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RESEARCH ARTICLE

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The inter-trial effects of stimulus and saccadic direction on prosaccades and antisaccades, in controls and schizophrenia patients

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Abstract We investigated the influence of the direction of preceding saccadic trials on the latency of current prosaccades and antisaccades, in healthy subjects and patients with schizophrenia. When prosaccades and antisaccades were performed in separate, single-task blocks, we found that only prosaccades were delayed if the saccade in the prior trial was in the same direction, consistent with the expected directional effect from an 'inhibition of return'-like alternation advantage. However, both types of saccades were executed more quickly when the saccade in the penultimate trial was in the same direction, consistent with previous demonstrations of directional plasticity in monkeys. In blocks of randomly mixed prosaccades and antisaccades, the directional effects in healthy subjects were greatest when a prosaccade was preceded by an antisaccade, consistent with a summation of effects of alternation advantage (from the prior stimulus) and directional plasticity (from the prior saccade). Schizophrenic patients showed an additional phenomenon, a directionally specific inhibition of upcoming saccades by preceding antisaccades. These results suggest that saccades in humans are modulated by inter-trial effects attributable to both an 'inhibition of return'-like alternation advantage and directional plasticity.

Keywords Saccades · Plasticity · Inhibition of return · Antisaccades · Alternation advantage

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Introduction

What impact does recent behavior have upon current action? This issue has significant implications for both daily life and psychological research. In the latter, a single trial is usually embedded in a block of trials, yet responses are often analyzed without considering the effects of preceding trials. However, a growing body of literature shows that the response to a stimulus can be modified by its history, by both the prior stimuli and prior responses (Fecteau and Munoz 2003).

Research in monkeys has produced simple and elegant demonstrations of inter-trial influences on saccadic behavior. Using saccades made to right or left targets randomly, Dorris et al. (2000) showed that the latencies of saccades made to a target were lower if they were made in the same direction as in the prior trial. This directional effect was evident even from the trial preceding the prior one (the penultimate trial), indicating that the effect persists over several seconds at least. In neurons of the superior colliculus, this behavioral effect was accompanied by changes in the preparatory activity that preceded the appearance of the target. A saccade increased the future pre-target activity of neurons coding for its direction, making it easier and more rapid in the next trial for a pulse of neural firing to reach the threshold to trigger a similarly directed saccade. This phenomenon was labeled a type of "immediate neural plasticity".

Whether such directional plasticity also exists in humans is unclear. Other studies suggest a contradictory

effect. It may be harder rather than easier for humans to make a saccade back to the same location (Rafal et al. 1989) or when the stimulus direction is repeated (Fecteau et al. 2004). This has been called an "alternation advantage" (Fecteau et al. 2004), which has similarities to "inhibition of return" (Klein 2000). In inhibition of return, if a target is preceded by more than 300 ms by another stimulus at its location, the perceptual processing of the target is degraded and saccades to it are delayed. Inhibition of return has been hypothesized to play a role in facilitating visual search, by decreasing the saliency of locations already visited or attended (Klein 2000).

Which of these inter-trial effects dominates human saccades? Our goal was to examine for persistent directional effects in a string of randomly directed horizontal saccadic trials. As Dorris et al. (2000) did in monkeys, we examined the effects of both the prior trial and the penultimate trial. We analyzed the effects both for prosaccades, in which the subject looks at the target when it appears, and antisaccades, in which the subject makes a more unusual response, looking in the direction opposite to the target (Hallett and Adams 1980). The antisaccade, by dissociating the direction of the stimulus and the required motor response, allows us to determine whether directional effects depend upon the direction of the stimulus, the direction or the response, or the conjunction between the direction of the saccadic stimulus and that of the response.

We assessed these effects in two groups of human subjects, healthy subjects and a cohort of patients with schizophrenia. We have reported that schizophrenia patients show abnormally persistent inhibitory effects of antisaccades on subsequent trials (Barton et al. 2005). If heightened persistence characterizes other inter-trial effects in schizophrenia, they may be a good group in which to detect subtle effects from directional plasticity. On the other hand, there are also reports of reduced inhibition of return in schizophrenia (Huey and Wexler 1994; Gouzoulis-Mayfrank et al. 2004, 2006). A combination of strong directional plasticity and weak inhibition of return might predict that alternation advantage in this type of saccadic paradigm might also be reduced in schizophrenia.

Experiment 1 (Single-task blocks)

Methods

Participants

The details of the methods have been described in our previous reports on the inter-trial effects of antisaccades in the same subjects (Cherkasova et al. 2002; Manoach et al. 2002). We studied 16 healthy subjects, 5 women and 11 men with mean age of 40.3 years (SD 8.7), and 21 outpatients with schizophrenia, 4 women and 17 men with mean age of 43.7 years (SD 8.0). All patients had been maintained on stable doses of antipsychotic drugs for at least 6 weeks. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al. 1997). Healthy and schizophrenia groups did not differ in mean age, sex distribution, handedness score or parental socioeconomic status (Hollingshead 1965; see Manoach et al. 2002 for subject details). The committee on clinical investigations at the Beth Israel Deaconess Medical Center approved the study and all subjects gave written informed consent.

Apparatus and eye movement protocol

We recorded eye movements with a magnetic search coil technique (Crist Instruments, Bethesda, MD, USA). Displays were generated by a Power Macintosh 9600/233, using programs written in C++ on the Vision Shell programming platform (http://www.kagi.com/visionshell), and back-projected with an Eiki LC-7000U projector. Eye position was digitized at 500 samples/s and a five-point central difference algorithm (Bahill and McDonald 1983) derived velocity from eye position.

The initial display had a dark background with a white 1° fixation ring at the center. The fixation ring was flanked by two 0.7° white dots right and left. Trials started when the subject's eye was within 3° of center. After 1–1.5 s, the fixation point was replaced by one of the two prompts—a yellow 'O' of 4.5° diameter for prosaccade trials or a blue 'X' spanning 4.5° for antisaccade trials. Prompts were replaced after 300 ms by the white fixation ring. After a mean interval of 2 s (range 1,850–2,150 ms) the ring target shifted to one of the two peripheral dots. After the subject fixated within 3° of the desired target location, the ring returned to the center, and the next trial began when the subject had returned to within 3° of the central fixation mark.

Experiment 1 consisted of blocks of 26 trials with a single type of saccadic task, either all prosaccades or all antisaccades. Four blocks were given of each, resulting in 104 prosaccade and antisaccade trials. The blocks of experiment 1 were interleaved with the blocks of experiment 2 in a counterbalanced order in the same test session. All subjects had a practice session of 20 trials for each of the prosaccade and antisaccade blocks of experiment 1, and the mixed saccade blocks of experiment 2.

Analysis

We identified saccades as eye movements with velocities exceeding 47°/s. The onset of a saccade was taken as a point at which the velocity of the eye first exceeded 31°/s. The first saccade after target onset was considered the saccadic response. The first saccade of each block was eliminated from analysis. We excluded trials whose saccadic responses had latencies less than 130 ms, as these would be anticipatory responses in advance of rather than in response to the appearance of the target. We also excluded trials with latencies greater than 800 ms as being too prolonged to accurately reflect the processes

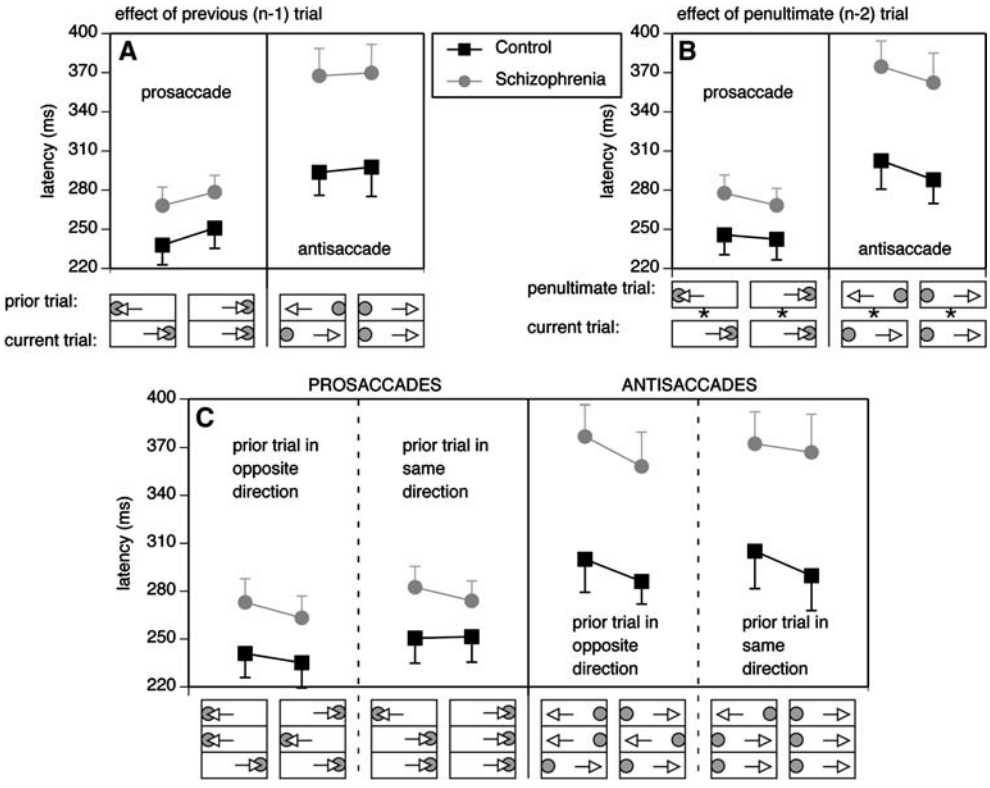

Fig. 1 Experiment 1: directional effects of the prior and penultimate trials on saccadic latency during single-task blocks. Trials are divided into those following trials with the same saccadic direction and those following trials with the opposite saccadic direction. Mean latencies of saccades across subjects are shown, with *error bars* indicating one standard error. *Symbols at the bottom* indicate the congruence between stimulus and the response during previous and current trials, with the *arrow* indicating the saccade direction and the *gray dot* the location of the stimulus. **a** The effect of the prior trial (irrespective of the penultimate trial). For prosaccades, saccades are slower when preceded by saccades in the same direction than when preceded by saccades in the opposite direction, consistent with alternation advantage. For antisaccades the effect is not significant. **b** The effect of the penultimate trial (irrespective of the prior trial). For both antisaccades and prosaccades, saccades are faster when preceded by saccades in the same direction than when preceded by saccades in the opposite direction, consistent with directional plasticity. **c** Data for all different directional sequences. The directional plasticity effect of the penultimate trial is fairly consistent across all different sequences. Note that the results for schizophrenia are very similar to those for healthy subjects

we wished to isolate. Saccades were classified as directionally correct if their vector was in the appropriate direction, regardless of their amplitude.

Trials were classified by the congruence of the direction of the saccades in the prior two trials with the direction of the saccade in the current trial. Thus a *YYX* trial is one in which both the prior and the penultimate responses (saccades in the *Y* direction) differ from the current response (saccade in the *X* direction). This would include both a right saccade preceded by two left saccades and a left saccade preceded by two right saccades. We included only directionally correct trials that were preceded by two correct trials. ANOVA with repeated measures was employed to examine the effects of subject group (healthy vs. schizophrenia), saccade type (prosaccade vs. antisaccade), congruence of prior trial (same direction vs. different direction) and congruence of penultimate trial, with subject as a random effect nested within group. This was done using the JMP 3.2.6 program (SAS Institute, Cary, NC, USA).

Results

Latency effects

The effects of the direction of the response in the immediately preceding trial were more consistent with alternation advantage than with directional plasticity (Fig. 1a). The mean latency of saccades in the same direction was about 9 ms slower than that for saccades in the direction opposite to the prior trial [$F(1,34) = 6.26$, $P < .013$]. Alternation advantage was greater for prosaccades [interaction of directional congruence with saccade type: $F(1,34) = 7.12$, $P < .008$]. Linear contrasts showed a significant effect of the direction of the prior prosaccade on the latency of a current prosaccade ($t = 4.19$, $P < .0001$), but no effect of the direction of the preceding antisaccade on the latency of a current antisaccade ($t = 0.11$, n.s.).

However, the results from the penultimate trial were the opposite (Fig. 1b). Here the effects were more consistent

Table 1 Number of trials and error frequency in experiment 1

Group	Current saccade	Direction	Mean *n* of trials	Mean %error	Standard deviation
$n-1$ analysis					
Control subjects	Prosaccade	Different	50	0.88	3.04
		Same	45	0.71	1.81
	Antisaccade	Different	44	11.22	10.06
		Same	44	7.02	10.62
Schizophrenic patients	Prosaccade	Different	47	1.49	2.57
		Same	44	1.06	2.42
	Antisaccade	Different	35	32.11	21.07
		Same	31	24.39	19.95
$n-2$ analysis					
Control subjects	Prosaccade	Different	47	1.20	3.15
		Same	44	0.65	2.59
	Antisaccade	Different	42	9.72	7.90
		Same	36	6.09	6.77
Schizophrenic patients	Prosaccade	Different	45	2.01	3.27
		Same	41	0.48	1.27
	Antisaccade	Different	25	30.43	21.12
		Same	23	30.77	26.13

with directional plasticity than alternation advantage. The mean latency of saccades in the same direction as the saccade two trials back was about 8 ms faster, not slower [$F(1,34) = 10.05$, $P < .002$]. Furthermore the results were similar for both prosaccades and antisaccades, as indicated by a lack of interaction of directional congruence of the penultimate trial with saccade type.

As expected, schizophrenic patients had longer antisaccade latencies than control subjects, as indicated by an interaction between the subject group and current saccade type [$F(1,34) = 739$, $P < .0001$]. However, there were no significant interactions involving subject group and directional congruency of either the prior or penultimate response. Hence we conclude that the directional effects for the schizophrenia patients were not different from those in the healthy subjects in this single-task block design.

Directional error effects (Table 1)

There was a significant effect of saccade type, with more error on antisaccades than prosaccades [$F(1,34) = 130$, $P < .0001$] and a significant main effect of directional congruence from the immediately preceding trial, with more errors when direction changed (12%) than when it stayed the same (8%) [$F(1,34) = 7.1$, $P < .009$]. There was a significant interaction between saccade type and directional congruence of the preceding trial [$F(1,34) = 6.2$, $P < .013$], with a small repetition advantage for antisaccades ($t = 3.64$, $P < .0003$) but not prosaccades ($t = 0.12$, n.s.). There were no significant effects involving the directional congruence of the penultimate trial. Hence speed accuracy trade-offs cannot explain the effects of the direction of the preceding trial on prosaccade latency or the effects of the direction of the penultimate trial on the latency of either prosaccades or antisaccades.

Group effects showed a significant main effect, with schizophrenic patients making more errors [$F(1,34) = 14.3$, $P < .0006$], and an interaction between group and saccade type, with schizophrenic error rate similar to that of controls for prosaccades ($t = 0.87$, n.s.) but elevated for antisaccades ($t = 9.95$, $P < .0001$). As with the latency data, no other group interactions were significant.

Comment

These results provide evidence of both directional plasticity and an alternation advantage in human saccades. The 'inhibition of return'-like alternation advantage dominates the effects of the preceding trial on the next, but its effects weaken rapidly, so that by two trials later directional plasticity is evident instead. The alternation advantage was only evident for prosaccades. Previous studies have been variable on this point. One recent study reported that there was no interaction between saccade type and direction repetition, but their figure suggests that the antisaccade data were more variable and it is unclear if a specific comparison of direction for antisaccades would have yielded a significant result (Reuter et al. 2006). Another study has reported that both prosaccades and antisaccades show inhibition of return following a preceding prosaccade under some cuing conditions, but only prosaccades and not antisaccades manifest this directional effect with other cues (Rafal et al. 1994). (However, the relevance of these findings to the current data is limited by the fact that in that study the antisaccades were all preceded by prosaccades.)

We suggest that a finding of alternation advantage with prosaccades but not antisaccades may imply that this phenomenon is dependent upon a stimulus at the prior saccade's goal. This stimulus dependency accords with the hypothesis that inhibition of return serves to facilitate visual exploration, does not require the execution of a prior response (Klein 2000) and is consistent with recent data suggesting that alternation advantage originates in sensory rather than motor biases (Fecteau et al. 2004). In contrast, directional plasticity from the penultimate trial was present for both prosaccades and

antisaccades, indicating that this effect depends more on the penultimate saccade than on the penultimate stimulus. Hence directional plasticity may reflect changes generated by motor responses.

The results in the schizophrenic patients were no different from the controls. Thus there is no evidence of a reduced alternation advantage from weakened inhibition of return or excessively strong directional plasticity effects from the penultimate trial.

The fact that we found influences of directional plasticity from the penultimate trial (in that a saccade in the same direction as a saccade two trials back is faster than one in the opposite direction) suggests that similar effects might be present from the immediately prior trial, but masked by stronger 'inhibition of return' in the opposite direction. To investigate this, we turned to the blocks of randomly mixed pro- and antisaccade trials of Experiment 2.

Experiment 2 (mixed-task blocks)

Blocks with all prosaccades or all antisaccades allow only a limited exploration of the influence of the stimulus and response of the prior trial on the response in the next trial. Consider a block of antisaccades alone. If one knows that the required response in the current antisaccade trial is in the opposite direction to that of the previous antisaccade, then it automatically follows that the current antisaccade must be in the same direction as the previous stimulus. Thus in a block of pure antisaccades, the direction of the stimulus and the direction of the response will always be opposite and it is not possible to disentangle their discrete effects on subsequent trials. To explore both stimulus-based and response-based intertrial effects, it is desirable to have a paradigm in which one can independently dissociate the relation between the current trial's response and the prior stimulus direction on one hand and the prior response direction on the other. Blocks with a random mixture of both prosaccades and antisaccades provide such a dissociation. For example, with two prosaccades in the same direction, both the prior saccade and the prior stimulus are congruent with the direction of the current prosaccade. However, if the trial before the prosaccade was an antisaccade in the same direction, then the prior saccade is congruent but the prior stimulus is not. If there are both stimulus-based and response-based effects from the prior trial, the contrast between these two types of sequences will show additive interactions of these effects in one case and subtractive interactions in the other (Fig. 2). A similar strategy has been used recently to support conclusions that sensory rather than motor processes in the prior trial generate alternation advantage (Fecteau et al. 2004).

We formulated a key prediction based upon three assumptions derived from experiment 1. First, we proposed that the prior trial generates both alternation advantage and directional plasticity. Second, we hypothesized that alternation advantage derives from the prior

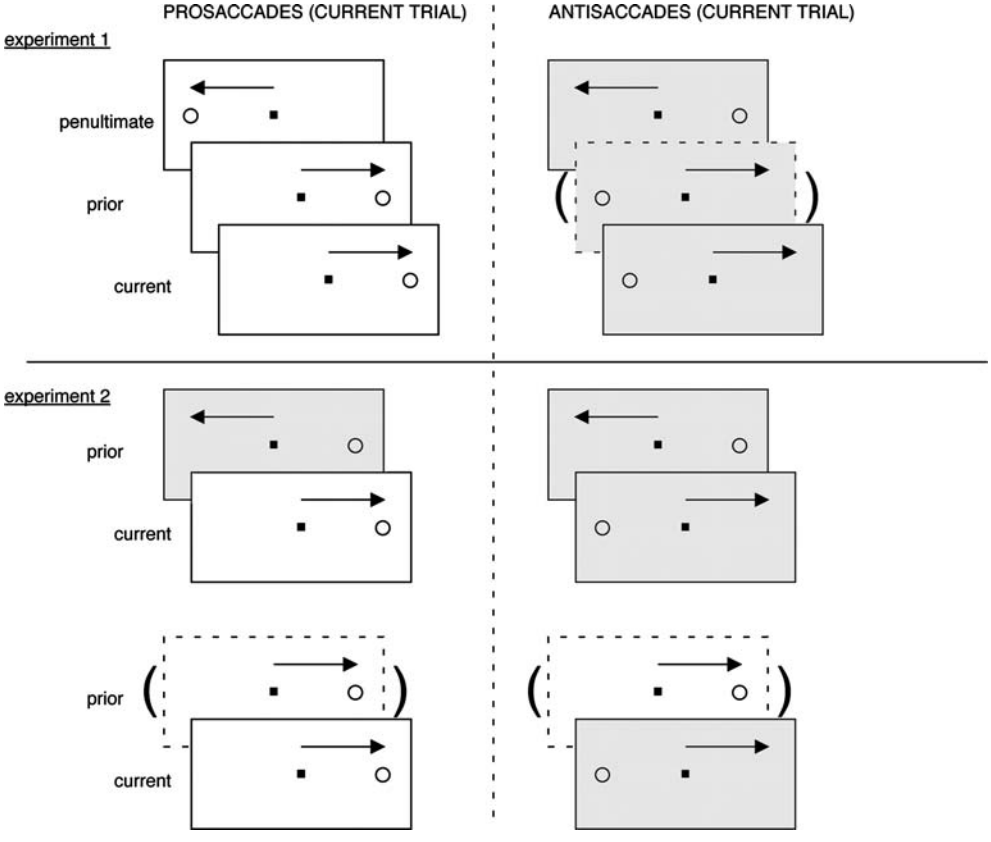

Fig. 2 Depiction of inter-trial inhibitory effects. *Left side* indicates results for current prosaccades, *right side* for current antisaccades. Antisaccade trials are shaded *light gray*. In each *rectangle* depicting a trial, the *black dot* indicates the screen center, the *arrow* the direction of the saccade and the *disc* the location of the stimulus. The sequences that generate the greatest inhibition (longest latencies) of the current trial are shown. Trials in *parentheses with dashed outlines* indicate where effects of preceding trials are minimal. In experiment 1, a penultimate saccade in the opposite direction and a prior stimulus in the same direction both inhibit prosaccades, while antisaccades show only an inhibitory effect from a penultimate saccade in the opposite direction. In the healthy subjects in experiment 2, the greatest inhibition was seen for a prior antisaccade in the opposite direction to the current saccade, whether prosaccade or antisaccade. Prior prosaccades had little effect

stimulus and therefore causes a slowing of a saccade in the same direction as the stimulus of the prior trial. Third, we hypothesized that directional plasticity derives from the previous response and therefore facilitates a saccade in the same direction as the saccade in the prior trial. If these assumptions are correct, then the longest prosaccade latencies should occur when a prosaccade is preceded by an antisaccade in the opposite direction. In such a sequence the prosaccade is preceded by a stimulus in the same direction and a response in the opposite direction and the effects of alternation advantage and directional plasticity should coincide, leading to a larger overall effect on latency. In contrast, a preceding prosaccade in either direction would have less effect, since the effects of alternation advantage and directional plasticity would not coincide but instead compete (Fig. 2).

Methods

As stated above, data for experiment 2 were collected in the same subjects in the same testing session as experiment 1, with experimental blocks interleaved in a counterbalanced order. The same trial design was used, with the same stimuli and timing parameters. In contrast to experiment 1, experiment 2 consisted of blocks of 52 trials that contained a random mix of prosaccades and antisaccades. Each block was repeated four times, generating 104 prosaccade and antisaccade trials.

In these mixed-task blocks, trials were classified not only by the congruence of the direction of the prior saccade with the direction of the current saccade, but also by the type of the saccade in the prior trial. Here the ANOVA with repeated measures examined the effects of subject group (healthy vs. schizophrenia), current saccade type (prosaccade vs. antisaccade), prior saccade type and directional congruence (same vs. different response direction), again with subjects as a random effect nested within group. Again, we included only correct trials that had also been preceded by a correct trial and omitted the first trial of each block from analysis. For specific a priori comparisons or explorations of the bases of significant interactions, we used linear contrasts within the ANOVA analysis.

Results

Latency effects

We first report the results that do not involve subject group. Main effects and interactions that are not mentioned were not significant. As expected, both antisaccades in the current trial [$F(1,34) = 305$, $P < .0001$] and having an antisaccade in the prior trial [$F(1,34) = 19.8$, $P < .0001$] were associated with increased latency, consistent with reports from other subjects (Fecteau et al. 2004; Barton et al. 2006). The only effect involving the directional congruence of responses was a significant three-way interaction between directional congruence, current saccade type and prior saccade type [$F(1,34) = 4.29$, $P < .039$]. The predictions from interacting effects from both a stimulus-based alternation advantage and a response-based directional plasticity were supported in prosaccades (Fig. 3). There was significant inhibition (longer prosaccade latencies) from a prior antisaccade in the opposite direction compared to one in the same direction ($t = 2.01$, $P < .043$), consistent with a hypothesized combination of effects from both alternation advantage and directional plasticity operating to slow the response. This effect was particularly evident in the healthy subjects ($t = 2.96$, $P < .004$). Also, the direction of a prior prosaccade had no significant effect on the latency of a current prosaccade, which would be the expected result when the opposing effects of alternation advantage and directional plasticity cancel out each other. However, for current antisaccade trials the effect of direction of the prior response was less evident, regardless of the type of prior saccade (Table 2).

When the effects of subject group were studied, an interesting difference emerged in the directional analysis between healthy and schizophrenia subjects. As expected, schizophrenia patients had longer antisaccade latencies than the healthy controls, seen in a significant interaction between current saccade type and subject group [$F(1,34) = 17.3$, $P < .0001$]. However, there was also a significant interaction between subject group and directional congruence [$F(1,34) = 5.9$, $P < .016$] and a three-way interaction between subject group, directional congruence and prior saccade type [$F(1,34) = 6.48$, $P < .011$]. Figure 3 shows that two chief differences generated these interactions. First, schizophrenia patients did not show the significant delay of prosaccade latencies that healthy subjects had when the prior trial had an antisaccade response in the opposite direction. Second, there was a paradoxical slowing of a current antisaccade by another antisaccade in the same direction ($t = 2.74$, $P < .006$), which did not occur in healthy subjects. This paradoxical slowing is opposite to the predicted effects of either alternation advantage or directional plasticity. Rather, a different phenomenon must be present.

Directional error effects

There was a significant main effect of saccade type, with antisaccades less accurate than prosaccades [$F(1,34) = 179$, $P < .0001$]. There was a significant interaction of current saccade type with prior saccade type [$F(1,34) = 46.1$, $P < .0001$], with both prosaccades and antisaccades more inaccurate when the prior trial was a different saccade type—again, a finding we have already reported in this group (Manoach et al. 2002) and consistent with reports from other subjects (Fecteau et al. 2004; Barton et al. 2006). There was a main effect of directional congruence of the responses [$F(1,34) = 6.16$, $P < .02$], with slightly more errors when the direction was changed, but no significant interactions involving directional congruence.

Looking at group effects, controls were more accurate than schizophrenia patients [$F(1,34) = 26.5$, $P < .0001$].

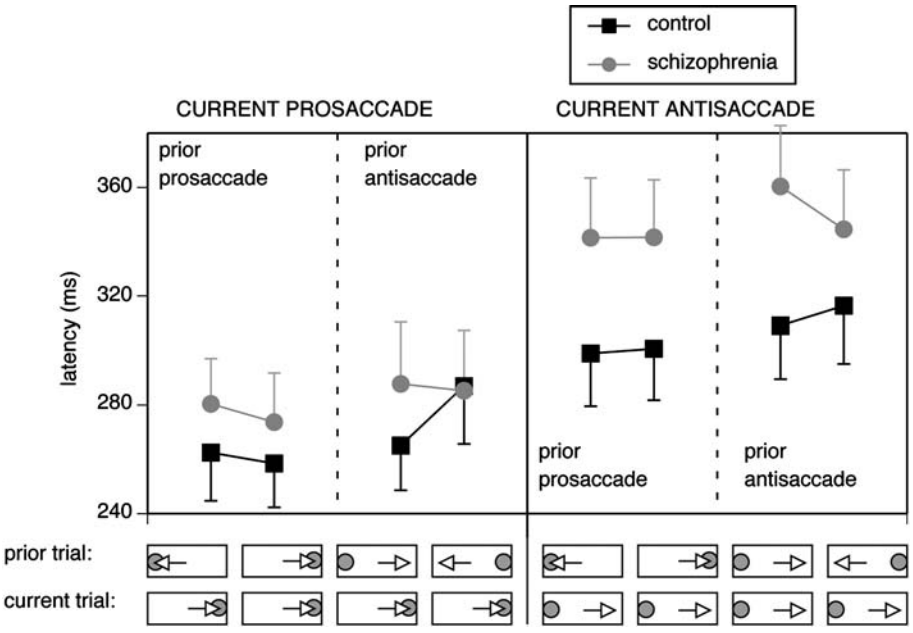

Fig. 3 Experiment 2: prior trial effects from preceding prosaccades versus antisaccades. Mean latencies of saccades across subjects are shown, with *error bars* indicating one standard error. *Symbols at the bottom* indicate the congruence between stimulus and the response during the prior and current trials, with the *arrow* indicating the saccade direction and the *gray dot* the location of the stimulus. In this experiment a prosaccade (or an antisaccade) could be preceded by either a prosaccade or an antisaccade, allowing the directional effects of the prior stimulus and the prior saccade to be dissociated. We hypothesized that inhibition of a current saccade is generated by a stimulus in the same direction (alternation advantage) or a saccade in the opposite direction (directional plasticity). When these coincide, the effects of prior direction on latency are maximized; when they compete, they cancel each other. This pattern of results is seen in the healthy subject data. However, schizophrenic patients show a paradoxical increase in latency from a prior antisaccade in the same direction

Table 2 Number of trials and error frequency in experiment 2

Group	Current saccade	Prior saccade	Response direction	Mean *n* of trials	Mean %error	Standard deviation
Control subjects	Prosaccade	Prior prosaccade	Different	25	1.94	2.85
			Same	23	0.19	0.79
		Prior antisaccade	Different	22	8.20	8.31
			Same	22	8.98	10.43
	Antisaccade	Prior prosaccade	Different	25	16.94	9.90
			Same	25	14.86	12.34
		Prior antisaccade	Different	23	10.02	11.09
			Same	23	7.57	6.74
Schizophrenic patients	Prosaccade	Prior prosaccade	Different	24	3.98	5.63
			Same	22	4.47	6.03
		Prior antisaccade	Different	19	16.63	11.10
			Same	17	11.02	11.58
	Antisaccade	Prior prosaccade	Different	24	35.91	17.45
			Same	23	35.21	15.21
		Prior antisaccade	Different	17	34.43	20.18
			Same	17	23.04	16.88

There was a significant interaction of group with saccade type [$F(1,34) = 46.5$, $P < .0001$], with schizophrenia patients only slightly worse than controls on prosaccades ($t = 2.59$, $P < .01$), but far worse than controls for antisaccades ($t = 12.2$, $P < .0001$). There was also a significant three-way interaction between group, prior saccade type and directional congruence [$F(1,34) = 4.29$, $P < .04$]. Schizophrenia patients showed an effect of directional congruence when the preceding response was an antisaccade ($t = 3.82$, $P < .0002$), with fewer errors when the saccade was in the same direction as the prior antisaccade response, but no effect of prior prosaccades ($t = 0.04$, n.s.). Control subjects did not show an effect of directional congruence from either prior prosaccades ($t = 0.81$, n.s) or prior antisaccades ($t = 0.35$, n.s.).

Thus, schizophrenia patients not only have paradoxically longer-than-expected latencies of any saccade when it is preceded by an antisaccadic response in the same

direction, but also make fewer errors in this circumstance. Thus the anomalous effect of prior antisaccades in schizophrenia has characteristics of a speed accuracy trade-off, but none of the other directional effects on latency do.

Comment

For healthy subjects performing prosaccades, the prediction that prosaccades preceded by antisaccades in the opposite direction would have the longest latencies of the four types of prosaccade sequences was confirmed. Also confirmed was the prediction that the direction of a prior prosaccade would modulate current prosaccade latencies less than the direction of a prior antisaccade. This is because the hypothesized effects of alternation advantage and directional plasticity would oppose each other with a prior prosaccade, but act synergistically with a prior antisaccade. However, the directional effects of prior antisaccades do not emerge so clearly in the data for current antisaccades. While Fig. 3 suggests a trend for prior antisaccades to have longer latencies when preceded by a prior antisaccade in the opposite direction, the linear contrast failed to reach significance. This may suggest that these directional inter-trial effects are muted with antisaccades, whose generation involves more complex processes such as prosaccade suppression and vector inversion (Munoz and Everling 2004).

The anomalous finding in schizophrenia patients is also of interest. We have previously shown that antisaccades increase the latencies of either prosaccades or antisaccades in the next trial (Cherkasova et al. 2002), and that this effect is more persistent in schizophrenia (Barton et al. 2005). If there is a directionally specific component to this enhanced antisaccade-induced inhibition of the saccadic system in schizophrenia, then antisaccades might also delay any subsequent saccade made in the same direction. If so, this would create a paradoxical slowing of antisaccades made in the same direction as a prior antisaccade, as observed in the current data. Also, this antisaccade effect could mitigate against the synergistic effects of alternation advantage and directional plasticity in current saccades preceded by antisaccades. This would explain why the prosaccades of healthy subjects benefit from a preceding antisaccade in the same direction, but schizophrenia patients show no directional effect of a prior antisaccade. Thus a proposed directional antisaccadic inhibition specific to schizophrenia could explain both of the statistical anomalies related to subject group.

We can formulate a simple explanatory model incorporating these three carry-over effects: directional plasticity, inhibition of return and an additional directionally selective antisaccadic inhibition specific to schizophrenia (Fig. 4). The variable we wish to explain is the difference between latencies of saccades in the same versus opposite direction of the stimulus in the prior trial. Thus we consider the inhibitory costs that each process adds to a saccade in the same direction as the stimulus in the prior trial. For simplicity, we assume that the magnitudes of alternation advantage and directional plasticity are equivalent and that the interaction between all three effects is linear and additive. We also assume, as above, that both effects are attenuated partially in antisaccades. Whether all of these assumptions are justified can be debated, but, as Fig. 4 shows, simple addition of these effects creates a pattern that reasonably approximates the results with our blocks of randomly mixed trials.

However, this modest model is limited in that such linear interactions do not appear to account for the latency data in the single-task blocks, where alternation advantage appears to be much stronger than directional plasticity in the effect of a prior prosaccade on a current one. Others have also recently noted discrepancies between single-task and mixed-task blocks for directional effects (Reuter et al. 2006). It may be that the differential demands on attention and working memory between single-task and mixed-task blocks modulate the relative strength of these different inter-trial influences, much as the different demands of prosaccades and antisaccades appear to modulate the strength of alternation advantage in the single-task blocks. Specifically, these factors may attenuate the alternation advantage in mixed-task blocks, allowing the influence of directional plasticity to be more apparent. Furthermore, the atypical effects of a prior antisaccade are not evident in the schizophrenia data in the single-task blocks, again suggesting that the additional demands inherent to the mixed-task blocks may be important for the unmasking of this anomaly.

It is also important to note that these results are somewhat discordant with the report of Fecteau et al. (2004), who used a similar paradigm of randomly mixed prosaccades and antisaccades and a similar inter-target interval of 3.7 s, in a smaller group of 12 subjects. They found an alternation advantage for all combinations of prosaccades and antisaccades, in terms of the relation of the current stimulus to the side of the preceding stimulus, but without the interaction of directional congruence with current or prior saccade type that we found. The reason for this discrepancy is unclear. Apart from other methodological differences, it may be that, just as the weights of the different inter-trial influences may vary with task demands, so too they may vary between individuals. It may be, for example, that directional plasticity effects were particularly weak in the subjects in the prior report. Our results at least have the advantage in that they were obtained in the same subjects and test sessions as the single-task blocks, which showed directional plasticity effects, and whose results were used to generate predictions that were examined and confirmed in the mixed-task design.

On the other hand, there is some support for this model from one other recent study that examined mixtures of prosaccades and antisaccades in normal subjects (Reuter et al. 2006). This study found that the only significant effect of the prior saccade's direction on latency was that a prior antisaccade in the opposite direction

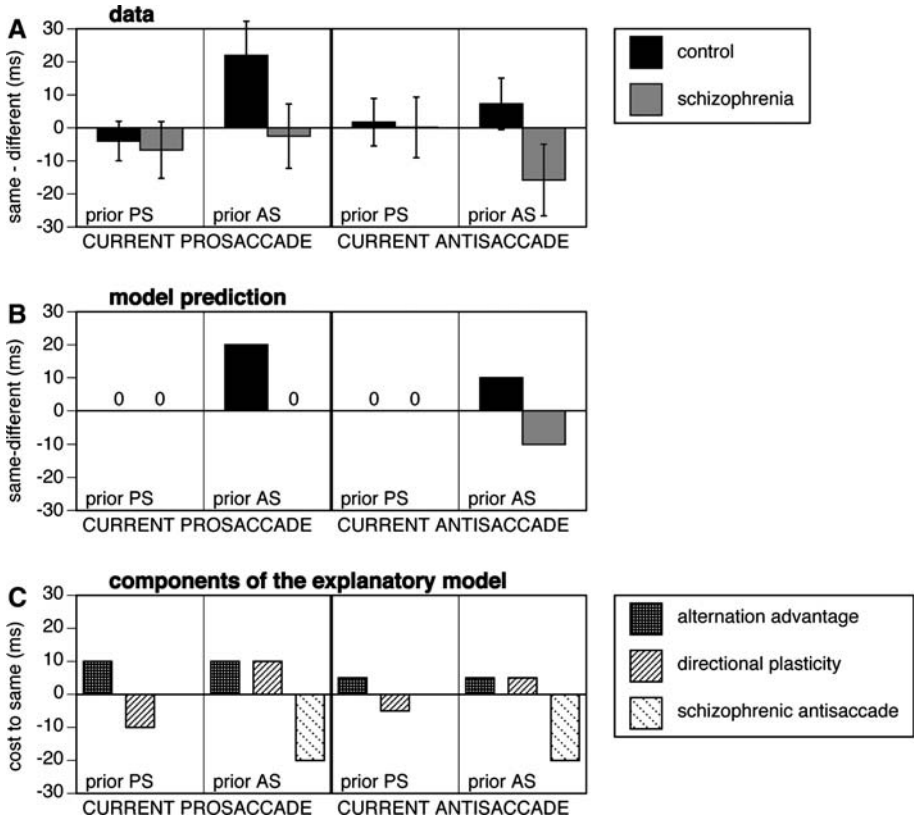

Fig. 4 Modeling the directional effect in experiment 2. To quantify the effect of the prior trial's direction, we subtract the latency for responses preceded by stimuli in the opposite direction, from the latency for responses preceded by stimuli in the same direction ('same − different'). Current prosaccades are on the *left half* of each graph, antisaccades are on the *right half*. Each half shows the effect of a prior prosaccade (*PS*) or a prior antisaccade (*AS*). **a** Data from the patients for this same/different directional measure. **b** Model of the results from simple addition of the individual effects in **c**. **c** Hypothetical effects of alternation advantage, directional plasticity and the proposed directionally specific antisaccade inhibition in schizophrenia. These are modeled as their effect on the latency of trials preceded by trials with stimuli in the same direction as the current saccade, the "cost to same". Alternation advantage always adds to the latency of these trials (increasing cost). However, the directional plasticity effect will differ depending on whether the prior trial was a prosaccade or an antisaccade. If a prosaccade, its effect will be opposite to that of alternation advantage, because directional plasticity facilitates repetition of saccades in the same direction. If an antisaccade it will add to alternation advantage. The model speculates that both alternation advantage and directional plasticity may be reduced for current antisaccades. The schizophrenic antisaccade effect is a response-based effect that increases latency of saccades in the same direction as the prior antisaccade but opposite to the prior stimulus. Therefore there is a reduction in the latency cost to trials with the same direction as the prior antisaccade's stimulus

increased the latency of a current prosaccade. This in fact is the prediction of our model that the longest prosaccade latencies should occur when a prosaccade is preceded by an antisaccade in the opposite direction, and it is also consistent with our results that the largest directional effect is from a prior antisaccade on a current prosaccade, and all other effects are insignificant (Fig. 4).

Finally, we caution that the consistency of our model with the results and the a priori prediction from hypotheses generated in experiment 1 does not exclude other explanations for the pattern of results in experiment 2. For example, since an antisaccade requires suppression of a prosaccade in the opposite direction, persistence of this may prolong a prosaccade in the opposite direction in the next trial, as we found. An antisaccade in the next trial may not be affected if this directionally selective inhibition is specific to the prosaccade task set. However, such an explanation fails to incorporate the directional effects seen in experiment 1 and in fact would predict no directional effects in that setting.

Discussion

The results in these experiments confirm the existence of directionally selective inter-trial effects on saccadic latency. The findings from blocks of randomly mixed prosaccades and antisaccades provide evidence that alternation advantage is not the only factor operating from the immediately prior trial, even though it dominates when prosaccades are performed in a uniform block. The results also provide support for the concept that alternation advantage is based upon the prior stimulus, not the prior response. If it was the latter, alternation advantage would always compete with directional plasticity and one would be unlikely to find any difference between the effects of a prior prosaccade or a prior

antisaccade. The fact that dissociating the stimulus from the response in the prior trial leads to very different patterns in latency argues that alternation advantage and directional plasticity must derive from separate aspects of the prior trial, one possibly stimulus-based, the other possibly response-based. When the effects of the two are aligned the directional effect of the prior trial is magnified, as seen in the prosaccades of our healthy subjects; when they compete the directional effect is reduced.

Experimentally, alternation advantage is seen as an inter-trial effect in a series of responses separated by several seconds, even up to 11 s (Fecteau et al. 2004), whereas inhibition of return is traditionally studied as the effect of a preceding cue on a response that follows hundreds of milliseconds later and hard to detect after 2–3 s (Samuel and Kat 2003). Despite these differences, Fecteau et al. (2004) offer plausible arguments why both may reflect the same underlying neural phenomena. While inhibition of return is classically demonstrated with a first visual stimulus that attracts attention to a specific location, following which manual or saccadic responses to a second stimulus at that location are delayed, several studies show that inhibition of return can also occur when the first stimulus also requires a saccade of its own (Vaughan 1984; Posner et al. 1985; Rafal et al. 1994; Tanaka and Shimojo 1996; Taylor and Klein 2000). Thus it is plausible that inhibition of return is operating between saccades in a series of trials, as with alternation advantage.

In most studies of inhibition of return, the magnitude of the effect on either manual or saccadic reaction times is a function of the interval between the first and the second stimulus, ranging from a peak of 30 to 50 ms when the interval is about 300 to 500 ms and decaying to 20 ms or less when the interval is greater than 2,000 ms (for reviews, see Klein 2000; Samuel and Kat 2003). The 9 ms magnitude of our effect, occurring at an average inter-trial interval of around 3–4 s, is small but consistent with the size of inhibition of return effects seen at around 3,200 ms (Fig. 1 of Samuel and Kat 2003) and in the original report showing inhibition of return in a second saccade after a first one (Posner et al. 1985) and is also consistent with the alternation advantage reported for inter-target intervals of 3.7 s (Fecteau et al. 2004).

Although others and we propose that alternation advantage arises from the stimulus in the preceding trial, one point of remaining ambiguity is which aspect of the current trial is affected by alternation advantage. While we view the preceding stimulus as facilitating an upcoming saccade in the opposite direction, Fecteau et al. (2004) view it as facilitating an upcoming stimulus in the opposite direction. This was based on their mixed-block data showing such an effect regardless of whether the current or prior trial was an antisaccade or a prosaccade. Our results and those of Reuter et al. (2006) differ, though, showing in particular no significant effect with current antisaccades. The operation of an alternation advantage facilitating the current stimulus as the sole inter-trial influence would not explain the interaction we found. Rather, an interaction fits best with a combination of effects from directional plasticity (prior saccade affecting current saccade) and alternation advantage (prior stimulus affecting current trial). With such a combination, what would be the difference between an alternation advantage affecting the current stimulus versus one operating on the current saccade? Both would predict the same directional effects on current prosaccades, namely little effect from prior saccades, because directional plasticity and alternation advantage act in opposing directions, and a large effect from prior antisaccades, because their effects would summate. Where these two concepts of alternation advantage differ is in the effect on current antisaccades. Alternation advantage acting on the current saccade predicts that directional effects would summate for an antisaccade preceded by an antisaccade and cancel for an antisaccade preceded by a prosaccade, whereas alternation advantage acting on the current stimulus predicts the opposite. Unfortunately, our results and those of Reuter et al. (2006) show that the effects on a current antisaccade are modest: while we find a non-significant but slightly higher latency effect for an antisaccade preceded by an antisaccade, they find a non-significant but slightly higher latency effect for an antisaccade preceded by a prosaccade. Since the key differences predicted by these two concepts of alternation advantage cannot be confirmed with significant findings from the available data, this issue is unsettled.

In schizophrenia patients, our single-task blocks showed that their alternation advantage was no different from that of controls. While alternation advantage has not been previously studied in schizophrenia, there are a few reports on inhibition of return in this condition, though with conflicting findings. Some report that inhibition of return is reduced (Huey and Wexler 1994; Gouzoulis-Mayfrank et al. 2004, 2006), but others report that it is normal (Carter et al. 1992; Fuentes et al. 1999; Fuentes and Santiago 1999) or only abnormal in the paranoid subtype of schizophrenia (Carter et al. 1994). Differences cannot be attributed to medication status, since all studies involved medicated subjects except for two (Carter et al. 1992, 1994). Rather, Gouzoulis-Mayfrank et al. (2004, 2006) suggested two possible methodologic reasons for the discrepancy. First the studies with normal results studied inhibition of return at longer intervals of about 1,200 ms. Since one study suggested that inhibition of return may be more delayed than reduced in schizophrenia, in that it began at around 300 ms in controls but at 500 ms in schizophrenic patients (Larrison-Faucher et al. 2002), the magnitude of inhibition of return at long intervals may be similar in the two groups. Second, the studies with normal results used a 'cue-back' procedure, in which the cue at the peripheral location is followed by a cue at fixation. Another study showed that the reduced inhibition of return without this 'return to fixation' cue normalized in schizophrenic patients when the cue was provided (Sapir et al. 2001). Since sequences of saccadic trials are characterized by relatively long inter-target intervals with a return to a fixation cue at the start of

each trial, our study shares key conditions with the trials showing normal inhibition of return in schizophrenia. Thus the finding in experiment 1 of normal alternation advantage in schizophrenia is consistent with current proposals about inhibition of return in this condition.

In the mixed-trial blocks the inter-trial directional effects were more complicated in schizophrenia patients, in whom we found that a preceding antisaccade inhibited any subsequent saccade in the same direction. In monkeys, the instruction to perform an antisaccade reduces the pre-target preparatory activity in the frontal eye field and superior colliculus, an effect that correlates with increased response latency and reduced error rate (Everling et al. 1999; Everling and Munoz 2000). We have hypothesized that, just as the directional plasticity has carry-over effects on the pre-target activity of the next trial, this depressive effect of antisaccades might also carry over to subsequent saccades. This would explain our finding that antisaccades delay any type of saccade in the next trial (Cherkasova et al. 2002). In schizophrenia, there is significant difficulty in performing antisaccades, with a high error rate that suggests difficulty inhibiting the reflexive prosaccade. However, when schizophrenia patients make a successful antisaccade, the inhibition generated by the antisaccade appears to be prolonged, as it delayed the latencies of saccades two trials later in these subjects but not in healthy controls (Barton et al. 2005). The results here suggest that there is a directionally specific aspect of this antisaccadic inhibition of the saccadic system, which is also abnormally strong in schizophrenia. We have suggested that this excessive inhibition may be an adaptive response to the difficulty these subjects have in suppressing reflexive errors during the antisaccade task. To correctly perform an antisaccade may require much stronger inhibitory control of the saccadic system in schizophrenia patients. This could be implemented through greater depression of preparatory activity in ocular motor structures. This would not only increase latency but also help mitigate against their high error rate, thus partially counteracting their marked difficulty in suppressing reflexive prosaccades. Persistence into the next trial of a directional aspect of this preparatory modulation could account for the reduced errors and increased latencies for saccades in the same direction as a prior antisaccade that we found in schizophrenia in this report. This directional carry-over from a prior antisaccade is also reflected in our prior report from these same patients that schizophrenia patients make perseverative errors (errors repeating the same direction as a prior response) after an antisaccade but not a prosaccade, an effect not found in healthy subjects (Barton et al. 2005).

Hence we suggest that schizophrenic patients have difficulty not so much with inhibition but with implementing inhibitory control, reflected in a highly variable ability to inhibit a reflexive prosaccade from one trial to the next. Difficulty in implementing inhibition may be reflected in decreased activity in brain areas such as prefrontal cortex (McDowell et al. 2002): these could be due to primary deficits in initiating inhibitory mechanisms but could also reflect secondary effects of abnormalities in other cognitive domains, such as working memory (Roberts et al. 1994), goal activation (Nieuwenhuis et al. 2004) or context processing (Cohen and Servan-Schreiber 1992, 1993; Cohen et al. 1999). To overcome this barrier to implementation requires excessive deployment of inhibition, possibly leading to greater depression of preparatory activity in ocular motor structures, with the consequence of the abnormally strong and persistent inhibitory inter-trial effects from a prior antisaccade we have documented.

In conclusion, we demonstrate that the effects of a prior saccade include both an 'inhibition of return'-like alternation advantage from the preceding stimulus and directional plasticity from the prior saccade. Alternation advantage serves to depress trials with the same stimulus location, whereas directional plasticity facilitates repeated saccades in the same direction as the prior response. Alternation advantage may have a shorter time course than directional plasticity in our paradigm, since it is only evident from the prior trial, while the effects of the penultimate trial are consistent with directional plasticity instead. In blocks of randomly mixed prosaccades and antisaccades, patterns can be seen that suggest that both effects are present from the prior trial and interact in their effects on latency. Schizophrenia patients have an additional effect, in which a prior antisaccade inhibits any future saccade in the same direction. These findings illustrate the complexity of inter-trial effects and the modulation of current behavior by past events in human subjects and reveal some important differences in directional inter-trial influences between humans and monkeys (Dorris et al. 2000).

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References

Bahill T, McDonald J (1983) frequency limitations and optimal step size for the two-point central difference derivative algorithm with applications to human eye movement data. IEEE Trans Biomed Eng 30:191–194

Barton J, Cherkasova M, Lindgren K, Goff D, Manoach D (2005) What is perseverated in schizophrenia? Evidence of abnormal response plasticity in the saccadic system. J Abnorm Psychol 114:75–84

Barton J, Greenzang C, Hefter R, Edelman J, Manoach D (2006) Switching, plasticity, and prediction in a saccadic task-switch paradigm. Exp Brain Res 168:76–87

Carter C, Robertson L, Chaderjian M, Celaya L, Nordahl T (1992) Attentional asymmetry in schizophrenia: controlled and automatic processes. Biol Psychiatry 31:909–918

Carter C, Robertson L, Chaderjian M, O'Shora-Celaya L, Nordahl T (1994) Attentional asymmetry in schizophrenia: the role of illness subtype and symptomatology. Prog Neuropsychopharmacol Biol Psychiatry 18:661–683

Cherkasova M, Manoach D, Intriligator J, Barton J (2002) Antisaccades and task-shifting: interactions in controlled processing. Exp Brain Res 144:528–537

Cohen J, Servan-Schreiber D (1992) Context, cortex and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev 99:45–77
Cohen J, Servan-Schreiber D (1993) A theory of dopamine function and its role in cognitive deficits in schizophrenia. Schizophr Bull 19:85–104
Cohen JD, Barch DM, Carter C, Servan-Schreiber D (1999) Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. J Abnorm Psychol 108:120–133
Dorris M, Paré M, Munoz D (2000) Immediate neural plasticity shapes motor performance. J Neurosci 20:RC52
Everling S, Munoz DP (2000) Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. J Neurosci 20:387–400
Everling S, Dorris MC, Klein RM, Munoz DP (1999) Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. J Neurosci 19:2740–2754
Fecteau J, Munoz D (2003) Exploring the consequences of the previous trial. Nat Rev Neurosci 4:435–443
Fecteau J, Au C, Armstrong I, Munoz D (2004) Sensory biases produce alternation advantage found in sequential saccadic eye movement tasks. Exp Brain Res 159:84–91
First M, Spitzer R, Gibbon M, Williams J (1997) Structured clinical interview for DSM-IV axis I disorders, research version, patient edition with psychotic screen (SCID-I/P W/PSY SCREEN). Biometrics Research, New York State Psychiatric Institute, New York
Fuentes L, Santiago E (1999) Spatial and semantic inhibitory processing in schizophrenia. Neuropsychology 13:259–270
Fuentes L, Boucart M, Alvarez R, Vivas A, Zimmerman M (1999) Inhibitory processing in visuospatial attention in healthy adults and schizophrenic patients. Schizophr Res 40:75–80
Gouzoulis-Mayfrank E, Heekeren K, Voss T, Moerth D, Thelen B, Meincke U (2004) Blunted inhibition of return in schizophrenia—evidence from a longitudinal study. Prog Neuropsychopharmacol Biol Psychiatry 28:389–396
Gouzoulis-Mayfrank E, Arnold S, Heekeren K (2006) Deficient inhibition of return in schizophrenia—further evidence from an independent sample. Prog Neuropsychopharmacol Biol Psychiatry 30:42–49
Hallett P, Adams B (1980) The predictability of saccadic latency in a novel voluntary oculomotor task. Vis Res 20:329–339
Hollingshead A (1965) Two factor index of social position. Yale University Press, New Haven
Huey ED, Wexler BE (1994) Abnormalities in rapid, automatic aspects of attention in schizophrenia: blunted inhibition of return. Schizophr Res 14:57–63
Klein R (2000) Inhibition of return. Trends Cogn Sci 4:138–147
Larrison-Faucher A, Briand K, Sereno A (2002) Delayed onset of inhibition of return in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 26:505–512
Manoach DS, Lindgren KA, Cherkasova MV, Goff DC, Halpern EF, Intriligator J, Barton JJS (2002) Schizophrenic subjects show deficient inhibition but intact task-switching on saccadic tasks. Biol Psychiatry 51:816–825
McDowell J, Brown G, Paulus M, Martinez A, Stewart S, Dubowitz D, Braff D (2002) Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. Biol Psychiatry 51:216–223
Munoz D, Everling S (2004) Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 5:218–228
Nieuwenhuis S, Broerse A, Nielen M, de Jong R (2004) A goal activation approach to the study of executive function: an application to antisaccade tasks. Brain Cogn 56:198–214
Posner M, Rafal R, Choate L, Vaughan J (1985) inhibition of return: neural basis and function. Cogn Neuropsychol 2:211–228
Rafal R, Calabresi P, Brennan C, Sciolto T (1989) Saccade preparation inhibits reorienting to recently attended locations. J Exp Psychol Hum Percept Perform 15:673–685
Rafal R, Egly R, Rhodes D (1994) Effects of inhibition of return on voluntary and visually guided saccades. Can J Exp Psychol 48:284–300
Reuter B, Philipp A, Koch I, Kathmann N (2006) Effects of switching between leftward and rightward pro- and antisaccades. Biol Psychol 72(1):88-95
Roberts R, Hager L, Heron C (1994) Prefrontal cognitive processes: working memory and inhibition in the antisaccade task. J Exp Psychol Gen 123:374–393
Samuel A, Kat D (2003) Inhibition of return: a graphical meta-analysis of its time course and an empirical test of its temporal and spatial properties. Psychon Bull 10:897–906
Sapir A, Henik A, Dobrusin M, Hochman EY (2001) Attentional asymmetry in schizophrenia: disengagement and inhibition of return deficits. Neuropsychology 15:361–370
Tanaka T, Shimojo S (1996) Location versus feature: reaction time reveals dissociations between two visual functions. Vis Res 36:2125–2140
Taylor TL, Klein RM (2000) Visual and motor effects in inhibition of return. J Exp Psychol Hum Percept Perform 26:1639–1656
Vaughan J (1984) Saccades directed at previously attended locations in space. In: Gale A, Johnson C (eds) Theoretical and applied aspects of eye movement research. Elsevier, Amsterdam, pp 143–150