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Abstract

Prospective memory has emerged as an important cognitive construct and one that is essential to everyday functioning. Prospective memory is thought to involve cognitive processes that are mediated by prefrontal systems and are executive in nature. Given that individuals with Parkinson's disease (PD) frequently show executive dysfunction, it is important to determine whether these individuals may have deficits in prospective memory that could impact daily functions such as taking medications. Although it has been reported that individuals with PD evidence impairment in prospective memory, it is still unclear whether they show a greater deficit for time- versus event-based cues. The present study investigated prospective memory functioning in individuals with PD and demographically similar healthy adults using a standardized measure of prospective memory that allows for a direct comparison of time-based and event-based cues. In addition, participants were administered a series of standardized measures of retrospective memory and executive functions. Individuals with PD demonstrated impaired prospective memory performance compared to the healthy adults, with a greater impairment demonstrated for the time-based tasks. Time-based prospective memory performance was moderately correlated with measures of executive functioning, but only the Stroop Neuropsychological Screening Test emerged as a unique predictor in a linear regression. Findings are interpreted within the context of McDaniel and Einstein's (2000) multi-process theory to suggest that individuals with PD experience particular difficulty executing a future intention when the cue to execute the prescribed intention requires higher levels of cognitive control.

Keywords. Parkinson's disease, prospective memory, episodic memory, basal ganglia, time perception, memory for intentions

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Deficits in episodic memory and executive functions are the most common neuropsychological sequelae of Parkinson's disease (PD). Mild-to-moderate impairment in verbal and visual episodic memory and executive functions may already be observed at (or very near) the time of diagnosis of PD (Foltynie et al., 2004; Muslimovic et al., 2005). Although there is considerable heterogeneity among individuals (Filoteo et al., 1997), the profile of episodic memory impairment at the group level is probably best characterized as a mixed encoding/retrieval deficit that is broadly consistent with the primary fronto-striato-thalamo-cortical neuropathogenesis of the cognitive impairment in PD (Braak et al., 2004). Acquisition of new information is slowed (Faglioni et al., 2000) and marked by limited use of higher-level encoding strategies, such as semantic clustering during list learning (e.g., Buytenhuijs et al., 1994). Impaired immediate and delayed free recall is contrasted by relatively better – although not necessarily normal – recognition (Whittington et al., 2000), suggesting a general retrieval deficit. Retrieval deficits are also evident in poor use of semantic strategies during verbal fluency tasks (Raskin et al., 1992; Henry & Crawford, 2004). In contrast, episodic memory deficits characteristic of Alzheimer's disease, including consolidation deficits (i.e., rapid forgetting) and intrusion errors, are unusual in non-demented patients with PD (Massman et al., 1990), but may be evident in PD with dementia (PDD; e.g., Stern et al., 1993). Importantly, episodic memory impairments in PD are associated with poorer health-related quality of life (e.g., Klepac et al., 2008) and incident PDD (e.g., Woods & Tröster, 2003).

A vast majority of the episodic memory literature in PD has focused on "retrospective memory (RetM)," which involves the recollection of past events in response to an explicit prompt. Many fewer studies have examined the nature, extent, and cognitive mechanisms of

prospective memory (ProM) impairment in PD (Altgassen et al., 2007; McDaniel & Einstein, 2007; Choudhry & Saint-Cyr, 2001; Costa et al., 2008a; 2008b; Foster et al., 2009; Katai, 1999; Katai et al., 2003; Kliegel et al., 2005; Tröster, & Fields, 1995). ProM is a unique component of episodic memory that refers to one's ability to independently execute a prescribed intention in response to an appropriate cue at some point in the future (i.e., "remembering to remember"). Thus, ProM is hypothesized to place more demands on self-initiated monitoring and retrieval processes as compared to RetM (e.g., McDaniel & Einstein, 2007). In fact, ProM is dissociable from RetM at the neural (e.g., Simons et al., 2006; Woods et al., 2006), cognitive (e.g., Salthouse et al., 2004), and functional (e.g., Woods et al., 2008a) levels and is posited to play a critical role in everyday functioning, making it a construct of considerable clinical importance to the neuropsychology of PD. A convergence of data indicates that normal ProM functioning is dependent on the fronto-striato-thalamo-cortical loops that are disrupted in PD. The involvement of prefrontal systems in ProM is supported by neuroimaging and electrophysiological studies, which implicate the fronto-polar and superior rostral aspects of the frontal lobes, particularly Brodmann's area 10 (e.g., Burgess et al., 2001; 2003). While successful ProM depends partly on the integrity of the posterior parietal and medial temporal lobes and RetM (e.g., Adda et al., 2008), it is mostly dependent upon frontal systems and executive functions, including planning, cognitive flexibility, strategic monitoring, and self-initiated retrieval processes (e.g., McDaniel et al., 1999).

Considering the prominent frontal systems neuropathophysiology of PD and its adverse effects on executive functions and episodic memory (see Tröster & Fields, 2008), it is reasonable to hypothesize that PD is associated with impairment in ProM. Although disruptions in ProM have been suspected in patients with PD for quite some time (Tröster & Fields, 1995; Knight et al., 1998) only recently have empirical studies directly examined this issue. As compared to healthy adults, patients with PD report more frequent and severe day-to-day ProM

failures, especially on self-cued tasks (e.g., Foster et al., 2009) and short-term routine activities (Choudhry & Saint-Cyr, 2001). Katai and colleagues (1999; 2003) were the first to report evidence of objective, performance-based ProM impairment in PD, which was characterized by deficits in event-based ProM (i.e., a simple motor response to two target words that were embedded in a semantic decision task). Subsequent studies suggest that the event-based ProM deficit is driven by impairment in the intention formation (e.g., Kliegel et al., 2005) and cue detection (Katai et al., 2003; Kliegel et al., 2005) aspects of retrieving future intentions, rather than by failure of RetM (Katai et al., 2003; Kliegel et al., 2005). For example, event-based ProM may be particularly affected in PD when the retrieval cue is non-focal to a background task, suggesting that executive dyscontrol of attentional monitoring and shifting may be critical to task success (Foster et al., 2009). In fact, the PD-associated ProM deficit can be ameliorated by directing attention away from the background task and toward the prescribed intention, perhaps because of enhanced (i.e., more active) cue monitoring (Altgassen et al., 2007).

McDaniel and Einstein's (2000) multi-process theory posits that the strategic encoding, monitoring, and retrieval demands of a given ProM task may vary by the particular characteristics of the target cue. For example, using an event-based ProM paradigm, Foster et al. (2009) found that PD was associated with a disproportionate deficit on trials in which the cue was not focal to the ongoing task, which is theorized to amplify demands on strategic monitoring and cue detection processes. Another common application of this conceptual framework is the evaluation of time- versus event-based ProM. In a time-based (TB) ProM task, the intention is executed after the passage of a specified time interval (e.g., taking a medication every eight hours), whereas the retrieval and execution of an event-based (EB) task is based on an external, environmental cue (e.g., taking a medication before going to bed). A considerable body of research shows that – all other things being equal – time-based ProM tasks place greater demands on self-initiated monitoring and retrieval processes linked to frontal systems (e.g.,

Einstein et al., 1995). As such, it might be anticipated that TB tasks would be disproportionately affected in PD; however, whether PD is associated with a differential deficit in time- versus event-based ProM remains unclear as the literature on this topic is quite mixed. The only two prior studies on this topic reached starkly contrasting findings. Costa and colleagues (2008b) showed the expected differential effect of TB (i.e., performing 3 actions after a 20-min delay) versus EB (i.e., performing 3 actions upon hearing a timer ring) ProM in 23 patients with PD and 25 healthy adults. In contrast, Katai et al. (2003) reported the opposite (and counterintuitive) pattern in which EB ProM (i.e., tap the desk when target words appeared) was more affected than TB ProM (i.e., tap the desk after 10- and 15-min intervals) in 20 patients with PD as compared to 20 healthy adults. Several factors likely contribute to these discrepant findings, most notably small sample sizes (i.e., limited statistical power) and variability in ProM task construction, which is critical since some event-based tasks place considerable demands on strategic processes (e.g., those ProM tasks with non-focal cues) and thereby more closely parallel the putative cognitive demands of time-based measures (e.g., Henry et al., 2004). The latter point is particularly important in studies aiming to clarify a differential deficit. Psychometric differences between TB and EB tasks (e.g., task complexity, nature of the environmental cue, scoring, reliability, and sensitivity), like psychometric differences between any tasks used to demonstrate differential impairments (Chapman & Chapman, 1973), can introduce a major confound.

Accordingly, this study aimed to examine the effects of PD on ProM using a standardized, well-validated task that includes psychometrically comparable indices of TB and EB performance (i.e., the Memory for Intentions Screening Test [MIST]; Raskin, 2004). The MIST contains four TB and four EB trials that are balanced on scale (i.e., scoring and range), ongoing task complexity (i.e., a shared word-search task), delay interval (i.e., 2- and 15-minute delays), and response modality (i.e., action versus verbal). Considering the literature reviewed

above, most notably the work of Foster and colleagues (2009) on non-focal cues, it was hypothesized that PD would be associated with a differential deficit in TB ProM relative to demographically comparable healthy adults. In addition, we aimed to extend prior research on ProM in PD by examining specific error types, which may be informative regarding the cognitive mechanisms of ProM failures. The MIST allows for the measurement of five different types of errors (e.g., omissions and task substitutions) and previous work has suggested that different clinical populations are likely to make different types of errors (see Raskin, 2009). In this case, given previous findings of deficits in executive control in individuals with PD, it was predicted that participants with PD would be more likely to make no response, loss of time (i.e., respond at an incorrect time), and task substitution errors than the healthy adult participants. Finally, we sought to examine the association between ProM and measures of executive functions and RetM. Given that the MIST is designed as a clinical measure, it is necessarily complex and successful performance requires a number of cognitive processes, including executive functions and RetM. As such, we also aimed to determine whether the hypothesized ProM deficit in PD was associated with executive dysfunction (e.g., planning, impulsivity) and/or failures in RetM (e.g., consolidation).

Method

Participants

A total of 88 participants, including 54 individuals with PD and 34 healthy adults (HA), were drawn from two study sites. Participants assessed in Connecticut (n = 23 PD and n = 34 HA) were recruited from Parkinson's disease support groups, a movement disorders clinic, and the general community. Participants recruited in North Carolina (n = 31 patients with PD) were attendees at an academic medical center movement disorders clinic. Exclusions for study participation included current psychiatric disorders and histories of cardiovascular or other

neurologic disease, dementia, prior neurosurgery, current substance use disorders, or a visual impairment that would interfere with reading the testing materials. There were no significant differences between the PD and HA groups for age, education, gender, or self-reported ethnicity (see Table 1). All PD participants were prescribed medication for parkinsonian symptoms and were tested in their "on" state. PD participants were in stages 0-4 of the Hoehn and Yahr scale (Hoehn & Yahr, 1967), with the majority in stages 1-3 (see Table 1). No patients were on anticholinergic medications.

[Insert Table 1 about here]

Materials and Procedure

All participants provided informed consent prior to completing the neurocognitive test battery, which is detailed below.

Prospective Memory Assessment. The primary measure of interest was the Memory for Intentions Screening Test (MIST; Raskin, 2004), which is a 30-min, 8-trial test during which participants engage in a word search puzzle as the ongoing task. A complete description of the MIST administration and scoring procedures can be found in Raskin (2009) and Woods et al. (2008b). We examined the following primary MIST variables: 1) summary score; 2) time-based scale; and 3) event-based scale. Briefly, the MIST is comprised of four trials with event-based cues (e.g., "When I hand you a postcard, self-address it.") and four trials with time-based cues (e.g., "In 15 minutes, tell me it is time to take a break."), with each item scored from 0-2 points; thus, the separate event-based and time-based scales have scores ranging from 0 to 8. The time- and event-based trials were balanced for delay interval (i.e., 2- and 15-min delay periods) and response modality (i.e., verbal and action responses). The MIST allows for separate scoring of time-based trials (8 points possible), event-based trials (8 points possible), 2-minute delay periods (8 points possible), 15-minute delay periods (8 points possible), verbal response trials (8

points possible) and action response trials (8 points possible), which are summed for a total of 48 possible points. However, this involves inclusion of the score of each trial three times in the total score (e.g., Trial 1 is a 2-minute delay trial, time-based cue, and verbal response, thus contributing to the 2-minute delay, time-based cue, and verbal response scores). A large digital clock is in full view of the participant at all times. For the event-based trials, the cues were considered to be ecologically relevant, meaning they are related to the response required and could naturally elicit that required response (e.g., When I hand you a request for records form, please write your doctors' names on it). The ongoing task is non-focal as the word search is not related to the prospective memory items. Prior studies support the reliability (Raskin, 2009; Woods et al., 2008b) and construct validity (e.g., Raskin & Buckheit, 2001; Woods et al., 2009) of the MIST.

At the completion of the eight MIST trials, participants are given eight multiple choice recognition items (e.g., "At any time during this test, were you supposed to: 1) tell me to make an appointment; 2) tell me when I can call you tomorrow; 3) tell me to call for a prescription."). The recognition scale is included as a way to determine whether ProM failures are due encoding versus retrieval failures. Impairment on recognition items is likely to reflect deficits in retrospective rather than prospective memory functions. Furthermore, a 24-hr delay trial was administered for which examinees were instructed to leave a voicemail message for the examiner the day after the exam indicating the number of hours the participant slept the night after the evaluation. In addition, the following error types were coded: 1) no response (i.e., response omission errors); 2) task substitutions (e.g., replacement of a verbal response with an action or vice-versa); 3) loss of content (e.g., acknowledgment that a response is required to a cue, but failure to recall the content); and (4) loss of time (i.e., performance of an intention greater than ± 15% before or after the target cue). No response errors are presumed to be directly due to failure of ProM (i.e., cue detection). Task substitution errors (e.g., intrusions and

perseverations) are likely multidetermined, but presumed to be due to executive control deficits (e.g., Carey et al., 2004). Loss of content errors most likely reflect RetM failures and loss of time errors seem to be due to difficulty with strategic monitoring or timing.

Basic Neuropsychological and Mood Assessment. Participants also completed several standard clinical measures of RetM, attention and executive functions, including the Logical Memory (recall total raw scores) and Digit Span (total raw score) subtests of the Wechsler Memory Scale-III (Psychological Corporation, 1997), the Tower (total achievement raw), Verbal Fluency (condition 1 total raw score) and Trail Making (condition 4 raw score) tests from the Delis-Kaplan Executive Function Scale (D-KEFS) (Delis et al., 2001), and the Stroop Neuropsychological Screening Test (Color-Word trial raw score; Trenerry et al., 1988). Finally, participants also completed the Profile of Mood States (POMS; McNair et al., 1992) to assess current affective distress across four specific areas (i.e., Depression/Dejection, Fatigue/Inertia, Vigor/Activity, and Tension/Anxiety). A Total Mood Disturbance score was derived, for which higher scores indicate greater distress.

Data Analyses

The primary study hypothesis was evaluated with a parametric repeated measures analysis of variance (ANOVA) in which between-subjects factor was diagnosis (i.e., PD versus healthy adults) and the within-subjects factor was ProM cue type (i.e., time- versus event-based). Although the MIST variables were non-normally distributed (i.e., negatively skewed) as determined by a Shapiro-Wilk W test (*ps* < .01), the results of the primary analysis did not change when a nonparametric approach to testing the statistical interaction was used. Planned follow-up pair-wise comparisons were conducted using a series of Wilcoxon Rank-Sum tests, which were complemented by Cohen's *d* effect size estimates. Spearman's rank correlation coefficients (ρ) were used to examine the associations between ProM and *a priori* selected measures of neuropsychological functions and psychiatric distress in the PD sample. Both

Spearman's ρ (for continuous variables) and Wilcoxon Rank-Sum tests (for categorical variables) were conducted to evaluate the relationship between ProM and indicators of PD disease severity and treatment status. A critical alpha level of .05 was used for all analyses.

Results

Descriptive data on the MIST in the PD and HA groups are displayed in Table 2. A repeated measures ANOVA revealed a significant main effect of PD diagnosis, F (1, 86) = 13.1, $p = .0005$, $\eta^2 = 0.13$), as well as a significant main effect of cue type, F (1, 86) = 35.3, $p < .0001$, $\eta^2 = 0.29$). These main effects were accompanied by a significant interaction between PD diagnosis and cue type, F (1, 86) = 7.9, p = .006, $\eta^2 = 0.08$). Pair-wise comparisons revealed a significant effect of PD on the TB scale ($p < .0001$) that was accompanied by a large Cohen's d value (see Table 2). In contrast, the PD effect on the EB scale was at the level of a statistical trend ($p < .10$), which was associated with a small-to-medium Cohen's d value. This effect was complicated by ceiling effect in this particular group of healthy subjects, of who 64.7% (n = 22) showed perfect performance on the EB scale; however, this proportion did not differ significantly from the 48.2% (n = 26) of PD patients who showed ceiling effects (p = .19). Of note, the PD sample achieved significantly fewer words on the ongoing task as compared to the healthy adults (p < .0001). Nevertheless, a follow-up regression with the TB scale as the criterion and PD diagnosis and ongoing task performance as the predictors showed that only PD was a significant predictor (p < .0001).

Component process analysis showed that the PD group made significantly more No Response and Task Substitution errors than the HA sample ($ps < .05$). These error type differences were associated with medium-to-large effect sizes (see Table 2). Finally, the PD group performed below the HA sample on the multiple-choice recognition post-test ($p < .05$). No significant difference was found between the groups for the 24-hour item.

[Insert Table 2 about here]

Between-group differences on the standard cognitive tasks are displayed in Table 3. The correlations between the MIST TB scale and standard neuropsychological measures in the PD sample are presented in Table 4. These data show that the TB ProM impairment was moderately associated with deficits on several measures of executive functions (i.e., DKEFS Letter Fluency, SNST Color-Word), including a trend-level association with a test of planning (i.e., DKEFS Tower). A significant correlation was also observed between the MIST TB scale and RetM (i.e., WMS-III Logical Memory II). To determine the uniqueness of these executive and RetM predictors for TB ProM, we conducted a follow-up linear regression predicting TB ProM in the PD group from the four standard clinical tests that showed a univariate effect. The overall regression model was significant (adjusted R^2 = .26, p = .001), but only the SNST Color-Word trial emerged as a unique predictor of TB ProM (p = .007). Table 3 shows the same basic pattern of correlations for the EB ProM scale, with the exception of a slightly stronger association with the WMS-III Logical Memory I subtest as compared to TB ProM. In fact, in contrast to the TB scale, a follow-up regression in the PD sample using the same four standard clinical tests used above (adjusted R^2 = .37, p < .0001) showed that both LM and SNST were independent predictors of the EB scale (ps < .05). Finally, neither TB nor EB ProM was associated with study site, POMS total score, side of disease onset, or Hoehn & Yahr staging (*ps* > .10).

[Insert Tables 3 and 4 about here]

Discussion

Several prior studies indicate that Parkinson's disease (PD) is associated with deficits in prospective memory (ProM), but the limited research regarding the differential impact of PD on

time- versus event-based ProM has been hampered by several methodological limitations (e.g., task selection and small sample sizes). Drawing from McDaniel and Einstein's (2000) multi-process theory, and extending the prior work by Foster et al. (2008), the present study evaluated the hypothesis that, based on its prominent frontal systems neuropathophysiology and associated executive dysfunction, PD is associated with a disproportionate deficit on time-based as compared to event-based ProM. The study results supported this hypothesis by revealing a significant interaction between PD diagnosis and ProM cue type, which pair-wise comparisons confirmed was driven by a larger PD-associated deficit in time- (Cohen's d = .95) versus event-based (d = .46) ProM. The finding of a disproportionate deficit in TB ProM is discordant with the study conducted by Katai et al. (2003), who used a non-focal cue for the event-based task, but echoes the findings of Costa et al. (2008b), who reported similar effect sizes for both TB (d = .92) and EB (d = .54) in PD using a different experimental ProM paradigm. The current investigation extends that prior work in several important ways, expanding on the work of Costa and colleagues by demonstrating a significant statistical interaction in a larger sample using procedurally comparable TB and EB scales within a standardized task with known psychometric properties (Woods et al., 2008b) and considerable evidence for construct validity (see Raskin, 2009 for a review). Despite this notable psychometric advantage over prior studies, one limitation of the current findings was the presence of ceiling effects on the EB scale, which may have limited our ability to detect group differences. Ceiling effects are a common problem for EB tasks, including the MIST subscale, and represent a serious challenge for both clinical and experimental ProM researchers. Yet the ceiling effects did not differ significantly across the PD and HA cohorts and were weak enough such that we still observed a trend-level finding for the EB scale, which was associated with a medium effect size. Thus, although our results suggest that individuals with PD were relatively more impaired on TB ProM, there was nevertheless evidence for mild impairment on EB tasks,

as well. Before considering the nature and extent of the EB impairment in PD, however, we first discuss the implications of the more prominent TB deficit.

Within the context of McDaniel and Einstein's (2000) multi-process theory, the observed disproportionate TB ProM impairment extends the work of Foster et al. (2009) in suggesting that individuals with PD experience particular difficulty executing a future intention when the cue to execute the prescribed intention requires higher levels of cognitive control, which is linked to the integrity of frontal systems and associated executive functions (Einstein et al., 1995) that are affected in PD (see Tröster & Fields, 2008 for a review). Indeed, Foster and colleagues demonstrated that PD was associated with a differential deficit in non-focal versus focal cues using an exclusively EB paradigm, which was interpreted as evidence of impairment in strategic/executive control of ProM. To this end, neuroimaging studies show that ProM tasks with increased self-initiated demands are associated with increased activation in the lateral aspects of the prefrontal cortex (i.e., Brodmann's area 10; Gilbert et al., 2009). Time-based ProM tasks generally place greater demands on self-initiated monitoring (e.g., clock checking) and retrieval (e.g., time perception) processes as compared to event-based tasks, which tend to involve more salient response cues. Nevertheless, PD patients are also susceptible to impairment on event-based ProM that place considerable demands on cognitive control mechanisms; for instance, impairment in PD is amplified when the retrieval cue is not focal to an ongoing task (Foster et al., 2009), although it was not tested directly whether time-based tasks still require more demands on monitoring than non-focal event-based items. This interpretation is consistent with research in other aspects of episodic memory and executive functions that highlight PD patients' particular difficulties on tasks that require strategy generation and the utilization of internally-generated rules to guide behavior (Taylor & Saint-Cyr, 1995; Owen et al., 1995).

While the possible contribution of a deficit in automatic processing cannot be dismissed

(e.g., Smith et al., 2003), the increased rate of omission (i.e., no response) errors suggests that the PD cohort experienced particular difficulty managing the concurrent cognitive demands of the ongoing task (i.e., a word search) and the strategic time monitoring required for successful TB ProM. A limitation of the current study was that time monitoring was not recorded, as the MIST was designed as a clinical measure. However, Costa and colleagues (2008b) reported that patients with PD monitored time less frequently than healthy adults during performance of a time-based ProM task. Less frequent time monitoring performance during the time immediately preceding the target was strongly related to poorer task performance, which is a phenomenon that has also been observed in healthy adults and individuals with schizophrenia (e.g., Shum et al., 2004). As such, it is reasonable to hypothesize that strategic time monitoring may have played a prominent role in the time-based ProM deficit observed in the present PD cohort. Considering the importance of the basal ganglia in other aspects of temporal processing (e.g., Pastor et al., 1992), future studies may wish to examine the role of time estimation and/or production in the PD-associated impairment in time-based ProM. An alternate interpretive possibility is that the PD group allocated greater resources to the ongoing task, while the healthy subjects focused their resources on the ProM tasks. Yet our results showed the opposite pattern; that is, the PD group performed significantly worse than the HA sample on the ongoing task, which suggests that the HA group was better to able to manage the simultaneous demands of the ongoing task and ProM cue monitoring.

Further supporting the contribution of cognitive dyscontrol to the present findings, correlational analyses showed that measures of executive functions, including prepotent response inhibition, letter fluency, and planning (at a trend level) were significantly related to time-based ProM in PD. Although the delayed recall trial of the WMS-III Logical Memory subtest was also correlated at the univariate level, multiple regression analyses revealed that response inhibition (i.e., the color-word trial of the SNST) was a unique predictor. Similar results were

reported by Costa and colleagues (2008b), who demonstrated a strong correlation between a test of executive functions (i.e., abstraction and set-shifting on the Wisconsin Card Sorting Test) and time-based ProM. In contrast to Costa et al., however, we did not observe a significant correlation between TB ProM and attention/working memory (i.e., digit span), which may be related to differences between our ProM tasks and/or study samples (e.g., education). Despite this minor discrepancy, these studies collectively support the relationship between time-based ProM impairment and executive dysfunction in PD and may inform future studies using more complex analytic approaches (e.g., confirmatory factor analysis) with larger sample sizes to more rigorously evaluate this question. A slightly different pattern of correlations was observed for the EB ProM scale in the PD group. Specifically, although EB also correlated with SNST, DKEFS Tower and Letter Fluency, and LMII, it also correlated with LMI. A follow-up linear regression showed that both SNST and LM II were significant independent predictors of EB. These data suggest that both executive control and RetM are important components of EB deficits in individuals with PD.

Along these same lines, the present study also provided evidence of possible deficits in the encoding and retrospective memory components of ProM in PD. The high prevalence of task substitution errors indicates that the PD sample was more likely than healthy adults to misremember the content of the intention, which is considered to be a function of retrospective memory. Further evidence for impairment in the retrospective memory component of ProM is provided by the PD sample's relatively poorer performance on the post-test recognition task (which was associated with a medium effect size). These data are consonant with the findings of Costa et al. (2008b), who found that individuals with PD were impaired in recalling the content of their intention after failing to respond to the prescribed cue (after a grace period). Interestingly, Costa also reported associations between time-based ProM and retrospective memory tasks (e.g., prose recall) that were of approximately the same magnitude as were

reported in the current study, but did not reach statistical significance due to the small sample size in that prior investigation. Thus, it may be that both the prospective and retrospective memory components of ProM are disrupted in PD. Whether this reflects executive dyscontrol of encoding and/or retrieval aspects of retrospective memory, as has been shown with other retrospective memory tasks, such as list learning (Filoteo et al., 1997), remains to be determined.

It is of note that the groups did not differ in their performance on the 24-hour item. This item can be likened to more naturalistic memory tasks, whereas the rest of the MIST is more similar to laboratory-based tasks. As such, this finding is consistent with investigations of the age-prospective memory paradox (e.g., Bailey et al., 2010) and may reflect greater use of compensatory devices or reminders outside the lab. By virtue of having a neurologic condition, the PD patients presumably have greater experience in complying with these sorts of health care requests than do the healthy adults and may have therefore developed effective adaptive strategies (e.g., reminders from caregivers). Further studies of this population with naturalistic tasks, perhaps to including multiple trials with varying load and intention realization demands, may shed more light on the functional ProM performance of individuals with PD in daily life.

ProM has emerged as an important cognitive construct and one that is essential to everyday functioning. As such, results from the present study have potential implications for the assessment and remediation of everyday functioning problems in PD. A growing literature shows that individuals with impaired ProM are more likely to experience problems independently managing their instrumental activities of daily living (e.g., Schmitter-Edgecombe et al., 2009; Smits et al., 1999; Twamley et al., 2008; Woods et al., 2008a). In fact, ProM demonstrates preliminary evidence of incremental ecological validity in this regard, predicting dependence in daily functioning above and beyond impairment in other cognitive domains (e.g., retrospective memory, executive functions), disease severity, and psychiatric factors (e.g., Woods et al.,

2009). Time-based ProM appears to be a particularly strong predictor of everyday functioning, including medication non-adherence (Woods et al., 2009). Future studies are therefore needed to evaluate the role of ProM in important functional outcomes in PD, including various IADLs (e.g., medication adherence and financial management) and health-related quality of life.

Considering the magnitude of the deficits observed in recent study magnitude and potential role in everyday functioning declines, ProM might be an appropriate target for pharmacological and cognitive neurorehabilitation. One prior study reported that time-based ProM impairment in PD may improve with levodopa therapy (Costa et al., 2008a), but the possible role of other drugs, such as memantine (e.g., Aarsland et al., 2009) remains to be determined. It is also possible that cognitive-behavioral approaches may be employed to improve and/or compensate for the PD-associated deficit in time-based ProM (Raskin & Sohlberg, 2009). Extending literature on the role of cue focality in the expression of ProM deficits in PD, Altgassen et al. (2007) reported that PD participants demonstrated improved ProM performance when their attention was explicitly directed to the prescribed intention, rather than the ongoing task. The present findings suggest that investigations that aim to enhance strategic encoding (e.g., Kliegel et al., 2007) and monitoring (e.g., Fish et al., 2007), as well as the use of salient cues (see recent review by Raskin & Sohlberg, 2009), may be particularly effective.

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References

Aarsland, D., Ballard, C., Walker, Z., Bostrom, F., Alves, G., Kossakowski, K., et al. (2009). Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurology, 8*, 613-618.

Adda, C. C., Castro L. H., Alem-Mar e Silva, L. C., de Manreza, M. L., & Kashiara, R. (2008). Prospective memory and mesial temporal epilepsy associated with hippocampal sclerosis. *Neuropsychologia, 46,* 1954-64.

Altgassen, M., Zollig, J., Kopp, U., Mackinlay, R., & Kliegel, M. (2007). Patients with Parkinson's disease can successfully remember to execute delayed intentions. *Journal of the International Neuropsychological Society, 13*, 888-892.

Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research, 318*, 121-134.

Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia, 39*, 545-555.

Burgess, P. W., Scott, S. K., & Frith, C. D. (2003). The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation. *Neuropsychologia, 41*, 906-918.

Buytenhuijs, E. L., Berger, H. J., Van Spaendonck, K. P., Horstink, M. W., Borm, G. F., & Cools, A. R. (1994). Memory and learning strategies in patients with Parkinson's disease. *Neuropsychologia, 32*, 335-342.

Chapman, L. J., & Chapman, J. P. (1973). Problems in the measurement of cognitive deficit. *Psychological Bulletin, 79*, 380-385.

Choudhry, R.K. & Saint-Cyr, J. (2001) Self-Report on memory abilities and prospective memory in Parkinson's disease [abstract]. *Brain and Cognition, 47*, 266-269.

Costa, A., Peppe, A., Brusa, L., Caltagirone, C., Gatto, I., & Carlesimo, G. A. (2008a). Levodopa improves time-based prospective memory in Parkinson's disease. *Journal of the International Neuropsychological Society, 14*, 601-610.

Costa, A., Peppe, A., Caltagirone, C., & Carlesimo, G. A. (2008b). Prospective memory impairment in individuals with Parkinson's disease. *Neuropsychology, 22*, 283-292.

Delis-Kaplan Executive Function System (D–KEFS). San Antonio, TX: Pyschological Corporation; 2001.

Einstein, G. O., McDaniel, M. A., Richardson, S. L., Guynn, M. J., & Cunfer, A. R. (1995). Aging and prospective memory: examining the influences of self-initiated retrieval processes. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 2,* 996-1007.

Faglioni, P., Saetti, M. C., & Botti, C. (2000). Verbal learning strategies in Parkinson's disease. *Neuropsychology, 14*, 456-470.

Filoteo, J. V., Rilling, L. M., Cole, B., Williams, B. J., Davis, J. D., & Roberts, J. W. (1997). Variable memory profiles in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 19*, 878-888.

Fish, J., Evans, J. J., Nimmo, M., Martin, E., Kersel, D., Bateman, A., et al. (2007). Rehabilitation of executive dysfunction following brain injury: "content-free" cueing improves everyday prospective memory performance. *Neuropsychologia, 45*, 1318-1330.

Foltynie, T., Brayne, C. E. G., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain, 127*, 550-560.

Foster, E. R., McDaniel, M. A., Repovs, G., & Hershey, T. (2009). Prospective memory in Parkinson disease across laboratory and self-reported everyday performance. *Neuropsychology, 23*, 347-358.

Gilbert, S. J., Gollwitzer, P. M., Cohen, A., Oettingen, G., & Burgess, P. W. (2009). Separable brain systems supporting cued versus self-initiated realization of delayed intentions. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 35, 905-915.

Henry, J. D., & Crawford, J. R. (2004). Verbal fluency deficits in Parkinson's disease: a meta-analysis. *Journal of the International Neuropsychological Society, 10*, 608-622.

Henry, J. D., MacLeod, M. S., Phillips, L. H., & Crawford, J. R. (2004). A meta-analytic review of prospective memory and aging. *Psychology and Aging, 19*, 27-39.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*, 427-442.

Katai, S. (1999). Everyday memory impairment in Parkinson's disease. *Rinsho Shinkeigaku, 39*, 913-919.

Katai, S., Maruyama, T., Hashimoto, T., & Ikeda, S. (2003). Event based and time based prospective memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 74*, 704-709.

Klepac, N., Trkulja, V., Relja, M., & Babic, T. (2008). Is quality of life in non-demented Parkinson's disease patients related to cognitive performance? A clinic-based cross-sectional study. *European Journal of Neurology, 15*, 128-133.

Kliegel, M., Phillips, L. H., Lemke, U., & Kopp, U. A. (2005). Planning and realisation of complex intentions in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 76*, 1501-1505.

Kliegel, M., Martin, M., McDaniel, M. A., Einstein, G. O., & Moor, C. (2007). Realizing complex delayed intentions in old and young adults: The role of planning aids. *Memory & Cognition, 35*, 1735-1746.

Knight, R. G. (1998). Prospective memory in aging and neurodegenerative disease. In A.I Tröster (Ed), *Memory in Neurodegenerative Disease* (pp. 172-183). Cambridge, UK: Cambridge University Press.

Massman, P. J., Delis, D. C., Butters, N., Levin, B. E., & Salmon, D. P. (1990). Are all subcortical dementias alike? Verbal learning and memory in Parkinson's and Huntington's disease patients. *Journal of Clinical and Experimental Neuropsychology, 12*, 729-744.

McDaniel, M. A. & Einstein, G. O. (2007) *Prospective Memory: An overview and systhesis of an emerging field*. Thousand Oaks, CA: Sage Publications.

McDaniel, M. A. & Einstein, G. O. (2000) Strategic and automatic processes in prospective remembering: A multiprocess framework. *International Journal of Psychology, 35,* 296-296.

McDaniel, M. A., Glisky, E. L., Rubin, S. R., Guynn, M. J., & Routhieaux, B. C. (1999). Prospective memory: a neuropsychological study. *Neuropsychology, 13*, 103-110.

McNair, D., Lorr, M., & Droppleman, L. (1992). *Profile of Mood States (POMS) manual.* San Diego, CA: Educational and Industrial Testing Services.

Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology, 65*, 1239-1245.

Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E., & Robbins, T. W. (1995). Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia, 33*, 1-24.

Pastor, M. A., Artieda, J., Jahanshahi, M., & Obeso, J. A. (1992). Time estimation and reproduction is abnormal in Parkinson's disease. *Brain, 115*, 211-225.

Psychological Corporation. (1997). *WAIS-III and WMS-III technical manual.* San Antonio, TX: Author.

Raskin, S. A. (2004). Memory for intentions screening test [abstract]. *Journal of the International Neuropsychological Society, 10,* 110.

Raskin, S. A. (2009). Memory for intentions screening test: Psychometric properties and clinical evidence. *Brain Impairment, 10,* 23-33.

Raskin, S. A., & Buckheit, C. (2001). Prospective memory functioning after brain injury [Abstract]. *Journal of International Neuropsychological Society, 7,* 249-250.

Raskin, S. A., & Sohlberg, M. M. (2009). Prospective memory intervention: A review and evaluation of a pilot restorative intervention. *Brain Impairment, 10,* 76-86.

Raskin, S. A., Sliwinski, M., & Borod, J. C. (1992). Clustering strategies on tasks of verbal fluency in Parkinson's disease. *Neuropsychologia, 30*, 95-99.

Salthouse, T. A., Berish, D. E., & Siedlecki, K. L. (2004). Construct validity and age sensitivity of prospective memory. *Memory & Cognition, 32*, 1133-1148.

Schmitter-Edgecombe, M., Woo, E., & Greeley, D. R. (2009). Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology, 23*, 168-177.

Shum, D., Ungvari, G. S., Tang, W. K., & Leung, J. P. (2004). Performance of schizophrenia patients on time-, event-, and activity-based prospective memory tasks. *Schizophrenia Bulletin, 30*, 693-701.

Simons, J. S., Scholvinck, M. L., Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2006). Differential components of prospective memory? Evidence from fMRI. *Neuropsychologia, 44*, 1388-1397.

Smith, R. E. (2003). The cost of remembering to remember in event based prospective memory: Investigating the capacity demands of delayed intention performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 29,* 347-361.

Smits, C. H., Deeg, D. J., Kriegsman D. M., & Schmand B. (1999). Cognitive functioning and health as determinants of mortality in an older population. *American Journal of Epidemiology, 150,* 978-986.

Stern, Y., Marder, K., Tang, M. X., & Mayeux, R. (1993). Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology, 43*, 1690-1692.

Taylor, A. E., & Saint-Cyr, J. A. (1995). The neuropsychology of Parkinson's disease. *Brain and Cognition, 28*, 281-296.

Trenerry, M. R., Crosson, B., DeBoe, J., & Leber, W. R. (1988). *Stroop Neuropsychological Screening Test manual.* Odessa, FL: Psychological Assessment Resources.

Tröster, A. I., & Fields, J. A. (1995). Frontal cognitive function and memory in Parkinson's-disease: toward a distinction between prospective and declarative memory impairments. *Behavioural Neurology, 8*, 59-74.

Tröster, A. I., & Fields, J. A. (2008). Parkinson's disease, progressive supranuclear palsy, corticobasal generation, and related disorders of the frontostriatal system. In J. E. Morgan & J. H. Ricker (Eds.), *Textbook of Clinical Neuropsychology* (pp. 536-577) New York, NY: Taylor & Francis.

Twamley, E. W., Woods, S. P., Zurhellen, C. H., Vertinski, M., Narvaez, J. M., Mausbach, B. T., et al. (2008). Neuropsychological substrates and everyday functioning implications of prospective memory impairment in schizophrenia. *Schizophrenia Research, 106*, 42-49.

Whittington, C. J., Podd, J., & Kan, M. M. (2000). Recognition memory impairment in Parkinson's disease: power and meta-analyses. *Neuropsychology, 14*, 233-246.

Woods, S. P., Dawson, M. S., Weber, E., Gibson, S., Grant, I., & Atkinson, J. H. (2009). Timing is everything: antiretroviral nonadherence is associated with impairment in time-based prospective memory. *Journal of the International Neuropsychological Society, 15*, 42-52.

Woods, S. P., Iudicello, J. E., Moran, L. M., Carey, C. L., Dawson, M. S., & Grant, I. (2008a). HIV-associated prospective memory impairment increases risk of dependence in everyday functioning. *Neuropsychology, 22*, 110-117.

Woods, S. P., Moran, L. M., Dawson, M. S., Carey, C. L., & Grant, I. (2008b). Psychometric characteristics of the memory for intentions screening test. *The Clinical Neuropsychologist, 22*, 864-878.

Woods, S. P., Morgan, E. E., Marquie-Beck, J., Carey, C. L., Grant, I., & Letendre, S. L. (2006). Markers of macrophage activation and axonal injury are associated with prospective memory in HIV-1 disease. *Cognitive and Behavioral Neurology, 19*, 217-221.

Woods, S. P., & Troster, A. I. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *Journal of the International Neuropsychological Society, 9*, 17-24.

Table 1.

Demographic and Disease Characteristics of the Study Participants

Variable	HA (n = 34)	PD (n = 54)	p
Demographic Characteristics			
Age (years)	61.0 (2.6)	61.9 (7.6)	0.47
Education (years)	14.5 (2.1)	14.7 (2.1)	0.68
Sex (% men)	67.6	63.0	0.65
Handedness (% right)	82.4	96.3	0.03
Ethnicity (% Caucasian)	91.2	81.5	0.36
Disease Characteristics			
Hoehn & Yahr (%)			
Stage 0	-	5.6	-
Stage 1	-	13.0	-
Stage 2	-	53.7	-
Stage 3	-	21.4	-
Stage 4	-	3.7	-
Side of Onset (% right)	-	78.8	-

Table 2.

Prospective Memory Performance in the Study Samples.

Variable	HA (*N* = 34)	PD (*N* = 54)	*p* [a]	*d* [b]
MIST				
Summary Score (of 48)	45 (39, 45.8)	39 (27, 42.8)	0.0011	0.76
Time (of 8)	7 (6, 8)	5 (3, 7)	<0.0001	0.95
Event (of 8)	8 (6, 8)	7 (5.8, 8)	0.0605	0.46
Recognition (of 8)	8 (8, 8)	8 (8, 8)	0.0194	0.44
24-Hour (of 2)	1 (0, 2)	1 (0, 2)	0.6275	0.12
Ongoing Task (of 40)	22 (17.8, 28.5)	14.5 (9, 18.3)	<0.0001	-1.06
Errors				
No Response	0 (0, 1)	1 (0, 2)	0.0020	0.63
Task Substitution	0 (0, 0)	0 (0, 1)	0.0002	0.73
Loss of Time	0 (0, 1)	0 (0, 1)	0.6502	0.08
Loss of Content	0 (0, 1)	1 (0, 1)	0.8369	0.05

Note. Data represent medians and interquartile ranges. [a] P-value based on one-way ANOVA, [b] Cohen's d effect size estimate. MIST = Memory for Intentions Screening Test. PLO = Place losing omissions.

Table 3.

Cognitive Test Performance in the Study Samples.

Cognitive Test	HA (*N* = 34)	PD (*N* = 54)	*p* [a]	*d* [b]
WMS-III Logical Memory I	32.7 (6.0)	37.4 (10.5)	0.0097	0.52
WMS-III Logical Memory II	19.7 (4.7)	21.6 (7.6)	0.1429	0.29
WMS-III Digit Span	16.6 (1.9)	15.0 (3.5)	0.0051	-0.54
DKEFS Tower	15.6 (4.2)	13.7 (3.9)	0.0368	-0.47
DKEFS Letter Fluency	49.6 (6.4)	36.7 (13.0)	<0.0001	-1.18
DKEFS TMT Condition 4	44.2 (10.0)	111.7 (58.4)	<0.0001	1.49
SNST Color-Word	81.0 (15.2)	71.9 (21.4)	0.0249	-0.48

Note. Data represent means and standard deviations [a] P-value based on one-way ANOVA, [b] Cohen's d effect size estimate. WMS= Wechsler Memory Scale, DKEFS= Delis-Kaplan Executive Function System, SNST= Stroop Neuropsychological Screening Test; TMT = trail making test.

WMS-III Digit Span PD N=52
DKEFS Tower PD N=53
DKEFS TMT Condition 4 PD N=48
SNST Color-Word PD N=50

Table 4
Correlations between the MIST and other neurocognitive tests in the PD group (*N*=54)

Cognitive Tests	MIST Time-Based	MIST Event-Based
WMS-III Logical Memory I	0.21	0.39**
WMS-III Logical Memory II	0.38**	0.45**
WMS-III Digit Span	0.20	0.19
DKEFS Tower	0.26^{+}	0.29*
DKEFS Letter Fluency	0.38**	0.35**
DKEFS TMT Trial 4	-0.15	-0.13
SNST Color-Word	0.52**	0.50**

Note. MIST= Memory for Intentions Screening Test, WMS= Wechsler Memory Scale, DKEFS= Delis-Kaplan Executive Function System, SNST= Stroop Neuropsychological Screening Test; TMT = trail making test. Values based on Spearman's rho.

$^{+}$ $p < .10$, *$p<.05$, **$p<.01$