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ORIGINAL PAPER

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Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part I. Saccadic velocity

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Abstract Saccadic eye movements were elicited in 30 schizophrenic patients before and in 17 of these 30 during antipsychotic treatment with neuroleptics, and compared with those of 12 age-matched controls under three different conditions: (a) the gap paradigm, which tests the visually triggered and visually guided saccades; (b) the anti-task paradigm, which tests the internally guided, visually triggered saccades; and (c) the memory paradigm, which tests the internally triggered and guided saccades. Eye movements were recorded by DC electro-oculography, and the peak eye velocities for the different saccades were calculated. We found that antipsychotic treatment with neuroleptics reduces the peak saccadic eye velocity. This effect is larger for internally guided saccades than for externally triggered and guided eye movements. The saccadic velocity of the unmedicated schizophrenic patients did not differ from that of the controls. Since patients with diseases of the basal ganglia primarily show abnormalities of the internally guided and triggered saccades, our findings indicate that neuroleptics influence the oculomotor loop through the basal ganglia and that this loop, by means of neuroleptic influence on the brainstem saccadic burst generator, also influences the peak velocity of the internally guided saccades. This contradicts the current idea of the role of the cortical input to the brainstem saccadic burst generator, which is thought to not be involved in the determination of saccadic velocity.

Key words Saccadic velocity · Internally guided saccades · Visually guided saccades · Neuroleptics

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Introduction

Abnormalities of the eye movements of schizophrenic patients have been described since the beginning of the twentieth century (Diefendorf and Dodge, 1908). While several recent studies (Holzman et al. 1973; Holzman 1985; Levy et al. 1993; Arolt et al. 1993) have investigated especially the abnormalities of smooth-pursuit eye movements, fewer studies have reported on the performance of saccadic eye movements of schizophrenic patients (Arolt et al. 1993; Fukushima et al. 1988; Fukushima et al. 1990). This is somewhat surprising, since the currently accepted concepts of anatomy and physiology of the saccadic-eye-movement system (overview in Pierrot-Deseilligny 1994; Pierrot-Deseilligny et al. 1995; Fuchs et al. 1985) allow us to use the abnormalities of saccades to topographically allocate underlying defects. In this way, saccadic eye movements can contribute to a better understanding of the functional and morphological changes of the central nervous system in schizophrenia. Furthermore, only one study (Crawford et al. 1995) has investigated neuroleptic-free schizophrenic patients, and no study has yet compared saccadic eye movements in schizophrenic patients before taking neuroleptics and after improved psychopathology under neuroleptics. Since most of these patients take neuroleptics during the acute state of their disease, global performance of the eye movement task is probably influenced.

In general, there are two different types of saccadic eye movements: internally and externally guided saccades (Pierrot-Deseilligny 1991). We investigated the influence of antipsychotic medication with neuroleptics on the gain, fixation error rate, and velocities of externally triggered saccades to visual targets (gap saccades), and of externally triggered saccades to internal targets (anti-saccades and memory saccades) by comparing the eye movements in unmedicated patients with an acute exacerbation of schizophrenic psychosis and later after improvement during antipsychotic medication. In part I we describe the influence of the antipsychotic treatment on the saccadic veloc-

ity under different paradigms compared with that of healthy controls in order to determine the influence of the cortical input to the brainstem on saccadic velocity. In part II we describe the influence of neuroleptics and the psychopathological state of schizophrenic patients on the latency, gain, and rate of fixation suppression errors of saccades, elicited under the same paradigms.

Subjects and methods

We examined 30 schizophrenic patients (14 females, 16 males; average age 34.2 ± 11.1 years) who had been diagnosed with the Structured Clinical Interview (American Psychiatric Association 1990) according to the diagnostic criteria of the DSM-III-R. All patients were inpatients of the psychiatric university hospital. The patients gave their informed consent, and the study was approved by the local ethics committee. Twelve healthy age-matched volunteers (5 females, 7 males; average age 37.9 ± 13.0 years) served as controls.

Before being included in the study but after admission to the hospital, 18 patients received no drug treatment; 12 patients (8 females, 4 males) received benzodiazepines (average: 10.6 ± 4.9 mg diazepam) for a short time (1–3 days) if it was clinically indicated for sleep disturbances, agitation, or tension. All patients had a medical and neurological examination and a blood test. None of them showed any signs of an additional somatic disease. Patients with alcohol or drug abuse (urine screening test) were excluded from the study.

Twenty-four (8 females, 16 males) of these patients had had a first episode of schizophrenia or were admitted to psychiatric treatment for the first time but had not been treated with neuroleptics before ("neuroleptic naive"); 3 patients had been off neuroleptic treatment for at least 4 weeks. Seventeen (7 females, 10 males; average age 37.0 ± 12.7 years) of these 27 patients were reexamined before being discharged. These 17 patients had been treated as inpatients for at least 1 month in order to hold the treatment conditions as stable as possible. The duration of treatment ranged from 1 to 4 months (mean duration 2.6 ± 1.8 months). Treatment included butyrophenone derivates, phenothiazine derivates, thioxanthenes, clozapine, and other atypical neuroleptics. The antipsychotic treatment regimen was based on the natural clinical conditions (e.g., individual history of response or side effects, necessity of sedation, sleep disturbances). The mean dosage for antipsychotic therapy was 275 ± 209 chlorpromazine equivalents per day. Three of the patients were examined only while under treatment with neuroleptics. The total duration of the disease before admission to the study was from 6 to 300 months; the mean duration was 54.5 ± 77.9 months.

Psychopathology was assessed according to the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1976) and the Scale for Assessment of Negative Symptoms (SANS; Andreasen and Olsen 1982).

The BPRS total score mean value was at admission 56.1 ± 9.7 points and after the treatment 37.5 ± 9.8. This decrease was highly significant ($p < 0.001$).

The SANS total score at admission was 70.3 ± 25.5 points and after treatment 49.3 ± 19.4 points, also showing a significant decrease ($t = 2.53$; $p \leq 0.02$).

Apparatus

The subjects were seated in a chair 1.2 m in front of a semi-spherical screen. The head was immobilized by a head rest. Eye movements were recorded by binocular horizontal and vertical DC electro-oculography (EOG) in complete darkness. Silver-silver chloride electrodes were placed above and below the right eye to record vertical eye movements and at the outer canthi to record binocular horizontal eye movements (DC amplifier, cut-off filters at 50 Hz). After a pause of 5 min to reduce the drift of the cornea retinal potential, the experimental session started with the calibration paradigm used for off line calibration of the data. This calibration paradigm was repeated in the middle and at the end of the session. Data were stored on a seven-channel analog tape (Teac XR-310, Teac, Tokyo, Japan). Additional paper charts were made on-line.

Testing paradigms

Saccades were elicited by different paradigms (Fig. 1). All paradigms consisted of a series of trials that always began with fixation of a laser spot, presented centrally for 1 s. Another laser spot was used to elicit a saccade to one excentric position. At the end of each trial the subject returned to fixation of the central laser spot that reappeared. These saccades back to the center were not used in the analysis. For each paradigm a minimum of 16–40 trials were recorded. All paradigms were tested twice; there was a short rest of 1–3 min between each paradigm. To calibrate the eye movements the subjects were asked to follow a spot moving periodically between the excentricities -30, 0, and +30°. Thus, the direction as well as the amplitude and timing of the next step were predictable. Subjects were instructed to follow the target as fast and accurately as possible. At least one of the investigators administered and supervised the test. The following paradigms were used:

1. Gap: 200 ms before the peripheral target appeared, the central fixation LED was switched off (Fig. 1 A): The peripheral target then appeared at random positions between ± 20°.

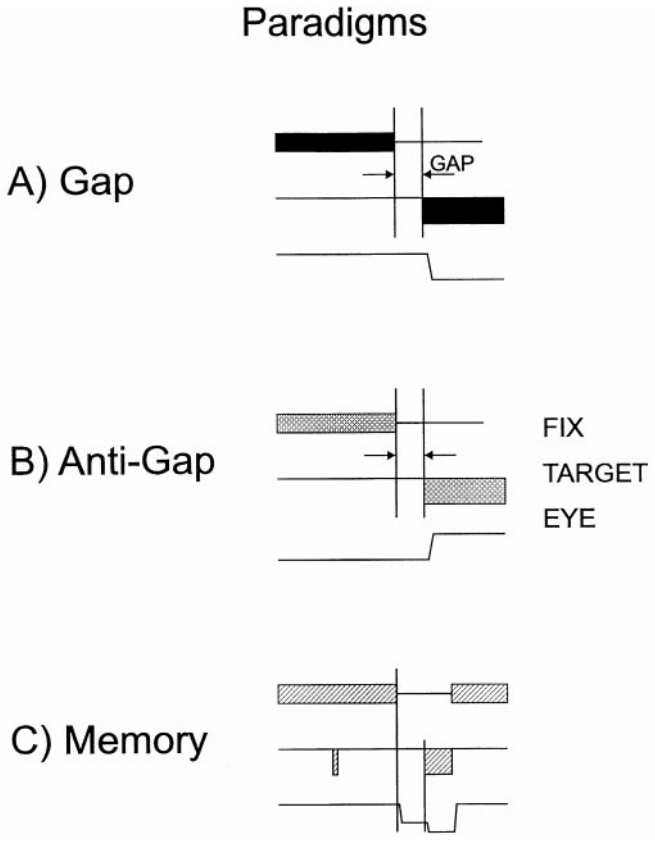


Fig. 1 A–C Paradigms used to elicit externally triggered, visually guided, or internally triggered/guided saccades. **A** Gap paradigm; **B** anti-gap paradigm; **C** memory paradigm. The fixation spot *(FIX)*, the peripheral target *(TARGET)*, and the schematic eye position *(EYE)* are indicated. The peripheral target in the memory paradigm was flashed for 50 ms

2. Anti-gap: As in the gap paradigm the fixation spot disappeared before the presentation of the peripheral target. But in contrast, the subjects had to make a saccade to the side opposite to the position where the target appeared (Fig. 1 B).
3. Memory: The subject had to fixate a central LED for at least 2000 ms, then at random peripheral locations (± 10, ± 20, and ± 30° right or left); the target appeared for a period of 50 ms. The central fixation LED disappeared 2000 ms later. The subject was asked to make a saccade to the remembered target location. The target reappeared 500 ms after this saccade was completed (Fig. 1 C).

Data analysis and statistical evaluation

The recordings were digitized off-line (sampling rate 200 Hz) and stored on a hard disk. A commercial interactive eye movement analysis program (AMTECH, Heidelberg, Germany) was then used to calculate the gain (eye amplitude to target amplitude), the latency (the time between target onset or fixation offset and first saccade), the duration, and the peak velocity of the initial saccade. The program marked the onset and offset of the saccade. These automatic markings were then verified and, if necessary, corrected by the operator. Saccade amplitudes and peak velocities were calibrated using the periodic 30° target steps from the calibration paradigm. Despite the large offset drifts that are frequently observed in the EOG signal, previous recordings have shown an almost linear relation between the AC component of the EOG signal and the saccade amplitude, although the overall noise of the AC signal is high. This linearity is maintained up to excentricities of ± 30°.

Fig. 2 The differences in the average peak velocity of saccades with an amplitude range of 5–10, 10–15, 15–20, and 20–25° between unmedicated patients and controls are shown. For saccades > 10° the saccades of the unmedicated patients tend to be slightly faster than the saccades of the controls

Saccades with latencies less than 130 ms and more than 800 ms, as well as amplitudes less than 5° or more than 35° under the GAP paradigm, were excluded from further analysis, because they had to be predictive and/or not goal directed.

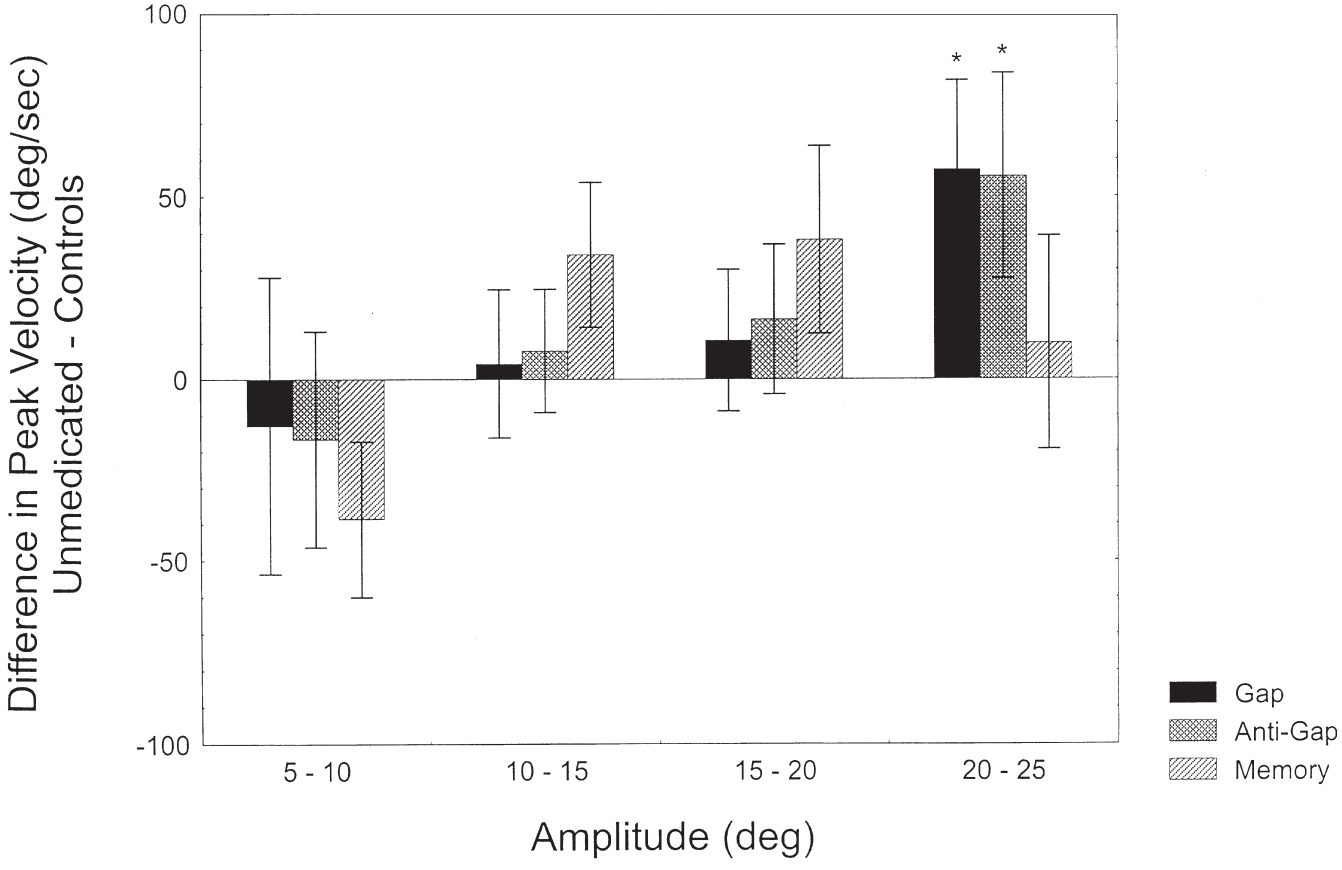
The mean and standard deviation for the peak velocity under each condition for untreated and treated patients as well as the controls were calculated using a commercial statistics package (Statistica, Tulsa, Oklahoma). The average velocities were computed separately for four classes of saccade amplitudes (5–10, 10–15, 15–20, and 20–25°), for each stimulus condition, and for each group. Because the patients and the controls represent different individuals, pairs of these groups were compared using Student's *t*-test for independent groups. The degree of freedom of the *t*-value (n1 + n2-2) was computed. The significance level for group differences was set at $p \leq 0.05$. To compare the effect of neuroleptics a paired sample test was performed.

Results

General observations

The schizophrenic patients selected for the study did not generally manifest specific problems under the different test conditions. Most of the patients were able to finish the eye movement recording in a time comparable to that of the controls.

Approximately 4500 saccades were included in the analysis. Figures 2 and 3 show the differences of these average velocities between the unmedicated patients and the controls (Fig. 2) and the medicated and unmedicated patients (Fig. 3).



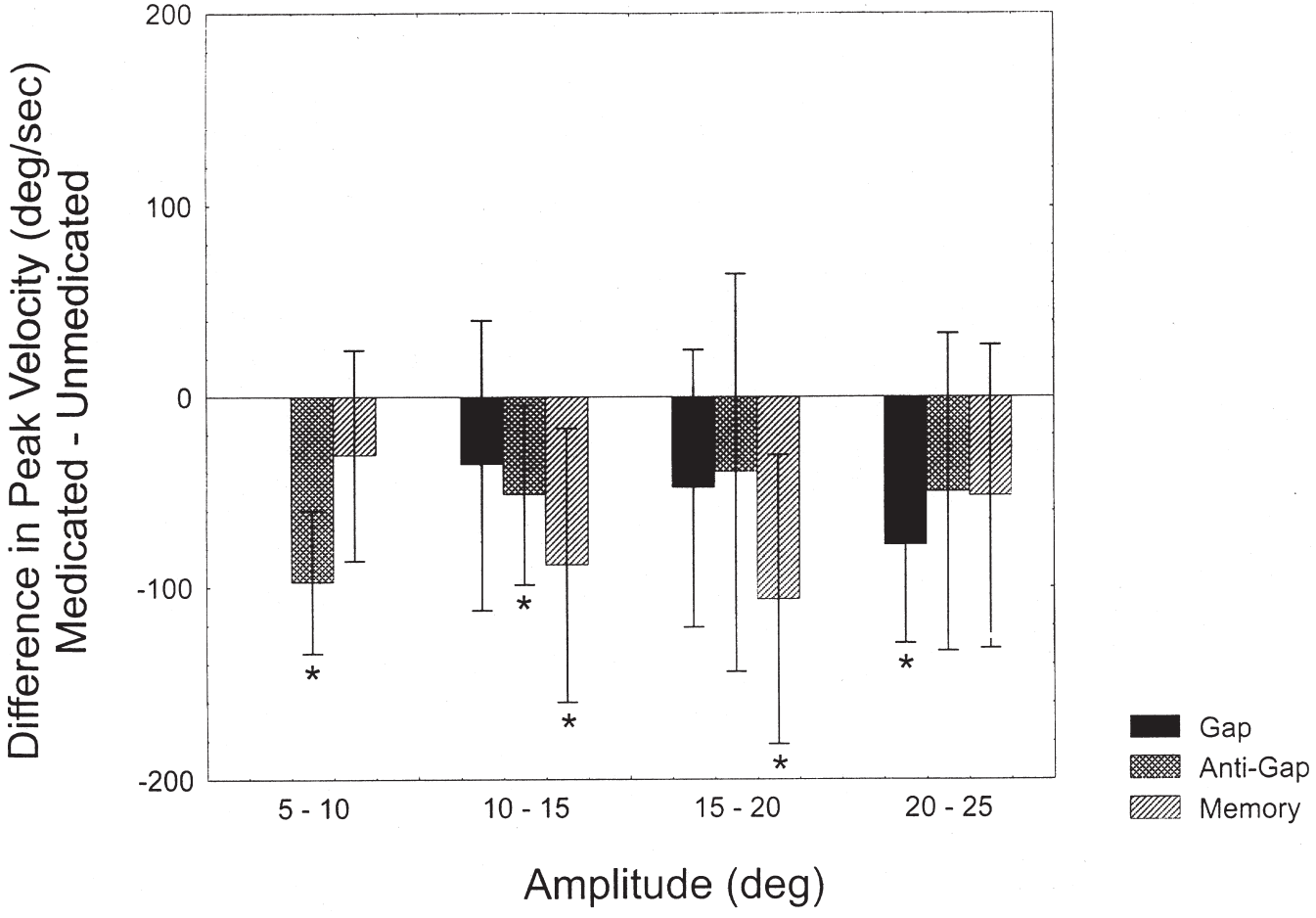


Fig. 3 The differences in the average individual peak velocity of the saccades with an amplitude range of 5–10, 10–15, 15–20, and 20–25° in the ten patients who were tested as medicated and unmedicated are shown. The saccades of the patients when medicated were slower, especially the anti-saccades and the memory saccades

Unmedicated patients compared with controls

The peak velocity of the memory-guided saccades, the antisaccades, and the visually guided saccades < 20° was not significantly different between the controls and the unmedicated patients. Only the gap saccades and anti-gap saccades > 20° were slightly, but significantly, faster in the unmedicated patients than in the controls ($p < 0.05$, *df* 29; Fig. 2).

Medicated patients compared with controls

Saccadic velocities were generally slower for the medicated patients than the controls, especially the smaller saccades and the anti- and memory-guided saccades. The gap saccades were less affected. The maximal difference was 60°/s for the 5–10° memory-guided saccades. Since the standard deviation of the difference was large, this difference is significant only for the smaller memory-guided and anti-saccades (5–10°, $p < 0.05$, *df* 13; $p < 0.01$, *df* 18).

Medicated compared with unmedicated patients

A similar result was found when we compared medicated and unmedicated patients. The peak velocities of the saccades were maximally different in the memory-guided saccades (Fig. 3), especially for the amplitudes from 10 to 20° ($p < 0.04$, *df* 4 and 6); less different in the anti-saccades (5–15°; $p < 0.05$, *df* 6), although the saccades of the unmedicated patients always had higher velocities than the saccades of the medicated patients. As in the controls, the difference was not significant for saccade amplitudes between 5–20° in the gap paradigm, and only the 20–25° saccades were significantly faster in the unmedicated schizophrenic patients ($p < 0.01$, *df* 6; Fig. 3).

In summary, only the largest tested saccades of the unmedicated patients were faster than the equal-sized saccades of the controls. Otherwise, the saccades of the medicated patients were slower than the saccades of the unmedicated patients as well as those of the controls. This difference was always less obvious in the externally guided saccades (gap paradigm) than in the internally guided saccades (memory-guided and anti-saccades).

Discussion

Our results show that the internally guided as well as the externally guided saccades of the unmedicated patients

and the controls have nearly equal velocities. There was only a slight tendency to faster saccades with larger amplitudes (> 20°) in the unmedicated patients. In contrast, the peak velocities of the memory-guided and the antisaccades were lower in the medicated patients than in the unmedicated patients or the controls. The velocities of the externally guided saccades did not differ between the groups tested, with the exception of the saccades with amplitudes > 20°. Thus, neuroleptics reduce almost exclusively the velocities of the internally guided saccades and have only minor effects on the velocities of visually guided saccades. Schizophrenia alone does not alter saccadic velocities.

Among authors of recent publications only Fukushima et al. (1990) have analyzed the saccadic velocities of schizophrenic patients and controls. They found that the larger anti-saccades and memory-guided saccades, but not the visually guided saccades, had smaller peak velocities in the patients than in the controls. All patients except one were on neuroleptic medication. These authors did not investigate unmedicated patients. Thus, their results were similar to our finding that neuroleptics mostly reduce the saccadic velocities of the internally guided saccades.

This differential effect of neuroleptic medication on the velocities of internally and externally guided saccades resembles the differential effect of disorders of the basal ganglia on voluntary saccades (Crawford et al. 1989; Hikosaka et al. 1995). The parkinsonian syndrome primarily affects the internally guided saccades (Vidailhet et al. 1994; Kennard and Lueck 1989; Hikosaka and Wurtz 1989). Similar results have also been reported for patients with Gilles de la Tourette syndrome (Straube et al. 1997). Typically, the internally guided saccades (e.g., memory guided saccades) are hypometric, and the latencies are prolonged. In contrast, the externally (visually) guided saccades are almost normal. The results suggest that the basal ganglia are involved in the pathophysiology of saccade abnormalities in schizophrenic patients on neuroleptics, probably reflecting a dopamine-receptor blocking effect. We discuss this in more detail together with the results on latency, gain, and suppression errors in externally and internally guided saccades in part II of this paper.

Velocity of saccades and the concept of the burst generator

It is generally accepted that the final pathway for all saccades is the saccadic burst generator, a neuronal network located in the brainstem (Fuchs et al. 1985; Wurtz 1996). According to the Robinson model (Robinson 1973, 1975), the velocity of a saccade is terminated solely by the behavior of the local feedback loop in the brainstem. Since our results show a differential effect of neuroleptic medication on the peak velocity of the internally and externally guided saccades, we conclude that the input to this local feedback loop by the afferences from the superior colliculus and cortex influences the dynamics (velocity) of the triggered saccade. Moreover, these dynamics are solely defined by intrinsic properties of the local feedback loop. The findings of Berthoz and colleagues (1986) that neurons in the superior colliculus may code the dynamics of the saccade agree with our conclusion. The concept of a burst generator proposed that the output of the superior colliculus regulates not only the amplitude but also the velocity of the saccade. This implies that all models introducing a *scalar* value are unsuitable for explaining our findings. In contrast, the model of Tweed and Vilis (1990) introduces a *vector* at this point, which reflects the angle as well as the velocity of the ongoing saccade and thus is more suitable for explaining our results.

In conclusion, saccadic velocities in unmedicated schizophrenic patients are normal or even slightly supranormal. Antipsychotic treatment with neuroleptics selectively decreased the velocity of the memory-guided saccades. They also reduced the velocity of the anti-saccades, but to a lesser extent. These findings indicate that the cortical input through the basal ganglia to the brainstem saccade burst generator is under dopaminergic control during internally guided saccades. This input, however, influences not only saccade initiation but also saccade dynamics, a finding that contradicts the general concept that only the performance of the brainstem saccade burst generator is responsible for the saccade dynamics.

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