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Prospective Memory Impairment in Parkinson Disease without Dementia: Cognitive Mechanisms and Intervention

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by

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List of Abbreviations

BA = Brodmann area

BDI-II = Beck Depression Inventory, Second edition

CEQ = Credibility Expectancy Questionnaire

COMT = Catechol-O-methyl transferase

fMRI = Functional magnetic resonance imaging

GDS = Geriatric Depression Scale

II = Implementation intentions

LEDD = Levodopa equivalent daily dose

MAO = Monoamine oxidase inhibitor

MCI = Mild cognitive impairment

MMSE = Mini-Mental State Examination

MoCA = Montreal Cognitive Assessment

PD = Parkinson disease

PM = Prospective memory

PRMQ = Prospective and Retrospective Memory Questionnaire

RR = Rehearsal (or rote rehearsal)

UPDRS Motor, UPDRS III = Unified Parkinson Disease Rating Scale, Motor subscale

VR = Verbal rehearsal

WU = Washington University in St. Louis

WUSM = Washington University School of Medicine

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ABSTRACT OF THE DISSERTATION

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Cognitive impairment among non-demented individuals with Parkinson disease (PD) produces significant disability, reduced quality of life, and restricted participation. This dissertation will cover PD-related impairment in *prospective memory*, or the ability to remember to execute delayed intentions at the appropriate moment in the future. Prospective memory impairment in PD is increasingly recognized as a functionally and clinically relevant problem and viable target for cognitive intervention. To lay the groundwork for the development of effective interventions for prospective memory in PD, this dissertation examines the cognitive mechanisms underlying prospective memory impairment in PD and the potential of training in a targeted strategy to improve prospective memory in PD. Specifically, it focuses on the efficacy of an associative encoding strategy called *implementation intentions* for addressing PD-related deficits in prospective memory in a laboratory setting and as reported in everyday life. Results indicate that implementation intentions training holds promise for improving prospective memory in PD. A synthesis and analysis of the dissertation studies reveals avenues for future research that will bolster the scientific and clinical impact of this line of work.

Chapter 1: Introduction

1.1 Cognitive impairment in Parkinson disease

Parkinson disease (PD) is the second most common neurodegenerative disorder, affecting approximately 1-2% of the population over the age of 65 [1]. It is classified as a movement disorder, and clinical diagnosis is based on the presence of motor manifestations (i.e. bradykinesia, rigidity, and/or resting tremor) [2]. However, non-motor manifestations are also highly prevalent in PD and contribute significantly to reduced function and quality of life [3-5]. Cognitive dysfunction is a well-established non-motor feature of PD. It can range in severity from overt decline that significantly interferes with daily function (i.e. dementia) [6] to subtle deficits in discrete domains detectable by sensitive experimental tests [7]. About 30% of people with PD have dementia [8], and greater than 80% of people who survive more than 20 years with PD will develop dementia [9]. Accumulation of synucleinopathy in the cerebral cortex and limbic system is likely the primary substrate of dementia in PD [10,11]. In addition, at least 30% of people in the earliest stages of PD have mild cognitive deficits that can persist for years without or before progressing to dementia [12-14]. These deficits are attributed to frontostriatal circuitry dysfunction due to dopamine depletion in the basal ganglia and prefrontal cortex [15,16].

1.1.1 Functional relevance of cognitive impairment in Parkinson disease without dementia

Cognitive deficits among non-demented people with PD relate to disability, reduced quality of life, and restricted participation early in the course of the disease, potentially to a larger extent than motor impairment [17-24]. For example, subtle decline in global cognition is associated with poorer performance of cognitively-demanding instrumental activities of daily living such as managing medication and money [22]. In addition, executive function difficulties in daily life result in reduced participation in instrumental, leisure and social activities, difficulties managing daily routines, lowered self-confidence, and an increased need for caregiver support [21,25]. Existing pharmacologic and surgical treatments for PD do not prevent or treat cognitive impairment and may even exacerbate the problem [15,26-28]. As such, cognitive rehabilitation interventions that mitigate the negative functional consequences of cognitive impairment in people with PD are a top research priority [28-33].

1.2 Prospective memory

Prospective memory has received increasing attention in PD research over the past decade, as it is a highly functionally, clinically and theoretically relevant aspect of cognition [34,35]. Prospective memory is a multi-faceted cognitive construct encompassing the ability to remember to execute delayed intentions at the appropriate moment in the future [36]. Examples of everyday prospective memory tasks include remembering to call a friend on his/her birthday, attend meetings or appointments, pay bills on time, take medications as prescribed, turn the stove off after using it, include an attachment to an email before sending it, or pick the children up after school. Prospective memory plays a central role in daily occupational performance and participation, as it serves to bind together goal-directed actions and enables people to carry out their plans and wishes meaningfully and appropriately [37,38]. Good prospective memory is essential for independent living, employment, and social relationships [37,39,40]. It is also necessary for adherence to important health-related behaviors (e.g. taking medications, doing home exercises) [41,42], which are a fundamental component of clinical care and well-being for individuals with chronic conditions like PD.

1.2.1 Time- and event-based tasks

There are two main types of prospective memory tasks. In *time-based* prospective memory tasks, a certain time or the passage of a specified amount of time serves as the cue that signals the appropriate moment for execution [43]. Examples of everyday time-based prospective memory tasks include remembering to attend a meeting at 3:00pm or re-fill the parking meter in two hours. In *event-based* prospective memory tasks, the occurrence of an event serves as the cue that signals the appropriate moment for execution [43]. Examples of everyday event-based prospective memory tasks include remembering to take medications with breakfast or stop by the store for an item on the way home from work.

1.2.2 Prospective and retrospective components

Prospective memory tasks can be described as having two cognitive components. The *prospective component* refers to detecting prospective memory cues and interpreting them as cues for action and is thought to involve executive control processes that support monitoring for the event and initiating the intention (e.g. working memory, shifting) [38,44,45]. The *retrospective component* refers to remembering the cues themselves and the specific action to be performed and is thought to involve encoding and retrieval processes similar to those of other episodic memory tasks (e.g. associative encoding, cued recall) [44,46-49].

1.2.3 Process model

A more nuanced view of prospective memory tasks and their underlying cognitive demands has been presented by Kliegel, Altgassen, Hering, Rose [50]. Their conceptual model, depicted in Figure 1.1, describes the process of prospective memory as encompassing four phases: (1) *intention formation* – the intention to execute an action at a particular moment in the future is formed and encoded; (2) *intention retention* – the intention is retained in long term memory over a delay period while performing other unrelated tasks (i.e. ongoing activity); (3) *intention* *retrieval* – the appropriate moment (i.e. cue) occurs and the intended action is retrieved from memory and initiated; (4) *intention execution* – the intention is successfully carried out. Each phase demands distinct underlying cognitive processes, the extent to which depends on characteristics of the particular prospective memory task (Figure 1.1; discussed further in section 1.3.2). Following this model, prospective memory impairment is conceptualized as a mismatch between the cognitive resources required by the particular task and the individual's available (or deployment of available) cognitive resources. Of note, this model can be viewed as an expansion of the Multiprocess Theory of prospective memory [51] (described in section 1.3.2), which was developed earlier by McDaniel and Einstein to explain intention retrieval specifically.

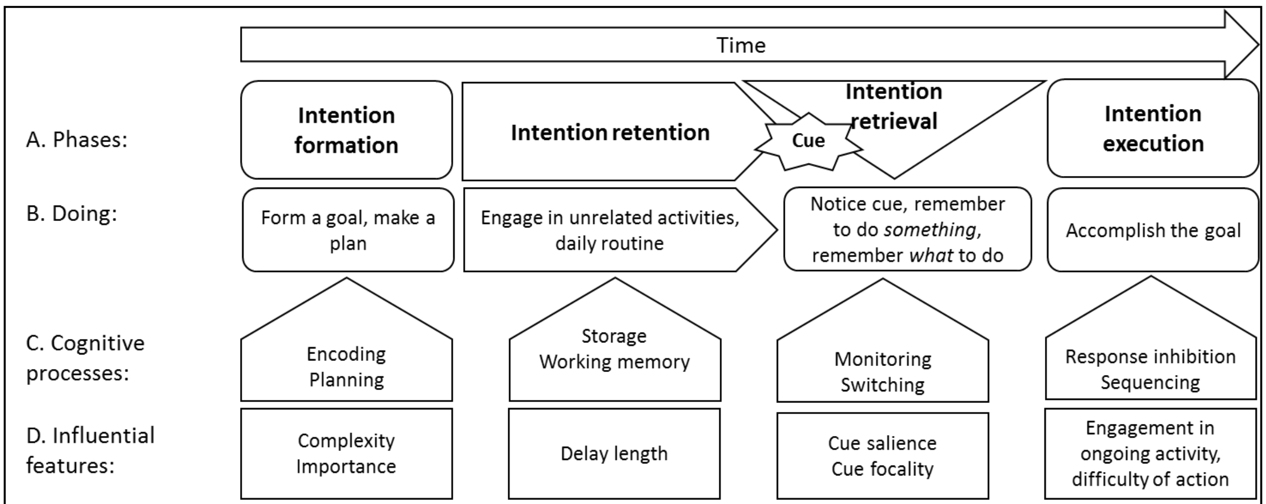

Figure 1.1. Process model of prospective memory. (A) The four sequential phases of prospective memory tasks. Includes cue occurrence, which signals intention retrieval. (B) Connection to "doing" in daily life. (C) Hypothesized cognitive processes that underlie each phase. (D) Examples of task-related features that can determine the demand on the underlying cognitive process. Expanded from Kliegel et al. (2011).

1.3 Prospective memory impairment in Parkinson disease

1.3.1 Functional relevance

People with PD consistently demonstrate both time- and event-based prospective memory deficits in laboratory studies [52]. In addition, they report more everyday prospective memory failures compared to healthy older adults [53,54], and prospective memory problems in people with

PD relate to poorer daily function [54-56]. Specifically, impaired laboratory prospective memory performance is associated with worse performance on tests of financial capacity and medication management [54], and poorer self-reported everyday prospective memory is associated with poorer reported instrumental activities of daily living function, medication management, and health-related quality of life [54-56]. In a recent qualitative study investigating everyday function in PD, people with PD and their care partners commonly mentioned prospective memory failures and their negative impact on aspects of daily life such as independence and safety, social obligations, and self-management of their health condition [25]. These findings highlight the need for interventions for prospective memory impairment in PD. Interventions that improve prospective memory in people with PD could positively impact daily function and clinical care for this population.

1.3.2 Cognitive mechanisms

Prospective memory requires the integration of retrospective memory processes and executive control processes [36,50], both of which can be impaired in PD [15,57,58]. Initial investigations attempting to pinpoint which is the source of prospective memory impairment in PD compared performance on the prospective and retrospective components of prospective memory tasks. These studies found that PD participants fail to carry out intentions despite remembering their contents upon later questioning (i.e. they remembered *what* they were supposed to do but did not do it at the appropriate moment) [53,59,60]. This lead to the conclusion that the retrospective memory processes involved in encoding and retention of intentions were intact, while the executive processes underlying self-initiated intention retrieval (i.e. the prospective component) were impaired in PD. However, the opposite performance pattern has been reported, with PD participants demonstrating intact intention retrieval but impaired recall of the intended action (i.e. they remembered *that* they were supposed to do something at the appropriate moment but not *what* they were supposed to do) [61]. In another study, PD participants committed more task substitution errors (performing the wrong intended action) and had poorer recognition of intentions at posttest compared to healthy older adults [62] indicating PD-related retrospective component deficits. These findings conflict with the interpretation of intact retrospective but impaired prospective component functioning in PD and suggest the need for more refined examinations of the cognitive mechanisms underlying prospective memory impairment in PD. The following discussion applies the notion – initially put forth by the Multiprocess Theory [51] and expanded by Kliegel and colleagues' process model [50] – that characteristics of prospective memory tasks can influence their underlying cognitive requirements to guide such an examination and to explain the aforementioned seemingly discrepant findings.

Prospective component

In terms of the prospective component, the Multiprocess Theory of prospective memory [36,51,63] can be used to investigate the intention retrieval phase of prospective memory in PD. In a typical experimental prospective memory paradigm, participants are instructed to perform a specific action upon the occurrence of a cue that is embedded in an ongoing activity. The ongoing activity does not change when the cue appears, so for intention retrieval to occur participants must somehow recognize the prospective memory cue as a cue for action [63,64]. According to the Multiprocess Theory, individuals can either use strategic attentional resources to detect the cue during the ongoing activity (an executive control process), or they can rely on spontaneous processes to retrieve the intention upon encountering the cue. The Multiprocess Theory proposes that, among other things, particular features of the prospective memory cue can determine whether executive resources are employed to support intention retrieval. For example, tasks with cues that are perceptually salient or distinctive relative to the existing context (e.g. an alarm, a different color font) produce involuntary orienting and automatic attentional switching from the ongoing activity, eliminating the need for self-initiated attentional control [51]. One study of prospective memory in PD used such a cue (a timer ring) and found that intention retrieval was unimpaired [61].

Another cue-related feature thought to strongly influence the executive control requirements of intention retrieval is *cue-focality*, or the degree to which the ongoing activity encourages processing of critical features of the prospective memory cue [51,65]. *Non-focal* cues are not fully processed as a consequence of the ongoing activity in which an individual is engaged and thus require strategic attentional control such as monitoring and shifting for detection and intention retrieval. In contrast, *focal* cues are processed as a part of the ongoing activity and thus elicit automatic intention retrieval when encountered in the context of the ongoing activity. Of note, the terms focal and non-focal are typically used in reference to event-based prospective memory tasks, but time-based cues are also considered non-focal because time is not usually processed as a part of ongoing activities. Intention retrieval in prospective memory tasks with non-focal or time-based cues are impaired in PD [53,61,62], and this impairment has been associated with executive control processes such as working memory, set-shifting, and response inhibition [53,61,62]. By contrast, intention retrieval in prospective memory tasks with focal or salient cues is not impaired in PD [53,61]. Thus, the prospective component is not necessarily impaired by PD but instead can be supported by cue-related features that reduce executive control demands and thereby facilitate automatic intention retrieval.

Retrospective component

The idea that prospective memory task characteristics can alter their demand on executive control can also be used to investigate the retrospective component of prospective memory. The number of different intentions within a prospective memory paradigm or the complexity of their contents likely influence the amount of executive control required to effectively encode and retrieve them [50]. The studies reporting intact retrospective component functioning in PD used paradigms with a minimal number of simple intentions (e.g. "press a button when you see the word 'cookie'") [53,59,66] or intentions that were simpler than those of the comparison group [60] and thus had relatively low retrospective memory demands. In contrast, the two studies mentioned previously which found PD-related impairments in the retrospective component used more complex or numerous intentions. Costa and colleagues [61] used a relatively complex intention of performing three unrelated actions (e.g. "ask the experimenter to turn off the computer, write your name on a paper, and replace the telephone receiver"), and Raskin and colleagues [62] used an experimental paradigm with eight different intentions. Thus, it appears that when intentions require controlled encoding or retrieval processes, the retrospective component may be impaired in PD.

In general, much of the existing research on prospective memory in PD has not sufficiently challenged retrospective memory. This may have resulted in an underestimation of the role of controlled memory processes in PD participants' prospective memory performance. In addition to underestimating the role of retrospective memory processes in prospective memory, another potential consequence of minimizing the retrospective memory demands of prospective memory tasks may be a failure to represent real-world prospective memory. In everyday life, people often manage a number of intentions simultaneously, many of them with memory-demanding content [67]. Given that the ultimate goal of this work is to improve individuals' prospective memory in everyday life, it is important to understand how PD-related prospective memory deficits manifest in real-life-like contexts.

Conclusion

Taken together, previous work suggests that the prospective component is not necessarily impaired in PD, nor is the retrospective component necessarily intact. Rather, prospective memory performance in PD depends on the executive control requirements of these components. PD-related prospective memory impairment is most apparent when tasks require the self-initiation of executive control processes such as strategic encoding and attentional control (e.g. monitoring, shifting). However, a more comprehensive evaluation that explicitly manipulates retrospective component demand is warranted to draw stronger conclusions about the cognitive mechanisms underlying prospective memory impairment in PD. In addition, more ecologically valid paradigms should be used to more closely represent people's real-world prospective memory functioning. Studies with these features can better inform the development of targeted interventions to improve everyday prospective memory among people with PD.

1.3.3 A note on neural mechanisms

The above interpretation of the cognitive mechanisms underlying prospective memory impairment in PD is in line with the longstanding notion that PD produces a fundamental deficit in the allocation of attentional resources without explicit external cues or structure [68,69]. PD-related performance decrements on tasks that require self-initiated generation and use of internal organizational strategies to optimize goal-directed behavior have been found across a variety of domains [70]. This deficit is thought to arise from frontrostriatal circuitry dysfunction [71], particularly the circuit encompassing the dorsal portion of the caudate nucleus and its projections to the dorsolateral prefrontal cortex (Brodmann Area [BA] 45/46) [16,72]. The neural mechanism of

PD-related prospective memory impairment has not been studied directly, but dorsolateral prefrontal cortical activity has been linked to executive aspects of prospective memory in healthy participants [38,73,74]. However, the brain region most consistently associated with prospective memory in neuroimaging studies is the anterior prefrontal cortex (BA 10) [75], and the specific effect of PD on this region is not well studied. Further research is required to delineate the neural mechanisms underlying the effect of PD on prospective memory.

1.4 Improving prospective memory in Parkinson disease

Prospective memory impairment in PD is increasingly recognized as a functionally and clinically relevant problem and a viable target for cognitive intervention [35,76]. In light of the view that prospective memory impairment in PD stems primarily from executive dysfunction, two general approaches to improving prospective memory in PD can be pursued. The first is direct training to augment or restore the deficient executive control processes that underlie prospective memory impairment (*cognitive process training*), and the second is training in strategies to compensate for or circumvent deficits in the executive control processes that underlie prospective memory impairment (*strategy training*) [77,78].

1.4.1 Cognitive process training versus strategy training

Cognitive process training

Almost all cognitive interventions for PD to-date have taken the cognitive process training approach, using repetitive practice of tasks that challenge specific cognitive processes to enhance underlying neural physiology and strengthen those cognitive processes (e.g. working memory, processing speed) [30,79-83]. This approach has produced small, specific and short-term improvements on neuropsychological tests [30]. Unfortunately, these benefits do not translate to improved daily function in PD [30,79,81,84].

Aside from Aims 2 and 3 of this dissertation (Chapters 3-4; published versions of record: [85,86]), there is only one other published prospective memory intervention study in PD. This small study (*N* = 17) used the cognitive process training approach and found that direct training of shifting ability (an executive control process involved in intention retrieval) improved PD participants' performance on a laboratory prospective memory task compared to placebo [76]. Everyday prospective memory or other daily function outcomes were not assessed in this study; however, given the lack of generalization of process training in other cognitive domains, it is reasonable to assume a similar outcome in prospective memory.

Strategy training

In contrast to cognitive process training, a strategy training approach to cognitive intervention provides ways to maintain cognitive task performance despite the presence of cognitive deficits. It involves teaching people to use compensatory or adaptive techniques to bypass or work through cognitive processing limitations and achieve task-related goals [87]. Whereas practice-based process training tends to produce skills that are tightly tied to the training context, strategy training can produce flexible skills that people can apply across situations (i.e. transfer or generalize) [88,89]. This is because strategy training relies on explicit learning, can deal directly with functional cognitive goals and tasks, and can incorporate specific techniques to support transfer, such as emphasizing metacognition, teaching general problem-solving skills, encouraging self-generation, training in different contexts, and making connections between activity experiences and contexts [90-95].

Strategy training is recommended for those with mild (vs. more severe) cognitive decline because it requires learning, capitalizes on existing cognitive resources, and aims to prevent or delay functional decline [87,96]. Although strategy training does not specifically target neurodegeneration or aim to improve cognition per se (which may be unrealistic in the context of neurodegeneration [97]), it can facilitate metacognitive control and continued activity engagement which may promote neuroplasticity, maintain cognition, or slow cognitive decline [98-100]. Strategy training is a Practice Standard (strongest evidence) for rehabilitation of mild memory, attention and executive function deficits after stroke or brain injury [101]. It also has a larger impact on daily function than restorative approaches in older adults with mild cognitive impairment (MCI) [97,102]. Because non-demented people with PD have similar cognitive problems and cognitive rehabilitation goals as these populations, strategy training may also be beneficial for them [103-105].

Indeed, the few cognitive rehabilitation studies that have incorporated strategy training show promise for improving daily function in PD [106-108]. This pattern of results dovetails with a study of prospective memory in healthy older adults, which found that strategy training (specifically implementation intentions, see section 1.4.2) was better than process training (shifting ability) for improving everyday prospective memory performance [78].

Conclusion

Given the above evidence and the need for interventions that mitigate the impact of PD-related prospective memory impairment on daily function, this dissertation examines a prospective memory strategy training intervention for people with PD.

1.4.2 Implementation intentions

Evidence from retrospective and prospective memory studies implies that while people with PD do not self-initiate effective encoding strategies, they can make use of externally guided encoding to improve their performance [109-111]. Thus, teaching people with PD specific prospective memory encoding strategies may improve their prospective memory performance. The *implementation intentions* (II) [112] strategy is a method of encoding and planning intentions that was originally designed to facilitate goal attainment and has since been applied to prospective memory. The II strategy is thought to reduce the executive control demands of prospective memory tasks [113] and has been shown to improve prospective memory performance in healthy older adults [114], stroke [115], multiple sclerosis [116], and very mild Alzheimer's disease [117]. The strategy involves specifying the intended action (Y) and the appropriate moment or cue for action (X) and creating a "When X, I will do Y" statement (e.g. "When I eat breakfast, I will take my medication") during intention formation [112]. Full use of II requires the person to repeat the statement aloud several times and visualize him or herself encountering the future moment or cue and executing the intended action. By forcing elaborate and specific encoding, II are thought to heighten the accessibility of prospective memory cues and strengthen the association between prospective memory cues and their intended actions, thereby facilitating more automatic cue detection and intention retrieval when the cue is encountered [112,113,118-120]. The proposed general mechanism of II, that they promote a shift from controlled to automatic processing, is supported by an fMRI study showing that use of II shifted brain activity from a region associated with top-down control of prospective memory processing (lateral BA 10) to one associated with bottom-up prospective memory cue responding (medial BA 10)[121].

To summarize, II target aspects of prospective memory tasks that can be challenging for people with PD due to executive dysfunction. They provide an explicit structure for good associative encoding of intentions that may compensate for the PD-related deficit in internally-generated intention formation strategies. This then should reduce the need for controlled intention retrieval processes (which are impaired in PD) by fostering reliance on more automatic retrieval processes (which are spared in PD) [113].

1.5 Aims of the dissertation

This dissertation examines the cognitive mechanisms underlying prospective memory impairment in PD and the potential of II training to improve prospective memory in PD. The specific aims are as follows: (1) Determine the cognitive mechanisms underlying prospective memory impairment in PD, (2) Determine the effect of II training on laboratory prospective memory performance in PD, and (3) Determine the effect of II training on reported everyday prospective memory in PD.

Aim 1 is addressed in an observational study comparing the performance of non-demented PD participants and healthy older adults on the Virtual Week test [122,123] (see Appendix). The Virtual Week test was designed to simulate the prospective memory requirements of everyday life and involves the coordination and execution of multiple intentions that resemble real world tasks (e.g. taking medications, running errands). Importantly for present purposes, while possessing naturalistic features, the Virtual Week remains a controlled laboratory test and allows for the manipulation of characteristics thought to influence the demand on underlying cognitive processes. Relevant to the above analysis of prospective memory in PD, it includes tasks that vary in prospective component and retrospective memory demands (cue focality and regularity, respectively). This study is the first to explicitly manipulate and factorially combine the executive control requirements of the prospective and retrospective components of prospective memory tasks. Compared to existing work, it is a more ecologically valid and comprehensive evaluation of prospective memory in PD.

Due to the overlap of the cognitive mechanisms underlying prospective memory impairment in PD (determined, in part, by Aim 1) and the mechanisms of action of II, Aims 2 and 3 of this dissertation examine the potential of the II strategy to improve prospective memory in PD. These aims are addressed in a randomized controlled trial that compares the effect of a single session of laboratory-based training in either II or verbal rehearsal (control/placebo strategy) on prospective memory in non-demented individuals with PD. Within this study, Aim 2 seeks to provide “proof of concept” of II in PD – in other words, that when people with PD use the strategy, it improves their prospective memory performance in predictable ways based on our understanding of cognitive mechanisms. To this end, it uses the Virtual Week as the primary outcome measure and tests the effect of strategy training on performance of the various prospective memory task types (focal/less focal and regular/irregular crossed factorially). Aim 3 explores issues relevant to clinical application by seeing if people with PD can generalize the use or benefit of II to everyday prospective memory, as measured by a self-report questionnaire [124]. It also investigates individual characteristics that may influence response to II training because knowledge of such potential effect modifiers can inform future tailoring, targeting, or modification of the intervention.

Chapters 2-4 contain the detailed reports of Aims 1, 2 and 3, respectively (published versions of record: Aim 1 [125], Aim 2 [85], Aim 3 [86]).

Chapter 2: Aim 1: Cognitive mechanisms of prospective memory impairment in Parkinson disease

Foster, E.R., Rose, N.S., McDaniel, M.A., & Rendell, P.G. (2013). Prospective memory in Parkinson disease during a virtual week: Effects of both prospective and retrospective demands. *Neuropsychology*, *27*(2),170-181.

2.1 Abstract

Objective: This study investigated the effect of Parkinson disease (PD) on event-based prospective memory tasks with varying demand on (1) the amount of strategic attentional monitoring required for intention retrieval (prospective component) and (2) the retrospective memory processes required to remember the contents of the intention or the entire constellation of prospective memory tasks. **Method:** Twenty-four older adults with PD and 28 healthy older adults performed the computerized Virtual Week task, a multi-intention prospective memory paradigm that simulates everyday prospective memory tasks. The Virtual Week included *regular* (low retrospective memory demand) and *irregular* (high retrospective memory demand) prospective memory tasks with cues that were *focal* (low strategic monitoring demand) or *less focal* (high strategic monitoring demand) to the ongoing activity. **Results:** For the regular prospective memory tasks, PD participants were impaired when the prospective memory cues were less focal. For the irregular prospective memory tasks, PD participants were impaired regardless of prospective memory cue type. PD participants also had impaired retrospective memory for irregular tasks, which was associated with worse prospective memory for these tasks during the Virtual Week. **Conclusions:** When retrospective memory demands are minimized, prospective memory in PD can be supported by cues that reduce the executive control demands of intention retrieval. However, PD-related deficits in self-initiated encoding or planning processes have strong negative effects on the performance of prospective memory tasks with increased retrospective memory demand.

2.2 Introduction

Cognitive impairment is a well-recognized feature of Parkinson disease (PD) and is present in the earliest disease stages and in the absence of dementia [58,126]. Although subtle, this impairment independently predicts reduced function and quality of life [20,21]. Cognitive impairment in PD without dementia involves, most prominently, deficits in executive control functions such as planning, working memory and cognitive flexibility [127-130]. Individuals with PD also demonstrate declarative memory impairments, which are thought to stem from deficits in the executive control of encoding or retrieval processes rather than from deficits in retention [57,110,131-133].

Prospective memory, or remembering to carry out previously formed intentions at the appropriate moment, is a complex cognitive construct [36] that has received increasing attention in PD. Prospective memory tasks include such common everyday examples as remembering to take medication as prescribed, remembering to keep appointments, and remembering to return a library book on the due date. In event-based prospective memory, the appropriate moment is signaled by an external event. In terms of a single task, successful event-based prospective memory requires detecting the event and interpreting it as a cue for action (the *prospective component*) as well remembering the specific action to be performed (the *retrospective component*) [44]. On some accounts, the prospective component is thought to involve frontally mediated executive control processes that support monitoring for the event and initiating the intention [38,45]. Once the event is interpreted as a cue for action, retrieval processes similar to those involved in other associative memory tasks, such as recognition and cued-recall, support the retrospective component [46-49]. In everyday life, people often manage a number of intentions simultaneously (e.g. [67]) so another source of retrospective memory demands in prospective memory is memory for all of the different tasks one has formulated for a given future period.

A number of studies have found that PD participants fail to carry out intentions despite remembering their contents upon later questioning [53,59,60]. This suggests that the retrospective memory processes involved in encoding and retention of intention contents are intact, while the executive processes underlying self-initiated intention retrieval or execution at the appropriate moment in the future are impaired (the prospective component). However, the opposite performance pattern has been reported, with PD participants demonstrating intact event-based intention retrieval but impaired recall of the intended action (i.e. they remembered they were supposed to do something, but not what they were supposed to do [61]).

The notion that particular features of prospective memory tasks can influence their executive control requirements has begun to guide more refined examinations of prospective memory in PD and can help to explain the above seemingly discrepant findings. In terms of the prospective component, the Multiprocess Theory [36,51] proposes that intention retrieval can be supported by either controlled or automatic processes depending on, among other things, the nature of the prospective memory cue. A cue-related feature thought to strongly influence the executive control requirements of intention retrieval is c*ue-focality*, or the degree to which critical features of the prospective memory cue are processed during the ongoing activity [65]. Non-focal cues (those that are not fully processed as a consequence of the ongoing activity in which an individual is engaged) require controlled attentional processes such as strategic monitoring for detection and intention retrieval; as such, performance on prospective memory tasks with non-focal cues has been linked to prefrontal cortical functioning [75]. In contrast, focal cues are thought to elicit spontaneous intention retrieval when encountered in the context of the ongoing task, a process which is associated with the hippocampus [134]. Foster et al. [53] manipulated cue-focality within an event-based prospective memory paradigm and found that while PD participants were impaired on tasks with non-focal cues, they were unimpaired on tasks with focal cues. Taken together, these studies suggest that the prospective component is not necessarily impaired by PD, but instead can be supported by cue-related features that facilitate automatic intention retrieval, thereby reducing executive control demands.

The idea that prospective memory task characteristics can alter demand on executive control can also be applied to more thoroughly investigate the contribution of retrospective memory processes to prospective remembering. The number of different intentions within a prospective memory paradigm (single vs. multiple, see [50]) or the complexity of their contents likely influence the amount of executive control required to effectively encode and retrieve the intentions and thus may affect memory for the entire prospective memory task (both the cue and action) or for the intention contents (the specific action associated with the cue), respectively. Although several studies have reported that retrospective problems do not interfere with prospective memory performance in PD, they used paradigms with a minimal number of simple intentions (e.g. “press a button when you see the word ‘cookie’”) [53,59,66] or intentions that were simpler than those of the comparison group [60]. Therefore, much existing work has not sufficiently challenged the retrospective memory processes involved in prospective memory.

Two studies that used more numerous or complex intentions did find PD-related impairments in the retrospective component [61,135] and in retrospective memory for the entire task [135]. These apparent retrospective memory failures may have resulted from poor executive control during intention encoding and/or retrieval. For example, in the case of Costa, Peppe, Caltagirone et al. [61], recalling the relatively complex intention of performing three unrelated actions (e.g. “ask the experimenter to turn off the computer, write your name on a paper, and replace the telephone receiver”) in response to a timer ring may have required a controlled memory search after spontaneous retrieval of the intention to do “something.” Deficits in controlled memory retrieval are a commonly-cited manifestation of frontostriatal circuitry dysfunction in PD [136].

Paradigms with numerous or more complex intentions may also require higher-level encoding strategies or planning during the intention formation phase, and individuals with PD have been found to make limited use of such strategies [110,133]. These findings indicate the need for a more focused examination of the effect of retrospective memory demand on prospective memory performance in PD.

Specifically, the common practice of minimizing retrospective memory demands may result in an underestimation of the role of controlled declarative memory processes in PD participants' prospective memory performance. It may also result in a failure to capture the true demands of real-world prospective memory, which often involves multiple intentions with memory-demanding content. Given the prevalence of prospective memory tasks in daily life and their relevance for health and independence (e.g. [137,138]), it is important to understand how PD-related prospective memory deficits manifest in real-world contexts. Unfortunately, experimental paradigms used thus far may have low predictive validity for everyday prospective memory performance (e.g. [53]). The Virtual Week task [122,123] may help overcome this limitation, as it was designed to simulate the prospective memory requirements of daily life. The Virtual Week task takes the form of a board game that requires the coordination and execution of multiple intentions that resemble the types of prospective memory tasks people perform throughout their day (e.g. running errands, taking medications, making phone calls). Importantly, while possessing these naturalistic features, the Virtual Week is a controlled laboratory task, allowing for the manipulation of characteristics thought to influence the underlying cognitive requirements of various prospective memory tasks. Critical to the above discussion of prospective memory in PD, the Virtual Week includes event-based prospective memory tasks that vary in prospective-component and retrospective-memory demands (*cue-focality* and *regularity* [described below], respectively). Moreover, the Virtual Week has been found to be a more reliable index of prospective memory than traditional paradigms, as it includes a comparatively large number of prospective memory target trials (e.g. [139]).

In this study, we employed the Virtual Week to conduct a more ecologically valid examination of prospective memory in PD. Specifically we aimed to replicate, in a more realistic context, the finding of Foster et al. [53] that non-demented individuals with PD are preferentially impaired on event-based prospective memory tasks that require executive control for intention retrieval. We included event-based prospective memory tasks with *focal* and *less focal* cues, whereby focal cues served as an external trigger for intention retrieval and less focal cues required attentional strategies for detection and intention retrieval (details of how this factor was operationalized are in the description of the Virtual Week below).

A second objective was to investigate the effect of retrospective memory demand on prospective memory in PD, an issue that has received little attention to-date. To vary the demand on retrospective memory processes we included *regular* and *irregular* tasks. As outlined in previous reports of Virtual Week, retrospective memory demand is reduced for regular compared to irregular tasks (e.g. [122,139-141]). In the current study, the retrospective memory demands of regular tasks were reduced in four ways. First, regular tasks received enhanced encoding relative to the irregular tasks because regular tasks were learned to criterion at the beginning of the game whereas irregular tasks were learned on the participants' own terms throughout the game. Second, the regular tasks were to be repeatedly performed across days and also within each day at the same moments in the game, whereas irregular tasks changed from day to day, both in terms of the intention and the specific cue to which that intention was linked. Third, because regular tasks were repeated across days and each irregular task was unique, there were fewer total cue-action associations to learn and remember for the regular tasks (4) compared to the irregular tasks (20) for the duration of the Virtual Week. Fourth, the content of the four regular tasks was of minimal complexity, as it only involved two relatively simple actions (taking antibiotics and using an asthma inhaler) that were related to one topic (dealing with a health problem). Irregular tasks, on the other hand, involved distinct actions and cues that were unrelated to each other. Thus, there were not only fewer total regular tasks compared to irregular tasks to learn and remember, but the content of the regular task intentions (i.e. the retrospective component) was less difficult.

Previous research has found that when retrospective memory demands are minimized, PD participants have a selective impairment for event-based prospective memory tasks with non-focal cues [53,59]. Accordingly, we predicted that for the *regular* tasks (those that presumably minimize the retrospective memory demand), PD participants would be impaired on those with less focal cues (challengind the prospective component [36]) but unimpaired on those with focal cues relative to a comparison group of healthy older adults.

By contrast, for the *irregular* tasks (that we assume increase the retrospective memory demand), we anticipated that PD participants would be impaired regardless of whether cues were more or less focal. This expectation stems from our theoretical analysis presented above and from recent studies suggesting that PD participants had impaired prospective memory when demands on retrospective memory were relatively high [61,135]. It should be noted, though, that these studies used time-based tasks. Such tasks are analogous to less focal event-based tasks in that they require strategic monitoring of the environment [142], thereby placing high demands on the prospective component. Thus, these recent studies leave uncertain the degree to which challenges to retrospective memory versus the prospective component contribute to the observed

PD-related prospective memory deficits. By examining prospective memory performance on a task with relatively high retrospective memory demands (the irregular prospective memory task) but lower prospective memory demands (a focal event-based irregular task), the current experiment allows a more penetrating evaluation of the role of retrospective memory processes in PD-related changes in prospective memory.

To provide support for our manipulation of retrospective memory demand, we assessed participants' retrospective memory for the various prospective memory tasks at the end of the Virtual Week (see *Retrospective memory test* below). We anticipated that for all participants, retrospective memory would be better (and almost perfect) for regular compared to irregular tasks. Due to the PD-related retrospective memory deficit hinted at in previous studies with more numerous or complex intentions [61,135], we predicted that the PD group would have impaired retrospective memory for irregular tasks relative to the comparison group. Impaired retrospective memory for an intention likely interferes with its prospective execution. We predicted that this pattern would manifest on an individual level, with those with worse retrospective memory having worse prospective memory performance, as well as on a group level, with a PD-related deficit in irregular task retrospective memory contributing to a PD-related deficit in irregular task prospective memory performance.

2.3 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.

2.3.1 Participants

Study participants were 24 older adults with PD and 28 healthy older adults. PD participants were recruited from the WUSM Movement Disorders Center, and non-PD participants were volunteers from the community. All PD participants had been diagnosed with idiopathic PD by a movement disorders neurologist and were Hoehn and Yahr stage II (indicating relatively mild signs of disease) [143]. Of the PD participants, 15 were receiving carbidopa-levodopa exclusively and 9 were receiving carbidopa-levodopa in conjunction with a dopamine agonist, COMT-inhibitor, or both (n = 3 each). Exclusionary criteria included possible dementia or global cognitive impairment (Mini-Mental State Examination (MMSE) score < 27) [144], treatment with anticholinergic medications, treatment with certain dopaminergic or benzodiazepine medications known to interfere with cognitive functioning, history of neurosurgery or other neurological conditions (aside from PD for PD participants), history or current psychotic disorder, significant current psychiatric disorder, or any condition which would interfere with testing (e.g. non-English speaking, severe dyskinesias, inability to see testing materials, etc.).

2.3.2 Design

The type of prospective memory task was manipulated within-subjects, with the regularity of the task (regular, irregular) factorially combined with the cue type (focal, less focal) to yield 4 types of prospective memory tasks. As detailed (and justified) below, the focal cue prospective memory task was cued by an event card, whereas the less focal cue task was cued by a time square. In sum, the design constituted a 2 (Group: PD, non-PD) x 2 (Regularity of the prospective memory task: regular, irregular) x 2 (Cue type: focal, less focal) mixed factorial.

2.3.3 Procedure

Each participant underwent testing during one session that lasted about three hours. Because our goal was to conduct an investigation more representative of real-world prospective memory functioning, PD participants were tested while on their regular antiparkinsonian medications. Our previous study in a similar sample of PD participants found no effect of medication status on event-based prospective memory performance [53] (for different findings in relation to time-based prospective memory, see [145,146]). Demographic information for both groups was obtained through interview. PD-related clinical characteristics, including on-medications motor dysfunction severity ratings within three months of the testing session (the Unified Parkinson's Disease Rating Scale Motor subscale, UPDRS [147]), were obtained from clinical chart review. All participants completed the Mill Hill Vocabulary Test [148] as a proxy for general intelligence and the 15-item Geriatric Depression Scale (GDS; [149]) to assess for depressive symptoms. Then they proceeded to cognitive testing, the details of which are described next.

Prospective memory test: Computerized Virtual Week

A recently computerized version of the Virtual Week board game was used for this study [122,139,150] (see Appendix). Participants performed this task on a desktop computer, using the mouse to interact with the software and move a game token around a "board" on the screen. Participants moved their token around the board by rolling a die (clicking on it in the middle of the screen) and then clicking on the corresponding square of the board. The consecutive hours of the day that people are typically awake (7:00am-10:00pm) were marked on the board, and each circuit of the board represented one day. As participants circuited the board, they progressed through the virtual time of day and encountered time-appropriate activities for which they were required to make decisions. Each time the token landed on or passed an event square (labeled "E") participants were required to click on the "Event Card" button to reveal an event card that described a specific activity and three options relevant to the activity (e.g. "It's breakfast. Do you have a) eggs, b) cereal, c) only coffee?"). Participants read each card, pretended to be engaged in that activity, and selected the preferred option. After the option was selected, the event card indicated a number to be rolled on the die in order to continue with the day (e.g. "You must roll an even number to continue."). Rolling the die, circuiting the board, reading event cards, and making decisions about activity details served as the *ongoing activity* of this prospective memory paradigm.

Eight prospective memory tasks were embedded within each day: four regular tasks and four irregular tasks. Participants did not physically carry out the prospective memory tasks; rather they clicked on the "Perform Task" button when they felt it was the appropriate moment and selected the task from a list of possibilities (prospective memory tasks and distracters). The four *regular tasks* were repeated every day. These were "take antibiotics at breakfast and dinner" and "take asthma medication at 11 a.m. and 9 p.m." Thus, upon reading the breakfast event card, participants were to remember to take their antibiotics by clicking on the "Perform Task" button and selecting "take antibiotics" from the list. Similarly, when the token landed on or passed the 9 p.m. square, participants were to remember to take their asthma medication by selecting it from the Perform Task list. All participants were required to learn the regular tasks to criterion (i.e. 100%) by completing a recall test three times with feedback provided following each test.

The four *irregular tasks* were different each day. Examples of irregular tasks were "drop off dry cleaning when you go shopping" and "phone the plumber at 4 p.m." At the beginning of each day, participants were required to click on the "Start Card" button, which revealed a start card that described two of the irregular tasks for that day. The remaining two irregular tasks for each day were administered sometime during the day on event cards. For example, one event card read "You visit your nephew at school for lunch. He asks you to buy him some multi-colored pens when you go shopping today. In the meantime, do you have a) pizza, b) a sandwich, or c) a salad for lunch?" Then, later in the afternoon of that day, an event card informed participants that they were shopping. Upon reading this event card, participants were to remember to buy a multi-colored pen by selecting it from the Perform Task list.

As described above, participants were cued for the prospective memory tasks by either reading an event card that described a particular activity or by passing the token across a particular time square on the board[1]. Rose et al. [139] suggested that Virtual Week tasks cued by event cards and time squares are event-based tasks[2] that differ in their *cue-focality*, or degree to which the ongoing activity encourages processing of features of the cue emphasized during intention formation. Tasks to be performed on event cards were considered to have *focal* cues because reading and pretending to be engaged in the activity described on the card is central to the ongoing activity of the Virtual Week. In contrast, tasks to be performed at specified time squares were considered to have *less focal* cues because attending to the time square that one's token passed was not critical to the ongoing activity of the Virtual Week. Consistent with this hypothesis, Rose et al. [139] showed that age differences were larger for tasks with less focal cues (i.e. the time-square cues) and that individual differences in working memory were correlated with performance on tasks with less focal cues, but not tasks with focal cues (the tasks associated with the event cards).

Participants completed five days with eight prospective memory tasks per day: four regular and four irregular. Within the regular and irregular tasks for each day, two of each had

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[1] We did not include the time-check tasks that can be a part of the Virtual Week (i.e. check lung capacity at 2min 15sec and 4min 30sec after the start of each day) in this study because our purpose was to investigate event-based prospective memory in PD. A number of previous studies with Virtual Week as the primary measure have excluded these tasks.

[2] Because the times were marked on the squares of the board, the "time-based" tasks of the present version of the Virtual Week did not require monitoring a clock or the passage of real time as in true time-based prospective memory tasks. Instead, moving one's token past a time square can be conceptualized as an event, as it involved encountering an external cue.

focal cues (event cards) and two had less focal cues (time squares). This yielded a total of 40 prospective memory tasks across four task types: 10 regular focal, 10 regular less focal, 10 irregular focal and 10 irregular less focal. For regular and irregular less focal tasks, responses were considered correct if they occurred within one virtual hour of the target time. For regular focal tasks, responses were considered correct if they occurred between the event cards immediately preceding and following the target event card, a period which roughly corresponds to the on-time criteria set for the less focal tasks. Therefore, in the regular focal condition and in both of the less focal conditions slightly early responses were considered correct because the breakfast and dinner event cards and the time squares could reasonably be anticipated within the context of the game. In contrast, in the irregular focal condition, only responses occurring at the target event card or before the next event card were considered correct (because participants did not know when the irregular events would occur and thus presumably could not have anticipated the target event card for the irregular focal task). Additional performance errors including number of perform task list cancellations (opening the list but not selecting a task), number of distracters selected, and “double doses” were also recorded. A double dose indicates the repeated selection of a specific prospective memory task. In some cases, a task is completed early and then repeated at the correct time (second correct); thus, the repeat appears to be a correction.

Participants received detailed verbal instructions on the Virtual Week and were guided through one trial day with four irregular tasks (two focal, two less focal) by the experimenter. During this time they were free to ask questions, and the experimenter ensured they were comfortable with the computer and the task. After the trial day but before beginning the test days, participants were introduced to the regular tasks and were required to learn them to criterion (i.e. 100%) by completing a recall test three times, with feedback provided following each test. The participants were instructed to perform the same four regular tasks each test day and were reminded that, similar to the trial day, they would be given four different irregular tasks to perform each test day that would not be repeated (two would be given at the beginning of each day and two would be given during each day). Participants then completed the five test days (Monday-Friday) of the Virtual Week on their own.

Retrospective memory test

Immediately following the Virtual Week, participants completed a recognition test to assess their retrospective memory for the various prospective memory tasks of the Virtual Week. The test involved matching each intended action with its cue. Participants were presented with a list of the actions (e.g. take antibiotics, phone the plumber) on the left side of a sheet of paper and a list of the cues (e.g. dinner, 4:00 pm) on the right. They were to draw lines connecting the appropriate pairs and were encouraged to connect every action with a cue even if they were unsure. There were 24 items on the test: 4 regular tasks (2 focal, 2 less focal) and 20 irregular tasks (10 focal, 10 less focal). Proportion correct was calculated for each task type (regular focal, regular less focal, irregular focal, irregular less focal).

2.4 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).

2.4.1 Participant Characteristics

Demographic and clinical characteristics of the participants are presented in Table 2.1. Due to experimenter error (score sheets misplaced), a portion of the non-PD groups' GDS and MMSE data are missing; however, no non-PD participants scored < 27 on the MMSE or above the GDS screening cutoff for depressive disorder. The sample was 54% female and 96% Caucasian. There were no significant group effects with regard to age, education, MMSE score, or Mill Hill score (ps > 0.19). The PD group reported significantly more depressive symptoms than the control group as measured by the GDS, $t = -2.93$, $p = 0.006$; however, only one PD participant scored above the GDS screening cutoff for depressive disorder (cutoff = 5, participant's score = 9). Depression was not associated with prospective memory performance within the PD group (rs < 0.15, ps > 0.47).

Table 2.1. Characteristics of the participants for Aim 1, N=52.

Variable	PD	non-PD
n	24	28
Age (years)	67.0 (5.9)	69.2 (5.9)
Education (years)[a]	15.3 (2.8)	16.5 (2.8)
GDS[b]	2.3 (1.8)	0.7 (0.9)*
MMSE[c]	29.4 (0.7)	29.1 (0.9)
Mill Hill Vocabulary	14.7 (1.7)	15.0 (2.4)
Disease duration (years)	5.7 (4.3)	--
UPDRS Motor	19.5 (9.0)	--
LEDD (mg)	1039 (579)	--

Values are shown as mean (standard deviation) or number of participants. Variables with missing data are indicated with superscript letters as follows: [a]control n=26; [b]control n=13; [c]control n=16. * $p < 0.05$

2.4.2 Virtual Week

Reliability

The reliability coefficients (Cronbach's α) for the four prospective memory task types of the Virtual Week are presented in Table 2.2. The data for the PD participants (see top row in Table 2.2) indicate that the computerized Virtual Week is a reliable measure of prospective memory in PD.

Table 2.2. Reliability of Virtual Week: Cronbach's alpha assessing internal consistency.					
	Regular focal	Regular less focal	Irregular focal	Irregular less focal	Overall
Number of items	10	10	10	10	40
PD	0.79	0.79	0.73	0.63	0.89
non-PD	0.74	0.75	0.74	0.70	0.81

Prospective memory

Proportions of correct prospective memory responses are presented in Figure 2.1. These data were submitted to a mixed analysis of variance (ANOVA) with group (PD, non-PD) as the between-subjects factor and regularity (regular, irregular) and cue type (focal, less focal) as the within-subjects factors. In general, PD participants were disadvantaged in prospective memory relative to the non-PD participants, $F(1, 50) = 8.33$, $p = 0.006$, $\eta^2 = 0.14$. In addition prospective memory performance was generally higher with regular than with irregular cues, $F(1, 50) = 226.12$, $p < 0.001$, $\eta^2 = 0.82$, and higher with focal than with less focal cues, $F(1, 50) = 15.20$, p < 0.001, $\eta^2 = 0.23$. These main effects were qualified by a marginally significant three-way interaction, $F(1, 50) = 3.81$, $p = 0.06$, $\eta^2 = 0.07$ (see Figure 2.1). To help interpret this interaction and to evaluate the predictions outlined in the introduction, separate two-way ANOVAs for regular and irregular tasks (with group and cue type as variables) were performed. For regular tasks, there was a significant two-way interaction between group and cue type, $F(1, 50) = 3.92$, $p = 0.05$, $\eta^2 = 0.07$. A test of simple effects showed that PD participants performed worse than non-PD participants on less focal tasks, $F(1, 50) = 6.46$, $p = 0.01$, $\eta^2 = 0.11$, but not focal tasks, $F(1, 50) = 0.87$, $p = 0.36$, $\eta^2 = 0.02$. For irregular tasks, PD participants performed worse than non-PD participants, $F(1, 50) = 9.18$, p = 0.004, $\eta^2 = 0.16$, and this effect did not interact with cue type, $F = 0.95$. Also, all participants performed worse on less focal compared to focal tasks, $F(1, 50) = 26.38$, $p < 0.001$, $\eta^2 = 0.35$. To summarize, as anticipated PD participants were impaired on regular less focal, irregular focal and irregular less focal prospective memory tasks compared to non-PD participants.

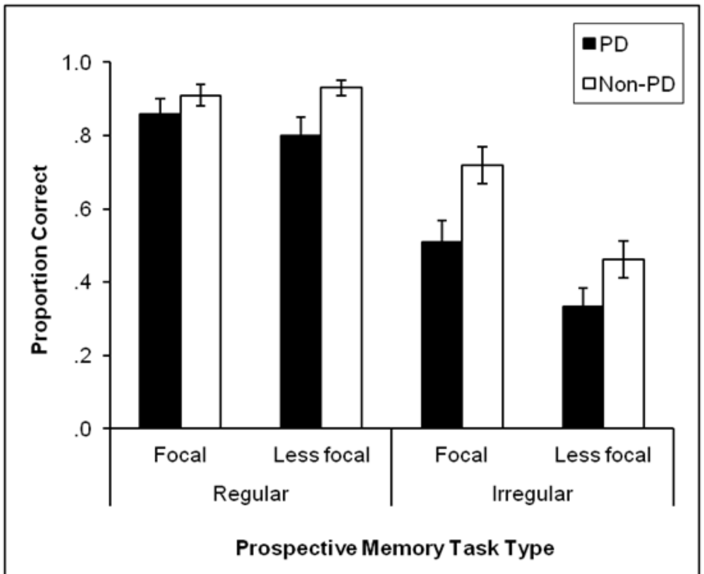

Figure 2.1. Prospective memory performance: Mean proportion of correct responses on prospective memory tasks in the Virtual Week as a function of clinical group, cue type and task regularity. Error bars depict standard error of the mean.

We performed two additional analyses to (a) determine the effect of repeatedly performing the same prospective memory task (regular tasks) across the days of the Virtual week and (b) determine whether enhanced encoding per se contributed to the advantage of regular tasks relative to irregular tasks. Proportions of correct prospective memory responses for regular tasks (collapsed across focal and less focal cues) on each day of the Virtual Week were submitted to a 2 (group) X 5 (day of the week) ANOVA. Regular task prospective memory performance improved over the course of the week in both groups, $F(4, 47) = 3.70$, $p = 0.006$, $\eta^2 = 0.07$. This effect did not interact with group, $F(4, 47) = 0.63$, $p = 0.64$, $\eta^2 = 0.01$, indicating that PD and non-PD participants benefitted similarly from repetition.

To isolate the potential benefit of enhanced encoding associated with the regular prospective memory tasks, we analyzed the proportions of correct prospective memory responses for regular and irregular tasks on the first day of the Virtual Week (Monday). The 2 (group) X 2 (regularity) ANOVA indicated that prospective memory was better for regular tasks ($M = 0.81$, $SD = 0.24$) than for irregular tasks ($M = 0.43$, $SD = 0.29$) on the first day of the game, $F(1, 50) = 83.06$, $p < 0.001$, $\eta^2 = 0.62$. PD participants had worse prospective memory performance than non-PD participants on the first day of the game, $F(1, 50) = 8.15$, $p = 0.006$, $\eta^2 = 0.14$, but this effect did not interact with regularity, $F(1, 50) = 2.25$, $p = 0.14$, $\eta^2 = 0.04$. Thus, both the enhanced encoding that regular tasks received before beginning the test and the repetition of these regular tasks contributed to the enhanced prospective memory performance.

Retrospective memory

Proportions of correct retrospective memory responses for each group and task type are presented in Table 2.3. Due to the limited variance in retrospective memory for regular tasks (only one non-PD and two PD participants had less than 100% accuracy on these items), we did not analyze these data further. Irregular task retrospective memory scores were submitted to a mixed ANOVA with group (PD, non-PD) as the between-subjects factor and cue type (focal, less focal) as the within-subjects factor. In line with the expectations outlined in the introduction, PD participants had worse retrospective memory for irregular tasks than non-PD participants, $F(1, 50) = 5.42$, $p = 0.02$, $\eta^2 = 0.10$. In both groups, memory was better for irregular tasks with focal cues compared to those with less focal cues, $F(1, 50) = 48.91$, $p < 0.001$, $\eta^2 = 0.49$.

Table 2.3. Retrospective memory performance: Proportion of correct retrospective memory responses for the prospective memory tasks of the Virtual Week.		
Type of task	PD	non-PD
Regular focal[a]	0.96 (0.14)	0.98 (0.09)
Regular less focal[a]	0.96 (0.14)	0.98 (0.09)
Irregular focal[b]	0.55 (0.21)	0.68 (0.21)*
Irregular less focal[b]	0.37 (0.22)	0.50 (0.22)*

Values are shown as mean (standard deviation). [a] Out of 2 items, [b] Out of 10 items; * PD worse than non-PD, $p < 0.05$

Association of prospective and retrospective memory for the irregular tasks

Retrospective memory for irregular tasks was strongly correlated with prospective memory for irregular tasks for both groups (PD: $r = 0.78$, $p < 0.001$; non-PD: $r = 0.76$, $p < 0.001$). We conducted a pair of stepwise linear regression analyses predicting prospective memory for irregular tasks with focal or less focal cues to determine if retrospective memory completely or partially mediated the effect of PD. For irregular focal tasks, retrospective memory accounted for 27% of the variance, $F(1, 50) = 18.36$, $p < 0.001$, and group added an additional 6% of the variance, $F\Delta(1, 49) = 4.26$, $p = 0.04$. For irregular less focal tasks, retrospective memory accounted for 66% of the variance, $F(1, 50) = 97.60$, $p < .001$, but group did not add a significant amount of variance ($p = 0.72$). Thus, retrospective memory partially mediated the effect of PD on prospective memory for irregular focal tasks and completely mediated the effect of PD on prospective memory for irregular less focal tasks.

Prospective memory conditionalized on retrospective memory for the irregular tasks

Proportions of correct prospective memory responses for only those irregular tasks for which retrospective memory was accurate are presented in Table 2.4. These data were submitted to a mixed ANOVA with group (PD, non-PD) as the between-subjects factor and cue type (focal, less focal) as the within-subjects factor. There were no significant effects of group, $F(1, 50) = 2.90$, $p = 0.095$, $\eta^2 = 0.06$, or cue type, $F(1, 50) = 0.09$, $p = 0.769$, $\eta^2 < 0.01$, nor was there an interaction effect, $F(1, 50) = 2.54$, $p = 0.117$, $\eta^2 = 0.05$. Therefore, when the content of the irregular prospective memory tasks were accurately remembered by those with PD on the retrospective memory post-test, their prospective memory was similar to non-PD participants.

Table 2.4. Proportion of correct prospective memory responses conditionalized on correct retrospective memory responses for irregular tasks.

Type of task	PD	non-PD
Focal	0.56 (0.32)	0.75 (0.24)
Less Focal	0.66 (0.27)	0.68 (0.30)

The formula for this index is #PMcorrect|RMcorrect/(#PMcorrect|RMcorrect + #PMincorrect|RMcorrect). Values are shown as mean (standard deviation).

Additional performance errors on the Virtual Week

There were no significant group effects in terms of the additional errors recorded (all *p*s > 0.17; Table 2.5). Double doses were notably low in both groups (PD $M = 2.17$, $SD = 1.76$; non-PD $M = 2.36$, $SD = 2.8$) relative to the total number of prospective memory tasks (40).

Table 2.5. Number of additional errors on the Virtual Week.

	PD	non-PD
Perform Task List cancellations	8.92 (10.48)	5.36 (5.18)
Distracters selected	0.67 (1.24)	0.29 (0.71)
Double doses[a]		
2nd correct	1.38 (1.24)	1.82 (2.13)
All other	0.79 (1.10)	0.54 (1.07)

Values shown as mean (standard deviation). [a] Out of 40 tasks

2.5 Discussion

Our purpose was to investigate the cognitive mechanisms underlying complex event-based prospective memory performance in PD. We aimed to determine whether the previously found preferential impairment on tasks requiring executive control for intention retrieval (i.e. less focal prospective memory tasks) could be replicated in a more realistic context. We also addressed the effect of retrospective memory demand on prospective memory performance in

PD, an issue that has been largely disregarded in studies to-date. To this end, we used the Virtual Week task, a multi-intention paradigm that mimics daily life, and compared the effects of cue-focality and regularity on the prospective memory performance of non-demented individuals with PD and healthy comparison participants. As hypothesized, we found that PD participants were impaired on prospective memory tasks that required attentional strategies for intention retrieval (i.e. tasks with less focal cues) regardless of retrospective memory demand. However, when retrospective memory demand was higher (i.e. irregular tasks), PD participants were also impaired on tasks thought to rely on relatively automatic retrieval processes (i.e. tasks with focal cues).

Our data are consistent with previous research in that, at least when retrospective demand is minimized (i.e. the regular tasks), non-demented individuals with PD demonstrate a preferential impairment for less focal event-based prospective memory tasks—tasks that require attentional control strategies for intention retrieval [53,59]. Focal and less focal regular tasks were encoded in the same manner and elicited nearly perfect post-test recognition, so it is unlikely that the impairment for less focal regular tasks was a result of deficits in intention formation or retention. In addition, both of these conditions required inhibition of the ongoing activity and switching to actions required to perform the prospective memory task after intention retrieval, so deficits in the intention execution phase also cannot account for the impairment on less focal regular tasks.

The primary difference between focal and less focal regular tasks was the degree to which the ongoing activity encouraged processing of the prospective memory cue[3]. Tasks cued

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[3] Although there was no effect of cue-focality on regular task performance in the non-PD group, which is somewhat at odds with what would be expected based on the Multiprocess Theory, it should be noted that the conceptualization of cue-focality in the present version of the Virtual

by event cards are considered to be more focal because they are processed more fully during the ongoing activity of Virtual Week, which involves reading event cards and pretending to be engaged in the events. Tasks cued by passing one's token over a particular square on the board are considered to be less focal because this action is peripheral to the ongoing activity in the game [139]. Whereas focal cues can elicit automatic intention retrieval when encountered within the context of the ongoing activity, less focal cues require additional attentional control processes to be recognized [51,65]. This notion has been supported in PD, as performance on prospective memory tasks with less focal, but not focal, cues is associated with ongoing activity response time costs and performance on executive control tasks [53,61]. The PD-related deficit for less focal tasks could be due to impaired active maintenance of the intention in working memory [38], impaired monitoring of the environment for the cue while also engaging in the ongoing task [73], or impaired internally-driven shifting of attention from stimuli relevant to the ongoing activity to a less relevant or salient cue [151]. Our study was not designed to determine the potential differential contributions of these executive control processes. Regardless, our results indicate that intention retrieval in PD is facilitated by cues which reduce demand on these processes.

When retrospective memory processes were challenged (i.e. the irregular tasks), the PD group had impaired prospective memory for both focal and less focal tasks. This impairment was

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Week task was not as strictly controlled as in other prospective memory paradigms. The exact event-card (focal) cues were not presented during task encoding, and it is possible that these cues were not fully processed when encountered later due to the other demands of the ongoing activity (selecting activity options). In addition, although attending to the times marked on the squares was not critical to the ongoing activity of the Virtual Week, participants may have nonetheless done it while moving their tokens or as a general way of keeping track of the progression of the virtual day. Cue-focality is a matter of degree in the current study rather than an absolute distinction, which is why these tasks were termed "*less* focal" instead of "*non*-focal". This may also help to explain why the group difference was larger (although not significantly so) for Irregular Focal tasks than for Irregular Less Focal tasks, although it is important to note that both groups had the most difficulty with the Irregular Less Focal tasks largely accounted for by deficient retrospective memory for the irregular tasks as measured by the post-test recognition task. The irregular condition of Virtual Week is thought to impose greater demands on retrospective memory processes than the regular condition because it involves twenty different and unrelated cue-action associations (compared to just four related and repeated cue-action associations in the regular condition) which do not receive enhanced encoding (as do tasks in the regular condition) [122]. The nearly perfect retrospective memory for regular tasks but significantly reduced retrospective memory for irregular tasks among all participants in the present study supports this claim. The PD group had worse retrospective memory for irregular tasks than the non-PD group, and this was strongly associated with worse prospective memory for irregular tasks during Virtual Week. Furthermore, when only those tasks with accurate retrospective memory were considered (the conditional analyses), the PD-related prospective memory deficit for irregular tasks went away. These findings are consistent with those of Raskin et al. [62], who found a PD-related post-test recognition deficit for irregular intentions and significant associations between retrospective and prospective memory performance within PD. Previous studies have also found increased task substitution errors (indicating misremembering of intention contents; [62]) and impaired recall of the intended action after intention retrieval in PD [61]. Taken together, these results suggest that the retrospective memory processes involved in prospective memory can be disrupted by PD.

It should be noted that the retrospective memory post-test in the current study is only a general indicator of retrospective memory for the prospective memory tasks because it was not administered until the end of the five virtual days. Factors such as interference with new tasks that were to-be-remembered or the length of the retention interval (up to approximately 40 minutes for Monday’s tasks) could have affected performance on the retrospective memory post-test without necessarily being indicative of retrospective memory load-related forgetting during the game. This may account for the partial mediation of irregular task prospective memory performance by irregular task retrospective memory. In addition, the retrospective memory post-test does not allow determination of the potential source of impaired task performance during the course of the game. For example, failure on the post-test could indicate that the participant forgot only the cue-action association (which means s/he could have retrieved the intention to do *something* upon encountering the cue during the game but could not retrieve the contents of the intention, i.e. a retrospective component failure), or it could indicate that the participant forgot the entire task (and thus did not even retrieve the intention to act during the game). Since these data were collected, the Virtual Week has been upgraded to include a retrospective component assessment at the end of each virtual day. Meanwhile, a more complete picture may be provided by the additional performance errors on the Virtual Week. If the retrospective memory problem is an associative one, it should be characterized by Perform Task list cancellations and selection of distracters from the Perform Task list. There were no group differences in these measures, and Distracter selection was a rare error in both groups, suggesting that participants were forgetting the entire prospective memory task.

Given that non-demented individuals with PD consistently demonstrate intact memory retention [57] and that the recognition format of the Perform Task list and of the retrospective memory post-test placed few demands on controlled retrieval processes, it is unlikely that the PD-related retrospective memory deficit for irregular tasks was related to impaired storage or retrieval of intention contents. Instead, we propose that it was largely a function of poor executive control of encoding during the intention formation phase. Although we did not directly assess the differential effects of encoding and retrieval, previous research on memory dysfunction in PD supports this explanation. Participants were left to encode irregular tasks on their own throughout the duration of the game, so optimal encoding of these tasks required a high degree of self-initiation. In contrast, the experimenter guided regular task encoding at the beginning of the game by supplementing computer administration with verbal explanation and requiring participants to recall the tasks while providing corrective feedback until the tasks were learned to criterion. In this way, full encoding of the regular tasks was externally-enforced. The self-initiation of good encoding strategies is a frontally-mediated executive process [152]. Studies of retrospective memory have shown that individuals with PD fail to self-initiate effective encoding strategies, and this contributes to deficient recall [57,110,133]. However, when provided with explicit encoding strategies, PD patients can use them to essentially normalize their performance [111,153].

In the present study, it is likely that without explicit instruction the PD participants did not optimally encode the irregular intentions, which resulted in the prospective memory deficit. This explanation is consistent with the findings of two studies of prospective memory in PD by Kliegel and colleagues. In a paradigm which involved self-directed formation of a complex delayed intention, individuals with PD formed less elaborate plans for accomplishing the intention relative to a control group and subsequently were less likely to retrieve and initiate the intention when the target event occurred [60]. In a follow-up study, Altgassen, et al. [109] more closely examined the intention formation phase by using instructions that differentially emphasized the importance of the prospective memory task relative to the ongoing activity in two versions of a challenging event-based paradigm. PD participants had impaired prospective memory when the ongoing activity was emphasized, but they performed just as well as controls when the prospective memory task was emphasized. Therefore, it appears that when challenging intentions are involved, individuals with PD do not spontaneously implement higher-order encoding or planning strategies necessary to support later remembering, but this process can be facilitated by externally-guided direction of attention to the intention during encoding. Working memory capacity was strongly associated with the intention formation effects in both of the studies just described ([60,109]), which is consistent with the idea that deficits in executive control underlie this retrospective memory problem in PD.

Still at issue is why retrospective memory for the less focal irregular tasks was poorer than for the focal irregular tasks. In this experiment, retrospective memory for the less focal irregular tasks may have been especially compromised by the arbitrary relation between the cues and intended actions. For instance, the less focal cues were time squares (virtual times) that did not inherently relate to the intention (4 PM—phone the plumber). By contrast, focal cues were events (go shopping) that could be meaningful linked to the intended action (pick up dry cleaning), and may have even reflected the participants' everyday experiences. Certainly, the relatively arbitrary cue-action association for the less focal irregular tasks could have compromised encoding. However, it is theoretically plausible that the poorer retrospective memory by both PD and non-PD groups for less focal compared to focal tasks may reflect difficulty retrieving less well-related cue-action associations. Greater retrieval difficulty for these associations (in the less focal irregular tasks) could have also been the reason that retrospective memory for the cue-action pairings entirely mediated the PD-related prospective memory deficit for the less focal irregular tasks (a finding that was not expected a priori). These findings leave open the possibility that a memory retrieval deficit, rather than or in addition to an encoding deficit, impairs the retrospective memory involved in prospective memory in PD. We could not parse the effects of these component processes in the current experiment, but it is clear that the retrospective memory demands of prospective remembering warrant further investigation in this population.

Our findings and interpretation are in line with the notion that PD produces a fundamental deficit in the allocation of attentional resources without explicit external cues [68,69]. PD-related performance decrements on tasks that require the generation and use of internal organizational strategies to optimize goal-directed behavior have been found across a variety of domains [70]. This deficit is thought to arise from frontrostriatal circuitry dysfunction [71], particularly the circuit encompassing the dorsal portion of the caudate nucleus and its projections to the dorsolateral prefrontal cortex [16,72]. Dorsolateral prefrontal cortical activity has been linked to the maintenance of a delayed intention in healthy participants [38], particularly in tasks with high working memory load [73,74]. However, the region most consistently associated with prospective memory in neuroimaging studies is the anterior prefrontal cortex [73,75], and the specific effect of PD on this region is not well-studied. Further research is required to delineate the neural mechanisms underlying the effect of PD on prospective memory.

In summary, our data highlight the negative effect of executive control requirements on prospective memory performance in PD using a reliable and complex multi-intention paradigm. In addition to affecting the prospective component (i.e. self-initiated intention retrieval), deficits in strategic attentional processing among individuals with PD can also interfere with retrospective memory processes critical to prospective memory performance. While intention retrieval may be supported by features that facilitate automatic processing of prospective memory cues, deficits in self-generated encoding strategies or planning at intention formation can preclude this benefit. This implies that the presence of multiple intentions with complex content may call for the additional provision of explicit intention formation strategies (e.g.

implementation intentions [112]). Prospective memory is considered essential for everyday function and is associated with important clinical outcomes in other neurological populations, including independence in activities of daily living [138,154] and caregiver burden [155]. A better understanding of what causes prospective memory impairment in PD will guide the development of targeted interventions to improve it. Because the ultimate goal is to improve individuals' prospective memory in everyday life, it is important that we begin conducting investigations that capture the complexity of real-world prospective memory tasks. This includes using assessments that are more representative of people's daily lives and acknowledging the fact that many real-world prospective memory tasks challenge retrospective memory. Tasks like the Virtual Week, which have better face validity and psychometric properties compared to previous paradigms used to investigate prospective memory in PD (e.g. [53,135]), may provide better insight into the factors that influence real-world prospective memory in PD and perhaps a clearer path to intervention.

Chapter 3: Aim 2: Strategy training and laboratory prospective memory in Parkinson disease

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3.1 Abstract

Background: Prospective memory is essential for productive and independent living and necessary for compliance with prescribed health behaviors. Parkinson disease (PD) can cause prospective memory deficits that are associated with activity limitations and reduced quality of life. Forming implementation intentions is an encoding strategy that may improve prospective memory in this population. **Objective:** To determine the effect of implementation intentions on prospective memory performance in PD. **Methods:** This was a laboratory-based randomized controlled trial. Participants with mild to moderate PD without dementia (N = 62) performed a computerized prospective memory test (Virtual Week) under standard instructions. One week later they were randomly allocated to perform it again while using either implementation intentions or a rehearsal encoding strategy. **Results:** Prospective memory performance was better with the use of both strategies relative to standard instructions. This effect was larger for tasks with event-based compared to time-based cues. In addition, implementation intentions resulted in a larger effect than rehearsal for the non-repeated tasks. **Conclusions:** Strategies that support full encoding of prospective memory cues and actions can improve prospective memory performance among people with PD, particularly for tasks with cues that are readily available in the environment. Implementation intentions may be more effective than rehearsal for non-repeated tasks, but this finding warrants verification. Future work should address transfer of strategy use from the laboratory to everyday life. Targeted strategies to manage prospective memory impairment could improve function and quality of life and significantly impact clinical care for people with PD. (NCT01469741)

3.2 Introduction

Cognitive impairment is a well-established feature of Parkinson disease (PD) without dementia and is associated with activity limitations, reduced quality of life, and restricted participation [7,18,20-22,156]. Prospective memory (PM) has received increasing attention in PD research over the past decade, as it is a highly functionally, clinically and theoretically relevant aspect of cognition [34,35]. PM is the ability to remember to execute delayed intentions at the appropriate moment in the future. In time-based PM tasks, a certain time or the passage of a specified amount of time serves as the cue that signals the appropriate moment for execution. In event-based PM tasks, the occurrence of an event serves as the cue that signals the appropriate moment for execution. Examples of everyday time-based PM tasks include remembering to attend a meeting at 3:00pm or re-fill the parking meter in two hours, and examples of everyday event-based PM tasks include remembering to take medications with breakfast or stop by the store for an item on the way home from work. Laboratory studies consistently demonstrate PD-related impairments in PM for both time- and event-based tasks [52]. In addition, people with PD report more PM failures in everyday life compared to their healthy peers (e.g. forgetting appointments), and PM impairment in PD is associated with worse instrumental activities of daily living function (e.g. financial capacity, medication management) and health-related quality of life [53,54]. These findings highlight the need for interventions for PM impairment in this population.

Successful PM performance depends on the ability to formulate and plan an intention (intention formation), retain its contents in long term memory over a delay while performing other unrelated tasks (intention retention), recognize when the appropriate moment occurs for it to be carried out and retrieve its details from memory (intention retrieval), and, finally, execute it (intention execution) [50]. This multi-phase process requires the integration of episodic memory processes and executive or attentional control processes such as planning, working memory, and cognitive flexibility [50], all of which can be impaired in PD [15,16,57,58].

PM impairment in PD is thought to stem from deficits in the intention formation and intention retrieval [50]. While retention of well-formed intentions and execution of intentions once they are retrieved are fairly intact in PD, encoding, planning and/or retrieval of intentions can be impaired, particularly under conditions of high executive control demand [52,53,59,60,125]. This impairment is attributed to frontostriatal circuitry dysfunction due to dopamine depletion in the prefrontal cortex and basal ganglia [50]. For example, Kliegel et al. [60] found that PD participants formed less elaborate plans for accomplishing a complex intention compared to healthy older adults and, subsequently, were less likely to initiate the intention at the appropriate moment. In another study, PD participants had poorer PM for intentions that required self-initiated encoding at intention formation relative to those for which encoding was externally guided[17]. In terms of intention retrieval, PM tasks with cues that are not integral to performing the ongoing activity (e.g. time-based tasks) and require strategic monitoring of the environment are impaired in PD [53,59,62,125,146]. By contrast, PM tasks with cues that are integrated into the processing of the ongoing activity (e.g. some event-based tasks) and can be processed relatively automatically are not impaired in PD [61,125]. However, although intention retrieval in PD may be supported by features that facilitate automatic processing of PM cues, deficient intention formation can preclude this benefit [125].

These findings indicate that suboptimal intention formation is a key barrier to successful PM performance in PD and suggest that a PM intervention for PD should focus on improving intention formation, one aspect of which is encoding. Indeed, evidence from retrospective and prospective memory studies implies that while people with PD do not self-initiate effective encoding strategies, they can make use of externally guided encoding to improve their performance [109-111,125]. Thus, a cognitive rehabilitation approach that teaches specific PM encoding strategies may improve PM in PD. The formation of *implementation intentions* [112] is a method of encoding and planning intentions that was originally designed to facilitate goal attainment and has since been applied to PM. The strategy involves specifying and stating aloud the circumstances under which one will carry out an intention ("When X, I will do Y"; e.g. "When I eat dinner, I will take my medication") and visualizing oneself encountering those circumstances and executing the intention. By forcing elaborate and specific encoding, implementation intentions are thought to heighten the accessibility of PM cues and strengthen the association between PM cues and their intended actions, thereby facilitating more automatic cue detection and intention retrieval [112,113,118-120]. Of relevance to PD, implementation intentions provide an explicit structure for good associative encoding of intentions that may compensate for the PD-related deficit in internally-generated intention formation strategies. This then should reduce the need for controlled intention retrieval processes (which are impaired in PD) by fostering reliance on more automatic retrieval processes (which are spared in PD) [50,113,125].

There is evidence for the beneficial effect of implementation intentions on PM performance in healthy older adults [114], stroke [115], multiple sclerosis [116], and very mild Alzheimer's disease [117]. To our knowledge, this strategy has not been tested in PD. The purpose of this study was to investigate the effect of implementation intentions on PM performance in PD. We used Virtual Week (a computerized board game that mimics everyday life PM tasks) to assess PM, as it is reliable and sensitive in PD and importantly for present purposes allows for the analysis of different PM task types (repeated, non-repeated) and cues (event, time) [122,123,125]. Repeated tasks are those that occur multiple times throughout the game (e.g. take antibiotics each day at breakfast) whereas non-repeated tasks occur only once (e.g. get a haircut at 1pm on a specific day). We expected that the efficacy of implementation intentions relative to a less elaborate encoding strategy would come to the fore with the non-repeated tasks. The less elaborate encoding strategy was unspecified repetition of PM tasks without visualization (rehearsal).

We hypothesized that an instructed encoding strategy (implementation intentions, rehearsal) would be associated with greater gains in event-based compared to time-based PM performance. We reasoned that strategic encoding of the PM cue and the intended action would be of less value for the time-based tasks, for which detection of the PM cue presumably requires strategic monitoring. That is, we would not expect strategic encoding of intentions to obviate the need for strategic monitoring in time-based tasks; thus, impaired monitoring in PD would still interfere with time-based PM task performance.

In addition, we anticipated that implementation intentions would be particularly beneficial relative to rehearsal for the non-repeated PM tasks. Repeated tasks are re-instructed on each virtual day and thus receive multiple encodings. By contrast, the non-repeated tasks are presented for encoding only once and amidst other PM tasks. Here the encoding challenges are high, and thus the advantage of a mnemonically superior strategy (implementation intentions) should be especially important.

3.3 Methods

This study was approved by the university's human research protection office, and all participants gave written informed consent.

3.3.1 Participants

Participants were community-dwelling volunteers with PD recruited from the university's movement disorders center. Inclusion criteria included at least 50 years of age, diagnosed with idiopathic PD [157], and classified as Hoehn & Yahr stage I-III [143]. Exclusion criteria included suspected dementia (determined by physician or caregiver report or Mini Mental Status Exam score < 27) [144], medications that interfere with cognitive function (e.g. anticholinergics, tricyclic/tetracyclic antidepressants), change in medication over the course of the study, other neurological disorders, history of brain surgery, significant psychiatric conditions, or any other features that would interfere with study participation (e.g. non-English speaking).

3.3.2 Design

This was a randomized controlled trial (NCT01469741) (Figure 3.1). Participants performed a computerized PM test upon enrollment (Virtual Week). One week later, they returned to the laboratory and were randomly assigned to encoding strategy group—Implementation Intentions (II) or Rehearsal (RR)—stratified by sex and age (+/- 62 years). Participants were then taught their respective encoding strategy and used it while performing a parallel version of Virtual Week.

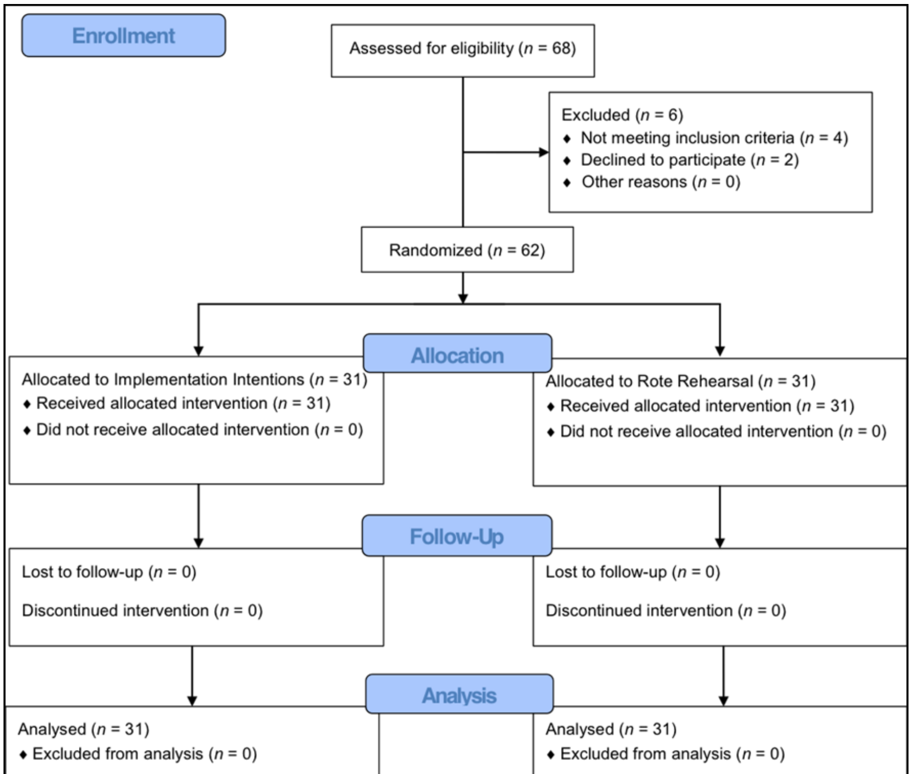

Figure 3.1. CONSORT flow diagram illustrating participant recruitment, randomization, attrition and analysis for Aim 2.

3.3.3 Assessment

Assessment was conducted at the university while participants were on their regular antiparkinsonian medications. Participants' testing sessions were scheduled for the same time of day to control for potential dosage timing effects within subject. During the baseline testing session, participants provided demographic information and completed the Montreal Cognitive Assessment (MoCA) [158] to asses global cognition and the Beck Depression Inventory II (BDI-II) [159] to assess depressive symptoms. Clinical characteristics related to PD (e.g. Unified Parkinson's Disease Rating Scale Motor Scale score from within 3 months of testing [UPDRS] [160], Hoehn & Yahr stage, disease duration, medications) were accessed through clinical records.

Primary outcome measure: Virtual Week

A computerized version of the board game Virtual Week was used to measure PM [122,123,139]. At each testing session, participants first completed a practice day during which detailed automated messages and the experimenter explained the game. Then they completed three test days (Monday, Tuesday, Wednesday). Two equivalent versions of the test days were counterbalanced across testing session to reduce practice and order effects. Participants played the game on a desktop computer, using the mouse to interact with the software. They moved their token around the board on the screen by clicking a die in the middle of the board and clicking the corresponding square of the board. One circuit around the board represented one day (7:00am to 10:00pm), and a clock in the middle of the board displayed the virtual time of day calibrated to the position of the token on the board. As participants progressed through each day, they encountered Event Cards that described time-appropriate activities for which they were required to make decisions (e.g. “You go shopping. Do you buy (a) groceries, (b) a hardware item, (c) clothes”). Rolling the die, circuiting the board, encountering Event Cards and making decisions about activities constitutes the ongoing activity of this PM paradigm.

Each day had eight embedded PM tasks: four repeated and four non-repeated tasks. The *repeated* tasks were health-related tasks that were repeated every day, and the *non-repeated* tasks were different each day. In this version of the game, the repeated tasks did not receive enhanced encoding at the onset of the game (as in Foster et al., 2013 [125]) but instead were administered at the beginning of each day similar to the non-repeated tasks. Half of the repeated and non-repeated tasks each day were cued by Event Cards (*event-based*), and half were cued by the virtual time of day displayed on the clock in the middle of the board (*time-based*). Thus, the event based tasks had cues that were integrated into the ongoing activity of playing the game, whereas the time-based task had cues that required monitoring for information that was not integrated into playing the game. The repeated event-based tasks were “Take antibiotics at breakfast and dinner”, and the repeated time-based tasks were “Take asthma medication at 11am and 9pm”. A non-repeated event-based task was “Drop off dry-cleaning when you go shopping”, and a non-repeated time-based task was “Get a haircut at 1pm.” To perform each PM task, participants clicked on the Perform Task button when they felt it was the appropriate moment and selected the task from a list that consisted of PM tasks and distractors. For example, upon reading the dinner event card each day, participants were to remember to take their antibiotics by clicking the Perform Task button and selecting “take antibiotics” from the list. Similarly, when the clock in the middle of the board read 1pm on a certain day, participants were to remember to get a haircut by clicking the Perform Task button and selecting “get haircut” from the list. There was a total of 24 PM tasks per testing session: 6 repeated event, 6 repeated time, 6 non-repeated event and 6 non-repeated time.

3.3.4 Intervention

For the first testing session, all participants completed Virtual Week under standard instructions. For the second testing session one week later, the practice day incorporated encoding strategy training and practice. Participants in the II group were told that each time they encountered a PM task, they should create a “When X, I will do Y” statement, repeat the statement out loud three times, and close their eyes and visualize themselves performing the task at the appropriate moment within the context of the game. Those in the RR group were told to repeat the administered PM tasks out loud three times but were given no specific instructions on how to do so. During the test days, automated messages (and, if necessary, the experimenter) reminded participants to use their strategy when PM tasks were administered (see Appendix). In addition, for the second session the game was programmed to display the PM tasks on the screen for at least 30 seconds before allowing participants to continue. These features ensured that participants used the strategy they were taught and controlled for time spent on the PM tasks across conditions.

3.3.5 Sample size determination

In a pilot study, 12 PD participants completed Virtual Week under standard instructions during one testing session and then returned to the laboratory 1-3 weeks later to complete it a second time either while using implementation intentions ($n = 6$) or under standard instructions ($n = 6$). There was a large between-group effect in favor of the II group at the second testing session (II $M = 0.75$, control $M = 0.50$, pooled $SD = 0.28$; $d = 0.89$). A sample size of 20 participants per condition was estimated to detect such an effect with $\alpha = 0.05$ and 80% power. Since our pilot study did not employ an active control condition, we increased our target sample size for the current study to 30 participants per group and recruited 68 to account for potential attrition. Of relevance to the current results, there was no difference in Virtual Week performance between testing sessions for the control group (i.e. no apparent practice or learning effect). Further, a test-retest study of Virtual Week with standard instructions in older adults that used the same counter-balanced parallel versions as the current study also showed no practice or learning effect [161].

3.3.6 Analysis

Data were stored and managed using REDCap electronic data capture tools [162] and analyzed with IBM SPSS Statistics 22. Descriptive statistics were calculated for all variables, and independent samples *t*-tests and Chi-squared tests were used for group comparisons of demographic and clinical characteristics. To determine the effect of strategy use on PM performance, proportions of correct PM responses were submitted to a 2 x 2 x 2 x 2 mixed ANOVA with the between-group variable encoding strategy group (II, RR) and within-group variables PM task (repeated, non-repeated), PM cue (event, time) and time of assessment (T0, T1). Interactions were followed up with ANOVA and pairwise comparisons. All statistical tests were two-tailed. An alpha level of $p < 0.05$ was considered significant. Effect sizes were estimated using partial eta squared (η_p^2) and Cohen's *d*.

3.4 Results

3.4.1 Participant characteristics

Sixty-two participants ($n = 31$ per group) had usable data for this study (Figure 3.1). The II and RR groups were equivalent on all demographic and clinical characteristics (Table 3.1). Antiparkinsonian medication regimens included levodopa-carbidopa only (16 II, 18 RR), levodopa-carbidopa with a dopamine agonist, COMT inhibitor, or both (11 II, 11 RR), dopamine agonist only (1 II, 0 RR), MAO inhibitor only (1 II, 0 RR), and no antiparkinsonian medications (2 II, 2 RR) and did not differ between groups, $\chi^2 = 2.84$, $p = 0.83$.

Table 3.1. Demographic and clinical characteristics of the Aim 2 sample ($N = 62$).

Variable	Implementation Intentions Group	Rote Rehearsal Group	Group Comparison Statistic	*p* value
n	31	31		
Age (years)	62.5 (5.7)	62.7 (5.4)	$t_{60} = -0.14$	0.89
Male/Female ratio (*n*)	15/16	15/16	$\chi^2 < 0.001$	1.00
Education (years)	16.1 (2.7)	16.0 (2.3)	$t_{60} = 0.10$	0.92
Duration of diagnosis (years)	4.3 (3.4)	5.1 (3.3)	$t_{60} = -0.95$	0.35
UPDRS III	15.7 (9.6)	15.9 (7.3)	$t_{60} = -0.10$	0.92
LEDD (mg)	804 (606)	1022 (648)	$t_{60} = -1.35$	0.18
MoCA	26.8 (1.9)	26.3 (2.2)	$t_{60} = 0.93$	0.35
BDI-II	11.0 (7.6)	9.7 (5.4)	$t_{60} = 0.78$	0.44

Values represent mean (standard deviation) or number of participants.

3.4.2 Effect of encoding strategy on PM performance

Proportions of correct PM responses are presented in Table 3.2 and the initial ANOVA results are in Table 3.3. Overall, performance was better for repeated tasks, event cues, and at T1 (with strategy use) compared to non-repeated tasks, time cues and at T0 (baseline, without strategy use), respectively, Fs ≥ 23.54, ps < 0.001, $\eta_p^2 \geq 0.28$. There was an interaction between PM cue and time of assessment, $F(1, 60) = 3.96$, $p = 0.05$, $\eta_p^2 = 0.06$, such that event-based tasks showed a larger improvement at T1 than time-based tasks. There was a three-way interaction between PM task, group and time of assessment, $F(1, 60) = 7.55$, $p = 0.008$, $\eta_p^2 = 0.11$. Group did not interact with any other variable.

Table 3.2. Group mean (standard deviation) proportion of correct prospective memory responses for each task type without and with strategy use. Comparisons (paired samples *t* tests) and associated effect sizes (Cohen's *d*) are for the within-group difference in prospective memory performance between T0 and T1.

	Without encoding strategy (T0)	With encoding strategy (T1)	t_{30}	*d*
Repeated Event				
Implementation Intentions	0.58 (0.30)	0.80 (0.23)	-3.30*	0.62
Rote Rehearsal	0.56 (0.35)	0.78 (0.28)	-4.37*	0.82
Repeated Time				
Implementation Intentions	0.61 (0.29)	0.71 (0.26)	-2.81*	0.54
Rote Rehearsal	0.54 (0.27)	0.69 (0.27)	-3.18*	0.44
Non-repeated Event				
Implementation Intentions	0.53 (0.32)	0.83 (0.19)	-5.58*	1.07
Rote Rehearsal	0.58 (0.33)	0.77 (0.28)	-3.85*	0.70
Non-repeated Time				
Implementation Intentions	0.33 (0.27)	0.53 (0.30)	-3.78*	0.69
Rote Rehearsal	0.35 (0.26)	0.45 (0.30)	-1.78	0.33

*$p < 0.05$

Table 3.3. Results from the 2 x 2 x 2 x 2 mixed ANOVA. The between-subjects variable was group (II, RR) and within-subjects variables were PM task (repeated, non-repeated), PM cue (event, time) and time of assessment (T0, T1).

Effect	*df*	*MSE*	*F*	*p*
Group	1	0.33	0.45	0.51
PM task	1	0.06	23.54	<0.001*
PM cue	1	0.05	59.54	<0.001*
Time	1	0.08	61.39	<0.001*
Group x PM task	1	0.06	0.65	0.43
Group x PM cue	1	0.05	1.56	0.22
Group x Time	1	0.08	0.18	0.68
PM task x PM cue	1	0.04	0.23	0.63
PM task x Time	1	0.03	0.09	0.77
PM cue x Time	1	0.05	3.96	0.05*
Group x PM task x PM cue	1	0.04	0.23	0.63
Group x PM task x Time	1	0.03	7.55	0.008*
Group x PM cue x Time	1	0.05	0.81	0.32
PM task x PM cue x Time	1	0.03	0.56	0.44
Group x PM task x PM cue x Time	1	0.03	1.11	0.30

$^{*}p \leq 0.05$

To follow up the three-way interaction, separate 2 (group) x 2 (time of assessment) ANOVA were conducted for non-repeated and repeated tasks. On non-repeated tasks, there was an effect of time of assessment, $F(1, 60) = 47.29$, $p < 0.001$, $\eta_p^2 = 0.44$, such that performance was better at T1. There was also a marginally significant interaction between group and time of assessment, $F(1, 60) = 3.29$, $p = 0.08$, $\eta_p^2 = 0.05$, such that the II group had a larger improvement at T1 than the RR group (II $d = 1.02$, RR $d = 0.59$; Figure 3.2). On repeated tasks, there was an effect of time of assessment, $F(1, 60) = 40.62$, $p < 0.001$, $\eta_p^2 = 0.40$, such that performance was better at T1, but there was not an interaction of group and time of assessment, $F(1, 60) = 1.21$, $p = 0.28$, $\eta_p^2 = 0.02$.

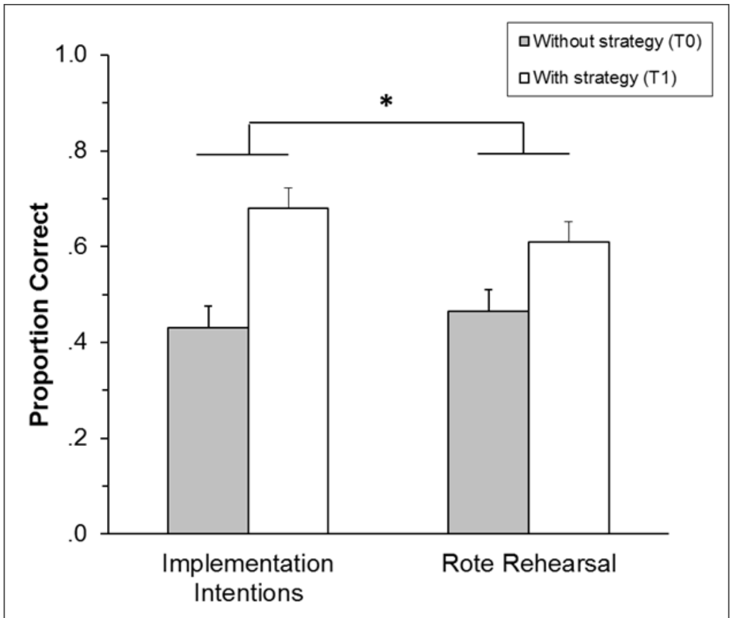

Figure 3.2. Mean proportion of correct prospective memory responses on non-repeated tasks as a function of encoding strategy group and time of assessment. Error bars depict standard error of the mean. (* group X time of assessment, $p = 0.08$)

3.5 Discussion

This study tested the effect of encoding strategies on PM performance in non-demented individuals with PD. Specifically, we aimed to determine the types of PM tasks for which various encoding strategies would benefit PD individuals. We also were interested in whether a mnemonically-enhanced encoding strategy (implementation intentions) would produce greater improvements in PM performance for PD individuals than a typically less effective encoding strategy (rehearsal). We used the Virtual Week PM test, which includes repeated and non-repeated PM tasks cued by events or time. PD participants were randomly assigned to perform Virtual Week under standard instructions (T0) and also while using either the implementations intentions or rehearsal encoding strategy (T1). Both strategies improved PM performance relative to standard instructions, particularly for tasks cued by events. In addition, implementation intentions resulted in a larger effect than rehearsal, but only for non-repeated tasks.

Our data are consistent with the view that poor executive control of intention formation, namely poor self-initiated strategic encoding, is a key cognitive mechanism underlying PM impairment in PD [50]. Previous studies have suggested this by showing that people with PD naturally form less elaborate intentions and are then less likely to initiate those intentions than their healthy peers [60] but have better PM performance when external testing conditions facilitate better encoding of intentions [109,125]. This study expands on previous work to demonstrate that when people with PD use explicit encoding strategies, their PM performance improves substantially, especially for event-based PM tasks. It provides support for cognitive rehabilitation approaches that train people with PD to use PM encoding strategies.

As predicted, the encoding strategies were more effective for event-based compared to time-based tasks. The event-based tasks were cued by specific Event Cards that appeared throughout the day and that the person interacted with to play the game. In contrast, the time-based tasks required the person to periodically disengage from the game to check the clock in the middle of the board. Thus, whereas event cues were processed as a part of the ongoing activity, time cues required the deployment of strategic attentional resources (i.e, monitoring the virtual time of day, which involves internally driven shifting of attention from the ongoing activity) to be processed. Our results support the notion that specification and repetition of PM intentions during encoding heightens perceptual readiness for and facilitates detection of cues encountered in the environment [112,113], in this case, the event cues. However, heightened cue accessibility would not facilitate detection of time cues in the absence of strategic monitoring (or shifting) because those cues would not be encountered. Some evidence suggests that implementation intentions increase monitoring for non-focal PM cues [163] (cues that are not processed as a part of the ongoing activity), which may explain the improvement in time-based tasks; however, consistent with other studies, our findings indicate that this mechanism is less robust than the automatic processing facilitated by implementation intentions for tasks with focal event cues [114] (cues that are processed as a part of the ongoing activity). Direct assessment of monitoring by recording time checks would have helped to confirm this explanation and should be considered for future studies. Regarding PM intervention, these results suggest that in addition to the provision of intention formation strategies, people with PD may need support to enhance their monitoring for time cues. Alternatively, a more effective approach could be to teach them to associate intentions with externally available cues that do not require monitoring (essentially turning time-based tasks into focal event-based tasks; e.g. feed the dog when you turn on the evening news rather than at 5:00pm) and then use encoding strategies that support automatic cue detection and intention retrieval.

More novel was that implementation intentions tended to produce greater gains than rehearsal for PM tasks with challenging encoding conditions: the non-repeated tasks which were instructed only once and amidst other PM tasks. In fact, implementation intentions produced non-repeated task performance in PD participants in the current study that was better than that of a healthy older adult group from a previous Virtual Week study [125]. Thus, implementation intentions presumably compensated for PD-related difficulties with intention formation and substantially improved PM performance for these difficult tasks that arguably are often present in the lives of older adults—one-off PM tasks that are encoded along with other tasks the adult has to perform during the day.

This pattern is consistent with, though possibly not as robust as, past findings with non-PD patients that implementation intentions are superior to rehearsal for non-repeated tasks [116], purportedly because they force specification of the PM cue and intended action rather than allowing one to simply state the intention ("I will Y"), which could occur with rehearsal. Still, this finding is suggestive rather than definitive since it was only of marginal statistical significance.

The absence of an advantage of implementation intentions (relative to rehearsal) for repeated tasks suggests that repeated encoding reduces encoding challenges for the PM task so that any explicit strategy, even rehearsal, is sufficient for PD. Alternatively, this could have stemmed from overlap in the application of the two strategies in the context of this particular experimental paradigm. In Virtual Week, PM task administration specifies the PM cue and intended action. Although rehearsal participants were not explicitly trained to form "When [cue], I will [action]" statements, their rehearsals would have involved co-verbalization of the cue and action if they were repeating the information provided to them. In this way, rehearsal may have facilitated cue accessibility and strengthened associative encoding to a similar degree as implementation intentions.

The neural mechanism of PD-related PM impairment has not been studied directly but is often attributed to disruption of prefrontal cortical regions responsible for the executive control of intention retrieval [50,53,59]. In contrast, the hippocampal networks thought to underlie more automatic intention retrieval are relatively spared in PD [71,134]. This aligns with the proposed mechanism of implementation intentions, which is that they promote a shift from controlled to automatic processing. Specifically, they allow intention retrieval to occur in a reflexive, stimulus-driven fashion rather than require self-initiated retrieval processes [112,113]. This notion is supported by an fMRI study showing that implementation intentions shifted brain activity from a region associated with top-down control of PM processing (lateral BA 10) to one associated with bottom-up PM responding (medial BA 10) [121]. However, BA 10 (the region most consistently implicated in PM studies [75]) is not one of the regions directly disrupted by frontostriatal circuitry dysfunction in PD. Thus, the underlying neural mechanisms of PM impairment and recovery in PD are unclear and warrant further investigation.

We designed this study to examine the potential benefits of encoding strategies (implementation intentions and rehearsal) on PM in PD, but there are some issues that limit our conclusions. We cannot rule out the potential effect of practice; however, it is unlikely to have caused the observed pattern of improvement in PM performance. First, there is no reason that practice alone would be more beneficial for event-based compared to time-based tasks. Instead, we contend that the larger improvement on event-based tasks was due to enhanced encoding of the PM cue and associated intention, thereby allowing environmental (event) cues and their associated actions to be more automatically detected and retrieved. Second, if practice was a major driver of improvement, then performance on repeated tasks, which were repeated within and across testing sessions, should have increased proportionately more than performance on non-repeated tasks, but this was not the case. In addition, the limited differentiation between implementation intentions and rehearsal could have been due to insufficient power. Our pilot study found a larger between-group effect of implementation intentions compared to standard instructions and, similar to a test-retest study of Virtual Week, no practice effect with standard instructions [161]. We increased our sample size to account for the use of an active control condition, but our estimate may have been inadequate. A larger study with a no-strategy control condition would help address these limitations and substantiate our conclusions regarding the relative effects of implementation intentions and rehearsal.

This study is the first to evaluate a cognitive strategy training intervention for PM in PD. PM is essential for productive and independent living and necessary for compliance with prescribed health behaviors (e.g. taking medications, keeping therapy appointments, performing home exercises). Targeted strategies that enable people with PD to successfully perform PM tasks could improve function and quality of life and significantly impact clinical care for this population. We have demonstrated that when people with PD use simple encoding strategies at intention formation, they can improve their performance on a variety of PM tasks in a laboratory setting and that such strategies may be most helpful for tasks with cues that are readily available for processing in the environment (event-based tasks). The specific strategy of implementation intentions may be particularly effective for non-repeated PM tasks, but further work is required to verify this finding. This provides a valuable starting point for research on PM strategy training in PD and cognitive rehabilitation approaches for PM impairment in PD. Additional work is required to directly inform clinical application. A next step is to understand whether – or how training should be structured so that – people with PD can independently initiate the use of intention formation strategies to support their PM performance. Future studies should also address the degree to which strategy use and effectiveness transfer to people's real-world PM tasks.

Chapter 4: Aim 3: Strategy training and everyday prospective memory in Parkinson disease

Goedeken, S., Potempa, C., Prager, E.M., & Foster E.R. (2017). Encoding strategy training and self-reported everyday prospective memory in people with Parkinson disease: A randomized controlled trial. *The Clinical Neuropsychologist*, DOI: 10.1080/13854046.2017.1387287

4.1 Abstract

Objective: To compare the effects of laboratory-based training in implementation intentions (II; experimental strategy) and verbal rehearsal (VR; control strategy) on self-reported everyday prospective memory among people with Parkinson disease (PD) and to investigate potential correlates of change in self-reported everyday prospective memory in response to this training. **Method:** This was a randomized-controlled trial. Participants with mild to moderate PD without dementia underwent one session of training in either II (n = 25) or VR (n = 27). Then they were instructed to use their strategy as much as possible in their everyday lives to help them remember to do things. The Prospective and Retrospective Memory Questionnaire Prospective Scale (PRMQ-Pro) administered at baseline and one month after training assessed training-related change in self-reported everyday prospective memory. Baseline depressive symptoms, perceptions of the strategy (credibility, expectancy), prospective memory-related awareness, global cognition, and disease severity were correlated to PRMQ-Pro Change scores (post minus pre) to determine their association with response to training. **Results:** The VR group's PRMQ-Pro scores declined from pre to post training, while the II group's remained stable (p = 0.03). This effect was driven by change in self-cued everyday prospective memory tasks. Higher baseline depressive symptoms, treatment expectancy, and global cognition related to better response to training in the II group (rs $\leq$ -0.40, ps $\leq$ 0.05). **Conclusions:** II training may prevent everyday prospective memory decline among people with PD. In addition, people with higher depression, stronger expectations of improvement from strategy training, or better global cognition may benefit the most from II training.

4.2 Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder, affecting approximately 1-2% of the population over the age of 65 [1]. It is classified as a movement disorder, and clinical diagnosis is based on the presence of bradykinesia, rigidity, and/or resting tremor [2]. However, about one third of people in the earliest stages of PD have mild cognitive deficits, typically in memory, executive and attentional control functions [12,13]. These deficits are attributed to frontostriatal circuitry dysfunction due to dopamine depletion in the basal ganglia and prefrontal cortex [15,16]. Importantly, they relate to disability, reduced quality of life, and restricted participation early in the course of PD, potentially to a larger extent than motor impairment [18-22]. Pharmacologic and surgical treatments for PD do not prevent or treat cognitive impairment and may even exacerbate the problem [15,26-28]. As such, interventions that mitigate the negative functional consequences of cognitive impairment in people with PD are a top research priority [28-33].

Due to its high functional and clinical relevance, PD-related prospective memory impairment is a prime target for cognitive intervention [34,35]. Good prospective memory, or the ability to remember to execute delayed intentions at the appropriate moment in the future [36], is essential for independent living (e.g. paying bills on time, turning the stove off after using it) and adherence to important PD-related health behaviors (e.g. taking medications, doing home exercises). People with PD consistently demonstrate prospective memory deficits in laboratory studies [52] and report more everyday prospective memory failures compared to healthy older adults [53,54]. Further, prospective memory problems in people with PD relate to activity limitations and reduced health-related quality of life [54-56]. Interventions that improve prospective memory in people with PD could positively impact daily function and clinical care for this population.

In their conceptual model, Kliegel, Altgassen, Hering, Rose [50] describe the process of prospective memory as encompassing in four phases: (1) *intention formation* – the intention to execute an action at a particular moment in the future is formed and encoded; (2) *intention retention* – the intention is retained in memory over a delay period that involves unrelated tasks (i.e. ongoing activity); (3) *intention retrieval* – the appropriate moment (i.e. cue) occurs and the intended action is retrieved from memory; (4) *intention execution* – the intention is successfully carried out. Each of these phases requires distinct underlying cognitive resources, the extent to which depends on characteristics of the particular prospective memory task. Following this model, prospective memory impairment is conceptualized as a mismatch between the cognitive resources required by the particular task and the individual's available cognitive resources.

In relation to PD, prospective memory impairment is thought to stem from deficits in executive control processes that can underlie intention formation and intention retrieval [50,125]. For example, tasks with complex intentions may require strategic encoding or planning during intention formation. Studies show that people with PD fail to self-initiate these processes, which then relates to subsequent failures in intention retrieval and execution [60,109,125]. Regarding intention retrieval, tasks with cues that are perceptually salient or are processed as a part of the ongoing activity (i.e. focal cues) can be retrieved relatively automatically and thus do not require much executive control, whereas those with cues that are not processed as a part of the ongoing activity (i.e. non-focal and time-based cues) require strategic attentional control – namely, monitoring and shifting – to be retrieved [51]. People with PD are impaired on prospective memory tasks with non-focal and time-based cues relative to those with salient or focal cues [53,61,125,135].

Thus, PD-related prospective memory impairment is most apparent when intention formation or intention retrieval require the self-initiation of executive control processes such as planning, strategic encoding, and attentional control.

In light of the view that prospective memory impairment in PD stems primarily from executive dysfunction, two general approaches to improving prospective memory in PD can be pursued. The first is direct training to augment or restore the deficient executive control processes that underlie prospective memory impairment (i.e. process training), and the second is training in strategies to compensate for or circumvent deficits in the executive control processes that underlie prospective memory impairment (i.e. strategy training) [77,78]. In terms of the first approach, direct training of shifting ability (an executive control process) significantly improved PD participants' performance on a laboratory prospective memory task [76]. This finding is consistent with the bulk of the cognitive rehabilitation research in PD, which has shown that process training produces improved performance on neuropsychological tests that assess the cognitive processes that are trained (e.g. working memory, processing speed) [30]. However, the process training approach has had limited effect on daily function in PD (e.g. [30,79,81,84]). In contrast, the few cognitive rehabilitation studies that have incorporated strategy training show promise for improving daily function in PD [106-108]. This pattern of results dovetails with a study of prospective memory in healthy older adults, which found that strategy training was better than process training (shifting ability) for improving everyday prospective memory performance [78]. Given the above evidence and the need for interventions that mitigate the impact of PD-related prospective memory impairment on daily function, we pursued a prospective memory strategy training intervention for people with PD.

A strategy that circumvents the executive control demands of tasks and improves prospective memory performance across a variety of populations is the *implementation intentions* (II) strategy [113,114]. This associative encoding and planning strategy involves specifying the intended action (Y) and the appropriate moment or cue for action (X) and creating a "When X, I will do Y" statement (e.g. "When I eat breakfast, I will take my medication") during intention formation [112]. Full use of II requires the person to repeat the statement aloud several times and visualize him or herself encountering the future moment or cue and executing the intended action. The elaborate, specific, and dual verbal/visual encoding that occurs with forming II is hypothesized to increase the accessibility of the cue and strengthen the association between the cue and intended action and thus facilitate automatic cue detection and intended action retrieval when the cue is encountered [112,113,118-120] [4]. Therefore, II target both aspects of prospective memory tasks that can be challenging for people with PD due to executive dysfunction: intention formation and intention retrieval [50,125]. II facilitate strategic encoding of intentions during the intention formation phase, which should then reduce the attentional monitoring demands of intention retrieval. In line with this proposed mechanism of action, II have been found to improve prospective memory in populations with subtle frontal-executive decline similar to that experienced by non-demented people with PD, such as healthy older adults, multiple sclerosis, and very mild Alzheimer's disease [114,116,117], whereas they appear to be less effective in the context of concomitant retrospective memory impairment that may interfere with intention retention, such as that which occurs with traumatic brain injury [164].

[4] It is worth noting that evidence for the added value of visualization (versus simply creating the "When X, I will do Y" statement) is inconsistent in the existing literature on II (Chen et al., 2015; McDaniel et al., 2008; McFarland & Glisky, 2012).

Following this reasoning, we conducted a randomized controlled trial comparing the effects of II and verbal rehearsal (VR) on prospective memory in PD [85]. In line with previous studies (e.g. [78,116,165,166]), we selected VR as an active control condition to ensure equal exposure to the prospective memory tasks (in terms of time spent attending to the tasks and verbalization) without explicit facilitation of strategic or elaborate associative encoding [167]. We used a single session of training, which has been shown to improve both laboratory and real-world prospective memory in healthy older adults (e.g. [78,89,166,167]) and neuroclinical populations [115-117]. We found that training in both encoding strategies improved non-demented PD participants' performance on the Virtual Week [122], a life-like laboratory prospective memory test. Whereas both strategies produced greater gains in focal compared to non-focal tasks, II tended to be more effective than VR for nonrepeated and non-focal tasks. These results show that people with PD can use intention formation strategies to improve their performance on a variety of prospective memory tasks and that II may be particularly effective for tasks with challenging encoding and retrieval conditions (nonrepeated and non-focal tasks, respectively). However, just because people with PD can successfully apply strategies in the controlled environment in which they were learned, we cannot assume they will spontaneously transfer the use of those strategies to everyday prospective memory challenges [88]. Therefore, the purpose of this study was to determine whether the encoding strategy training provided during the above-described study may enhance everyday prospective memory in people with PD. After receiving laboratory-based training and practice in either II or VR, participants were instructed to use their respective strategy as much as possible in their daily lives for the next month. We hypothesized that the II group would report greater improvements in everyday prospective memory after one month than the VR group.

Although we predicted significant group-related effects of strategy training on self-reported everyday prospective memory, we also anticipated that there would be considerable variation within groups in terms of this effect. As discussed by Kliegel and colleagues [50], individual characteristics such as motivation and metacognitive awareness may influence the tendency to use prospective memory strategies in daily life. For example, limited awareness of prospective memory abilities could reduce recognition of situations in which to use strategies and result in limited or inconsistent use [92]. Similarly, one's perceptions of the validity of a strategy or its likelihood of producing benefits may determine whether he or she chooses to adopt the strategy at all [168]. In addition, PD in particular is associated with features such as depression, global cognitive decline, and motor and non-motor dysfunction that may impact a person's motivation or ability to learn and apply strategies in daily life. Therefore, our second objective was to investigate potential correlates of change in self-reported everyday prospective memory in response to training. We hypothesized that individual differences in certain cognitive, motivational and disease-related characteristics would be associated with the direction and magnitude of change in everyday prospective memory from before to after training. Finally, to gain additional insight into real-world strategy use after training, we conducted an exploratory interview with participants about their strategy use during the one-month follow-up period.

4.3 Methods

This study was approved by the Human Research Protection Office at Washington University in St. Louis (WU). All participants gave written informed consent before testing.

4.3.1 Participants

Participants were community-dwelling volunteers with PD recruited from the WU Movement Disorders Center. Inclusion criteria were as follows: at least 50 years of age, diagnosed with idiopathic PD based on UK Brain Bank Criteria [157], and classified as Hoehn & Yahr disease stage I-III (mild to moderate disease) [143]. Exclusion criteria were as follows: suspected dementia or global cognitive impairment determined by Movement Disorders Society diagnostic criteria [6] or Mini Mental Status Examination score < 27 [144], currently taking medications that interfere with cognitive function (e.g. anticholinergics), change in medication over the course of the study, other neurological disorders (e.g. stroke), history of brain surgery (e.g. deep brain stimulation), history of or current psychotic disorder, current psychiatric conditions that could interfere with study participation (e.g. severe depressive symptoms, major depressive episode), or any other features that would interfere with study participation (e.g. non-English speaking).

The final sample consisted of 52 participants (25 II, 27 VR) (Figure 4.1). There were no significant differences between included participants and those lost to follow-up in any demographic, clinical, primary or secondary variables; however, MoCA scores were slightly lower (although not significantly) in the group lost to follow-up, $t(60) = 1.81$, $p = 0.10$. Demographic and clinical characteristics of the analyzed sample are presented in Table 4.1. There were no group differences in any of these characteristics. Using a MoCA cutoff score of 25/26 [169], 3 II and 4 VR participants met criteria for possible mild cognitive impairment in PD (PD-MCI) [170], $\chi^2 = 0.09$, $p = 0.77$. According to BDI-II criteria, 19 II and 19 VR had no or minimal depressive symptoms, 3 II and 6 VR participants had mild depressive symptoms, and 3 II and 2 VR had moderate depressive symptoms, $\chi^2 = 1.13$, $p = 0.57$. Antiparkinsonian medication regimens included levodopa-carbidopa only (14 II, 15 VR), levodopa-carbidopa with a dopamine agonist, COMT inhibitor, or both (8 II, 10 VR), dopamine agonist only (1 II, 0 VR), MAO inhibitor only (1 II, 0 VR), and no antiparkinsonian medications (1 II, 2 VR) and did not differ between groups, $\chi^2 = 4.71$, p = 0.58.

Table 4.1. Demographic and clinical characteristics of the Aim 3 sample ($N = 52$).

Variable	Implementation Intentions ($n = 25$)	Verbal Rehearsal ($n = 27$)	Statistics	Effect size*
Male/female ratio	12/13	13/14	χ^2<0.01, p=0.99	-0.001
Age (years)	63.8 (4.6)	62.7 (5.5)	t=0.78, p=0.44	0.22
Education (years)	16.4 (2.6)	16.0 (2.3)	t=0.64, p=0.52	0.16
Race			χ^2=2.28, p=0.32	0.21
White	23	24		
Other	2	3		
Age at diagnosis (years)	60.2 (5.4)	58.7 (6.1)	t=0.91, p=0.37	0.26
Duration of diagnosis (years)	4.2 (3.6)	5.0 (3.0)	t=0.83, p=0.41	-0.24
Primary motor sign			χ^2=1.65, p=0.44	0.18
Tremor	16	15		
Bradykinesia/rigidity	6	5		
Mixed	3	7		
Hoehn & Yahr Stage			χ^2=2.49, p=0.47	0.22
1	2	3		
2	18	21		
2.5	4	1		
3	1	2		
UPDRS (on medications)	17.2 (10.0)	15.3 (6.9)	t=0.79, p=0.43	0.22
BDI-II	11.0 (8.3)	10.4 (5.3)	t=0.32, p=0.75	0.09
MoCA	26.9 (1.8)	26.4 (2.0)	t=0.95, p=0.35	0.26

Note. Numbers represent means (standard deviation) or number of participants. * Phi (r) for $\chi 2$ tests or Cohen's d for t-tests.

4.3.2 Design

This was a single-blind randomized controlled trial (NCT01469741) with an in-person baseline testing session, an in-person training session, and mailed or in-person post-training data collection (Figure 4.1). All data were collected while participants were on their regular antiparkinsonian medications.

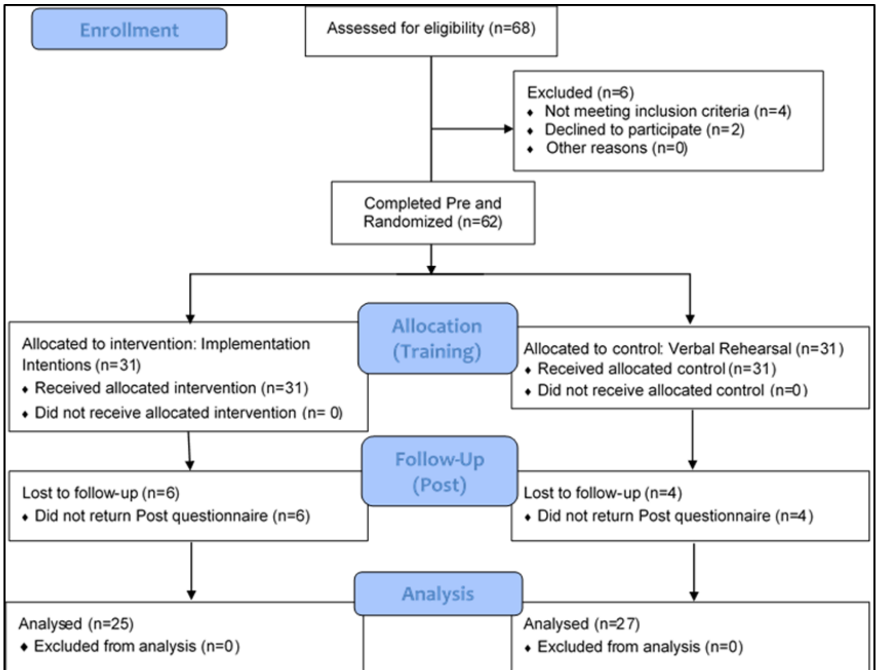

Figure 4.1. CONSORT flow diagram illustrating participant recruitment, randomization, attrition and analysis of final sample for Aim 3.

Baseline Testing Session (Pre)

Demographic information was collected through interview. Clinical characteristics related to PD were collected from clinical records (e.g. Hoehn & Yahr stage, disease duration, medications). The primary outcome measure, the Prospective and Retrospective Memory Questionnaire Prospective Scale (PRMQ-Pro) [124], was administered at this time (described below). In addition, we measured a number of characteristics that we hypothesized might influence a participant’s response to prospective memory strategy training (i.e. the direction and magnitude of change in reported everyday prospective memory). General constructs relevant to PD included motor dysfunction severity (Unified Parkinson’s Disease Rating Scale Motor Examination, UPDRS) [147], global cognitive function (Montreal Cognitive Assessment, MoCA) [158], and depressive symptoms (Beck Depression Inventory, Second Edition, BDI-II) [159]. Constructs more specifically related to prospective memory or the strategy training itself included prospective memory-related awareness and perceived credibility and expectancy of the strategy, respectively (described below).

Training Session

One week after the baseline testing session, participants returned to the laboratory for the training session. They were randomly assigned to the experimental (implementation intentions [II]) or control (verbal rehearsal [VR]) encoding strategy group and completed laboratory-based strategy training. Training occurred in the context of the computerized Virtual Week prospective memory test by instructions from the examiner and automated messages from the Virtual Week (for overview see also [122]; for full description and screen shots of the specific version used in this study, see Chapter 3 and the Appendix). The Virtual Week takes the form of a board game, with one circuit of the board representing one day. Participants use the mouse to interact with the game (e.g. roll the die, move their token around the board, perform prospective memory tasks). As they progress through each day, they encounter time-appropriate activities displayed in boxes on the screen for which they make decisions (i.e. the ongoing activity of this prospective memory paradigm). They also encounter prospective memory tasks (8 tasks per day) that they have to remember to "perform" sometime later that day by clicking a box on the screen and selecting the task from a list. In this study, participants played 3 days of the Virtual Week, which involved 24 total prospective memory tasks. II group participants were taught to form a "When X, I will do Y" statement when they encounter prospective memory tasks during the Virtual Week, recite the statement aloud three times, and imaging themselves performing the prospective memory task during the Virtual Week in accordance with the statement for 30 seconds. For example, when they encountered the prospective memory task, "Drop in dry cleaning when you go shopping," they were to form the statement "When I go shopping, I will drop in my dry cleaning," say it out loud three times, and imagine themselves reaching the shopping activity and performing the dry cleaning task. In contrast, VR group participants were simply told to recite the prospective memory tasks they encounter aloud at least three times and study them for 30 seconds. After this instruction, participants used their respective strategy during a practice day and three test days of the computerized Virtual Week, with the test days alone providing over 30 minutes (M = 33.9, SD = 11.5) of strategy practice. Automated messages (and the examiner, if necessary) prompted participants to use their strategy when prospective memory tasks were administered, thus ensuring that participants were at least completing the verbal recitation portion of the strategies. Additionally, in both conditions the prospective memory tasks remained on the screen for 30 seconds to prevent participants from moving ahead too quickly. Upon completion of the Virtual Week, participants in both groups were instructed to use their respective strategy as much as possible in their everyday lives to help them remember to do things. They were given a handout with strategy instructions as reference, and the examiner answered questions and provided clarification if necessary.

Post-training Data Collection (Post)

One month after the training session, Post data were collected. Participants either came to the laboratory to complete the PRMQ-Pro and a follow-up interview (described below) or they completed the PRMQ-Pro by mail and the follow-up interview by phone.

4.3.3 Measures

Primary Outcome: Reported Everyday Prospective Memory

We administered the self-report Prospective and Retrospective Memory Questionnaire Prospective scale (PRMQ-Pro) [124] at Pre and Post to measure reported everyday prospective memory. It consists of eight items describing everyday prospective memory failures that participants rate according to the frequency with which they occur. The scale can be divided into self-cued (Pro-Self; 4 items) and environment-cued (Pro-Env; 4 items) subscales. For example, the item “If you tried to contact a friend or relative who was out, would you forget to try again later?” measures self-cued prospective memory. The item “Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?” measures environment-cued prospective memory. Each item is rated on a five-point scale (1 = Never; 5 = Very Often), with higher scores indicating more frequent failures or worse everyday prospective memory. This study used the PRMQ-Pro (range 8-40), Pro-Self (range 4-20), and Pro-Env (range 4-20) scores as outcome variables.

Secondary Variables: Characteristics Associated with Everyday Prospective Memory Change

We used the Credibility and Expectancy Questionnaire (CEQ) [168] to measure how convincing and logical participants found the strategy (Credibility; 3 items) and how strongly participants felt their everyday prospective memory would improve as a result of strategy use (Expectancy; 3 items). Items had 0-10 response scales. Item scores were averaged within each construct to yield separate Credibility and Expectancy scores, with higher scores indicating higher credibility or expectancy.

To measure prospective memory-related awareness, we asked participants to predict and “postdict” their prospective memory performance on the computerized Virtual Week [85,122]. After completing the Virtual Week practice day but before the test days, participants predicted how many of the 24 prospective memory tasks they would execute accurately during the test. Then after completing the test days, participants postdicted how many of the 24 prospective memory tasks they executed accurately. The difference between their prediction and actual performance is an indicator of their “metacognitive knowledge” (i.e. existing knowledge or beliefs of their prospective memory abilities), while the difference between their postdiction and actual performance is an indicator of their “on-line awareness” (i.e. ability to monitor and appraise their prospective memory performance in real time) [92,171]. We used the absolute difference for both components, so larger values corresponded to poorer prospective memory-related awareness.

Exploratory Follow-up Interview about Everyday Prospective Memory Strategy Use

At Post, we asked the participants several questions about their strategy use in everyday life during the month following training. First, we asked if they remembered the strategy they learned and, if so, asked them to state or describe it. Answers were written down verbatim and later coded into the following categories: No memory/accuracy, Partially correct, Correct. The remaining questions and their response options were as follows: Did you use the strategy? (No, Yes); How often/much did you use the strategy? (Never, 1x/week or 1-5 times total, 2-5x/week or 6-20 times total, 1x/day, More than 1x/day); Do you think the strategy worked? (No, Not sure, Yes).

4.3.4 Statistical Analysis

Study data were stored and managed using REDCap electronic data capture tools hosted at WU [162] and analyzed with IBM SPSS Statistics 22. Descriptive statistics were calculated for all variables. Independent samples t-tests and Chi-squared tests were used for group comparisons of demographic and clinical characteristics, secondary variables, and follow-up interview data. Mixed general linear models (GLM) with planned pairwise comparisons were used to determine strategy training effects on reported everyday prospective memory (separate models for PRMQ-Pro, Pro-Self, and Pro-Env) with group (II, VR) as the between-subjects factor and time (Pre, Post) as the within-subjects factor. PRMQ-Pro Change scores (Post minus Pre) were calculated and then correlated (partial correlations controlling for Pre PRMQ-Pro) with potential influential variables (e.g. depression, global cognitive function, credibility) to investigate possible effect modifiers of prospective memory strategy training. All statistical tests were two tailed, and an alpha level of $p < 0.05$ was considered significant.

4.4 Results

4.4.1 Effect of Implementation Intentions and Verbal Rehearsal Training on Self-reported Everyday Prospective Memory

For PRMQ-Pro, there was a time X group interaction, $F(1, 50) = 4.98$, $p = 0.03$. The VR group reported worse everyday prospective memory from Pre to Post, $F(1, 50) = 8.15$, $p = 0.006$, while the II group had no change, $F(1, 50) = 0.01$, $p = 0.92$ (Figure 4.2A). There were no main effects of time or group for PRMQ-Pro (Fs ≤ 2.99, ps ≥ 0.09). For Pro-Self, there was a main effect of time, $F(1, 50) = 7.35$, $p = 0.009$, that was qualified by a time X group interaction, $F(1, 50) = 4.45$, $p = 0.04$. The VR group reported worse self-cued everyday prospective memory from Pre to Post, $F(1, 50) = 12.08$, $p = 0.001$, while the II had no change, $F(1, 50) = 0.17$, $p = 0.68$ (Figure 4.2B). There were no effects for the Pro-Env scale (Fs ≤ 0.15, ps ≥ 0.70) (Figure 4.2B).

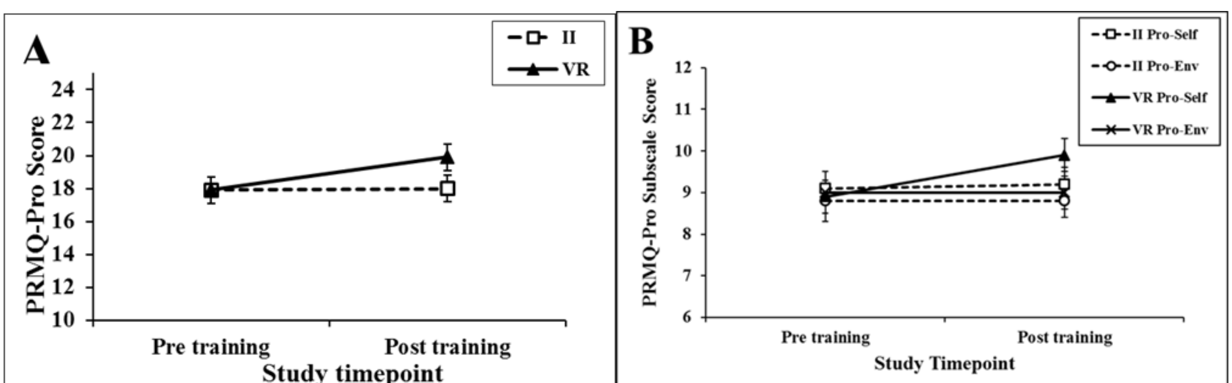

Figure 4.2. Group Pre and Post strategy training PRMQ scores for the (A) Prospective scale and (B) Prospective Self-cued and Prospective Environment-cued subscales. Error bars depict standard error of the mean.

4.4.2 Characteristics Associated with Self-reported Everyday Prospective Memory Change

PRMQ-Pro Change is presented in Table 4.2, and data for the variables assessed as potential correlates of reported everyday prospective memory change are in Table 4.1 (UPDRS, MoCA, BDI-II) and Table 4.2 (CEQ, prospective memory-related awareness). There were no group differences in CEQ or prospective memory-related awareness (*p*s ≥ 0.13). The VR group had higher PRMQ-Pro Change (i.e. greater decline) than the II group, $t(50) = 2.23$, $p = 0.03$.

Table 4.2. Change in reported everyday prospective memory, perceptions of prospective memory strategy training, and prospective memory-related awareness.

Variable	Implementation Intentions ($n = 25$)	Verbal Rehearsal ($n = 27$)	Statistics	Effect size (d)
PRMQ-Pro change [a]	-0.08 (3.66)	2.22 (3.92)	t=2.23, p=0.03	-0.61
CEQ Credibility	6.52 (1.52)	7.14 (1.49)	t=1.54, p=0.13	-0.41
CEQ Expectancy	4.21 (1.24)	4.78 (1.95)	t=1.44, p=0.19	-0.34
Prospective memory-related awareness				
Metacognitive knowledge [b]	5.16 (3.46)	5.59 (3.46)	t=0.45, p=0.65	-0.12
Online awareness [c]	4.64 (3.92)	4.42 (4.37)	t=0.19, p=0.85	0.05

Note. Numbers represent means (standard deviation). [a] Calculated as Post minus Pre; higher scores indicate more reported everyday prospective memory problems at Post compared to Pre. [b] Absolute difference between prediction of Virtual Week score and actual Virtual Week score; higher scores indicate less accurate predictions (poorer metacognitive knowledge). [c] Absolute difference between postdiction of Virtual Week score and actual Virtual Week score; higher scores indicate less accurate postdictions (poorer online awareness).

As illustrated in Figure 4.3, there was substantial variation in the magnitude and direction of PRMQ-Pro Change scores in both groups. Within the II group, PRMQ-Pro Change correlated with MoCA ($r = -0.46$, $p = 0.02$), BDI-II ($r = -0.40$, $p = 0.05$), and CEQ Expectancy ($r = -0.46$, $p = 0.02$), such that higher cognition, depressive symptoms and expectancy were associated with greater improvement in reported everyday prospective memory from Pre to Post. There were no significant correlations between PRMQ-Pro Change and UPDRS, CEQ Credibility, and prospective memory-related awareness within the II group (*r*s ≤ 0.18, *p*s ≥ 0.39) or between PRMQ-Pro Change and any variables within the VR group (*r*s ≤ 0.27, *p*s ≥ 0.19).

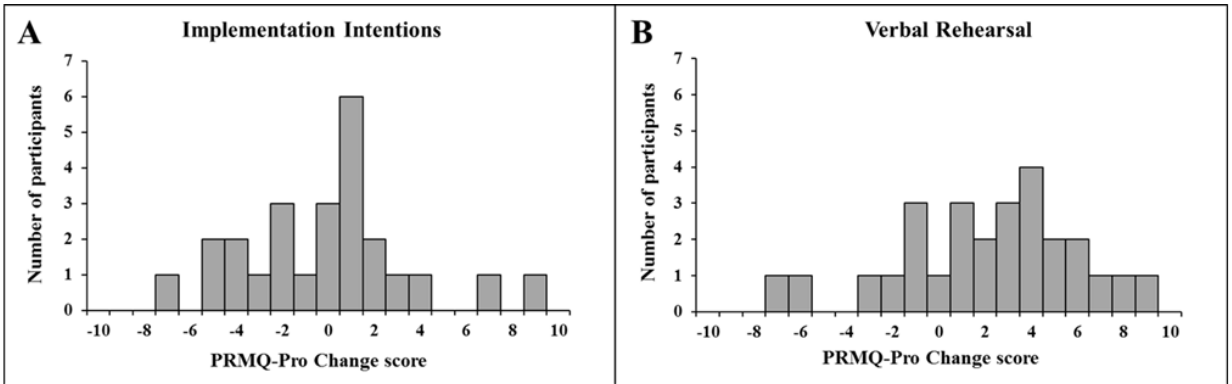

Figure 4.3. Distribution of Prospective and Retrospective Memory Questionnaire Prospective scale Change scores for the (A) implementation intentions and (B) verbal rehearsal groups. Higher scores indicate more reported everyday prospective memory problems at Post compared to Pre strategy training.

4.4.3 Exploratory Follow-up Interview Data

Descriptive data for the follow-up interview are in Table 4.3. There were no group differences in the distribution of answers for any of the questions, χ^2s $\leq$ 2.07, *p*s $\geq$ 0.36.

Table 4.3. Numbers and percentages (in parentheses) of participants responding to each response option for each question of exploratory follow-up interview about everyday prospective memory strategy use.

Question and response option	Implementation Intentions (n =25)	Verbal Rehearsal (n = 27)	Statistics	Effect size (r)
1. Do you remember the strategy? Describe.			χ^2=2.07, p=0.36	0.20
No memory/accuracy	5 (20)	2 (7)		
Partially correct	12 (48)	17 (63)		
Correct	8 (32)	8 (30)		
2. Did you use the strategy?			χ^2<0.01, p=0.94	0.01
No	2 (8)	2 (7)		
Yes	23 (92)	25 (93)		
3. How often/much did you use the strategy?			χ^2=1.32, p=0.86	0.16
Never	2 (8)	2 (7)		
1x/week; 1-5 times	9 (36)	6 (22)		
2-5x/week; 6-20 times	7 (28)	9 (33)		
1x/day	3 (12)	4 (15)		
> 1x/day	4 (16)	6 (22)		
4. Do you think the strategy worked?			χ^2=0.27, p=0.88	0.07
No	2 (8)	2 (7)		
Not sure	5 (20)	4 (15)		
Yes	18 (72)	21 (78)		

4.5 Discussion

This study tested the effect of laboratory-based encoding strategy training on self-reported everyday prospective memory in people with PD without dementia. Specifically, we aimed to determine whether the associative encoding strategy of II would produce greater improvements than the less elaborate encoding strategy of VR. We also investigated potential correlates of change in self-reported everyday prospective memory in response to training. Specifically, whether individual differences in several cognitive, motivational, and disease-related characteristics related to the direction and magnitude of change in everyday prospective memory from before to after training. After a single session of instruction and practice in either II or VR using the Virtual Week prospective memory test, participants were instructed to use their respective strategy as much as possible to accomplish their real-life prospective memory tasks over the following month. The self-report PRMQ Prospective scale administered before and one month after training showed significant decline in self-reported everyday prospective memory in the VR group but not in the II group. In addition, better global cognition, higher expectancy of improvement, and more severe depressive symptoms related to a more positive response to II training.

Our data are consistent with the notion that II is a more robust prospective memory strategy than VR and may help to compensate for PD-related deficits in executive control processes that underlie intention formation and retrieval [50,85]. Previously, we found that although both strategies improved laboratory prospective memory performance among people with PD, II produced larger effects for tasks with higher strategic encoding and attentional monitoring demands (nonrepeated and non-focal tasks, respectively) [85]. This study expands on our previous work to show that training in II may also benefit everyday prospective memory among people with PD.

Our primary results are somewhat surprising for a number of reasons. First is the finding that the group-related post-training difference in self-reported everyday prospective memory was due to decline in the VR group rather than improvement in the II group. This pattern contrasts with laboratory performance from the same sample, which improved in both groups after training and to a larger extent in the II group [85]. However, it is consistent with a recently-proposed function of cognitive intervention in PD as something which may mediate cognitive decline rather than improve cognition [33]. Specifically, our results are in line with the notion that cognitive intervention may briefly prevent or delay PD-related cognitive decline [33]. However, evidence on the trajectory of cognitive decline in early, non-demented PD and time-course effects of cognitive intervention in PD is limited [30,33], so it is not entirely clear how to interpret the VR group's self-reported decline over the relatively short one-month follow-up period used in this study.

The second counterintuitive finding is that the training effects were driven by changes in self-cued rather than environment-cued prospective memory. II are typically thought to support intention retrieval in part by facilitating detection of environmental cues [112,113]. However, everyday prospective memory tasks with environmental cues showed no change in response to II training in this study. In contrast, II appeared to maintain PD participants' self-reported everyday prospective memory on tasks for which there are no environmental cues. There is evidence that II can enhance performance on non-focal tasks (which are similar to the self-cued PRMQ tasks, see [53]) by increasing attentional monitoring [163], so perhaps this is what occurred in the current study. Alternatively, it may be that the formation of II forced people to define environmental cues for previously self-cued tasks, thereby reducing their attentional monitoring demands and allowing for more automatic cue detection and intention retrieval. The current study design did not allow for the examination of such mechanisms.

As anticipated, there was variability within both groups in terms of the direction and magnitude of improvement reported after strategy training. Our correlational data suggest that treatment expectancy, global cognitive function and level of depression may contribute to these individual differences in response to II training. Evidence from physical and cognitive-behavioral intervention studies supports the finding that higher treatment expectancy is a positive predictor of outcomes, likely because it motivates engagement in treatment and application of treatment techniques [168,172,173]. This finding has important clinical implications because expectancy can be increased before treatment through the use of a strong therapeutic rationale and motivational interviewing [172,173].

The finding that better MoCA scores were associated with a better response to training likely reflects the general cognitive demands of learning something new and transferring or generalizing it across situations. None of our participants had dementia, but several in each group met screening criteria for possible PD-MCI (MoCA score ≤ 25), which could have been a determining factor in their level of improvement from II training. Although studies show that people with MCI can benefit from strategy-based interventions [97,102], external strategies or environmental approaches that require less self-initiation (e.g. setting alarms, visual reminders, care partner support) may be more appropriate for them. Alternatively, a small study conducted by Costa, Peppe, Serafini, Zabberoni, Barban, Caltagirone, Carlesimo [76] suggests that shifting training may improve prospective memory in PD participants with MCI.

We initially expected that higher depression would relate to poorer response to training through its negative effects on motivation and engagement in training [174,175], but we found the opposite. This may be explained in relation to a cognitive initiative framework, whereby people with depression do not necessarily lack cognitive resources but instead fail to strategically engage their cognitive resources in tasks naturally [176-178]. However, when their attention is directed toward key features of cognitive task or a useful strategy (as occurred with II training in the current study), they can make use of such information to improve their performance, potentially to a greater extent than people without depression [176-178] (for evidence to support this notion in prospective memory, see [179]). Another potential explanation for our finding is the empowering nature of strategy training in general. Strategy use enables people to have better control over their functioning and provides mastery experiences through which to develop self-efficacy [180]. These effects may have been particularly salient for people with initially higher levels of depressive symptoms.

Knowing who responds to certain treatments can aid in the tailoring of interventions and guide clinicians in selecting appropriate clients to whom they should administer said treatments (i.e. people who are likely to benefit). Alternatively, it can reveal potentially modifiable characteristics (e.g. expectancy) to address before beginning the treatment to maximize the likelihood that the person will engage at a level necessary to derive benefit. Ultimately, these practices will result in more effective and cost-effective intervention delivery. Continued and more thorough examination of heterogeneity in response to treatment and treatment effect modifiers will be critical to the successful translation of findings from strategy training research to clinical practice.

Although there were group differences in the laboratory and self-reported everyday effects of prospective memory strategy training, the follow-up interview results showed no differences in terms of participants' accuracy of strategy recall, reported daily life strategy use, or perceptions of strategy effectiveness. Given that the training itself required minimal time and resources, it is encouraging that almost all participants reported using their strategy at least once per week and a majority thought that it worked. However, about two-thirds of participants in both groups did not have fully accurate memory for their strategy, so it is unclear how effectively or appropriately they were using it in daily life. This may help to explain the relatively small self-reported everyday effects and suggests that a more rigorous training program may have produced more robust effects.

This study has some design-related issues that limit our conclusions. The sample size was relatively small and, in light of the finding that global cognition was related to response to training, inclusion of data from the participants who were lost to follow up could have influenced our group-related findings. Furthermore, we did not conduct a comprehensive neuropsychological assessment, so we do not know the cognitive status of our sample and our ability to interpret results related to potential PD-MCI and the influence of other cognitive processes on response to prospective memory strategy training is limited. In addition, the one month follow-up period was likely too short to provide information on any sustainable effects of training.

Another potentially problematic feature is that our primary outcome measure and follow-up interview were self-reported, so we do not have objective evidence of prospective memory performance or strategy use in daily life. In particular, the validity of the PRMQ as an indicator of prospective memory ability in PD is inconclusive. In some studies it discriminated between

PD and healthy participants (specifically the Pro-Self scale) [53,54], whereas other studies found no differences [171]. Similarly, in some studies it correlated with objective prospective memory test scores [55,171], whereas in other studies it did not [53,54]. This may explain the different pattern of training-related findings across the laboratory reported in [85] and self-reported everyday prospective memory measures in the current sample. Lack of association between self-reported and objectively-measured prospective memory could be due to issues such as depressive symptoms, limited insight, and reporter bias. However, it is likely also due to a number of important aspects of “reality” that are not captured by many objective prospective memory tests, such as variation in real-world prospective memory challenge, additional daily demands, compensatory strategy use, task importance, and motivation [181-187]. This is especially true of laboratory-based tests, but even so-called “naturalistic” paradigms are artificial in that they use experimenter-generated tasks and thus may not tap into personal and motivational aspects of real-life prospective memory [187]. Thus, self-report measures of cognition can be informative in the absence of agreement with objective measures of cognitive ability [186,188]. Furthermore, because they incorporate the individual’s experience and perspective, they are critical for delivering patient-centered care [189]. We were interested in understanding these real-life and clinically-relevant issues, so we selected self-report over an objective measure of everyday prospective memory for this study.

This study revealed a number of issues for further investigation. In terms of intervention development, a more intense multi-session training program that incorporates methods to explicitly “train for transfer” (e.g. variable training tasks, spacing, homework, metacognitive framework) [89] may produce more conclusive findings related to meaningful real-world change. Future studies should include comprehensive neuropsychological assessment to fully characterize participants’ cognition, informant-report and/or naturalistic performance-based outcome measures to help corroborate self-report or at least provide more complete information about a person’s prospective memory and strategy use outside of the laboratory or clinic, and longer term tracking of prospective memory after strategy training. In addition, research should aim to gain a better understanding of the potential effect of II on everyday self-cued prospective memory tasks.

In summary, our results suggest that the use of II may prevent decline in everyday prospective memory among non-demented people with PD. Furthermore, training in this strategy may be particularly beneficial for those with better global cognition, worse depressive symptoms, or higher expectations of improvement from strategy-use. Although there were statistically significant findings, the degree of change on the PRMQ that should be considered clinically significant is unclear. Regardless, this study has provided information to contribute to the development of future strategy training interventions for people with PD that take into consideration not only what to train, but also who to train and how. Further, it provides support for the value of strategy training for prospective memory impairment in PD.

Chapter 5: Conclusion

5.1. Summary and synthesis

Prospective memory impairment is a well-established and functionally disabling problem for people with PD without dementia [52,54-56]. The purpose of this dissertation was to provide a foundation for the development of effective prospective memory interventions for people with PD by better understanding the nature of prospective memory impairment in PD and testing a targeted strategy, II, to address it. Specifically, it aimed to (1) Determine the cognitive mechanisms underlying prospective memory impairment in PD, (2) Determine the effect of II training on laboratory prospective memory performance in PD, and (3) Determine the effect of II training on reported everyday prospective memory in PD. A summary and synthesis of the major findings from these studies follows.

5.1.1 Aim 1

The first aim was addressed by an observational study comparing the performance of non-demented PD participants and healthy older adults on an experimental test that stimulates real-world prospective memory challenges, the Virtual Week [122,123]. The Virtual Week allows for the analysis of prospective memory under conditions of high and low demand on specific underlying cognitive processes and, thus, the pinpointing of cognitive deficits that give rise to prospective memory impairment in PD. This study possessed key methodological advancements compared to prior work. First, it explicitly manipulated both the prospective and retrospective component demands of prospective memory tasks in a single experimental paradigm and used a full factorial design, which permitted a more thorough and conclusive analysis of the cognitive mechanisms underlying prospective memory impairment in PD. Second, it used the Virtual Week test to conduct a more ecologically valid investigation of prospective memory in PD. By simulating real-world prospective memory tasks, the Virtual Week is not only more face valid than typical experimental paradigms but is also more representative of the cognitive requirements of real-world prospective memory. Furthermore, it is a more reliable index of prospective memory than traditional experimental paradigms [139,161]. The Virtual Week proved to be a reliable measure of prospective memory in PD, which supports its use in future studies.

Findings from this study replicated, in a more realistic context, the PD-related preferential impairment for tasks with less focal cues [53], which likely stems from poor executive control during intention retrieval (e.g. monitoring, shifting). More novel was the finding that when intentions are more complex, as they tend to be in real-life, deficits in retrospective memory processes can interfere with prospective memory performance in people with PD. When considered in the context of prior retrospective and prospective memory research in PD, the data from this study indicate that PD-related retrospective component problems likely stem from poor executive control of encoding during intention formation, namely, failure to self-initiate strong associative encoding of the cue-action pair. Critically, this impaired intention formation results in prospective memory task failure even under conditions that should facilitate automatic intention retrieval (i.e. focal irregular tasks). Thus, suboptimal intention formation is a key barrier to successful prospective memory performance in PD, so a prospective memory intervention for people with PD should target intention formation.

5.1.2 Aims 2 and 3

The insight gained from Aim 1 – along with the perspective that strategy training (rather than cognitive process training) is the appropriate cognitive intervention approach for PD – prompted a randomized controlled trial to test the effect of the II strategy on prospective memory in PD. II target intention formation by forcing good associative encoding of the cue-action pair. This then has the downstream effect of fostering more automatic intention retrieval when the cue is encountered [113]. The II strategy was pitted against the placebo strategy of simple verbal rehearsal (VR) to control for time spent thinking about the intentions and verbalization.

Aim 2 investigated the effect of strategy training on laboratory prospective memory performance using the Virtual Week as the outcome measure. Results showed that both II and VR improved prospective memory performance relative to standard instructions (no strategy use). Importantly, II resulted in a larger effect than VR for the irregular tasks, i.e. those tasks with increased intention formation demands for which PD participants were most impaired in Study 1. In fact, the II group in Aim 2 had irregular task performance that was better than that of the healthy older adult group in Study 1. Thus, II compensated for PD-related intention formation deficits. The effect of strategy use was larger for tasks with focal compared to non-focal cues. This finding suggests that intention formation strategies do not eliminate the need for strategies or task modifications that support cue detection for non-focal tasks (discussed further in section 5.2).

The results from Aim 2 show that people with PD can use intention formation strategies to improve their performance on a variety of prospective memory tasks in a controlled laboratory setting and that II are particularly effective for tasks with challenging encoding conditions and focal cues. They also provide “proof of concept” for II in PD in that when people with PD use the strategy, it works. However, although people with PD can successfully apply strategies in the controlled environment in which they were learned, we cannot assume they will spontaneously transfer the use of those strategies to everyday prospective memory challenges [88]. This issue –

whether people with PD can transfer strategy use and benefit from the laboratory to everyday life with minimal training – was addressed in Aim 3.

Aim 3 investigated the effect of laboratory-based strategy training on everyday prospective memory using a widely-used self-report questionnaire, the PRMQ [124], as the outcome measure. In addition to examining group-related effects, it also investigated individual characteristics that may influence response to strategy training. Results showed that the VR group's self-reported everyday prospective memory worsened from before to after training, while the II group's remained stable. In addition, higher baseline depressive symptoms, treatment expectancy and global cognition related to better response to training in the II group. These findings further support the potential value of II for addressing prospective memory impairment in PD, suggesting that II training may prevent, delay or slow everyday prospective memory decline in this population. They also suggest that II training may be particularly beneficial for those with better global cognition, worse depressive symptoms, or higher expectations of improvement from strategy-use.

5.1.3 Significance and clinical implications

Interventions that enable people with PD to successfully perform prospective memory tasks could improve function and quality of life and significantly impact clinical care for this population. The studies in this dissertation were designed to answer basic questions to inform the development of such an intervention. Although additional work is required to more conclusively guide clinical practice (see section 5.2), the results suggest that training in II may be a useful approach, especially for focal tasks and people with minimal global cognitive decline. Establishing good treatment expectancy (e.g. conveying therapeutic rationale, motivational interviewing) [172,173] may bolster the beneficial effects of training.

5.2 Issues to address in future research

This dissertation provides a strong foundation for research on prospective memory intervention for people with PD. The specific limitations of each aim are discussed in their respective chapters. The following discussion summarizes some key issues revealed during the course of this work that will be addressed in future studies.

The studies included PD participants without dementia but did not specify anything else about their cognitive status. This likely resulted in cognitively heterogeneous samples, which may have limited statistical power. In addition, there was no confirmation of objective cognitive decline or deficits (e.g. diagnosis of PD-MCI [170]). In light of the fact that several participants in each group met screening criteria for possible PD-MCI (MoCA score ≤ 25) [169,170], the finding that global cognition was associated with response to strategy training, and recent work suggesting that prospective memory impairment is specific to PD-MCI [55,56,190], this factor should be explored more thoroughly in future research. Further, the MoCA was the only cognitive assessment administered outside of the Virtual Week test, so there was very limited information on the participants' cognitive profiles (i.e. strengths and limitations in specific cognitive processes or domains). A full neuropsychological assessment would provide additional insight into the specific cognitive abilities associated with prospective memory and response to strategy training in PD.

A fundamental assumption of this work is that strategy training is a more appropriate approach to cognitive intervention than process training for producing meaningful real-world functional cognitive benefits in people with PD. However, these two approaches have not been tested against each other in PD, so this assumption must be supported with data before moving forward. Relatedly, a more focused examination of transfer of training effects must take place.

Aim 2 had no transfer requirements because II were trained using the Virtual Week, and participants were reminded to use the strategy during their post-test. Although Aim 3 assessed and supported the occurrence of far transfer, the use of self-reported outcomes, inconsistencies with laboratory findings and theorized cognitive mechanisms, and results from the follow-up interview (e.g. only 30% of participants remembered the strategy accurately) indicate further investigation is needed to more fully understand whether and how people are applying trained strategies in their daily lives.

A more comprehensive training program should be developed for clinical application. It is reasonable to assume that a single session of training in the “right” strategy could be an effective way to improve real-world prospective memory [89], and there is some evidence to support this notion [78,114,166]. However, it is likely that a more rigorous training program is required for optimal benefit, especially for people with PD who have slower learning rates and require more repetition to acquire new skills than healthy adults [191]. In addition to (and perhaps more important than) increasing the number of training sessions, future training programs should incorporate techniques known to support learning and transfer such as variable training contexts, spaced and interleaved practice, grading, feedback, and making explicit connections between training and real-life [88,90,91,93,94,192]. Training should emphasize metacognitive processes to build awareness of deficits and task demands so that people can recognize when learned strategies may be helpful and, thus, apply them in the appropriate situations [90-92]. Additionally, therapist mediation to facilitate strategy self-generation and testing may be more effective for promoting transfer than directive instruction. This technique is rooted in constructivism theories that suggest learning and transfer are enhanced when the learner actively engages in the process of discovering, testing, and evaluating solutions to challenging experiences [193-196]. Best practice rehabilitation practices such as client-centeredness and collaborative goal-setting should also be employed to maximize the likelihood of robust and clinically meaningful outcomes.

In terms of prospective memory intervention specifically, effective strategies for prospective memory tasks with non-focal and time-based cues should be pursued. Although there was some effect of II training on these types of tasks in Aims 2 and 3, strategies or task modifications to support cue detection should augment this effect. For example, there is evidence that older adults and people with PD who use attentional control strategies such as event monitoring and strategic clock checking perform better on non-focal or time-based tasks [59,89]. Another option is to associate intentions with environmental cues that do not require monitoring or shifting to detect, essentially turning non-focal or time-based tasks into focal event-based tasks. Furthermore, while the current focus is on internal strategies, studies should also test external strategies such as using alarms or other reminders, particularly for people with more pronounced cognitive decline.

More work is required to understand how prospective memory impairment manifests in daily life and the functional relevance of prospective memory impairment in PD. The Virtual Week is thought to be more ecologically valid than existing experimental prospective memory paradigms; however, its predictive validity for real-world prospective memory functioning has yet to be tested. This issue is compounded by the fact that the available methods for assessing real-world prospective memory function – so-called “naturalistic” prospective memory paradigms and self- or informant- report measures – are far from perfect (discussed section 4.5). Until a gold-standard assessment is established, studies should incorporate multiple methods to provide a more comprehensive picture and, ideally, converging data regarding people’s prospective memory performance in everyday life. More research on the association of prospective memory with broader occupational performance and participation outcomes is also warranted. Such knowledge would permit stronger conclusions about the clinical significance of intervention effects.

5.3 Contribution to rehabilitation and participation science

This work leverages conceptual and methodological features to advance rehabilitation research in PD. It is consistent with the emerging recognition in the field of the need to directly address *functional cognition*, or the ability to use and integrate thinking and processing skills to accomplish everyday activities [197], in order to develop cognitive interventions that have meaningful effects on people's daily lives. It focuses on prospective memory, a cognitive construct that people recognize and value in their daily lives, rather than on isolated and abstract cognitive processes with little relevance to daily performance. It is also concerned with ecologically valid assessment and understanding how prospective memory impairment manifests in everyday life. Relatedly, it aims to not only determine the *efficacy* of strategies for prospective memory but to develop an *effective* intervention that supports peoples' everyday prospective memory function. This will be accomplished by incorporating training techniques thought to maximize the likelihood of transfer of learning as well as by taking a phased and incremental approach to intervention development. Complex behavioral intervention development requires such an approach to ensure that the resources required for clinical trials are not wasted on inadequately designed interventions [198-201]. Knowledge and experience gained from this work in prospective memory can inform the development of interventions for other functional cognitive deficits experienced by people with PD that can be implemented in clinical practice to optimize peoples' function in their homes, work and communities and promote their full participation in life.

Historically, PD-related rehabilitation science and practice has focused on motor dysfunction and physical disability. While evidence suggests that rehabilitation can benefit specific physical performance skills in PD, large improvements in broader occupational performance outcomes, participation, and quality of life have been elusive [202]. Cognitive impairment in particular is considered a major unmet need and important target for treatment by patients, families, practitioners, and scientists in the PD community [28,29]. This dissertation has begun to address this need by taking a systematic and hypothesis-driven approach to facilitate the translation of knowledge acquired from basic cognitive science into a practical intervention. Ultimately, it aims to improve the overall effectiveness of rehabilitation for people with PD by producing cognitive interventions that can be integrated with existing physical and self-management interventions to more comprehensively address daily function and quality of life among people with PD.

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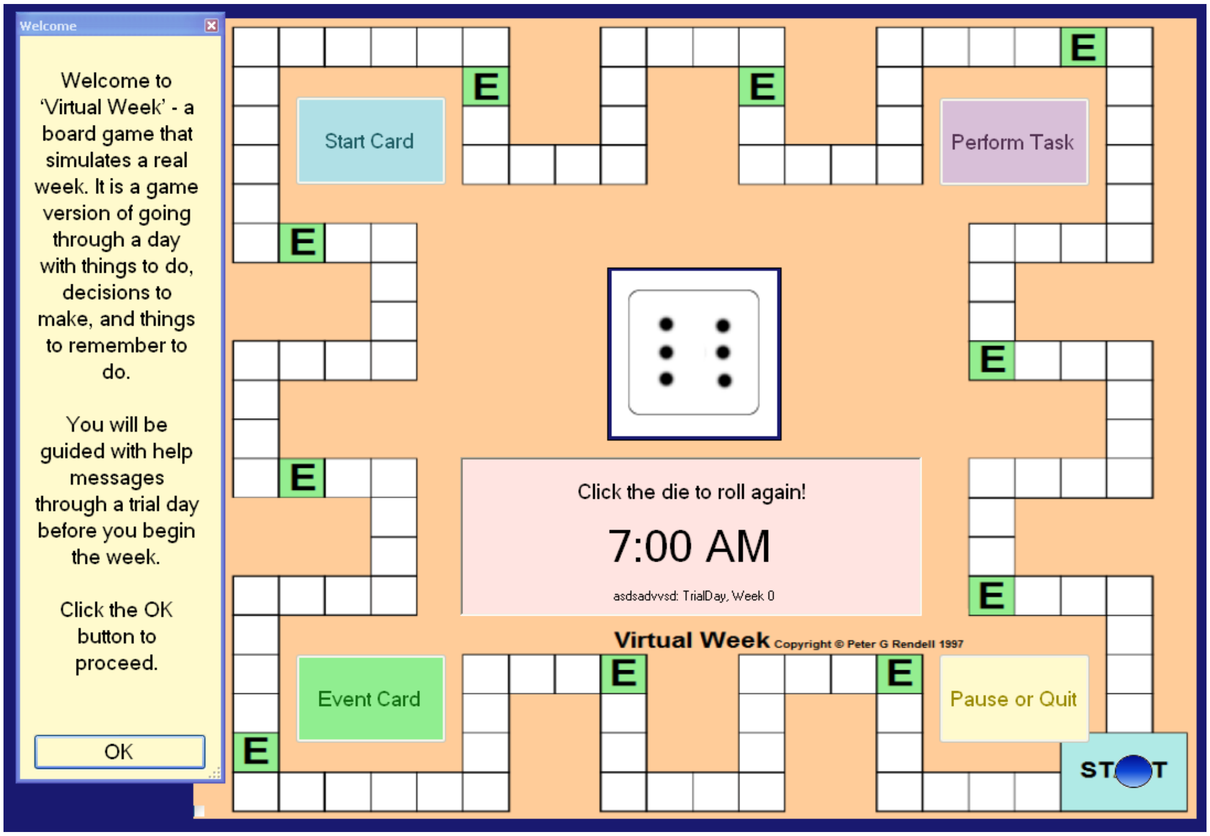
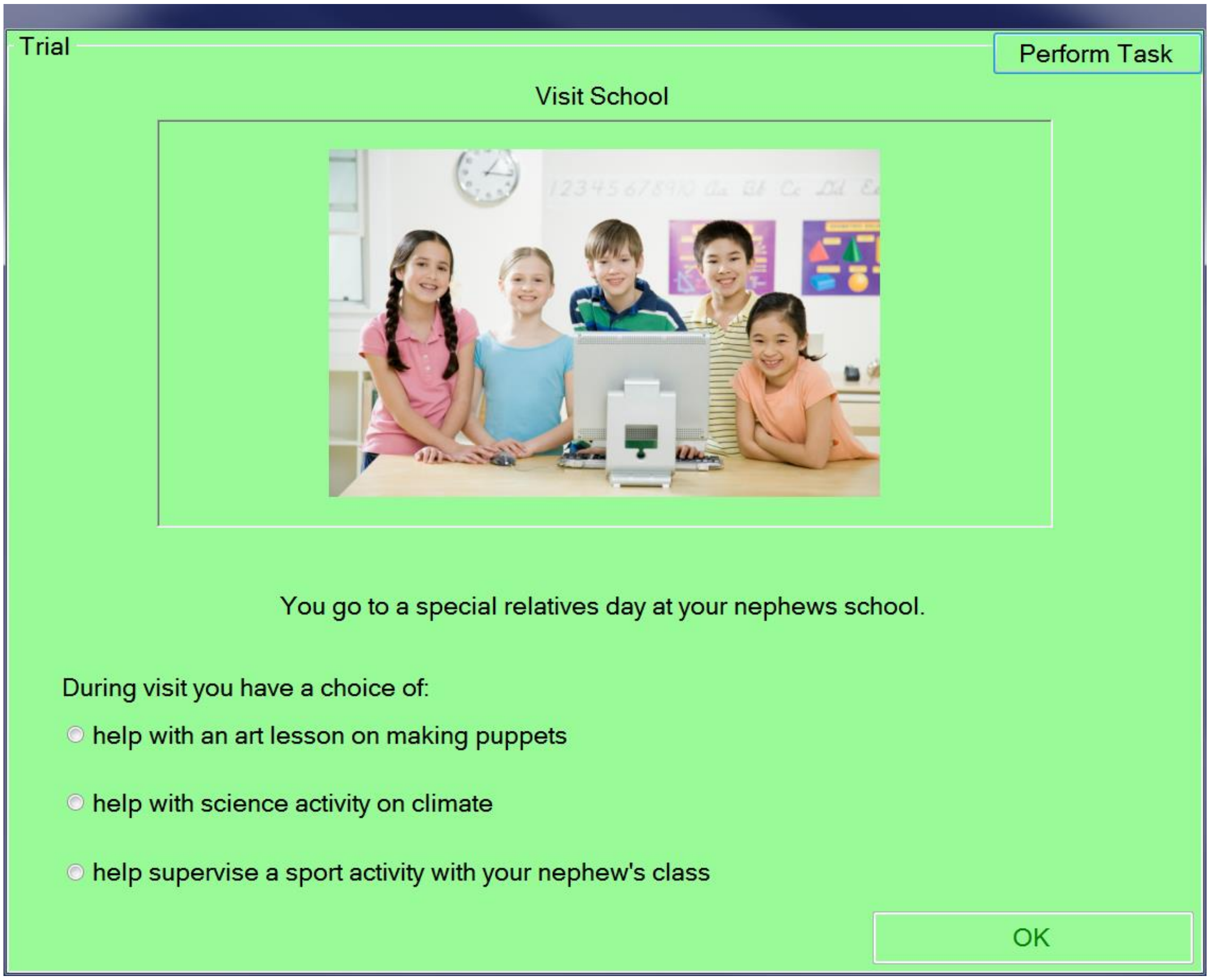
Appendix

Screen shots from the Virtual Week

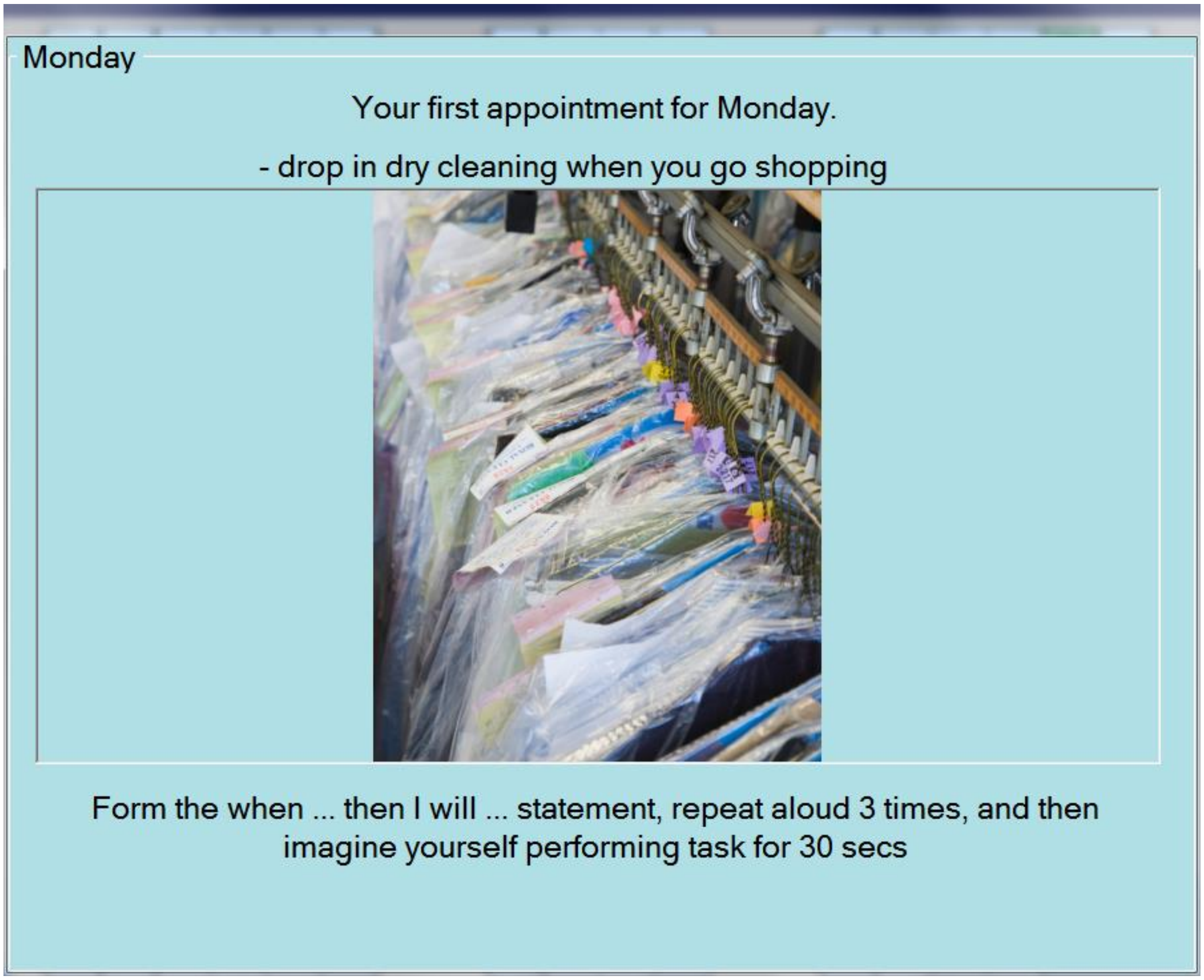


1. The board and welcome message at the beginning of the trial (practice) day.

2. Example task card for the standard instructions (no encoding strategies). This is an example of a non-repeating event-based task.



3. Example Event Card. This is the target Event Card (visiting a school) for the above task card (take favourite children's book). Thus, when the participant encounters this card, s/he is to click the "Perform Task" button on this card or on the board to select the appropriate task (take favourite children's book) from the list of options.



4. Example task card with strategy encoding instructions for the Implementation Intentions group (non-repeating event-based).

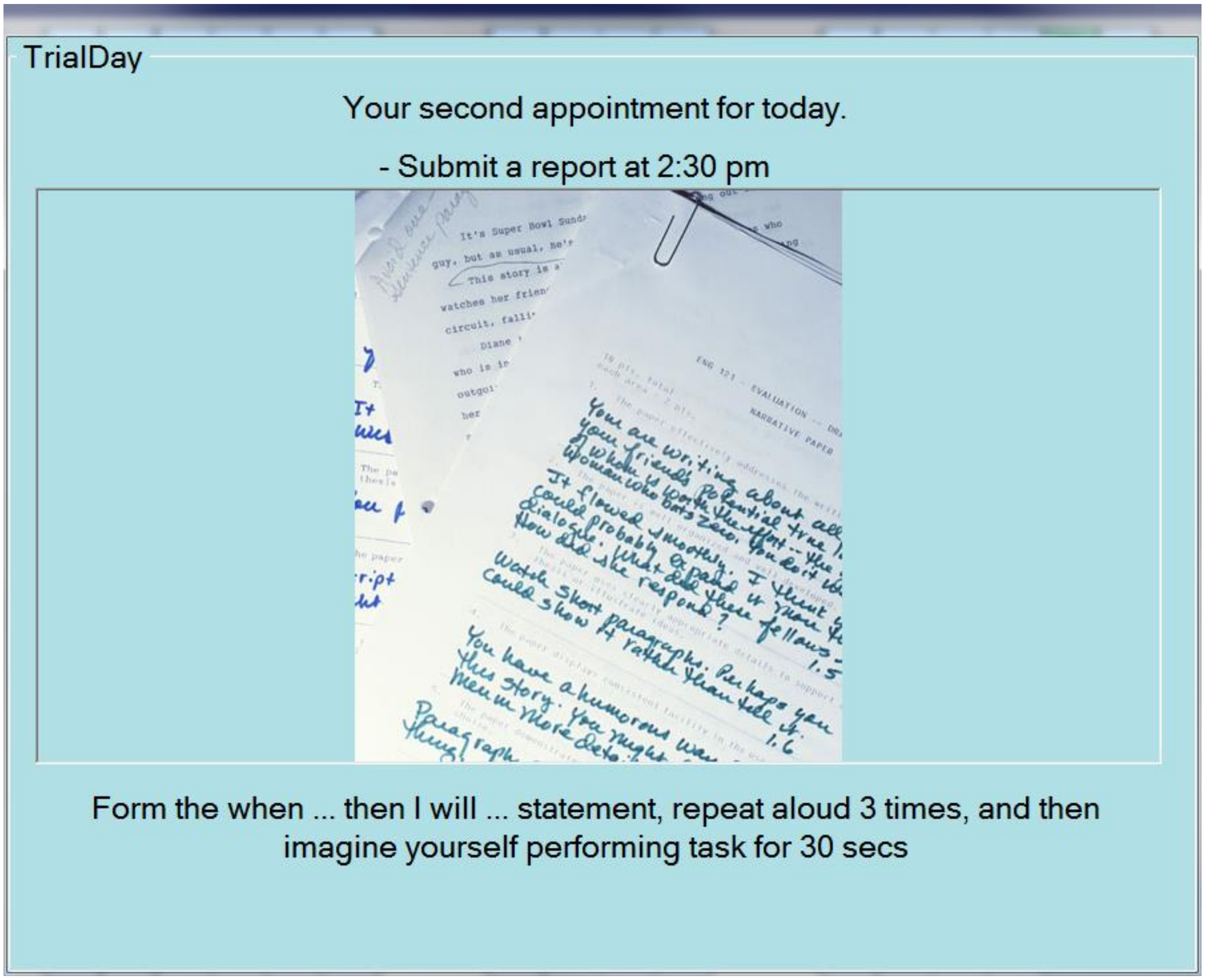
You are asked to perform the following health tasks every day

- take antibiotics at breakfast

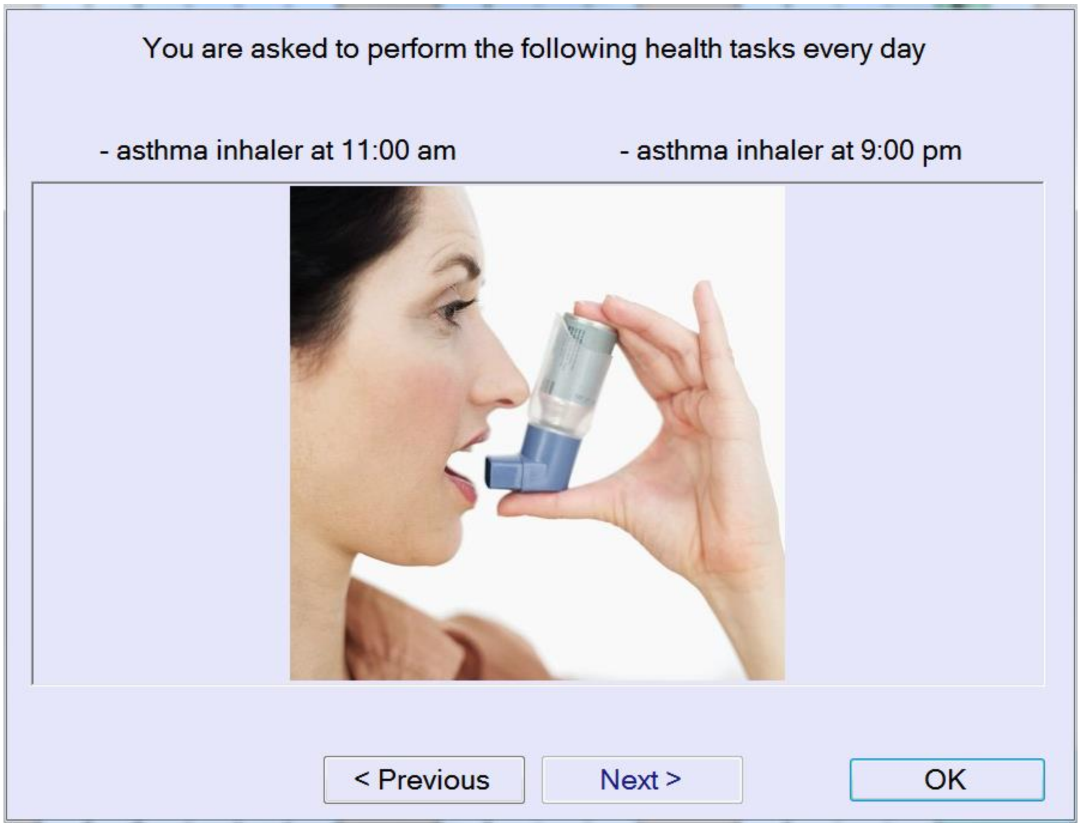
- take antibiotics at dinner

Repeat aloud each task and study for 30 secs

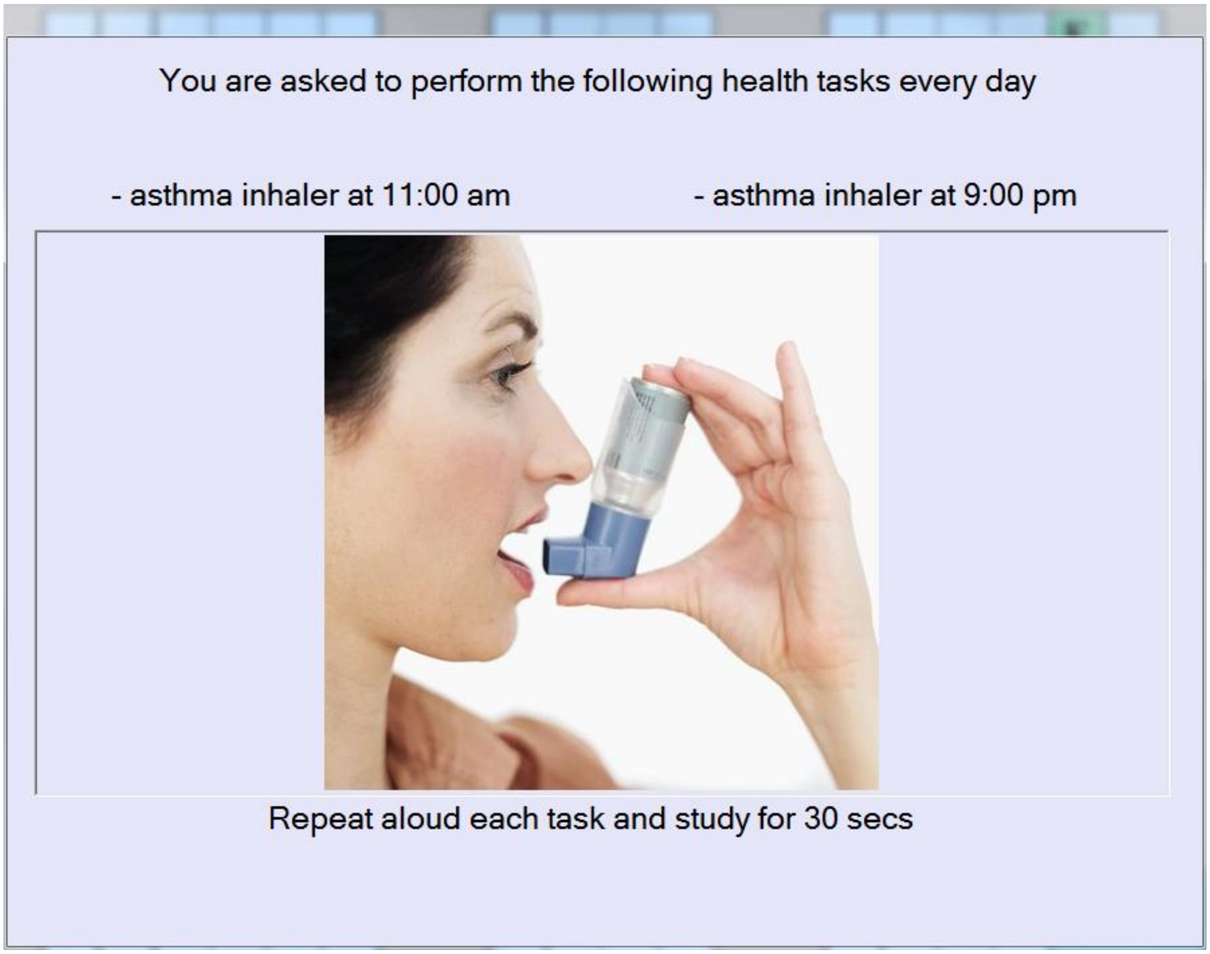
5. Example task card with strategy encoding instructions for the Rehearsal group (two repeating event-based)



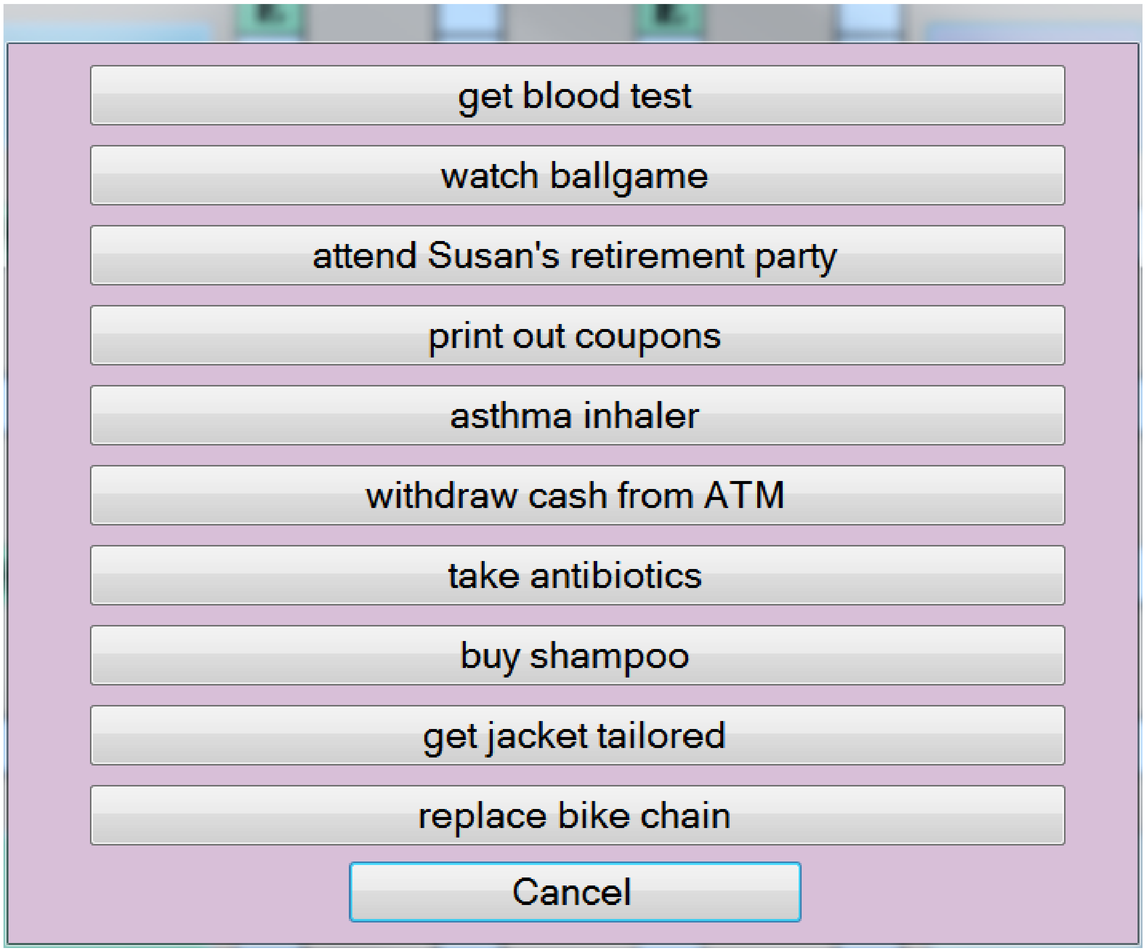
6. Example task card with strategy encoding instructions for the Implementation Intentions group (non-repeating time-based).



7. Example task card with standard instructions for the repeating time-based tasks.



8. Example task card with strategy encoding instructions for the Rehearsal group (repeating time-based).



9. Example Perform Task List. The list always includes the possible prospective memory tasks for the day and 4 distractors.