

The Origin of Working Memory Deficits in Parkinson's Disease

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In Partial Fulfillment of the Requirements for the Degree
Doctor of Philosophy

by

Eun-Young Lee, Diplom

Steven A. Hackley, Ph.D, Dissertation Supervisor

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The undersigned, appointed by the Dean of the Graduate School, have examined the
dissertation entitled

The Origin of Working Memory Deficits in Parkinson's Disease

presented by Eun-Young Lee

A candidate for the degree of Doctor of Philosophy

and hereby certify that in their opinion it is worth of acceptance.

Professor Steven A. Hackley

Professor Nelson Cowan

Professor Shawn Christ

Professor Jeffrey Johnson

Professor Terry Rolan

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The Origin of Working Memory Deficits in Parkinson's Disease

Eun-Young Lee

Dr. Steven A. Hackley, Dissertation Supervisor

ABSTRACT

Two experiments were conducted to examine the mechanisms underlying deficits of visual working memory in Parkinson's disease (PD). One study combined behavioral methods with event-related potentials (ERPs), the other, behavioral methods with structural and functional magnetic resonance images (MRIs). In both experiments, participants viewed an array of colored rectangles, some of which were task-irrelevant. Then, after a brief delay, they reported whether the orientation of any relevant figures had changed.

By comparing trials with and without task-irrelevant items, it was shown that poor attentional filtering contributes to poor memory, both in people with and in those without PD. Measures of basal ganglia activation prior to the retention interval were generally consistent with claims that this structure serves as a “gate-keeper” to working memory. Structural analyses identified three regions for which disease-specific atrophy was negatively correlated with capacity—the right intraparietal sulcus (IPS) and the left and right pre-supplementary motor area (pre-SMA). Thus, converging evidence from behavior, electrophysiology, and MRI indicate that lowered capacity and poor attentional filtering both underlie deficits of working memory in people with Parkinson's disease.

Chapter I

General Introduction

The purpose of this research was to determine the neural mechanisms underlying compromised working memory performance in patients with Parkinson's disease.

Parkinson's disease (PD) is a slowly progressing neurodegenerative disorder with predominant loss of dopaminergic neurons in SNc (substantia nigra pars compacta) and subsequent depletion of dopamine levels in the basal ganglia. Prominent characteristics of Parkinson's disease include motor symptoms such as tremor, rigidity and bradykinesia. While the motor symptoms of PD dominate the clinical picture, many patients with PD experience a wide range of non-motor symptoms. These include fatigue, pain, depression, anxiety, sleep disturbance, constipation, bladder and other autonomic disturbances, sensory complaints such as numbness, burning or tingling sensation, and decline in cognitive functions which include planning, set shifting, reward learning and working 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), patients' cognitive symptoms are often ascribed to compromised information flow through this pathway (Lewis et al., 2003). In fact, the pattern of cognitive deficits in patients with Parkinson's disease appears to be similar to that observed in frontal lobe patients (Morris et al., 1988, Owen, 1995; West et al., 1998). However, recent studies suggest that the basal ganglia may be even more directly involved in a variety of cognitive functions (Frank, 2005; Gruber et al., 2006; Cools et al., 2008; Cohen and Frank, 2009).

Working memory deficits in Parkinson's disease

Impairment of working memory is one of the cognitive deficits observed in patients with Parkinson's disease. Both the measurement methods and conceptual basis for this type of memory vary (Miyake and Shah, 1999). Working memory has been traditionally considered as a capacity-limited storage system, previously known as short term memory, which maintains information over a period of seconds (Miller, 1956; Atkinson and Shiffrin, 1968). In conventional psychometric tasks, the capacity of working memory is measured by means of simple digit or word span tasks in which participants are presented with a series of digits or words, and asked to recall them in the presented order. However, these types of span tasks are considered to be flawed because people can utilize rehearsal and grouping (chunking) to improve their performance. This can lead to an artifactual inflation of the measured memory capacity depending on individual's skills and strategies.

Baddeley and Hitch (1974) pointed out that working memory is more than a passive storage of information and, therefore, they incorporated an information processing component to their definition. According to Baddeley and Hitch, as well as subsequent authors, working memory is a capacity limited system which not only temporarily maintains and stores information in a highly active and accessible state but also manipulates that information in the service of ongoing cognitive tasks (see also Baddeley, 2003; Conway et al., 2005; Cowan et al., 2005).

Based on this notion, Daneman and Carpenter (1980) developed a reading span task to measure individual's working memory capacity, a task which was designed to tax both the storage and processing of information. Participants are asked to read a series of

sentences aloud and recall the last word of each sentence in the presented order. The rationale behind this kind of storage-and-processing span task is that the two working memory components may share a common resource which is limited in capacity. Thus, the ability to simultaneously process and maintain information would be crucial to measure the capacity of this common resource (e.g., Just and Carpenter, 1992; Daneman and Merikle, 1996; Unsworth et al., 2009).

Since then, various kinds of storage-and processing span tasks have been developed including counting and operation span tasks (Case, Kurland, and Goldberg, 1982; Turner and Engle, 1989). However, these kinds of storage-and-processing paradigms have been criticized due to their dual-task characteristics. Note that they require participants to simultaneously retain information (e.g., words) while carrying out processing (e.g. responding to a sentence or mental arithmetic). Thus, it is difficult to determine the extent to which variation in test results reflect processing efficiency, storage ability, or both (Cowan et al., 2005).

To overcome this weakness, new lines of span tasks were introduced, such as visual array comparison, multi-object tracking, running span and memory-for-ignored-speech tasks (for details see Cowan et al., 2005). These tasks focus on information storage while not including a processing component. According to Cowan and colleagues (2005), working memory is a capacity limited system which temporarily maintains information online for performing tasks. What is crucial to successfully and effectively measuring working memory capacity is preventing rehearsal and chunking processes rather than including a processing component in the task.

An example relevant to the present study is the visual array comparison paradigm of Luck and Vogel (1997), one of the most widely used spans tasks in the field. In this task, a to-be-remembered array of visual items (e.g., colored rectangles) is followed by a short retention interval. During the test phase following the retention interval, either a single probe stimulus or a probe array of several items is presented. Participants are asked to indicate whether or not the probe is identical with the memory array. Since the visual memory array is usually presented very briefly (e.g., 200 ms), participants would not have enough time to employ a strategy of verbal rehearsal or of encoding enhancement via perceptual grouping.

Regarding working memory capacity in patients with Parkinson's disease, many studies have shown that patients with Parkinson's disease appear to suffer from reduced memory capacity, especially when capacity is measured by means of storage-and processing tasks. For example, Kensinger and colleagues (2003) reported that patients with Parkinson's disease exhibited lower span scores in reading span tasks (see also Hochstadt et al., 2006). Similarly, Gabrieli and colleagues (1996) found that Parkinson's patients had only half the memory capacity of neurologically normal individuals in an operation span task. In their task, participants were asked to both report whether a series of mathematical operations was correct and also to recall the words that followed each arithmetic operation.

Unfortunately, due to the dual-task characteristics of such storage-and processing paradigms, it is not clear whether patients' poor performance is due to reduced storage capacity per se, inability to effectively process information, or both (Cowan *et al.*, 2005). Moreover, some studies have failed to document any differences in capacity for patients

with Parkinson's disease, especially when simple digit or word span tasks were administered (Cooper et al., 1991; Dalrymple-Alford et al., 1994; Kensinger et al., 2003; Gilbert et al., 2005; Lewis et al., 2005). Interestingly, in a study by Kensinger and colleagues (2003) Parkinson patients showed reduced capacity in a reading span task whereas the very same patients showed span scores in the digit and word span tasks that were comparable to those of control participants. This suggests that some span tasks (e.g., simple span tasks) may not be sensitive enough to detect patients' deficits in working memory.

Attentional filtering as an explanation of deficits

If there are genuine deficits in working memory for patients with Parkinson's disease, one possible cause may be a reduced ability to filter out irrelevant information. By nature, working memory is assumed to have limits in its capacity. Although there are individual differences, many studies have suggested that working memory capacity may be limited to three or four information units (Sperling, 1960; Luck and Vogel, 1997; Cowan, 2001).

For example, in a study by Luck and Vogel (1997) healthy young adults were presented with a memory array of 1-12 colored squares and then, after a brief delay, a test array. Participants were asked to indicate whether or not the test array was identical to the memory array. Results showed that accuracy monotonically decreased with increasing number of to-be-remembered items regardless of whether the to-be-remembered objects were simple with a single feature or complex with many features (see also Awh et al., 2007). As in the present study, Luck and Vogel converted their proportion correct data to

“ K ” statistics (Cowan, 2001; Pashler, 1988; see Appendix A), which estimate the number of task-relevant items stored in, and retrieved from working memory. The asymptotic value for K scores as a function of array size showed that healthy, young participants were able to maximally hold about four items in working memory.

Due to the sharp limitation of this capacity (Luck & Vogel, 1997; Cowan, 2001), it would be important not to let irrelevant items take up space. This general idea is supported by the findings of Vogel and coworkers (2005a), who used EEG methods to show that effective attentional filtering may be necessary to ensure that working memory is filled with only relevant information.

In Vogel and colleagues’ experiment, participants were required to remember the orientations of red rectangles on the side of the display cued by a central arrow. (Figure 1 shows the trial structure for Dissertation Experiment 1, which is quite similar.) Trials in which there were two red and two blue rectangles (2-red-2-blue) in the attended half of the display were the most theoretically critical. These trials were compared with two other types that lacked any blue distracters: One consisted of four (4-red) and the other of two (2-red), to-be remembered rectangles on each side of the display screen. The critical question was whether retention during the 2-red-2-blue trials would be more similar to the 2-red or the 4-red condition. If the participant can successfully filter out the blue distracters, then he or she only needs to hold two items in memory. If the subject cannot ignore distracters, then he or she has to retain four items. Retention of task-irrelevant items is hereafter referred to as “wasteful” or “unnecessary” storage.

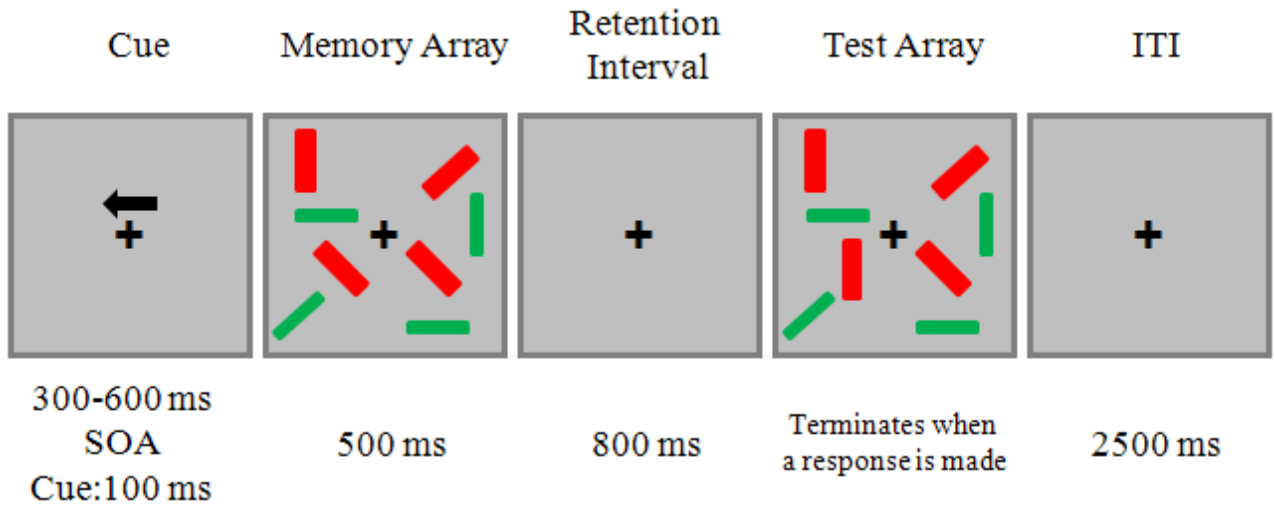


Figure 1. Sequence of events of a typical trial of Experiment 1. Specifically, this is an example of a 2-red-2-green condition in which the left hemifield was task-relevant.

From the scalp EEG recordings, an event-related potential (ERP) was extracted that is known to reflect the amount of information held in visual working memory irrespective of task-relevance. This component is referred to as either contralateral delay activity (CDA; Vogel and Machizawa, 2004) or sustained posterior contralateral negativity (SPCN; Jolicoeur et al., 2008). These terms convey the fact that it is a surface-negative brain wave observed over the back part of the head, on the side opposite to the attended stimulus, and that it is sustained during the delay between the memory and test arrays. Its cognitive correlates are quite specific: The amplitude is proportional to the number of items held in visual working memory (Vogel and Machizawa, 2004).

As in the experiments reported in this dissertation, the (young, healthy) participants of Vogel and colleagues' (2005a) study were split into two groups based on their behavioral performance. For the high-capacity group, CDAs were equivalent in the 2-red and the 2-red-2-blue condition, which implies that these participants were

successful at keeping irrelevant distracters from their memory. For people with low capacity, however, CDAs were significantly larger when two red rectangles were presented with distracters than without. In fact, amplitudes in the 2-red-2-blue condition were comparable to those observed in the 4-red condition. Based on this finding, the authors suggested that attentional filtering ability critically determines a person's working memory capacity. Individuals who perform well on memory span tests may simply excel at filtering out irrelevant information; they may not have large memory spans, per se (see also Awh and Vogel, 2008).

Basal ganglia dysfunction as the cause of impaired filtering

As will be seen in Chapter 2, my colleagues and I successfully used the Vogel paradigm to test impaired attentional filtering in Parkinson's disease (published as Lee, Cowan, Vogel, Rolan, Valle-Inclán and Hackley, 2010). This EEG-based paradigm has a number of limitations, some of which were addressed in the follow-up study using fMRI methods (Chapter 3). The main limitation is that the CDA component can only be extracted using a task in which the participant focuses their attention to the left or right of fixation in different trials. This implies that subjects in the Lee et al. study needed to ignore not just the rectangles that were of the wrong color, but additionally, all rectangles that were on the wrong side of the display. Failure to restrict attention to one hemifield will diminish the size of CDA irrespective of any true reduction in capacity. The methods of Experiment 2 (Dissertation Chapter 3) allowed memory-related brain activity to be measured without the need for unilateral attention on the part of the subject.

A second limitation of my earlier experiment was that CDA can only index the number of items held in memory as that quantity is manifest within the specific but poorly defined cortical regions that generate the CDA. The main generator is thought to be the intraparietal sulcus (IPS), but pertinent data are scarce (reviewed in Lee et al., 2010). By contrast, fMRI allows memory-related activity throughout the brain to be identified. Experiment 2 made use of whole-brain functional analysis to assess filtering deficits. It also employed a focused, region-of-interest approach to test the specific hypothesis that dysfunction of the basal ganglia is a cause of filtering deficits in Parkinson's disease.

The possibility that patients with basal ganglia disease might be especially vulnerable to filtering deficits is supported by a recent functional MRI study of healthy young adults by McNab and Klingberg (2008; see also Praamstra et al., 1998; Praamstra and Plat, 2001; Verleger et al., 2010). In that study, an instructional precue was followed by a memory display consisting of a set of 16 small, open squares arranged in a circle. A few of the squares contained a small colored disk. This memory array vanished during the retention interval, and then the array of squares reappeared with a question mark inside one of them. The subject's task was to indicate whether or not there had been a colored disk at that particular location.

Similar to the Vogel paradigm, the critical condition in McNab and Klingberg's experiment comprised trials in which there were three red and two yellow disks, and in which the precue had instructed subjects that the yellow disks should be ignored. (This is analogous to Vogel and colleagues's 2-red-2-blue condition.) During the second type of trial, there were only three red disks (analogous to the 2-red condition). The third

category entailed three red and two yellow disks, but with a precue indicating that all five should be remembered (roughly analogous to the 4-red condition).

The BOLD (blood oxygenation level-dependent) signal from the intraparietal sulcus during the retention interval was used as an index of the amount of information held in working memory (Cowan et al., 2011; Todd and Marois, 2004). Greater amplitudes were observed on 3-red-2-yellow distraction trials than on the 3-red trials for people with low memory capacity, reflecting unnecessary storage of the irrelevant items in memory. This is consistent with the EEG results by Vogel and colleagues (2005a).

The relevant new insight concerns the left and right middle frontal gyri and the left basal ganglia. Greater activation was observed in these three regions when the precue indicated that the two yellow disks should be ignored than when it indicated that the yellow disks should be attended and remembered. This preparatory activity was more robust in participants with larger working memory capacity.

Importantly, the activity of part of the basal ganglia called the globus pallidus in response to the ‘ignore’ cue was inversely correlated with the unnecessary storage of the irrelevant items in memory: Less pallidal activity, more intrusion of irrelevant items. The amount of information held in memory—irrelevant as well as relevant—was estimated by the parietal lobe activation during the retention interval. By implication, the basal ganglia may be involved in filtering out distracters so that they do not usurp space in memory. Congruent with these results, several neuroimaging studies have shown that the basal ganglia are engaged during working memory tasks (Skeel *et al.*, 2001; Lewis *et al.*, 2004; Cools *et al.*, 2008).

Basal ganglia dysfunction is, of course, of central importance to Parkinson's disease (Lewis et al., 2003; Owen et al., 2004). Regarding PD patients' filtering ability, patients do seem to be vulnerable to attention deficits in a general sense. Studies have shown, for example, that patients have more difficulty inhibiting automatic response to ignored salient but irrelevant stimuli such as flanking distracters (Praamstra & Plat, 2001; Verleger et al., 2010).

Deficits in storage capacity, per se

Independent of any filtering problems, it is possible that patients' poor performance on working memory span tasks might be due to a reduction of storage capacity. If so, the CDA measures of Experiment 1 should be sensitive to such a deficit. As noted above, CDA varies in amplitude according to the number of items held in visual working memory, and its maximum amplitude is at a scalp site overlying posterior parietal cortex (Vogel and Machizawa, 2004).

Recent evidence indicates that the maintenance of information in visual working memory is better correlated with the activity the parieto-occipital region than that of the frontal lobes as had previously been thought. For example, Postle and colleagues (2006) used transcranial magnetic pulse stimulation to show that the posterior parietal lobe is vulnerable to disruption during both retention and manipulation of items in working memory, whereas dorsolateral prefrontal cortex is sensitive only during the manipulation of information.

The localization of short-term storage of visual information within parietal cortex was identified more specifically in a functional MRI study by Todd and Marois (2004).

These authors showed that activation within the intraparietal sulcus linearly increases with memory load, reaching an asymptote at about four objects. A recent study by Cowan and colleagues (2011) also showed that there was an increase in left IPS activity with increasing memory set sizes, and this increase was apparent irrespective of whether the modality of presented memoranda were auditory or visual.

Whether patients with Parkinson's disease have impairments in posterior parietal functioning that might lead to reduced storage capacity is unclear. Diffusion tensor imaging of white matter tracts does reveal a loss within the left parietal lobe of patients with Parkinson's disease (Matsui *et al.*, 2007). However, other studies have found preserved parietal lobe function, at least in the context of tasks involving visuospatial orienting or sequential finger movements (Bennett *et al.*, 1995; Hsieh *et al.*, 1996; Samuel *et al.*, 1997). With this in mind, Experiment 2 examined differences in gray matter density between participants with PD and those without, within the parietal cortex. Atrophy within other regions was examined on an exploratory basis, and was correlated with memory deficits, disease state, and other relevant variables.

Chapter II

Experiment 1 (EEG and Behavior)

Introduction

In this study, I examined whether patients' poor performance on working memory span tasks is due to a reduced storage capacity *per se*, attentional filtering deficits, or both (Lee et al., 2010). To overcome the weakness of previous, purely behavioral, studies that used combined storage-and-processing tasks, a simple visual array comparison task was administered. Medication-withdrawn patients with Parkinson's disease and age-matched control subjects were asked to remember the orientation of red rectangles on the cued side of a computer display while ignoring all green distracters. The initial display consisted of two red, two red and two green, or four red rectangles on each side of the screen. After a short retention interval, the array was presented again. Participants then judged whether the orientation of any of the red rectangles on the attended side had changed slightly.

The number of relevant items held in and retrieved from working memory was estimated by a behavioral measure, K scores, defined as $K = N*(H-FA)$, where N is the relevant set size, H is the hit rate and FA is the false alarm rate (Cowan, 2001). H reflects the proportion of changes between arrays correctly detected and FA reflects the proportion of unchanged arrays incorrectly judged to have changed. The formula assumes that the participant truly knows the answer if the relevant item or items are in working memory and otherwise simply guesses whether there has been a change.

This measure was more appropriate for my goals than reaction time, percentage correct, sensitivity (d') or other more familiar dependent variables. K scores have become

standard in the field because they specifically estimate the number of relevant items held in and retrieved from working memory, independent of array size, while correcting for guessing and response bias. When array size is manipulated across a range of values (e.g., 2-6 items in the “outside-the-scanner” task described in Chapter 3), the asymptotic value of K estimates the participant’s memory capacity (Cowan, 2001; Cowan et al., 2005).

Because K scores estimate the amount of information retained in memory, they can be directly compared with the electrophysiological index of retention, CDA (Vogel et al., 2005a). These two measures provide distinct perspectives on the processes and representations of interest. Whereas CDA amplitudes reflect the number of items stored in working memory irrespective of task-relevance, K scores index the number of items stored in and then retrieved from working memory that were in fact task relevant.

If patients with Parkinson’s disease have impaired attentional filtering, they would be expected to exhibit lower K scores and higher CDA amplitudes when distracters are present than when they are absent. By contrast, age-matched controls who have good memories should exhibit little difference in CDA amplitudes and K scores as a function of the presence versus absence of distracters, similar to the high-capacity young adults studied by Vogel and colleagues (2005a).

If patients have reduced storage capacity *per se*, but no particular deficit in filtering, then the presence of the distracters should not matter for them any more than it does for controls. However, K scores and CDA amplitudes should be generally reduced, especially in the demanding 4-red condition. On the other hand, if patients have impaired updating, the presence of the distracters would not matter as well. K scores and CDA amplitudes would also be reduced as if they have reduced storage capacity.

Methods

Participants. Twenty-one patients with idiopathic Parkinson's disease and 28 age- and education-matched control subjects comprised the final sample (demographics are shown in Table 1.) All participants reported having normal color vision and normal or corrected-to-normal acuity. None exhibited evidence of dementia as assessed by the Mini-Mental State Examination [$M = 28.5$ for patients and $M = 29.2$ for controls (Folstein et al., 1975)]. Depression was evaluated by means of Geriatric Depression Scale-short form (Sheikh and Yesavage, 1986). All controls and all but two patients scored under 10 on the 15-point scale (overall $M = 2.3$ for patients and $M = 1.3$ for controls). The two highest-scoring patients were above 10, the criterion for depression (Geriatric Depression Scale, GDS = 11 and 12). Five patients, including the two who scored highest on the Geriatric Depression Scale, as well as two of the control subjects, were taking duloxetine as an antidepressant at the time of the study.

Patients were free from other neurological disorders with three exceptions: The first had an old lacunar infarct in the left thalamus and another in the cerebellar vermis. The second had a history of epilepsy. At the time of his participation he was taking antiepileptic medication. The third had mild atrophy and diffuse atherosclerotic disease, but no well-defined abnormality was said to be visible on T1-weighted scans. The general pattern of results was essentially the same with or without these three patients; therefore their data have been retained. The same was true for the seven participants who were taking antidepressants.

Sixteen patients were receiving the dopamine precursor levodopa as treatment. One patient was taking pramipexole (a dopamine agonist) in addition to levodopa. The

remaining five patients were receiving either Azilect (a monoamine oxidase inhibitor) alone or in conjunction with trihexyphenidyl (an anticholinergic agent) or pramipexole. On the morning of the experiment, patients skipped their initial dose of antiparkinsonian medication. The mean withdrawal period of 14 h (at least 11 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 patient's neurologist was contacted to obtain approval for this brief withdrawal as well as to confirm the diagnosis. The severity of the disease was reassessed prior to the start of the experiment using the Hoehn and Yahr scale (1967). Scores averaged 1.98 on the 5-point scale, with a range of 1 (mild unilateral tremor) to 3 (apparent balance problems). This indicates a mild to moderate stage in the progression of the disease (years of disease, $M = 6.7$). 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. Subjects were paid \$15 per hour for their participation.

Stimuli and procedures. Stimulus arrays were presented within two, $4 \times 7.3^\circ$ rectangular regions that were centered 3° to the left and right of a central fixation cross on a dark background (8.2 cd/m²), and were viewed at a distance of ~70 cm. Arrays consisted of two or four colored rectangles in each hemifield. Item positions were randomized across trials. Rectangles in red subtended $0.65 \times 1.15^\circ$ of visual angle and those in green subtended $0.32 \times 1.15^\circ$, with orientations selected randomly from a set of four possible values (vertical, horizontal, left-tilting 45° and right-tilting 45°).

Each trial began with a 100 ms, arrow-shaped cue presented above the fixation cross (Figure 2). This cue was followed at a 300–600 ms onset asynchrony by a 500 ms-long memory array, then an 800 ms blank period with fixation cross and finally, the test array. The 800 ms blank period was intended to provide sufficient time for development of the CDA while extending beyond the limits of iconic memory (~300-500 ms; Lu et al., 2005) and lateralized transients such as the visuospatial orienting component, N2pc (Luck & Hillyard, 1994). The test array ended as soon as the subject pressed a response key. Following a 2.5 s interval, the next trial commenced, starting with the arrow cue.

There were three different types of memory arrays: On 2-red-2-green trials, there were two relevant red rectangles interspersed with two green distracters on each side of the display. On 2-red trials, there were two red rectangles within each hemifield. Finally, on 4-red trials, four relevant red items were shown on each side of the screen. The three trial types were presented in random order in each block. On half of the trials, the memory and test arrays were identical, while on the other half the tilt of a single red rectangle within the to-be-remembered hemifield was altered for the test array. Participants responded by pressing one of two mouse keys to indicate whether such a change occurred. Participants used their preferred hand, which, in all cases, was the right hand. Accuracy was emphasized over speed, and participants were allowed to correct their response before the next trial began.

Participants were tested in a single session comprising two practice and 10 experimental blocks of 80 trials. All participants took part in the study in the morning beginning at 8:00 or 9:00 a.m. The experiment took about 1.5 h, and the whole session, including the training blocks and electrode attachment, lasted about 4 h. Each trial block

lasted 6 min, including a 20 s break at the halfway point. Between blocks, participants were allowed to take as long a break as they wished. Subjects performed 200 trials of the 2-red, 200 of the 4-red, and 400 of the 2-red-2-green variety.

Psychophysiological recordings. The EEGs were recorded using Ag/AgCl electrodes embedded in an elastic cap (Electrocap International; Eaton, OH) and filled with Grass electrode gel (Astro-Grass Instrument Co.; Quincy, MA). Measurements were obtained at frontal, central, parietal, temporal and occipital electrode sites (F3, Fz, F4, C3, C4, P3, P4, T5, T6, O1 and O2). Scalp derivations employed a left-mastoid reference during acquisition. Bipolar recordings of horizontal eye movements (horizontal electro-oculograms) were obtained with electrodes placed approximately 2 cm lateral to the outer canthus of each eye. Bipolar recordings of the vertical electro-oculograms were obtained with electrodes positioned above the right eyebrow and below the lower orbital rim to detect blinks and vertical eye movements.

The EEG and electro-oculograms were amplified and filtered by a Grass model 12 amplifier with a band pass of 0.01–30 Hz. To reduce artifacts due to alpha waves (8-12 Hz) and tremor (4-8 Hz), the EEG data were low-pass filtered off-line using a 5 Hz cut-off. Analogue-to-digital conversion was performed at a rate of 500 Hz via a PC-compatible computer. Acquisition was carried out with Neuroscan software; preprocessing and waveform measurement with *EEG lab* (version 5.02). Horizontal and vertical electro-oculogram recordings were supplemented with infrared eye tracking for all elderly controls and the first 17 patients (Applied Science Laboratories Eye-Tracker, Model 504; Bedford, MA, USA).

Gaze control. Controlling the direction of the gaze was important in this experiment both to avoid contamination of lateralized event related potentials and to ensure that the relevant and irrelevant sides of the memory display were encoded in separate hemispheres. The problem with encoding is that, if participants moved their eyes after arrow onset and looked at say, the middle of the cued half of the display, then the CDA would not reflect the difference between the relevant and irrelevant halves of the bilateral display. Once encoding is completed, eye movements are of less concern because CDA still reflects lateralized representations within the original, recipient hemispheres (Eimer & Kiss, 2010).

The problem with contamination is that the back of the eyeballs has a negative charge. Consequently, if participants shift their gaze toward the cued half of the display, this negativity would propagate to contralateral scalp sites and would mimic the CDA. Although volume-conducted ocular potentials are extremely small at the back of the head (Mangun & Hillyard, 1991), they would compromise our ability to infer that negativity contralateral to the cued half of the display reflects working memory.

To minimize gaze shifts, two training blocks of 40 trials each were conducted prior to the main experiment. In these blocks, participants were given verbal feedback whenever loss of fixation ($>30 \mu\text{V}$, $\sim 2^\circ$) occurred during the arrow, memory array or retention interval. The data from subjects who were unable to adequately control their gaze in the main experimental blocks (fixation loss on $>70\%$ of trials) were rejected. For the other subjects, trials that were contaminated by horizontal gaze shifts ($>20\text{--}45 \mu\text{V}$) during the arrow cue or memory array were excluded from analysis. Supplementary

analyses using a more conservative approach (strict 20 μV criterion during cue, memory array, and retention interval) yielded similar results.

To test the effectiveness of these training and data cleansing procedures, the horizontal electro-oculogram data were signal averaged separately for left- and right-pointing cues. Mean amplitudes during the interval used for CDA measurements averaged well below 3 μV for all control subjects ($M = 0.19 \mu\text{V}$, $SD = 0.48$ for attend left, and $M = -0.34 \mu\text{V}$, $SD = 0.64$ for attend right). The corresponding values for 20 of the patients were also well below 3 μV ($M = 0.37 \mu\text{V}$, $SD = 0.65$ for attend left, and $M = -0.82 \mu\text{V}$, $SD = 0.58$ for attend right). One patient had higher but acceptable values (3.77 μV for attend left and -4.70 μV for attend right). His data were retained in order to keep as many participants and trials as possible but the statistical outcome was the same with or without this patient.

Data analysis. The final sample comprised 21 patients and 28 neurologically normal participants, however data from seven additional subjects were excluded from the analyses. Two patients and one control subject were rejected because they made horizontal eye movements on more than 70% of trials. Data were rejected from two patients and one control subject because their task performance was at chance level (~50%). Finally, one control subject was eliminated due to problems with the EEG recording equipment.

Behavioral data analysis. The primary behavioral measure was the K score (see Appendix A), which is 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. Results using K scores based on the formula suggested by Cowan (2001) are reported, but the pattern of results regarding group differences was similar using either percentage of correct responses or K scores based on Pashler's (1988) formula.

When the number of relevant items is varied across a range of values (e.g. 1-7), healthy young adults exhibit an asymptotic value for K at about four items (Cowan, 2001). On the assumption that remembering the orientations of four simultaneously presented rectangles would be slightly beyond the ability of the majority of older adults, I used the K score in the 4-red condition to estimate working memory capacity for each of the participants.

Psychophysiological data analysis. Trials with both correct and incorrect responses were included (Vogel et al., 2005b) but analyses including only correct responses yielded generally similar results. Given that CDA amplitudes reflect how many items are held in working memory irrespective of their task relevance, the amplitudes from the incorrect trials should also be sensitive to the number of items kept in memory. It is important to retain incorrect trials as participants may err because they hold irrelevant items in their working memory rather than relevant ones.

The CDA at 600-1200 ms following memory array onset was measured at posterior parietal (P3, P4), posterior temporal (T5, T6) and occipital (O1, O2) electrode sites relative to a 700 ms pre-memory array baseline. The 600-1200 ms time window

following onset of the memory array was selected *a priori* to assess the portion of the retention interval that is most specific to visual working memory. As noted above, this window was intended to avoid overlap with encoding, iconic memory and target onset transients, as well as retrieval processes during perception of the test array. Waveforms recorded at scalp sites on the same side as the attended array are subtracted from analogous waveforms on the opposite side to calculate CDAs (Vogel & Machizawa, 2004).

Behavioral and psychophysiological data were analyzed using repeated measures analyses of variance, with group (Patient, Control) as a between-subject factor and trial type as the within-subject factor (2-red, 2-red-2-green, 4-red) along with the pair-wise comparisons among the three trial types. Additional analyses were performed in which participants were categorized dichotomously according to their estimated memory capacity (high and low *K* scores, relative to an absolute cut-off). This planned analysis was motivated by the finding of Vogel and colleagues (2005*a*, discussed above) that healthy young adults with low but not high capacity exhibit impaired filtration of irrelevant information. An absolute cut-off was employed rather than a median split to allow comparison of patients and controls with similar mnemonic abilities.

Along with the repeated measures ANOVAs and the pair-wise comparisons, intercorrelations among the main behavioral and psychophysiological measures are reported. All *P*-values vulnerable to sphericity violations were adjusted in accordance with the Greenhouse–Geisser epsilon value. An alpha level of 0.05 was adopted as the critical value, but marginally significant effects are reported when they are judged likely to be of interest to the reader.

Results

Behavioral data. In the 2×3 factorial analysis of K scores there were significant main effects for both group [Patient, Control; $F(1,47) = 8.1, p = 0.007$] and trial type [2-red, 2-red-2-green, 4-red; $F(2,94) = 7.0, p = 0.01$], but the interaction was not significant [$F(2,94) = 0.6, p = 0.464$]. Planned comparisons tested group differences between the theoretically critical 2-red-2-green and 2-red trials. Consistent with the assumption that patients with Parkinson's disease are more vulnerable to distraction, the interaction of group and trial type (2-red, 2-red-2-green) was significant [$F(1,47) = 7.7, p = 0.008$]. As shown in Figure 3, K scores in the 2-red-2-green condition were in fact lower than those in the 2-red condition for controls as well as patients ($F_s > 30.5, p_s < 0.001$), indicating that both groups had some difficulty ignoring distracters. K scores for the 2-red-2 green condition were also lower than those for the 4-red condition for both controls and patients [$F(1,27) = 6.1, p = 0.02$ for controls, and $F(1,20) = 4.4, p = 0.049$ for patients], whereas the difference between 2-red and 4-red conditions failed to be significant for either group ($F_s < 1.8, p_s > 0.201$).

In the analyses that incorporated a breakdown by memory capacity, patients and controls were assigned to high and low subgroups based on an absolute cut-off ($K = 1.92$ items). The absolute cut-off was determined by looking for the natural discontinuity (Figure 4) that was closest to the cut-off found to be meaningful by Vogel and colleagues (2005a) in their study of healthy young adults. The proportion of patients and controls in the high-capacity category was 33% and 43%, respectively.

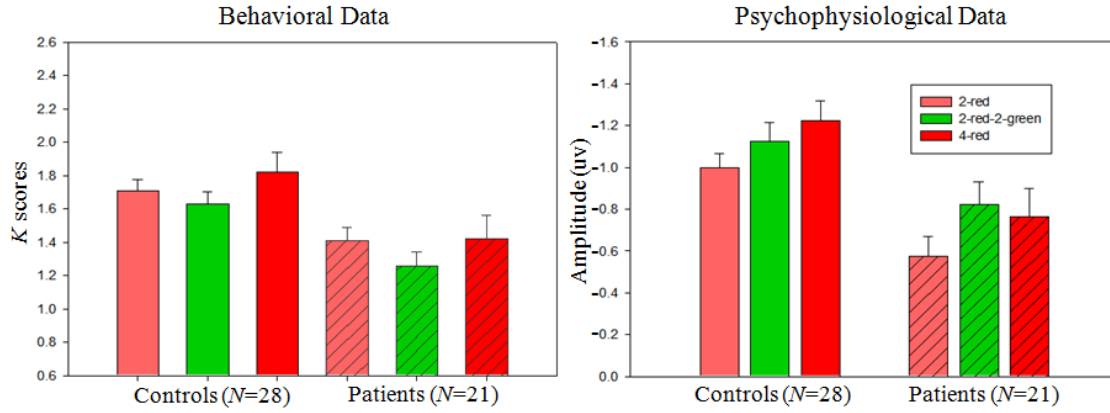


Figure 2. Left panel: Mean K scores of control subjects and Parkinson's patients ($N=28$ and 21 , respectively) as a function of trial type: $K = N * (H - FA) / (1 - FA)$, where N is the relevant set size, H is the hit rate and FA is the false alarm rate. Right panel: Mean amplitudes of CDA (Contralateral Delay Activity) at 600-1200 ms after memory array onset as a function of trial type for controls and patients. Error bars represent standard errors of the mean.

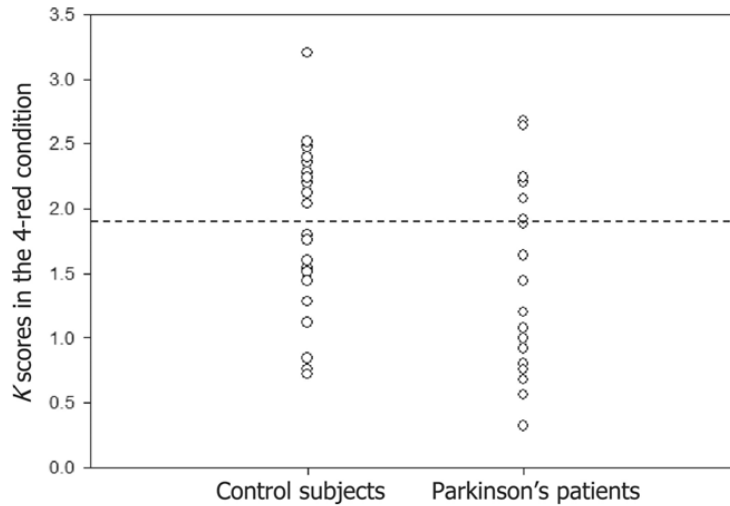


Figure 3. K scores (number of relevant items held in and retrieved from working memory) in the 4-red condition for control subjects and patients with Parkinson's disease, respectively.

In the 2×3 analysis (Group, Trial type) of patients and controls with high capacity, there was a significant effect for trial type [$F(2,34) = 55.8$, $p < 0.001$; Figure 5, upper left panel] but not for Group [$F(1, 17) = 0.07$, $p = 0.403$]. Pair-wise comparisons revealed that K scores for both controls and patients were lower on 2-red and 2-red-2-green trials than on 4-red trials ($F_s > 12.1$, $p_s < 0.013$). The critical comparisons between the 2-red-2-green and the 2-red trials also showed reliable differences for these subgroups

of patients and controls [$F(1,11) = 5.9, p = 0.034$ for controls and $F(1,6) = 37.6, p = 0.001$ for patients]. Although the effect of distracters (2-red-2-green < 2-red; Figure 5) was numerically small, both controls and patients with high capacity seemed to experience some difficulty in filtering out irrelevant information. However, the corresponding group by trial-type interaction did not achieve significance, as it had for the full sample of 49 participants (noted above).

In the 2×3 analysis of low-capacity participants, there were significant main effects of trial type [$F(2, 56) = 14.1, p < 0.001$] and group [$F(1,28) = 12.3, p = 0.002$; Figure 5, upper right panel]. Pair-wise comparisons revealed that K scores for the 2-red-2-green condition were lower than those for the 2-red condition ($F_s > 30.3, p_s < 0.001$). The theoretically critical interaction between group and 2-red versus 2-red-2-green trials was significant [$F(1,28) = 4.8, p = 0.037$]. This indicates that the disruptive effect of distracters in the 2-red-2-green condition was worse in patients.

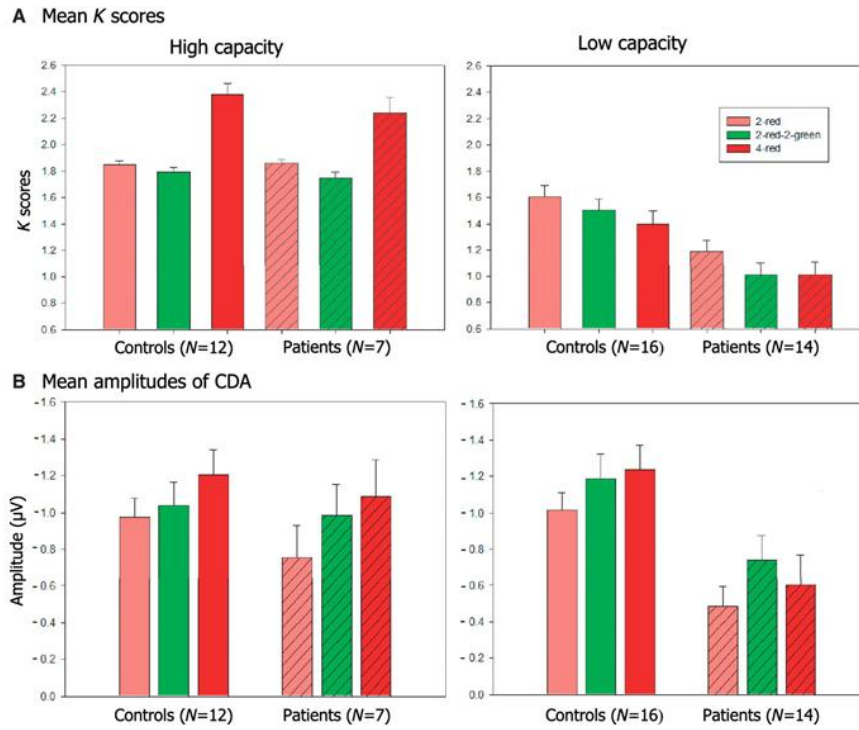


Figure 4. (A) Mean K scores of high- and low-capacity controls and patients as a function of trial type: $K = N \cdot (H - FA)$, where N is the relevant set size, H is the hit rate and FA is the false alarm rate.

A categorical breakdown of participants by capacity was necessary to allow performance data to be directly compared to group-averaged CDA waveforms. However, the underlying relationship between capacity and impaired filtering was apparently not dichotomous. In the scatter plots shown in Figure 6, the interfering effect of distracters is portrayed on the Y -axes as ‘unnecessary storage’, defined as the difference in K scores between 2-red and 2-red-2-green conditions. For the patients ($n = 21$) this quantity was negatively correlated with memory capacity as estimated by K scores in the 4-red condition (Pearson correlation coefficient, $r = -0.50$, $p = 0.023$; Table 2). This association supports Vogel and colleagues’ (2005a) conclusion that apparent reductions in capacity might actually be due to usurpation of available space by irrelevant information. Our neurologically normal control subjects exhibited a similar relationship ($r = -0.35$, $p = 0.07$, $n = 28$; Table 2).

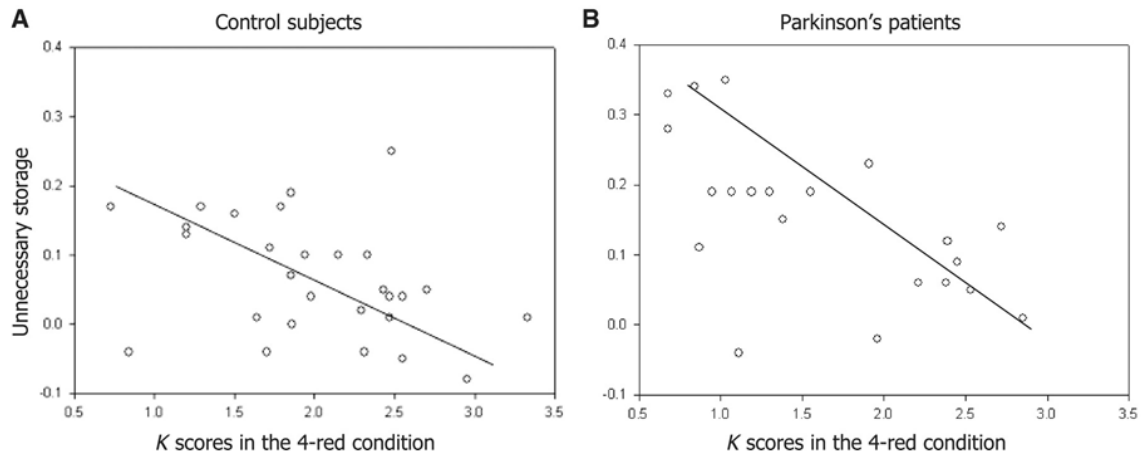


Figure 5. Correlation between estimated capacity of visual working memory (K score in the 4-red condition) and unnecessary storage (K score difference: 2-red minus 2-red-2-green) for control subjects (A) and patients with Parkinson's disease (B).

In addition to problems with filtering out distracters, patients with Parkinson's disease might also have less storage space to start with. This possibility is supported by the finding that patients' *K* scores were lower than those of controls for all trial types, even those without explicit distracters. In the analysis of all 49 participants, $F_s(1,47) > 8.9$, $p < 0.004$ for 2-red and 2-red-2-green; $F(1,47) = 4.6$, $p = 0.037$ for 4-red; Figure 3, left panel. In the separate analyses of participants with high and low capacity, there was a main effect of group (patient versus control) for the low-capacity subgroups, as noted earlier ($p = 0.002$), which was true for all three trial types [$F_s(1,28) > 7.4$, $p < 0.011$].

Psychophysiological data. The pattern of results for retention-interval CDAs supported inferences drawn from behavioral data (Figure 3 right panel and Figure 7). Although some theoretically critical effects failed to reach significance, these electrophysiological data provide converging evidence concerning group differences and help determine whether behavioral effects are due to maintenance or retrieval processes. In the 2×3 overall analysis there were significant main effects of Trial type [$F(2, 94) = 9.7$, $p <$

0.001] and Group [$F(1, 47) = 9.6, p = 0.003$], but no interaction [$F(2,94) = 1.3, p = 0.287$].

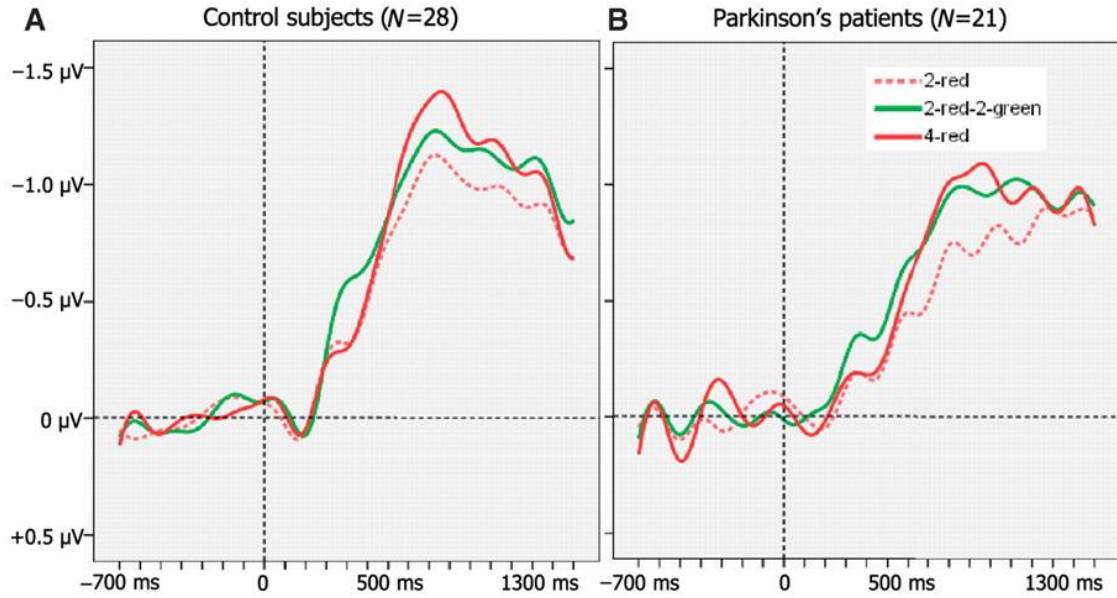


Figure 6. Grand averaged CDA waveforms time-locked to the onset of the memory array averaged across the posterior parietal, posterior temporal and occipital electrode sites for controls (A) and patients with Parkinson's disease (B) as a function of trial type.

Pair-wise comparisons showed that CDA was larger in the 4-red than 2-red condition for controls [$F(1, 27) = 14.7, p = 0.001$; Figs 2 and 6] implying that these neurologically normal individuals were able to hold more items in memory when they were presented with a larger array size. Patients had smaller CDAs than controls for each of the three types of trials [$F(1,47) > 4.5, ps < 0.039$]. Amplitudes in the 2-red-2-green condition were significantly higher than in the 2-red condition for both healthy participants and patients with Parkinson's disease [$F(1, 27) = 6.2, p = 0.019$ for controls; $F(1, 20) = 10.1, p = 0.005$ for patients], implying that both groups experienced some difficulty in ignoring the green bars. Although the averaged waveforms shown in Figures 3 and 7 would seem to suggest that distracter effects were more severe in the patient

group, this was not reflected in a reliable interaction of group by trial type [2-red, 2-red-2-green; $F(1, 47) = 1.9, p = 0.177$].

In the analysis of high-capacity participants there was a significant main effect of trial type [$F(2, 34) = 5.5, p = 0.013$] but not of group [$F(1, 17) = 0.5, p = 0.491$]. For control subjects, pair-wise comparisons showed that amplitudes in the 2-red-2-green condition were lower than in the 4-red condition [$F(1, 11) = 8.1, p = 0.016$] but comparable to the 2-red condition, suggesting good exclusion of distracters. As would be expected for an index of working memory, the size of the CDA was greater in the 4-red than 2-red condition [$F(1, 11) = 8.9, p = 0.013$]. For the patients with high capacity, CDA waveforms for the 2-red-2-green condition appeared to be more similar to the 4-red condition than to the 2-red condition, suggesting poor filtration of irrelevant information. However, neither this difference nor its interaction with group approached significance.

For the low-capacity subgroups, there were significant main effects of trial type [$F(2, 56) = 5.8, p = 0.008$] and group [$F(1, 28) = 10.1, p = 0.004$], but the interaction was not significant [$F(2, 56) = 1, p = 0.365$]. Pair-wise comparisons showed that for both subgroups, CDA amplitudes in the 2-red-2-green condition were significantly higher than in the 2 red-condition [$F(1, 15) = 5.9, p = 0.028$ for controls; $F(1, 13) = 12.6, p = 0.004$ for patients]. The critical interaction between group and 2-red versus 2-red-2-green was not significant [$F(1, 28) = 0.7, p = 0.418$]. Pair-wise comparisons showed that the pattern of larger amplitudes in controls than patients was reliable across the three trial types [$F(1, 28) > 5.4, ps < 0.027$], consistent with a difference in overall memory capacity. The CDA amplitudes were larger in the 4-red than in the 2-red condition for controls [$F(1, 15) = 6.5, p = 0.022$], but not for patients [$F(1, 13) = 0.1, p = 0.336$].

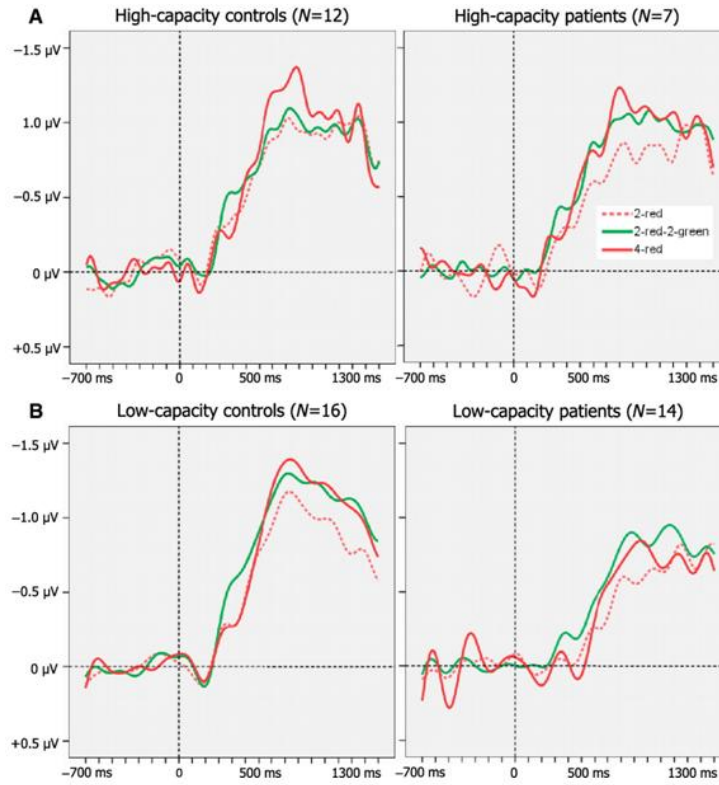


Figure 7. Grand averaged CDA waveforms as a function of trial type for high-capacity controls and patients (A, upper panel) and low-capacity controls and patients (B, lower panel).

Relation to demographic variables. Controls and patients with Parkinson's disease did not differ with regard to demographic variables such as age, gender or years of education [$F_s(1, 47) < 0.6$, $p_s > 0.43$ for age and education, $\chi^2(1) = 1.7$, $p = 0.187$ for gender; Table 1]. Regarding the relationship between demographic and memory variables, both controls and patients showed a significant negative correlation between age and K scores for the 2-red and 4-red conditions (Pearson correlation coefficients, $r_s > -0.38$, $p_s < 0.045$ for 2-red and $r_s > -0.41$, $p_s < 0.032$ for 4-red; Table 2).

Congruently, CDA amplitudes in the 4-red condition decreased with increasing age for patients ($r = -0.47$, $p = 0.032$). The unnecessary storage of distracters, as indexed by the difference in K scores between the 2-red and 2-red-2-green conditions, increased as a function of disease severity in the patient group, which was measured by the Hoehn

and Yahr scale (1967; $r = 0.46$, $p = 0.036$). Although age was highly correlated with the disease severity ($r = 0.58$, $p = 0.006$), only the stage of disease was a significant predictor of unnecessary storage [$t(46) = 3.6$, $p = 0.001$], whereas both age and stage of disease were significant predictors of memory capacity, as indexed by K scores in the 4-red condition [$t(46) = -4.1$, $p < 0.001$ for age and $t(46) = -3.3$, $p = 0.002$ for stage of disease].

Discussion

In this study, I examined whether the poor performance of patients with Parkinson's disease in working memory span tasks is due to a reduced storage capacity per se, inability to filter out distracters or both. Participants were asked to remember the orientations of red rectangles on the cued side of a display while ignoring all green rectangles, and then to judge whether any relevant items changed. Behavioral and psychophysiological measures provided converging evidence that patients with Parkinson's disease had both impaired attentional filtering ability and reduced storage capacity.

Impaired attentional filtering. Both controls and patients had some difficulty ignoring distracters. They showed reduced K scores and enhanced CDA amplitudes when distracters were present. The interfering effect of distracters, however, was greater for the patient group as evidenced by a larger decline of K scores in the presence of distracters. This difference was also supported by patterns in the surface electrophysiological data, although the greater increase in patients' CDA amplitudes failed to reach statistical significance due in part to tremor-induced noise in the EEG recordings.

It should be kept in mind that the behavioral and psychophysiological measures are complementary: CDA amplitudes reflect how many items within the cued display are being stored in memory irrespective of their task-relevance, whereas *K* scores provide an index of the number of items stored in and then retrieved from working memory that were in fact task-relevant. In this regard, patients' enhanced CDAs and reduced *K* scores in the 2-red-2-green condition imply that they allocated some of their limited memory space to irrelevant information.

Considering subgroups separately, even the high-capacity controls experienced some difficulty in ignoring distracters. They showed a small but reliable fall in *K* scores when distracters were present. However, it is possible that the problem these individuals had with filtering might have occurred during retrieval and comparison with the test array, because their average CDA amplitudes for trials with two relevant items were the same regardless of whether distracters were or were not present. Hence, older adults who are neurologically normal and have good memories seem to be effective at blocking out distracters, at least during the encoding and maintenance phases. By contrast, control participants with low working memory capacity had reduced *K* scores and enhanced CDA amplitudes when distracters were present, a pattern indicating impaired filtration during encoding and maintenance.

For participants whose basal ganglia had been impaired by Parkinson's disease, the situation was different. Consider first the subgroup of patients identified as having a working memory of ample size. Their behavioral performance was as good as that of healthy participants who were mnemonically well endowed. However, the data for these patients indicated that they were probably impaired at keeping distracters from memory

since these participants showed larger K scores and increased CDAs in the 2-red-2-green condition. For low-capacity patients, both behavioral and electrophysiological indices of unnecessary storage were highly significant.

Why should basal ganglia disease lead to an impaired ability to exclude irrelevant information from working memory? A plausible answer comes from the functional MRI study by McNab and Klingberg (2008) that was described earlier. Their study showed that subjects in whom pallidal activity greatly increased following the ‘ignore’ command were better able to filter out the irrelevant information. Similarly, the present data from patients with Parkinson’s disease showed that disease severity was a significant predictor of the unnecessary storage, which in turn exhibited a strong negative correlation with memory capacity. Regarding the present findings, it seems plausible that the loss of dopaminergic input to the basal ganglia in patients with Parkinson’s disease leads to a diminished ability of the globus pallidus to regulate which items are loaded into working memory (O’Reilly and Frank, 2006).

It is worth mentioning that the current data are less consistent with the model suggested by Cohen and Frank (2009; see also Wiecki and Frank, 2010). According to their model, patients’ reduced striatal dopamine level would result in hypoactivity in the striatonigral direct but hyperactivity in the striatopallidal indirect pathways, which would in turn lead to increased threshold for gating information into working memory so that both relevant and irrelevant information would be blocked for updating into working memory. However, the current result of patients’ impaired filtering suggests that patients may not be able to block distracters, at least when the distracters are presented simultaneously with to-be-remembered items.

An alternative interpretation based on the common Parkinson's disease symptom of bradyphrenia should be considered as well. Parkinsonian patients often demonstrate slowed thinking and slow responses to questions, but get the answers right if enough time is provided. In the present study, the memory array was presented only briefly (500 ms) in order to minimize eye movements and discourage strategic grouping of individual rectangles into meaningful units (Luck and Vogel, 1997). It is possible that patients with Parkinson's disease are generally able to filter out distracters but that they do so at a much slower rate than neurologically normal, older adults.

Reduced storage capacity. In addition to problems with filtering, the data suggest that patients with Parkinson's disease have less space in working memory. Their *K* scores and CDA amplitudes were smaller than those of control subjects across trial types, including trials without distracters. However, those patients categorized as having ample storage space were as good at retaining relevant items as similarly categorized control subjects. Furthermore, although CDA amplitudes were reliably larger for control subjects on trials with four than with two targets, this was not the case for patients, particularly those in the low-capacity subgroup (Fig. 4, upper right and Fig. 7, lower right). Equivalence or even paradoxical reversal during 2-red and 4-red trials for low-capacity patients is congruent with previous findings in which parietal cortex activation was markedly reduced when neurologically normal subjects were presented with memory loads beyond their capacity, as if they were simply overwhelmed (Linden et al., 2003; Vogel and Machizawa, 2004; see also Experiment 2 of this dissertation).

A possible explanation of how basal ganglia disease might lead to reduced capacity comes from a study by Matsui and colleagues (2007) in which fractional anisotropy values of white matter were compared in patients with Parkinson's disease with and without impaired executive functions (e.g., Wisconsin Card Sorting Test scores). Abnormalities of left parietal white matter were observed in patients with impaired executive functions. On the assumption that the retention of information in visual working memory occurs within parietal cortex (Todd and Marois, 2004; Postle *et al.*, 2006), pathological changes of the parietal lobe in our patients with Parkinson's disease may have led to reduced storage capacity. Preliminary attempts to compare patients and controls in Experiment 2 with regard to fractional anisotropy failed to generate useful findings. As will be seen, though, volume-based morphometry of gray matter identified a number of useful differences.

Reduced parietal function might also be secondary to impairments in the basal ganglia. This view is supported by a study of Chang and co-workers (2007), in which brain activation during a high memory-load condition was compared with that of a low-load condition in healthy young adults performing a modified Sternberg Task. Participants were asked to remember five successive numbers. In the high-load condition, the stimuli consisted of five different digits (e.g. 5 2 9 1 4), whereas in the low-load condition the same number was successively presented (e.g. 3 3 3 3 3). Memory load-dependent activation was observed in the basal ganglia, prefrontal and posterior parietal cortices during encoding and maintenance phases.

What made this study special in comparison with other studies was that the authors used multiple regression approaches to determine which brain regions are

functionally connected with the basal ganglia activations under high- versus low-memory load. They found enhanced connectivity between the left anterior caudate and ventrolateral prefrontal and posterior parietal cortices under high memory load condition. Given that memory load was manipulated in the absence of any explicit distracters, this study suggests that basal ganglia control of visual working memory extends beyond blocking the entry of distracters (McNab and Klingberg, 2008).

Our conclusion that reduced storage capacity contributes to impaired performance in Parkinson's disease is asserted with some caution though, because of a limitation imposed by our use of bilateral displays. To successfully perform the task, participants needed to ignore the uncued side of the display. This would have imposed a filtering requirement even for those conditions in which no green rectangles were presented. Consequently, patients' lower K scores and CDA amplitudes for the 2-red and 4-red conditions might actually have been due to an impaired ability to filter the to-be-ignored half of the display rather than to any reduction in storage capacity *per se*. As an example, consider the fact that patients' CDA amplitudes were significantly increased when distracters were present. This indicates that patients with Parkinson's disease were in fact able to hold significantly more information than they did on 2-red trials, although some of that information was task-irrelevant.

Chapter III

Experiment 2 (MRI and Behavior)

Introduction

Experiment 1 identified possible origins of working memory deficits in Parkinson's disease by means of behavioral and EEG correlates of working memory. Both impaired filtering and reduced storage capacity were implicated. However, there were some limitations in Experiment 1. That study used a bilateral display to measure CDA, which, as noted above, required additional filtering by the participant even in conditions with no distracters. So it is possible that patients' lower K scores and CDA amplitudes could be due to impaired filtering rather than diminished storage capacity, *per se*. Another problem is that, although EEG methods excel with respect to temporal precision, they are poor in terms of spatial localization. Consequently, Experiment 1 could not identify the neural source of the mnemonic dysfunction within the patients' brains.

To overcome these limitations of Experiment 1, I investigated the fMRI correlates of working memory in Experiment 2. The second study also extended the earlier one by examining the role of specific subcortical structures (e.g., basal ganglia) and cortical structures in attentional filtering and storage capacity.

Using the visual-array comparison paradigm, patients with Parkinson's disease and age-matched control subjects were presented with a memory array that was preceded by an instructional precue. Similar to the McNab and Klingberg (2008) study discussed earlier, the precue indicated whether participants should ignore the green rectangles as distracters or remember them along with the red rectangles, which were always relevant.

After a delay period, a single probe stimulus was displayed. Participants judged whether the tilt of this particular rectangle was the same as it was in the memory display.

Methods

Participants. The final sample comprised 19 patients and 23 neurologically normal participants for the outside the scanner task. Data were rejected from one additional control subject because she showed evidence of a stroke in the frontal cortex. One of the 19 patient's data was excluded from the analysis for the fMRI analysis and the inside-the-scanner task because his key press responses failed to register. One additional patient's data were excluded from the fMRI data analysis because his head movements exceeded the exclusion criterion of 3 mm. Demographics are shown in Table 3.

All participants 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 participant 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. None of the subjects exhibited evidence of dementia as assessed by the Mini-Mental State Examination (MMSE; $M = 29$, $SD=1.3$, for patients and $M = 29.5$, $SD=1$, for controls; Folstein, Folstein, and McHugh, 1975). Depression was evaluated by means of Geriatric Depression Scale-long form (GDS; Sheikh and Yesavage, 1986). All controls and all but one patient scored under 10 on the 30-point scale (overall $M = 4.1$, $SD=3.2$, for patients and $M = 2.6$, $SD=2.2$, for controls). The highest-scoring patient was above 10 (specifically, 11), which is the criterion for depression.

Three patients, including the one who scored highest on the GDS scale 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. The same was true for the seven participants who were taking antidepressants.

Patients were free from other neurological disorder. Fifteen patients were receiving the dopamine precursor Levodopa as treatment. One patient was not taking 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 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 patient's neurologist was contacted to obtain approval for this brief withdrawal as well as to confirm the diagnosis. The severity of the disease was reassessed just before the start of the experiment using the Hoehn and Yahr scale (1967). Scores averaged 2 on the 5-point scale, with a range of 1 (mild unilateral tremor) to 3.5 (apparent balance problems). This indicates a mild to moderate stage in the progression of the disease (years of disease, $M = 6.7$ and $SD = 4.8$).

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. Subjects were paid \$25 per hour for their participation. Participant exclusion varied across measures and is described below.

Stimuli and Procedures. Stimulus arrays were presented within a $4 \times 7.3^\circ$ 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 $.65 \times 1.15^\circ$ of visual angle, with orientations selected randomly from a set of four possible values (vertical, horizontal, left-tilting 45° , and right-tilting 45°).

Prior to the task in the MRI scanner, participants performed a brief practice session prior to entering the scanner room in order to become familiar with the task. This practice session comprised 5 trials in the Low-Load condition with faster timing and then 4 trials of each of the three conditions with exactly the same timing as for the inside-the-scanner task. Another purely behavioral version of the task followed the MRI session, and will be referred to as the “outside-the-scanner task.” This procedure was designed to estimate the maximum number of colored rectangles that could be held in memory (described below).

During the fMRI session, visual stimuli were displayed in the scanner using an LCD projector, and responses were recorded using fiber-optic keypads. Each trial began with a 2 s get-ready signal (3 yellow crosses). Next there was a 1, 3 or 5 s long instructional cue, which was followed by a 1 s long memory array, consisting of either two red or two red and three green rectangles (see Figure 8). The duration of the cue was

the only jittered time segment within the trial. All fMRI analyses were time-locked either to the onset of the cue, or the onset of the encoding period.

The instructional cue indicated whether participants should ignore the green rectangles as distracters (“**X**”: Low Load+ Distracter) or remember them as part of target memory array (“**o**”: No Distraction Low Load, or “**O**”: No Distraction High Load conditions). Note that the cue indicated the color and number of items would need to be retained (**X** = 2 red rectangles, **o** = 2 red rectangles, **O** = 2 red and 3 green rectangles).

After a 7 s retention interval, subjects were presented with a single probe stimulus for 2 s. They were 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. Following a varying 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 participants were allowed to correct their response before the next trial began. The inside-the-scanner task was structured as twelve blocks of 12 trials, with each block lasting about 4.5 minutes.

All participants took part in the study in the morning beginning around 7:00 or 8:00 a.m. The inside-the-scanner task took about 1.5 hour. Between blocks, participants were allowed to take as long a break as they wished.

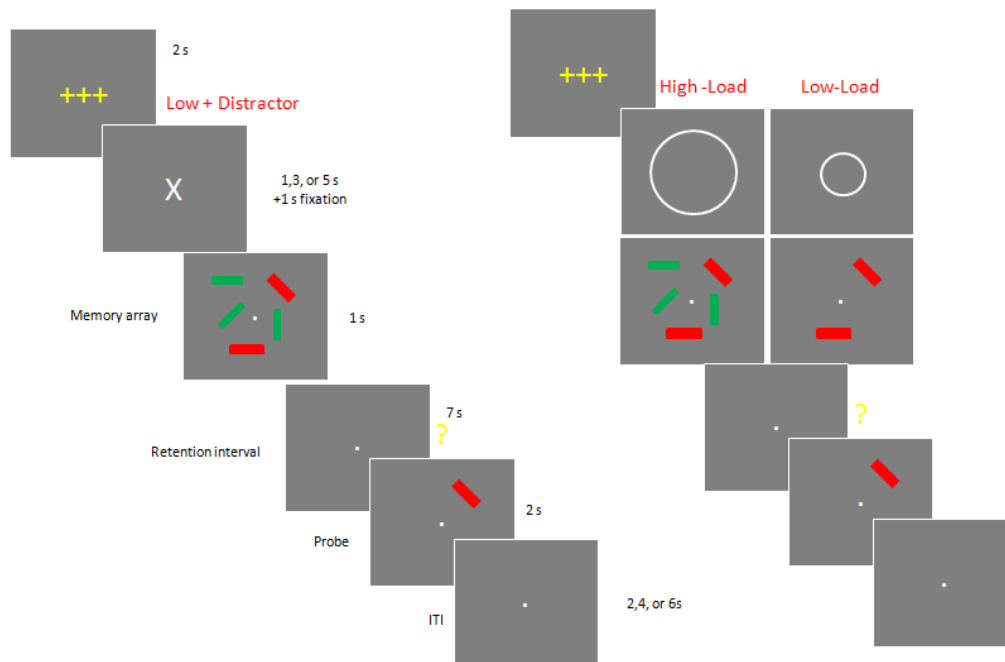


Figure 8. Example of a typical trials for each condition. In the Low+Distracter condition, participants were asked to ignore the green distracters whereas, in the High-Load condition, they were asked to remember both red and greens. In the Low-Load condition, only two to-be-remembered-red bars were presented.

Following the MRI session, participants performed the-outside-the-scanner-task to provide a more precise estimate of 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 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 retention interval, 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 participants were allowed to correct their response before the next trial began. This version of the task was structured as five blocks of 32 trials, and each block

lasted about 5 minutes. Experiment 2 was conducted in a single session, lasting about 3 hours in its entirety.

Behavioral analysis. The behavioral data were analyzed primarily as K scores, which are 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; see Appendix A).

The mean K score at set size 5 in the outside-the-scanner task was used as an estimate of the individual's working memory capacity. This measure is justified by previous findings showing that healthy young adults exhibit an asymptotic K value at about four items when the number of relevant items was varied across a range of values (e.g. 1-7; Luck and Vogel, 1997; Cowan, 2001). Note that the orientations of five simultaneously presented rectangles would be slightly beyond the ability of the majority of older adults. Set size 5 is used instead of 6 (the largest array in the outside-the-scanner task) in order to achieve greater comparability with the High Load (5-item) condition of the inside-the-scanner task. It is worth mentioning that there were abrupt drop in K scores for some of participants even if they showed reliable increase in K scores up to set size 5. Part of the reason could be that, for some participants, there simply was not enough time to perceptually encode all 6 rectangles. Once these individuals realized that they could not encode all position-orientation conjunctions, they may have given up for that trial.

Behavioral and imaging data were analyzed using repeated measures analyses of variance (ANOVA), with group (Patient, Control) as a between-subject factors and trial

type as the within-subject factor (Low Load, Low Load + Distracter, High Load), followed-up with pair-wise comparisons among the three trial types. Additional analyses were performed in which participants were categorized dichotomously according to their estimated memory capacity (high and low *K* scores, relative to an absolute cut-off). This planned analysis was motivated by Experiment 1 (Chapter 2) as well as by the finding of Vogel and colleagues (2005a, discussed above) that healthy young adults with low but not high capacity exhibit impaired filtration of irrelevant information.

All *p*-values vulnerable to sphericity violations were adjusted in accordance with the Greenhouse–Geisser epsilon value. An alpha level of .05 was adopted as the critical value, but marginally significant effects are reported when they are judged likely to be of interest to the reader.

Hypothesis 1. One of the goals of Experiment 2 was to test whether patients' reduced filtering ability was due to impaired function of the frontostriatal circuitry, especially the basal ganglia. To assess the filtering ability, increased activity within the intraparietal sulcus for Low Load + Distracter condition was compared to that of the Low Load trials during the 7-s retention interval. Based on the findings of Experiment 1 (Lee et al., 2010), it was expected that such wasteful storage would be greater in the patient group. Based on the findings by McNab and Klingberg (2008), it was further expected that unnecessary storage would be inversely correlated with the activity in the basal ganglia, within which the globus pallidus was of greatest relevance. Given the known impairment of basal ganglia function in PD, this relationship should be abnormal in the patient group.

Hypothesis 2. A second goal of the Experiment 2 was to identify the source of the observed reduction in patients' overall capacity in Experiment 1. Capacity was estimated outside the scanner using a similar task but larger range of to-be-remembered items. It must be acknowledged that no difference might be observed between people with Parkinson's disease and control participants in terms of behavioral correlates of working memory (Cooper et al., 1991; Dalrymple-Alford et al., 1994; Kensinger et al., 2003; Gilbert et al., 2005; Lewis et al., 2005). If no group differences are found, it might be inferred that the apparent reduction of capacity for patients in Experiment 1 was actually due to impaired attentional filtering of the to-be-ignored half of the bilateral display. If a genuine capacity difference between patients and controls is observed with the non-lateralized stimuli of Experiment 2, neuroimaging methods can determine whether this difference is mirrored in activation within parietal cortex. Reduced capacity is quantified both in terms of *K* scores and intraparietal sulcus activation differences between High- and Low-Load trials (See Table 4).

MRI acquisition and imaging data analysis. Images were acquired on the 3-Tesla Siemens scanner at the University of Missouri's Brain Imaging Center. The session began with a T1-weighted structural scan, upon which the functional images were ultimately co-registered. 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 = 9°, 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. For the twelve runs of functional images—one for each block of trials—the scans were T2*-weighted, echo-planar images with a TR = 2 s, TE = 30 ms, flip angle = 90°, 32 axial slices, voxel size = 3 x 3 x 3 mm, 4 mm slice thickness, FoV = 256 mm, with 64 x 64 grid.

Shape analysis.¹ The basal ganglia were segmented from T1-weighted structural image and their shapes were analyzed by means of FIRST (Patenaude et al., 2011), a model-based segmentation/registration tool within FSL (Smith et al., 2004; Woolrich et al., 2009). Structural differences were correlated with age, gender, time since diagnosis, and memory capacity (high, low). Subjects were classified as 'high' or 'low' memory capacity according to their *K* scores at the set size 5 condition in the outside-the-scanner task. These variables were also used as covariates in the analysis involving group differences, and thus the effects attributed to them were independent of the differences between the two groups (patients, controls).

Grey matter density analysis.¹ Voxel-based morphometry (VBM) was used to assess grey matter (GM) differences between the patients and controls (Ashburner and Friston, 2000). Voxel-wise changes in the grey matter density were assessed following the optimized VBM protocol implemented in FSL, which was developed by Good and colleagues (2001).

The first step was to create a study-specific GM template. For this purpose, brain images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The GM images were then non-linearly registered to the GM ICBM-152

¹ These analyses were carried out by my colleague, Professor Fernando Valle-Inclán.

template and averaged. The final GM template was 2x2x2 mm in standard MNI (Montreal Neurological Institute) space. The next step was to non-linearly register the participant's GM images to the newly created template. In order to obtain GM density at each voxel, it was necessary to compensate for the contraction/enlargement introduced by the non-linear component of the registration (see Good et al., 2001). The modulated images were then smoothed with a Gaussian kernels (sigma = 3 mm). Statistical tests were conducted using a randomize tool (in FSL) with 10,000 iterations for each contrast.

FMRI data analysis. Preprocessing and statistical analyses were carried out with *BrainVoyager QX* software (version 2.30; Brain Innovation, Maastricht, the Netherlands). Preprocessing steps included slice-time correction, motion correction for head movements smaller than 3 mm, a modest amount of spatial smoothing (e.g., 8-mm FWHM, full width at half maximum) and high-pass filtering (0.0175 Hz). Recorded head movements were used as covariates during statistical analyses. Functional runs from participants with movements larger than 3 mm were rejected without further analysis.

The comparisons of interest were carried out by means of planned contrasts. The analysis of activity at each point in the brain (*voxel*) was done in two stages: Contrast images were generated for each individual participant in the first level, and then these maps were compared across subjects in the second level analysis, treating subjects as a random factor. This is the random effects general linear model (rfx GLM) approach. Estimated parameter values were derived separately for the 6 combinations of two time periods of interest by three trial types: Cue (Low Load + Distracter), Cue (Low Load),

Cue (High Load), Retention (Low Load + Distracter), Retention (Low Load), and Retention (High Load).

To better distinguish the cue- and the encoding- and-retention-related time periods, an FIR (finite impulse-response) model was employed instead of a canonical hemodynamic response function. Encoding- and retention-related activity was modeled for 2 time points (4s) following 4 seconds after the onset of the memory display, whereas cue-related activity was modeled for 2 time points (4s) starting from 6 seconds after the onset of the get-ready signal.

I conducted regions of interest (ROI) analyses focusing on bilateral IPS (intraparietal sulcus), BG (basal ganglia, especially globus pallidus), MFG (middle frontal gyrus), and pre-SMA (supplementary motor area). The first three regions were selected as the regions of interest based on the findings reported by McNab and Klingberg (2008). Note that the cue-related activity in the globus pallidus was inversely correlated with the encoding-and-retention related IPS activity. The pre-SMA was selected as ROI based on the VBM analysis of the present study in which there was a meaningful relationship between grey matter density and *K* score measure of memory capacity. Subgroup analyses with high- and low-capacity controls and patients were also conducted on these ROIs. Because the IPS, MFG and GP regions of the right hemisphere showed similar but more reliable group differences than the analyses with left side ROIs, only analyses for the right hemisphere are reported. An uncorrected alpha level of .05 was adopted as the critical value for all ROIs.

RESULTS

Performance for inside-the-scanner task. In the 2×3 factorial analysis of K scores there were significant main effects for group [Patient, Control; $F(1,39) = 5.6, p = 0.023$] and trial type [Low Load, Low Load + Distracter, High Load; $F(2,78) = 18.5, p < 0.001$], but the interaction was not significant [$F(2,78) = 2.4, p = 0.121$; Figure 9, right panel]. Planned comparisons tested differences between the Low Load + Distracter and Low Load conditions. As shown in Figure 9, K scores in the Low Load + Distracter condition were less than those in the Low Load condition for both controls and patients [$F(1,22) = 4.3, p = 0.05$ for controls and $F(1,17) = 6.6, p = 0.02$ for patients], indicating that both groups had some difficulty ignoring distracters. In contradistinction to Experiment 1, however, wasteful storage was not more prevalent in participants suffering from PD. The interaction of the group by trial type (Low Load, Low Load + Distracter) failed to be significant [$F(1,39) = 1.6, p = 0.216$].

Interestingly, K scores for the High Load condition [$M = 1.2$ ($SD = 1.2$) for controls and $M = 0.5$ ($SD = 1.0$) for patients] were actually less than those for the Low Load condition [$M = 1.7$ ($SD = 0.4$) for controls and $M = 1.5$ ($SD = 0.4$) for patients] for both groups [$F(1,22) = 4.5, p = 0.046$ for controls and $F(1,17) = 24.7, p < 0.001$ for patients]. Contrast this surprising pattern with the analogous conditions for the outside-the-scanner task (left side of Figure 9). As would be expected, K scores in that task were higher on trials with set size 5 than 2. Performance in the High Load trials also tended to be diminished as compared to Low Load + Distracter trials [$M = 1.6$ ($SD = 0.4$) for controls and $M = 1.2$ ($SD = 0.7$) for patients; $F(1,22) = 3.3, p = 0.083$ for controls and

$F(1,17) = 12.4, p = 0.003$ for patients]. These unexpected differences between the two tasks might be related to length of the retention interval (2 vs. 7 s).

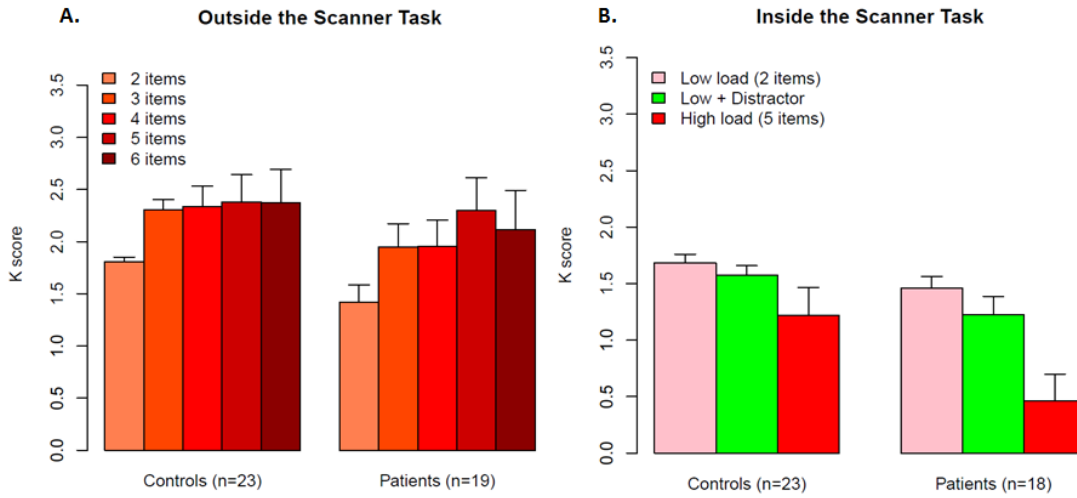


Figure 9. (A) Mean K scores of controls and patients as a function of trial type in the Outside the Scanner Task. (B) Mean K scores of controls and patients as a function of trial type in the Inside Scanner Task:

$K = N*(H - FA)$, where N is the relevant set size, H is the hit rate and FA is the false alarm rate.

In the analyses that incorporated a breakdown by memory capacity, high and low subgroups were defined based on performance in the outside-the-scanner task, using the median value of $K = 2.75$ as cutoff (see the study by Vogel et.(2005a) in which the median was also used as a cutoff criterion for the subgroup analysis). Performance in the set size 5 condition was employed to maximize comparability to the High Load trials of the inside-the-scanner task. Results were similar when slight variations were used, such as a cut-off value of $K = 3$ or performance assessment in the set size 6 condition.

In the 2×3 analysis (group, trial type) of patients and controls with high capacity, there were significant effects for trial type [$F(2,42) = 4.8, p = 0.033$; Figure 10, left panel] and an interaction of group by trial type [$F(2, 42) = 4.2, p = 0.045$], but there was no

main effect of group [$F(1, 21) = 3.4, p = 0.08$]. Pair-wise comparisons revealed that there were no differences in K scores between Low Load + Distracter and Low Load conditions (i.e., wasteful storage) for either group [$F(1,12) = 0.1, p = 0.757$ for controls and $F(1,9) = 0.6, p = 0.461$ for patients]. Interestingly, whereas there were no differences among three trial types for controls ($F_s < 0.1, p_s > 0.7$), patients' K scores on the High Load trials were lower than those on Low Load + Distracter and Low Load trials ($F_s > 4.6, p_s < 0.06$). This led to a significant interaction of group by trial type [(Low Load, High Load); $F(1,21) = 5.1, p = 0.035$].

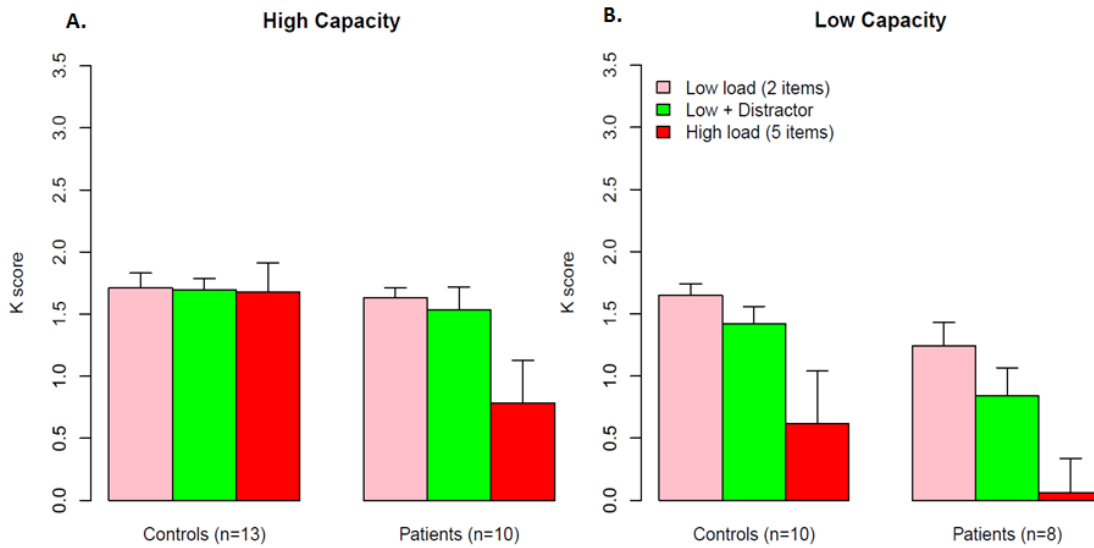


Figure 10. (A) Mean K scores of high capacity controls and patients as a function of trial type in the Inside the Scanner Task. (B) Mean K scores of low capacity controls and patients as a function of trial type in the Inside the Scanner Task: $K = N*(H - FA)$, where N is the relevant set size, H is the hit rate and FA is the false alarm rate.

In the 2×3 analysis of low-capacity participants, there was a significant main effect of trial type [$F(2, 32) = 18.4, p < 0.001$], but neither the main effect for group [$F(1,16) = 3.2, P = 0.093$] nor the group by trial type interaction [$F(1,32) = 0.1, p = 0.759$; Figure 10, right panel] achieved statistical significance. For both low-capacity groups, K scores on the High Load trials were lower than those on Low Load + Distracter

and Low Load trials ($F_s > 5.5$, $p_s < 0.043$ for controls and $F_s > 10.1$, $p_s < 0.015$ patients). Although somewhat surprising, a similar pattern was observed in Experiment 1.

For the individual trial types, low capacity patients' K scores on the Low Load and Low Load + Distracter conditions were significantly diminished compared to those of control subjects [$t(17) = 2.03$, $p = 0.059$ for Low Load, and $t(17) = 2.28$, $p = 0.037$ for Low Load + Distracter]. Pair-wise comparisons revealed that K scores for the Low Load + Distracter condition were lower than those for the Low Load condition for both groups [$F(1,9) = 6.8$, $p = 0.028$ for controls and $F(1,17) = 13.9$, $p = 0.007$ for patients], indicating that both groups had some difficulty ignoring distracters. However, the interaction between group and Low Load + Distracter versus Low Load trials failed to be significant [$F(1,16) = 1.6$, $p = 0.219$].

The interfering effect of distracters, quantified as the difference in K scores between Low Load and Low Load + Distracter conditions, was negatively correlated with memory capacity, as estimated by K scores in the 5 items condition for both controls (Pearson correlation coefficient, $r = -0.308$, $p = 0.077$, $n = 23$, one-tailed) and patients ($r = -0.436$, $p = 0.035$, $n = 18$, one-tailed). As in Experiment 1, unnecessary storage was positively correlated with disease severity ($r = 0.583$, $p = 0.006$, $n = 18$, one-tailed).

Outside-the-scanner task. In the 2×5 factorial analysis of K scores there was a significant main effect for trial type [2-6 item set size; $F(4,160) = 6.0$, $p = 0.003$], but no significant effect for group [$F(1,40) = 1.2$, $p = 0.29$] or interaction (Figure 10, left panel). Pair-wise comparisons revealed that there was a significant increase in K scores from set size 2 to 3 condition for both groups [$F(1,22) = 26.6$, $p < 0.001$ for controls and $F(1,18) =$

14.5, $p = 0.001$ for patients]. After set size 3, there were no differences in K scores among different set sizes for controls, whereas there was a significant increase from set size 4 to 5 for patients [$F(1,18) = 5.2, p=0.035$].

In the 2×5 analysis (group, trial type) of patients and controls with high capacity, there was a significant effect for trial type [$F(4,84) = 14.3, p < 0.001$; Figure 11, left panel], but no main effect for group or interaction. Pair-wise comparisons revealed that K scores linearly increased with increasing set size for both high capacity controls and patients [$F(1,12) = 11.3, p = 0.006$ for controls and $F(1,9) = 9.0, p = 0.015$ for patients] reaching an asymptote at 5 items. These results indicate that both high capacity controls and patients were able to hold more information when they were presented with more information.

In the 2×5 analysis of low-capacity participants, there was a significant main effect for group [$F(1,17) = 4.6, p = 0.046$] but no main effect for trial type or interaction of group by trial type. The group effect indicated that low-capacity patients' memory capacity was even lower than that of low-capacity controls. Pair-wise comparisons documented no significant differences among the 5 set sizes for either group. These mnemonically challenged participants were not able to retain more items when more to-be-remembered items were presented.

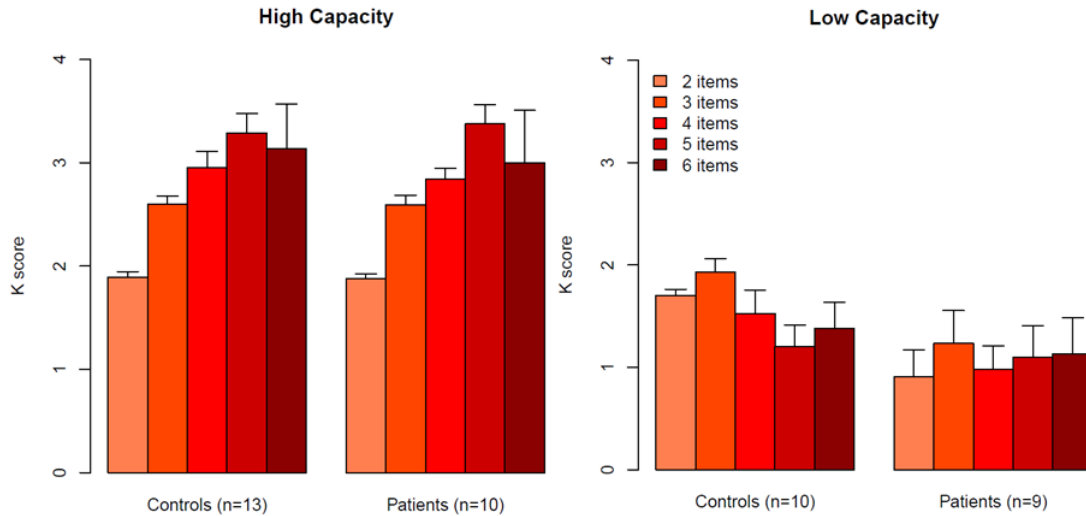


Figure 11. (A) Mean K scores of high capacity controls and patients as a function of trial type in the Outside the Scanner Task. (B) Mean K scores of low capacity controls and patients as a function of trial type in the Outside the Scanner Task: $K = N*(H - FA)$, where N is the relevant set size, H is the hit rate and FA is the false alarm rate.

Structural imaging data. Subcortical surface analysis documented age-related atrophy, after accounting for the possible effects of PD and gender, in the right caudate (Monte Carlo-based test, full sample, corrected for multiple comparisons, $p = 0.03$), right putamen ($p = 0.009$), left thalamus ($p = 0.02$) and right thalamus ($p = 0.02$). Memory capacity, as estimated in the outside-the-scanner task, correlated negatively with localized atrophy at the caudal surface of the left thalamus ($p = 0.0003$) and with more extensive atrophy in the left putamen ($p = 0.01$). When the difference between patients and controls were taken into account, only the atrophic zones in the left putamen correlated with memory capacity.

Cortical density analysis using VBM methods revealed that PD patients showed less GM density than controls over an area corresponding to the pre-SMA in both hemispheres: right pre-SMA (MNI coordinates: $X=2/12$; $Y=0/14$; $Z=48/66$, threshold at

$p < 0.0005$, uncorrected; Figure 12). Patients also showed a tendency toward reduced gray matter density within the right intra-parietal sulcus (MNI coordinates: $X=24/38$, $Y=-68/-78$, $Z=26/46$) and the superior frontal gyrus, bilaterally ($p < .005$, uncorrected).

Additional analyses showed that these effects were not due to differences in age or gender between the two groups.

For the control group, gray matter density in the subcortical and cortical areas described above exhibited no correlation with performance. For patients, however, the gray matter density within parietal cortex and pre-SMA was positively correlated with K scores, except when the task was particularly easy (set size 2; Table 5, Figures 13 and 14). This is consistent with the recently discovered role of pre-SMA in the maintenance of working memory or, more specifically, “a state of preparedness for selecting a motor response based on information held on-line” (Petit et al., 1998).

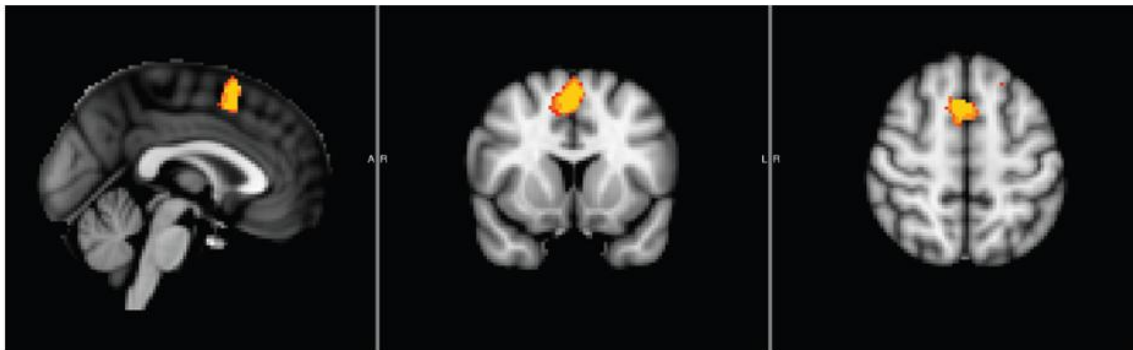


Figure 12. Pre-SMA: A region in which controls showed greater grey matter density than patients ($p < 0.0005$, uncorrected).

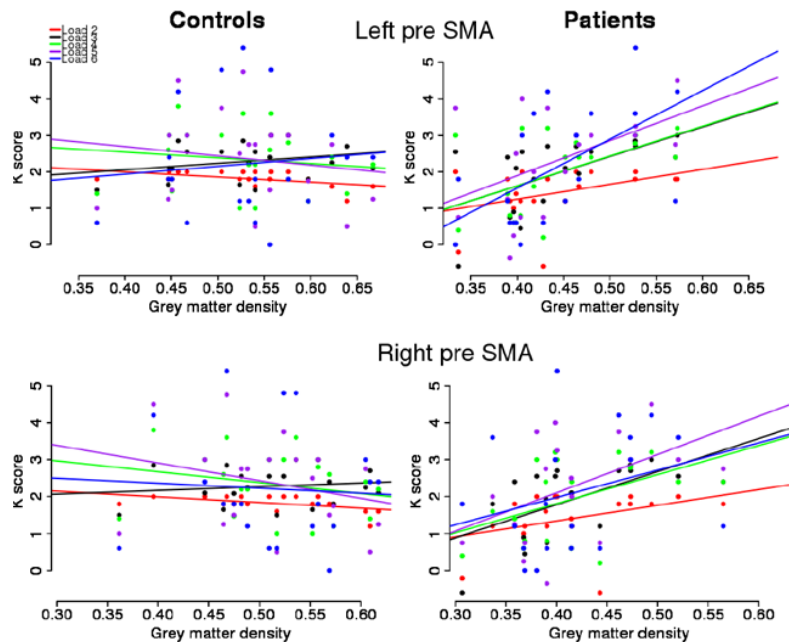


Figure 13. Scatter plot showing the relations between K scores and grey matter density in the left (upper panel) and right (lower panel) pre-SMA ($p < 0.0005$, uncorrected). The five curves represent set size variations from 2 to 6. The darkest line is set size 5.

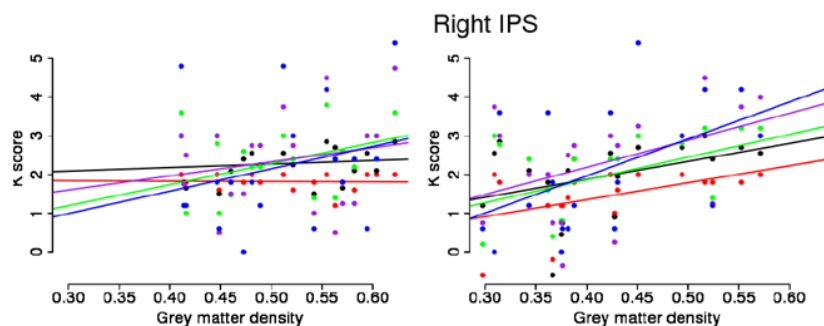


Figure 14. Scatter plot showing the relations between K scores and grey matter density in right IPS ($p < 0.0005$, uncorrected). The five curves represent set size variations from 2 to 6. The darkest line is set size 5.

Functional imaging data: ROI analyses

For the hypothesis-driven Region of Interest (ROI) analyses, seven brain areas were considered: IPS, MFG, GP (bilaterally), and pre-SMA. The center of MFG (41, -8, 31) was visually determined on the T1-weighted structural image according to the reported area by McNab and Klingberg (2008). The peak coordinates of IPS (36, -64, 38) were derived from the center of the cluster coordinates reported by McNab and Klingberg (2008) after the transformation of MNI coordinates to Talairach space (MNI coordinates: $x=24/59$, $y=-50/-77$, $z=36/51$) and boundaries of pre-SMA (MNI coordinates: $x=2/12$; $y=0/14$; $z=48/66$) were derived from the structural VBM analysis of the current study. For the peak coordinates of GP, the center of the entire segmented GP area was used based on the report by Suman et al. (2011). In that study, the entire GP area was automatically segmented by means of automatic segmentation software (AutoSeg) (Gouttard et al., 2007; Joshi et al., 2004). Each ROI was drawn with a 12 mm diameter sphere centered at the peak coordinates except for pre-SMA, in which the whole cluster extent was used based on the VBM analysis result.

This a priori, ROI approach justified the use of a relaxed threshold, $p < 0.05$, uncorrected.

The analysis results for the left IPS, MFG, and the pre-SMA are not reported because they failed to reveal meaningful group differences; only results for the right hemisphere are presented.

To detect cue-related activity, the 4-s time period following 6 s after onset of the get-ready signal was used for the planned comparisons. To detect encoding- and retention-related activity, the 4-s time period that followed 4 s after memory array onset was used.

Intra-parietal Sulcus fMRI analyses. I will first describe findings for the right intra-parietal sulcus (IPS: centered at 36, -64, 38; see Figure 15). For the ROI analysis of IPS, only encoding-and-retention related interval was considered for the analysis. The planned comparison of High- versus Low-Load conditions showed increased activity in the High-Load condition for controls [$t(22) = 3.82, p = .0009$]. This supports the assumed involvement of the IPS in the maintenance of working memory (Todd and Marois, 2004; Cowan et al., 2011) and implies that controls in my study held more items in memory when more were presented. For patients, there was no significant increase in IPS activity when more-to-be-remembered items were presented ($p = .92$). This result led to a significant group difference for the comparison of High- versus Low-Load [$t(38) = 2.73, p = 0.009$, an interaction of group and High/Low load]. This is consistent with evidence from Experiment 1 that neurologically normal individuals may be able to hold more items in memory than can those with Parkinson's disease. It is worth noting that, for patients, the IPS activity in the High-Load condition started increasing about 2s later as compared to other two conditions and correspondingly it reached a peak activity about 2 s later than other conditions. For that reason, a separate 4-s time period that followed 6 s after the memory array onset was additionally used for the contrast comparison of High- versus Low-Load conditions. Nevertheless, the increased IPS activity during this time window also failed to be significant [$t(16) = 0.81, p = 0.43$].

The contrast between Low Load + Distracter versus Low Load conditions revealed that there was increased activation in the former condition for controls [$t(22) = 5.42, p < .0001$], implying unnecessary encoding and retention of distracters whereas the extent of the unnecessary storage failed to be significant for patients [$t(16) = 1.55, p =$

0.14]. However, no group difference was observed for this unnecessary storage of the distracters [$t(38) = 1.15, p = 0.26$].

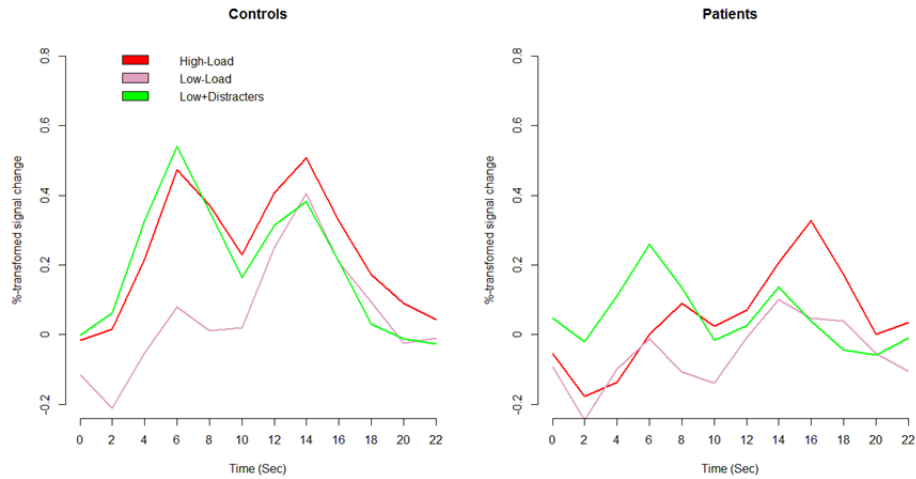


Figure 15. Percent-transformed signal change in the ROI region right IPS from a pretrial baseline for each memory load condition over 22 sec time period. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

In the analysis of high-capacity participants (Figure 16), there was enhanced right IPS activity with increasing memory load from the Low- to the High-Load condition for controls [$t(12) = 3.66, p = 0.003$] but not for patients [$t(8) = 0.17, p = 0.868$]. There was tendency for greater increase in IPS activity for controls than patients but this failed to be significant [$t(21) = 1.88, p = 0.07$]. The high capacity patients also showed delayed onset of IPS activity increase but the contrast comparison considering this delayed time window also failed to be significant [$t(8) = 0.64, p = 0.53$]. Surprisingly, there was significantly more IPS activity for high capacity controls [$t(12) = 8.27, p < 0.0001$] when distracters were present, whereas there was no such increase for high capacity patients [$t(8) = 0.72, p = 0.49$] although this group difference also failed to be significant [$t(21) = 1.24, p = 0.23$].

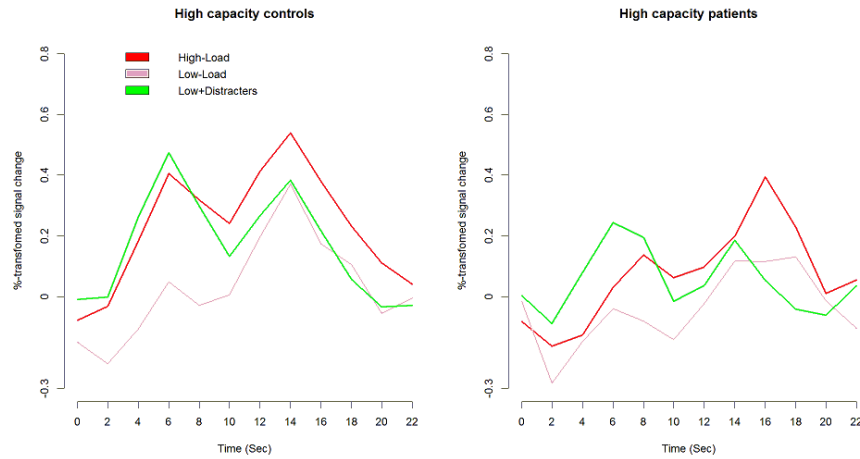


Figure 16. High capacity controls' and patients' percent-transformed signal change in the ROI region right IPS from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

In the subgroup analysis of low-capacity participants (Figure 17), there was increased activity with increasing memory load from 2 to 5 items for controls but this failed to be significant [$t(9) = 1.88, p = 0.09$]. For patients, there was no such increased IPS activity [$t(9) = -0.35, p = 0.74$]. The group difference failed to be significant as well [$t(16) = 1.59, p = 0.13$]. For both low-capacity controls and patients, the right IPS activity increased when distracters were present, indicating unnecessary storage [$t(9) = 2.27, p = 0.049$ for controls and $t(7) = 2.37, p = 0.049$ for patients]. There was no reliable difference between patients and controls in this regard [$t(16) = 0.50, p = 0.62$].

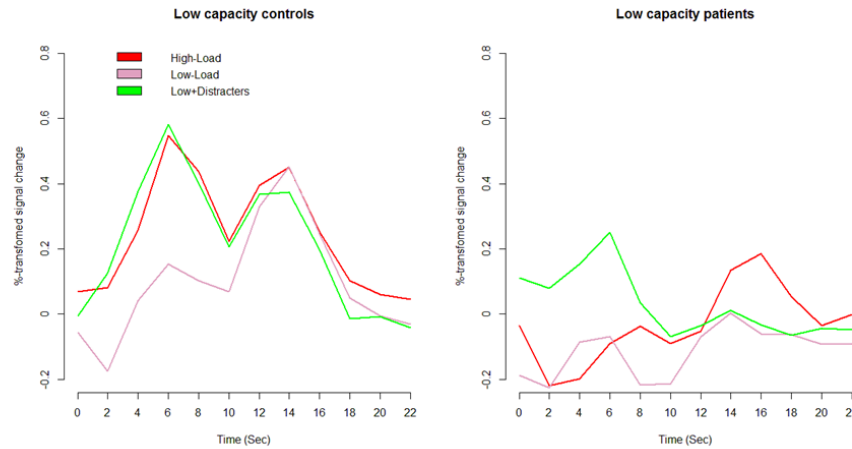


Figure 17. Low capacity controls' and patients' percent-transformed signal change in the ROI region right IPS from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

Middle frontal gyrus fMRI analyses. Turning now to the right MFG (Figures 18-21), this ROI was centered at Talairach coordinates 41, -8, 31. For the cue-related interval, anticipatory activity on Low Load + Distracter trials as compared to Low Load trials was greater for patients than controls [$t(38) = -2.24, p = 0.031$]. There was actually a directional reversal across groups. Controls had decreasing activity when they were instructed to ignore distracters [$t(22) = -2.88, p = 0.008$], whereas patients showed increased activity [$t(16) = 1.16, p = 0.26$], as compared to the post-cue intervals for the Low-Load trials. This is opposite to the group effect that had been predicted based on Parkinsonian deficits in fronto-striatal functioning.

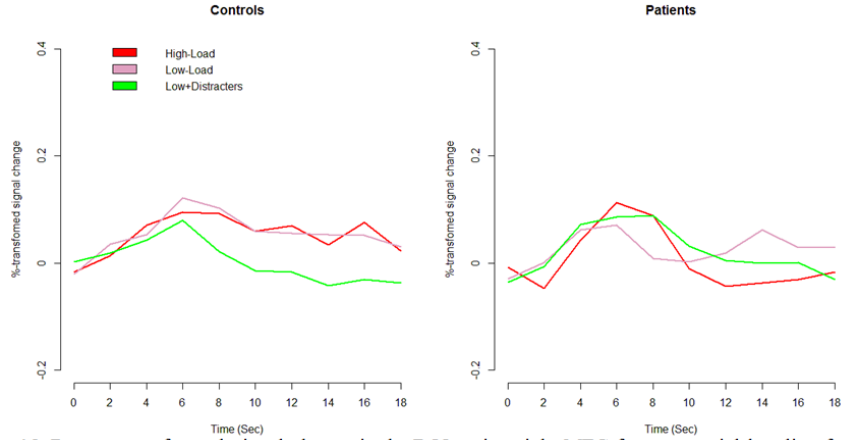


Figure 18. Percent-transformed signal change in the ROI region right MFG from a pretrial baseline for each memory load condition. The zero point depicts the onset of get-ready signal (2s) which was followed by a precue (1, 3, or 5 s).

During the encoding- and retention-related epoch (Figure 19), there was increased activity in the Low Load + Distracter condition compared to the Low Load condition for controls [$t(22) = 4.97, p < 0.0001$] but not for patients [$t(16) = 0.65, p = 0.53$] whereas there was no differences between the High-Load and Low-Load conditions for either group ($ts < 1.67, ps > 0.11$). There were no group differences in any of the contrast comparisons though ($ts < 1.32, ps > 0.15$).

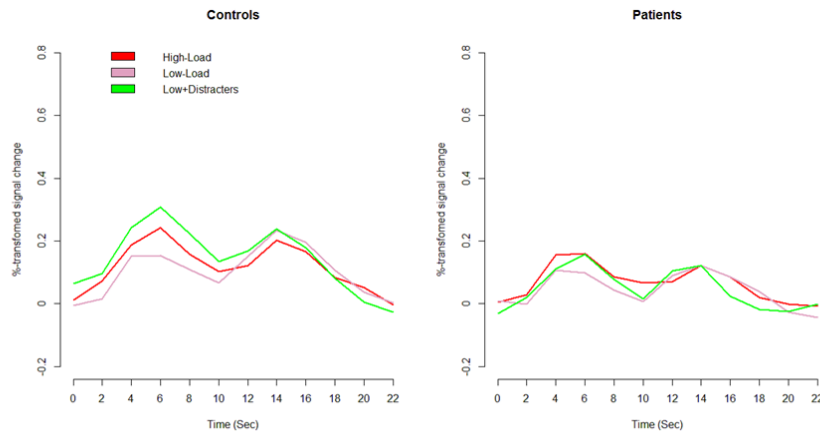


Figure 19. Percent-transformed signal change in the ROI region right MFG from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

In the cue-related analysis for the high-capacity participants (Figure 20), control subjects showed decreased anticipatory activity on distracter trials in right MFG [$t(12) = -2.1, p = 0.06$], whereas patients exhibited no such decrease [$t(8) = 0.59, p = 0.57$]. The group difference failed to be significant in this regard [$t(21) = -1.69, p = 0.1$].

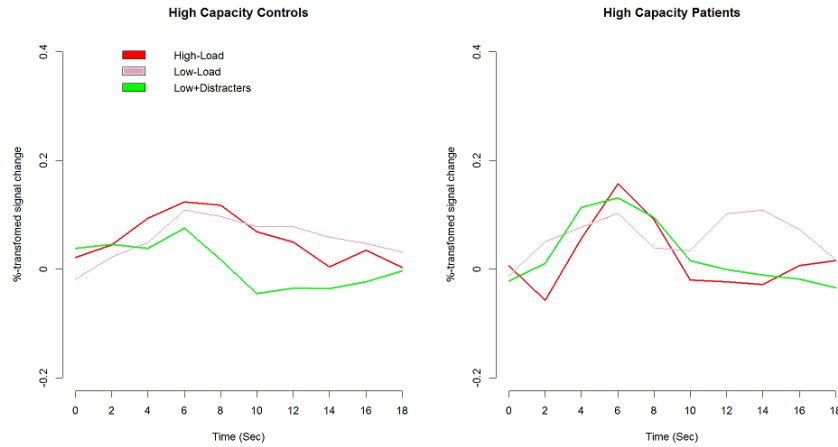


Figure 20. High capacity controls' and patients' percent-transformed signal change in the ROI region right MFG from a pretrial baseline for each memory load condition. The zero point depicts the onset of get-ready signal (2s) which was followed by a precue (1, 3, or 5 s).

Once the memory array was presented (Figure 21), high-capacity controls showed increased activity in the right MFG for both High Load and Low Load + Distracter conditions relative to the Low Load condition [High Load: $t(12) = 1.88, p = 0.08$; Low Load + Distracter: $t(12) = 3.99, p = 0.001$]. There were no differences among the three trial types for high capacity patients ($ts < 1.42, ps > 0.19$), although the pattern appeared roughly similar to that of controls. The group differences also failed to be significant for any of the contrast comparisons ($ts < 0.31, ps > 0.75$).

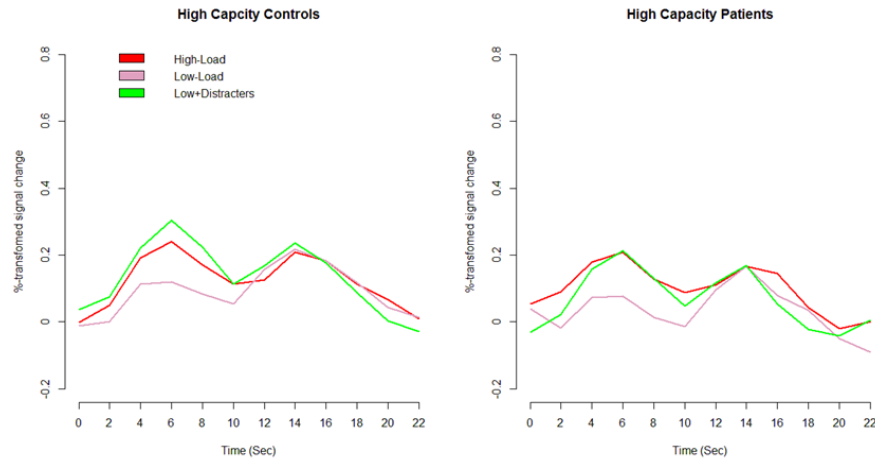


Figure 21. High capacity controls' and patients' percent-transformed signal change in the ROI region right MFG from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

In the subgroup analysis of low-capacity participants (Figures 22-23), there were significant group differences for both High-Load and Low Load + Distracter conditions relative to the Low-Load condition [High-Load: $t(16) = -2.03$, $p = 0.059$; Low Load + Distracter: $t(16) = -2.46$, $p = 0.025$] during the cue-related interval (Figure 22).

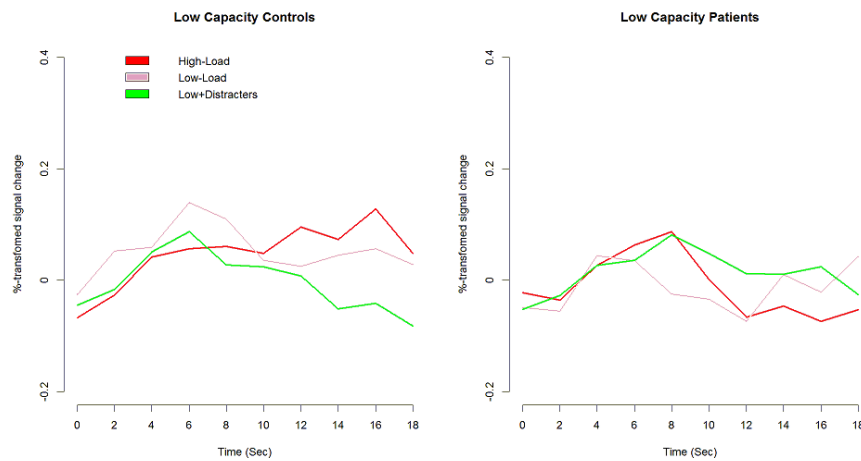


Figure 22. Low capacity controls' and patients' percent-transformed signal change in the ROI region right MFG from a pretrial baseline for each memory load condition. The zero point depicts the onset of get-ready signal (2s) which was followed by a precue (1, 3, or 5 s).

Once the memory array was present (Figure 23), low-capacity controls showed higher activity for the Low Load + Distracter condition than for the Low Load condition

[$t(9) = 2.39, p = 0.04$]. There were no comparable effects for patients in any of the contrasts ($ts < 1.09, ps > 0.3$).

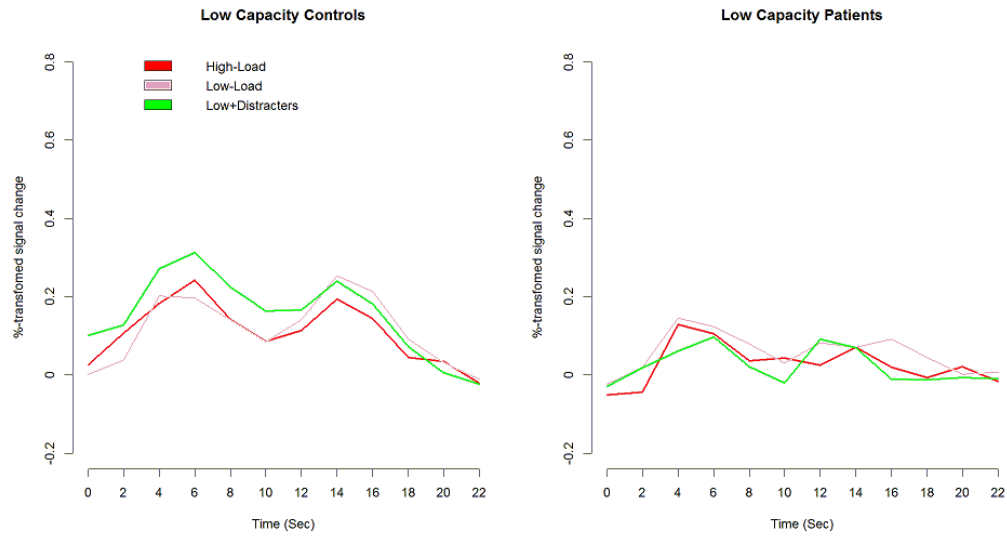


Figure 23. Low capacity controls' and patients' percent-transformed signal change in the ROI region right MFG from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

Globus pallidus fMRI analyses. The final ROIs to be considered were the brain regions most associated with Parkinson's disease, the basal ganglia. The right and left globus pallidus ROIs were centered at 20, -9, -1 and -20, -9, -1, respectively (following Suman et al., 2011).

There were no group differences for the planned comparison of the cue-related activity for High- versus Low-Load conditions [$t(22) = -0.46, p = .65$]. Anticipatory activity on Low Load + Distracter trials as compared to Low Load trials was greater for patients than controls showing a directional reversal across groups [$t(38) = -2.50, p = 0.017$ for right GP, and $t(38) = -1.83, p = 0.075$ for left GP]: Controls had decreasing activity when they were instructed to ignore distracters, whereas patients showed increased

activity, as compared to the post-cue intervals for either High- or Low-Load trials (Figure 24), which is opposite to the pattern predicted.

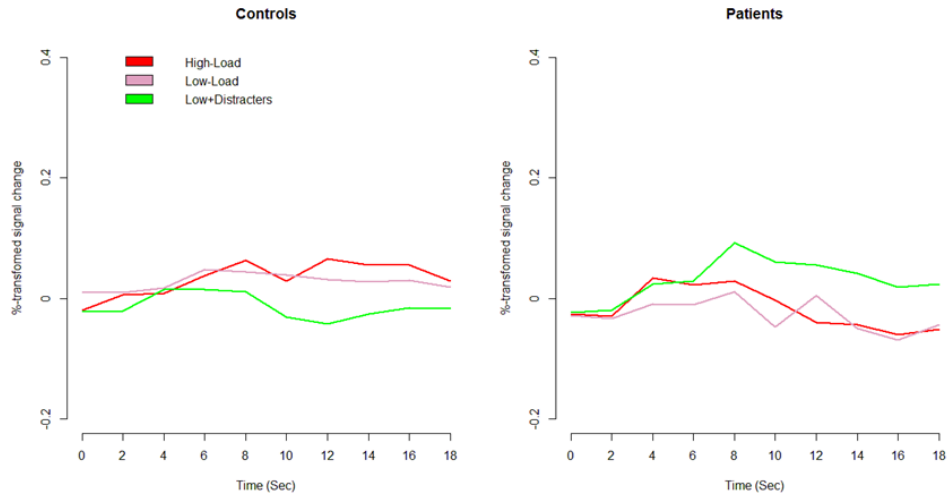


Figure 24. Percent-transformed signal change in the ROI region right globus pallidus (GP) from a pretrial baseline for each memory load condition. The zero point depicts the onset of get-ready signal (2s) which was followed by a precue (1, 3, or 5 s).

For the encoding- and retention-related interval (Figure 25), the planned comparison between High- versus Low-Load conditions showed no group differences [$t(38) = 0.85, p = 0.4$]. The contrast comparison, Low Load + Distracter versus Low Load, showed a larger activity increase for controls than patients [$t(38) = 2.16, p = 0.037$ for right GP, and $t(38) = 1.75, p = 0.089$ for left GP].

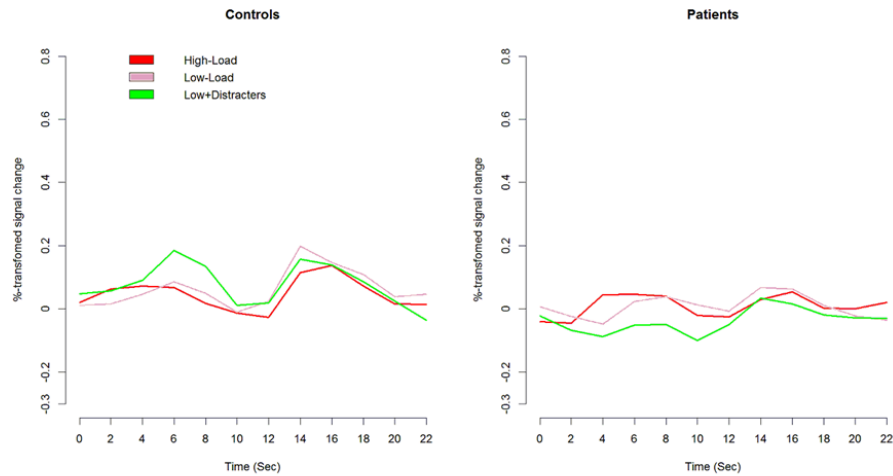


Figure 25. Percent-transformed signal change in the ROI region right globus pallidus (GP) from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

In the subgroup analysis of high-capacity participants (Figure 26-27), there were significant group differences for the contrast Low Load + Distracter versus Low Load during cue period showing the directional reversal across groups [$t(21) = -2.4, p = 0.025$].

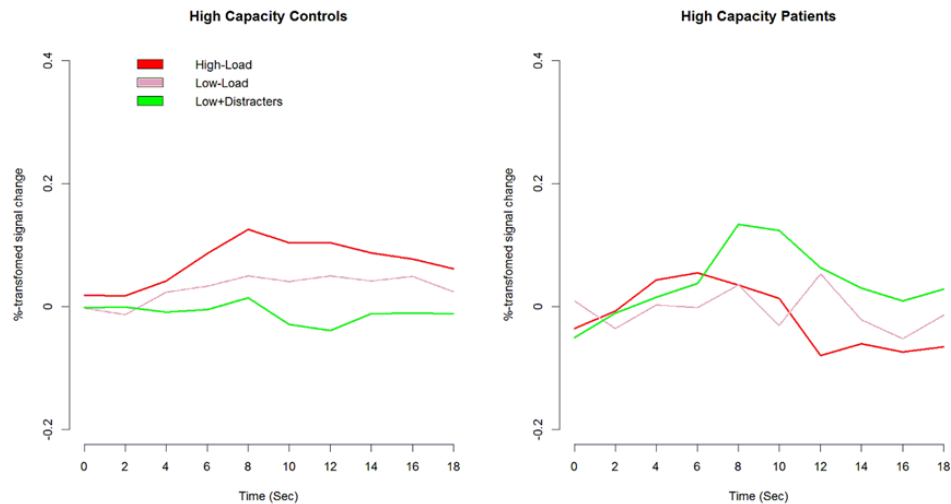


Figure 26. High capacity controls' and patients' percent-transformed signal change in the ROI region right globus pallidus (GP) from a pretrial baseline for each memory load condition. The zero point depicts the onset of get-ready signal (2s) which was followed by a precue (1, 3, or 5 s).

Once the memory array was presented (Figure 27), controls showed increased activity in the GP for Low Load + Distracter condition relative to the Low Load

condition while high capacity patients showed decreasing activity. However, this group difference failed to be significant [$t(21) = 1.41$, $p = 0.17$].

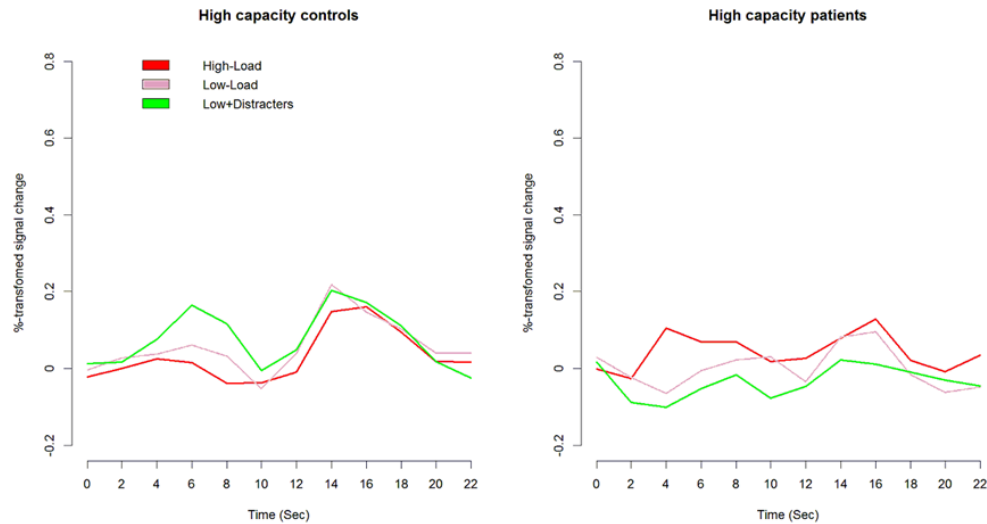


Figure 27. High capacity controls' and patients' percent-transformed signal change in the ROI region right globus pallidus (GP) from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

In the subgroup analysis of low-capacity participants, the observed directional reversal across groups during cue-related interval did not reach a significance for the contrast between Low Load + Distracter trials and Low Load trials [$t(16) = -1.27$, $p = 0.22$] while the contrast comparison between High and Low conditions revealed a significant group difference [$t(16) = -2.12$, $p = 0.05$]; low capacity controls showed a decreasing activity, whereas there was no such difference for patients.

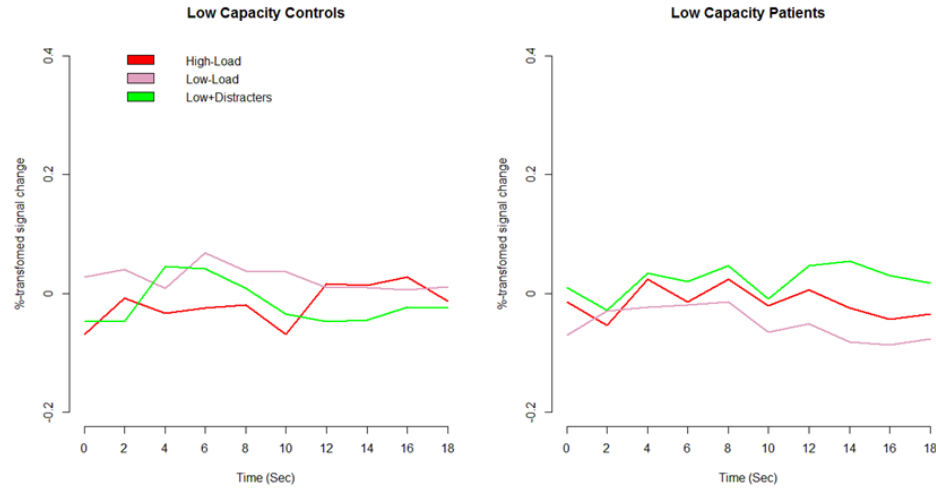


Figure 28. Low capacity controls' and patients' percent-transformed signal change in the ROI region right globus pallidus (GP) from a pretrial baseline for each memory load condition. The zero point depicts the onset of get-ready signal (2s) which was followed by a precue (1, 3, or 5 s).

During the encoding and retention period, low-capacity controls showed a trend towards higher activity increase for the Low Load + Distracter condition relative to the Low Load condition compared to patients, which failed to be significant [$t(9) = 1.76, p = 0.09$]. There was no reliable group difference in GP activation for the contrast between High and Low conditions [$t(16) = 0.69, p = 0.5$].

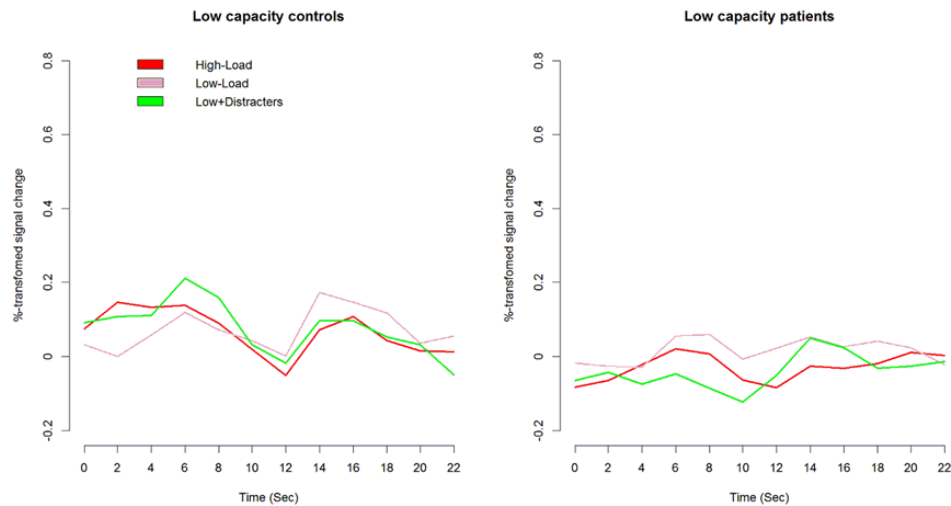


Figure 29. Low capacity controls' and patients' percent-transformed signal change in the ROI region right globus pallidus (GP) from a pretrial baseline for each memory load condition. The zero point depicts the onset of encoding (1s) which was followed by retention (7s) and test (2s) periods.

Correlation analyses. Two of the correlation analyses, one involving the right GP and one involving the right MFG, examined the relation between cue-related activity for the contrast (Low Load + Distracter vs. Low Load) and the same contrast, but for IPS activity during the encoding and retention interval. A second pair of correlations assessed cue-related activity in GP and MFG and memory capacity, as estimated by *K* scores in the set size 5 condition of the outside-the-scanner task. All four analyses failed to detect significant relationships ($-0.17 < r_s < 0.31$, $p_s > 0.2$ for both groups). The cue-related activity increase in GP for the Low Load + Distracter relative to the Low Load condition was correlated negatively with the *K* score measure of unnecessary storage for the patient group but it failed to be significant ($r = -0.30$, $p = 0.12$, $n = 17$, one-tailed) whereas the GP activity for the same contrast positively correlated with the *K* score measure of unnecessary storage for the control group ($r = 0.35$, $p = 0.05$, $n = 23$, one-tailed). This opposite pattern of the correlation between GP activity and *K* scores is probably due to a directional reversal of GP activities across groups. Collapsed across groups, the absolute activity changes in GP were marginally negatively correlated with *K* score measure of unnecessary storage ($r = -0.21$, $p = 0.096$, $n = 40$, one-tailed).

The parietal unnecessary storage was not significantly correlated with disease severity ($r = 0.01$, $p = 0.49$, $n = 17$, one-tailed). However, the GP activity for the contrast of Low Load + Distracter vs. Low Load condition during cue period was marginally negatively correlated with the disease severity ($r = -0.34$, $p = 0.089$, $n = 17$ for right GP, one-tailed) suggesting that with progressing disease stage patients may not be able to increase the GP activity when they were asked to ignore distracters.

Controls and patients with Parkinson's disease did not differ with regard to demographic variables such as age, gender or years of education [$F_s(1, 40) < 1.6$, $p_s > 0.22$ for age and education, $\chi^2(1) = 2.04$, $p = 0.153$ for gender]. Regarding the relationship between demographic and memory variables, both controls and patients showed negative correlations between age and K scores at set size 6 in the outside-the-scanner-task ($r = -0.36$, $p = 0.046$, $n = 23$ for controls and $r = -0.69$, $p = 0.001$, $n = 19$ for patients). Only patients showed a negative correlation between age and K scores at set size 5 ($r = -0.59$, $p = 0.004$, $n = 19$).

The unnecessary storage of distracters, as indexed by the difference in K scores between the Low Load + Distracter versus Low Load conditions, increased as a function of disease severity in the patient group, which was measured by the Hoehn and Yahr scale (1967; $r = 0.58$, $p = 0.006$, $n = 18$, one-tailed) indicating that patients with progressing disease stage exhibited greater unnecessary storage. A similar relationship was observed in Experiment 1.

When considering age and the stage of disease to account for memory capacity and unnecessary storage, only the stage of disease was a significant predictor of unnecessary storage [$t(17) = 2.77$, $p = 0.014$], whereas both age and stage of disease were significant predictors of memory capacity, as indexed by K scores in the 5 items condition [$t(18) = -3.41$, $p = 0.004$ for age and $t(18) = -2.71$, $p = 0.015$ for stage of disease].

Discussion

In Experiment 2, I examined possible roles of frontostriatal and frontoparietal circuitry, in the impaired filtering and reduced storage capacity which were identified as characteristics of PD in Experiment 1. Participants were asked to remember the orientations of two red rectangles while ignoring three green rectangles or remember both red and green rectangles as relevant targets depending on the instructional precue.

Behavioral and imaging results provided evidence that patients with Parkinson's disease had both impaired attentional filtering ability and reduced storage capacity to a certain degree.

Impaired attentional filtering

Both controls and patients had some difficulty ignoring distracters. They showed reduced K scores and increased activity in right IPS when distracters were present. Considering subgroups separately, high-capacity controls and patients both seemed to be effective at blocking out distracters by the time they responded to the probe stimulus. Both controls and patients showed comparable K scores irrespective of the presence of distracters, which indicates effective filtering of distracters. Interestingly, imaging data revealed that high-capacity controls were unnecessarily holding distracters in memory during the encoding and maintenance period: Their IPS activity significantly increased when distracters were present. Thus, the effective filtering process seems to have occurred at the response stage for these participants. By contrast, high-capacity patients showed no significant increase in IPS activity in the presence of distracters, implying that

they might have been successfully able to keep distracters from memory during the encoding and maintenance period.

It is not clear why high capacity controls were unnecessarily holding distracters in their memory and employed filtering process first at the stage of retrieval. It may have been easier for them to remember everything on the memory array for both High-Load and Low-Load + Distractor conditions because they may have enough memory space to hold all 5 items. By contrast, high capacity patients seemed to have employed the filtering process not only for the Low-Load + Distractor condition but also for the High-Load condition although it was unnecessary and even harmful for the performance. IPS activity in the High-Load condition was comparable to that of the Low-Load condition, implying that they were not holding more items in memory even if more to-be-remembered items were presented. *K* scores in the High-Load condition were even lower than those of the Low-Load condition.

Note that green rectangles were task-relevant and used as probes 50% of the time in the High-Load condition whereas they were task-irrelevant and never used as probes in the Low-Load + Distractor condition. If high capacity patients generally kept green bars from memory, it would be beneficial for the performance in the Low-Load + Distractor condition whereas it would hurt task performance in the High-Load condition, leading to lower *K* scores, which was observed in the present study. It is not clear why high capacity patients were unnecessarily keeping task-relevant green bars from their memory in the High-Load condition. They may have not been flexible enough to filter out information in one condition, e.g., Low-Load + Distractor condition, while inhibiting the filtering process and encoding the same information into memory in another condition, e. g.,

High-Load condition (negative priming). This interpretation is consistent with previous findings showing that patients with Parkinson's disease particularly had difficulty to perform tasks when task requirements kept changing (Cools et al., 2001; 2006; Woodward et al, 2002; Cameron et al., 2010) and they also showed greater negative priming effects compared to controls (Wylie and Stout, 2002). Another possibility is that it may have been too demanding for high capacity patients to hold 5 items in memory over 7s of delay period. Note that high capacity patients were able to hold more items in memory as shown in the outside-the-scanner-task. In that task, the retention interval was as short as 2s and only red bars were presented with no changes in task requirements.

For people with low memory capacity, both subgroups revealed reduced K scores and enhanced IPS activity in the presence of distracters, a pattern indicating impaired filtration. They were not able to keep distracters from memory even if it would have been beneficial for them because of their restricted memory space.

The lack of reliable group differences for the disrupting effect of the distracters may be due to small number of trials in Experiment 2. Note that there were only 42 trials for the Low Load + Distracter condition, whereas there were 400 distracter trials in Experiment 1. It is also possible that the task demand to ignore the interfering distracters may be higher in Experiment 1, in which participants were asked to ignore the half of the display screen in addition to ignoring distracters on the relevant cued side. For Experiment 2, the distracting stimuli were presented around the fixation dot, which may have made it easier for participants to ignore distracters, thereby making the current task paradigm less sensitive to group differences.

It is worth mentioning that the activity increase in the GP and MFG, especially GP, during the cue interval seemed to be associated with effective filtering at the consecutive processing stage. For example, high capacity patients showed increased GP activity in the Low-Load + Distractor condition during cue period and they were able to filter out distracters at following encoding and retention period. High capacity patients were probably preparing for filtering out upcoming distractors so that they could make more room for task-relevant items. For them, it would have been too demanding to hold both red and green rectangles in memory and filter out distracters at later stage as high capacity controls could do. This result is consistent with the previous findings by McNab and Klingberg (2008) showing that a preparatory activity in the GP during cue period reliably predicted whether distracters would be unnecessarily held in memory during encoding and retention period, implying that dysfunction in GP may lead to impaired filtering ability.

Regarding the present findings for people with Parkinson's disease, loss of dopaminergic input to the basal ganglia in Parkinson's disease may lead to a diminished ability of the GP. Given that the disease severity was a significant predictor of memory capacity even after accounting for age effect, it may be plausible to assume that high capacity patients were still able to regulate GP activity thereby showing effective filtering ability because they were at the earlier stage of the disease. By contrast, low-capacity patients were not able to enhance their GP activity and so were not successful at filtering out distracters because their already advanced stage of the disease may have interfered with regulation of GP function. This finding is consistent with previous findings showing that even newly diagnosed, drug-naïve Parkinson's patients showed under-activation in

basal ganglia including caudate nuclei, putamen and globus pallidus during an updating process (Marklund et al., 2009)

Reduced storage capacity

Present results showed that patients' K scores were comparable to those of controls when their memory was tested 2 s after the memory array offset. This result would suggest that patients with Parkinson's disease may not have reduced storage capacity, per se. Instead, PD patients may have difficulty to continue holding information in memory over a prolonged period of time, 7 s, as shown in the inside-the-scanner task. This was especially true for high capacity patients. High capacity controls showed increased IPS activity with increasing set size whereas there was no such activity increase for high capacity patients, despite the fact that they showed greater K scores with increasing memory load in the outside-scanner-task in which memory was tested 2s after the memory array offset.

By contrast, low-capacity patients seemed to have even less space in working memory than similarly categorized control subjects. Their K scores were overall lower than those of low capacity controls when their memory was tested 2 s or 7 s after the memory array offset. Their IPS activity did not significantly increase with increasing memory load, suggesting that they were not encoding and maintaining more information when presented with more to-be-remembered-information.

It is worth mentioning that equivalence or even paradoxical reversal from Low-Load to High-Load trials for low-capacity patients is congruent with previous findings in which parietal cortex activation was markedly reduced when neurologically normal

subjects were presented with memory loads beyond their capacity, as if they were simply overwhelmed (Linden et al., 2003; Vogel & Machizawa, 2004). This phenomenon was also apparent in Experiment 1.

Patients' failure to increase IPS activation despite of increasing memory load is consistent with the VBM analysis results showing a reduction in grey matter density over the right IPS. The structural analysis also indicated that patients had a reduction in grey matter density over pre-SMA (see also Jubault et al., 2011), which was positively correlated with patients' *K* scores of the outside the scanner task. However, the ROI analysis failed to document any group differences in the pre-SMA activation.

General Discussion

The purpose of the present dissertation study was to identify possible cognitive and neural origins of working memory deficits in Parkinson's disease by means of behavioral, EEG, and MRI correlates of working memory. Participants were asked to remember red rectangles while ignoring green distracters, and then to report whether any of the relevant items had changed.

Filtering or storage capacity?

The behavioral and EEG correlates of working memory suggested that PD patients may be unnecessarily holding irrelevant distracters during encoding and maintenance period irrespective of their basic memory capacity. In addition to this unnecessary storage problem, patients seemed to have less space than controls to begin with. This was especially true for those who were already categorized as having low capacity.

In the follow-up experiment using slightly different task paradigms, behavioral performance was measured at two different delay periods (2s vs. 7s), and MRI correlates were used to examine neural correlates of patients' impaired filtering and reduced storage capacity. Patients, who had ample size of memory, showed comparable behavioral performance to the similarly categorized control subjects in the outside-scanner-task. This suggests that those patients were able to encode and maintain as much information as controls when memory was tested within 2s of delay period and there were no changes in task requirements. However, patients' performance level dramatically dropped in the

inside-the-scanner-task, especially for the High-Load condition in which the delay period was extended to 7s and three different types of trials were intermixed.

High-capacity patients were successful at keeping distracters from memory, which is inconsistent with the findings observed by means of EEG in Experiment 1. Instead, it was the control subjects in Experiment 2 who were in fact unnecessarily holding distracters in memory, which is also inconsistent with the findings by McNab and Klingberg (2008). The discrepancy between the two experiments' results may be due to different task demands and characteristics. It may be possible that participants generally try to hold as many items in memory as possible including both targets and distracters as long as their memory space allows them to do so. This avoids expending additional efforts to filter out distracters. Once the memory array goes beyond participants' capacity limits, they may start employing filtering process at encoding and maintenance stage in order to make more space for relevant information.

Note that one memory array was presented on each side of the screen in order to extract CDA waveforms in Experiment 1. This would lead to a supra-capacity array size even for healthy young adults (Luck and Vogel, 1997; Cowan, 2001). Since memory resources were challenged by this supra-capacity memory set size, high-capacity controls in Experiment 1 may have tried to keep distracters from their memory so that they could make more room for relevant targets. The findings reported in the study by McNab and Klingberg (2008) is consistent with this interpretation. In that study, 16 grids were presented as possible target locations and 5 colored disks were randomly assigned to 5 out of these 16 grids during encoding period. It may have been challenging even for high capacity younger adults to hold all 16 grid positions along with the target and distracter

disks because it would be beyond their memory capacity forming a supra-capacity memory load. Thus, high capacity younger adults may have tried to keep distracters from their memory so that they could make more room for the task-relevant target stimuli. As for the Experiment 2, only 5 items were presented, which was less demanding for high-capacity controls. Thus, they may have kept both targets and distracters in memory because they had enough memory space to hold 5 items.

By contrast, high-capacity patients may have more difficulty keeping distracters from memory when the memory set size far exceeded their memory space, e.g., bilaterally arranged 8 items in Experiment 1, as did low capacity controls and patients in both Experiments 1 and 2. However, high capacity patients may still be able to keep distracters from memory as long as the memory load is reasonably higher than their capacity, such as 5 items as seen in Experiment 2.

For patients with low memory capacity, the data were consistent across experiments and measures. There was converging evidence that these participants have less memory space than similarly categorized controls, and that they have impaired filtering ability as indicated by three correlates of working memory: Behavior, EEG, and MRI.

In addition to filtering and storage problems, PD patients seemed to have difficulty with flexibly adjusting themselves to different task requirements. When patients were challenged by higher memory load, even high capacity patients, who were capable of filtering out distractors, could not encode previously task-irrelevant items into memory by inhibiting the filtering process, which ultimately led to less storage of information in memory. This result is consistent with previous findings showing that PD

patients were not flexible enough to alter their behaviors in response to changes in task requirements (Cools et al., 2001; 2006; Woodward et al, 2002; Cameron et al., 2010).

The results of Experiment 2 suggest that patients' impaired filtering and reduced storage capacity cannot be ascribed to the common symptom of bradyphrenia, slowness of mental processing. Suppose that patients with Parkinson's disease are generally able to filter out distracters as well as hold as much information as controls do, but that they do so at a much slower rate. If so, the extended delay period of 7s should not interfere with their performance but even be beneficial for them. This was apparently not the case in the MRI experiment. People with Parkinson's disease may indeed experience genuine impaired filtering and reduced storage capacity, at least those who begin their disease progression with a low base level of capacity.

Role of globus pallidus in filtering

Experiment 2 showed that the cue-related activity changes in GP for the contrast (Low Load + Distracter vs. Low Load) were associated with the extent of the unnecessary storage. Patients' GP activity was negatively correlated with *K* score measure of unnecessary storage whereas controls' GP activity was positively correlated with the *K* score measure of unnecessary storage because of a directional reversal in GP activity. Collapsed across groups, the absolute activity changes in GP during cue period were marginally negatively correlated with the *K* score measure of unnecessary storage. This result is generally consistent with the findings by McNab and Klingberg (2008), who studied healthy younger adults.

The present finding is consistent with the computational models of basal ganglia suggested by O'Reilly and Frank (2006; Cohen and Frank, 2009). Accordingly, basal ganglia may adaptively gate information flow into frontal cortex: Goal-related representations in the frontal cortex are facilitated by this gating function of the basal ganglia, while goal-irrelevant representations are suppressed. Regarding the present findings, the globus pallidus, the output nuclei of the basal ganglia, may have been activated to prevent the information flow of the task-irrelevant distracters into frontal cortex.

Interestingly, present results showed that PD patients with ample memory size were able to activate GP and thereby effectively filter out distracters from memory probably because they were still at earlier stage of the disease. With progressing stage of the disease, patients' memory capacity and filtering ability decreased. Correspondingly, there was a reduction in GP activity when they were asked to ignore distracters. This finding is less consistent with the claim raised by Wiecki and Frank (2010; see also Moustafa et al., 2008). According to the authors, dopamine may play an important role to modulate the gating function of the basal ganglia: It selectively increases signal-to-noise ratio for the goal-related representations through the direct (striatonigral) pathway while suppressing goal-irrelevant signals via the indirect (striatopallidal) pathway. With decreased striatal dopamine level, basal ganglia may not be able to facilitate task-relevant representation, but still be able to inhibit task-irrelevant representation by enhancing inhibitory indirect pathway. Given the compromised striatal dopamine level in Parkinson's disease, it would have predicted reduced performance for task-relevant information but still intact or even enhanced inhibitory activity of task-irrelevant information, which is inconsistent with the

findings observed in both Experiments 1 and 2. Instead, the current results suggest that reduced striatal dopamine level in Parkinson's disease may lead to inefficient gating of information irrespective of its task-relevance resulting in reduction in performance for both task-relevant as well as task-irrelevant information.

Role of Intra-parietal sulcus in information storage

Control participants showed increased activity in IPS, especially in right IPS when they were presented with High-Load compared to Low-Load memoranda whereas there was no such increase in IPS activity for patients. There was a significant group difference in this regard. Similar result was also found in the structural analysis: PD patients had reduced grey matter density over right IPS. The present MRI results are consistent with previous findings (Todd and Marois, 2004; see also Postle et al., 2006) suggesting that the activity increase in IPS is sensitive to the number of items held in memory and may serve as reliable neural correlates of working memory storage.

It is worth mentioning that IPS may not be place storing working memory for visuo-spatial information (Harrison et al., 2010) or even abstract or multimodal information (Cowan et al., 2011) per se but place storing attentional pointers to the information which is stored elsewhere in brain (Ruchkin et al., 2003). For both hypotheses, IPS activity would be sensitive to the number of items held in memory. Another alternative to interpret the role of IPS is that it may reflect the amount of general effort involved in performing the task. In support of this interpretation, note that low-capacity patients in Experiment 2 showed increased IPS activity during maintenance period when they were presented with distracters whereas their IPS activity in the High-

Load condition was lower than that of the Distracter + Low-Load condition and even comparable to that of Low Load trials.

If IPS reflects storage capacity for visuo-spatial information or pointers to the information stored elsewhere in brain, low capacity patients' IPS activity in the High-Load condition should have been at least comparable to that of Low Load + Distracter condition because they should be able to hold at least as much information in the High-Load condition as they could do in the Low-Load + Distracter condition, which is inconsistent with the findings observed in Experiment 2.

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Table 1 Demographics and memory variables

	Age		Gender		Years of education		Hoehn & Yahr scale		Years of disease	
	M	SD	Male	Female	M	SD	M	SD	M	SD
Patients (N=21)	66.71	9.83	13	8	14.29	2.99	1.98	0.58	6.7	4.2
Controls (N=28)	68.57	6.77	12	16	14.59	2.9	-	-	-	-
	Hit and False Alarm rates									
	2-red		2-red-2-green				4-red			
	Hit	False Alarm			Hit	False Alarm			Hit	False Alarm
Patients (N=21)	0.84	0.25			0.79	0.29			0.62	0.39
Controls (N=28)	0.93	0.24			0.91	0.27			0.73	0.44
	K scores									
	2-red		2-red-2-green		4-red		Unnecessary storage			
	M	SD	M	SD	M	SD			M	SD
Patients (N=21)	1.41	0.47	1.26	0.51	1.42	0.71			0.16	0.1
Controls (N=28)	1.71	0.22	1.63	0.25	1.82	0.59			0.08	0.08
	CDA amplitudes									
Patients (N=21)	-0.58	0.43	-0.82	0.49	-0.77	0.62			-0.25	0.36
Controls (N=28)	-1.00	0.37	-1.12	0.49	-1.22	0.51			-0.13	0.27

Note. Descriptive data for participants' demographics (age, gender, years of education, patients' Hoehn & Yahr scale, and years of disease) and memory performance indexed by hit and false alarm rates, *K* scores and CDA amplitudes across three trial types (2-red, 2-red-2-green, and 4-red conditions).

Table 2 Correlation matrix

Parkinson's patients								
	1	2	3	4	5	6	7	8
1. <i>K</i> score for 2-red	-							
2. <i>Unnecessary storage: K</i>	-.27	-						
3. <i>K</i> score for 4-red	.84**	-.50*	-					
4. <i>CDA</i> for 2-red	.56**	.38	.49*	-				
5. <i>Unnecessary storage: CDA</i>	.03	.14	.04	.19	-			
6. <i>CDA</i> for 4-red	.50*	.32	.47*	.60**	.37	-		
7. <i>age</i>	-.64**	.31	.69**	.25	.23	-.47*	-	
8. <i>Hoehn & Yahr scale</i>	-.41	.46*	-.53*	.28	.23	.14	.58**	-
9. <i>Years of disease</i>	-.18	-.20	-.19	.10	.16	.06	.13	.31
Control subjects								
	1	2	3	4	5	6	7	
1. <i>K</i> score for 2-red	-							
2. <i>Unnecessary storage: K</i>	-.23	-						
3. <i>K</i> score for 4-red	.82**	-.35	-					
4. <i>CDA</i> for 2-red	.02	.20	.04	-				
5. <i>Unnecessary storage: CDA</i>	.31	.05	.15	.24	-			
6. <i>CDA</i> for 4-red	.03	.07	.06	.79**	.30	-		
7. <i>age</i>	-.38*	.24	-.41*	.20	.29	.22	-	

Note. Correlations between *K* scores (relevant items held in working memory) at 2-red and 4-red conditions, *CDA* amplitudes, age and stage of disease factors for Parkinson's patients and Control subjects. "*Unnecessary storage: K*" indicates the difference in *K* scores between 2-red and 2-red-2-green condition; "*Unnecessary storage: CDA*" is the difference in *CDA* amplitude between those two conditions. The negative signs for *CDA* amplitudes have been dropped so that larger values indicate more items stored in memory.

* $p < .05$, ** $p < .01$

Table 3 Demographics

	Age		Gender		Years of education		Hoehn & Yahr scale		Years of disease	
	M	SD	Male	Female	M	SD	M	SD	M	SD
Patients (N=19)	66.16	8.81	14	5	16.63	3.25	2.03	0.77	6.65	4.76
Controls (N=23)	68.04	6.62	12	11	15.26	3.85	-	-	-	-

Note. Descriptive data for participants' demographics (age, gender, years of education, patients' Hoehn & Yahr scale, and years of disease).

Table 4 Hypotheses

Hypothesis 1.

Patients' reduced filtering ability is due to impaired function of the basal ganglia

Predictions and test methods:

BG activity (t-test): patients < controls

Negative correlations (correlation analyses)

- 1) between parietal unnecessary storage during retention & BG activity
- 2) between parietal unnecessary storage during retention & working memory capacity
(*K* score)

=> patients > controls

Hypothesis 2.

Behavioral working memory estimate (*K* score) & parietal activations: patients < controls

Table 5 Correlations

Memory load	left pre-SMA	right pre-SMA	right IPS
2	$r = 0.389$, ns	$r = 0.383$, ns	$r = 0.500$, $p=0.029$
3	$r = 0.577$, $p = 0.0095$	$r = 0.603$, $p = 0.0062$	$r = 0.395$, ns
4	$r = 0.522$, $p = 0.021$	$r = 0.474$, $p = 0.04$	$r = 0.448$, $p = 0.054$
5	$r = 0.479$, $p = 0.037$	$r = 0.490$, $p = 0.032$	$r = 0.419$, $p = 0.07$
6	$r = 0.564$, $p = 0.011$	$r = 0.295$, ns	$r = 0.483$, $p = 0.035$

Note. Correlations between *K* scores and grey matter density in bilateral pre-SMA and right IPS for patients.

Appendix A. Behavioral capacity estimate of working memory

The number of task-relevant items loaded into working memory termed as K can be estimated using a formula suggested by either Pashler (1988) or Cowan (2001). In a typical visual-array task, a to-be-remembered memory array of visual items is followed by a short retention interval. In the following test phase, in which either a single probe stimulus or an array of many to-be-tested probe stimuli is presented, participants are asked to respond whether or not the single probe stimulus/or the array of probe stimuli is identical with the memory array. When number of relevant items in the memory array is varied across a range of values (e.g. 1-7), a typical finding with healthy young adults exhibits an increasing K value with increasing set size but the K reaches an asymptotic at about four items (Luck and Vogel, 1997; Todd and Marois, 2004). The asymptotic value of K is then suggested as estimate for the participant's working memory capacity (Pashler, 1988; Cowan, 2001; Cowan *et al.*, 2005).

The K estimate formula developed by Pashler (1988) is based on hit and false alarm rates, and suited when the probe has as many items as the memory array and no one item is cued. It is assumed that when a memory array of N items is presented, the participant is able to hold a certain fixed number of items in working memory, k . If the changed item is in working memory, the change will be detected with the probability of k/N , and otherwise the participant will guess with probability of g . Thus, the formula for the hit rate is

$$p(\text{hit}) = (k/N) + (1 - k/N)g \quad (1)$$

N is the number of items in the memory array and g is the rate of guessing that a change occurred, given that the item is not in working memory.

The false alarm rate for the cases in which the participant incorrectly reports that there was a change even if there was no change is estimated with g which is guessing rate,

$$p(\text{false alarm})=g \quad (2)$$

Combining equations 1 and 2 yields Pashler's formula:

$$p(\text{hit})=(k/N)+(1-k/N)*p(\text{false alarm})$$

$$p(\text{hit})=k/N + (p(\text{false alarm})/ N)- (k*p(\text{false alarm})/N)$$

$$N*(p(\text{hit}))=k+ (p(\text{false alarm})- (k*p(\text{false alarm})))$$

$$N*(p(\text{hit})) = k(1- p(\text{false alarm})) + p(\text{false alarm})$$

$$N*(p(\text{hit})/(1- p(\text{false alarm}))) - (p(\text{false alarm})/(1- p(\text{false alarm}))) = k$$

$$k=N[p(\text{hit})-p(\text{false alarm})]/[1-p(\text{false alarm})] \quad (3)$$

To the contrary, Cowan (2001)'s estimate is suited to procedures in which the probe contains only one item. If that item is changed compared to the corresponding item in the memory array and the change is reported, that is considered a hit and it is expected to occur with the probability described below (equation 4)), which is same as the hit rate according to the Pashler's hit rate:

$$p(hit) = (k/N) + (1 - k/N)g \quad (4)$$

Again, N is the number of items in the memory array and g is the rate of guessing that a change occurred, given that the item is not in working memory. When there is no change, the participant will know that when the item is in working memory and otherwise will guess. It is considered a false alarm if the participant incorrectly reports that there was a change which, under this model, only occurs if the item is not in working memory.

Therefore, false alarms are assumed to occur with the following probability:

$$p(false\ alarm) = (1 - k/N)g \quad (5)$$

Combining the two equations 4) and 5) leads to the Cowan's (2001) formula:

$$p(hit) = (k/N) + p(false\ alarm)$$

$$N * (p(hit)) = k + (p(false\ alarm) * N)$$

$$N * (p(hit)) - (p(false\ alarm) * N) = k$$

$$k = N[p(hit) - p(false\ alarm)] \quad (6)$$

Appendix B. Parkinson's disease

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder with predominant loss of dopaminergic neurons in SNc (substantia nigra pars compacta) and subsequent depletion of dopamine levels in the basal ganglia. Although Parkinson's disease can develop at any age, it mostly begins in older adults with a peak onset age around 60 years. The likelihood of developing the disease increases with age with a lifetime risk of about 2% but it increases to about 4 % in the presence of positive family history. Except for a few identified genetic mutations (e.g., PARK1, 2, 5 and 7 mutated genes) the cause of the disease remains unknown so that Parkinson's disease is often described as idiopathic disease.

The pathology seems to start even well before the substantia nigra is affected by the disease. For example, Braak and colleagues (2003) found Lewy bodies, which are histopathological hallmarks of Parkinson's disease and mainly consist of aggregated form of protein alpha-synuclein, not only in the substantia nigra but also outside of the substantia nigra. According to them, the neuronal damage begins in fact in dorsal motor nucleus of the vagal nerve and anterior olfactory structures with ascending course of the pathology, which eventually reaches the neocortex. The damage to the substantia nigra then occurs at an intermediate stage (stage III) out of six stages.

Pathophysiology of Parkinson's disease

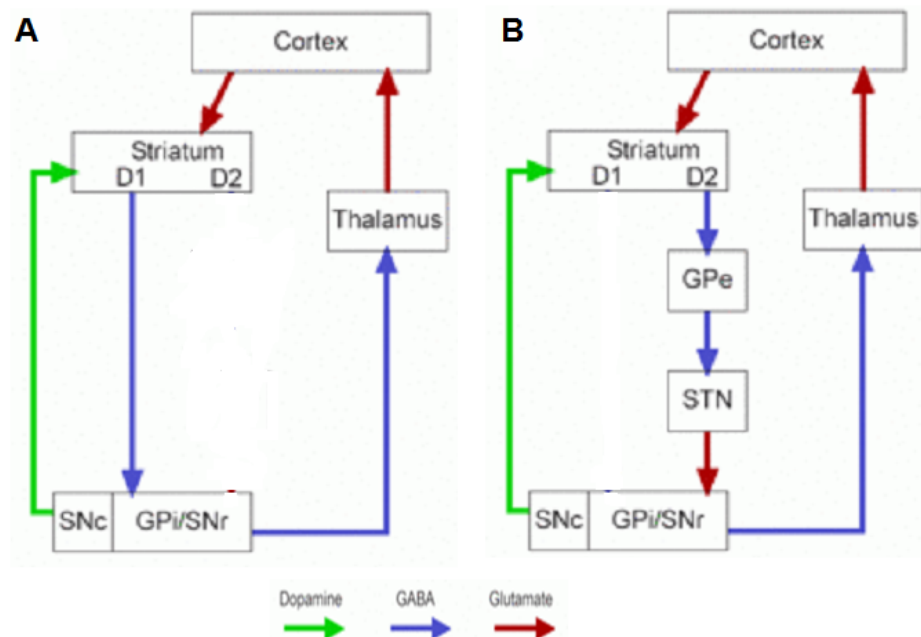
Organization of BG

Basal ganglia are a constellation of several nuclei in the midbrain area which consists of striatum (caudate nucleus, putamen, and nucleus accumbens), subthalamic nucleus, substantia nigra pars compacta (SNc) and pars reticulata (SNr), and globus pallidus

interna (GPi) and externa (GPe). Studies indicate that segregated areas of the striatum, the input nuclei of the basal ganglia, receive inputs from different areas of the frontal cortex, and GPi, the output nuclei of the BG, project the information into separate parts of the thalamus. The thalamic areas, in turn, project back to the same areas of the cortex from which the input originates by forming the basal ganglia-thalamo-cortical circuits (Alexander & Crutcher, 1990; DeLong et al., 2007). Five circuits have been identified based on their main cortical projection areas and presumed functions, which are considered functioning in parallel: motor, oculomotor, associative/or dorsolateral prefrontal, limbic, and orbitofrontal circuits. As an example for a parallel organization of each circuit, consider the motor circuit which originates from the precentral motor field (Brodmann areas 4 & 6, and supplementary motor area). The inputs from the cortex are projected to the posterolateral putamen, posterolateral globus pallidus pars externa and pars interna, as well as the dorsolateral subthalamic nucleus, and then to the ventrolateral thalamus which are projected back to the precentral motor field. Unlike the motor circuit, the associative/prefrontal circuit originates from the dorsolateral prefrontal cortex (Alexander et al., 1986; Obeso et al., 2008) and the inputs terminate within the dorsolateral head of the caudate nucleus, which are in turn projected to the dorsomedial one-third of the globus pallidus and to the rostral portions of the SNr, and then to the ventral anterior or medial dorsal part of the thalamus.

It has been traditionally considered that the striatum, the BG input nuclei, receives inputs from various regions of the cortical areas and projects to the GPi/SNr, the BG output nuclei, via two pathways: striatonigral direct vs. striatopallidal indirect pathways (see the Figure below). These two pathways were known to function in parallel within each basal

ganglia circuit while having opposing effects on the activity of the basal ganglia output nuclei. In the direct pathway, medium spiny neurons (MSNs), which are striatal efferent neurons and mainly contain D-1 receptors, directly project from the striatum to GPi/SNr, whereas the MSNs in the indirect pathway, which largely contain D-2 receptors, indirectly project to GPi/SNr through GPe and STN.



Direct (A) vs. indirect (B) pathways of the basal ganglia modified from Albin and colleagues (1989). In the direct pathway, medium spiny neurons (MSNs) directly project from the striatum to GPi/SNr, whereas the MSNs in the indirect pathway indirectly project to GPi/SNr through GPe and STN. Excitatory glutamatergic connections are depicted as red, inhibitory GABAergic connections as blue, and modulatory dopaminergic connections as green.

In the absence of striatal firing, neurons in GPi/SNr are tonically active, which inhibits the thalamic activation and the inhibited thalamic activity in turn leads to inhibition of the frontal activity. By contrast, in the presence of striatal firing, the striatum directly sends inhibitory projections to the GPi/SNr through the direct pathway, which has disinhibitory (or excitatory) effects on the thalamic activity. For the indirect pathway, the striatum

sends inhibitory projections to the GPe, which in turn sends focused inhibitory signals to GPi/SNr so that a specific response can be suppressed (Mink, 1996; Obeso et al., 2008). Due to this additional inhibitory projection via GPe, the activity through the indirect pathway leads to the inhibition of the thalamic activity.

Recent findings incorporated STN as another BG input nucleus, which receives inputs from the cortex and exerts broad and diffuse projections to GPi forming a cortico-STN-pallidal hyperdirect pathway (Nambu et al., 2002; Miller, 2008). This hyperdirect pathway is faster in signal conduction than the direct and indirect pathways, and exerts excitatory effects on GPi neurons because it only consists of excitatory glutamatergic connections. The excited GPi neurons in turn inhibit the thalamic activity. According to this distinct pathway model view (Nambu et al., 2002), at least in context of the motor control, the signals from the frontal cortex are directly and diffusely transmitted to many GPi neurons via the STN (hyperdirect pathway), which inhibits the thalamic and cortical activities and all responses, rather than just one, are initially prevented from being executed. Then, another signal is conveyed through the direct pathway by inhibiting the GPi activity, which leads to the facilitation of the thalamic and cortical activities. By doing so, specific responses are facilitated. Finally, signals project to GPi through the indirect pathway by suppressing the thalamic and cortical activations. Other competing responses are also suppressed. In this way, movements are initially widely suppressed through the hyperdirect pathway and a single movement is selectively facilitated via the direct pathway while all other unnecessary movements are suppressed via the indirect pathway (Nambu et al., 2002).

Parkinson's disease as deficits in BG function

The functional hallmark of Parkinson's disease is associated with the striatal dopamine (DA) depletion and increased activities in STN and GPi, the BG output nuclei. The reduced DA in the striatum is caused by the loss of pigmented dopaminergic cells in the substantia nigra pars compacta, which has extensive connections to the striatum by forming the nigrostriatal pathway. The striatal dopamine depletion is estimated to be around 70% by the time of the diagnosis but the depletion is even higher for the posterior putamen which is part of the motor circuit. In this region, the dopamine loss may reach up to 90% even at the early stage of PD.

The increased activities in STN and GPi may be resulted from the reduced dopamine level in the striatum. It is suggested that DA plays an important modulatory role in BG functions (Gerfen, 2000; Gruber et al., 2006; Moustafa et al., 2008). At D-2 receptors, which are abundant in the striatopallidal indirect MSNs, DA plays an inhibitory role: phasic DA burst reduces glutamate release. The postsynaptic responsiveness to the released glutamate is also reduced. On the other hand, DA release enhances signal-to-noise ratio at D-1 receptors, which are in abundance on the MSNs of the striatonigral direct pathway: DA facilitates responses to active and strongly coordinated glutamatergic inputs whereas it decreases weak and asynchronous signals as noise (Surmeier et al., 2007; Cohen and Frank, 2009). These modulatory actions of the DA release facilitate activities in the direct pathway but inhibit activities in the indirect pathway, which has inhibitory effects on the activity of the BG output nuclei. To the contrary, the DA depletion reduces the signal-to-noise ratio on the D-1 receptors as well as inhibitory activity on the D-2 receptors, which leads to hypoactivity in the striatonigral

direct pathway while leading to hyperactivity in the striatopallidal indirect pathway. This will result in the overactivity of the BG output nuclei. By implication, Parkinson patients' reduced dopaminergic inputs to the striatum may lead to increased activities in the indirect pathway, which result in the increased activities in the BG output nuclei, GPi. In fact, the clinical motor symptoms of Parkinson's disease such as bradykinesia and rigidity may be due to the overactivity in the indirect pathway (Nambu et al., 2002). For example, an animal study by Kravitz and colleagues (2010) showed that activating MSNs in the indirect pathway *in vivo* was associated with the increased bradykinesia, freezing and decreased movement initiation whereas stimulating the direct pathway ameliorated those movement features.

By contrary, the mechanism underlying cognitive symptoms for patients with Parkinson's disease is less clear. Because the basal ganglia have extensive interconnections with the prefrontal cortex (Jellinger, 2001; Lewis *et al.*, 2003) forming the frontostriatal circuitry, patients' cognitive symptoms in planning, set shifting, reward learning or working memory capacity (Gabrieli *et al.*, 1996; Zgaljardic *et al.*, 2003; Owen, 2004) were often ascribed to the compromised information flow through the frontostriatal circuitry (Lewis et al., 2003). Indeed, the pattern of cognitive deficits in patients with Parkinson's disease appear to be similar to that were observed in frontal lobe patients (Morris et al., 1988, Owen, 1995; West et al., 1998). However, recent studies suggested that the basal ganglia may be directly involved in various cognitive functions including reward learning and working memory (Frank, 2005; Gruber et al., 2006; Cools et al., 2008). Cohen and Frank (2009) even suggested that the basal ganglia may modulate cognitive functions in a similar way as they do motor functions (see also

Moustafa et al., 2008; Wiecki and Frank, 2010). For example, their model predicts that Parkinson patients' reduced signal-to-noise ratio in the direct pathway and the hyperactivity in the indirect pathway would impair learning from positive outcomes but preserve learning from negative outcomes in terms of reward learning. However, other studies argue that cognitive functions are far more complicated than motor functions so that the mechanism underlying the cognitive deficits in patients with Parkinson's disease may be different from those underlying motor deficits. Whether or not Parkinson patients' cognitive deficits are modulated in the similar way as the motor symptoms are, it seems that there is a growing evidence showing that the basal ganglia may be directly involved in the motor as well as cognitive functions implying the direct involvement of the basal ganglia in the cognitive deficits in patients with Parkinson's disease (Gruber et al., 2006; Cools et al., 2008; McNab and Klingberg, 2008).

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Appendix C. Consent form

**INVESTIGATORS' NAMES: MS. EUN-YOUNG LEE, MA, NELSON COWAN, PH.D.,
FERNANDO VALLE-INCLAN, M.D., TERRY ROLAN, M.D., DAVE BEVERSDORF, M.D.
AND STEVE HACKLEY, PH.D.**

VERSION OF FORM: CONTROL/PILOT VERSION

PROJECT #: 1170557

FOR HS IRB USE ONLY
APPROVED _____ HS IRB Authorized Representative Date EXPIRATION DATE: _____

**Study Title: Target Intervention Sites for Treatment of Memory Deficits in
Parkinson's
Disease**

INTRODUCTION

As with all human research conducted at this university, our study includes only people who freely choose to participate. As a potential subject, you have the right to know about the procedures that will be used so that you can make an optimal decision as to whether or not to participate. The information presented here is simply intended to make you better informed so that you may give or withhold your consent to participate in this study. If you choose to be in this experiment, signing at the bottom of this form will document your consent. You can quit the study at any time, even after signing this form.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to identify structures in brain for a new approach to the treatment of Parkinson's disease. Brain scans performed on a magnetic resonance imaging (MRI) machine will be made to determine brain regions which are responsible for compromised memory process in people with Parkinson's disease.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 40 people with Parkinson's disease and 44 age- matched elderly people are expected to take part in this study. About 20 college students will participate in this study serving as pilot subjects.

WHAT IS INVOLVED IN THE STUDY?

Participants with Parkinson's disease:

Prior to arrival at the imaging center today, please do not take your morning dose of antiparkinsonian medication. This will give the investigator an accurate assessment of your visual memory related to your Parkinson's disease.

You are allowed to resume your medication as soon as the computer game is over.

All participants:

In this study, you will lie inside of an MRI scanner while looking at a computer screen. The measurements will be obtained while you play computer games that involve looking at a set of colored rectangles on the screen and then remember the orientations of the colored rectangles.

We will measure the anatomy and activity of your brain using a brain-imaging camera called an MRI scanner. MRI scanners measure brain anatomy using very strong magnets. You will be required to lie completely motionless while you are playing the computer games. Cushions will be placed inside the tube for your comfort and to keep your head still.

Before starting the games, you will first be asked to accurately and completely complete the fMRI Screening Questionnaire, which will be analyzed by the investigator. Then you will be given a tour of the fMRI facility and will be familiarized with the screening and safety procedures associated with the MRI scanner.

HOW LONG WILL I BE IN THE STUDY?

The study usually takes a little over two hours. The procedure could end early if the investigator decides that something is going wrong with the study or if, for whatever reason, you should decide to quit the study. You can stop participating at any time, even after signing this form. Your decision to withdraw from the study will not affect in any way your medical care or benefits.

WHAT ARE THE RISKS OF THE STUDY?

While participating in the study, you are at risk for the side effects described below. You should discuss these with the investigator. There may also be other side effects that we cannot predict.

Unlike x-rays or CT-scans, MRI does not involve any ionizing radiation. However, the tasks may cause some fatigue similar to reading a book or doing homework. You may also experience discomfort from lying still. If this happens, please let us know and we will arrange for you to adjust your position. Additionally:

- The safety of MRI has been evaluated over the past 20 years and no short-term effects have been observed. However, the long-term effects of MRI on the body are not fully known. Some individuals with claustrophobia (fear of closed or confining spaces) may find the MRI equipment too confining. In that case, you can request to be removed from the scanner and this will be done immediately. If you have any concerns about this, you can be placed in a MRI simulator to determine if the confining aspects and noises are too uncomfortable.
- The MRI scanner makes sounds variously described as “thumping”, “pounding”, “banging”, “chirping” and “buzzing”; these sounds can be loud. You will be required to wear protective earplugs and headphones during scanning to reduce the noise. However, you will be able to hear the Technologist and he/she can hear your voice when you respond.
- The Investigators for this research project are not Licensed or Trained Diagnosticians or Clinicians. The testing performed in this project is not intended to find abnormalities, and the images or data collected do not comprise a diagnostic or clinical study. The Investigators and the University of Missouri are not responsible for failing to find abnormalities. However, on occasion the Investigators may perceive possible abnormalities. When this occurs, the Brain Imaging Center will consult with a Specialist. If the Specialist determines that additional inquiry is warranted, a staff person from the

Brain Imaging Center will contact you. In such case, you are advised to consult with a Licensed Physician to determine whether further examination or treatment would be prudent. The Investigators, Specialist, Brain Imaging Center and the University of Missouri are not responsible for any decision you make with regard to examination or treatment. Because the images collected for this research project do not comprise a diagnostic or clinical study, the images will not be made available for diagnostic or clinical purposes.

- No short-term effects to a fetus from this procedure have been observed. However, the long-term effects of MRI on the fetus are not fully known. Therefore, if you are sexually active and capable of becoming pregnant, you must use an effective method of birth control while participating in this research. If you are a subject in a multi-session study and become pregnant during the course of that study, you will no longer be able to participate in this MRI research study for the duration of your pregnancy.
- You **cannot** have an MRI if you have **any metal in or near your brain** such as an aneurysm clip or a cochlear implant, or other contra-indicated implants such as a pacemaker for your heart or metal-containing prostheses (like a ‘stent’ or a heart valve, hearing aids, etc.). For example, welders and metal workers may be at risk for a MRI because they may have gotten small metal fragments in their eyes. This would be dangerous inside the magnet. There are also possible risks for participants if metal objects are drawn to the magnet while a participant is within or near the bore. Accordingly, you will be asked to leave all jewelry and metal objects outside of the testing area. No loose metal objects will be allowed near the magnet. Many items of clothing contain metal hooks, wires, etc. and some of these cannot be worn in the MRI device. We have clean garments that you can wear in this case.
- There may be some unanticipated risks or side effects involved with your participation in this research study. Since 1981, there is no evidence that high magnetic fields endanger health on a short or long term basis. Therefore the potential health risk is thought to be minimal, if any.

IT IS VERY IMPORTANT THAT IF YOU HAVE ANY KIND OF METALLIC OBJECT IN YOUR BODY OR HAVE EXPERIENCED HEART RHYTHM DISTURBANCES THAT YOU NOT PARTICIPATE IN THIS STUDY.

If you have any questions about the procedure after leaving the lab, please feel free to contact the researchers: Eun-Young Lee (1-573-673-2989) or Steven Hackley, Ph.D. (1-573-882-3277).

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Participating in the present study is unlikely to be any medical benefit for you as an individual. Most participants consider the main benefits of participation to be the knowledge that they have contributed to biomedical science.

Potential benefit to others may result from the knowledge gained from your participation in this research study. For example, the present study can contribute to the identification of structures in brain for a new approach to the treatment of memory problems in people with Parkinson's disease.

THE MRI SCAN YOU WILL RECEIVE IS NOT INTENDED TO BE DIAGNOSTIC AND DOES NOT REPLACE A CLINICAL MRI SCAN REVIEWED BY A QUALIFIED RADIOLOGIST.

WHAT ABOUT CONFIDENTIALITY?

Information produced by this study will be stored in the investigators' file and will not be given to anyone unaffiliated with Dr. Hackley's laboratory in a format that could identify you. The results of this study may be published in scientific books or journals, or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law.

WHAT ARE THE COSTS?

There are no costs to you associated with participating in this study. Neither you nor your insurance company will be billed for the brain scan, which would normally cost about \$1400.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

There is a small payment (\$25/hour) for your participation.

[For college students as pilot subjects: one course credit will be awarded per half hour of your participation. In the summer, there will be a small payment (\$25) along with a CD copy of your brain image.]

WHAT IF I AM INJURED?

As noted above, it is very unlikely that you will be injured in any way during your participation in this research. Your safety and well being are of the utmost importance to us.

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number 1-573-882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Your participation in this experiment is voluntary. You do not have to be in the study if you don't want to. If you decide to participate, you can still change your mind and drop out of the study at any time. In addition, the investigators for this study may decide to end your participation in this study at any time, and will explain the reasons for doing so.

You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Health Sciences Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at 1-573-882-3181.

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact Eun-Young Lee (1-573-673-2989) or Steven Hackley, Ph.D. (1-573-882-3277).

A copy of this consent form will be given to you to keep.

SIGNATURE

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

_____	_____
Subject/Patient	Date
_____	_____
Additional Signature (if required, identify relationship to subject)	Date

**The presence and signature of an impartial witness is required during the entire informed consent discussion if the patient or patient's legally authorized representative is unable to read.

***The "Additional Signature" line may be used for the second parent's signature, if required. This line may also be used for any other signature which is required as per federal, state, local, sponsor and/or any other entity requirements.

"If required" means that the signature line is signed only if it is required as per federal, state, local, sponsor and/or any other entity requirements.

SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

_____	_____
Study Representative****	Date

****Study Representative is a person authorized to obtain consent. Per the policies of the University of Missouri Health Care, for any 'significant risk/treatment' study, the Study Representative must be a physician who is either the Principal or Co-Investigator.

If the study is deemed either 'significant risk/non-treatment' or 'minimal risk,' the Study Representative may be a non-physician study investigator.

Appendix D. HIPAA authorization form

Authorization for the Use and Disclosure of Personal Health Information Resulting from Participation in a Research Study

Principal Investigator's Name: Eun Young Lee

Project #: 1170557

Project Title: Target Intervention Sites for Treatment of Memory Deficits in
Parkinson's
Disease

You have agreed to participate in the study mentioned above. This authorization form gives more detailed information about how your health information will be protected.

1. Description of the information

My authorization applies to the information described below. Only this information may be used and/or disclosed in accordance with this authorization:

- medicine I am taking for Parkinson's disease and other disorders that affect the nervous system
- diagnosis
- physician's name
- demographic data (e.g., age, gender, education)

2. Who may use and/or disclose the information

I authorize the following persons (or class of persons) to make the authorized use and disclosure of my PHI:

- Drs. Hackley and Rolan, Ms Lee, and the co-investigators

3. Who may receive the information

I authorize the following persons (or class of persons) to receive my personal health information

- The information will be used in a confidential, aggregate format in publications and talks, but I will not be identified as an individual.
- Institutional Review Board, accounting office, and other regulatory bodies

4. Purpose of the use or disclosure

My PHI will be used and/or disclosed upon request for the following purposes:

- | | |
|---|--|
| <input type="checkbox"/> Auditing | <input type="checkbox"/> My treatment during the study |
| x <input type="checkbox"/> Study outcomes including safety and efficacy | x <input type="checkbox"/> Administrative and billing |
| x <input type="checkbox"/> Submission to government agencies that may monitor the study | |
| x <input type="checkbox"/> Publications and presentation of results that may identify me as a subject | |
| <input type="checkbox"/> Other: _____ | |

5. Expiration date or event

This authorization expires upon:

- ☐ The following date: _____

- ☐ End of research study
x ☒ No expiration date
☐ Other: _____
-

6. Right to revoke authorization

I understand that I have a right to revoke this authorization at any time. My revocation must be in writing in a letter sent to the Principal Investigator at __University of Missouri--Columbia_____. I am aware that my revocation is not effective to the extent that the persons I have authorized to use and/or disclose my PHI have already acted in reliance upon this authorization.

7. Statement that re-disclosures are no longer protected by the HIPAA Privacy Rule

I understand that my personal health information will only be used as described in this authorization in relation to the research study. I am also aware that if I choose to share the information defined in this authorization to anyone not directly related to this research project, the law would no longer protect this information. In addition, I understand that if my personal health information is disclosed to someone who is not required to comply with privacy protections under the law, then such information may be re-disclosed and would no longer be protected.

8. Right to refuse to sign authorization and ability to condition treatment, payment, enrollment or eligibility for benefits for research related treatment

I understand that I have a right not to authorize the use and/or disclosure of my personal health information. In such a case I would choose not to sign this authorization document I understand I will not be able to participate in a research study if I do not do so. I also understand that treatment that is part of the research project will be conditioned upon my authorization for the use and/or disclosure of my personal health information to and for use by the research team.

9. Suspension of right to access personal health information

I agree that I will not have a right to access my personal health information obtained or created in the course of the research project until the end of the study.

10. If I have not already received a copy of the University of Missouri Healthcare Privacy Notice, I may request one. If I have any questions or concerns about my privacy rights I should contact, the HS Privacy Officer at 573-882-9054 or the Campus Privacy Officer at 573-882-7254.

11. Individuals' signature and date

I certify that I have received a copy of the authorization.

Signature of Research Participant

Date

Research Participant's Legally Authorized Representative

Date

Describe Representative Authority to Act for the Participant

VITA

Eun-Young Lee was born on October 16, 1974, in Seoul, Korea. She received her bachelor's degree in German from Hankuk University of Foreign Studies, Seoul, Korea, in February, 1998. After graduation, she went to Germany to study psychology. She received her Diplom in psychology from University of Goettingen, Germany, in 2004. From 1999 to 2003, she worked as a research assistant in cognitive psychology laboratory at the University of Goettingen. She received her Ph.D. in psychology from University of Missouri-Columbia, USA, in 2012. Her graduate study was funded by Life Sciences Fellowship from the University of Missouri-Columbia.

She is married to Junhwan Jung since June, 2008, and has one daughter whose name is Hannah.