions for experiment 2 ($p > 0.06$). In addition, PD patients had lower thickness in the left superior temporal gyrus ($p = 0.02$). Lower thickness values in the left superior temporal gyrus were significant predictors of lower delayed memory performance in Low-Load and Low-Load with Distractor conditions (ps'< 0.044) and working memory performance of memory load conditions of 4 and 5 items (p's< 0.012). The present findings suggest that PD patients may have intact working memory storage capacity but impaired attentional filtering and memory consolidation that may lead to lower delayed memory scores. Lower delayed memory in PD may partly be associated with lower cortical thickness in the left superior temporal gyrus.

Keywords: visuospatial working memory; delayed memory; Parkinson's disease; attentional filtering; lower memory storage

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with predominant loss of dopaminergic neurons in subtantia nigra pars compacta and subsequent depletion of dopamine levels in the basal ganglia. Prominent characteristics of PD include motor symptoms such as tremor, rigidity and bradykinesia. While the motor symptoms dominate clinical pictures in PD, many patients with PD experience a wide range of non-motor symptoms. These may include autonomic disturbances (e.g., constipation and bladder control problems) and sensory complaints (e.g., numbness, burning or tingling sensation) but also include psychiatric (e.g., depression and anxiety) or non-psychiatric cognitive dysfunctions such as executive functions, attention, and memory (Gabrieli et al., 1996; Zgaljardic et al., 2003; Owen, 2004).

Given that the basal ganglia have extensive interconnections with the prefrontal cortex (Jellinger, 2001; Lewis et al., 2003), cognitive symptoms in PD are often ascribed to compromised information flow through this fronto-striatal pathway (Lewis et al., 2003). In fact, the pattern of cognitive deficits in PD appears to be similar to that observed in frontal lobe patients such as difficulties with planning, selective attention, and set shifting (Morris et al., 1988, Owen, 1995; West et al., 1998). Converging evidence, however, suggests that PD may experience various cognitive dysfunctions beyond frontal lobe-related executive dysfunctions.

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Working memory deficits in PD

Working memory is a capacity limited system which temporarily maintains information in a highly active and accessible state but also manipulates that information for performing tasks (Baddeley, 2003; Conway et al., 2005; Cowan et al., 2005). Theoretically, poor performance on working memory tasks can be due to reduced storage capacity per se, inability to effectively process information, or both (Cowan et al., 2005). Many studies have shown poor performance on various working memory tasks in PD patients and reported lower working memory capacity. One possible cause, however, may be a reduced ability to filter out irrelevant information so that they unnessarily usurp capacity-limited working memory space.

Episodic memory deficits in PD

Although PD present difficulties in various cognitive domains, learning/memory problems, particularly deficits in episodic memory (Bäckman et al. 2001) are one of the most common and devastrating cognitive symptoms in PD (Weintraub et al 2015, Yarnall 2014). Episodic memoryis a system that involves consciously retrieving information that was acquired in a particular time and space (Tulving 1984) and a key function of medial temporal lobe memory areas, especially hippocampus (Eichenbaum and Lipton 2008; Sugar and Moser 2019). Episodic memory problems have been reported as earliest neurobehavioral deficits observed in dementia patients (Bäckman et al. 2001). The prevalence of dementia in PD ranges between 24% and 50% and up to 80% PD patients may eventually develop dementia (Aarsland and Kurz 2010; Anang et al. 2014). Previous studies reported more than 20% of newly diagnosed PD patients had lower performance on episodic memory tasks (Breen and Drutyte 2013).

In the present study, two visual array comparison experiments were conducted to examine the mechanisms underlying potential memory deficits in PD patients. In both experiments, participants viewed an array of colored rectangles. In some trials, the presented array contained task-irrelevant items that should be ignored. After a short (2s) or relatively long (7s) delay, subjects reported whether the orientation of any relevant figures had changed. Structural differences were assessed by volumes or cortical thickness in brain areas related to attention (e.g., superior frontal gyrus, superior parietal lobe, and intraparietal sulcus for the dorsal attentional system and inferior and middle frontal gyri, inferior parietal lobe, and superior temporal gyrus for ventral attentional system), working memory storage capacity (e.g., intraparietal sulcus), and episodic memory (e.g., medial temporal lobe structures). Our central hypotheses were: 1) compared to controls, PD patients will show lower performance in both working memory and delayed memory tasks; 2) The memory performance in PD will be lower with distractors than without; 3) There will be significant structural differences in brain areas related to attention, working memory storage capacity, or episodic memory; 4) There will be positive associations between MRI structural metrics in ROIs and memory metrics.

2. Materials and Methods

2.1. Participants

Fourty one subjects (19 patients with Parkinson's disease (PD) and 22 age- and education-matched neurologically normal subjects) were recruited for the study. All subjects except for one patient and one control subject reported having normal color vision and normal or corrected-to-normal acuity. One patient and one control who were identical twins were partially color-blind, but they were able to tell the difference between red and green rectangles used in this study. All subjects had Mini-Mental Status Examination (MMSE) scores >=26. Depression was evaluated by means of Geriatric Depression Scale-long form (GDS; Sheikh and Yesavage, 1986). Three patients and one control subject were taking antidepressants (e.g., Fluoxetine, Bupropion, or Sertraline) at the time of the study. The general pattern of results was essentially the same with or without these three patients, so their data have been retained.

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PD patients were free from other neurological disorders. Fifteen patients were receiving the dopamine precursor Levodopa as treatment. On patient was not taking any anti-parkinsonian medication. Another patient was taking only Pramipexole (a dopamine agonist). The remaining two patients were receiving Ropinirole in conjunction with Trihexyphenidyl (an anticholinergic agent) or Azilect (an MAO inhibitor). On the morning of the experiment, PD patients skipped their initial dose of anti-parkinsonian medication. The mean withdrawal period of 11 h (at least 9 h) would not be enough to achieve complete clearance. Rather, it was intended to enhance differences between experimental groups while minimizing the burden imposed on patients. The severity of the disease was reassessed just before the start of the experiment using the Hoehn and Yahr scale (1967). Control subjects reported neither a history of neurological problems nor any significant current psychiatric disorder. All participants gave their informed consent according to procedures approved by the ethics board at the University of Missouri-Columbia (Approval number: 1170557).

2.2. Stimuli and Procedures for Neuropsychological Experiments

Stimulus arrays were presented within a 4 x 7.3° rectangular region centered at fixation on a dark background. Arrays consisted of either two or five colored rectangles. Item positions were randomized across trials. Both red and green rectangles subtended .65 x 1.15° of visual angle, with orientations selected randomly from a set of four possible values (vertical, horizontal, left-tilting 45°, and right-tilting 45°).

In experiment 1 (Figure 1), each trial began with a 2 s get-ready signal (3 yellow crosses). Next there was an instructional cue, which was followed by a 1 s long memory array, consisting of either two red or two red and three green rectangles. The instructional cue indicated whether subjects should ignore the green rectangles as distracters ("**X**": Low Load+ Distracter) or remember them as part of target memory array with no distracters ("**o**": Low Load, or "**O**": High Load).

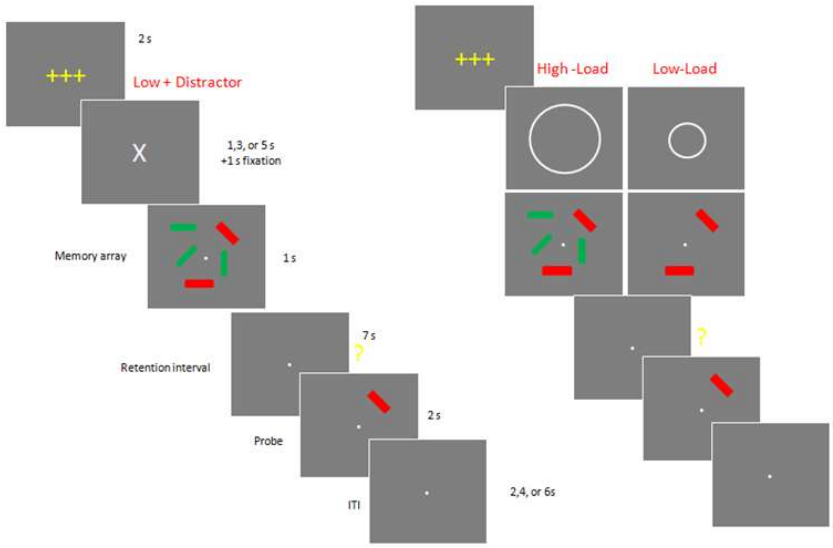

Figure 1. Example of a typical trials of Experiment 1. ITI: Inter-Trial-Interval.

After a 7-s long retention interval, subjects were presented with a single probe stimulus for 2 s and asked to press a specified button on either the left- or right-hand key pad to report whether the orientation of the tested rectangle changed (same or different). Following an inter-trial interval of 2, 4 or 6 s, the next trial commenced, starting with the yellow get-ready signal. Accuracy was emphasized over speed, and subjects were allowed to correct their response before the next trial began. The experiment 2 consists of twelve blocks of 12 trials (total 144 trials). Between blocks, participants were allowed to take as long a break as they wanted.

In experiment 2, subjects performed a change detection task to estimate their working memory capacity. Subjects sat upright in a comfortable chair and viewed the stimuli at a distance of ~70 cm. In this version of the task, there were neither precues nor green distracters, only relevant items. The

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number of to-be-remembered red rectangles varied from 2 to a maximum of 6, which slightly exceeds the typical capacity of an older adult. Each trial began with a 2 s get-ready signal followed by a 1 s long memory array. After a brief (200 ms) pattern mask and a 2 s delay period, the test stimulus was presented until a response was made. Following a 3 s inter-trial interval, the next trial commenced. Accuracy was emphasized over speed, and subjects were allowed to correct their response before the next trial began. This version of the task was structured as five blocks of 32 trials (total 160 trials).

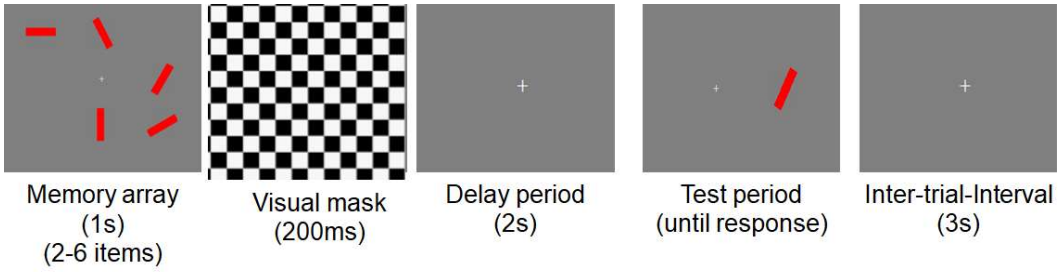

Figure 2. Example of a typical trials of Experiment 2.

2.3. MRI image acquisition and image processing

Images were acquired on the 3-Tesla Siemens scanner at the University of Missouri's Brain Imaging Center. Technical parameters for the structural scans were as follows: T1-weighted MPRAGE images: repetition time (TR) =1920 ms, echo time (TE) =2.92 ms, flip angle=9º, field of view (FOV) = 256 mm, matrix: 256 x 256, 176 slices in the sagittal plane, voxel size = 1x1x1 mm, slice thickness = 1 mm with acquisition time of 8 min, 13 s. T2-weighted images: TR = 3200 ms, TE = 402 ms, FOV = 256 mm, matrix = 258 x 256, slice thickness = 1 mm.

2.3.1. Brain regions of interest

Brain regions that previously had reported associated with attention including attentional filtering process (superior frontal gyrus, superior parietal lobe, and intraparietal sulcus for the dorsal attentional system and inferior and middle frontal gyri, inferior parietal lobe, and superior temporal gyrus for ventral attentional system; Figure 3a), working memory storage (retention; intraparietal sulcus) or episodic memory [medial temporal lobe (hippocampus, and entorhinal and parahippocampal cortices; Figure 3b) were selected as regions-of-interest (ROIs). The ROIs were defined for each subject using Freesurfer. The segmentation quality then was confirmed visually by a reviewer blinded to group assignment.

Figure 3

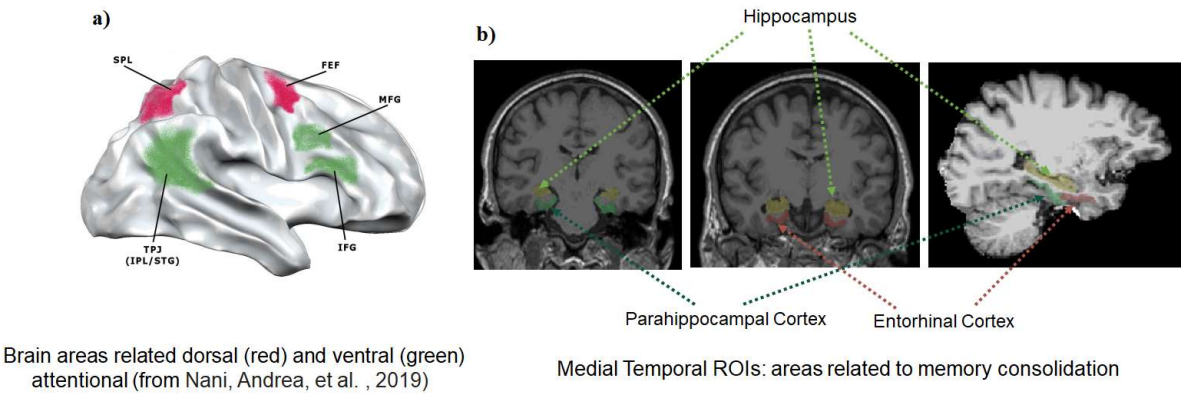

Figure 3. Brain regions of interests.

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2.3.2. Hippocampal volumes and cortical thickness

Volumetric segmentation and cortical parcellation for thickness calculation were performed with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The processing included motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al. 2004), automated Talairach transformation, and segmentation of the deep gray matter volumetric structures and parcellation of cortical gay matter structures (Fischl et al. 2002; Fischl et al. 2004).

2.4. Statistical Analysis

Group comparisons of demographic data were conducted using one-way analysis of variance (ANOVA) or χ^2 test. Group comparisons of neuropsychological and MRI structural ROI metrics were conducted using multivariate analysis of covariance (MANCOVA) in order to account for potential inter-correlations among outcome variables. For MANCOVA, age and education were used as covariates. To compare the performance differences between Low-Load and Low-Load with Distractor conditions, within-subjects analysis of covariance (ANCOVA) was performed using age and education as covariates. When comparing the hippocampal volume, total intracranial volume (TIV) additionally was used as a covariate. The primary neuropsychological metrics were *K* scores that were derived from hit rate (proportion of correct responses when a change was present) and false alarm rate (proportion of incorrect responses on no-change trials): $K = N * (H-FA)$, where N is the number of relevant, to-be-stored items, H is the hit rate and FA is the false alarm rate as suggested by Cowan (2001). Association analyses of MRI structural (volume and cortical thickness) with *K* scores were conducted for controls and PD patients separately using Pearson partial correlation analyses with adjustment for age and education. Following the association analyses, regression analyses were conducted for the variables that demonstrated significant associations between MRI structural and neuropsychological metrics after controlling for age and education. In order to determine structural metrics that could explain the variances of group differences in memory metrics, a stepwise regression analysis was conducted for controls and PD separately. For the stepwise regression analysis, structural metrics that showed significant associations with memory metrics were included in addition to age and education. Statistical significance was defined as α=0.05. The association analyses were corrected for multiple comparisons using the Holm-Bonferroni stepdown method (Holm 1979) to control the familywise error rate (*FWER*) at p=0.05. We report uncorrected raw p values but indicate significant results with *FWER*-correction. SAS 9.4 was used for all statistical analyses.

3. Results

3.1. Demographics

There were no significant group differences in age, gender, education, MMSE, and depression scores (p's >0.073).

Table 1. Demographics.

	Controls (N=22)	PD Patients (N=19)	p-values
	a. Demographics		
Age (y)	69.05 ± 5.58	66.16 ± 8.81	0.211
Gender (m/f)	12/10	14/5	0.205
Education (years)	14.77 ± 3.19	16.63 ± 3.25	0.073
MMSE	29.40 ± 0.99	29.00 ± 1.29	0.284
Hoehn & Yahr Scale	0	2.03 ± 0.77	

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Disease duration (years)	0	6.65 ± 4.76	
GDS	2.78	4.11 ± 3.11	0.147

Note. Descriptive data for participants' demographics. MMSE: Mini-Mental-State-Exam, GDS: Geriatric Depression Scale.

3.2. Group comparison of memory metrics

In Experiment 1, there were significant group differences of memory K scores in overall memory conditions [F(3,35)=3.04, p=0.042) and in each individual memory condition [F(1,37)=5.79, p=0.021, R^2=0.152 for Low-Load; [F(1,37)=8.33, p=0.007, R^2=0.206 for Low-Load with Distractor; F(1,37)=5.89, p=0.020, R^2=0.164 for High-Load; Figure 4a). The K socre in the Low-Load with distractor condition was significantly lower compared to that in Low-Load condition for PD (t=-2.81, p=0.008) but not for controls (t=-1.29, p=0.206).

In Experiment 2, there were no significant group differences in overall working memory condicitons (F(5,33)=0.84, p=0.534) and in each individual conditions with different memory set sizes (F's >0.49, p's >0.060, R^2<0.199; Figure 4b).

Figure 4

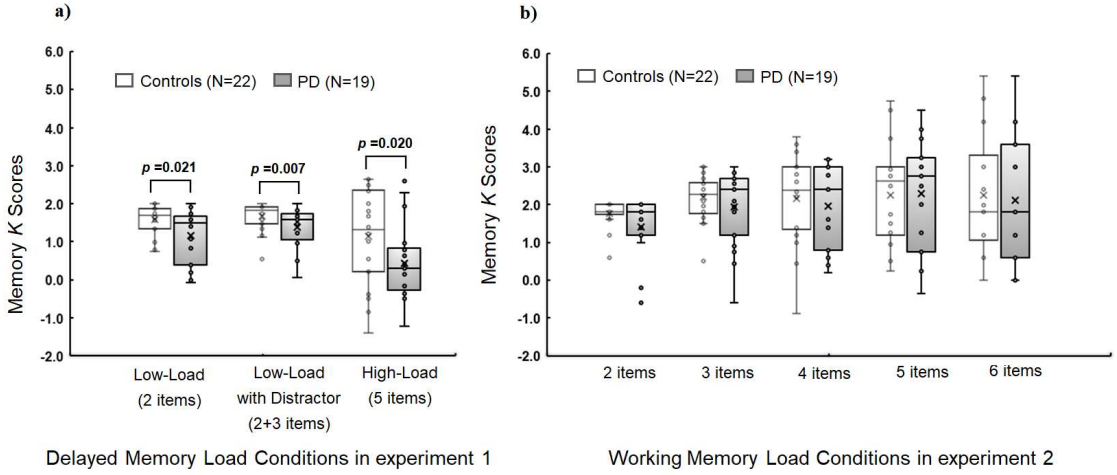

Figure 4. Mean *K* scores for controls and PD patients in a) experiment 1 and b) experiment 2 depending on different memory array conditions: *K = N * (H-FA)*, where *N* is the number of relevant, to-be-stored items, *H* is the hit rate and *FA* is the false alarm rate as suggested by Cowan (2001).

3.3. Group comparison of MRI structural metrics

There were no overall significant group differences in ROIs related to dorsal and ventral attentional systems (p's>0.121). When considering attention-related individual subregions, there was a significantly lower thickness in the left superior temporal gyrus for PD compared to controls [F(3,37)=5.92, p=0.020, R^2=0.270]. There were no significant group differences in bilateral intraparietal sulci (p's>0.064), entorhinal and parahippocampal cortices (p's>0.390). There also were no significant group differences in bilateral hippocampal volumes (p's >0.114).

3.4. Associations of MRI structural metrics with memory metrics

Within controls, higher thickness in the superior frontal gyrus was associated with higher memory K scores in the Low-Load condition of experiment 1 (R=0.466, p=0.038). There were no signficant correlations between structural metrics in other ROIs and memory K scores in experiment 1 (p's>0.083). For working memory conditions in experiment 2, higher thickness in the left inferior frontal-opercular gyrus and lower thickness in the left superior temporal gyrus were associated with higher *K* scores in memory load condition of 2 itmes (p's <0.048). Higher thickness in bilateral superior frontal gyri were associated with higher memory *K* scores in memory load condition of 6

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itmes (R's >0.460, p's<0.041). None of the associations, however, remained significant after *FWER*-correction. There were no signficant correlations between structural metrics in other ROIs and memory *K* scores in experiment 1 and 2 (p's>0.052; see Supplementary Materials 1 for details).

Subsequent regression analyses confirmed that higher thickness in the left superior frontal gyrus was a significant predictor of higher *K* scores in the Low-Load condition of experiment 1 after controlling for age and education (ß=2.0199, t=2.23, p=0.038, R^2=0.273). Higher thickness in the left inferior frontal-opercular gyrus and lower thickness in the left superior temporal gyrus were significant predictors of memory load of 2 items in experiment 2 (ß=1.2427, t=2.93, p=0.009 for inferior frontal gyrus and ß=-1.1137, t=-2.76, p=0.014 for superior temporal gyrus, total R^2=0.486).

Within PD patients, greater thickness in the left superior temporal gyrus was associated with higher *K* scores in the Low-Load and Low-Load with Distractor conditions of experiment 1 (R=0.563, p=0.019 for Low-Load and R=0.493, p=0.044 for Low-Load with Distractor; Figure 5a-b). Higher thicknessin in the right intraparietal sulcus was associated with higher *K* scores in the Low-Load condition (R=0.490, p=0.046). For memory conditions in experiment 2, greater thickness in the left superior temporal gyrus was associated with higher *K* scores in all memory load conditions of 2 to 6 items (R's>0.575, p's<0.016; Figure 5c for 4 items). The correlations between left superior temporal thickness and *K* scores in 3 and 4 items conditions remained significant after *FWER*-correction. Greater thickness in the right superior temporal gyrus also was associated with higher *K* scores in memory load condition of 2 itmes (R=0.514, p=0.035). Higher thickness in the left inferior frontal-opercular gyrus was associated with higher *K* scores in memory load conditions of 2, 3, 4, and 6 items (R's>0.489, p's<0.046). The association between left inferior frontal-opercular gyrus and memory load of 2 items remained significant after *FWER*-correction. Higher thickness in the right inferior frontal-opercular gyrus also was associated with higher *K* scores in memory load condition of 6 items (R=0.681, p=0.003) that remained significant after *FWER*-correction. Higher thickness in the left inferior frontal-triangular gyrus was associated with higher *K* scores in memory load conditions of 2 and 3 items (R's>0.489, p's<0.046). Higher thickness in bilateral supramarginal gyrus was associated with higher *K* scores of memory load condition of 6 items (R's>0.570, p's<0.017). The association between left supramarginal thickness and memory load of 6 items remained significant after *FWER*-correction. Greater left intraparietal sulcus thickness was associated with higher *K* scores of the memory load condition of 3 items (R=0.568, p=0.017). Higher thickness in the right superior frontal gyrus was associated with higher *K* scores of memory load conditions of 2 and 3 items (R's>0.550, p's<0.022). Greater thickness in the right superior parietal gyrus was associated with higher *K* scores in memory set load conditions of 2 and 3 items (R'2>0.568, p's<0.017). Higher thickness in the right intraparietal sulcus was associated with higher *K* scores of memory load conditions of 3 and 6 items (R's>0.569, p's<0.017). The correlations of right superior frontal and parietal gyri and intraparietal sulcus thickness with K scores in memory condition of 3 items remained significant after *FWER*-correction. For hippocampal volume metrics, there were no significant correlattions of hippocampal volumes with any memory metrics in both experiments 1 and 2 (p's >0.235; see Supplementary Materials 1 for details).

Subsequent regression analyses revealed that higher thickness in the left superior temporal gyrus was a significant predictor of higher *K* scores in the Low-Load with Distractor condition of experiment 1 (ß=2.5189, t=2.64, p=0.019, R^2=0.397) and memory load conditions of 4 and 5 items in experiment 2 (ß=4.1656, t=2.71, p=0.017, R^2=0.655 for 4 items and ß=4.4272, t=2.86, p=0.012, R^2=0.580 for 5 items). Higher thickness in the left supramarginal gyrus was associated with higher *K* scores in the memory load condition of 6 items (ß=6.6444, t=2.63, p=0.025, R^2=0.891).

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Figure 5

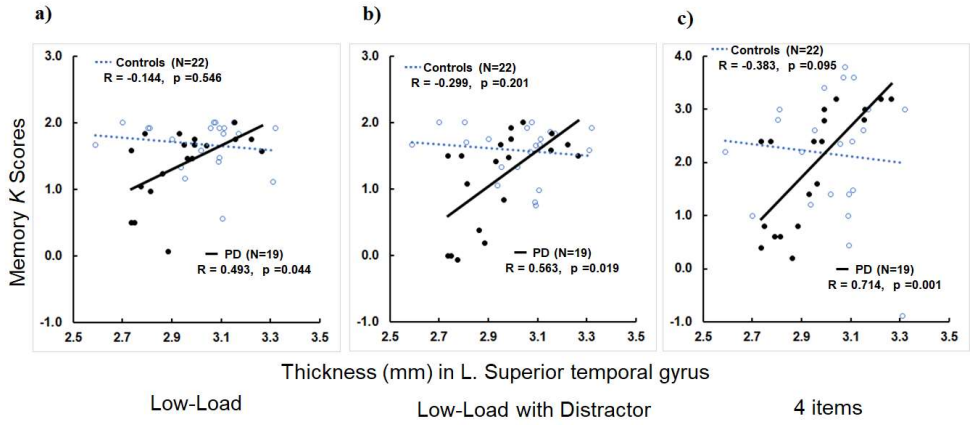

Figure 5. Scatter plots show memory *K* scores (y-axis) in Low-Load (a), Low-Load with Distractor (b), and memory load of4 items (c) versus thickness values (mm) in the left superior temporal gyrus (x-axis) for controls and PD: $K = N * (H-FA)$, where N is the number of relevant, to-be-stored items, H is the hit rate and FA is the false alarm rate as suggested by Cowan (2001).

3.5. Stepwise regression analysis to determine factors predicting memory metrics

The stepwise regression analyses were conducted using structural metrics that showed significant associations with memory metrics. In controls, left inferior frontal-opercular and superior temporal gyri and bilateral superior frontal gyri thickness values were used for stepwise regression analyses in addition to age and education as predictors for K scores of Low-Load in experiment 1 and memory load conditions of 2 and 6 items in experiment 2 (see Supplementary Materials 1 for association analysis results). For PD, thickness values in left inferior frontal-triangular and right superior frontal and parietal gyri, and bilateral inferior frontal-opercular, supramarginal, superior temporal gyri and bilateral intraparietal sulci were used as predictors analyses in addition to age and education.

In controls, higher thickness in the left superior frontal gyrus was a significant predictor of higher *K* scores in the Low-Load condition of experiment 1 (ß=2.0199, p=0.038, partial R^2=0.202). Higher thickness in the left inferior frontal-opercular gyrus and lower thickness in the left superior temporal gyrus were significant predictors of memory load of 2 items in experiment 2 (ß=1.2427, p=0.009, partial R^2=0.260 for inferior frontal gyrus and ß=-1.1137, t=-2.76, p=0.014 for superior temporal gyrus, partial R^2=0.229). Higher thickness in the right superior frontal gyrus was a significant predictor of higher *K* scores of memory load condition of 6 items (ß=7.3819, p=0.021, partial R^2=0.218).

In PD, higher thickness in the left superior temporal gyrus was a significant predictor for higher *K* scores of Low-Load (ß=1.6034, p=0.044, partial R^2=0.203) and Low-Load with Distractor (ß=2.5189, p=0.019, partial R^2=0.279) conditions in experiment 1. Higher thickness in the left inferior frontal-opercular gyrus was a significant predictor for higher *K* scores of memory condition of 2 items in expediment 2 (ß=3.2703, p=0.006, partial R^2=0.365). Higher thickness in the right superior parietal thickness was asignificant predictor for higher *K* scores of memory condition of 3 items (ß=4.8596, p=0.007, partial R^2=0.315). Higher thickness in the left superior temporal gyrus a significant predictor for higher *K* scores of memory load conditions of 4 items (ß=4.3709, p=0.001, partial R^2=0.360) and 5 items (ß=4.4272, p=0.012, partial R^2=0.228). Higher thickness in the right inferior frontal-opercular and supramarginal gyri were significant predictors for higher *K* scores of memory condition of 6 items (ß=4.7980, p=0.019, partial R^2=0.242 for inferior frontal and ß=6.2697, p=0.019, partial R^2=0.093 for supramarginal).

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4. Discussion

The present study examined mechanisms underlying memory deficits in PD patients and their associations with structural metrics. Compared to controls, PD patients had lower delayed memory whereas there were no group differences in working memory performance for any memory load conditions. In addition, PD patients had lower thickness in the left superior temporal gyrus, aregion related ventral attentional system. To the contrary, there were no structural differences in ROIs related to dorsal attentional system, working memory storage, and episodic memory. Lower thickness values in the left superior temporal gyrus were significant predictors of lower delayed memory performance in Low-Load and Low-Load with Distractor conditions and working memory performance of memory load conditions of 4 and 5 items. The present findings suggest that PD patients may have intact working memory storage capacity but impaired attentional filtering and memory consolidation that may lead to lower delayed memory scores. Lower delayed memory in PD may partly be associated with lower cortical thickness in the left superior temporal gyrus. Future studies should be warranted to elucidate early brain structural or functional changes related to poorer delayed memory in PD.

4.1. Lower dealyed memory due to reduced memory consolidation

In the present study, 2 different delay periods (2s vs. 7s) were utilized between memory and test arrays to mimic working memory and episodic memory formation processes. Interestingly, PD patients' memory *K* scores were comparable to those of controls when their memory was tested 2s after the memory array offset whereas their memory performance became significantly worse with a 7s delay period. This result suggests that PD patients may have intact working memory storage capacity compared to neurologically normal controls. PD patients' ability to encode and retrieve visual information may also be intact compared to those in controls. This result is inconsistent with a previous finding demonstrating that PD patients had lower *K* scores and CDA (contralateral delay activity) amplitudes, EEG correlates reflecting items held in working memory, in memory load conditions even with no distractors (Lee et al. 2010). In that study, however, a bilateral display was utilized to measure CDA, which required additional filtering by the participant even in conditions with no distracters. So, it is possible that patients' lower *K* scores and CDA amplitudes in that study could be due to impaired filtering rather than diminished working memory storage capacity. The current finding supports this interpretation.

Instead, PD patients seemed to have difficulty to continue holding information in memory over a prolonged period of time where memory consolidation may increasingly gain importance to form stable episodic memory. Memory consolidation is a process by which a temporary and unstable memory trace is transformed into a more stable and long-lasting memory (Squire et al. 2015) and may serve as a critical component for successful episodic memory formation process. Note that studies that reported impaired episodic memory performance in PD typically tested memory performance after a 20 min delay period (Weintraub et al. 2015; Yarnall et al. 2014). The current finding, however, suggests that impaired episodic memory formation process may be detected as early as within a 7s delay period. Thus, the curent finding of lower delayed memory performance in PD without difference in working memory performance suggests intact working memory storage but impaired memory consolidation process in PD.

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder, comprising about 50-70% of dementia cases (Brookmeyer et al. 2011) and the major and early AD-related behavioral deficits entail learning/memory problems (Bäckman et al. 2005), particularly episodic memory (Bäckman et al. 2001). Given that selective episodic memory decline may occur in AD-at-risk-populations (Bäckman et al. 2001; Lim et al. 2014), current finding of lower *K* scores in delayed memory conditions suggests that AD-related early neurobehavioral differences may occur in PD despite still intact working memory performance.

4.2. Lower delayed memory due to impaired attentional filtering

Both controls and patients had some difficulty ignoring distracters. They demonstrated lower *K* scores compared to Low-Load condition although the number of to-be-remembered items was same for both conditions with and without distractors. Interestingly, *K* score difference between these two memory conditions was significant only for PD patients, suggesting difficulty to ignore irrelevant information (attentional filtering difficulty) in PD. This finding is consistent with a previous study (Lee etal., 2010) reporting that PD patients had lower *K* scores but higher CDA (contralateral delay activity) amplitudes in memory load conditions with distractors suggesting lower memory performance for to-be-remembered task-relevant information probably due to unnessary storage for task-irrelevant items. The current finding also is in line with previous findings reporting a critical role of fronto-striatal pathway in controlling the access of incoming information into memory system (McNab and Klingberg, 2008; Cohen and Frank, 2009). Patients with impaired fronto-striatal pathway may especially be vulnerable to filtering deficits. The loss of dopaminergic input to the basal ganglia in Parkinson's disease may lead to a diminished fronto-striatal functions and reduced ability to filter out distracters so that they do not unnecessarily usurp memory space. Indeed, PD patients do seem to be vulnerable to attention deficits in a general sense. Studies have shown that PD patients have more difficulty inhibiting automatic response to ignored salient but irrelevant stimuli such as flanking distracters (Praamstra & Plat, 2001; Verleger et al., 2010).

4.3. Structural correlates of lower delayed memory in PD

In the present study, we examined structural metrics (volumes and cortical thickness) in brain areas that were known to be related to attentional processes including attentional filtering, working memory storage, or episodic memory including memory consolidation processes. Consistent with comparable working memory storage capacity throughout different memory load conditions, there were no significant group differences in the intraparietal sulcus, an area known to be sensitive to working memory storage (Postle et al., 2006). Instead, PD patients had lower thickness in the left superior temporal gyrus. Moreover, lower thickness in the left superior temporal gyrus was a significant predictor of both lower delayed memory performance and working memory performance. The superior temporal gyrus is known to be part of ventral attention network that is generally associated with bottom-up detection of salient stimuli by shifting attention to unexpected information while a dorsal attention network employs top–down goal-directed attentional shifts to designated features of stimuli (Nani et al. 2019). Both ventral and dorsal attention netwkrs, however, seem to simultaneously influence and integrate each other in real life situations (Nani et al. 2019). The volume of the left superior temporal gyrus has been reported to sensitively reflect verbal working memory capacity and ability to comprehend spoken sentences (Leff et al. 2009). Since properly understanding spoken sentences may be involved in accessing to long-term storage of lexico-semantic representations of verbal information, the role of the left superior temporal gyrus in accessing to long-term storage especially for verbal information has been implicated (Leff *et al.*, 2008; Schofield *et al.*, 2009). The significant associations of the left superior temporal gyrus thickness with working memory and delayed memory capacity observed in the present study may extend previous findings suggesting that the role of the left superior temporal gyrus may be multimodal and generic to working memory capacity and transferring information to and accessing to long-term storage. Future studies are waranteed to replicated current findings and test this inriguing hypothesis.

It is intriguing to note that there were no volumetric or thickness differences in any of medial temporal ROIs or associations with memory metrics although PD patients demonstrated robust decline in delayed memory performance. It is possible that our sample size was too small reliably to detect structural differences in medial temporal areas. It also is possible that patients' lower delayed memory observed in this study may partly be associated with early brain microstructural or functional changes that may occur before medial temporal morphological changes. For example, studies report that diffusion tensor imaging (DTI) metrics that measure random translational water motion may reflect early microstructural changes (Le Bihan et al. 2001). These DTI measures have

been suggested to be more sensitive than volume or thickness measures in capturing AD-related early brain changes including changes in the medial temporal lobe (Douaud et al. 2013; Fellgiebel et al. 2006; Lancaster et al. 2016; Müller et al. 2007). Further studies utilizing brain imaging markers that sensitiely capture early brain microstructural or functional changes should be warranted to confirm current findings and to elucidate neural correlates of delayed memory in PD.

5. Conclusions

Lower attentional filtering and memory consolidation problems may contribute to lower delayed memory performance in PD that may partly be associated with lower cortical thickness in the left superior temporal gyrus.

Supplementary Materials: Supplementary Materials 1.

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