

Reflex Suppression in the Anti-Saccade Task Is Dependent on Prestimulus Neural Processes

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Everling, Stefan, Michael C. Dorris, and Douglas P. Munoz. Reflex suppression in the anti-saccade task is dependent on prestimulus neural processes. *J. Neurophysiol.* 80: 1584–1589, 1998. Reflexive responses often must be suppressed to correctly execute a voluntary behavior. It is largely unknown why this control sometimes fails. To examine the neural processes responsible for these failures, we recorded single-neuron activity in the superior colliculus (SC) in behaving monkeys during an anti-saccade task in which they had to suppress a saccade to a visual stimulus that suddenly appeared in the periphery and generate a saccade to the opposite side. We found that the level and distribution of prestimulus activity of buildup neurons in the SC was highly predictive of whether a correct response or an error occurred. A high level of prestimulus activity in buildup neurons at the location in the SC where the visual stimulus was represented was associated with the generation of a reflexive saccade to the stimulus. These findings suggest that the successful suppression of reflexive saccades is dependent on prestimulus neural processes in the SC.

tions, why can subjects suppress a reflexive response on some trials yet fail on others?

It is widely assumed in cognitive neuroscience that reflexive responses can be inhibited by a stopping process initiated after stimulus appearance (Hanes and Schall 1996; Logan and Cowan 1984). Accordingly, it was proposed that reflexive saccades in the anti-saccade task occur when the stopping signal is generated too late (Guitton et al. 1985). However, the reaction time to a stimulus is also influenced by the prestimulus activity in motor areas (Coles 1989; Dorris et al. 1997; Riehle and Requin 1993). It was shown recently that the variability in saccadic reaction times is related to the variability of prestimulus activity in buildup neurons in the SC (Dorris et al. 1997). These neurons display low-frequency prestimulus activity when there is high predictability of stimulus appearance (Basso and Wurtz 1997; Dorris et al. 1997; Munoz and Wurtz 1995). Moreover, many of these neurons have a high-frequency visual burst before their saccade-related motor burst (Dorris et al. 1997; Munoz and Wurtz 1995). We hypothesized that a high level of prestimulus activity in the SC, which shortens the reaction time of saccades, would also reduce the ability to suppress a reflexive saccade to the stimulus by allowing the visual burst to trigger a reflexive saccade. To test this hypothesis, we recorded the activity of buildup neurons while monkeys performed a task with randomly interleaved pro-saccade (saccade toward the stimulus) and anti-saccade (saccade to the opposite direction) trials.

INTRODUCTION

The “visual grasp reflex” (Hess et al. 1946; Ingle 1973) moves the line of sight to a newly appearing visual stimulus in the peripheral visual field with a fast eye movement called a saccade. This reflex is primarily mediated by the superior colliculus (SC) in the midbrain (Dorris et al. 1997; Edelman and Keller 1996; Schiller et al. 1987; Wurtz and Goldberg 1972), whose intermediate layers receive visual inputs and project directly to the precollicular neurons in the brain stem (for reviews see Moschovakis et al. 1996; Wurtz and Goldberg 1989). Humans, however, can suppress the reflex and can even be instructed to generate a saccade to the side opposite to the stimulus in a task known as the anti-saccade task (Hallett 1978; Hallett and Adams 1980). The suppression of reflexive saccades seems to be mediated by direct and indirect cortical projections to the SC (for review see Wurtz and Goldberg 1989) because subjects with certain psychiatric and neurological diseases that involve the frontal cortex or the basal ganglia have difficulties suppressing reflexive saccades to the stimulus in this task (Fukushima et al. 1988; Guitton et al. 1985; Lasker et al. 1987; Pierrot-Deseilligny et al. 1989 1991). However, normal subjects also make frequently errors in the anti-saccade task, especially when the initial fixation stimulus is extinguished before the peripheral stimulus appears (Fischer and Weber 1992). Given identical task condi-

METHODS

Single-cell activity was recorded from the SC of two male monkeys (*Macaca mulatta*, 6–10 kg). All experimental protocols were in accordance with the Canadian Council on Animal Care policy on use of laboratory animals and approved by the Queen's University Animal Care Committee.

The surgical procedures and standard electrophysiological techniques for single neuron recording in the SC and eye movement monitoring in head-fixed monkeys were described previously (Dorris et al. 1997). The monkeys were trained on a task with randomly interleaved pro- and anti-saccade trials. The experiments were conducted in total darkness. The monkeys faced a tangent screen 86 cm in front of them, onto which light-emitting diodes (green and red, 0.3 cd/m²) were back-projected to produce visual stimuli. The screen was illuminated diffusely between trials (1.0 cd/m²) to prevent the animal from becoming dark-adapted. Each trial started with the appearance of a central fixation point (FP) on the screen. The monkey was required to look at it and maintain fixation for 700–900 ms. A red FP signaled a pro-saccade trial

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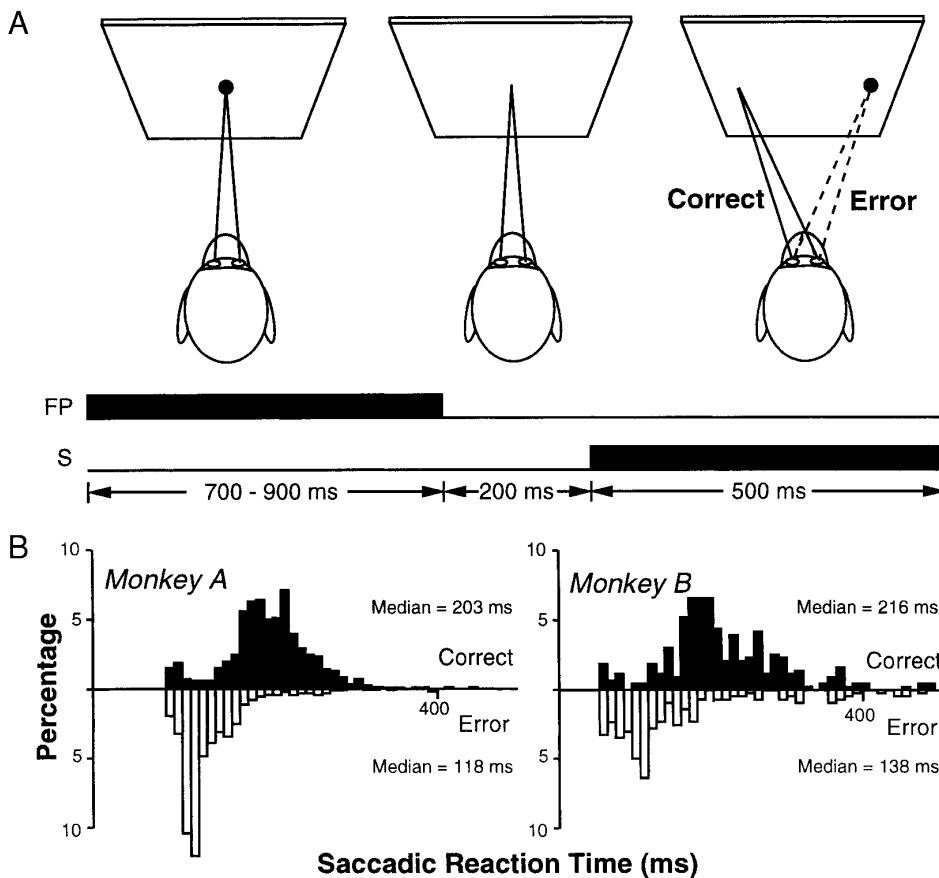


FIG. 1. Schematic representation of the gap anti-saccade condition (A) and distribution of saccadic reaction times in this condition observed while recording from 40 buildup neurons (binwidth 10 ms) (B). The monkeys were required to fixate a central fixation point (FP) that was extinguished 200 ms before a peripheral visual stimulus was presented. When the stimulus was presented, the monkeys had to suppress a saccade to the stimulus (---, Error) and generate an anti-saccade (—, Correct) to the mirror location of the stimulus to receive a reward. Both monkeys made errors in this task (B). The majority of errors had shorter reaction times than the correct responses.

and a green FP signaled an anti-saccade trial. On half of the trials the FP was extinguished for 200 ms (gap period) before stimulus presentation (gap condition, Fig. 1A). On the other half of the trials the FP remained illuminated during stimulus presentation (overlap condition). A red visual stimulus was then pseudorandomly projected with equal probability either at the position, which yielded the optimal saccade-related response of the neuron, or at the mirror location on the opposite side of the horizontal and vertical meridians. The monkeys received a liquid reward if they made a saccade within 500 ms to the correct position and maintained fixation there for ≥ 200 ms. Trials with reaction times < 80 ms were excluded as anticipations and trials with reaction times > 500 ms were excluded as no response trials.

A postsynaptic activation function with a growth time of 1 ms and a decay time of 20 ms was used to construct continuous spike density waveforms and to obtain the levels of neural activity (for details see Thompson et al. 1996).

To be classified as a buildup neuron, a neuron had to display 1) a significant higher discharge at the end of the gap period (50 ms before stimulus appearance to 50 ms after stimulus appearance) compared with the visual fixation period (100 ms before the gap period) on pro-saccade trials (t -test, $P < 0.05$) and 2) a saccade-related discharge > 100 spikes/s for pro-saccades into the neuron's response field (Dorris et al. 1997).

RESULTS

The monkeys often generated pro-saccades in the gap condition when they were instructed to generate an anti-saccade, similar to previous human studies (Fischer and Weber 1992; Pierrot-Deseilligny et al. 1991). These pro-saccades had shorter reaction times than correct anti-saccades (Fig. 1B).

These errors were less frequent in the overlap condition, and the monkeys almost never made an anti-saccade when they were instructed to generate a pro-saccade. We were specifically interested in the neural processes that distinguish correct from reflexive responses. Therefore we compared the activity levels of buildup neurons in the gap anti-saccade task between correct trials in which an anti-saccade was generated away from the stimulus with error trials in which a reflexive saccade was generated toward the stimulus.

Of the 73 saccade-related neurons recorded in the SC of two monkeys, 40 neurons were identified as buildup neurons (see METHODS). Sufficient data for an extended analysis (≥ 5 correct anti-saccade trials and 5 error trials) were obtained from 28 neurons for stimulus presentations into the neuron's response field and from 20 neurons for stimulus presentations at the mirror position.

Figure 2A shows the response of a representative buildup neuron on correct trials and on error trials when the stimulus was presented into the response field of the neuron. The activity of this buildup neuron began to increase during the gap period on correct trials and on error trials. However, the activity before the arrival of the visual signal in the SC was significantly higher on error trials, i.e., when the monkey generated a reflexive saccade toward the stimulus (t -test; $P < 0.0001$). The appearance of the stimulus elicited a visual response on correct trials that occurred at the same time as the motor burst on most of the error trials. On trials where the stimulus was presented at the mirror location of the neuron's response field (Fig. 2B), no differences in the

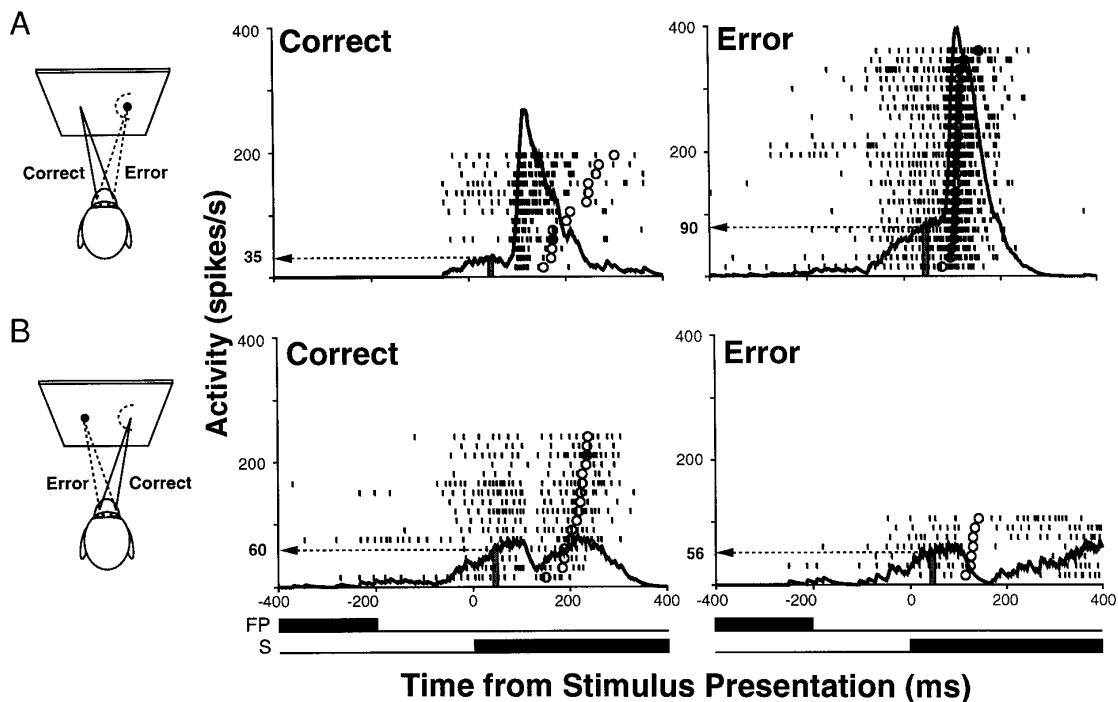


FIG. 2. Activity of a superior colliculus (SC) buildup neuron on correct and error trials. Each tick mark indicates the time of an action potential relative to stimulus presentation, and each row represents one trial. Trials are sorted according to saccadic reaction times (open circles). Superimposed on the rasters is the average spike density waveform. Horizontal dashed arrows indicate the average level of activation 40–50 ms after stimulus presentation (shaded region), which represents the period before the arrival of the visual signal in the intermediate layers of the SC.

level of prestimulus neural activity were observed between correct and error trials in this neuron. After stimulus presentation, the neuron had a transient decrease in discharge that may have been mediated by lateral inhibition in the SC (Munoz and Istvan 1998). On correct trials, the neuron then displayed a weak motor burst for the anti-saccade. The magnitude of the motor burst tended to be weaker for anti-saccades compared with pro-saccades. Anti-saccades also had lower peak velocities than pro-saccades. These results require a detailed quantitative analysis, which is beyond the scope of this paper. The late increase in discharge on error trials corresponds to the discharge for a correction saccade away from the stimulus after an error.

To determine when the levels of prestimulus activity started to differ between correct anti-saccade trials and error trials, we compared for the sample of buildup neurons the mean activity levels in 10-ms bins. On trials where the stimulus was presented into the response field of the neurons, error trials started to differ significantly from correct trials in the period 130–140 ms before stimulus presentation (t -test, $P < 0.05$). On trials where the stimulus was presented at the mirror position, significant differences started in the period 40–50 ms after stimulus presentation (t -test, $P < 0.05$). In both cases, the differences between correct anti-saccades and errors started before the arrival of the visual signal in the intermediate layers of the SC (>50 ms for all neurons with stimulus-related responses in our sample). For the quantitative analysis to be described, we used the period 40–50 ms after stimulus presentation because the activity in this period was not influenced by any changes related to the appearance of the stimulus.

Figure 3A shows the activity of the population of buildup neurons on trials where the stimulus was presented into the response field. The mean discharge rate of buildup neurons was 31 ± 6 (SE) spikes/s (range 0–121 spikes/s) before correct anti-saccades and 57 ± 6 spikes/s (range 14–124 spikes/s) before errors (t -test, $P < 0.0001$). Almost all neurons in our sample (26/28, 93%) showed a higher activity level before errors compared with correct anti-saccades (Fig. 3B). Significant differences (t -test, $P < 0.05$) were obtained for 50% (14/28) of the neurons. This finding shows that a high level of prestimulus neural activity in the SC at the location where the visual stimulus is represented is associated with the generation of a reflexive saccade to the stimulus.

Next we compared the prestimulus activity of buildup neurons before correct anti-saccades and errors when the stimulus was not presented into the response field of the neuron but at the mirror location (Fig. 3C). In this case, the neurons discharged a saccade-related motor burst for the correct anti-saccades into their response field but not for the errors toward the visual stimulus. The mean discharge rate of buildup neurons was 44 ± 6 spikes/s (range 2–114 spikes/s) before correct anti-saccades and 34 ± 5 spikes/s (range 0–107 spikes/s) before errors (t -test, $P = 0.028$). The majority of neurons (15/20, 75%) was more active on a correct trial compared with an error trial (Fig. 3D). These differences were significant (t -test, $P < 0.05$) only for some neurons (6/20, 30%). Thus a higher level of prestimulus activity in neurons that subsequently discharged for the anti-saccade was associated with the generation of correct responses.

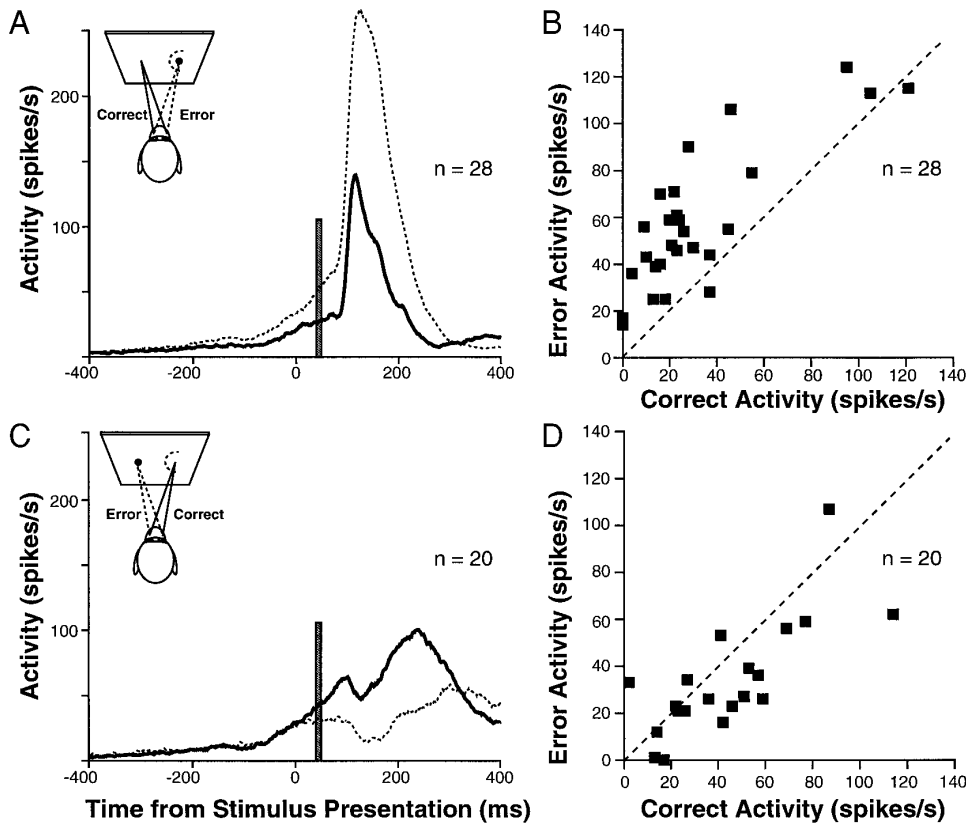


FIG. 3. Activity of the sample of buildup neurons on correct trials and error trials. *A*: mean spike density on correct trials (solid line) and error trials (dashed line) for stimulus presentations into the response field of the neurons. *B*: activity levels in the time 40–50 ms after stimulus presentation (shaded region in *A*) of individual buildup neurons (squares) are plotted before correct anti-saccades (abscissa) against the activity levels before errors (ordinate). The oblique dashed line represents the unity line (slope is 1). *C* and *D*: same as in *A* and *B* but for stimulus presentations at the mirror position.

Despite the significant differences in discharge between correct trials and error trials, it was not clear how well the prestimulus activity of buildup neurons on a single trial could predict the response behavior of the monkeys. To address this question, we performed a discriminant analysis (Miller et al. 1993; Snedecor and Cochran 1967) on the activity in the period 40–50 ms after stimulus presentation. This analysis determined the success rate by which a single trial could be classified into the appropriate response population (correct anti-saccade trials or error trials). The average of the means of the two populations served as the boundary point for the classification. Because the response behavior of the monkey could either be a correct anti-saccade or an error, a chance classification rate would be 50% for each neuron. For stimulus presentations into the response field, the mean successful classification rate was 68% (range 40–88%). This was significantly greater than chance (t -test, $P < 0.0001$). The mean classification rate for stimulus presentations at the mirror location was 59% (41–76%). This rate was also significantly greater than chance (t -test, $P < 0.001$).

DISCUSSION

We provided evidence for the hypothesis that a high level of prestimulus activity in the SC at the location where the stimulus is represented predicts the generation of reflexive saccades in the anti-saccade task. Previous studies emphasized the role of stopping processes after stimulus appearance in reflex inhibition (Guitton et al. 1985; Hanes and Schall 1996; Logan and Cowan 1984). Our findings indicate

that prestimulus neural processes also have a major influence on the ability to prevent reflexive responses.

Buildup neurons in the SC display different event-associated activities: 1) a low-frequency prestimulus activity when there is a high predictability of stimulus appearance, 2) many neurons have a phasic increase in discharge after the presentation of a visual stimulus into their response field, and 3) a motor burst for saccades into their response field (Dorris et al. 1997; Munoz and Wurtz 1995). The target neurons of buildup neurons in the saccadic burst generator in the brain stem (for review see Moschovakis et al. 1996) cannot decode these different event-associated activities because they are simply action potentials of the same neuron at different times. Therefore any increase in discharge of buildup neurons leads to an increased excitation of the target neurons. A saccade is elicited once the burst threshold of these target neurons is surpassed.

In the gap saccade task, the disappearance of the FP leads to an increase in discharge rate in buildup neurons (Munoz and Wurtz 1995). If the stimulus is subsequently presented into the response field of buildup neurons that already have a high discharge rate, less increase in discharge is required to surpass the burst threshold of target neurons to elicit a saccade. Therefore a high level of prestimulus activity should shorten saccadic reaction times by shortening the time required to reach the threshold. This hypothesis is supported by the negative correlation between the level of prestimulus activity in buildup neurons and saccadic reaction times (Dorris et al. 1997). Express saccades, which have latencies that approach the minimal conduction time in the oculomotor system (for review see Fischer and Weber

1993), are preceded by a high level of prestimulus activity in buildup neurons (Dorris et al. 1997). In this case, the level of prestimulus excitation of neurons in the saccadic burst generator may be so high that the stimulus-related burst of saccade-related neurons is sufficient to bring the activity over the threshold to trigger the saccade. Indeed, a single burst, which is equally correlated to the onset of the stimulus and the onset of the saccade, was found before express saccades in SC saccade-related neurons (Dorris et al. 1997; Edelman and Keller 1996). Similarly, in an anti-saccade trial when a visual stimulus is presented into the response field of buildup neurons that already have a very high level of prestimulus activity, the threshold may either be passed directly by the stimulus-related burst or before a stopping process can be completed in time to prevent the occurrence of a reflexive pro-saccade. Indeed, the majority of reflexive saccades generated by the monkeys in this study had latencies in the range of express saccades (Fig. 1B). Consequently, it seems that a crucial prerequisite for the prevention of reflexive saccades in the anti-saccade task is the suppression of preparatory processes before stimulus presentation.

The reaction times of correct anti-saccades are longer than the reaction times of pro-saccades in humans (Fischer and Weber 1992; Hallett 1978; Hallett and Adams 1980). It was hypothesized that this extra delay is the result of the necessity to shift the representation of the stimulus from the contralateral hemisphere to the ipsilateral hemisphere, i.e., contralateral to the movement (Hallett 1978). This hypothesis is in accordance with our data, which show that the generation of a correct anti-saccade is associated with a motor burst of buildup neurons in the SC ipsilateral to the stimulus (Figs. 2B and 3C).

Human studies also revealed that subjects cannot generate anti-saccades with the reaction times of express saccades (Fischer and Weber 1992). The two monkeys in our study also lacked correct anti-saccades within the range of express saccades (see Fig. 1B). We suggest that the transient decrease in discharge in buildup neurons in the SC ipsilateral to the stimulus at ~90 ms after the presentation of the stimulus (Figs. 2B and 3C) prevents the generation of short latency saccades in the anti-direction. This decrease in discharge may be mediated by lateral inhibition between the two SC (Munoz and Istvan 1998).

The intermediate layers of the SC receive projections from all brain areas implicated in the successful performance of the anti-saccade task (for review see Everling and Fischer 1998). Therefore we assume that the different discharge patterns in the SC before correct anti-saccades and reflexive saccades result from different prestimulus processes in the frontal cortex and/or basal ganglia. Indeed, Schlag-Rey et al. (1997) recently demonstrated that neurons in the SEF had higher discharges before anti-saccades compared with pro-saccades. These differences were already present in many neurons before the visual stimulus was presented (Amador et al. 1996). Moreover, event-related potentials in humans also showed differences in the prestimulus activation level between correct anti-saccades and reflexive saccades (Everling et al. 1998).

Taken together, these findings indicate that an important aspect of the control of reflexive responses is the state of neural activity in motor systems before stimulus appearance.

We speculate that a general imbalance in favor of motor preparation over inhibitory processes may account for the poor voluntary control over reflexive responses associated with many psychiatric and neurological disorders.

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