Eye Movements in the "Morris Maze" Spatial Working Memory Task Reveal Deficits in Strategic Planning

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Abstract

■ Analysis of eye movements can provide insights into processes underlying performance of cognitive tasks. We recorded eye movements in healthy participants and people with idiopathic Parkinson disease during a token foraging task based on the spatial working memory component of the widely used Cambridge Neuropsychological Test Automated Battery. Participants selected boxes (using a mouse click) to reveal hidden tokens. Tokens were never hidden under a box where one had been found before, such that memory had to be used to guide box selections. A key measure of performance in the task is between search errors (BSEs) in which a box where a token has been found is selected again. Eye movements were found to be most commonly directed toward the next box to be clicked on, but fixations also occurred at rates higher than expected by chance on boxes farther ahead or back along the search path. Looking ahead and looking back in this way was found to correlate negatively with BSEs and was significantly reduced in patients with Parkinson disease. Refixating boxes where tokens had already been found correlated with BSEs and the severity of Parkinson disease symptoms. It is concluded that eye movements can provide an index of cognitive planning in the task. Refixations on locations where a token has been found may also provide a sensitive indicator of visuospatial memory integrity. Eye movement measures derived from the spatial working memory task may prove useful in the assessment of executive functions as well as neurological and psychiatric diseases in the future. ■

INTRODUCTION

Performing everyday tasks, such as making a cup of tea or driving a car, requires the coordination of complex sequences of eye movements (Land & Furneax, 1997). Analysis of this aspect of behavior can provide insights into processes of visual attention, working memory, and executive function during neuropsychological tasks (Kaller, Rahm, Bolkenius, & Unterrainer, 2009; Huddy et al., 2007; Mosimann, Felblinger, Ballinari, Hess, & Muri, 2004; Hodgson & Golding, 2003; Hodgson, Tiesman, Owen, & Kennard, 2002; Kennard, 2002; Hodgson, Bajwa, Owen, & Kennard, 2000). Eye tracking also has the potential to provide enhanced metrics for the diagnosis and assessment of psychiatric and neurological disorders by providing more sensitive measures of cognitive and neurological integrity (Shakespeare et al., 2015; Benson et al., 2012; Kaufman, Pratt, Levine, & Black, 2012). This article describes the characteristics of eye movements made during the performance of a memory-guided token foraging task widely used in the assessment of human executive function. We were interested in determining whether eye movements might provide insights into cognitive function in this task as it has for other tests. We were also interested in whether eye-tracking measures might have potential for the development of enhanced approaches to neuropsychological assessment in the future.

Originally described as the "Morris Maze" task (Morris et al., 1988) and later incorporated into the Cambridge Neuropsychological Test Automated Battery (CANTAB[1]), the spatial working memory (SWM) task was originally developed as a human analogue of tests of memory in animals (Passingham, 1985; Olton, 1982; Petrides & Milner, 1982). In the SWM task, patients have to find reward tokens hidden within an array of boxes displayed on a computer screen. Patients are asked to search through the boxes by selecting them using a mouse click or touch screen response. Following a box selection, the contents of the box are revealed as either a token (a colored square) or empty (a blank space). The patient is told that there is only ever one token hidden at a time, but when a token has been found, another one is immediately hidden. Crucially, a token is never hidden under a box where a token has been found. In a given token set, the same number of tokens needs to be found as there are boxes displayed on the screen. The difficulty of the task can be varied by changing the total number of boxes in the array from four boxes (easy) to eight boxes (hard).

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Thus, the four-box condition will comprise a set of four discrete token searches, whereas the eight-box condition will comprise a set of eight token searches.

As with the radial arm maze version developed for rats, humans need to keep track of where they have found reward tokens in the SWM task and only search boxes where rewards have not already been found in the current set. As the number of boxes and tokens increases, there is a concomitant increase in the number of previously searched locations that the patient must try to keep in mind to avoid making errors. The task produces two basic types of errors indicative of memory failures: "within search errors" (WSEs) when a box is reselected even though it has already been revealed to have been empty within the current token search and "between search errors" (BSEs) when a box where a token has already been found is reselected during a later token search within the same set.

Investigations comparing patients with focal brain lesions and patients with idiopathic Parkinson disease (PD) in different disease states have revealed deficits in the SWM task compared with healthy controls (Owen et al., 1992; Owen, Downes, Sahakian, Polkey, & Robbins, 1990). Patients with moderately severe PD as well as focal frontal lesions show increased BSEs. Patients also differ with respect to their strategy score, defined as the percentage of searches that commence at the same box in a given set. Subsequent investigations in patients with PD on and off dopaminergic medication showed that these impairments were unlikely to be attributable to the effects of dopaminergic medication alone and most likely reflect disordered strategic planning of the search sequence rather than deficient memory for spatial location (Owen, Iddon, Hodges, Summers, & Robbins, 1997).

No studies to date have investigated how eye movements are used in the SWM task (although the lead author's informal observation of patients performing the task over many years suggest that eye movements play an important role). Interestingly, previous studies of patients with PD have reported a correlation between the SWM task and performance of a sequential memory-guided eye movement test (Hodgson, Dittrich, Henderson, & Kennard, 1999). Walker, Husain, Hodgson, Harrison, and Kennard (1998) have also described a patient with a focal lesion affecting the ventrolateral frontal cortex who was impaired in the SWM task against both BSE and strategy score criteria. Interestingly, the patient also made close to 100% errors in the antisaccade task, in which an eye movement toward a peripheral onset has to be suppressed and directed toward the opposite location. These findings suggest that there may be an association between oculomotor control and impairments in the SWM task, although this possibility has not been explored directly.

Studies and theories of visuospatial working memory contrast with respect to the importance attributed to eye movements in processes of encoding and maintenance. Much previous work has used variants on the forward (but not backward) spatial span or "Corsi block" task, in which a sequence of spatial locations is cued by the experimenter and the participant must then point sequentially to the same locations in the same order (Corsi, 1972). Recently, Smith and colleagues devised an ingenious series of experiments in which viewers were instructed to abduct eye position to an eccentric fixation location while performing a version of the spatial span test. Using this technique, it was shown that memory for visual locations must place demands on oculomotor representations in some form, as performance was disrupted when eye abduction brought the coordinates of memorized locations outside the effective oculomotor range (Pearson, Ball, & Smith, 2014; Ball, Pearson, & Smith, 2013). Yet recordings of naturally occurring eye movements made by participants during the spatial span task show that an adaptive strategy is to maintain fixation during stimulus presentation and maintenance. One explanation for this apparent contradiction is that shifts in fixation disrupt retinotopic encoding and maintenance of visuospatial coordinates, meaning that it is advantageous to maintain correspondences between retinotopic and craniotopic reference frames during visuospatial memory tasks (Martin, Tapper, Gonzalez, Leclerc, & Niechwiej-Szwedo, 2017; Patt et al., 2014).

The SWM task differs from the Corsi block task as it requires patients to actively search an array of locations while simultaneously maintaining memory for spatial locations in working memory. This makes it difficult to adopt a strategy of maintaining a constant fixation point. The importance of working memory in guiding eye movements in search has been investigated by a number of authors (Hollingworth & Luck, 2009; Gilchrist & Harvey, 2000; Klein & MacInnes, 1999; Horowitz & Wolfe, 1998). Using a multitarget visual search task based on the Mesulam cancellation test (Weintraub & Mesulam, 1985), Mannan and colleagues have investigated processes of attentional control and working memory in patients with hemispatial neglect and PD using a multitarget visual search task, which has parallels with the SWM test investigated here (Mannan, Hodgson, Husain, & Kennard, 2008; Mannan et al., 2005; Husain et al., 2001). In the multitarget search task, patients must make a mouse click each time they find a new target among distractors (e.g., "T" shapes among "L"s) and avoid revisiting and reclicking on targets they have already discovered. Healthy control participants are found to adopt an ordered search strategy, in which locations are rarely refixated. Patients often show higher rates of refixations, but this can have different explanations in different patient groups. Repeated mouse click selections on locations that have already been searched suggest that patients with hemispatial neglect fail to remember searching locations (Mannan et al., 2005; Husain et al., 2001). In contrast, patients with PD refixate but do not reclick on previously found targets, suggesting an attentional rather

than a working memory origin for refixations in search (Mannan et al., 2008).

Experiment 1 aimed to investigate whether analysis of eye movements might provide insights into cognitive processes in the SWM task. The spontaneous (i.e., uninstructed) patterns of eye movements made by young healthy participants while performing the task were recorded. Analysis tested whether eye movements more or less randomly sampled the array of boxes or instead reflected prospective action planning and memory processes. This was achieved by categorizing each possible response box according to its instantaneous relationship to past and future search events, that is, was it the next box to be selected, the next plus one box, or the last box selected, or so forth. Rates of occurrence of fixations were compared with what might be expected according to a chance distribution across all boxes. A higher-than-chance rate of fixations on boxes that were to be selected in the future would indicate cognitive planning ahead. In contrast, refixations on previously searched boxes might reflect failure to recall that these locations had been searched or rehearsal of the preceding search path. In the latter case, one might expect these fixations to be negatively rather than positively correlated with task performance, as defined by mouse click selection errors.

EXPERIMENT 1

Methods

SWM Task

The task was programmed using Experiment Builder software (SR-Research Ltd.), a Python-based object-oriented programming environment that allows seamless integration and synchronization of experiment display and event timing with eye movement data recordings. Although closely based on the CANTAB SWM test, several features were different in our version of the task. First, only four- and eight-box conditions were used. This was because the complexity and size of the resulting eye movement data sets were such that it was deemed that two levels of difficulty would be a sufficient number for the analysis. Second, we removed the token accumulator bar, which appears in the original version of the task, as we anticipated that this would attract a large number of "checking" fixations and detract from the focus of our analysis, which was planning and rehearsal of the search path. Finally, rather than a touch screen response being used to select boxes, mouse movements controlled a screen pointer (a small white square subtending 5 × 5 screen pixels) and a left mouse click was used to select boxes. This was done to avoid reaching arm movements, obstructing head position tracking (EyeLink II) or the remote eye-tracking camera (EyeLink 1000). At each level of the task (four or eight boxes), participants completed four token sets where a full set of either four or eight reward tokens had to be found. Between token sets, the color and spatial distribution of boxes and tokens was pseudorandomly varied.

As in the original task, errors were defined as either WSEs, when a box was reclicked having already been selected during the current token search, or BSEs, when a box was selected where a token had already been found before in the current set. A simple measure of strategy was derived based on that described by Owen et al. (1997): For each set of token searches, the box that was most often chosen as the first box to be clicked on in a token search was identified, and the total number of searches commencing at the preferred starting box was summed to give the "strategy score."

Participants

Twelve young control (YC) participants (mean age = 22.7 years, SD = 1.6 years; eight women) performed four sets each of the four- and eight-box versions of the task.

Eye Movement Recording

Eye movements were recorded using a helmet-mounted EyeLink II eye tracker located at the University of Exeter (SR Research Ltd.), configured to operate in combined corneal reflex and pupil-tracking mode. Participants were instructed to find a comfortable operating position for the computer mouse and to keep head movements to a minimum during performance of the task. Continuous recordings were taken during performance of the task, and fixation coordinates were outputted to a results file, along with timings of task events (Figure 1A). A separate behavioral results file recorded details of box selections. For five of the participants, eye movement recordings were not deemed of sufficient quality due to loss of calibration, head band slippage, or excessive interference of eye blink artifacts in either the four- or eight-box condition or both. Good records were obtained for eight participants in the four-box condition and nine in the eight-box condition. For six YC participants, good eye movement recordings were obtained in both the four- and eight-box conditions.

Eye Movement Analysis

DataViewer software (SR Research Ltd.) was used to parse the gaze position data into periods of saccades and fixation (based on an eye rotational velocity criterion of 30°/sec combined with a rotational acceleration criterion of 3000°/sec^2). Fixations are defined as the periods in between saccades when the eye is stationary, whereas saccades are the rapid shifts in eye position that occur between fixation. As vision is actively suppressed during saccades (Volkmann, Schick, & Riggs, 1969), the spatial and temporal distributions of fixations are typically the focus of studies that measure eye movements to investigate cognitive processing. DataViewer was also used

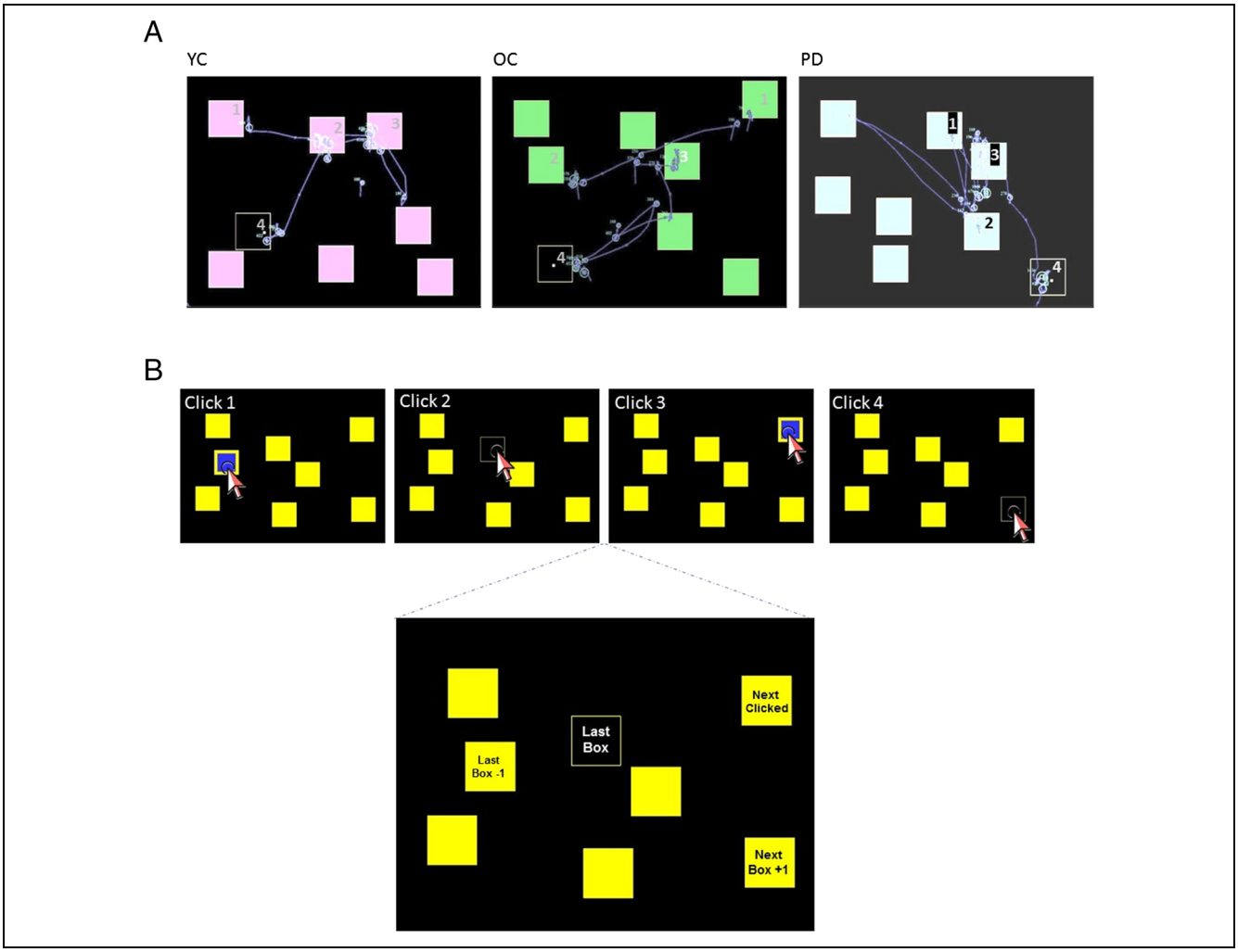

Figure 1. (A) Examples of typical eye movement scan paths for a YC, an OC, and a patient with PD in the SWM task (the location of the four consecutive box selections during the same period are numbered 1–4). (B) Schematic illustrating the approach taken to analyzing retrospective and prospective planning fixations, showing how fixations falling on the labeled boxes would be classified at the time point between mouse Clicks 2 and 3 given the example sequence of four-box selections shown.

to visualize eye movements and fixations for each set and participant via an eye position plot superimposed over an image of the array of boxes and video playback of the recorded eye movement sequence merged with a video of the sequence of box selections as seen by the participant (Figure 1A and video[2]). This was done to check that the recording was free from major artifacts and calibration errors (such as vertical position offset, which can arise from slippage of the EyeLink II helmet). The first token set for each participant was treated as practice and was excluded from the analysis. Each box location in the task was defined as an area of interest within DataViewer, and fixations were classified according to which was the nearest area of interest. Multiple consecutive fixations separated by small amplitude saccades within the same box were treated as a single "compound" fixation for the sake of subsequent analysis. Custom-written MATLAB and SPSS syntax scripts were then used to further process the resulting fixation output reports generated by DataViewer with respect to the box selection event sequence captured by Experiment Builder.

Basic measures of eye movement characteristics were derived for each condition and participant. These were total number of fixations, mean duration of each fixation (fixation duration), and saccade amplitude (size) for eye movements between fixations.

Fixations were classified as "refixations" if a return saccade was made to a box that had already been fixated within the same period between any two consecutive box selections.

In the highest level of the analysis, fixations were classified as "prospective" or "retrospective" (Figure 1B), according to whether the box fixated fell into one or more of the following task-related classifications:

- "Clicked/Not Clicked": Fixations on boxes that had been searched with a mouse click to reveal its contents or not during a single token search;

- "Token Found/Token Not Found": Fixations on boxes where a token had already been found or not on a preceding search in the same token set;
- "Last Box Clicked"/"Last Box − 1 Clicked": Fixations on boxes that were either the box most recently clicked or had been searched one click earlier;
- "Next Box Clicked"/"Next Box + 1 Clicked" Fixation on boxes that were prospectively searched either as the next box to be selected or after one intervening box click.

The percentage of fixations that corresponded to each of these categories was calculated for each participant and task difficulty level. Fixations coincident or immediately following the mouse click, which revealed the contents of a box, were excluded from this analysis, which only considered fixations following the first and subsequent saccade away from the most recently clicked box.

Results

WSEs, BSEs, and Strategy Score

For WSEs, a mean of only 0.25 errors per participant were made in the four-box condition and 0.2 errors in the eight-box condition. These error rates were so low that they were not analyzed further. No BSEs were recorded in the four-box task, but an average of 5.25 BSEs per participant were made in the eight-box condition.

Strategy score varied significantly between the four- and eight-box conditions, $F(1, 10) = 6.68$, $p = .027$. An average of 50% of four-box searches started from the same box, whereas only 42% of eight-box searches started from a common location.

Basic Eye Movement Measures

On average, each participant executed 16 and 63 discrete shifts in fixations per token set in the four- and eight-box task, respectively (four-box vs. eight-box paired comparison t test: $t(5) = 7.25$, $p < .001$), but neither the mean duration of each fixation ($t(5) = 0.347$, *ns*) nor the mean amplitude (size) of saccades ($t(5) = 0.08$, *ns*) varied significantly between the four- and eight-box conditions. Twenty-four percent of all fixations were classified as refixations, where the box had already been fixated during the same period between consecutive box selections. The rate of refixations as a proportion of all fixations was not significantly different between the four- and eight-box conditions (four-box: $M = 25.4$, $SE = 0.04$; eight-box: $M = 23.3$, $SE = 0.04$; $t = 0.38$, *ns*).

Fixations on Previously Selected Boxes

Fixations were rarely directed toward boxes that had already been selected with a mouse click during the current token search (main effect of box type Clicked/Not Clicked: $F(1, 5) = 614.69$, $p < .0001$), but there was a significant interaction between Clicked/Not Clicked and difficulty, such that more fixations on previously Clicked boxes occurred in the eight-box version compared with the four-box version ($F(1, 5) = 7.08$, $p < .05$; % of all fixations; four-box, Clicked: $M = 4.3$, $SE = 2$, Not Clicked: $M = 95.7$, $SE = 2$; eight-box, Clicked: $M = 10.4$, $SE = 2$, Not Clicked: $M = 88.5$, $SE = 2$).

A similar analysis examined fixations on locations where a token had been found before or not. There was no difference in the percentage of fixations landing on Token Found compared with Token Not Found for either condition ($F(1, 5) = 0.11$, *ns*), nor was there any interaction between difficulty and Token Found/Token Not Found ($F(1, 5) = 0.14$, *ns*; four-box, Token Found: $M = 28.0$, $SE = 10\%$, Token Not Found: $M = 21.8$, $SE = 4$; eight-box, Token Found: $M = 23.0$, $SE = 3.96$, Token Not Found: $M = 26.17$, $SE = 3.91$).

Prospective and Retrospective Fixations

Two-way ANOVAs with Difficulty (four-/eight-box) and Prospective/retrospective box type (Last Box − 1 Clicked, Last Box Clicked, Next Box Clicked, Next Box + 1 Clicked) as factors were used to analyze differences in the proportion of fixations according to their relevance to past, future, and current mouse clicks (see Experiment 1: Methods: Eye Movement Analysis above).

This showed a main effect of Difficulty, $F(1, 5) = 48.48$, $p < .001$, Box type, $F(3, 15) = 144.49$, $p < .001$, and interaction of Difficulty × Box Type, $F(3, 15) = 6.95$, $p = .004$. For all participants, the largest number of fixations was found to be directed toward the Next Box Clicked (Figure 2), that is, the target of the upcoming mouse selection.

Expected Probability Analysis

This analysis was carried out to determine if fixations on boxes that had recently been selected or were to be selected in the future occurred at a rate higher than expected by chance. For each participant, the expected probability of fixations occurring by chance on boxes other than the immediately Next Box Clicked was determined by dividing observed probability of fixations landing on any other box type by the total number of boxes − 1 (i.e., the number of boxes left over after excluding the Next Box Clicked):

$$\mathrm{Exp}_{(\text{Not Next Clicked})} = \left(1 - P_{(\text{Next Clicked})}\right)/(N-1)$$

The mean expected probability in each condition determined in this manner is indicated for each condition by the dashed lines shown in Figure 2. Paired-samples t tests were carried out between the observed and expected probabilities to determine whether fixations occurred at rates higher than expected by chance on the different categories of boxes.

This analysis showed that, in the four-box condition, fixations on the Last Box Clicked were significantly lower than predicted by chance ($t = -2.65$, $df = 7$, $p = .033$),

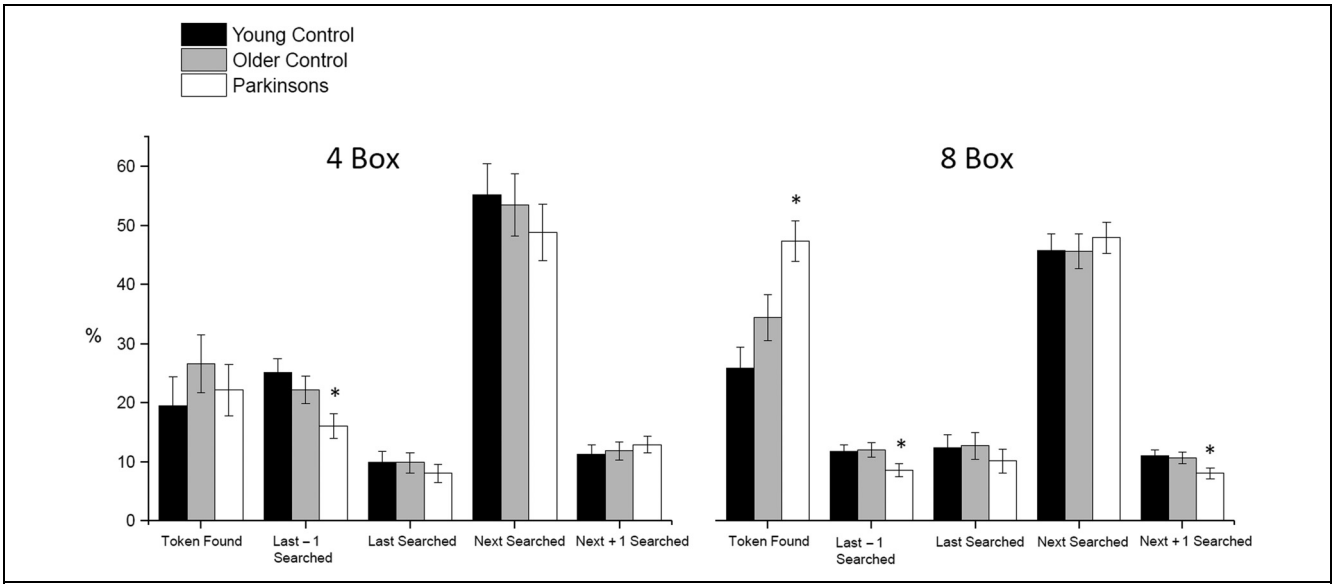

Figure 2. Prospective and retrospective planning fixations in patients and control participants during performance of the SWM task. *$p < .05$ between patients with PD and controls. Dashed line indicates mean expected probability of fixation given a random distribution of fixations across all boxes (excluding the Next Box Clicked).

whereas fixations on the Last Box − 1 Clicked were significantly more common than chance ($t = 2.93$, $df = 7$, $p = .022$). For the eight-box condition, fixations on the Last Box Clicked, Last Box − 1 Clicked, and Next Box + 1 Clicked were all significantly more likely than predicted by a random model ($t = 4.05$, $df = 8$, $p = .005$; $t = 3.68$, $df = 8$, $p = .006$; and $t = 3.88$, $df = 8$, $p = .005$, respectively; Figure 2).

Correlations between Eye Movements and Performance

A final analysis examined whether there was a relationship between eye movements and overall performance as indexed by BSEs. As BSEs were zero for all participants in the four-box task, this analysis was based on performance in the eight-box task only, although cross-condition correlations between the distribution of fixations in the four-box task and BSEs in the eight-box were explored.

There was a correlation between eye movements in the four-box condition and BSEs in the eight-box version of the task. The total number of fixations in the four-box task was found to correlate with the number of BSEs in the eight-box task ($r = .94$, $p = .001$). Furthermore, the proportion of all fixations that were directed toward Token Found boxes in the four-box task also correlated strongly with the number of BSEs in the eight-box task ($r = .80$, $p < .017$; Figure 3A).

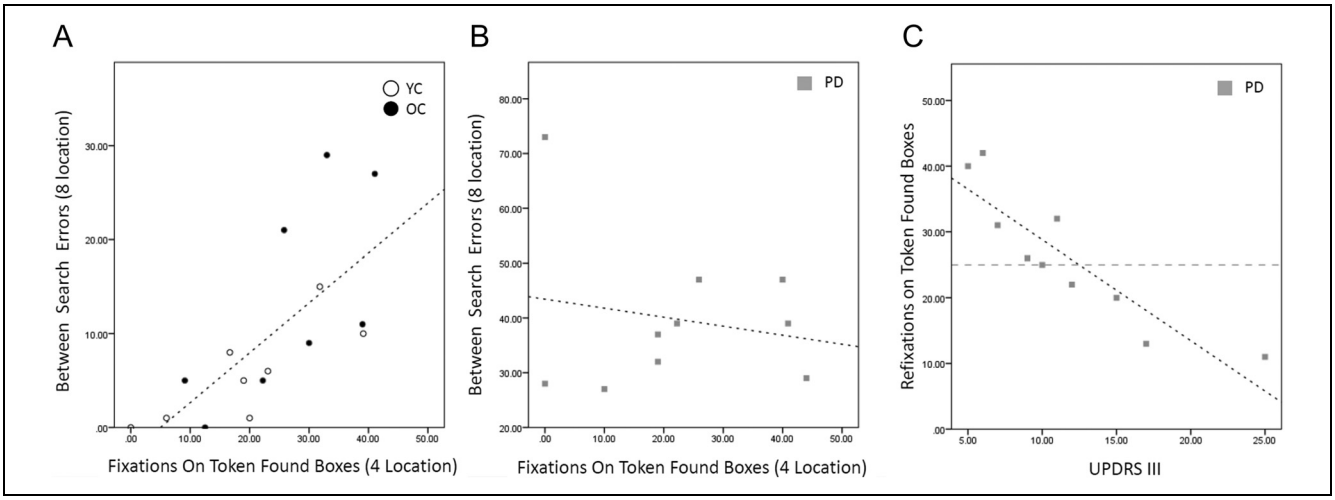

Figure 3. (A) Scatter plot illustrating correlation between Token Found box fixations in the four-box task and BSEs in the eight-box condition for young (YC) and older (OC) healthy participants. (B) Correlation between Token Found fixations in the four-box task and BSEs in the eight-box condition for participants with PD. (C) Negative correlation between PD severity (UPDRS III) and refixations on Token Found boxes.

There was no significant correlation between fixations on Token Found locations and BSEs within the eight-box condition. All correlations relating to retrospective and prospective fixations and BSEs within the eight-box condition were also found to be nonsignificant ($p = .37$ or greater).

Discussion

The pattern of eye movements made by healthy participants in the SWM task is consistent with a role for fixational eye movements in processes of cognitive planning and memory rehearsal in the SWM. The next box to be selected was the most commonly fixated box and accounted for around 50% of all fixations, and boxes that had already been clicked on in the current token search were found to be rarely fixated, indicating that eye movements were strongly guided by memory for past box selections. However, fixations on boxes that ended up being selected one mouse click into the future or had been clicked on one or two selections back in the past were also more likely to be fixated than would be expected by chance.

A potential criticism of this analysis of eye movements and prospective/retrospective planning is that boxes that had recently been clicked upon were also often selected one or two clicks into the future. This is particularly the case in the four-box version where tokens are typically found within two or three box selections. This may explain why fixations on the Last Box − 1 Clicked were so frequent (Figure 2), as fixations falling into this category might reflect both rehearsal of recent box selections and planning of future selections. However, this inevitable overlap between planning ahead and rehearsal of the search path does not affect the conclusion that eye movements may be important in strategic planning, although their relative importance in planning ahead and keeping track cannot be determined.

A very interesting finding of Experiment 1 was that the number of eye movements made in the four-box condition correlated with how well participants performed the eight-box condition (as defined by BSEs). The percentage of fixations directed specifically toward Token Found boxes in the four-box condition also predicted performance in the eight-box task. One possibility is that fixations on Token Found boxes reflect a weak memory trace for whether or not a token had been found at that location. Refixating boxes might actually help to refresh memory for whether or not a token has been found there before or not. Under low memory load, this compensatory strategy is effective such that BSEs are avoided in the four-box condition. However, under the higher memory load present in the eight-box condition, refixations are unable to adequately compensate for memory failures such that the box is reselected with a mouse click and a BSE is committed.

One aspect of the finding that runs against the suggestion that eye movements play an important role in the task is the absence of correlations between eye fixations and BSEs within the eight-box condition (as opposed to the correlations between the four- and eight-box tasks discussed above). It might be expected that increased strategic planning would lead to lower BSEs, but significant correlations with retrospective and prospective "planning" fixations were not found. One problem might be that performance of young healthy controls is generally high, and there is not enough variability in their performance to reveal such correlations. To investigate this, Experiment 2 recorded eye movement in older controls (OCs) and patients with mild to moderate PD during performance of the same task. Rather than reflecting a deficit in spatial memory, previous work has indicated that increased BSEs in the SWM task in PD are due to impairments in cognitive planning and strategy (Owen et al., 1992, 1997). If this were the case and eye movements truly reflected planning processes in the task, then patients should show reduced rates of fixations on previously selected and to be selected boxes.

EXPERIMENT 2

Methods

Participants

Eight OC participants (age $M = 67$ years, $SE = 6.4$ years) and 10 patients with mild to moderate idiopathic PD ($M = 68.5$ years, $SE = 9.5$ years) participated in the study. All patients with PD had taken dopaminergic medication at the time of the midmorning testing session. Six of the eight OCs were spouses of patients with PD. The majority of patients and OCs completed a forward/backward digit span task, the Mini-Mental State Examination, and the National Adult Reading Test. Statistical comparison of these test scores revealed no significant difference between OCs and patients with PD on any of the test scores. PD symptoms were assessed immediately before testing using both the United Parkinson Disease Rating Scale (UPDRS) III motor score and the Webster assessment (Webster, 1968). The Webster Scale is an older assessment scale with a question set closely aligned to the UPDRS III but has the advantage of also incorporating questions assessing quality of life and self-care as well as a Hoehn and Yahr (1967) rating. We have previously found Webster scores to correlate with cognitive and oculomotor performance measures (Hodgson, Sumner, Molyva, Sheridan, & Kennard, 2013; Ketcham, Hodgson, Kennard, & Stelmach, 2003). All participants reported that they were familiar with mouse cursor control and were confident in selecting boxes by clicking in this manner.

Task and Procedure

The task and procedure were as for Experiment 1, except for the following: Eye movements were recorded

using either the helmet-mounted EyeLink II eye tracker (University of Exeter) or a remote desktop camera-configured EyeLink 1000 eye tracker (University of Lincoln). The EyeLink II eye tracker utilizes infrared illuminated screen markers and a helmet-mounted camera to compensate for rotational head movements, whereas the EyeLink 1000 remote camera utilizes a target sticker placed on the participant's forehead to maintain eye tracking during small head movements. Both systems use the combined pupil and corneal reflex technique to track point of gaze (rather than eye position in head), which is robust to small translational movements of the head. Two patients with PD and two OCs were tested using the EyeLink II, and a further eight patients and six controls were tested with the EyeLink 1000. Before completing the SWM task, participants also completed four other tasks selected from a battery of oculomotor tests previously used to investigate cognitive control of eye movements in neurological patients (described in Hodgson et al., 2007, 2013). Patients with PD were assessed for PD symptomology (Webster/UPDRS III see above) at the start of the testing session. Pencil-and-paper assessments of cognitive function (Mini-Mental State Examination, National Adult Reading Test, digit span) were interleaved between eye movement tests. Good eye movement recordings were obtained for all participants in both the four- and eight-box conditions.

Results

WSEs, BSEs, and Strategy Scores

Fewer than one WSE per participant was made in the four-box condition for both groups, such that these errors were not analyzed further. There was no significant difference in BSEs between OCs and patients with PD in the four-box condition (OC vs. PD: $t = -0.24$, $df = 16$, $p = .814$), with patients with PD committing slightly fewer errors than OCs (means per participant per set: OC: $M = 0.65$ errors, PD: $M = 0.55$).

For the eight-box task, WSEs were increased for patients with PD compared with OCs ($t = 2.24$, $df = 16$, $p = .049$), and BSEs were also significantly increased for patients with PD versus OCs ($t = 5.72$, $df = 16$, $p < .001$; OCs: $M = 3.34$ errors per participant per set, PD: $M = 9.95$).

Strategy score was significantly higher in the four-box condition relative to the eight-box condition, $F(1, 16) = 43.65$, $p < .0001$, with more four-box condition searches starting from the same box location. However, there was no significant difference in strategy score between the OC and PD groups (OC: $M = 49\%$, $SE = 3.6\%$; PD: $M = 45\%$, $SE = 2.4\%$). OCs were found to have higher Strategy Scores relative to the YCs tested in Experiment 1 for the four-box search ($M = 57\%$ searches starting from same box, relative to $M = 50\%$ for YCs), but lower strategy scores compared with YCs in the eight-box condition ($M = 36\%$ relative to $M = 42\%$; interaction of Difficulty × Group: $F(1, 17) = 9.26$, $p = .007$).

Basic Eye Movement Measures

An average of 18 and 80 discrete shifts in fixations per set were recorded per participant in the four-and eight-box conditions, respectively. Between groups, t tests showed no significant difference due to group (OC vs. PD) in the total number of fixations recorded in the four- ($t = 1.143$, $df = 16$, $p = .27$) or eight-box conditions ($t = 0.484$, $p < .63$). Mean fixation durations also did not differ between groups for the four- ($t = 1.596$, $p = .13$) or eight-box conditions ($t = 0.484$, $p = .635$), neither did mean saccade amplitude (size) for the four- ($t = 0.623$, $p = .542$) or eight-box ($t = 0.75$, $p = .464$) conditions.

Refixations on Previously Clicked Boxes

As with YCs, most fixations made by OCs and patients with PD were directed toward locations that had not already been clicked upon in the current token search (four-box, Clicked: $M = 3.20$, $SE = 0.68$ fixations per participant, Not Clicked: $M = 49.1$, $SE = 2.5$, $F(1, 23) = 395.11$, $p < .0001$; eight-box, Clicked: $M = 34.37$, $SE = 7.1$, Not Clicked: $M = 189.1$, $SE = 12.86$, $F(1, 24) = 105.41$, $p < .0001$). However, there was no difference between participant groups (YC, OC, PD) in this respect for either difficulty condition (effect of group for the four-box, $F(2, 23) = 1.19$, and eight-box, $F(2, 24) = 0.53$, conditions). The number of refixations (where a box was fixated having been fixated during the same period between two mouse clicks) also did not differ between groups (four-box: $F(1, 23) = 0.612$, *ns*; eight-box: $F(1, 24) = 0.137$, *ns*).

For four-box searches, there was no difference in the percentage of fixations falling on Token Found boxes between groups (OC: $M = 26.6$, $SE = 4.88$; PD: $M = 22.10$, $SE = 4.4$), but for the eight-box condition, fixations on Token Found boxes were significantly increased for patients with PD compared with OCs and YCs ($F(2, 24) = 9.44$, $p = .001$; YC: $M = 25.8$, $SE = 9.43$; OC: $M = 34.4$, $SE = 13.2$; PD: $M = 47.4$, $SE = 10.1$; Figure 2). Comparison between OCs and YCs showed no significant difference in fixations on Token Found boxes ($t = -1.55$, $p = .141$; Figure 2).

Prospective and Retrospective Planning Fixations

Two-way ANOVAs with Participant group and Box (Last Box − 1 Clicked, Last Box Clicked, Next Box Clicked, Next Box + 1 Clicked) as factors were used to analyze differences in the proportion of fixations with respect to past and future mouse click selections.

As was the case in Experiment 1, the majority of fixations were directed to the Next Box Clicked, $F(5, 115) = 73.84$, $p < .0001$, with no significant interaction of Group × Box Type in the four-box condition, $F(10, 115) = 0.67$,

although between-group t tests showed that patients with PD made fewer fixations than controls on the Last Box − 1 Clicked (t = 3.18, df = 24, p = .004), whereas no differences were found based on age of controls (OC vs. YC: t = 0.74, p = .471).

The same analysis for the eight-box condition showed a significant main effect of Box type, $F(5, 120)$ = 149.8, $p < .0001$, and a significant interaction of Group × Box Type, $F(5, 120)$ = 5.026, $p < .0001$. Significant differences between patients and controls were apparent in the proportion of fixations landing on the Next Box + 1 Clicked (t = 2.07, df 25, p = .049) and Last Box − 1 Clicked (t = 2.38, df = 25, p = .047; Figure 2).

The expected probability analysis (see Experiment 1: Methods) confirmed the finding of Experiment 1 as OCs showed significantly more fixations on the Last Box − 1 Clicked (t = 3.23, df = 7, p = .015) and Next Box + 1 Clicked (t = 3.47, df = 7, p = .01) during the eight-box condition. However, for patients with PD, there were no significant differences in the observed number of fixations on boxes previously or to be selected compared with that expected by chance (Figure 2).

Correlations between fixations and overall performance (BSEs) Unlike Experiment 1, Experiment 2 also revealed correlations between prospective and retrospective "planning" fixations and BSEs. Fewer fixations on the Next Box + 1 Clicked (r = −.625, p = .006) and Last Box − 1 Clicked (r = −.601, p = .008) were associated with greater BSEs across participants (Figure 4). These correlations were also found to be highly significant when the data from Experiments 1 and 2 were combined (the Pearson's r correlation statistics for OCs, YCs and patients with PD combined are shown in Figure 4). To examine if these correlations were due purely to the differences between patients and controls, data from OCs and YCs (Experiment 1) were examined separately. This again showed negative correlations between BSEs and fixations on Last Box − 1 Clicked (r = .685, p = .045) as well as a significant positive correlation between BSEs and fixations on the Next Box Clicked (r = .563, p = .18).

OCs in Experiment 2 also showed the interesting cross-condition correlation between rates of fixation on Token Found boxes in the four-box task and BSEs in the eight-box condition previously found in Experiment 1 (r = .70, p = .054) and when OCs were combined with data from YCs this correlation was highly significant (r = .714, p = .0002; Figure 3A). However, the same correlation was absent when patients with PD were examined in isolation (r = −.191, p = .60; Figure 3B).

Correlations between PD severity, cognitive and eye movement measures UPDRS III and Webster scores were tested for correlations with BSEs as well as with measures derived from the eye movement analysis. As this involved 12 separate correlations between behavioral measures and disease severity, a Bonferroni-adjusted significance criteria was applied ($p < .004$; although in fact all correlations other than those reported below were nonsignificant at $p > .05$).

Both UPDRS and Webster scores were found to be negatively correlated with refixations (UPDRS: r = −.874, p = .001; Webster: r = −.903, p = .001). This correlation

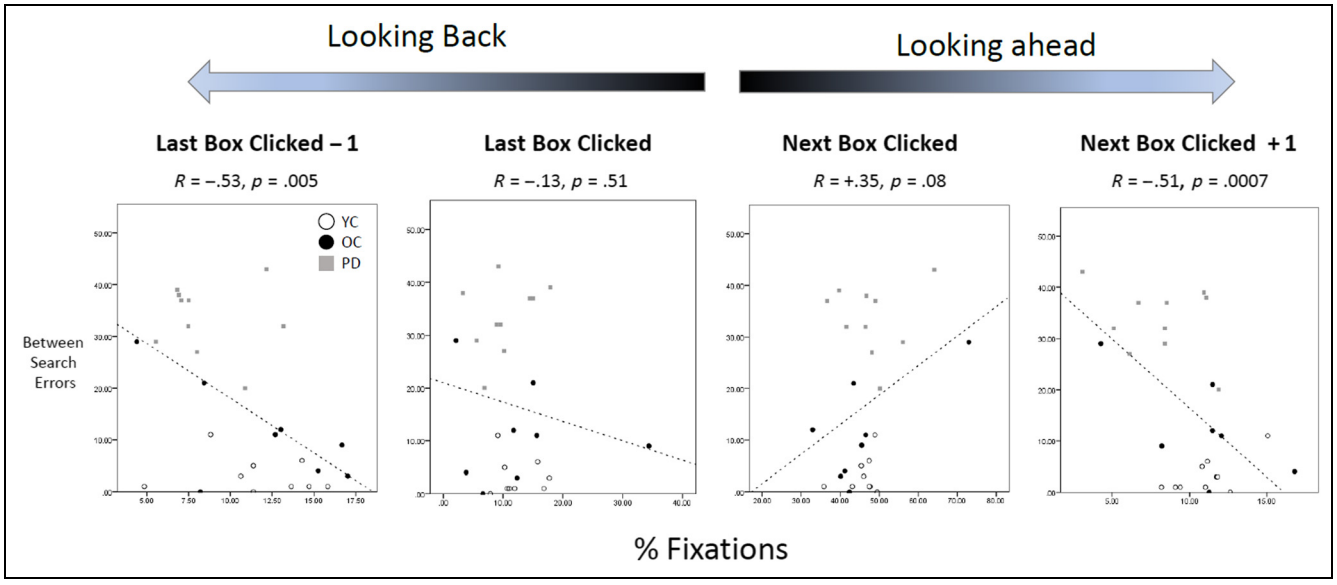

Figure 4. Correlations between BSEs and fixations on boxes, which were subsequently searched or previously selected with a mouse click for YCs, OCs, and participants with PD. Stronger correlations with performance (reduced BSEs) are seen for eye movements toward boxes farther ahead and back along the search path (Next Box + 1 Clicked and Last Box – 1 Clicked), compared with those more recently clicked or just about to be clicked (Last Box Clicked and Next Box Clicked), suggesting that eye fixations farther ahead and back along the search path are associated with better task performance.

was strongest for refixations on Token Found boxes ($r = -.895$, $p < .001$) but was also observed for refixations on No Token Found boxes ($r = -.796$, $p < .001$; Figure 4C).

GENERAL DISCUSSION

The aim of Experiment 2 was to replicate the findings of Experiment 1 in healthy older participants and also to test whether people with PD show differences in eye movements in the task reflective of a deficit in cognitive planning processes. The findings of Experiment 1 in YCs were replicated for older participants in Experiment 2. Fixations on boxes that had recently been selected or were to be selected further ahead along the search path occurred significantly above chance in OCs (Figure 2). Unlike Experiment 1, the rate of occurrence of prospective and retrospective planning fixations also correlated with task performance (as defined by BSEs), suggesting they play a functional role in the SWM task. Patients with PD also made significantly fewer of these "looking ahead" and "looking back" fixations compared with controls (Figure 2). Indeed, unlike controls, the frequency of such fixations in patients was not significantly above what would be expected in random scanning of the array of boxes. The findings are therefore consistent with eye movements playing a role in cognitive planning as well as an impairment in this mechanism in PD.

The cross-condition correlation between eye movements in the four-box task and BSEs in the eight-box condition was also replicated in Experiment 2. The proportion of fixations directed toward Token Found boxes in the four-box condition was found to predict BSEs in the eight-box condition (Figure 3A). An interesting explanation for this relationship is that fixations on Token Found locations might reflect partial forgetting of the box contents. Fixating a box may help facilitate recall for whether or not a box has been searched by reactivating/refreshing a memory for what the contents of the box were. Consistent with this idea, recent research has shown that visuospatial information is more accurately recalled for locations that are the target of an eye movement (Ma, Husain, & Bays, 2014; Bays & Husain, 2008). There is also evidence that maintaining memory for visuospatial location benefits from activation of oculomotor representations (Pearson et al., 2014) and that maintaining retinotopic correspondence between fixation and remembered locations supports recall (Martin et al., 2017; Patt et al., 2014).

Interestingly, patients with PD did not show the same relationship between fixations on Token Found locations in the four-box condition and BSEs in the eight-box task (Figure 3B). This could be seen as consistent with the idea that BSEs in patients with PD are not due to a deficit visuospatial memory per se but arise from deficits in cognitive planning. Variation in performance in healthy individuals may be more reflective of better/poorer visuospatial memory representations across different participants, and this is apparent as variation in the rates of compensatory fixations on Token Found boxes as well as BSEs. But in patients with PD, the analysis of eye fixations reported here along with previous work suggest that impaired performance arises from difficulties in strategic planning, rather than deficits in visuospatial memory representations (Owen et al., 1990, 1992, 1997).

PD severity was found to correlate with the rates of refixations of boxes within a token search period (i.e., refixations in this case refer to where a box was refixated during a period between two consecutive mouse clicks). This relationship was found to be particularly strong when refixations on Token Found boxes were examined in isolation (Figure 3C). Studies of visual search have linked refixations with failures to remember locations that have already been searched (Shen, McIntosh, & Ryan, 2014; Hollingworth & Luck, 2009; Husain et al., 2001; Gilchrist & Harvey, 2000), as well as attentional processes including mechanisms of inhibition of return, whereby attention and eye movements are normally inhibited toward recently attended locations (Klein & MacInnes, 1999).

The direction of the correlation between disease severity and refixations in this study was surprising as more severely affected patients showed lower rates of refixation compared with controls, whereas higher rates of refixation were found in patients with lower UPDRS scores (Figure 3C). However, this pattern can be seen as consistent with the hypothesized dual action of dopaminergic medication in ameliorating motoric function via its effect on the putamen while simultaneously "overdosing" cognitive and attentional circuits linking the pFC and striatum (Rowe et al., 2008). This leads to an "inverted U"-shaped relationship between prefrontal dopamine levels and working memory function (Fallon et al., 2015; Williams & Goldman-Rakic, 1995). In the case of refixations, too much dopamine in the prefrontal cortex (due to a medication overdose effect in mildly affected patients) might lead to a reduced suppression of return saccades leading to increased refixation rates. In contrast, too little dopamine within the same centers in some patients (at levels too low to be fully compensated for by medication) might evoke abnormally high levels of inhibition and significantly fewer refixations compared with controls.

Other work has shown differences between patients with PD and healthy controls in oculomotor tasks where participants are instructed to make a single saccade or a sequence of saccades to visual targets or a memorized target location. Although saccades made directly to visual stimuli are usually found to be of normal amplitude and response latency in PD, saccades made toward memorized locations or locations defined by a stimulus–response rule are found to be of reduced amplitude (Hodgson et al., 1999, 2013; Lueck, Tanyeri, Crawford, Henderson, & Kennard, 1990; Crawford, Henderson, & Kennard, 1989). This is consistent with a role for the caudate nucleus as a conduit for cognitive to motor transformations whereby spatially defined goals represented

within the pFC are converted into goals for spatiomotor action (Ketcham et al., 2003; Postle & D'Esposito, 1999). Many studies have also reported increased error rates in the antisaccade task, for which a saccade must be executed away from a target onset, suggesting impaired inhibitory control of saccades in PD (Antoniades, Demeyere, Kennard, Humphreys, & Hu, 2015; van Konningsbruggen, Pender, Machado, & Rafal, 2009; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Briand, Strallow, Hening, Poizner, & Sereno, 1999). These findings prompt the question as to how performance of patients with PD on classical eye movement tasks might relate to the pattern of spontaneous eye movements observed in patients in the SWM task.

Although saccades made under memory-guided conditions have been shown to be hypometric in PD (Hodgson et al., 1999, 2013; Lueck et al., 1990, 1992; Crawford et al., 1989), we found no difference in the amplitude of saccades between patients and controls in the SWM task. However, the majority of fixations and saccades in both patients and controls during the SWM task were found to be directed toward locations that had not been recently clicked. Therefore, eye movements in the SWM task are not memory-guided in the same sense as they are in the classical memory-guided saccade test as eye movements need to be directed away from, rather than toward, remembered locations in the SWM task. Previously reported deficits in the antisaccade task in PD could also be seen as consistent with eye movements in the SWM task. Increased refixations in mild medicated patients (see Figure 3C and discussion above) as well as increased fixations on Token Found locations (Figure 2) may be interpreted as failures to suppress saccades back toward salient or memorized spatial locations, similar to the failures to inhibit stimulus-driven saccades in the classical antisaccade task. Viewing things in this way, apparent cognitive deficits in PD might be characterized as impairments in high-level oculomotor control.

Finally, as well as being of pure interest with respect to understanding the role of eye movements in cognitive tasks, the present findings may have potential implications for improving the assessment of cognitive function in neurological and psychiatric disorders. Measures derived from fixational eye movements in the SWM may turn out to be more sensitive metrics for discriminating between diagnostic groups than BSEs and strategy score on their own. Key eye movement measures that our study suggests might be useful to examine in the future with respect to this possibility would be prospective and retrospective planning fixations (i.e., looking ahead and looking back along the search path) and rates of fixation and refixation on boxes where a token has been found.

Summary and Conclusions

Performance of a widely used test of SWM and executive function was found to be associated with a complex pattern of gaze-shifting eye movements in healthy participants and patients with PD. Rather than being random, fixational eye movements in the SWM task appear to reflect advanced planning and retrospective rehearsal of the path taken to find the hidden tokens. Fixations on locations where a token had been found are associated with more memory errors in the task. Patients with PD also showed significantly less looking ahead and looking back along the search path in the task. The findings contribute toward an accumulating body of evidence indicating that eye tracking has potential for enhancing the assessment of neurological and cognitive dysfunction.

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Notes

1. CANTAB [Cognitive assessment software]. Cambridge Cognition (2017). All rights reserved. www.cantab.com.
2. Video available at https://www.youtube.com/watch?v=PStfmW6q_c0.

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