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Kevin A. Briand · Daniel Strallow · Wayne Hening
Howard Poizner · Anne B. Sereno

Control of voluntary and reflexive saccades in Parkinson's disease

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Abstract Eight patients with idiopathic Parkinson's disease (PD) were compared with a group of age-matched controls on both reflexive saccade and antisaccade tasks. While reflexive, visually guided saccades led to equivalent performance in both groups, PD patients were slower, made more errors, and showed reduced gain on antisaccades (AS). This is consistent with previous results showing that PD patients have no difficulty with reflexive saccades but show deficiencies in a number of voluntary saccade paradigms. Moreover, visual information in the form of landmarks improves AS performance more for PD patients than controls, a finding analogous to results seen with other motor acts such as target-directed pointing. Results are discussed in terms of a two-process model of attention and eye movements.

Key words Parkinson's disease · Saccades · Antisaccades · Attention

Introduction

Investigation of saccadic performance in patients with Parkinson's disease (PD) has suggested that they have difficulty with certain classes of eye movements while other types are unaffected. However, previous studies reveal a major anomaly concerning this pattern, which the present study addresses. We begin by briefly summarizing previous work on saccadic performance in PD.

Saccade tasks may be grouped into two distinct categories, reflexive and voluntary, and converging evidence suggests that these two types of saccades may be under the control of separate neural systems. For example, gain adaptation of reflexive saccades does not transfer to voluntary eye movements, and similarly adaptation of voluntary saccades does not transfer to reflexive saccades (Deubel 1995). Reflexive, or visually guided saccades as they are sometimes referred to, require the subject to make a saccade to a single-target stimulus as soon as it appears. Ten studies have looked at reflexive saccade performance in PD (see Table 1); only one of these found any deficits for PD patients (Nakamura et al. 1991). Two studies (Kingstone et al. 1992; Roll et al. 1996) actually found enhanced performance for PD patients in the form of faster RT. Thus most evidence suggests that reflexive saccades are normal in PD (or may conceivably be superior).[1]

Voluntary saccades require volitional control over the eye movement, in contrast to the purely visually driven reflexive saccade. Different paradigms have been used to assess voluntary saccades in PD, including predictive, remembered, and purely volitional saccades (see Table 1). While reflexive saccade tasks show little evidence for deficits in PD, studies employing predictive, remembered and volitional saccades have almost universally found some problems in PD. As Table 1 illustrates, of the 15 studies which have assessed these latter types of

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K.A. Briand (✉) · D. Strallow · H. Poizner · A.B. Sereno
Center for Molecular and Behavioral Neuroscience,
Aidekman Research Center, Rutgers University,
197 University Avenue, Newark, NJ 07102, USA,
e-mail: briand@axon.rutgers.edu,
Tel.: +1 973 353 1080 ext. 3250, Fax: +1 973 353 1530

W. Hening
Robert Wood Johnson Medical School, Newark, New Jersey, USA

[1] Six additional studies required subjects to make saccades to a long sequence of targets, each occurring in random spatial locations at random times (Jones and De Jong 1971; White et al. 1983; Bronstein and Kennard 1985; Gibson and Kennard 1987; Gibson et al. 1987; Rascol et al. 1989). All six found some deficits for PD patients. Various factors, including task complexity, patient fatigue or even saccade amplitude could distinguish these studies from those which require discrete, single saccades. For this reason we limit consideration here to only those studies which require single saccadic movements, either reflexive or voluntary. It is also worth noting that motor sequencing itself is known to be an important basal ganglia function (Benecke et al. 1987; Aldridge and Berridge 1998)

Table 1 Summary of previous studies investigating simple eye movements in Parkinson's disease (– indicates PD worse than controls, + indicates PD better than controls, 0 indicates no significant difference)

Authors	Reflexive	AS	Predictive	Memory	Volitional
Corin et al. (1970)					–
De Jong and Jones (1971); Jones and De Jong (1970)					–
Corin et al. (1972)					–
Shibasaki et al. (1979)					–
Teravainen and Calne (1980)					–
White et al. (1983)			–		
Carl and Wurtz (1985)	0				–
Bronstein and Kennard (1985)			–		
Crawford et al. (1989a)			–		
Crawford et al. (1989b)	0			–	
Lueck et al. (1990)	0	0		–	
Nakamura et al. (1991)	–				
Lueck et al. (1992)	0			–	
Ventre et al. (1992)	0		–		
Kingstone et al. (1992)	+	+			0
Vidailhet et al (1994)	0	0			
Kitagawa et al. (1994)	0	–			
Fukushima et al. (1994)	0	0			
Nakamura et al. (1994)				–	
Vermersch et al. (1994)				–	
Roll et al. (1996)	+				
O'Sullivan et al. (1997)			–		
Crevits and De Ridder (1997)		–		–	
Hikosaka (1997)				–	–
Shaunak et al. (1999)	0			–	

saccades in PD, all but one have found their performance inferior to controls.

In general, then, PD patients appear to exhibit normal saccadic performance when reflexive saccades are required but are impaired in controlling voluntary eye movements. This is consistent with the suggestion that there is a deficit in the internal but not the external control of attention in PD (Brown and Marsden 1988). The voluntary-reflexive dissociation shown in saccadic movements has also been suggested to characterize certain limb movements (Benecke et al. 1986).

A notable exception to the prevalent pattern in saccadic behavior is the performance of PD patients on antisaccade (AS) tasks. In an AS paradigm, subjects are shown a target stimulus and must make a saccade as soon as it appears, but in the opposite direction to the stimulus (Hallett and Adams 1980). This is usually categorized as a voluntary type of saccade. Two aspects of this task make requirements on voluntary control processes. First, one must inhibit the tendency to make reflexive saccades to the target stimulus. Second, one must plan and execute a purely voluntary eye movement to a spatial location that is not driven by any type of visual input. In normal individuals, AS response latencies are much slower than latencies on the corresponding reflexive saccade task, and there is a tendency to make erroneous saccades to the target instead of in the opposite direction as required. Given the deficits shown by PD patients on other types of voluntary saccades, it is reasonable to expect that they would tend to show similar difficulties on an AS task.

Six studies have looked at AS performance in PD, and the results are mixed and contradictory. Three found no significant difference between the performance of PD patients and controls (Lueck et al. 1990; Fukushima et al. 1994; Vidailhet et al. 1994). Two studies (Kitagawa et al. 1994; Crevits and De Ridder 1997) reported poorer performance for PD patients, whereas the sixth actually reported superior performance for PD patients (Kingstone et al. 1992). Thus in contrast with the relatively uniform finding that PD patients have difficulty with other types of voluntary saccade tasks, the AS paradigm has so far failed to demonstrate similar deficits.

There were two aspects of task design that differed across studies and seemed to us to be potentially crucial to obtaining strong evidence for AS deficits. The first issue is the medication status of the patients. Four of the six previous studies (Lueck et al. 1990; Fukushima et al. 1994; Kitagawa et al. 1994; Crevits and De Ridder 1997) tested PD patients while medicated and one provided no information regarding medication status (Kingstone et al. 1992). Only one tested patients in the "off" state (Vidailhet et al. 1994). However, their definition of the "off" state is not further specified and the study did not provide any information concerning when the patients were tested with respect to their last dose of medication. Recently, a consensus standard for assessment of clinical state in PD was defined by Langston et al. (1992). In accordance with this standard, we tested patients in the morning prior to their taking medication and at least 12 h after their last medication dose.

The second design issue concerns the presence or absence of a "gap" procedure (Saslow 1967; Fischer and Ramsperger 1984). In a normal, "overlap" saccade task, the subject fixates a central spot, which remains in view for at least some time after the target appears. In a gap

paradigm, the fixation spot is removed shortly before target onset. While this speeds up reflexive saccades, it can disrupt antisaccades, since there is a strong tendency on such trials to erroneously make a saccade to the target when it appears (Weber 1995; McDowell and Clementz 1997). Such errors are much less likely when there is no gap. Only two of the previous studies of antisaccades in PD used a gap procedure (Vidailhet et al. 1994; Kingstone et al. 1992), while the remainder used a procedure where the fixation point was extinguished simultaneously with the onset of the target stimulus (gap=0 ms). A gap procedure was used in the experiments reported here, as we believed this would disrupt AS performance and improve our chances of detecting an AS deficit in Parkinson's patients.

One final issue prompted the experiments reported here. Previous research has demonstrated that PD patients show abnormal motor performance during targeted limb movements, such as pointing to or reaching for a target. These problems can be reduced if visual information concerning either the position of the limb or the target is presented (Flowers 1976; Flash et al. 1992; Klockgether and Dichgans 1994; Jackson et al. 1995; Adamovich et al. 1997; Poizner et al. 1998). It is interesting to note that analogous claims have been made regarding saccadic movements in PD. Parkinson's patients make fewer anticipations in predictive saccade paradigms (e.g., Bronstein and Kennard 1985; Gibson and Kennard 1987), suggesting that they require that the target stimulus be present in order to generate predictive voluntary saccades. Kennard and Lueck (1989) subsequently proposed that the tasks which cause most difficulty for PD (remembered or predictive saccades) have in common the fact that a novel visual eliciting stimulus is absent. Note, however, that this suggestion conflicts with the present interpretation that such tasks cause difficulty in PD because of their voluntary nature, not because of the presence or absence of target stimuli per se. Thus, we investigated whether the voluntary, or even reflexive, saccades of PD patients could be made more efficient by presenting visual information which could serve as "landmarks" for eye movements. In particular, if such landmarks have an effect on saccadic efficiency (i.e., in either latency, accuracy, or gain), we tested whether (a) such improvement would be limited to voluntary saccades and (b) whether PD patients would benefit from this visual information more so than control subjects.

To summarize, the present study had two main goals. First, we hypothesized that AS performance in PD patients could be shown to be deficient if they were tested under certain conditions that perhaps are important (i.e., in a relatively unmedicated state using a gap procedure). We also used multiple measures of performance to give a more complete picture of AS performance in PD patients than previous studies have provided. Second, we asked whether landmarks indicating target positions could improve saccadic performance for PD patients analogously to the pattern often observed with pointing behavior.

Materials and methods

Subjects

Eight patients with mild to moderate idiopathic Parkinson's disease (PD) were tested along with eight normal controls; all subjects were non-demented and non-depressed. Background statistics on the patients and controls are given in Table 2. Other than

Table 2 Background data for Parkinson's patients and control subjects (*L* L-dopa, *L-SR* sustained-release L-dopa, *T* trihexyphenidyl, *S* selegine, *A* amantadine, *R* ropinerole, *Bz* benztropine, *P* pergolide, *O* oxybutynin, *Lx* levothyroxine, *M* maprotiline, *C* clozapine, *B* buspirone)

	Age (years)	H&Y stage	UPDRS (motor)	Disease length (years)	MMSE	Medications	Education	Gender
Patients								
1	75	2	30	23	30	L, T, R, O	14	M
2	84	2	31	4	27	L	16	M
3	59	3	38	5	27	L, L-SR, S	16	M
4	67	2.5	41.5	12	24	L, A, O	9	M
5	78	3	28.5	11	25		16	M
6	79	3	16.5	4	28	L, S, A	12	F
7	72	1.5	19.5	2	27	L, Bz	13	F
8	77	2.5	33	8	26	T, S, P, Lx, M, C, B	12	M
Averages	73.9		29.8	8.5	26.8		13.5	
Controls								
9	66				28		14	M
10	74				28		20	M
11	67				26		12	M
12	66				28		11	M
13	74				26		12	M
14	79				25		12	M
15	73				27		12	M
16	82				28		12	M
Averages	72.6				27.0		13.1	

PD, none of the patients or control subjects tested had any known neurological disorder. All subjects were assessed using the Mini Mental State Examination (MMSE; Folstein et al. 1975) and PD patients were also given the motor section of the UPDRS (Goetz et al. 1995). None of the subjects showed any signs of dementia or abnormal cognitive functioning on the MMSE (score >22/30). With one exception, the Parkinson's patients were tested in the morning after having been off medication for at least 12 h. One patient had an early morning dosage 5 h prior to testing since he depended upon regular frequent dosing and "froze" in the morning without an initial dose. One additional control subject was tested but his results were not included in the analyses because his MMSE score was below the criterion for normal performance.

Apparatus and stimuli

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. Subjects placed their head on a chin rest positioned 72 cm from a computer monitor used to display the stimuli (Sony Trinitron Multiscan sf II). The monitor screen covered a visual area of 25° by 18° from this viewing distance. A gray central fixation spot of 0.15° was shown against a black background. Target locations were 7.3° to the left and right of this fixation spot. Target stimuli were 0.2° white squares. Landmark indicators, when shown, were plotted in gray against the background and had the same dimensions as the target stimuli, being plotted in the exact positions corresponding to the targets.

Procedure

Subjects were tested in four different saccade tasks (48 trials each). On each trial subjects fixated a central spot to initiate the trial sequence. If they successfully maintained fixation for 800 ms the sequence of trial events was initiated. However, if their estimated point-of-gaze shifted more than 3.0° from the center of the fixation point they were assumed to have broken fixation. In this instance the trial was cancelled and placed back in the pool of uncompleted trials. A "gap" paradigm was used in all tasks, which involved the removal of the fixation point 187 ms before the target appeared. The target then remained in view until the subject responded or until 1000 ms had elapsed.

Tasks

Examples of the stimulus sequence for the four tasks are shown in Fig. 1, with descriptions as follows:

Saccade no landmarks (SNL)

The fixation point was turned on to indicate the start of the trial, and the subject shifted his/her gaze to the center. After 800 ms, the fixation point was removed and the screen went blank for 187 ms. Then the target stimulus was displayed, with position (left or right) being chosen randomly. This was constrained only by the requirement that there be 48 trials, with equal numbers of targets presented in the left and the right sides. Simultaneous with target onset, a brief 13-ms tone sounded to provide an additional alerting stimulus. Subjects responded by making a saccade to the target item following its onset. At the conclusion of the response, the target stimulus was erased and the fixation point replotted to begin the next trial sequence.

Saccade with landmarks (SL)

This task was the same as the previous one with the exception that the possible target positions were indicated by two light-gray spots which acted as landmarks (see Fig. 1). These landmarks were turned on 500 ms after the reappearance of the fixation point, and remained in view for the duration of the trial. Since the landmarks were the same size as the target stimuli, onset of the target was indicated by simply changing the color of one of the landmarks from gray to white. Landmarks and targets were erased at the conclusion of the trial.

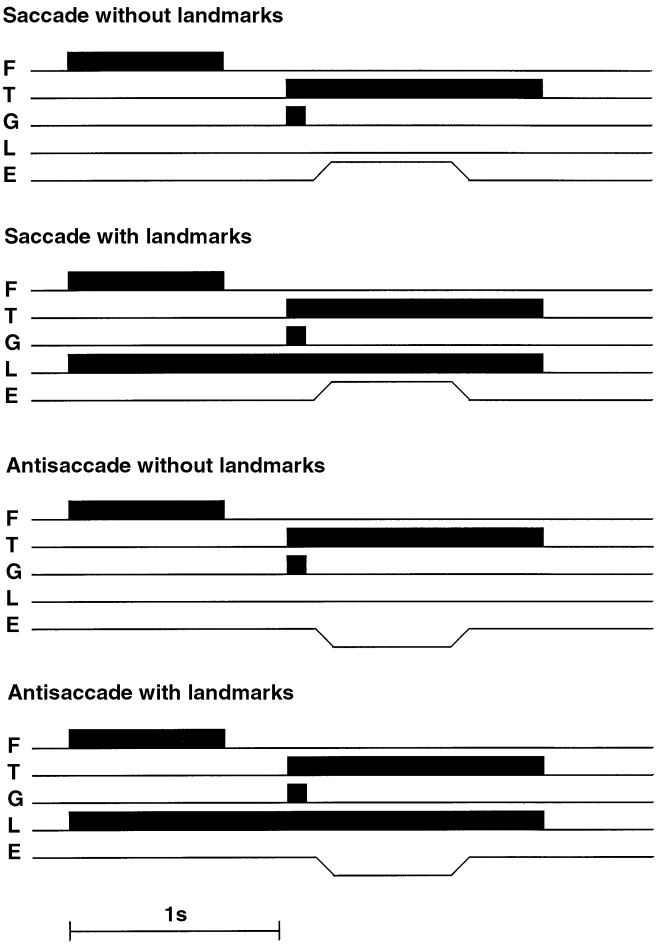


Fig. 1 Schematic representation of the stimulus sequences used in the four tasks (*F* fixation point, *T* target stimulus, *G* go tone, *L* landmarks, *E* eye position)

Antisaccade no landmarks (ASNL)

The sequence of events was identical with that used in the SNL paradigm, but the subject was required to make a saccade to the spatial position directly opposite where the target had appeared.

Antisaccade with landmarks (ASL)

Subjects again had to make a saccade in the direction opposite to the target, but the display sequence corresponded to that used in the SL paradigm.

The order in which these four conditions were given to subjects was counterbalanced, with half the subjects in each group doing the two saccade tasks first and half doing the AS tasks first. In addition, half the subjects did the "landmarks" versions of each task before the "no landmarks" versions.

Saccade latency was calculated using a velocity criterion. The start of a saccade was indicated as soon as the change in eye posi-

tion went above a velocity of 120°/s. The end of the saccade was indicated when (a) eye velocity fell below 12°/s and (b) eye position was within 4.4° of either the left or right target position. When resting eye position was determined, the saccade was determined to be "within target" or "in opposite position," and scored as correct or incorrect as appropriate for the task. If a saccade was not successfully completed within 1000 ms of target onset, that trial was replaced in the pool of unfinished trials to be completed later (a running count of such non-responses was maintained). Visual feedback following errors consisted of the message "Wrong Location" printed on the display screen, which remained in view for 500 ms.

After the completion of these four tasks all subjects performed a brief (4-s) task to collect normative data permitting measurement of saccade gain. Following the appearance of the fixation point, the left and right targets were shown sequentially for 2 s each. Subjects were required to look at each target while it was displayed. The estimates of eye position obtained in this fashion were used to scale the saccade amplitude measurements obtained during the previous four tasks. For each trial from the four tasks, "saccade amplitude" was defined as the point where the saccade first terminated. "Gain" was defined as the ratio of saccade amplitude to the normative estimate of eye position obtained while targets were actually being fixated (rather than the uncorrected screen coordinates of the target).

Statistics

Responses with latencies longer than 900 ms or faster than 90 ms were excluded from RT and gain analyses, but were scored as errors (these accounted for only 1.1% of all trials completed).

Each subject's mean correct response latency and gain for each of the tasks was then calculated. Statistical analyses were based on planned comparisons, either between the PD subjects and the controls for specific conditions, or between the landmark and no-landmark conditions of a task within a given group. Between group comparisons were based on parametric (*F*-tests) whereas within group comparisons were based on Wilcoxon matched pairs tests.

Results

Saccades

Figure 2 shows the average RTs and error rates on the S and AS tasks for both the control and the PD subjects. Landmark effects are presented separately below. For additional clarity, the distributions of the data from the two groups are provided in Fig. 3. PD and control subjects did not differ in either RT (251 vs 257 ms for PD and controls, respectively, $F_{(1,14)}<1$) or error rate on the saccade tasks (2.7 vs 4.5%, $F<1$).

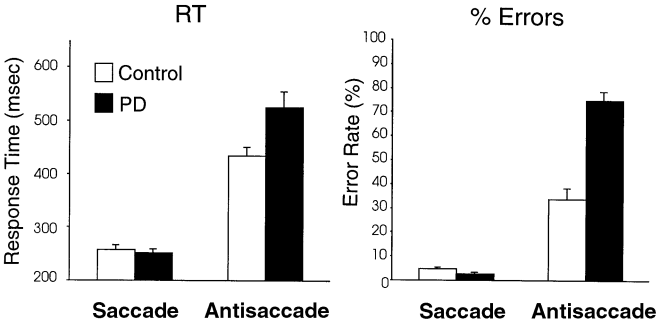


Fig. 2 Mean RT and error rate for the PD and control subjects on the reflexive saccade and antisaccade tasks

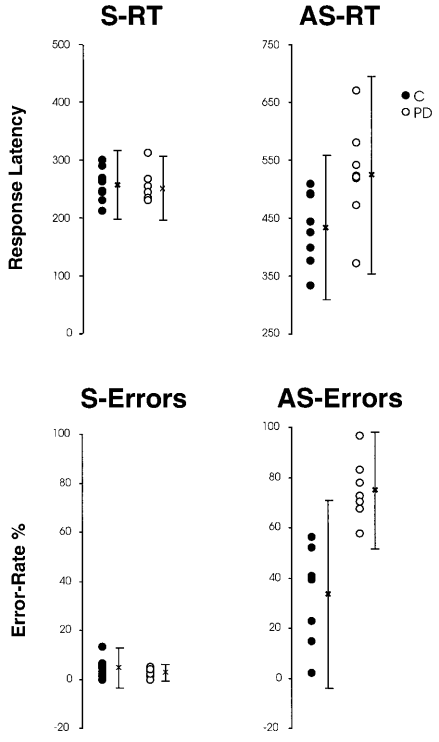


Fig. 3 Distributions of RTs and error rates in the S and AS tasks, for individual PD subjects (*open symbols*) and controls (*filled symbols*). The mean and 2 SDs of each distribution are also presented. The distributions differed significantly between groups only for the AS tasks

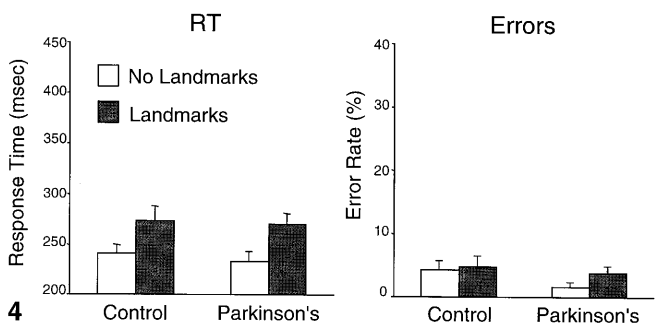
Antisaccades

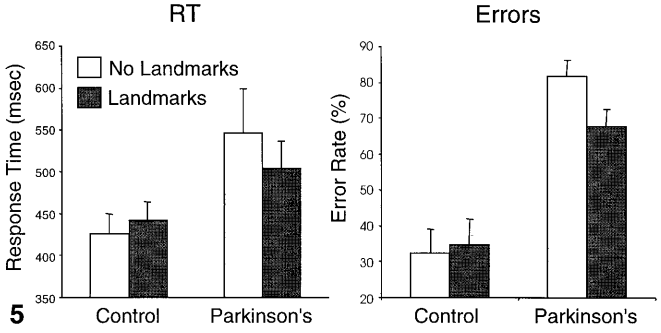
Also shown in Figs. 2 and 3 are the results from the AS paradigm for both groups. In striking contrast to the normal performance for PD patients on the saccade tasks, PD patients showed clear abnormalities on the AS tasks. PD patients had much slower RTs than controls (525 vs 433 ms), $F_{(1,14)}=4.83$, $P<0.05$. The increase in error rates for PD was even more striking (74.9% vs 33.5%), $F_{(1,14)}=33.94$, $P<0.001$.

As expected both RT and error rates were increased in the AS compared to the saccade tasks. Within group comparisons (Wilcoxon matched pairs) showed that, for controls, the increases in RT (178 ms, $T=0$, $P<0.006$) and in error rate (28.9%, $T=1$, $P<0.009$) were both significant. The RT (274 ms, $T=0$, $P<0.006$) and error rate (72.2%, $T=0$, $P<0.006$) increases in the AS tasks were also significant for the PD patients. These increases were greater for the PD patients, as evidenced by a significant Group by Task (S vs AS) interaction in RT ($F_{(1,14)}=5.45$, $P<0.04$) and in error rate ($F_{(1,14)}=37.10$, $P<0.001$).

Landmark effects: saccades

Figure 4 shows the mean RTs and error rates for both groups of subjects on the saccade tasks, this time ex-





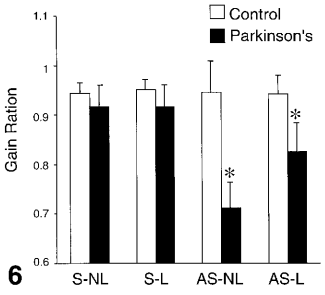


Fig. 4 Mean RT and error rates on reflexive saccade tasks, as a function of the presence or absence of landmarks

Fig. 5 Mean RT and error rates on AS tasks, as a function of the presence or absence of landmarks

Fig. 6 Mean gain on saccade and AS tasks, as a function of the presence or absence of landmarks

panding the data to show the results from the landmark and no-landmark conditions. Planned within-group comparisons showed that landmarks actually slowed RTs for both groups of subjects. For control subjects this increase was 32 ms (T=4, P<0.025), while for the PD patients it was 37 ms (T=1, P<0.009). There were no effects of landmarks on error rates for either group (P>0.25 for controls, P>0.12 for PD).

Landmark effects: antisaccades

Figure 5 shows the corresponding RT and error data for performance on the AS tasks with and without landmarks. Control subjects showed no significant effects of landmarks for either RT (P>0.20) or errors (P>0.28). In contrast, PD patients showed a significant 14.0% improvement in error rates when landmarks were included in the display (T=2, P<0.02). Although the PD group had faster RT in the landmark condition, this effect was not significant (44 ms, P>0.24).

Gain

For the two reflexive saccade tasks there was no significant difference in gain between the PD and control subjects (F<1, see Fig. 6). For voluntary saccades, however, PD patients showed decreased gain relative to controls in both the AS-L condition, $F_{(1,13)}$=6.63, P<0.05, and the AS-NL condition, $Fs_{(1,13)}$=58.29, P<0.001 (df=13 because gain data for one subject were not saved due to error).

Within group comparisons were also used to verify whether landmarks had any effects on gain for one group or the other. For the controls, landmarks had no effect on gain for either saccades (P>0.28) or antisaccades (P>0.50). The PD group showed no effects of landmarks on the saccade task (P>0.16); however, landmarks did improve gain on the AS task (T=6, P<0.05).

AS errors in PD patients

Due to the high error rate of PD patients in the AS tasks, we examined those trials where they incorrectly made a saccade to the target instead of in the opposite direction. Table 3 compares the mean RTs for PD patients on these erroneous AS trials with their average correct RT for the reflexive saccade tasks. The data are shown separately for the landmark and no-landmark conditions. Also included for illustrative purposes are their RT and gain from correct AS responses.

Analysis of variance on the RT revealed no difference between the latencies of incorrect AS responses (272 ms) and those of correct reflexive saccades (251 ms), $F_{(1,7)}$=1.57, P>0.25. There was an effect of Landmarks, with faster latencies in the No Landmark condition (243 vs 280 ms), $F_{(1,7)}$=26.10, P<0.002. Finally, landmarks appeared to have equivalent effects for correct saccades and incorrect AS, $F_{(1,7)}$=0.006, P>0.93 for the interaction.

The gain from these conditions was also analyzed. The gain for AS errors was less than that for correct reflexive saccades (0.845 vs 0.916), $F_{(1,6)}$=8.58, P<0.03. However, Table 3 makes it clear that the gain on erroneous AS was still greater than that for correct AS responses (0.745). An analysis of variance comparing gain for correct saccades, incorrect AS, and correct AS further revealed an interaction between Task and Landmarks,

Table 3 Response latency and gain for AS errors in PD patients, in comparison with their correct responses on saccade tasks (SEs in parentheses). Performance on correct AS trials is also included

	RT		Gain	
	No landmarks	Landmarks	No landmarks	Landmarks
AS errors	254 (16.4)	290 (19.8)	0.833 (0.037)	0.858 (0.049)
S correct	233 (10.2)	270 (11.1)	0.917 (0.051)	0.916 (0.044)
AS correct	547 (52.2)	503 (33.5)	0.691 (0.054)	0.857 (0.056)

$F_{(2,12)}$=11.37, P<0.002. Post hoc Wilcoxon comparisons confirmed that whereas landmarks improved gain for correct AS responses (T=6, P<0.05), they had no effect on gain for either correct saccades (P>0.30) or incorrect AS responses (P>0.33). Thus it appeared that AS errors were qualitatively very similar to correct reflexive saccades, suggesting that they were reflexive saccades to the target that failed to get suppressed.

Visual akinesia

Crevits and De Ridder (1997) reported that in an antisaccade task, PD patients had significantly more errors than controls involving a total failure to make an eye movement. In these errors, PD patients "froze" at fixation temporarily. Crevits and De Ridder (1997) referred to this phenomenon as "visual akinesia." Using a one-tailed *t*-test, we also found that Parkinson's patients made more of these errors than controls (2.78 vs 1.06, t=3.29, P<0.05). Since there was somewhat high variability in the data due to the fact that a single control subject showed a high number of these errors, a less stringent non-parametric test (Mann-Whitney) was used to assess this comparison. This test showed the increase in visual akinesia for PD to be significant with a one-tailed test (P<0.01).

Discussion

There were two main objectives to the present study: first, to test PD patients under conditions that might optimize the chances of finding AS deficits, and hence to clearly demonstrate a continuity between their AS performance and poor execution of other types of voluntary saccade tasks; second, to examine the effects of visual information in the form of landmarks on voluntary versus reflexive saccades in these same subjects. We will address each of these in turn.

The evidence from the present experiment is clear as to the first objective. Specifically, there was a marked dissociation between the performance of PD patients on reflexive versus voluntary saccade tasks. On the two tasks requiring subjects to make a reflexive, visually guided saccade, there was no evidence of deficits in PD patients. They did not differ from controls in the latency, error rates, or saccade accuracy (gain) of reflexive saccades. This is entirely consistent with the findings of previous studies, reviewed earlier, which almost universally found that PD patients had no deficits on such tasks.

The performance of PD patients on the voluntary AS tasks stands in stark contrast to this. When such voluntary saccades were required, PD patients were slower, made more errors, and made saccades which undershot the target. Thus the present study provides clear evidence that PD patients are deficient in voluntary antisaccades, just as they appear to have difficulty with other types of voluntary saccades (e.g., remembered, predictive, or volitional). We believe this AS deficit is the result of two factors. The first factor is poor inhibition of reflexive saccades (see Hikosaka 1997). This would explain the high rate of AS errors, and also would be consistent with our observation that these erroneous saccades look qualitatively very much like reflexive saccades in terms of their latency and gain. The second factor contributing to the AS deficiency is poor execution of voluntary saccades. This is demonstrated by the long latency and low gain found for AS, as well as perhaps by the increased rate of visual akinesia in the PD patients. The present study thus demonstrates that the poor AS performance in PD is observed simultaneously on a number of different dimensions of saccade execution (latency, error rate, and gain). None of the previous studies examining AS performance in PD measured all of these variables. Future studies should be considered that might allow the separate contributions of "reflexive saccade inhibition" and "voluntary saccade execution" to this AS deficiency to be examined in more detail.

Furthermore the present study is the first to demonstrate AS deficits in PD patients who are in the "mild to moderate" category (our subjects ranged from stage 1.5 to 3). Both of the previous studies that found an AS deficit in PD patients either used only advanced patients (stages III and IV; Crevits and De Ridder 1997) or found a deficit only in a subgroup of advanced patients (stage III) but not mild-moderate patients (stages I and II; Kitagawa et al. 1994).

Two factors most likely contributed to the robustness of the AS deficiency demonstrated in our study. The first factor was medication: every reasonable effort was made to test patients when medication effects would be minimal. Since PD patients were tested in the "off" state, their parkinsonian deficits could be more easily revealed. Our study appears to be the only one that tested patients following the current guidelines, which require a night without medication to produce a uniform "off" condition. We believe this contributed to our demonstration of robust AS deficits.

The second factor was the use of a gap paradigm in all of our saccade tasks. As mentioned earlier, gap paradigms have the dual effects of making reflexive saccades slightly more efficient, but they also make AS more difficult. Thus, by increasing the overall difficulty of the AS task we were able to make more apparent the problems PD patients have with this task, consistent with their problems in other voluntary saccade paradigms. We should note, however, that a review of the six previous studies of AS performance in PD patients does not reveal any particular trend regarding the effect of a gap paradigm. For example, Vidailhet et al. (1994) used a gap procedure but did not find any deficit for PD patients, whereas we did. Furthermore the two previous PD studies reporting an AS deficit did not use a gap procedure (Crevits and De Ridder 1997; Kitagawa et al. 1994).

Our rationale for choosing these particular testing procedures was to increase the opportunity to observe an AS deficit in PD. We did not systematically manipulate either the use of a gap or no-gap procedure, or the medication status of our patients.[2] Given the robustness of our findings, it would be worthwhile in the future to examine the effects of these variables.

Even considering the particular procedures we used, our results do seem at odds with many prior studies examining AS performance in PD. In particular, one could ask why we obtained such a high error rate compared to previous studies, and whether this may have contributed (artifactually) to the deficit we observed in our PD patients. Several possible issues can be raised, some of which relate to possible procedural differences between our study and previous ones.[3] These include the possibility that our subjects did not fully understand the AS task, as well as specific characteristics of our patients and stimuli.

Failure to understand AS task

The first question is potentially most critical. Could a failure of our subjects to understand the AS procedure have caused not only our higher overall error rates, but the deficit we observed in our PD patients? A number of reasons lead us to reject this possibility: (1) assuming that the PD patients misunderstood the task and instead responded directly to the target, one might expect that their rate of incorrect responses on AS trials (i.e., to the target) would be similar to their rate of correct responses during the reflexive saccade tasks (>95%). Yet the overall error rate in the AS task for the PD subjects was only 75%. Given this disparity, it seems unlikely that their performance on AS trials simply represented them making the same response they executed during these saccade trials (i.e., a saccade to the target). (2) Landmarks improved the performance of PD patients on AS trials, but they caused somewhat poorer performance on saccade trials, suggesting that the patients were not doing the same thing on AS as on saccade trials. Furthermore, these landmarks only provided external cues to possible target response positions and did not provide any additional information about which side was the correct response side. Hence unless the subject understood the task, it is not clear why this should have increased the number of correct responses for the AS task. (3) All of the subjects demonstrated visible distress during performance of the AS task and during subsequent debriefing, even apologizing that they were "ruining the experiment." They clearly understood that they were making errors on the task and showed frustration at not being able to perform correctly. (4) Finally, PD patients often made corrective saccades following an AS error (i.e., they followed a stimulus-directed saccade with an eye movement to the opposite side of the screen). Such corrective saccades spontaneously occurred following 55.6% of erroneous responses on AS trials, whereas the opposite pattern (i.e., following a correct AS response with a saccade to the stimulus) only occurred 1.6% of the time. Based on these factors, we are fully confident that all of our subjects understood the AS task and that this could not account for the error rates we obtained.

Age of PD patients

The average age of both our patients and controls was greater than in most prior AS studies, although Crevits and De Ridder (1997) observed AS deficits in both young (age 53 years) and old (age 72 years) groups of PD patients. Our patients were chosen specifically so as not to have early onset PD, which may well have a unique etiology (Tanner et al. 1999). Indeed most of our patients had onset of symptoms between the ages of 50–70 years, which is the typical age of onset for idiopathic PD. Thus, although our sample is older (average 73.9 years) than that typically observed in some of the previous studies, we feel that they are representative of idiopathic PD patients.

Working memory

A related question stems from the dual observations that working memory is believed to be involved in AS performance (e.g., Roberts et al. 1994) and that working

[2] While the use of a gap or no-gap procedure and medication status are obvious sources of interstudy variance, we did not systematically manipulate these variables for three reasons. First, our strategy was to first demonstrate that robust AS deficits could be obtained in a sample of PD patients, bringing coherence to the literature with regards to the voluntary versus reflexive saccade dissociation. Because the patients had been off medications for 12 h at the time we tested them, we made every effort to limit the workload of our patients to avoid fatigue or problems associated with withdrawal of medications. Finally, as we mention in the discussion, the existing literature does not show a consistent effect of these particular variables. Therefore any significant effects we obtained with, for example, manipulation of a "gap" procedure would still need to be reconciled with prior results

[3] The authors wish to thank two anonymous reviewers for pointing out these possibilities

memory declines with age (Salthouse 1992). It is also known that AS performance deteriorates with age (Fischer et al. 1997). If our patients were of sufficient age that they had working memory problems, this could explain their high AS error rate. We do not feel this is a plausible explanation for our findings since cognitive ability (as measured by the MMSE) was equivalent and reasonably high for both our control and patient groups (average score of 26.8 out of a maximum of 33). Furthermore our PD patients and controls were well matched in terms of age, rendering it unlikely that an age-related working memory decline could account for the AS deficit we found in our patients.

Role of anticholinergics

Even though our patients had been off medications for 12 h, a subgroup of them was being treated with anticholinergics. This is potentially important given that Kitagawa et al. (1994) reported that anticholinergics increased AS errors in their PD patients. However, our three patients who were on anticholinergics actually did somewhat better on the AS task (479 ms and 74% errors) than did the five not on anticholinergics (553 ms, 75.4%). The absence of any deleterious effect of anticholinergics on performance, in comparison with the results of Kitagawa et al. (1994), could be due to the fact that our PD patients were tested after withdrawing medications for 12 h.

Stimulus eccentricity

A potentially important aspect of our procedure is stimulus eccentricity. Increasing stimulus eccentricity is known to have a detrimental effect on AS performance (Fischer and Weber 1997). Thus, one might expect that varying stimulus eccentricity might alter the relative difficulty of an AS task, and that furthermore this might explain why some previous Parkinson's studies failed to observe an AS deficiency. That is, stimulus eccentricity may have been such that task difficulty was not great enough to see any deficit. However, an examination of the previous studies investigating AS in PD gives no support to this hypothesis. The stimulus eccentricities in the studies finding no AS deficit in PD range from 7.5° to 25°, while the corresponding range in the two studies finding a deficit is 8° to 24°; our stimulus eccentricity (7.2°) falls at the short end of this range. Thus stimulus eccentricity does not explain why some studies fail to observe AS deficits in PD, nor why we were successful.

Deficits in executing various types of voluntary saccades or in failing to inhibit reflexive saccades (i.e., errors on AS task) might be ascribed to a frontal or prefrontal dysfunction. The AS task becomes increasingly difficult as working memory load is increased (Roberts et al. 1994), and patients with frontal lobe lesions have problems with this task (Guitton et al. 1985). Given that PD is caused by the loss of dopaminergic-containing neurons projecting to the striatum, Crevits and De Ridder (1997), among others, have suggested that the voluntary eye movement control deficit in PD is caused by a dysfunction in the striato-pallidal-prefrontal projection. Most likely, what appears for this population to be a voluntary control deficit implicating higher neural structures is in fact a deficit caused by reduced or altered inputs to those areas from basal ganglia nuclei directly affected in PD.

Sereno (1992, 1996) proposed a model to account for attention and eye movements in schizophrenia, which might also apply to voluntary saccade deficits in PD. Sereno and Holzman (1993, 1995) found that schizophrenic patients had problems on a voluntary AS task, but that they showed hypereflexive (i.e., faster than normal) reflexive saccades. Sereno's (1996) model explained this pattern by proposing that two separate attentional systems control eye movements. One is a voluntary system which controls voluntary eye movements (e.g., remembered, predictive, volitional or antisaccades). Under normal circumstances, this system tonically inhibits a second, reflexive attention system that controls visually guided (reflexive) saccades. Sereno proposed that if the voluntary attention system were hypoactive or not functioning properly, this would cause voluntary saccades to become less efficient. However, reflexive saccades might actually become more efficient, as the neural system controlling these would no longer be subject to tonic inhibition from the voluntary attention system.

While the present data provide clear evidence for an AS deficit in PD, there is little evidence that their execution of reflexive saccades is more efficient than that of controls. While the PD group was both faster and more accurate than the control group on the reflexive saccade tasks, neither of these differences approached significance. The gap procedure we used might have inadvertently acted to make this latter hypothesis more difficult to support. Since the gap paradigm generally improves performance of reflexive saccades, it may have reduced any differences that existed. Evidence for this possibility comes from a separate experiment not described here (Briand et al. 1999). In a saccade task that used an overlap procedure, we found that these same PD patients were significantly faster than the controls.

The second objective of this study was to determine whether visual information in the form of landmarks had effects on saccadic performance, which were analogous to effects observed in other paradigms involving voluntary reaching or pointing movements (Flowers 1976; Flash et al. 1992; Klockgether and Dichgans 1994; Adamovich et al. 1997; Poizner et al. 1998). The data from the voluntary AS tasks are quite clear in this regard; landmarks improved AS performance for PD patients, in the form of reduced AS errors and improved gain. Landmarks had no detectable effect on the AS performance of control subjects. This pattern seems to be directly analogous to that observed in the motor control literature, where visual information has a greater benefi-

cial effect on performance for PD. While no doubt different neural circuits are involved in the case of voluntary eye movements as opposed to those implicated for reaching, it is striking that such apparent similarities in behavior exist.

Whereas landmarks had beneficial effects on AS execution for at least the PD patients, their influence on reflexive saccades was very different. For both patients and control subjects, landmarks actually hindered reflexive saccades. That this is not simply due to masking effects is indicated by the fact that AS performance was not similarly affected.

Why landmarks would benefit voluntary but not reflexive movements is unclear. One possibility is that providing visual cues prior to the execution of a reflexive eye movement hurts performance precisely *because* such cues induce the involvement of more voluntary control systems. According to Sereno's (1996) model, increasing activation of voluntary control processes should cause reflexive attention systems to be inhibited. Adding landmarks to the display in a reflexive saccade task could thus cause performance to deteriorate (relative to a reflexive saccade task with no landmarks) if some type of voluntary control system tried to integrate and make use of this information to guide eye movements. In direct contrast, since AS performance already requires voluntary control, visual information could be expected to improve performance. An increased benefit for PD patients would then be expected because of improved efficiency of hypoactive frontal control processes due to the provision of such contextual information (or because of the role of the basal ganglia in integrating contextual information in the execution of movements; Marsden and Obeso 1994).

In conclusion, we have addressed an anomaly in the literature regarding saccadic performance in PD. Previous investigations of single saccades in PD showed what appears to be a dissociation between reflexive and voluntary saccade tasks. However, this clear dichotomy was complicated by the failure to find robust deficits on AS tasks in PD. The present study robustly demonstrates that PD patients can be shown to have profound deficiencies on an AS task, which is completely consistent with previous reports using other voluntary saccade paradigms. The strength of our finding is enhanced by the fact that this AS deficit was reflected in three different performance measures (latency, accuracy and gain). It remains to be shown what variables in our study were critical to this robust finding. In addition, our study demonstrates that visual information in the form of landmarks facilitates voluntary saccades in PD, a finding that may be analogous to phenomena observed with goal-directed reaching or pointing in PD. Thus it appears that AS performance in PD nicely correlates with previous findings concerning voluntary movements, both saccadic eye movements and limb movements.

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