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Prospective Memory in Parkinson Disease across Laboratory and Self-reported Everyday Performance

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Abstract

Prospective memory is a complex cognitive construct ubiquitous in everyday life that is thought to sometimes rely on executive skills commonly affected by Parkinson disease (PD). The present study investigated the effect of PD on prospective memory tasks with varying demand on executive control processes, namely on the amount of strategic attentional monitoring required for intention retrieval. Non-demented individuals with PD and healthy adults performed laboratory event-based prospective memory tasks that varied in whether strategic attentional monitoring (nonfocal condition) or spontaneous processes (focal condition) were primarily involved in intention retrieval. Participants also completed a questionnaire rating their frequency of prospective memory failures in everyday life for both self-cued and environment-cued tasks. PD participants performed worse than non-PD participants in the nonfocal, but not focal, condition of the laboratory task. They also reported more everyday failures than non-PD participants for self-cued, but not environment-cued, prospective memory tasks. Thus, non-demented individuals with PD are preferentially impaired on prospective memory tasks for which higher levels of executive control are needed to support intention retrieval. This pattern is consistent across laboratory and reported real-world performance.

Keywords

Parkinsonian disorders; Intention; Cues; Executive function; Attention; Short term memory

Studies of non-demented, non-depressed individuals with Parkinson disease (PD) reliably show impaired executive functioning, even in the early stages of the disease (Pillon, Boller, Levy, & Dubois, 2001; Taylor & Saint-Cyr, 1995). Disruption of frontostriatal circuitry due to depletion of dopamine in the basal ganglia and prefrontal cortex is hypothesized as the primary underlying cause of these difficulties (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000). Affected executive processes in PD include planning (Owen et al., 1995), sequencing (Saint-Cyr, 2003), dual task processing (Brown & Marsden, 1991), working memory (Cooper, Sagar, & Sullivan, 1993; Lewis, Slabosz, Robbins, Barker, & Owen, 2005), temporal structuring (Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988; Vriezen & Moscovitch, 1990) and set shifting (Gauntlett-Gilbert, Roberts, & Brown, 1999). Although executive dysfunction in PD without dementia is relatively well-characterized in the laboratory,

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it is unclear whether or how experimentally-defined deficits manifest in the everyday lives of these patients.

Prospective memory, or remembering to carry out previously formed intentions, is a multifaceted cognitive construct (McDaniel & Einstein, 2007a) that is ubiquitous in everyday life. Real-world consequences of prospective memory failures can range in severity from the mildly annoying (e.g. forgetting to tape a television show) to the severe (e.g. forgetting to turn off the stove). Conceptually, intact prospective memory is essential for maintaining independence (e.g., medication adherence, Park & Kidder, 1996), employment (Dismukes, 2008), and social relationships (Morris, 1992). Recent clinical research provides evidence for the importance of prospective memory to daily functioning. For example, poor prospective memory is associated with impaired performance of various activities of daily living in individuals with human immunodeficiency virus (HIV) (Woods et al., 2008a; Woods et al., 2008b) and traumatic brain injury (Fortin, Godbout, & Braun, 2002; Fortin, Godbout, & Braun, 2003). The clinical significance of prospective memory is also apparent in that caregivers of individuals with Alzheimer's disease report prospective memory failures as being more frequent *and* more burdensome than retrospective memory failures (Smith, Della Sala, Logie, & Maylor, 2000).

Prospective memory is thought to involve cognitive processes and neural systems affected by PD. Successful prospective memory requires an individual to form an intention to do something at a particular moment in the future, maintain the intention over a delay while performing other unrelated activities, and then retrieve and execute the intention when the appropriate moment occurs. The moment, or cue, can be defined by time (time-based; e.g. go to a meeting at 2:00pm) or by the occurrence of a particular event (event-based; e.g., give a message to a colleague when you see her) (Kvavilashvili & Ellis, 1996). Although there is heterogeneity in the presence and nature of cognitive changes in early PD (Foltynie, Brayne, Robbins, & Barker, 2004), the hippocampal networks hypothesized to support encoding, retention and associative retrieval of prospective memory intentions (Martin et al., 2007; McDaniel et al., 2007a; see also Moscovitch, 1994) remain relatively intact in this population (Taylor, Saint-Cyr, & Lang, 1986). However, tasks with complex intentions or challenging retrieval contexts may require strategic encoding or self-initiated retrieval (Kliegel, McDaniel, & Einstein, 2000; Shallice & Burgess, 1991), and these processes are disrupted by frontrostriatal dysfunction in PD (Taylor, Saint-Cyr, & Lang, 1990). In addition to retrospective memory processes, prospective memory tasks involve the integration of many frontally-mediated executive processes, including planning how to accomplish the intention, maintaining the goals of both the intention and ongoing activity in working memory, interrupting the ongoing activity when the intention is retrieved, shifting attention to the intended action, and sequencing the execution of the intended action (McDaniel & Einstein, 2007a). Components of all of these functions are known to be impaired in individuals with PD (see review by Pillon et al., 2001). Furthermore, prefrontal cortical regions implicated by neuroimaging studies as involved in the executive aspects of prospective memory (e.g., Brodmann Area 45/46; Burgess, Quayle, & Frith, 2001) are affected by dopamine depletion in PD (Middleton et al., 2000). Thus, it is reasonable to expect impaired prospective memory in PD secondary to frontal-executive dysfunction.

The available studies generally support the above notion, finding that PD participants are impaired in event-based prospective memory tasks despite remembering the contents of the intentions (Altgassen, Zollig, Kopp, Mackinlay, & Kliegel, 2007; Katai, Maruyama, Hashimoto, & Ikeda, 2003; Kliegel, Phillips, Lemke, & Kopp, 2005) even when the intentions are complex (Altgassen et al.; Kliegel et al.). This suggests that individuals with PD have intact encoding and storage of the intention (the retrospective component) but are unable to employ efficient strategies to recall and execute it at the appropriate moment (the prospective component) (Einstein & McDaniel, 1990; Ellis, 1996). This pattern of impairment has been

attributed to disrupted executive control processes including self-initiated retrieval (Katai et al., 2003), planning (Kliegel et al., 2005), and working memory (Altgassen et al, 2007; Kliegel et al., 2005). Notably, Costa, Peppe, Caltagirone and Carlesimo (2008) found opposite results with their event-based task, whereby PD participants were less accurate than non-PD participants in recalling the intended actions even though they initiated performance of the actions just as often. The authors acknowledge, however, that the highly salient event-cue (a timer ring) may have eliminated the need for executive control processes to support intention retrieval. Further, the intention (perform three unrelated actions) was sufficiently challenging such that PD participants who were not impaired on traditional tests of declarative memory were unable to recall it. Taken together these data suggest that when executive processes are needed to support intention retrieval, prospective memory is impaired in PD. No studies to date have explicitly tested this assumption by manipulating, within an event-based prospective memory task, the degree of executive control required for intention retrieval.

In this article, we apply the Multiprocess Theory of prospective memory (McDaniel & Einstein, 2000; 2007a) to guide a more refined examination of prospective memory in PD and its relation to executive dysfunction. Specifically, the Multiprocess Theory proposes that particular features of the prospective memory task can determine whether or not executive resources are employed to support intention retrieval. In a typical experimental event-based prospective memory paradigm, participants are instructed to perform a specific action upon the occurrence of a cue that is embedded in an ongoing activity[1]. The ongoing activity does not change when the cue appears, so for intention retrieval to occur participants must somehow recognize the prospective memory event as a cue for action (McDaniel, Guynn, Einstein, & Breneiser, 2004; Smith, 2003). According the Multiprocess Theory, individuals can either use strategic attentional resources to monitor for the cue during the ongoing task, or they can rely on spontaneous processes to retrieve the intention upon encountering the cue. The model assumes that while strategic monitoring is an executive process that involves the prefrontal cortex, spontaneous retrieval requires little executive control and instead relies on a reflexive-associative medial temporal lobe system. Given the specific nature of cognitive and neuropathological dysfunction in PD and based on the above framework, we hypothesize dissociation within event-based prospective memory whereby individuals with PD are impaired only on prospective memory tasks that require strategic monitoring for intention retrieval.

To test this novel hypothesis, we manipulated the prospective memory task so that intention retrieval would require strategic attentional monitoring in one condition but would rely on more spontaneous retrieval processes in another condition. Following Einstein et al.'s (2005) event-based prospective memory paradigm, we varied the degree to which the ongoing activity encouraged processing of features of the prospective memory cue emphasized during intention formation (i.e., task instructions). The Multiprocess Theory and recent evidence (e.g., Einstein et al.; Rendell, McDaniel, Forbes, & Einstein, 2007) suggest that when the ongoing activity encourages processing of the prospective memory cue, intention retrieval will be relatively spontaneous (we label this the *focal* cue condition). By contrast, when the ongoing activity does not focus attention on the prospective memory cue, intention retrieval will involve strategic monitoring (*nonfocal* cue condition). Accordingly, we predicted that PD participants

[1]Typically in prospective memory paradigms, the ongoing activity is sufficiently engaging and unrelated to the prospective memory intention to discourage overt rehearsal, or maintenance in focal awareness, of the intention. Further, the prospective memory cue occurs as a natural part of the ongoing activity and does not directly demand performance of the intended action. These features contrast with most vigilance tasks, where all attention is presumably devoted toward detecting and reacting to a particular cue and the presentation of the cue is essentially a signal to perform the action. We acknowledge that theoretically, vigilance processes could nevertheless be involved in prospective memory tasks, particularly in those that involve monitoring. A recent study, however, found that vigilance, as assessed by a traditional vigilance task, accounted for only a small and non-significant portion of variance in prospective memory (using a different computerized prospective memory task) (Rose, McDaniel, & Rendell, 2008).

would perform worse than non-PD participants on the prospective memory task with nonfocal cues, whereas the groups would perform equivalently on the prospective memory task with focal cues.

To provide converging support for the theoretical claim that our participants would employ different prospective memory retrieval processes for focal versus nonfocal cue conditions, each participant also completed a block of ongoing activity trials without an accompanying prospective memory task. This control condition provided a baseline against which to compare response times for the ongoing activity when a prospective memory task also had to be performed. Following previous researchers (e.g., Einstein et al., 2005; Marsh, Hicks, & Cook, 2005; Smith, 2003), we assumed that significant increases in ongoing activity response times (relative to the control condition) would imply that executive resources were recruited to support strategic monitoring (as expected in the nonfocal cue condition). By contrast, no significant increases in response times would imply that intention retrieval was supported by spontaneous processes (as expected in the focal cue condition). Further, we assessed working memory capacity as an index of participants' executive resources. If the expected PD-related prospective memory decline for nonfocal tasks is indeed a consequence of declines in executive control, then working memory capacity should account for a significant proportion of the observed group differences in nonfocal prospective memory performance. Importantly from the perspective of the current theoretical framework, working memory capacity should not be related to focal prospective memory performance.

We were also interested in gauging the degree to which the anticipated patterns of laboratory prospective memory performance might parallel real-world prospective memory functioning for PD participants. To this end, we assessed self-reports of our participants' prospective memory difficulties in everyday life. We predicted that, like the laboratory tests, everyday prospective memory tasks with greater demand on executive control would be preferentially difficult for individuals with PD.

Finally, we wanted to control for the potential effect of dopaminergic medication on prospective memory performance in our PD group. It is hypothesized that optimal levels of dopamine increase the strength of cognitive signal relative to background noise in the prefrontal cortex, thereby enhancing executive control skills; however, levels that are too low or too high may dampen or diffuse the signal, leading to impaired performance (Braver, Barch, & Cohen, 1999; for review, see Cools, 2006; Williams & Goldman-Rakic, 1995). Given the complexity of previous findings regarding the cognitive effects of dopaminergic medication (e.g., Cools, Barker, Sahakian, & Robbins, 2001a; Gotham, Brown, & Marsden, 1988; Kulisevsky et al., 1996; Lange et al., 1992), it was unclear how medication status would influence prospective memory performance in the present study. Therefore, we tested PD participants while both on and off medications.

Method

This study was approved by the Human Research Protection Office at Washington University School of Medicine (WUSM) and was completed in accordance with the Helsinki Declaration. All participants gave written informed consent before testing.

Participants

Study participants were 24 PD and 30 healthy adult volunteers. Exclusionary criteria included: (1) current mood, anxiety or substance use disorders or history of psychosis (as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders, SCID; First, Spitzer, Gibbon, & Williams, 2002) (2) suspected dementia or global cognitive impairment (< 25 on the Mini-Mental State Examination; Folstein, Folstein, & McHugh, 1975), (3) history of head injury,

neurosurgery or other neurological condition aside from PD, (4) treatment with anticholinergic medication within the past 60 days (for PD participants), and (5) biological family history of PD (for non-PD participants). PD participants were diagnosed with idiopathic PD by a neurologist at the WUSM Movement Disorders Clinic and were all Hoehn and Yahr stage I or II (Hoehn & Yahr, 1967), indicating relatively mild signs of disease.

Procedure

Each participant performed cognitive testing during two testing sessions approximately one week apart. These included the prospective memory and working memory tasks (described below) and a motor-free version of the Tower of London task (Keefe et al., 2004). The Tower of London task was included as a brief, repeatable index of general executive function ability. PD participants performed testing once while on their regular antiparkinsonian medications and once after being off medications overnight (counterbalanced order). Non-PD participants performed both testing sessions in the same state (i.e., no antiparkinsonian medication); however, they received "on" and "off" testing session assignments in a counterbalanced order to control for differences in testing procedures across the sessions.

PD participants arrived to both testing sessions at least 8 hours after their last dose of antiparkinsonian medication (M = 12.6 hours, SD = 2.5). For their off testing session, they underwent a clinical motor rating (the Unified Parkinson's Disease Rating Scale Motor subscale, UPDRS; Fahn, Elton, & Members of the UPDRS Development Committee, 1987) and then proceeded to cognitive testing after about 30 minutes. For their On testing session, they underwent an initial UPDRS and then took their regular dose of antiparkinsonian medication. After they felt their medication had taken effect (30–60 minutes) they underwent a second UPDRS and then proceeded to cognitive testing.

During the wait period in the "on" testing session (before beginning cognitive testing), participants provided demographic information, completed various questionnaires and performed the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) as an estimate of premorbid intelligence. During the "off" session wait period, all participants were administered the SCID, and the non-PD participants received brief neurological evaluations to screen for any underreported or undiagnosed neurological conditions. A trained movement disorders research nurse performed all neurological screens and UPDRS ratings. The order in which the prospective memory and working memory tasks were administered relative to each other was counterbalanced across testing session. The details for the procedures of the cognitive tasks and questionnaire are provided next.

Laboratory event-based prospective memory—This computerized task was programmed according to the paradigm described in Einstein et al. (2005, Experiment 2). The task involved three conditions: a control condition in which only the ongoing activity was presented, and two prospective memory conditions (focal and nonfocal) in which a prospective memory task was added to the ongoing activity. The condition order was randomized across participants and testing session. We developed two equivalent versions that were counterbalanced across testing session for each participant (Foster et al., 2006). Each version used different prospective memory targets and different ongoing activity items (created from the Battig & Montague, 1969, norms).

The *ongoing activity* was a simple word-categorization task. Participants were presented with word pairs, and they decided whether the lower case word appearing on the left side of the screen belonged in the category represented by the capitalized word appearing on the right side of the screen. Participants were instructed to press keys labeled *Y* (5 on the number pad) or *N* (6 on the number pad) to indicate a *yes* or *no* response, respectively. They were instructed to make their responses as quickly and accurately as possible. The word pair stayed on the

screen until the participant responded, and the response triggered presentation of the next pair. There were 160 word pair trials, and the order of word pairs was randomly determined for each participant. Ongoing activity accuracy (proportion correct) and response time (in milliseconds) were recorded.

For the *prospective memory conditions*, in addition to performing the ongoing activity, participants were instructed to press the *Q* key whenever they saw a prospective memory cue. Because the word-categorization task requires the stimuli to be processed as unitized lexical items, it fosters focal attention to words but not syllables. Therefore, for the focal condition the cue was a word (either *tulip* or *cookie* depending on the particular version), and for the nonfocal condition the cue was a syllable (either *rad* or *com*). The nonfocal cue occurred at the beginning of four different exemplar words (e.g. for *com*, words were *comet*, *commercial*, *computer*, *command*), and the order of the four words was randomly determined for each participant and testing session. Prospective memory cues occurred 4 times out of 165 word pair trials during each prospective memory condition. Prospective memory responses were scored as correct if the participant pressed the *Q* key either during the prospective memory cue trial or within one word pair following the cue. Participants were given 1 point for each correct prospective memory response, yielding a total score of 0 to 4 for each prospective memory condition. After completing the entire task, participants were quizzed on their recall of the intended action (i.e. press *Q*) and their recall or recognition (if they did not have recall) of the focal and nonfocal cues.

Working memory: Serial Set—This computerized test is a modified Sternberg short-term memory task (Oberauer, 2001) that varies the demands on maintenance and manipulation aspects of working memory. Participants viewed a series of either 4 or 5 randomly generated letters presented sequentially in the center of a computer screen (e.g. *G A E B*). They were then given a task cue that instructed them to either remember the letters in the order they were presented (*maintain*) or rearrange them alphabetically and then remember the new, alphabetized order (*reorder*). A 10 second delay was imposed, and then a single letter and position-number probe was presented (e.g. *2A*). Participants decided if the letter resided in the position indicated by the number and then verbally responded *"Yes"* or *"No"* into a microphone. An experimenter coded their response and then triggered the next trial. Using the example provided above, if the task cue was *maintain*, the correct answer would be *"Yes"*; if the task cue was *reorder*, the correct answer would be *"No"* (because, in the alphabetized list, *A* would move to position *1*). There were four conditions in this test, representing the four combinations of set size (4 vs. 5) and task (maintenance vs. manipulation). There were 30 trials in each condition. Accuracy (proportion correct) and verbal response times were recorded.

Reported everyday memory: Prospective and Retrospective Memory Questionnaire—(PRMQ; Crawford, Smith, Maylor, Della, & Logie, 2003; Smith et al., 2000) This 16-item questionnaire measures self-reported prospective and retrospective memory failures in everyday life. Eight of the items enquire about prospective memory and eight about retrospective memory. Items can be further classified along the dimensions of short-term versus long-term memory and self-cued versus environment-cued memory. For example, the item *"Do you forget to tell someone something you had meant to mention a few minutes ago?"* measures prospective, short-term, self-cued memory, whereas the item *"Do you fail to recognize a place you have visited before?"* measures retrospective, long-term, environmentally-cued memory (see Crawford et al., Appendix 1, for a full list of the PRMQ items and their categorizations). In the current study, we considered the self-cued versus environment-cued memory distinction within the Prospective scale because it parallels the nonfocal versus focal manipulation in the experimental prospective memory paradigm. Self-cued prospective memory tasks are considered to require more executive control resources for intention retrieval, while environment-cued tasks are thought to rely more on automatic

retrieval (Craik, 1986). Participants rate each item on a 5-point scale according to how often they experience the memory failure it describes (1 = *Never* and 5 = *Very Often*). This yields a Total score of 16 to 80, Prospective and Retrospective scale scores of 8 to 40, and self-cued and environment-cued scores of 4 to 20 within each memory scale. Higher scores indicate worse subjective everyday memory. Participants completed this questionnaire one time.

Results

All statistical tests were 2-tailed. An alpha level of $p < 0.05$ was considered significant, and effect sizes were estimated using partial eta squared (η^2) for multivariable models and Cohen's *d* for planned pairwise comparisons.

Participant Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. There were no significant group effects with regard to gender, ethnicity, age, education or WTAR score (as determined by Mann-Whiney U tests, except for gender and ethnicity where Chi-square tests were used; all *p*s > 0.43). There were also no group differences in the number of correct items (out of 22) on the Tower of London task (on testing session: PD (*M* ± *SD*) = 18.2 ± 2.8, non-PD = 18.2 ± 3.7; off testing session PD = 17.8 ± 2.8, non-PD = 18.0 ± 2.6; all *p*s > 0.67). Of the PD participants, 11 were receiving carbidopa-levodopa exclusively, 11 were receiving carbidopa-levodopa with a dopamine agonist (i.e. pramipexole, ropinirole or pergolide) and 2 were receiving carbidopa-levodopa with a COMT inhibitor (i.e. entacapone). PD participants had significantly higher UPDRS scores (indicating worse motor dysfunction) while off compared to on their antiparkinsonian medications ($p = 0.01$). As per the brief neurological evaluation, no participants in the non-PD group had any notable neurologic abnormalities.

Laboratory Prospective Memory

Prospective memory performance—Prospective memory responses were scored as correct if the participant responded during the presentation of the prospective memory cue or the following word pair trial. Only 2.5% of all responses occurred at other times (6 from 5 PD participants, 5 from 3 non-PD participants) indicating that participants tended to respond quickly or not at all. Thus, the number of late or false-positive responses was too small to analyze quantitatively, and qualitative inspection revealed no apparent effects of group, prospective memory condition or testing session related to this outcome.

The group means and standard deviations for the number of correct prospective memory responses for each prospective memory condition and testing session are presented in Table 2. These data were submitted to a general linear model (GLM) with group (non-PD, PD) as the between-subjects factor and prospective memory condition (focal, nonfocal) and testing session (on, off) as the within-subjects factors. Performance was better in the focal compared to the nonfocal condition, $F(1, 52) = 44.47$, $p < 0.001$, $\eta^2 = 0.47$. There was also a significant main effect of group, $F(1, 52) = 10.27$, $p = 0.002$, $\eta^2 = 0.17$, that was qualified by a significant group × condition interaction, $F(1, 52) = 7.11$, $p = 0.01$, $\eta^2 = 0.12$. Planned comparisons (independent samples *t*-tests) confirmed that PD participants had worse prospective memory performance than non-PD participants in the nonfocal condition, $t(52) = 3.22$, $p = 0.002$, $d = 0.81$, but not in the focal condition, $t(52) = 0.91$, $p = 0.37$, $d = 0.24$ (see Figure 1). There were no effects of testing session in the full model (all *p*s > 0.21). Further, when analyzed within groups, there were still no significant effects of testing session (*p*s > 0.20). This indicates that medication status did not affect the PD participants' prospective memory performance.

When queried at the end of the experiment, 100% of the participants correctly recalled the prospective memory action (press the *Q* key). Combined across testing sessions, all but 2

participants (1 PD, 1 non-PD) correctly recalled the focal target and all but 3 participants (1 PD, 2 non-PD) correctly recalled the nonfocal target. However, all of these participants correctly recognized the targets. Thus, the prospective memory failures described above were most likely due to failures in the prospective, rather than in the retrospective, component of the task.

Ongoing activity performance—We examined response accuracies and latencies from the word-categorization task to determine whether performing the prospective memory task affected ongoing activity performance. We tabulated performance from the ongoing activity trials after excluding the first 5 trials (to allow response times to stabilize) and the 5 trials following each target event (to remove the possible influence of having just made a prospective memory response). This left 136 trials from which to calculate accuracy means. We calculated response time means from correct trials after trimming outliers within each participant and condition by removing trials for which response times were more than 2 SD's from the mean. The accuracy and latency data were submitted to separate GLM, with group as the between-subjects factor and prospective memory condition (focal, nonfocal, control) and testing session as the within-subjects factors (see Table 2 for the group means and standard deviations).

Ongoing activity accuracy was high overall ($M = 0.96$, $SD = 0.02$) and did not vary significantly across group, condition or testing session (all ps > 0.28). When analyzed within groups, there were no effects of testing session on ongoing activity accuracy (all ps > 0.26). This indicates that medication status did not affect word categorization accuracy in the PD group.

Ongoing activity response times were significantly affected by the prospective memory condition, $F(2, 52) = 51.52$, $p < 0.001$, $\eta^2 = 0.50$. Planned comparisons revealed that response times in the nonfocal condition ($M = 1578$, $SD = 396$) were significantly slower than in the focal and control conditions, whereas response times in the focal ($M = 1351$, $SD = 257$) and control ($M = 1338$, $SD = 244$) conditions were equivalent. The absence of a significant effect of the focal prospective memory task on ongoing activity response times was not a consequence of inadequate power, as there was extremely high power to find even a relatively small effect (power = 0.996 to detect an effect size of $f = 0.10$). There were no effects of group or testing session on ongoing activity response time in the full model (all ps > 0.17). When analyzed within groups, there were still no effects of testing session (all ps > 0.20). This indicates that medication status did not affect the PD participants' ongoing activity response times.

Laboratory Working Memory

The group means and standard deviations for working memory accuracy (proportion correct out of 30 trials) are presented in Table 2. We included these data in a GLM with participant group as the between-subjects factor and set size (4, 5), task (maintenance, manipulation), and testing session as within-subjects factors. As expected, performance was better with 4-letter lists compared to 5-letter lists, $F(1, 52) = 125.60$, $p < 0.001$, $\eta^2 = 0.73$, and there was a trend toward better performance on the maintenance compared to the manipulation task, $F(1, 52) = 3.36$, $p = 0.07$, $\eta^2 = 0.07$. PD participants performed worse than non-PD participants overall, $F(1, 52) = 4.70$, $p = 0.04$, $\eta^2 = 0.09$. There were no effects of testing session in the entire sample (all ps > 0.23) or when analyzed within groups (all ps > 0.39). This indicates that the PD participants' working memory performance was not significantly affected by their medication status. Because there were no interactions between any of the working memory task factors (all ps > 0.33), we calculated an overall working memory score for each participant by averaging his or her accuracy scores across all test conditions and both testing sessions. We used the resulting value for the following correlational analyses.

Associations between Laboratory Prospective Memory and Working Memory

To provide further evidence for our theoretical assumptions that executive control is required for nonfocal prospective memory (e.g., to support strategic monitoring implied by response time costs to the ongoing activity) but not focal prospective memory, we conducted linear regression analyses to determine the proportion of variance in nonfocal and focal prospective memory performance accounted for by working memory capacity. The dependent variables in these analyses were the number of correct prospective memory responses for each of the prospective memory tasks (nonfocal and focal) averaged across testing session. In the entire group of participants, working memory accounted for 22% of the variance in nonfocal prospective memory, $F(1, 52) = 14.59$, $p < 0.001$, but did not account for a significant proportion of the variance in focal prospective memory performance ($F < 1$, $p = 0.66$). When the groups were examined separately, working memory still accounted for a significant portion of the variance in nonfocal prospective memory in the non-PD group, $R^2 = 0.28$, $F(1, 28) = 10.60$, $p = 0.003$; this relationship was only marginally significant in the PD group, $R^2 = 0.12$, $F(1, 22) = 2.85$, $p = 0.10$. As with the combined group analysis, working memory was not a significant predictor of focal prospective memory performance within either group (Fs < 1, ps > 0.74). These results indicate that working memory capacity contributes more to nonfocal than to focal prospective memory performance.

To gain leverage on our hypothesis that PD disrupts nonfocal prospective memory because of compromised executive resources (as assessed by working memory) we conducted a pair of hierarchical linear regression analyses predicting nonfocal prospective memory. One model included only participant group as a predictor and the second model included working memory and participant group as predictors. In the first model, group accounted for 17% of the variance in nonfocal prospective memory performance, $F(1, 52) = 10.39$, $p = 0.002$. In the second model, working memory accounted for an initial 22% of the variance in nonfocal prospective memory, $F(1, 52) = 14.59$, $p < 0.001$, and the proportion of the variance accounted for by group was reduced to 9% but was still significant ($F(1, 51) = 6.41$, $p = 0.01$). Working memory explained almost half (47%) of the group-related variance in nonfocal prospective memory performance. Thus, the PD-related deficit in nonfocal prospective memory performance was partially, but not completely, mediated by working memory.

Self-reported Everyday Memory

Self-reported prospective memory—To determine if PD had a similar effect on prospective memory in everyday life as it did in the laboratory, we compared the PD and non-PD groups' reported everyday self-cued and environment-cued prospective memory failures. There were significant main effects of group, $F(1, 52) = 5.78$, $p = 0.02$, $\eta^2 = 0.10$, and cue type, $F(1, 52) = 13.80$, $p < 0.001$, $\eta^2 = 0.21$, that were qualified by a significant cue × group interaction, $F(1, 52) = 5.36$, $p = 0.03$, $\eta^2 = 0.10$. Planned comparisons showed that PD participants reported more self-cued but not environment-cued prospective memory failures than non-PD participants (self-cued: $t(52) = -3.36$, $p = 0.001$, $d = 0.89$; environment-cued: $t(52) = -1.19$, $p = 0.24$, $d = 0.33$). Additionally, self-cued prospective memory tasks elicited more failures than environment-cued prospective memory tasks in the PD group ($t(23) = 3.83$, $p = 0.001$, $d = 1.13$) but not in the non-PD group ($t(29) = 1.10$, $p = 0.28$, $d = 0.29$). See Table 3 for the means.

Self-reported retrospective memory—To determine whether the pattern of results described above was specific to prospective memory, we examined the PRMQ retrospective scale data in the same way. There were significant main effects of group, $F(1, 52) = 3.89$, $p = 0.05$, $\eta^2 = 0.07$, and cue type, $F(1, 52) = 50.70$, $p < 0.001$, $\eta^2 = 0.49$, but not a cue × group interaction ($p = 0.96$). The PD group reported more retrospective memory failures overall than the non-PD group, and all participants reported more self-cued than environment-cued

retrospective memory failures (see Table 3 for the means). The absence of a significant cue × group interaction for the retrospective memory scale indicates that the PD group's differential impairment in self-cued tasks (relative to the non-PD group) was specific to everyday prospective memory. Exploratory analyses confirmed this interpretation. Although there was a main effect of group in the omnibus analyses, there were no significant differences between groups in either self-cued or environment-cued retrospective memory failures when analyzed separately (self-cued: $t(52) = -1.65$, $p = 0.11$, $d = 0.44$; environment-cued: $t(52) = -1.64$, $p = 0.11$, $d = 0.46$).[2]

Associations between Laboratory and Self-reported Everyday Prospective Memory

To determine the relevance of laboratory prospective memory to self-reported everyday prospective memory, we performed within-groups bivariate correlations (Pearson's *r*) between nonfocal and focal prospective memory performance and PRMQ self-cued and environment-cued prospective memory scores. There were no significant correlations within either group (*p*s > 0.13). These data, with laboratory prospective memory performance collapsed across testing session, are presented in Table 4.

Discussion

Our results suggest that non-demented individuals with early PD are preferentially impaired on event-based prospective memory tasks that place high demand on executive control, namely on the use of attentional control strategies to support intention retrieval. This effect was observed consistently across laboratory task performance and self-reported real-world performance. PD participants performed worse than non-PD participants on an event-based prospective memory task that requires strategic attentional monitoring (nonfocal task), and they reported more failures than non-PD participants on everyday prospective memory tasks that require self-cued intention retrieval. In contrast, PD participants were not impaired on laboratory or everyday prospective memory tasks for which explicit external cues presumably automatically trigger intention retrieval (i.e., focal and environment-cued tasks).

In concordance with the Multiprocess theory of prospective memory (McDaniel & Einstein, 2000, 2007a), two independent results suggest that intention retrieval was supported by different processes in the nonfocal versus the focal prospective memory task. First, participants were significantly slower in responding to the ongoing activity in the nonfocal prospective memory condition than they were in the control condition even though ongoing activity demands were the same. These response time costs imply executive resources that would have quickened performance on the ongoing activity were instead deployed to monitor for the prospective memory cue during the nonfocal task (e.g., Einstein et al., 2005; Marsh et al., 2005; McDaniel et al., 2007a). In contrast, the focal task did not produce significant response time or accuracy costs to the ongoing activity. This implies that more automatic processes supported intention retrieval in the focal task because that task did not interfere with the processing necessary to perform the ongoing activity (Einstein et al., 2005; McDaniel et al., 2007a; 2007b). Second, working memory capacity was associated with nonfocal but not focal

[2]We were not interested in directly comparing everyday prospective vs. retrospective memory performance but wanted instead to use the Retrospective scale as a reference for our pattern of Prospective scale findings. However, in response to a reviewer's suggestion, we also analyzed the PRMQ data in a single model using memory scale as a factor (i.e., Group [PD, non-PD] x Memory scale [Prospective, Retrospective] x Cue [self, environment]). Our findings confirmed our interpretation of the differences between the separate memory scale analyses. There were main effects of Memory scale and Cue, such that participants reported more failures in everyday prospective and self-cued tasks vs. retrospective and environment-cued tasks (*p*s < 0.001). There was also main effect of Group, such that the PD group reported more everyday memory failures overall compared to the non-PD group ($p = 0.02$). However, this effect was qualified by a significant Group x Memory scale x Cue interaction that, when broken down, indicated the only significant group difference was in the Prospective scale self-cued score ($p = 0.04$).

prospective memory performance. This finding is also consistent with the idea that nonfocal but not focal prospective remembering requires executive control resources.

There are a number of other executive control processes that could contribute to a PD-related deficit on nonfocal tasks. Although working memory – which presumably was required to keep the intention active while also engaging in the ongoing activity – accounted for almost half of the group-related variance in nonfocal prospective memory, it did not completely mediate the effect. It is unlikely the case that this deficit resulted from impaired intention formation processes (e.g., less elaborate encoding of the intention or planning how to accomplish it) or from difficulty inhibiting response to the ongoing activity and executing the intended action because these processes were also required in the focal task (see, e.g., Kliegel et al., 2000; McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999; McDaniel, Robinson-Riegler, & Einstein, 1998). In addition, both groups demonstrated similar levels of attentional monitoring in the nonfocal condition (as indicated by response time costs to ongoing activity), which suggests that PD does not necessarily compromise the recruitment of strategies to support future intention retrieval (Einstein & McDaniel, 2008; Meeks, Hicks, & Marsh, 2007). Notably, however, the apparent monitoring strategies implemented by PD participants were not as effective in supporting prospective memory performance as those implemented by the non-PD participants. It appears that the PD participants were appropriately anticipating the nonfocal cue, but they were somehow unable to retrieve the intention when the cue occurred. The specificity of this deficit for nonfocal cues could reflect difficulty shifting attention to non-explicit or irrelevant features (per the ongoing activity) in the stimulus array (Brown & Marsden, 1988; Gauntlett-Gilbert et al., 1999). This impairment in cognitive flexibility is well described in the PD literature (e.g., Cools, Barker, Sahakian, & Robbins, 2001b; Gauntlett-Gilbert et al., 1999; Lewis et al., 2005) and it has been associated with dopamine depletion in the caudate in marmosets (Crofts et al., 2001). It also may be that the PD participants were unable to maintain attentional monitoring consistently across the experimental task (see McDaniel, Einstein, & Rendell, 2008, for evidence that monitoring can be difficult to maintain across the entire experimental task; Partiot et al., 1996).

Our findings provide new insight into the existing literature on prospective memory in PD. Katai et al. (2003) found that individuals with PD were impaired on event- but not time-based prospective memory while on antiparkinsonian medication. These results may initially appear to conflict with ours, as time-based tasks are thought to require more attentional control than event-based tasks (d'Ydewalle, Bouckaert, & Brunfaut, 2001). However, the presence of an external cue (a clock) in their time-based task could have reduced the need for internally-guided attentional monitoring. In contrast, the prospective memory cues in Katai et al.'s event-based task conceivably did not receive focal attention during ongoing task processing[3], which would have increased the need for strategic monitoring. In two studies by Kliegel and colleagues, PD participants had worse event-based prospective memory than non-PD participants (Altgassen et al., 2007; Kliegel et al., 2005). Both of these studies employed complex paradigms that placed high demand on a number of other cognitive processes including retrospective memory, planning and working memory. So while it is not surprising that the PD participants were impaired, it is unclear whether their impairment was specific to the prospective component or driven instead by overall task difficulty. We used a validated experimental paradigm that explicitly manipulates whether strategic attentional monitoring is employed for intention retrieval (Einstein et al, 2005) while holding all other task demands equal. This paradigm also

[3]The ongoing activity of Katai et al.'s (2003) event-based prospective memory task required participants to view 12-word lists and verbally report the two words that did not belong in the same category as the other ten words. Their prospective memory task was to tap the desk whenever a target word appeared (the Japanese word for "cow" or "orange"). The prospective memory target words were always members of the larger 10-word category (S. Katai, personal communication, December 8, 2004). This feature could have reduced the amount of focal attention the prospective memory target words received during the performance of the ongoing activity, particularly if they occurred later in the list than the two words that were selected out as a part of the ongoing activity.

isolates the prospective component of prospective memory by reducing ongoing task demands and retrospective memory load (participants needed only to remember a single cue and simple intended action). These methodological features, along with the growing body of literature supporting the Multiprocess theory of prospective memory (reviewed in McDaniel & Einstein, 2007a), allow us to draw stronger inferences regarding the cognitive mechanisms that underlie prospective memory impairment in PD.

Our discussion of the cognitive processes involved in nonfocal and focal prospective memory tasks (see McDaniel et al., 2007a, for more extensive discussion) and our data showing that the PD group was impaired on nonfocal but not focal prospective memory are consistent with the idea that PD produces a deficient executive control mechanism (e.g., Supervisory Attentional System; Shallice & Burgess, 1991; see also Brown & Marsden, 1988) but not a compromised reflexive-associative retrieval system (e.g., Moscovitch, 1994; see also Bondi et al., 1993). These disrupted and spared cognitive systems converge on the neuropsychological perspective that early PD disrupts prefrontal but not hippocampal functioning (e.g., Taylor et al., 1990). However, the prefrontal cortical areas associated with prospective memory function in neuroimaging studies of young, healthy volunteers are not completely overlapping with the regions affected by dopamine depletion in PD. PD is most commonly associated with alterations of the dorsolateral prefrontal cortex (BA 45/46), the anterior cingulate (BA 24), and the orbitofrontal cortex (BA 12) (Alexander et al., 1986). The dorsolateral prefrontal cortex has been linked to intention maintenance and execution (Burgess et al., 2001), but the most consistent region associated with intention retrieval (with nonfocal tasks) in prospective memory studies is the anterior prefrontal cortex (i.e., frontal pole, BA 10; Burgess, Scott, & Frith, 2003; Okuda et al., 2007; Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006). Further, our tasks were not designed to challenge retrospective memory or medial temporal functions directly, and so our data cannot address this dissociation optimally. This issue may warrant more focused examination, particularly in light of recent studies demonstrating retrospective component impairment in PD (Costa et al., 2008).

A novel feature of our study was the examination of prospective memory in PD in both the laboratory setting and as reported in everyday life. Although we found a parallel dissociation of prospective memory within the PD group for the laboratory and everyday measures, there were no correlations between the two sets of findings. This phenomenon is not new to neuropsychological research, as self-report measures of everyday cognitive functioning often correlate poorly with actual neuropsychological test performance (Burgess et al., 2006; Chaytor & Schmitter-Edgecombe, 2003). In fact, similar decouplings between PRMQ scores and various performance-based prospective memory tasks have been observed in studies of college students (Meeks et al., 2007), healthy older adults (Zeintl, Kliegel, Rast, & Zimprich, 2006) and individuals with presumed frontostriatal pathology (i.e., HIV; Woods et al., 2007). There are a number of possible explanations for the lack of association between laboratory and everyday prospective memory in our study.

First, due to the subjective nature of self-report questionnaires, it is possible that our measurement of everyday prospective memory was biased in some way. For example, older adults have been observed to have failures in output monitoring (Einstein, McDaniel, Smith, & Shaw, 1998; Marsh, Hicks, Cook, & Mayhorn, 2007), which occur when individuals think they have completed an intention when in fact they have not, or vice versa. Poor output monitoring could have influenced awareness, and thus report, of everyday prospective memory failures in our sample. Future studies could improve the reliability of self-reports of everyday prospective memory by checking them against informant reports. Alternatively, using more naturalistic measures of prospective memory may be a better way to address everyday prospective memory functioning than relying on self-report.

Second, our computerized prospective memory task may have failed to capture the complexities of real-world prospective memory tasks. By virtue of simplifying task demands to isolate intention retrieval, our laboratory task was unlike many everyday prospective memory tasks, which often depend on the integration of many executive and memory processes. Thus, to the advantage of increased experimental control we may have unintentionally weakened the ability of our laboratory task to yield an association with an everyday prospective memory measure that asks about complex, multifaceted and sometimes ambiguous (as to the underlying cognitive processes tapped) tasks (see Crawford et al., 2003, for a full list of the questionnaire items and latent structure data). Additionally, with only four prospective memory trials per condition and generally high performance overall, there was limited variance in our laboratory task data. Future studies may need to increase task complexity – and possibly difficulty – to broaden the range of performance and improve the ability to detect relationships with other measures. Small sample size and restricted range of the PRMQ scores may also have reduced our power to detect associations.

Finally, we did not take into account other factors that could influence the relationship between prospective memory performance in the laboratory and in the real-world, including the use of compensatory strategies (see, e.g., Maylor, 1990; Rendell & Thompson, 1999) and the amount of daily prospective memory challenge present in the participants' lives. Nonetheless, the striking parallel between our experimental task and questionnaire findings identifies a stable pattern in PD patients' prospective memory that translates across environments (laboratory versus real-world) and measurement approaches (performance versus self-report).

Antiparkinsonian medication did not have any acute effects on prospective memory or working memory performance in our sample of PD participants. The relationship between dopaminergic medication and executive control in PD is complex, potentially long lasting, and can depend on numerous factors including dosage, disease severity, basal dopamine levels and task demands (for review, see Cools, 2006). We did not design or power the current study to parse apart these issues or to determine the effect of dopaminergic medication on prospective memory. Instead, our purposes in testing PD participants while both optimally medicated and after overnight withdrawal from their antiparkinsonian medications (a practical "off" state) were to (1) isolate the effect of PD on laboratory prospective memory performance, and (2) examine prospective memory performance under conditions presumed to be more relevant to real-life in early PD, which is primarily an on-medication state. If anything, the consistency of our results across medication conditions further strengthens our general conclusion that prospective memory tasks requiring higher levels of executive control are problematic for individuals with PD whereas automatically-triggered tasks are not.

In summary, our data suggest that non-demented individuals with early PD have impaired prospective memory when internal attentional strategies are required for intention retrieval, and this preferential impairment is sufficient to be noticed in everyday life. The specificity of the deficit distinguishes non-demented individuals with PD from other non-demented clinical populations who demonstrate global prospective memory decline (e.g., multiple sclerosis, Rendell, Jensen, & Henry, 2007; closed head injury, Schmitter-Edgecombe & Wright, 2004), most likely because PD arises from disruption of a defined neural system (i.e., striatofrontal system) versus widespread white matter involvement. However, the neural mechanisms underlying these effects remain to be delineated. Importantly, the results of this study may suggest specific strategies for improving prospective memory in PD, such as adopting a system of obvious, external cues that reduce the necessity for monitoring and automatically prompt remembering (McDaniel & Einstein, 2007a). Another potentially useful strategy is using implementation intentions during encoding, which serve to increase the association between the intended action and specific features of the cue to facilitate more spontaneous retrieval of the intention when the cue is encountered (Gollwitzer, 1996; McDaniel, Howard, & Butler,

2008). Studies showing that implementation intentions improve prospective memory performance in individuals with both frontal lesions (Lengfelder & Gollwitzer, 2001) and dopaminergic dysfunction (e.g., schizophrenia, Brandstatter, Lengfelder, & Gollwitzer, 2001) point to their potential effectiveness in PD. The impact of such interventions on everyday prospective memory performance, functional capacity and quality of life in PD warrants future exploration.

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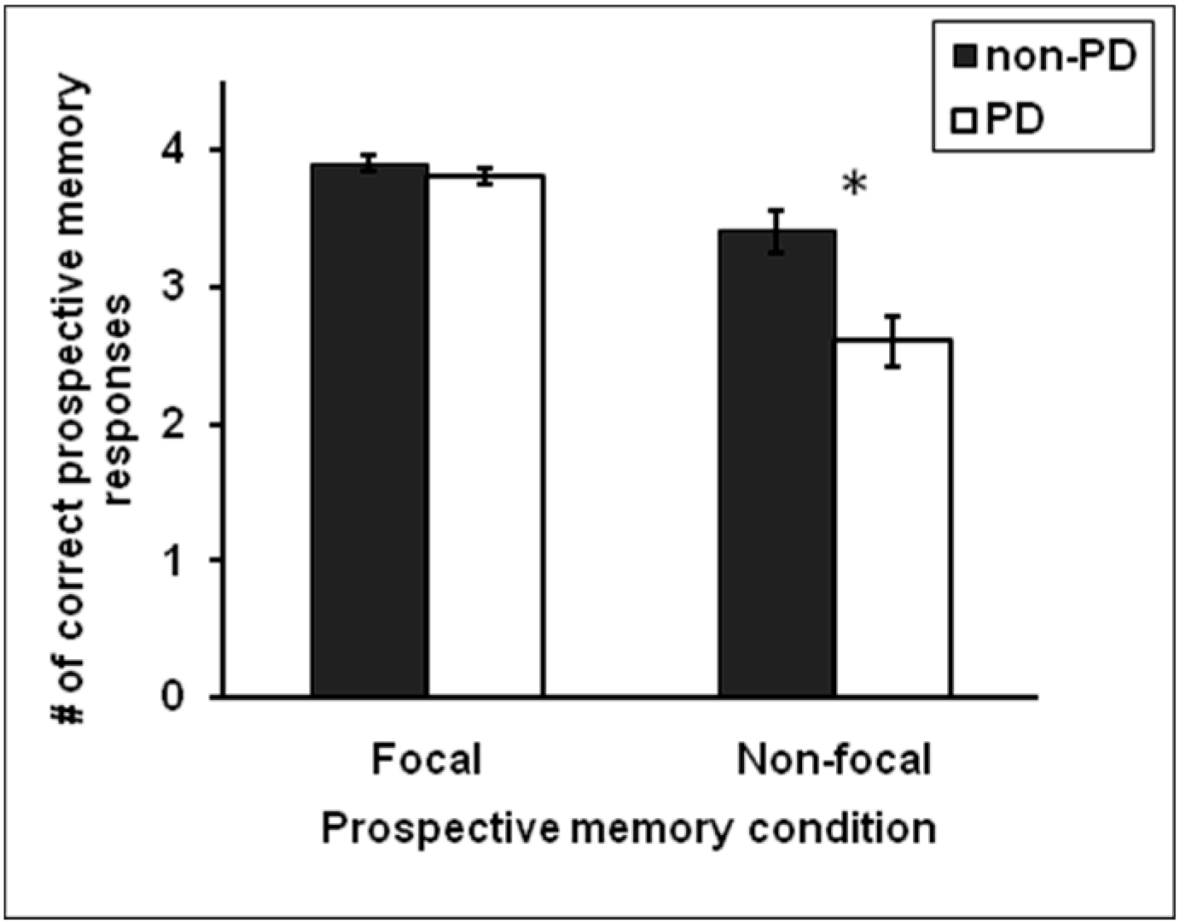

Figure 1.
Mean number of correct prospective memory responses (out of possible 4) collapsed across testing session. Error bars represent standard errors of the mean (* non-PD nonfocal > PD nonfocal, $p = 0.002$).

Table 1

Demographic and Clinical Characteristics for the Parkinson disease (PD) and non-PD Groups (N = 54).

Variable	PD	non-PD
n	24	30
Male/female ratio	14 / 10	14 / 16
Ethnicity		
Caucasian	24	28
African American	0	2
Age in years	59.0 (7.8)	60.0 (7.8)
Education level in years	14.9 (2.3)	15.3 (3.2)
WTAR	105.7 (14.2)	107.1 (9.2)
Disease duration in years	4.5 (2.6)	—
UPDRS On medications	17.2 (10.2)	—
UPDRS Off medications (averaged across two ratings)	20.7 (10.7)	—

Numbers represent means (standard deviation) or number of participants. WTAR = Wechsler Test of Adult Reading standard score; UPDRS = Unified Parkinson's Disease Rating Scale, Motor Subscale score

Table 2

Group Means (Standard Deviation) for the Laboratory Prospective Memory and Working Memory Task Dependent Variables by Testing Session.

	PD (n = 24)		non-PD (n = 30)	
Variable	**On**	**Off**	**On**	**Off**
Prospective memory task				
Prospective memory accuracy[a]				
Focal	3.87 (0.34)	3.75 (0.44)	3.90 (0.31)	3.86 (0.44)
Nonfocal	2.79 (1.02)	2.50 (1.14)	3.36 (0.88)	3.41 (1.05)
Ongoing activity accuracy[b]				
Control	0.96 (0.03)	0.96 (0.03)	0.97 (0.02)	0.97 (0.02)
Focal	0.96 (0.04)	0.96 (0.03)	0.96 (0.03)	0.96 (0.03)
Nonfocal	0.96 (0.03)	0.96 (0.04)	0.97 (0.02)	0.97 (0.03)
Ongoing activity response time (ms)[c]				
Control	1379 (300)	1381 (288)	1297 (182)	1302 (178)
Focal	1407 (366)	1394 (283)	1266 (200)	1330 (184)
Nonfocal	1628 (509)	1669 (441)	1469 (324)	1574 (471)
Working memory task accuracy[d]				
4-letter Maintenance	0.90 (0.09)	0.88 (0.10)	0.93 (0.05)	0.91 (0.08)
4-letter Manipulation	0.86 (0.16)	0.87 (0.13)	0.93 (0.06)	0.92 (0.09)
5-letter Maintenance	0.76 (0.14)	0.77 (0.16)	0.83 (0.14)	0.83 (0.11)
5-letter Manipulation	0.74 (0.14)	0.75 (0.16)	0.80 (0.13)	0.79 (0.10)

[a] Number of correct prospective memory responses out of 4 possible.

[b] Proportion of words correctly categorized out of 136 trials.

[c] Response latencies (in milliseconds) averaged over 136 ongoing activity trials.

[d] Proportion of letter and position-number probes correct out of 30 trials.

Table 3

Self-reported Frequency [Mean (Standard Deviation)] of Everyday Memory Failures.

Type of memory task	PD (n = 24)	non-PD (n = 30)
Prospective memory		
Self-cued	11.0* (2.1)	9.3 (1.5)
Environment-cued	9.7 (2.2)	9.0 (2.0)
Retrospective memory		
Self-cued	10.2 (2.4)	9.3 (1.6)
Environment-cued	8.1 (2.3)	7.2 (1.6)

Higher scores indicate more frequent everyday memory failures.

* Different from non-PD, $p = 0.001$

Table 4

Correlations (Pearson *r*) Between Participants' Laboratory Prospective Memory and Self-reported Everyday Prospective Memory Performance.

(a) Parkinson Disease (PD) Group, n=24

	Everyday Prospective Memory Scale	
Laboratory Prospective Memory	**Self-cued tasks**	**Environment-cued tasks**
Nonfocal cue condition	−0.31	0.14
Focal cue condition	0.04	−0.06

(b) non-PD Group, n = 30

	Everyday Prospective Memory Scale	
Laboratory Prospective Memory	**Self-cued tasks**	**Environment-cued tasks**
Nonfocal cue condition	−0.17	−0.09
Focal cue condition	0.13	0.10