Exp Brain Res (2002) 147:53–63
DOI 10.1007/s00221-002-1207-5

RESEARCH ARTICLE

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The antisaccade task in a sample of 2,006 young males

II. Effects of task parameters

Received: 30 January 2002 / Accepted: 14 June 2002 / Published online: 13 September 2002

Abstract Antisaccade performance was investigated in a sample of 2,006 young males as part of a large epidemiological study investigating psychosis proneness. This report summarizes the effects of task parameters on performance using a sample of 55,678 antisaccade trials collected from a subpopulation of 947 individuals. Neither the amplitude nor the latency of an error prosaccade in the antisaccade task was correlated with the latency of the ensuing corrective antisaccade that almost always followed an error. However, the latency of the corrective antisaccade decreased with increasing stimulus distance. Concerning the effects of specific task parameters, trials with stimuli closer to the central fixation point and trials preceded by shorter fixation intervals resulted in more errors and longer latencies for the antisaccades. Finally, there were learning and fatigue effects reflected mainly in the error rate, which was greater at the beginning and at the end of the 5-min task. We used a model to predict whether an error or a correct antisaccade would follow a particular trial. All task parameters were significant predictors of the trial outcome but their power was negligible. However, when modeled alone, response latency of the first movement predicted 40% of errors. In particular, the smaller this latency was, the higher the probability of an error. These findings are discussed in light of current hypotheses on antisaccade production mechanisms involving mainly the superior colliculus.

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Keywords Antisaccade · Saccade · Volitional saccade · Reflex saccade · Attention · Inhibition · Saccade programming · Saccadic latency · Frontal lobe · Superior colliculus

Introduction

The antisaccade task has been widely used in the study of neurological and psychiatric diseases as an indicator of frontal lobe dysfunction (Everling and Fischer 1998). Functional imaging studies investigating the anatomical substrate of antisaccade movements showed that, in fact, a complex network of cortical and subcortical areas are activated when humans perform this task (O'Driscoll et al. 1995; Sweeney et al. 1996). Studies with primates have identified that increased neuronal activity in the lateral intraparietal area (LIP) (Zhang and Barash 2000), supplementary eye field (SEF) (Schlag-Rey et al. 1997), frontal eye field (FEF) (Everling and Munoz 2000), dorsolateral prefrontal cortex (DLPC) (Funahashi et al. 1993) and superior colliculus (Everling et al. 1999) are related to the direction of an impending volitional antisaccade eye movement. Thus, neurophysiological data support the hypothesis that the volitional antisaccade is indeed programmed and executed by a complex circuit involving both cortical and subcortical areas.

In part I of this work (Evdokimidis et al. 2002), we reported the results from the analysis of antisaccade task performance indices in a sample of 2,006 young males recruited from the Greek Air Force. The analyses focused on indices of performance for each subject and the correlation of these indices with other data about the individual such as IQ. In this second part, we pooled together a large set of individual trials from a randomly chosen subpopulation of 947 subjects to study the specific effects of task parameters on performance. Thus, we categorized individual trials according to stimulus direction and distance, according to the preceding fixation interval, and according to the presence or absence of a sequence of trials that often precedes a perseveration

error. We also investigated the effect of the trial position within the trial sequence to test for the existence of learning and fatigue effects. We then included such stimulus parameters in regression models in an effort to predict a specific trial outcome (error or correct, latency of first eye movement, latency of corrective eye-movement after an error). This analysis provided some insights into the possible mechanisms of antisaccade generation that are discussed in conjunction with published neurophysiological data concerning the performance of antisaccades in primates.

Materials and methods

The subject population, the experimental setup for the antisaccade task and the recording procedures have been described in detail in part I of this report (Evdokimidis et al. 2002).

In the present analysis, we investigated the effects of task parameters on performance. We selected a random subset of 947 subjects (47% of the total population of 2,006 subjects) whose trials included all parameters of interest, thus forming a set of 55,678 individual trials. The reason for including a randomly selected subset of individuals was that of forming a smaller data set of single trial data. Using the whole population would result in over 100,000 individual trials and the statistical processing of such a huge data set presented technical problems. From a statistical point of view we did not expect an increase of n from 55,678 to 100,000 to affect the resulting inferences, as both numbers were already extremely large. The same criteria for validity of a trial were used as described in part I (Evdokimidis et al. 2002), namely that there where no artifacts occurring for 100 ms before the appearance of the stimulus for the antisaccade movement and that the response latency was more than 80 ms and less than 600 ms. All 947 subjects performed at least 40 valid trials. For each trial we evaluated:

1. The trial outcome (ER), which was either an error prosaccade (code =1) or correct antisaccade (code =0).
2. The latency of the first response (first eye movement) (L), irrespective of whether this response was a correct antisaccade or an error prosaccade.
3. The latency of the first eye movement if the trial was a correct antisaccade (LA).
4. The latency of the first eye movement if the trial was an error (LE).
5. The latency of correction (LC), which was the time interval between the end of the error prosaccade and the beginning of the corrective antisaccade in an error trial.
6. The latency to the corrective antisaccade from the appearance of the peripheral stimulus in error trials (LEC). For each error trial LEC = LE + duration of error prosaccade + LC.
7. The amplitude of the error prosaccade in degrees (EA).

We evaluated the above measures in relation to the following task parameters:

1. The stimulus direction, (DIR; right =1, left =0).
2. The stimulus distance (DIS) in degrees (2–10°). We also defined two categorical variables related to stimulus distance: the variable NEAR was set to 1 if the distance of the stimulus was 2° and 0 for all other distances; the variable FAR was set to 1 for distances of 8–10° and 0 for all other distances.
3. The time interval of fixation (FIX) before the appearance of the peripheral stimulus, which varied randomly from 1 to 2 s. This time interval reflected the inter-trial interval. We also binned the fixation time interval into ten categories of 100 ms intervals.
4. The running time in the task, measured in numbers of trials. Specifically, we divided the sequence of 90 trials into nine time intervals of ten trials each. We further defined two variables in our regression models related to the time in the task. The first, termed LEARN, was set to 1 if the trial was one of the first ten trials performed and was set to 0 for all subsequent trials. The second, termed FATIGUE, was set to 1 if the trial was one of the last 20 trials performed and was set to 0 for all other trials in the task.
5. Whether or not the trial was perseveration prone (PERS =1 or 0, respectively). A perseveration prone trial was defined as follows:

a. A sequence of two correct antisaccades was executed to the right or to the left and the instruction in the current trial was a break of the sequence direction (sequence RR current trial L, sequence LL current trial R).
b. A sequence of two alternations of right, left or left, right was performed and the current instruction was a break from the alternation pattern (sequence RLRL current trial L, sequence LRLR current trial R).

We used a logistic regression analysis to predict ER from the task variables. We included L in a separate analysis as a predictor. We used linear regression analysis to predict L, LA, LE, LC and LEC from the task variables as previously defined. For the prediction of LC, we also included LE and EA as predictors in a separate analysis. These analyses were implemented using Statstica v. 5.5 (Statsoft Co., Tulsa, Okla., USA) and SPSS 10.0 for Windows. In the results section SD refers to standard deviation and SEM to standard error of the mean.

Results

The mean error rate for all trials was 22%. The mean latency for the first response (L) was 249.25 ms (SD 68.46 ms); the mean latency for correct antisaccades (LA) was 263.89 ms (SD 64.84 ms); the mean latency for errors (LE) was 197.14 ms (SD 54.14 ms); the mean latency for corrections (LC) was 147.8 ms (SD 103.53 ms) and the mean latency for the antisaccades after an error (LEC) was 389.16 (SD 125.85 ms). There was a highly significant difference between LE and LA (Student's t =104, P<0.0001). Figure 1 shows the distributions for all latencies. The distribution of the latency for corrections included zero, illustrating that in some trials the error was reversed to the correct antisaccade with zero delay.

Relation of error to correction (Fig. 2)

Figure 2 shows the scatter plots of the correlations between the latency of correction and both the error amplitude (EA) (Fig. 2A) and the latency of error (LE) (Fig. 2B), as well as the correlation between LE and EA (Fig. 2C), for the set of all error trials in which a correction time was measured (n=10,915 out of 12,208 error trials). There was no correlation between LC and EA (r=0.00, P>0.1) or between LC and LE (r=0.02, P<0.05), thus indicating that neither the latency of the error prosaccade nor its amplitude has any effect on the time required for the generation of the corrective antisaccade. There is a small but highly significant negative correlation of LE with EA (r=0.08, P<0.01), indicating that larger error amplitudes accompany shorter error latencies.

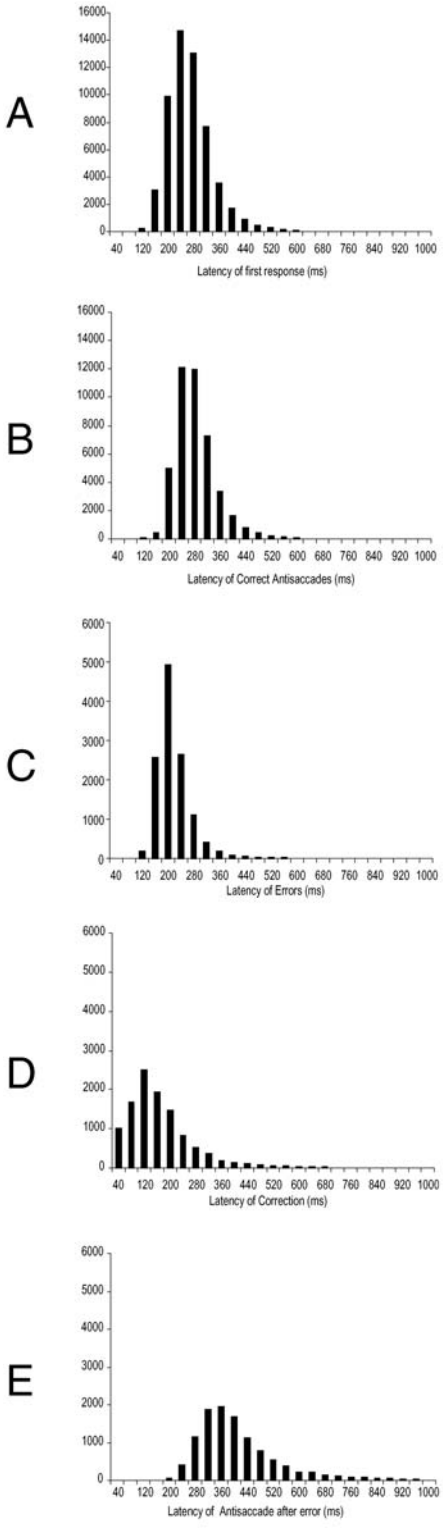

Fig. 1A–E Distributions of the different latency variables evaluated in each trial. **A** Latency of first response combining errors and correct antisaccades; **B** latency of correct antisaccades; **C** latency of errors; **D** latency for correction; **E** latency for the antisaccade in error trials

This effect is further explored in the section describing the regression results.

Effects of stimulus direction

When the stimulus appeared in the left visual hemifield, both error rates and amplitudes of the error saccades were smaller than those for trials in which the stimulus appeared in the right visual hemifield [21.4% (SEM 0.2%) versus 22.4% (SEM 0.2%), $P<0.0025$, and 5.17° (SEM 0.04°) versus 5.34° (SEM 0.04°), $P<0.006$, respectively]. In addition, left stimulus trials exhibited significantly longer latencies to the first response (L) [250 ms (SEM 0.4 ms) versus 248 ms (SEM 0.4 ms), respectively; $P<0.0006$] and longer latencies to error saccades (LE) [196 ms (SEM 0.7 ms) versus 199 ms (SEM 0.6 ms), respectively; $P<0.0014$] but the magnitude of these differences was extremely small (2–3 ms) to have any behavioral importance. The latency of correct antisaccades was not different for the two directions. Similarly, there was no effect of stimulus direction on latency of corrections (LC) or latency of antisaccades after an error (LEC).

In summary, trials in which the stimulus appeared in the left visual hemifield exhibited slightly lower error rates than trials in which the stimulus appeared in the right visual field. Response latencies did not result in a right-left asymmetry.

Effects of stimulus distance (Fig. 3)

Error rate decreased with increasing stimulus distance from the central fixation point ($\chi^2=131.8$, $P<0.0001$) (Fig. 3A). The maximum error rate (26%) was observed for the closest stimuli at a distance of 2° and the minimum (18%) for the farthest stimuli at a distance of 10°. As expected, the amplitude of the error saccade increased with increasing stimulus distance. In addition, there was a small overshoot of the stimulus for stimuli at 2° and 3° (0.7° and 0.5°, respectively) and a larger undershoot for stimuli at 8°, 9° and 10° (1.2°, 1.6° and 2.2°, respectively) (Fig. 3A). Latency of the first response and latency of correct antisaccades were affected similarly by stimulus distance, and the effects were significant ($F=11.7$, $P<0.0001$, and $F=7.45$, $P<0.0001$, respectively). Specifically, L and LA were longest at NEAR and FAR stimulus distances (Fig. 3B). The latency of errors also differed with stimulus distance ($F=8.04$, $P<0.0001$) but in a different way from L and LA. LE was highest for NEAR stimuli and lower for all others (Fig. 3B). The latency for corrections and the latency for the antisaccade after an error both decreased with increasing stimulus distance (Fig. 3C) ($F=29.21$, $P<0.0001$, and $F=16$, $P<0.0001$, respectively). The difference in latency between 2° and 10° was 47 ms for LC and 41 ms for LEC.

In summary, stimulus distance affected all indices of performance. However, the largest effects were on the

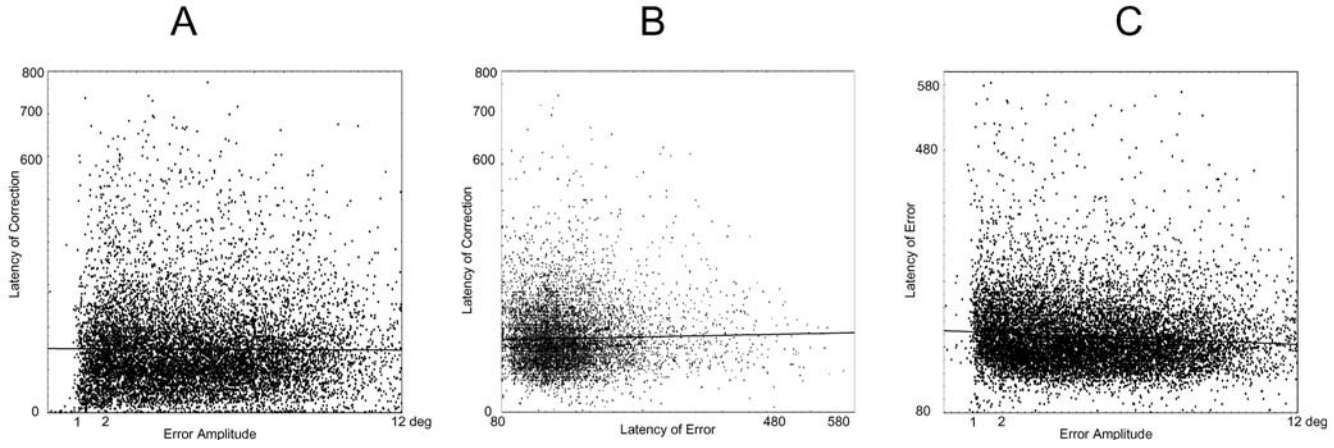

Fig. 2A–C Scatter plots with superimposed correlations of latencies and error amplitude. **A** Correlation of latency for corrections (*y*-axis) with error amplitude (*x*-axis); **B** latency of corrections (*y*-axis) and latency of errors (*x*-axis) and finally **C** latency for errors (*y*-axis) and error amplitude (*x*-axis)

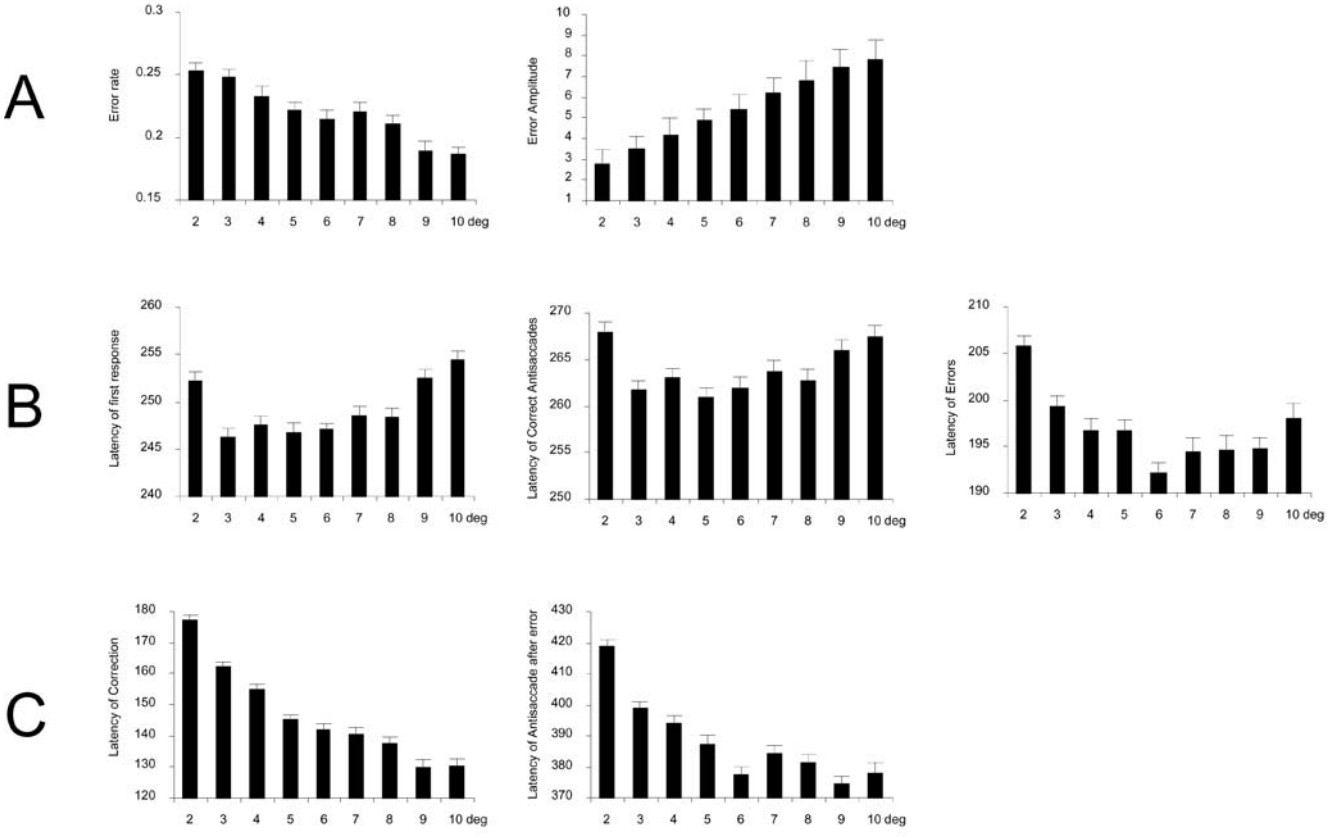

Fig. 3A–C Effects of stimulus distance (2–10°) on the error and latency variables measured in each trial. **A** Error rate, and error amplitude; **B** latency of first response, of correct antisaccades, and of error; **C** latency of correction, and of correct antisaccades after error (error bars represent SEM)

latency for correction (26% shorter at 10° versus 2°), and the error rate (24% lower at 10° versus 2°). Finally, the error saccade amplitude was 35% greater than actual stimulus distance at 2° and 22% smaller at 10°.

Effects of fixation interval (Fig. 4)

Increasing the fixation interval resulted in a decrease in error rate (χ^2=148.7, P<0.0001) from 27% for the 1100 ms interval to 20% for the 2000 ms interval, without a

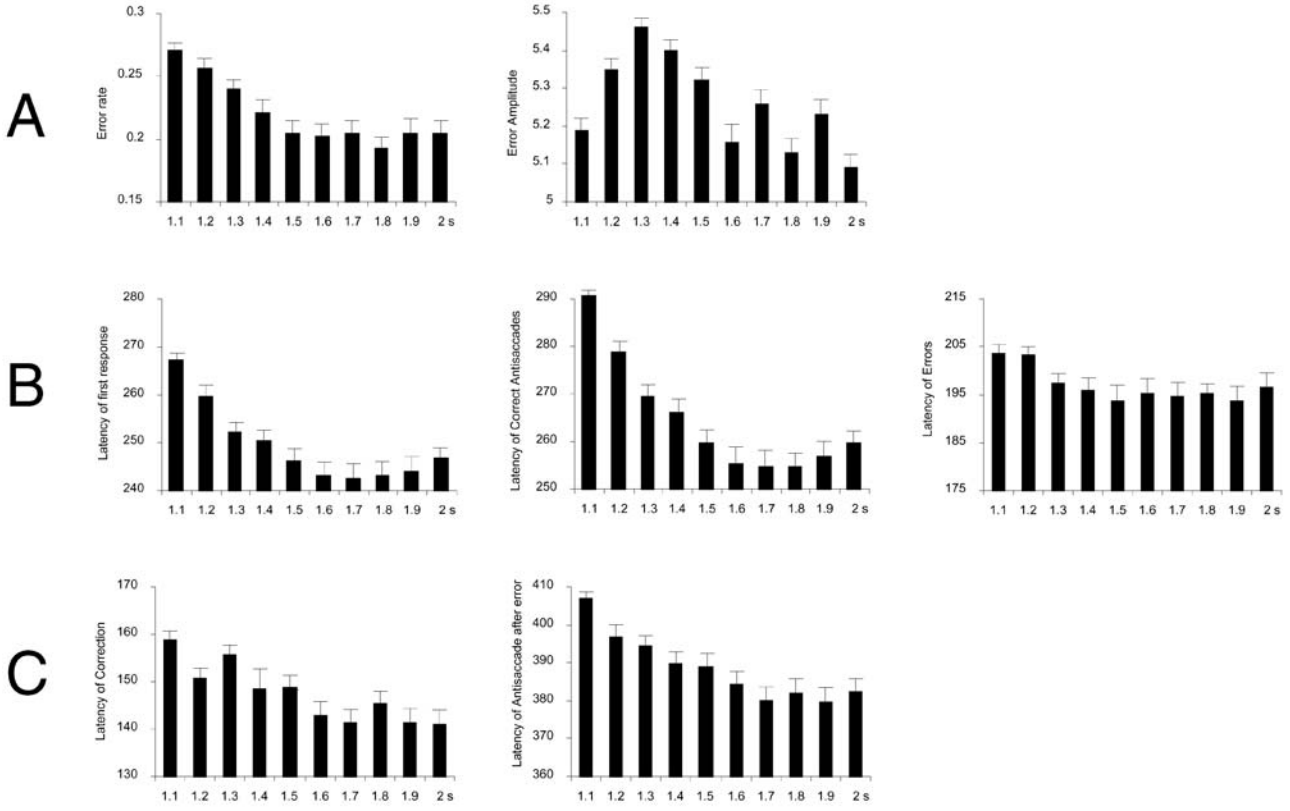

Fig. 4A–C Effects of prior fixation interval on the error and latency variables measured in each trial. Fixation interval was assigned to ten intervals starting from 1000 ms and increasing in steps of 100 ms. **A** Error rate, and error amplitude; **B** latency of first response, of correct antisaccades, and of error; **C** latency of correction, and of correct antisaccades after error (error bars represent SEM)

significant effect on the amplitude of the error saccade (Fig. 4A). The latency of the first response and the latency of correct antisaccades were also affected by fixation interval (F=76.8, P<0.0001, and F=142.5, P<0.0001, respectively), as evidenced by a general decrease in latency with increasing fixation interval (Fig. 4B). The longest L and LA were observed at 1100 ms (267 ms and 291 ms, respectively) and the shortest at 1700 ms (242 ms and 254 ms, respectively). The latency of errors was also affected by fixation interval duration (F=6.12, P<0.0001), but rather than a general decrease in latency with increasing fixation interval, there was a small decrease between 1200 and 1300 ms, which remained relatively stable thereafter (Fig. 4B). The maximum difference was 6 ms, which was observed between the 1100- and 1900-ms intervals. Finally, both the latency for correction and the latency for the antisaccade after an error decreased with increasing fixation intervals (Fig. 3C) (F=4.2, P<0.0001 for LC, and F=5.7, P<0.0001 for LEC) and the maximum difference was 18 ms for LC (between the 1100- and 2000-ms intervals) and 27 ms for LEC (between the 1100- and 1700-ms intervals).

Thus, shorter fixation intervals (less than 1300 ms) before the execution of the antisaccade resulted in an average 35%higher error rate than that observed for longer intervals of 1700–2000 ms with respect to short intervals of 1100–1300 ms and longer response latencies especially for correct antisaccades (where there was a 14% increase in latency).

Effects of time in the task (Fig. 5)

The error rate varied significantly during the course of the task (χ^2=172.9, P<0.0001), which lasted approximately 5 mins. In fact, there was an abrupt decrease in error rate between the first and the second block of ten trials (26% versus 20%, respectively). The performance was stable for the next 40 trials and then the error rate began to increase again, reaching 25% for the last block of ten trials. The amplitude of the error saccades was also significantly modulated with time, showing a tendency for larger error amplitudes for the first ten trials (5.7°) than for the other blocks (average of 5.1°) (F=5.2, P<0.0001) (Fig. 5A). The latency of the first response decreased after the first ten trials (from 254 ms to 250 ms) and then remained stable for the rest of the task (F=7.6, P<0.0001). The same phenomenon was observed for the latency of correct antisaccades (decrease from 272 to 262 ms; F=14.1, P<0.0001) and the latency of errors (decrease from 205 to 195 ms; F=4.65, P<0.0001) (Fig. 5B), for the latency of corrections (decrease from

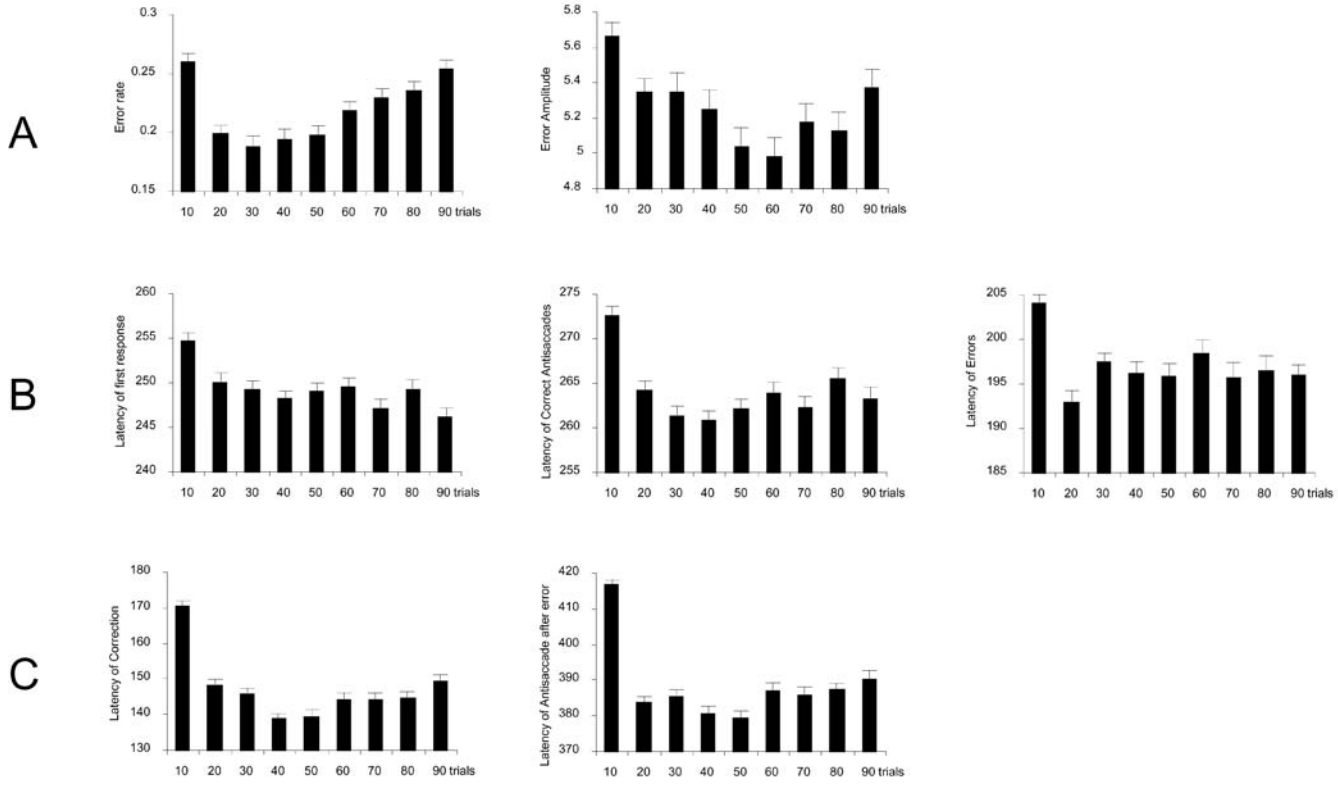

Fig. 5A–C The effects of time in the task (*x*-axis is block of trials) on the error and latency variables measured in each trial. **A** Error rate, and error amplitude; **B** latency of first response, of correct antisaccades, and of error; **C** latency of correction, and of correct antisaccades after error (error bars represent SEM)

170 ms to 145 ms; F=11.2, P<0.0001) and for the latency of antisaccades after an error (Fig. 4C) (decrease from 416 ms to 385 ms; F=10.7, P<0.0001).

Thus, all performance indices were significantly affected by time in the task. The error rate was modulated by as much as 30% for each value from the first ten trials as time evolved in the task, suggesting an initial learning effect (decrease in error rate) and a subsequent fatigue effect (an increase in error rate). All other performance indices showed learning but not fatigue effects.

Effects of perseveration prone trials

Neither error rate nor error amplitude was affected by perseveration prone trials. The latency to the first saccadic eye movement was not different for the two categories of trials and there was a significant, but too small to be important, increase in the latency of correct antisaccades and decrease in the latency for errors for perseveration versus non-perseveration prone trials [265 ms (SEM 0.8 ms) versus 262 ms (SEM 0.4 ms), P<0.0008, and 192 ms (SEM 1.2 ms) versus 196 ms (SEM 0.6 ms), P<0.0063, respectively]. There were decreases in both the latency for corrections and the latency to corrective antisaccade for perseveration versus non-perseveration prone trials (135 ms (SEM =2.3 ms) versus 147 ms (SEM 13.ms), P<0.0001, and 369 ms (SEM 2.9 ms) versus 386 ms (SEM 1.6 ms), P<0.0001, respectively].

In summary, the perseveration prone trials did not increase the error rate. However, when an error saccade occurred, the latency to corrective antisaccade, and thus latency of antisaccade after an error were all shorter in perseveration prone trials.

Regression analysis

The results of the descriptive analysis showed that every task index measured was modulated by a host of task parameters. The next question then was whether we could predict, on a trial-by-trial basis, the specific index of performance using specific task parameters and/or other performance indices in a regression model.

We first used logistic regression analysis to predict ER from all task parameters. The model was significant (χ^2=264.22). All task parameters had a significant effect on the trial outcome ER (Table 1). However, the model was not powerful in predicting the response outcome (Cox and Snell r^2=0.07) (Table 1). Considering the fact that 75% of trials were correct antisaccades, the power of the model is really measured by its ability to predict errors (25%). The model predicted all trial outcomes as correct antisaccades, i.e. it did not account for the errors. In a

Table 1 Prediction of trial outcome: parameter effects. The effect of each one of the task parameters on the trial outcome in the logistic regression model is shown (*DIR* stimulus direction, *NEAR* 2° eccentricity, *FAR* 8–10° eccentricity, *FIX* prior fixation interval, *LEARN* first ten trials, *FATIGUE* last 20 trials, *PERS* perseveration prone trials; see Materials and methods section for definitions)

Parameter	Regression β	Significance	
		Wald statistic	*P*-value
DIR	–0.088	12.39	<0.0001
NEAR	–0.143	13.73	<0.0001
FAR	0.211	43.87	<0.0001
FIX	0.000	109.76	<0.0001
LEARN	–0.184	18.76	<0.0001
FATIGUE	–0.232	61.28	<0.0001
PERS	–0.064	4.13	0.04

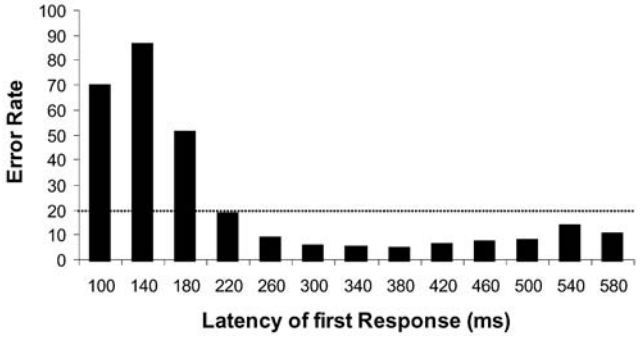

Fig. 6 Error rate for different latencies of first response. The latency of first response was assigned to 40-ms intervals and the total percentage of errors was computed for each interval. The *horizontal line* indicates the mean error rate for the total sample

separate analysis, we included the response time of the first eye movement in the model. The model was highly significant (χ^2=10096.65) and all task parameters again had a significant effect on the trial outcome ER. This model, however, was more powerful at predicting the response outcome (Cox and Snell r^2=0.22), predicting 42% of errors (Table 2). In fact, when we performed a logistic regression using the response latency as a single predictor, the model predicted 39% of errors. Thus, the response latency of the first eye movement was an important predictor of whether the trial was correct or erroneous. Figure 6 illustrates this relationship. The shortest response latencies (less than 200 ms) were associated with the highest error rates.

The linear regression model predicting the latency of the first response from task parameters was significant (r^2=0.01, regression ANOVA F=66.1, P<0.0001) (Table 3). Specifically, stimulus direction, stimulus distance (FAR versus NEAR) and fixation interval were significant predictors of response latency. In particular, fixation interval (β=0.9) accounted for most of the total predictive value of the model (r=0.11). The increase in fixation interval resulted in a decrease in response latency (see Fig. 5B). Similar results were obtained for the prediction of the response latency for correct antisaccades (stimulus

Table 2 Prediction of trial outcome: classification table. The classification table for the second logistic regression model that includes the latency of the first response as a predictor is shown. The columns show the predicted correct antisaccades and errors and the rows show the observed correct antisaccades and errors

Observed frequency	Predicted frequency		
	Errors	Correct antisaccades	% Correct
Errors	30,990	1,028	96.8%
Correct antisaccades	4,687	3,404	42.1%
% Total			85.8%

Table 3 Effect of each one of the task parameters on the latency of the first response in the linear regression model. (*DIR* stimulus direction, *NEAR* 2° eccentricity, *FAR* 8–10° eccentricity, *FIX* prior fixation interval, *LEARN* first ten trials, *FATIGUE* last 20 trials, *PERS* perseveration prone trials; see Materials and methods section for definitions)

Parameter	Regression β	Significance	
		t-value	*P*-value
DIR	–0.015	–3.08	0.002
NEAR	0.029	5.72	<0.0001
FAR	0.039	7.68	<0.0001
FIX	–0.09	109.76	<0.0001
LEARN	–0.003	–0.56	0.57
FATIGUE	–0.007	–1.4	0.16
PERS	–0.064	4.13	0.04

Table 4 Effect of each one of the task parameters on the latency of errors in the linear regression model. (*DIR* stimulus direction, *NEAR* 2° eccentricity, *FAR* 8–10° eccentricity, *FIX* prior fixation interval, *LEARN* first ten trials, *FATIGUE* last 20 trials, *PERS* perseveration prone trials; see Materials and methods section for definitions)

Parameter	Regression β	Significance	
		t-value	*P*-value
DIR	–0.03	–2.57	0.01
NEAR	0.07	6.27	<0.0001
FAR	0.014	1.27	0.2
FIX	–0.05	–4.34	<0.0001
LEARN	0.012	1.07	0.28
FATIGUE	0.02	1.76	0.08
PERS	–0.03	–2.72	0.006

distance and fixation interval, but not stimulus direction, predicted the latency, with fixation interval the most significant predictor; data not shown).

The linear regression model for the latency of errors was also significant (r^2=0.01, regression ANOVA F=10.9 P<0.0001) (Table 4). Specifically, stimulus direction, stimulus distance, fixation interval and perseveration proneness were significant predictors of the latency of errors. The strongest predictor was the NEAR stimulus distance, because a significant increase in the latency for

Table 5 Effect of each one of the task parameters on the latency of the correction in the linear regression model. (*DIR* stimulus direction, *DIS* stimulus distance, *FIX* prior fixation interval, *LEARN* first ten trials, *FATIGUE* last 20 trials, *PERS* perseveration prone trials; see Materials and methods section for definitions)

Parameter	Regression β	Significance	
		t-value	*P*-value
DIR	0.014	1.22	0.22
DIS	–0.126	–10.94	<0.0001
FIX	–0.067	–5.84	<0.0001
LEARN	0.025	2.22	0.025
FATIGUE	0.034	2.96	0.003
PERS	–0.046	–3.90	<0.0001

errors was observed for stimuli appearing at 2° from the central fixation point.

The linear regression model for the latency of corrections was significant (r^2=0.02, regression ANOVA F=25.3, P<0.0001), and all task parameters except stimulus direction were significant predictors. The most powerful predictors were stimulus distance (FAR and NEAR variables) and fixation interval. Given that the effect of increasing stimulus distance was a monotonic decrease in correction time (see Fig. 4), we performed the analysis using stimulus distance (DIS) as a continuous variable (Table 5). DIS was the strongest predictor of correction latency. We repeated the analysis using the amplitude of the error saccade instead of the stimulus distance. Although the amplitude of the error saccade was a significant predictor of the latency for correction, it was much weaker than the stimulus distance (β-value –0.02 versus –0.12, respectively), although the correlation between error amplitude and stimulus distance was, as expected, very high (r=0.68, P<0.0001). Finally, we included the latency for the error saccade in our model and observed that this factor was not a significant predictor of the latency for correction, as expected from our original correlation analysis.

The latency of the antisaccade after an error showed very similar results in the regression analysis to those for the latency for correction (data not shown) and again the stimulus distance was the most significant predictor of this latency.

Discussion

In this study, we investigated the effects of several parameters related to stimulus presentation in the antisaccade task on the latency of the response and on the response outcome (error prosaccade or correct antisaccade). We also formulated models for the prediction of the response outcome and the latencies of the first and the corrective eye-movements.

Correlation of error and correction

A robust finding of this analysis was the lack of correlation between latency and amplitude of error prosaccades and the ensuing time for their correction by the antisaccade. Furthermore, in many cases the correction latency was extremely small and in some cases the error prosaccade was reversed with zero delay. This phenomenon has been reported previously for the correction of erroneous prosaccades in the antisaccade task (Fischer and Weber 1997). Thus, the correction process seemed to be unrelated to the previous programming and execution of the error prosaccade and it could actually interrupt the execution of this movement in some cases.

Effects of stimulus location

A higher error rate was observed for stimuli presented in the right versus left visual field. Similar results have been reported previously (Fischer and Weber 1997; Fischer et al. 1997). Fischer and Weber (1997) found this difference specifically for stimuli at small eccentricities but not those at larger eccentricities. In the present study, the amplitude of error saccades was also larger for stimuli in the right visual hemifield. The absence of differences in latency for antisaccades to the right or to the left hemifield is in agreement with the results of the study of Fischer and Weber (1997).

Error rate decreased with increasing stimulus eccentricity. Fischer and Weber (1997) reported an increase in error rate with increasing stimulus eccentricity (from 2° to 12°). Although there are minor differences in the experimental paradigm used in that study (a gap between central fixation offset and stimulus onset varied from 0 to 600 ms, and the subjects were instructed to saccade to the mirror location of the peripheral stimulus as opposed to our subjects being instructed to saccade in the other direction), they do not seem able to account for opposite effects on error rate. In support of the current findings, in a recent study, monkeys performing the antisaccade task made more errors when stimuli were presented close to the central fixation point and the error rate declined with increasing eccentricity (Bell et al. 2001). The authors reported a preferred distance range of 8–10°. The authors suggested that small stimulus distances induce both fixation and saccade signals (considered as opposing signals) at the level of superior colliculus and this signal ambiguity leads to longer latencies and a higher probability of errors for small amplitude saccades.

Fischer and Weber (1997) observed an increase in latency with small distance stimuli. We also observed an increase in latencies when stimuli were presented at a close distance compared with those presented at larger distances. More interestingly, this increase in latency was very pronounced for the latency of corrections and the latency for the antisaccade after an error. Actually, the best predictor of both these latencies in a regression model was the distance of the stimulus. This effect of

stimulus distance on correction latency was not observed when we substituted the actual error amplitude for stimulus distance in our regression model, confirming our initial observation of a lack of correlation between error amplitude and correction latency. Nevertheless, the error amplitude increased with increasing stimulus distance. Perhaps the presence of a stimulus at a close distance interferes with the programming of the correct antisaccade (Bell et al. 2001). This interference was maximal in the cases where an actual error did occur resulting in a prolongation of the initiation of the antisaccade movement, irrespective of the actual amplitude of the error that was finally observed.

Fixation interval

The fixation interval preceding a response is as an index of the rate of stimulus presentation. Relatively high presentation rates (short fixation intervals) resulted in higher error rates and longer latencies, especially for correct antisaccades. The single most significant predictor of the latency for correct antisaccades in a regression model was the fixation interval. Manipulation of the state of fixation before the execution of the antisaccade leads to a difference in performance (Fischer and Weber 1992, 1996, 1997). For example, introducing a gap between fixation and stimulus presentation results in an increase of antisaccade errors (Fischer and Weber 1997). Similarly, a smaller fixation interval could result in a less stable fixation before stimulus appearance leading to an increase in error rate. Perhaps in an effort to compensate for a short fixation interval, response latency increases.

Learning and fatigue effects

Performance changed during the course of the task (task duration approximately 5 min, 90 trials) the. Time-dependent changes were observed for the percentage of errors, amplitude of errors and for the latencies. Error rate followed a U-shaped curve (Fig. 6), suggesting two well-known effects of time on performance: an initial “learning effect” reflected by higher error rates in early trials, and a “fatigue effect” reflected by similarly high error rates in final trials. In fact, many subjects reported at the end of the task that they were tired from the effort. A different effect of time in the task was observed for error amplitude and latencies, all of which decreased abruptly after the first ten trials and then remained lower throughout the task. Thus, fatigue was not reflected in error amplitude or response latencies.

Perseveration effects

Perseverative behavior has been reported in patients with frontal lobe lesions and consists of an inappropriate repetition or maintenance of a previous response when a new one is needed (Lezack 1995). In this study, we considered two types of perseveration prone trials, the trial after a repetition of two identical responses and the trial after an alternation of left-right or right-left responses. Surprisingly, the error rate was not different for perseveration prone trials versus non-perseveration prone trials. Only the latency corrections decreased in perseveration prone trials.

Predicting the response outcome

The final outcome for each trial of the antisaccade task was a choice between moving in the direction of the stimulus (error prosaccade) and moving in the opposite direction (correct antisaccade). We have discussed how stimulus parameters affected this outcome. We attempted to predict the trial outcomes based on the stimulus parameters. Although all the stimulus parameters were significant predictors of the trial outcome, their value for predicting error trials was negligible. As we have already mentioned, the power of such a model is really tested in the prediction of errors in performance due to the overall small percentage of errors (25% of trials). Thus, stimulus distance and direction, perseveration prone sequences, fixation interval (reflecting rate of trial transition) and task duration are of minimal significance in determining whether a particular trial will result in an error prosaccade. In contrast, response latency predicted 40% of errors. An increase in probability of error with decreasing response latency has been found in previous studies of performance in the antisaccade task (Fischer and Weber 1992, 1997). Nevertheless, given that less than half of errors are predicted by response latency, further experiments are required to determine which other variables may better predict performance. These variables could be related to the large variability of error rate among different subjects in our population (see part I of this study; Evdokimidis et al. 2002).

A combining hypothesis for antisaccade generation

In this study, we investigated the effects on antisaccade performance of several stimulus-related parameters. One important finding was that an error correction was always evident in the sample of trials we investigated (n=947) and it was observed in more than 99% of the total trials for all subjects in the study n=2,006). Fischer et al. (2000) have proposed that corrected errors in the antisaccade task have characteristically short latencies (in the range of express saccades) and result from a fixation instability, meaning a difficulty in maintaining fixation while the volitional antisaccade movement is still in preparation. In contrast, errors that are not corrected reflect a deficit in the volitional component of the antisaccade movement. These errors have larger latencies than the corrected ones and they might be related to pathology of the frontal lobes (Guitton et al. 1985).

A recent model of collicular neuronal activity actually proposes the activation of the superior colliculus (SC) by two competing signals in the antisaccade task, an endogenous signal based on the antisaccade instruction that comes from cortical processing of that instruction and an exogenous signal coming directly from visual areas (Trappenberg et al. 2001). Both these signals activate the SC buildup neurons but at the same time one signal inhibits the other. The result of the interplay between these competing signals could be an error prosaccade or a correct antisaccade. Neurons in the SC are indeed activated prior to the execution of antisaccades in the monkey (Everling et al. 1999). Moreover, an increased activity of fixation neurons in the SC has been observed in the preparatory period before the execution of an antisaccade (Everling et al. 1999). In yet another study of SC neurons, the increased activity of buildup neurons related to the error prosaccade stimulus location predicted well the occurrence of an error in the antisaccade task (Everling et al. 1998). Furthermore, activation of fixation neurons in the ipsilateral SC can inhibit saccade neurons in the contralateral SC via intercollicular inhibition (Munoz and Istvan 1998). Finally, SC saccade neurons are tonically inhibited by the basal ganglia (substantia nigra pars reticulata; Hikosaka and Wurtz 1983). The loss of striatal cholinergic neurons in Huntington's disease results in a high rate error-prosaccades in the antisaccade task (Lasker et al. 1987).

The neurophysiological data, combined with the psychophysical evidence from this and previous studies, suggest the existence of two parallel signals that may interact at the level of the SC: a volitional antisaccade (endogenous signal) and a reflex prosaccade (exogenous signal). The inhibition of the reflex prosaccade might rely both on the prior level of fixation activity, the intra- and inter-collicular inhibition, and on inhibitory signals to the SC coming from other brain areas such as the basal ganglia. Our data suggest a dissociation in programming between the erroneous prosaccade and the corrective antisaccade that follows. A very striking dissociation was that the latency of the ensuing antisaccade after an error was dependent on the distance of the stimulus and not on the actual error amplitude, indicating that the programming of the antisaccade in this case was affected by the original stimulus information and not on the error amplitude.

The dependence of the inhibition on the level of fixation activity prior to the onset of the antisaccade (fixation instability hypothesis) could explain the effects of the fixation interval. Thus, when the fixation interval preceding the antisaccade onset is short, the neuronal activity of fixation neurons could be less leading to a higher probability of error. A compensatory strategy would be to increase the level of activity of fixation neurons leading to an increase in response latency for the correct antisaccades.

In conclusion, our data could be viewed under a general hypothesis that antisaccade performance depends on the parallel processing of two distinct signals, one volitional involving cortical and subcortical structures and one reflexive involving mostly the SC. The successful inhibition of the reflexive signal could be mediated by the inter-play of fixation- and saccade-related activity at the level of SC, and the increase in error rate could be the result of a deficit in this mechanism, an effect named "fixation instability" (Fischer et al. 2000). We believe that the term "corrective antisaccade" is misleading for the antisaccade after the occurrence of an error because it supposes a serial process of error detection and a subsequent programming of a corrective antisaccade, whereas our data point to a parallel processing of two separate commands. It would be interesting to investigate at the behavioral level the error and correction parameters in neurological and psychiatric conditions, where antisaccade error rate was found to be increased (Everling and Fischer 1998).

Acknowledgements This work was supported by the grant EKBAN 97 to Professor C.N. Stefanis from the General Secretariat of Research and Technology of the Greek Ministry of Development. Intrasoft Co. provided the technical support for this project.

References

Bell AH, Everling S, Munoz DP (2001) Influence of stimulus eccentricity and direction on characteristics of pro- and antisaccades in non-human primates. J Neurophysiol 84:2595–2604

Evdokimidis I, Smyrnis N, Constantinidis TS, Stefanis NC, Avramopoulos D, Paximadis C, Thelcritis C, Efstratiadis C, Kastrinakis G, Stefanis CN (2002) The antisaccade TASK in a sample of 2006 young males. I. Normal population characteristics. Exp Brain Res DOI 10.1007/s00221-002-1208-4

Everling S, Fischer B (1998) The antisaccade: a review of basic research and clinical studies. Neuropsychologia 36:885–899

Everling S, Munoz DP (2000) Neuronal correlates for preparatory set associated with prosaccades and antisaccades in the primate frontal eye field. J Neurosci 20:387–400

Everling S, Dorris MC, Munoz DP (1998) Reflex suppression in the antisaccade task is dependent on prestimulus neural processes. J Neurophysiol 80:1584–1589

Everling S, Dorris MC, Klein RM, Munoz DP (1999) Role of primate superior colliculus in preparation and execution of antisaccades and prosaccades. J Neurosci 19:2740–2754

Fischer B, Weber H (1992) Characteristics of "anti" saccades in man. Exp Brain Res 89:415–424

Fischer B, Weber H (1996) Effects of procues on error rate and reaction times of antisaccades in human subjects. Exp Brain Res 109:507–512

Fischer B, Weber H (1997) Effects of stimulus conditions on the performance of antisaccades in man. Exp Brain Res 116:191–200

Fischer B, Biscaldi M, Gezeck S (1997) On the development of voluntary and reflexive components in human saccade generation. Brain Res 754:285–297

Fischer B, Gezeck S, Hartnegg K (2000) On the production an correction of involuntary prosaccades in a gap antisaccade task. Vision Res 40:2211–2217

Funahashi S, Chafee MV, Goldman-Rakic PS (1993) Prefrontal neuronal activity in rhesus monkeys performing a delayed antisaccade task. Nature 365:753–756

Guitton D, Buchtel HA, Douglas RM (1985) Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. Exp Brain Res 58:455–472

Hikosaka O, Wurtz RH (1983) Visual and oculomotor functions of the monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. J Neurophysiol 49:1285-1301

Lasker AG, Zee DS, Hain TC, Folstein SE, Singer HS (1987) Saccades in Huntington's disease: initiation defects and distractibility. Neurology 37:364–370

Lezak MD (1995) Neuropsychological assessment, 3rd edn. Oxford University Press, New York

Munoz DP, Istvan PJ (1998) Lateral inhibitory interactions in the intermediate layers of the monkey superior colliculus. J Neurophysiol 79:1193–1209

O'Driscoll GA, Alpert NM, Matthysse SW, Levy DL, Rauch SL, Holzman PS (1995) Functional neuroanatomy of antisaccade eye movements invastigated with positron emission tomography. Proc Nat Acad Sci 92:925–929

Schlag-Rey M, Amador N, Sanchez H, Schlag J (1997) Antisaccade performance predicted by neuronal activity in the supplementary eye field. Nature 390:398–401

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR (1996) Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol 75:454–468

Trappendberg TP, Dorris MC, Munoz DP, Klein RM (2001) A model of saccade initiation based on the competitive integration of exogenous and endogenous signals in the superior colliculus. J Cogn Neurosci 13:256–271

Zhang M, Barash S (2000) Neuronal switching of sensorimotor transformations for antisaccades. Nature 408:971–975