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Dissociating cognitive deficits involved in voluntary eye movement dysfunctions in Parkinson's disease patients

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Abstract

In an attempt to distinguish and define the altered cognitive processes associated with Parkinson's disease (PD), we examine and try to dissociate the components of an effective voluntary saccade: (1) the planning and execution of a voluntary saccade; (2) the suppression of reflexive eye movements; and (3) the working memory processes required. We tested 14 PD patients (off their medications) and 11 control subjects on antisaccade (AS), delayed antisaccade (DAS), and remembered antisaccade (RAS) paradigms. The three tasks required identical responses, each task only differing in a single manipulation for direct comparison – a delay period was added in the DAS, and the target was removed during the delay period of the RAS – allowing us to study the specific cognitive processes involved in the execution of a voluntary saccade. Voluntary saccade response times were longer in the PD group compared to controls on all three tasks, suggesting difficulties in voluntary saccade execution. Furthermore, PD patients showed difficulty suppressing reflexive saccades (increased number of errors in the AS task and increased number of disinhibitions in the DAS task). Finally, our study did not show significant differences in either response time or error rate between the RAS and the DAS tasks for either control subjects or PD patients. In sum, we report evidence for voluntary saccade execution deficits together with problems inhibiting reflexive saccades in Parkinson's disease patients. These findings were correlated with each other and disease severity, suggesting that eye movement measurement may be a useful tool for studying higher cognitive function.

Keywords: Endogenous; Antisaccade; Saccade inhibition; Working memory; Cognitive

1. Introduction

Anatomical and functional studies of the human brain support the idea of a voluntary system that not only programs and controls willed or purposeful actions, but also controls and modulates reflexive movements (Hikosaka, Takikawa, & Kawagoe, 2000; Mink, 1996; Sereno, 1992). Accordingly, over the last 30 years, studies have shown that Parkinson's disease (PD) patients are impaired in controlling voluntary or planned movements (Briand, Strallow, Hening, Poizner, & Sereno, 1999; De Jong & Jones, 1971; Shaunak et al., 1999), and recent studies have shown that PD patients exhibit normal or better performance when reflexive movements are required (Briand, Hening, Poizner, & Sereno, 2001), as elicited in a prosaccade task. The voluntary system is thought to critically involve prefrontal areas, including areas that imaging studies have shown to be hypoactive in PD patients (e.g., Playford et al., 1992). Additionally, on clinical measures that are thought to reflect frontal lobe function, such as scanpath tests, PD patients have impaired performance (Kennard, 2002). Further, some models such as the tonic inhibition model (Sereno, 1992) suggest that, with respect to orienting, a dysfunction of prefrontal areas (as seen in schizophrenia, autism, ADHD, PD) would release reflexive areas (e.g., superior colliculus) from a tonic inhibition, resulting in hyper-reflexive responding.

The antisaccade task (AS) is commonly used in PD patients to evaluate voluntary eye movement processing. In this task, the patient is asked to fixate a central spot until a peripheral target is presented (to the left or right of the fixation point) and then to make an eye movement to the mirror position in the opposite visual field. This differs from the prosaccade task (PS), where the correct response is to look at the target. Several studies report

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that PD patients, when compared to controls, show slower eye movements and increased number of errors (eye movements to the target) in the AS task, and that later stage patients can have increased deficits (Kitagawa, Fukushima, & Tashiro, 1994). The AS task requires three processes: (1) the programming of a voluntary saccade to the opposite side of the target; (2) the inhibition of a reflexive saccade to the target; and (3) the working memory recollection of the specific instructions (to look opposite) before producing the eye movement (Everling & Fischer, 1998; Hallett, 1978). The commonly observed deficits of PD patients in the AS task may be caused by deficits in any, or all three, of these cognitive processes.

The purpose of the present study is to examine performance of PD patients (versus controls) on three different eye movement tasks that each require an identical motor response to explicitly separate out and test performance on the different cognitive processes involved in producing a voluntary saccade. To evaluate *voluntary saccade generation*, we measure, primarily, the latency to generate the voluntary saccade in all three voluntary eye movement tasks. If PD deficits in the AS task are due solely to disinhibition of the reflexive system then, on trials when patients successfully inhibit an eye movement to the target, their antisaccade latency should not differ from the controls' latency. To evaluate the process of *reflexive saccade inhibition*, we introduce a delay in the typical antisaccade task before the eye movement response is required (delayed antisaccade; DAS). We measure, primarily, how many times the subjects break fixation during this delay (i.e., unable to suppress eye movements to the target) and, specifically, whether PD patients are more likely than controls to break fixation. Finally, to evaluate *working memory*, we compare performance on the DAS task with an identical remembered antisaccade (RAS) task that only differs in the duration of target presentation: in the DAS, the target remains present throughout the delay period, but in the RAS task, it is only briefly presented. Hence, in the RAS task, subjects must remember the location of the target over brief intervals in order to correctly program the eye movement to the opposite visual field.

Our battery of tasks is a much more comprehensive battery than other groups have used. For instance, previous studies have reported decreased performance on a delayed saccade (DS) or remembered saccade (RS) task when compared to a prosaccade (PS) task. Although the eye movement response appears identical, i.e., a prosaccade, the circuitry that is recruited to perform the tasks is vastly different. The PS is considered a reflexive task, but the DS and RS are considered voluntary tasks and require some differing cortical areas (Anderson et al., 1994; Mort et al., 2003). Other researchers have used the AS task instead of the PS task as a voluntary task with no delay. However, this comparison is also not carefully controlled because the AS and DS differ in the spatial congruence of sensory and motor activations which result in fundamentally different task demands. Two studies have used tasks (AS and DAS) similar to those in the present paper. In the first study, Armstrong, Chan, Riopelle, and Munoz (2002) tested PD patients, but did not directly compare their AS and DAS performance. In the second study, Reuter, Rakusan, and Kathmanna (2005) illustrated improved performance (decreased error rate) on the DAS task over the AS task for both schizophrenic patients and controls. In the present study, we directly compare performance of PD patients on an AS and a DAS task, expecting to find similar results as those found in schizophrenic patients. In addition, we are the first to add a third dimension (RAS) in an effort add clarity and depth to previous results.

In the present study, we test subjects on three tasks (AS, DAS, and RAS) that have the same visual target and require the same eye movement response, an antisaccade. The only difference between the three tasks is the addition of a delay period (DAS) and truncation of the cue duration (RAS), thus allowing direct comparisons, across tasks, of the effect of each manipulation under otherwise identical conditions. Our study, the first of its kind, tests for evidence of differences in voluntary eye movement generation, inhibition of reflexive eye movements, and working memory uncontaminated by non-parallel task demands.

2. Subjects and methods

2.1. Subjects

We examined 14 patients with moderate to advanced PD (eight males and six females) recruited from our movement disorders clinic. The patient group had a mean age of 60 years (range: 49–69 years), mean disease duration of 12 years (range: 2–25 years), mean Hoehn & Yahr of 3.62 (range: 2.5–5), and mean UPDRS of 85 (range: 45–121). Subjects were excluded from our study if they suffered from atypical Parkinsonism (due to trauma, brain tumor, infection, cerebrovascular disease, other known neurological disease, or to known drugs, chemicals, or toxins). They were also excluded if they had prominent oculomotor palsy, cerebellar signs, vocal cord paresis, orthostatic hypotension (<20 mmHg in mean arterial blood pressure standing), pyramidal tract signs, or amyotrophy. Subjects were not considered for the study if they had a history of substance abuse exceeding 5 years or if they scored less than 25/30 on the Mini Mental State Exam. No subjects suffering from dementia were included in the present study. Five patients had a previous pallidotomy (four unilateral, one bilateral). Careful analysis in the eye movement responses of these patients compared to those with no previous surgery history did not reveal any significant differences; therefore, all subjects were included in the patient group. Also, all findings reported here were significant without inclusion of these patients. The patients were tested while off their medication (not having any medications for the past 12 hours). Patients' data were compared to eleven matched control subjects (four males and eight females) with a mean age of 55 years (range: 44–70 years). All subjects gave informed consent before participating in the study, which was approved by the ethics committee of our institution and conducted in conformity with the Declaration of Helsinki.

2.2. Apparatus

The subjects sat 72 cm from a computer screen monitor and placed their head on a chin rest with their forehead against a restraint. The monitor screen covered a visual area of $25^\circ \times 18^\circ$ from this viewing distance. Subjects' eye movements were recorded using an ISCAN RK-426 eye tracking system, interfaced with an infrared-sensitive camera. Spatial resolution was approximately 0.5° of visual angle, while temporal resolution to detect saccades was set at 6 ms (180 Hz). At the beginning of the testing session, in order to calibrate the eye tracker, each subject was required to make eye movements to nine positions on the screen represented by $0.2^\circ \times 0.2^\circ$ white squares. For the three eye movement tasks, a light gray fixation point of 0.2° was shown against a black background, and target stimuli were $0.2^\circ \times 0.2^\circ$ white squares located 7° to the left and to the right of the fixation point. We used online velocity and areal criteria to determine saccade initiation and termination. Specifically, an eye movement had to be: (1)

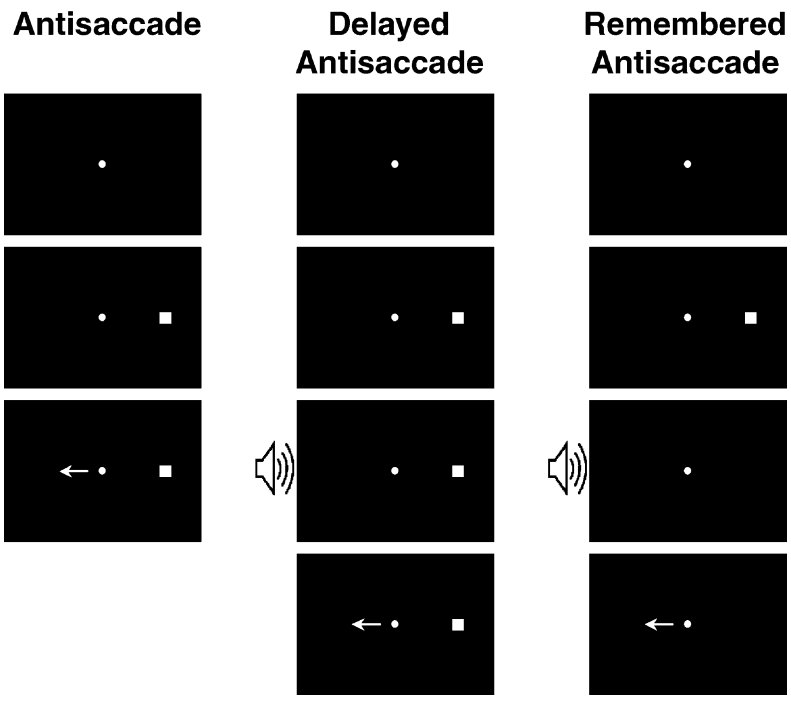

Fig. 1. Schematic representation of the stimulus sequences used in the three tasks (antisaccade, delayed antisaccade, and remembered antisaccade). The arrow represents the correct eye movement required.

above 120°/s for initiation, and (2) below 12°/s and within 4.4° of the target at termination of the saccade.[1]

2.3. Behavioral tasks

Three different eye movement tasks were given in the following order: antisaccade task (AS), delayed antisaccade task (DAS), and remembered antisaccade task (RAS), with 50 trials each (see Fig. 1). To reduce anticipatory eye movements, we used a variable fixation interval (400 or 800 ms) before the target onset. The target was presented in the left or right visual field in a random and balanced fashion.

In the AS task, the fixation point was presented to indicate the start of the trial. The patient had to maintain fixation during a variable period before target onset. The fixation point remained on throughout the trial. The target stimulus appeared 7° to the right or left of fixation requiring the patient to make an eye movement to the spatial position directly opposite to where the target appeared (Fig. 1). The DAS task varied from the AS task in that after the target presentation, the patient had to wait for a variable delay period (640–1440 ms) until a tone ("go" signal) indicated for the patient to execute the antisaccade. In the RAS task, the target was only briefly presented for 333 ms (unlike the DAS task, where the target stayed on throughout the delay), and the patient was required to remember the position of the target during the delay in order to make the correct antisaccade after the "go" signal (Fig. 1). Participants were given 5–10 practice trials before each task.

Outliers were not included in any of the data analyses and were defined as trials with response times less than 100 ms and greater than 900 ms with respect to the "go" signal (target onset in the AS task, auditory "go" signal in the DAS task and RAS). The percentages of outliers excluded from the analyses were 8.7% for the PD patients and 2.2% for the control subjects. Mean response time for all three tasks was then calculated by task and subject group across the remaining trials. Error rate in the AS task was defined as the number of eye movements directed to the target (errors) divided by all trials. Disinhibition rate in the DAS task was defined as the number of eye movements directed to the target during the delay period *before* the "go" signal divided by all trials. Error rate in the DAS and RAS tasks was defined as the number of eye movements directed to the target *after* the "go" signal divided by all trials less the number of trials that were disinhibitions:

$$\text{AS errors} = \frac{\text{number eye movements to target}}{\text{total number of trials}} \times 100$$

$$\text{DAS disinhibitions} = \frac{\text{number eye movements to target } \textit{during} \text{ delay}}{\text{total number of trials}} \times 100$$

$$\text{DAS and RAS errors} = \frac{\text{number eye movements to target } \textit{after} \text{ delay}}{\text{total number of trials} - \text{number disinhibitions}} \times 100$$

By comparing AS error rate to both DAS disinhibitions and DAS error rates, we determined whether most of the AS errors could be accounted for by a lack of inhibition of the reflexive saccade (DAS disinhibition rate) or whether the errors were due to difficulty with the execution of the voluntary saccade (DAS error rate). By comparing DAS and RAS response times and errors, we looked for significant differences in response time or error rate that could be attributed to the additional short-term memory requirement of the RAS task.

In order to measure differences in spatial accuracy between the patient group and the controls, gain was reported. Gain refers to the final amplitude of the first saccade (before any corrective eye movement) divided by the true amplitude of the target position. In this way, perfect responding would be a gain of 100%, while undershooting and overshooting the target would result in gains less than or more than 100%, respectively.

2.4. Statistical analyses

Response time, error rate, and gain were analyzed using a two-factor analysis of variance for repeated measures (ANOVA), with Group (PD and controls) as the between-group factor and Task (AS, DAS, and RAS) as the within-group factor. Percentage of errors was also compared to percentage of disinhibitions

[1] The velocity criterion used for detection of saccade initiation was higher than that typically found in the literature (30–50°/s). However, our criterion was optimal given our relatively slow sampling rate (180 Hz) and noise inherent in the ISCAN system, which resulted in random variation within about 0.5° from sample to sample. A lower criterion of 30°/s would correspond to an eye position shift of 0.17° between two consecutive samples at 180 Hz.

using a two-way ANOVA, with Group as the between-group factor and Task (AS errors, DAS errors, and DAS disinhibitions) as the within-group factor. Planned *t*-tests were used to test for within-group differences between task conditions. Pearson correlations were used to describe associations between performance and clinical variables. The significance level for all statistical tests was set to 0.05 (two-tailed).

3. Results

The group means and standard deviation for response time, error rate, disinhibition rate, and gain for each task are summarized in Table 1.

3.1. Response time

The ANOVA indicated significant main effects of Group ($F_{1,23} = 18.34$, $p < 0.001$) and Task ($F_{1,23} = 14.45$, $p < 0.001$). Respectively, these findings showed PD patients had significantly longer response times (486.7 ms) compared to the control group (373.4 ms), and the subjects' response time varied significantly among the different tasks: AS (510.2 ms), DAS (389.1 ms) and RAS (411.3 ms). There was not a significant interaction between Group and Task. Using the mean squared error value of 6757.7 from the two-way ANOVA, the following paired comparisons were calculated:

- *PD patients versus controls*. PD patients were significantly slower (more impaired) than controls in all three tasks (see Fig. 2): in the AS task, $t_{23} = 4.26$, $p < 0.001$ (572.2 ms versus 431.2 ms); in the DAS task, $t_{23} = 2.75$, $p < 0.009$ (429.1 ms versus 338.1 ms); and in the RAS task, $t_{23} = 3.26$, $p < 0.003$ (458.8 ms versus 350.9 ms).
- *Antisaccade versus delayed antisaccade task*. Both groups were significantly faster in the DAS task compared to the AS task: in the PD group, $t_{13} = 4.6$, $p < 0.001$ (429.1 ms versus 572.2 ms); and in the control group, $t_{10} = 2.53$, $p < 0.015$ (338.1 ms versus 431.2 ms). For AS and DAS task comparisons see left and middle bars in Fig. 2.
- *Delayed antisaccade versus remembered antisaccade task*. There was not a significant response time difference in the DAS task compared to the RAS task for either group: in the PD group, $t_{13} = 0.96$, $p > 0.3$ (429.1 ms versus 458.8 ms); and in the control group, $t_{10} = 0.35$, $p > 0.7$ (338.1 ms versus 350.9 ms). For DAS and RAS task comparisons see middle and right bars in Fig. 2.
- *Response time summary*. PD patients were significantly impaired (slow) compared to controls, but they performed significantly better on the DAS task than on the AS task.

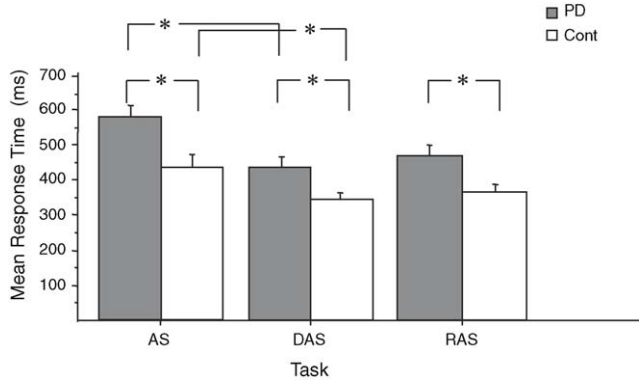

Fig. 2. Mean response time for the PD patients (filled bars) and controls (open bars) during the antisaccade (AS), delayed antisaccade (DAS), and remembered antisaccade (RAS) tasks. $^{*}p < 0.05$; error bars, S.E.M.

3.2. Error rate

The ANOVA showed main effects of Group ($F_{1,23} = 6.44$, $p < 0.02$) and Task ($F_{1,23} = 35.32$, $p < 0.001$). Respectively, these findings showed PD patients made more errors (16.4%) compared to the control group (7.0%), and the subjects' error rate varied significantly among the different tasks: AS (32.7%), DAS (1.9%), and RAS (2.3%). There was a significant Group by Task interaction ($F_{1,46} = 6.06$, $p < 0.005$). Using the mean squared error value of 197.3 from the two-way ANOVA, the following paired comparisons were calculated:

- *PD patients versus controls*. As shown in Fig. 3, PD patients made more errors than controls in the AS task, $t_{23} = 4.5$, $p < 0.001$ (43.9% versus 18.4%). In the DAS task as well as in the RAS task, the difference between patients and controls was not significant: in the DAS task, $t_{23} = 0.15$, $p > 0.88$ (2.3% versus 1.4%); and in the RAS task, $t_{23} = 0.33$, $p > 0.74$ (3.1% versus 1.3%).
- *Antisaccade versus delayed antisaccade task*. Both groups made fewer errors in the DAS compared to the AS (see Fig. 3): in the PD group, $t_{13} = 7.83$, $p < 0.001$ (2.3% versus 43.9%); and in the control group, $t_{10} = 2.83$, $p < 0.007$ (1.4% versus 18.4%).
- *Delayed antisaccade versus remembered antisaccade task*. There was not a significant difference in error rate in the DAS

Table 1
Group means of behavioral results

Measure	AS		DAS		RAS	
	Patient	Control	Patient	Control	Patient	Control
Response time (ms)	572.2 (108.9)	431.2 (113.8)	429.1 (106.8)	338.1 (70.4)	458.8 (77.4)	350.9 (69.9)
Error rate (%)	43.9 (28.2)	18.4 (20.3)	2.3 (3.0)	1.4 (1.6)	3.1 (3.3)	1.3 (1.6)
Disinhibition rate (%)	–	–	21.6 (15.6)	8.0 (10.7)	–	–
Timeouts (%)	3.1 (5.1)	5.8 (12.9)	1.6 (2.6)	0.6 (1.3)	3.2 (4.4)	0.4 (1.2)
Primary gain (%)	87.2 (27.0)	105.8 (13.2)	82.4 (23.6)	104.7 (18.5)	93.0 (34.9)	106.9 (19.4)

Values are the mean (S.D.) for the PD patient and control subject groups.

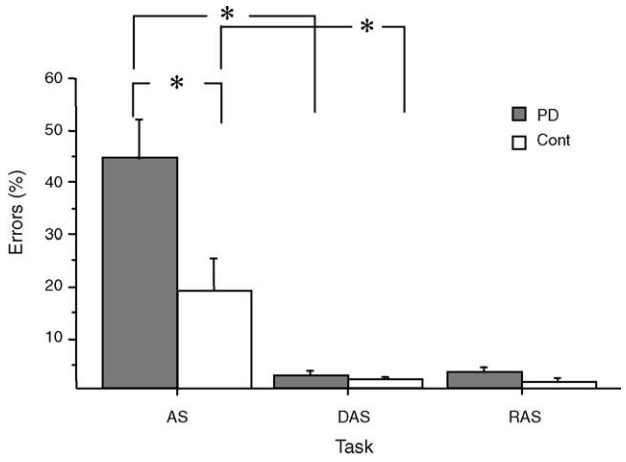

Fig. 3. Mean error rate for the PD patients (filled bars) and controls (open bars) during the antisaccade (AS), delayed antisaccade (DAS), and remembered antisaccade (RAS) tasks. $^{*}p<0.05$; error bars, S.E.M.

task compared to the RAS task for either group (see Fig. 3): in the PD group, $t_{13}=0.16$, $p>0.8$ (2.2% versus 3.1%); and in the control group, $t_{10}=0.03$, $p>0.9$ (1.4% versus 1.3%).

- *Error rate summary*. PD patients were significantly impaired (more errors than controls) on the AS task, but not on the DAS or RAS task.

3.3. Errors versus disinhibitions

A second ANOVA was done to compare the error rate in the AS task to the error rate and disinhibition rate in the DAS task, with Group as the between-group factor and Task (AS errors, DAS errors, and DAS disinhibitions) as the within-group factor (Fig. 4). Planned comparisons were made using the mean squared error value (183.2) of this ANOVA.

- *PD patients versus controls—disinhibitions*. PD patients' disinhibition rate was significantly higher than the controls', $t_{23}=2.5$, $p<0.02$ (21.6% versus 8.0%). This is illustrated by the middle bars in Fig. 4.
- *AS errors versus DAS disinhibitions and errors*. In PD patients, both the DAS disinhibition rate (21.6%) and the DAS error rate (2.3%) were significantly smaller than the AS error rate (43.9%) ($t_{13}=4.36$, $p<0.001$ and $t_{13}=8.13$, $p<0.001$, respectively; see Fig. 4). In control subjects, the DAS disinhibition rate (8.0%) was only marginally ($t_{10}=1.8$, $p>0.08$) smaller than the AS error rate (18.4%), whereas the DAS error rate (1.4%) was significantly lower ($t_{10}=2.94$, $p<0.005$) than the AS error rate.
- *Error and disinhibition summary*. PD patients performed significantly better (fewer errors) on the DAS task compared to the AS task, but they were still impaired compared to controls.

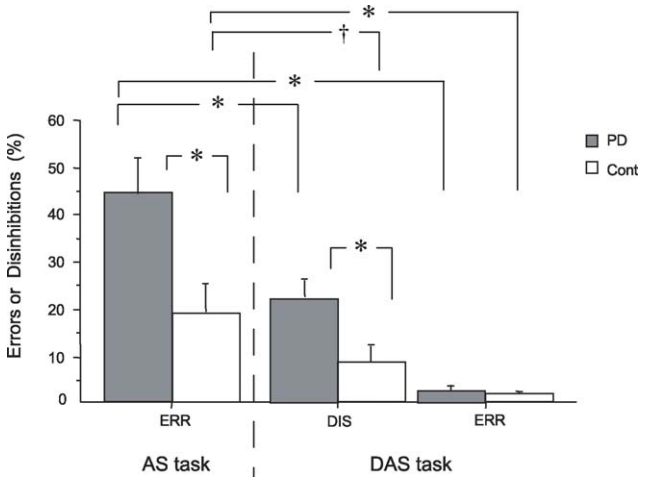

Fig. 4. Mean error rate (ERR) in the antisaccade (AS) task is compared to the mean error (ERR) and disinhibition (DIS) rates in the delayed antisaccade (DAS) task, for the PD patients (filled bars) and controls (open bars). $^{*}p<0.05$; $^{\dagger}p<0.08$; error bars, S.E.M.

3.4. Gain

The ANOVA of gain revealed no significant main effect of Task nor an interaction between Task and Group. There was a main effect of Group ($F_{1,23}=4.46$, $p<0.05$), signifying as a whole that the PD group significantly undershot the target compared to controls (87.5% versus 105.8%, average across all tasks). Further, compared to perfect amplitude (100%), the PD group significantly undershot the target on the DAS task ($t_{13}=2.8$, $p<0.02$; 82.4%) and had a similar trend on the AS task ($t_{13}=1.8$, $p<0.10$; 87.2%); the RAS task was not different from accurate amplitude ($t_{13}=0.75$, $p>0.47$; 93.0%). Based on parallel analyses, control subjects did not significantly overshoot the target.

- *PD patients versus controls*. Paired comparisons revealed the PD patients made responses with significantly lower amplitude compared to controls on each task: in the AS task, $t_{23}=5.8$, $p<0.001$ (87.2% versus 105.8%); in the DAS task, $t_{23}=6.9$, $p<0.001$ (82.4% versus 104.7%); and in the RAS task, $t_{23}=4.3$, $p<0.001$ (93.0% versus 106.9%).
- *Gain summary*. PD patients significantly undershot their responses to the target, whether it was visible or remembered.

3.5. Timeouts

The group means for percentage of timeouts (trials when a saccade was not generated in the time allowed) indicated a small, but highly variable percentage within both groups. There was a trend for a main effect of Task, $F_{1,23}=2.52$, $p<0.10$ (AS was 4.4%, DAS was 1.1%, and RAS was 1.8%) with no significant interaction. Follow-up analyses revealed no significant differences in performance between the three tasks and no significant difference between groups.

- *Timeouts summary*. PD patients did not differ from controls in percentage of non-response trials.

3.6. Correlations

Looking for associations between performance variables (response time, error rate, and disinhibition rate) in the PD

patients, we found a positive correlation between AS error rate and DAS disinhibition rate ($r_{12} = 0.95$, $p < 0.01$), a negative correlation between AS error rate and AS response time ($r_{12} = -0.73$, $p < 0.05$), and a positive correlation between AS error rate and RAS error rate ($r_{12} = 0.69$, $p < 0.05$). We also searched for associations between performance variables and clinical variables (Hoehn & Yahr stage and UPDRS Total score) and found that both AS error rate and DAS disinhibition rate positively correlated with Hoehn & Yahr scores ($r_{12} = 0.68$, $p < 0.05$ for AS errors; and $r_{12} = 0.67$, $p < 0.01$ for DAS disinhibitions).

- *Correlations summary*. Measures of voluntary saccade errors correlate between the tasks and with clinical measures of disease state.

4. Discussion

In the present study, patients with Parkinson's disease (PD) as well as controls performed antisaccade tasks that required the execution of a voluntary eye movement immediately after the onset of the target (antisaccade task; AS) or after a brief delay (delayed antisaccade task; DAS). Both groups of subjects were also tested on a modified delayed antisaccade task that assessed working memory (remembered antisaccade task; RAS). Comparison between these tasks was made with the intention of separating and evaluating the different cognitive processes thought to critically involve prefrontal cortex involved in the correct execution of an antisaccade in PD patients.

4.1. Voluntary saccade generation

Our PD patients had significantly longer latencies than controls to generate a correct eye movement on the AS (572.2 ms versus 431.2 ms), DAS (429.1 ms versus 338.1 ms) and RAS (458.8 ms versus 350.9 ms) tasks. Hence in all three tasks, PD patients were slower to execute voluntary eye movements, suggesting an intrinsic problem in voluntary saccade execution.

In addition, we showed that PD patients have difficulty generating voluntary saccades. Specifically, PD patients showed greater difficulty making the correct voluntary eye movement (43.9% versus 18.4% errors) on the AS task when compared to controls. However, on the DAS task, where the process of voluntary saccade generation was measured by error rate, PD patients were statistically normal compared to controls (2.3% versus 1.4% errors). Further, there was a significant decrease in errors on the DAS task compared to AS performance for both PD patients and control subjects. Reuter and colleagues (2005) found a similar pattern (improved performance on the DAS compared to the AS task) in patients with schizophrenia, who also demonstrate hypoactivity in the frontal cortex.

4.2. Reflexive saccade inhibition

Our results indicate PD patients' errors on the AS task are probably primarily due to an inability to inhibit a reflexive saccade. The PD patients show deficits in the control of unwanted reflexive saccades, as observed in the increased disinhibition rate compared to controls (21.6% versus 8.0% disinhibitions) in the DAS task. In other words, in the DAS task, PD patients were significantly less likely than control subjects to stay at fixation and wait for the go signal. This result is in agreement with the findings of Rafal, McGrath, Machador, and Hindle (2004) that show a lack of inhibition in a voluntary (verbal cue) prosaccade task in Parkinson's disease patients. Our findings are also supported by those of Armstrong and colleagues (2002) who concluded PD patients, compared to controls, were less able to inhibit reflexive responses (increased disinhibitions) on a mixed delayed prosaccade and delayed antisaccade task.

Further, we found that on trials when the PD patients were successfully able to stay at fixation during the delay period, the antisaccades were then correctly performed in most trials (2.3% errors), with no difference from the control subjects' error rate (1.4% errors). This suggests that differences in AS error rates between PD and control subjects may be primarily due to PD patients' inability to inhibit reflexive saccades to sudden target onsets rather than an inability to generate the voluntary saccade opposite to the target. That is, the majority of eye movements to the target in the DAS task by PD patients were caused by disinhibitions (90%) during the delay period and not errors (10%) after the delay period. Further, in both PD and control groups, the disinhibition rate plus error rate in the DAS task (totals: 23.8% in PD and 9.4% in control subjects) was smaller than error rates in the AS task (43.9% in PD and 18.4% in controls). These findings suggest that there are important differences between the two tasks that make the DAS task an easier task. In particular, the enhanced performance in the DAS task may be due to the fact that the delay allows the target to serve as a voluntary spatial attentional cue for the upcoming response; voluntary attentional cues have been shown to facilitate voluntary eye movements such as antisaccades (Seidlits, Reza, Briand, & Sereno, 2003).

4.3. How are these processes related?

Our results suggest that there is an interrelation or dependency between the processes of reflexive saccade inhibition and voluntary saccade generation because, if the two processes were functionally independent, no difference should be observed when they are required simultaneously (in the AS task) and when required separately (in the DAS task). In the present study, the separation of these two processes in the DAS task facilitated the successful execution of the voluntary saccade, as shown by decreased errors in both patients and controls in the DAS task compared to the AS task. Such a relation between reflexive and voluntary processing has been observed in different pathologies that involve frontal dysfunction, such as schizophrenia (Fukushima, Fukushima, Morita, & Yamashita, 1990; Fukushima et al., 1990b; Sereno & Holzman, 1995), PD (Briand et al., 1999; Crevits & De Ridder, 1997; Shaunak et al., 1999), autism (Goldberg et al., 2002; Minshew, Luna, & Sweeney, 1999), and ADHD (Munoz, Armstrong, Hampton, & Moore, 2003). In order to explain the interaction between these two processes, we have proposed a tonic inhibition model of orienting that suggests that the voluntary and reflexive sys-

tems are interrelated in such a way that the voluntary system exerts a tonic inhibition on the reflexive system, controlling and modulating reflexive attention and eye movements (Sereno, 1992). According to the tonic inhibition model, a deficit in the voluntary system would predict both impaired performance of voluntary saccades and decreased inhibition of reflexive saccades (e.g., more errors in an AS task and more disinhibitions in a DAS task).

4.4. Working memory

We did not find a significant memory deficit in the PD patients in our study (no difference between groups in RAS error rate). Some previous studies are in agreement with such a finding; however, several studies in the past have evaluated memory saccades in PD patients and found deficits in gain, latency, and direction (i.e., Crevits & De Ridder, 1997; Hikosaka, 1997; Shaunak et al., 1999). In the present study, we compared performance on the RAS task to an identical task (DAS) that did not require memory of the target in order to tease out a deficit that could be specifically related to an additional working memory demand. However, our design, although highly controlled, failed to show significant differences in either response time or error rate between the RAS and DAS tasks among control subjects or PD patients, suggesting that a more demanding RAS task may be needed to carefully test for such a specific working memory deficit. It is possible that longer delays (our longest was 1440 ms) may be necessary to elicit significant differences between DAS and RAS tasks.

Probably a more important difference between our study and previous research is that we tested working memory using a remembered *antisaccade* paradigm whereas previous studies have used a remembered *prosaccade* paradigm. Differences between a reflexive saccade (prosaccade) and a voluntary saccade (antisaccade) task have been reported, along with the specific effects voluntary attentional cues can have on response time in these two tasks. Specifically, antisaccades are facilitated by voluntary attentional cues (like presentation of the target with 100% predictive validity in our RAS task) whereas prosaccades show little or no cuing effects (Seidlits et al., 2003). This is also supported by the fact that remembered prosaccade tasks, compared to a standard prosaccade task, do not result in a significant decrease in response time. For example, Shaunak and colleagues (1999) report a 53 ms *increase* in saccade latency in a remembered prosaccade task compared to a standard prosaccade task in PD patients (287 and 235 ms, respectively) as well as a 63 ms *increase* in saccade latency for the remembered paradigm in matched normal control subjects (312 and 249 ms, respectively).

4.5. Correlation with clinical variables

In agreement with previous studies that describe a significant relationship between cognitive impairment and motor disability in PD (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Taylor, Saint-Cyr, & Lang, 1986; Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996), we found a strong positive correlation of increased AS error rate with more severe Hoehn & Yahr (H&Y) scores suggesting that the overall clinical stage evaluation provided by the H&Y scoring reflects the state of cognitive decline associated with the disease. DAS disinhibition rate also correlated with the H&Y scores in our patients showing that patients with higher scores in the H&Y were also more hyper-reflexive. The association of both these variables (AS errors and DAS disinhibitions) with the clinical scores also supports the idea that voluntary control and reflexive inhibition may be related. We did not see any significant correlations for disease state and RAS error as would be predicted by previous working memory studies that found correlations suggesting working memory declines with Parkinson's disease stage (e.g., Owen, Iddon, Hodges, Summers, & Robbins, 1997; Owen et al., 1992). This is not surprising considering the RAS task manipulation did not elicit robust deficits for the PD patients.

5. Conclusion

The study of higher cognitive functions in PD patients is essential for improving patients' quality of life and has only recently been the focus of investigation. Under highly controlled conditions, the present study demonstrates that PD patients have deficits in a number of higher cognitive processes including deficits in reflexive saccade inhibition and voluntary saccade generation. Further, we found that the eye movement deficits in PD patients were correlated with disease severity. The close physiological relationship between voluntary eye movements and higher cognitive functions, as well as the demonstrated clinical correlations, suggests that the study of eye movements may prove to be a simple, powerful, and direct measure of higher cognitive functions in Parkinson's disease.

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