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ORIGINAL PAPER

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Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part II. Saccadic latency, gain, and fixation suppression errors

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Abstract Saccades were elicited in 30 schizophrenic patients before medication, in 17 of them during medication with neuroleptics, and in 12 healthy controls using six paradigms that tested different types of saccades: (a) the externally triggered and visually guided saccades; (b) the externally triggered and internally guided saccades (anti-saccades); and (c) the internally triggered and internally guided saccades (memory-guided saccades). Latency of the primary saccade, gain (eye amplitude to target amplitude), and percentage of unwanted saccades (fixation suppression errors) were calculated. The externally triggered and externally guided saccades were only slightly affected in the patients, indicating that the function of parieto-tectal pathways was preserved. In contrast, the internally guided and externally triggered saccades showed abnormally long latencies, slightly smaller gains, and an increased rate of suppression errors regardless of the medication status. These findings were even more pronounced in the internally triggered and internally guided saccades such as memory-guided saccades. According to animal experiments and studies on patients with disorders of the basal ganglia, the performance of these saccades is based on the function of the pre- and dorsolateral frontal cortex and its connections to the basal ganglia. The minimal improvement of some of the parameters after clinical improvement and during treatment with neuroleptics suggests that the eye-movement deficits are associated with abnormalities of schizophrenia, which do not basically change under medication with neuroleptics. The observed effects of neuroleptics also argue against a primary abnormality in the dopaminergic input to the frontal cortex – basal ganglia oculomotor loop and support the view that there is a primary disturbance of the cortical input to the oculomotor loop through the basal ganglia in schizophrenics.

Key words Saccades · Latency · Gain · Fixation suppression error · Neuroleptics

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Introduction

Recent publications have reported several abnormalities of the saccadic eye movements in schizophrenic patients. These results are problematic since the studies have used different paradigms and most have not distinguished between unmedicated and medicated patients. Thus, it is not surprising that several studies have described prolonged latencies for visually guided saccades (Schmid-Burgk et al. 1982, 1983; Yee et al. 1987), whereas others did not (Levin et al. 1981, 1982; Iacono et al. 1981, 1982; Moser et al. 1990; Fukushima et al. 1988, 1990).

Thanks to animal experiments that have provided relatively elaborate concepts about the pathways and areas involved in the generation of reflectory as well as internally triggered voluntary saccades, it is now possible to use the differential pattern of saccadic abnormalities to allocate the underlying pathophysiology of the central saccadic system (Pierrot-Deseilligny 1994; Pierrot-Deseilligny et al. 1995). We thus have expanded our testing to include different types of saccades, e.g., visually guided saccades, memory-guided saccades, and anti-saccades, and our analysis to cover also saccadic latency and gain (ratio of eye amplitude to target amplitude) as well as the fixation suppression errors of unwanted saccades. Furthermore, we tried to estimate the effect of pharmacological treatment on saccadic eye movements by evaluating the psychopathological status of the patients before and after medication with neuroleptics and by correlating these changes in psychopathology with the eye movements.

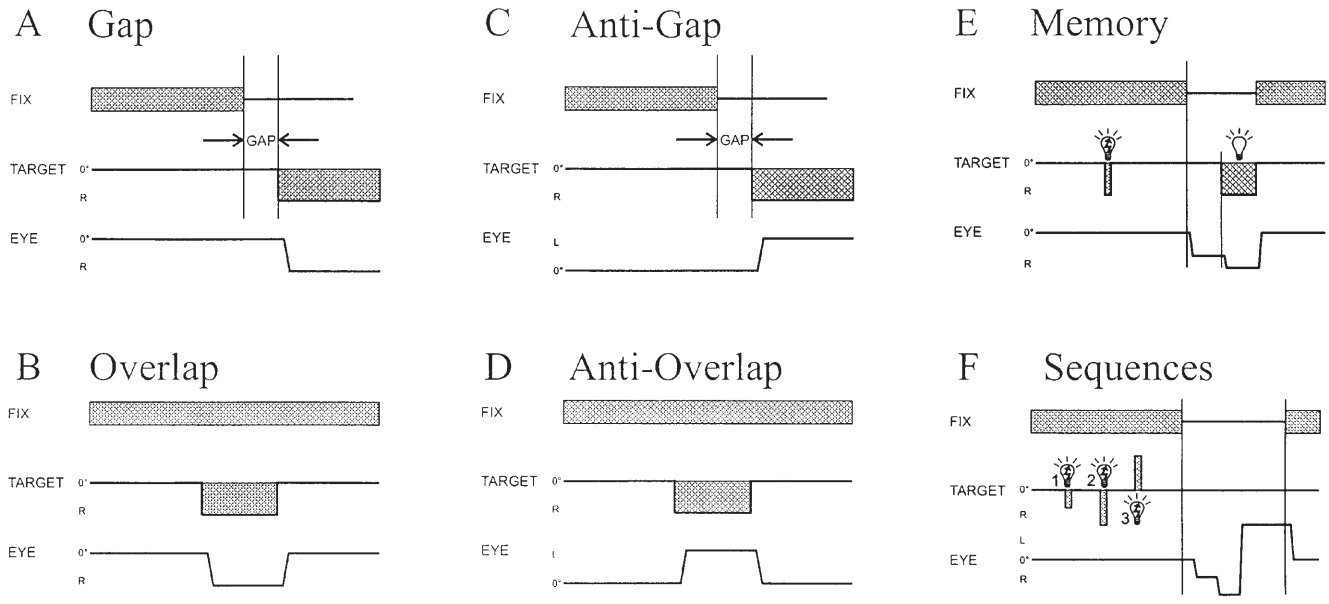

Fig. 1 A–F The paradigms used to elicit externally triggered, visually guided, or internally guided saccades are shown. **A** Gap paradigm; **B** overlap paradigm; **C** anti-gap paradigm; **D** anti-overlap paradigm; **E** memory paradigm; and **F** sequential memory paradigm. The fixation spot *(FIX)*,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

Patients and methods

The same 30 patients and 12 control subjects described in the accompanying paper (part I) participated in this analysis.

Apparatus

The apparatus and recording technique are described in detail in part I of this paper. Briefly, the eye movements were recorded by binocular horizontal DC electro-oculography (EOG) in complete darkness (DC amplifier, cut-off filters at 50 Hz). The experimental session started with the calibration paradigm used for off-line calibration of the data. The spot moved periodically between eccentricities of –30, 0, and +30°. The data were stored on a seven-channel analog tape (Teac XT-30, Teac, Tokyo, Japan) during the session for further off-line analysis.

Testing paradigms

Saccades were elicited by six different paradigms (Fig. 1). All paradigms consisted of a series of trials that always began with fixation of a laser spot presented centrally for 1s. Another laser spot was then used to elicit a saccade to one eccentric position. At the end of each trial the subject again fixated on the central laser spot that reappeared. These saccades back to the center were not used for analysis. A minimum of 16–40 trials were recorded for each paradigm. All paradigms were tested twice; there was a short rest of 1–3 min between each paradigm:

1. Gap: 200 ms before the target appeared, the central fixation light-emitting diode (LED) was switched off (Fig. 1A). The target then appeared at random positions between ± 20°
2. Overlap: The central LED stayed on for 750 ms after the peripheral target appeared at a random position between ± 20° (Fig. 1B).
3. Anti-gap: Similarly to the first paradigm, the fixation spot disappeared before the presentation of the peripheral target, but the subjects were instructed to make a saccade to the side opposite to where the target appeared (Fig. 1C).
4. Anti-overlap: Similar to the third paradigm, but the central fixation spot stayed on (Fig. 1D).
5. Memory: The subject had to fixate on 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. 1E).
6. Sequential memory: Similar to the fifth paradigm, but with the exception that more than one peripheral target was shown; the target appeared at three different peripheral locations (for 50 ms at each location) sequentially. The subject had to perform the saccades in the same sequence after a delay of 1000 ms (Fig. 1F).

Data analysis and statistical evaluation

The same analysis procedure described in part I of this paper was used here. The error rate of the visual suppression of unwanted saccades in the anti-saccade paradigms was defined as the number of saccades that initially began in the direction of the target, divided by the number of all performed trials.

The sequences of memory-guided saccades were characterized visually from the paper charts as either appropriate (no deviation from the target sequence, e.g. the temporal-spatial profile of the saccades reflects those of the targets; we did not use the saccade amplitude as a criterion) or inappropriate (at least one of the saccades of the sequence did not reveal the spatial structure of the target steps).

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

The mean and standard deviation for the latency, gain, and error rate for each condition in untreated and treated patients as well as the controls were calculated with a commercial statistics package (Statistica, Tulsa, Oklahoma). Since each of the control group and the patient group represent particular samples of subjects, 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 from the number of subjects per group. However, the mean values of each subject and each paradigm were averaged over several (up to 60) saccades. The significance level for group

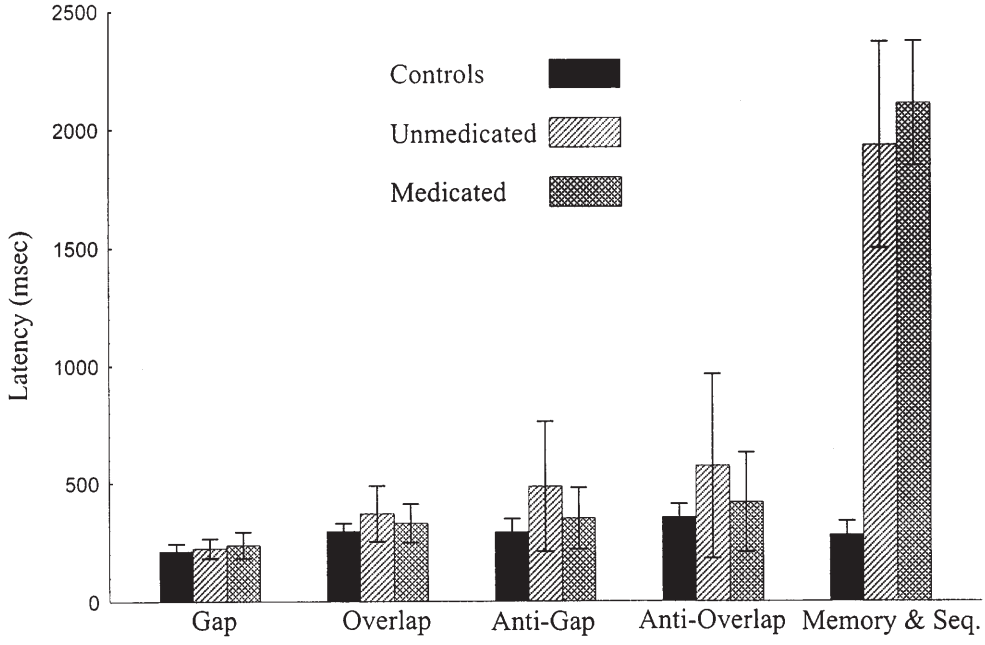

Fig. 2 The mean and standard deviation of the saccade latency (first saccade) in the different paradigms (gap, overlap, anti-gap, anti-overlap, and memory/sequential memory) are given for the controls *(black column)* and the schizophrenic patients without *(dotted diagonals)* and with *(dotted crosses)* neuroleptics. ■ Controls, ▨ unmedicated, ▩ medicated

differences was set at $p \leq 0.01$. To evaluate the differences between medicated and unmedicated subjects, Student's *t*-test for dependent groups was used based on the 17 patients that could be tested before and during medication with neuroleptics.

The χ^2 test was used for comparison of the error rates in the different groups. Pearson's product-moment correlation (two-tailed) was used to compute the relationship between the patients' scores on Brief Psychiatric Rating Scale (BPRS) tests grading degree of psychopathology and eye movements.

Results

Cap and overlap saccades

Latency

There was no significant difference in the latency of the saccades in the unmedicated schizophrenics (223.3 ± 41.1 ms, p 0.42) or the medicated schizophrenics (236.9 ± 55.1 ms, $p < 0.2$) compared with the controls (211.9 ± 31.4 ms) in the gap paradigm (Fig. 2). In the overlap paradigm, however, there was a tendency of increased latencies in unmedicated patients (370.6 ± 118.8 ms, $p < 0.07$) compared with controls (296.1 ± 32.7 ms), whereas a smaller difference was observed between medicated schizophrenics (329.8 ± 82.1 ms; $p < 0.24$) and controls (Fig. 2). Compared with the latencies in the gap paradigm, the latencies in the overlap paradigm were significantly longer for all three groups ($p < 0.002$); thus, the so-called gap effect was observed in both treated and untreated schizophrenics.

Gain

There were no significant differences in the gains, either between the medicated and the unmedicated or between patients and normals in both paradigms.

Anti-gap and anti-overlap saccades

Latency

Both the anti-gap and the anti-overlap paradigms showed similar results:

1. The latencies were longer in the gap and overlap paradigms.
2. The latencies were significantly longer in the unmedicated patients than in the controls (anti-gap 485.9 ± 276.7 to 291.7 ± 56.3 ms, $p < 0.02$; anti-overlap 572.3 ± 391.5 to 354.4 ± 56.7 ms, $p < 0.1$).
3. The medicated patients showed only an insignificant increase in the latencies compared with those of the controls (anti-gap: 349.2 ± 131.1 ms, $p < 0.18$; anti-overlap: 417.9 ± 211.1 ms, $p < 0.37$).
4. Similarly to the visually guided saccades, there were significantly longer latencies in the overlap paradigm than in the gap paradigm in all three groups ("gap effect"; Fig. 2).

Suppression errors

Unmedicated and medicated schizophrenics showed significantly increased error rates compared with healthy controls in both paradigms. Nearly 50% of the saccades of unmedicated patients and approximately 40% of those of medicated patients showed suppression errors in the anti-gap paradigm. The numbers were slightly smaller, 39 and 46%, respectively, in the overlap paradigm, but were still highly significant. Suppression errors were observed in only 13% (anti-gap paradigms) and 5% (anti-overlap paradigm) of the saccades in the controls (Fig. 3).

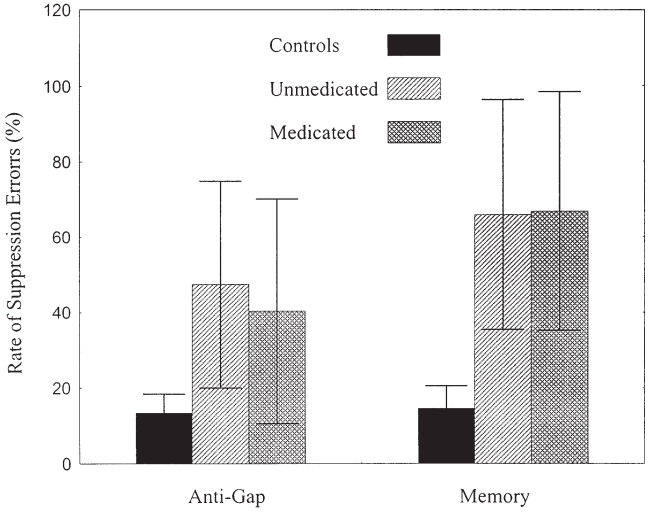

Fig. 3 The means and standard deviations are given for the suppression errors in percentage of all performed saccades in the controls and the schizophrenic patients without *(dotted diagonals)* and with *(dotted crosses)* neuroleptics in the anti-gap and memory paradigms. ■ Controls, ▨ unmedicated, ▩ medicated

Memory saccades and sequential memory saccades

Latency

There was a dramatic increase in the saccadic latencies in both the unmedicated and the medicated patients for the memory- and sequential-memory-guided saccades. The latencies in the unmedicated and the medicated schizophrenics were nearly nine times longer than the latencies in the controls (278.1 ± 58.3 ms; Fig. 2).

Gain

In the memory paradigm the unmedicated (0.80 ± 0.31, $p < 0.44$) and the medicated patients (0.76 ± 0.16, $p < 0.33$) exhibited a slight but not significant tendency toward a smaller gain than the controls (0.85 ± 0.24). We also analyzed the number of wrong saccadic sequences in the sequences of memory-guided saccades as described previously. The controls performed a wrong sequence in 18% of the sequences; the patients were not influenced by the actual treatment and made significantly more errors [63.3% (unmedicated) and 67.2% (medicated), $p < 0.001$].

Suppression errors

In the memory paradigm the patients (65.9% unmedicated and 66.9% medicated) had a significantly higher number of suppression errors as regards unwanted early saccades than the controls (14.6%; Fig. 3).

Psychopathology

During the treatment period psychotic symptoms decreased significantly. The total BPRS score decreased from 56.1 ± 9.8 points to 37.5 ± 9.8 points ($p < 0.001$). There were also significant reductions in the subscales Anxiety/Depression, Thought Disorder, Activation, and Hostility. The decrease in the subscale Anergy was not significant.

In parallel, the negative symptoms, measured by the SANS scale, also significantly improved in the subscales Alogia, Anhedonia, Attention, and the total score, whereas the decrease was not statistically significant in subscales Affective Flattening/Blunting and Abulia/Apathy (Fig. 4).

The correlation between psychopathology and saccades showed no significant relationship between the BPRS scores and the saccades. There were, however, several relationships between the SANS scores and the suppression errors in the anti-gap and anti-overlap paradigms (Table 1).

Discussion

This study examined acute schizophrenics twice: once before medication and once after psychopathological improvement under neuroleptic medication. The study design allowed us to separate the effects of the disorder from treatment effects; the psychopathological ratings allowed us to show relationships between eye-movement alterations and status variables.

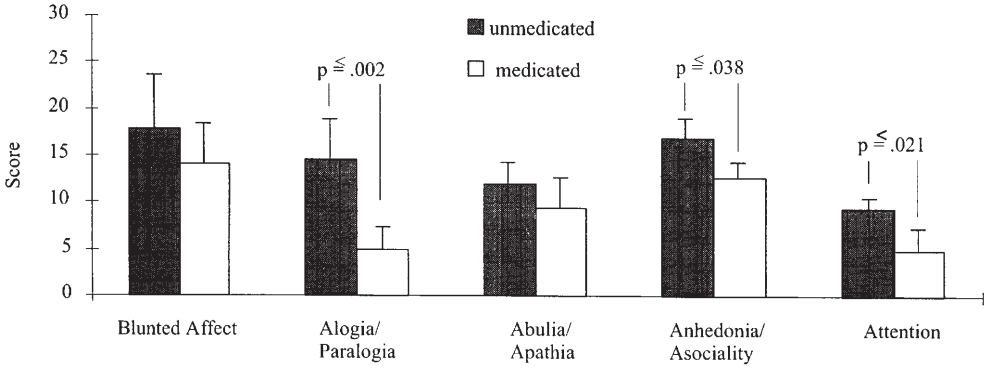

Fig. 4 Comparison of the SANS subscores for the unmedicated *(dark columns)* patients with the values at the reinvestigation of these patients under medication *(white columns)*. The *p*-values are indicated for each pair. ■ Unmedicated, □ medicated

Table 1 Relationship between error rates of medicated schizophrenics and the SANS subscales blunted affect, alogia/paralogia, and the total score

Saccades SANS	Anti-task saccades (n = 16)	Memory saccades (n = 17)	Sequential memory saccades (n = 17)
Blunted affect	$r = 0.51$ $p \leq 0.043$	$r = 0.62$ $p \leq 0.010$	n.s.
Alogia/paralogia	$r = 0.54$ $p \leq 0.0032$	$r = 0.67$ $p \leq 0.004$	$r = 0.51$ $p \leq 0.045$
Total score	$r = 0.48$ $p = 0.05$	n.s.	n.s.

In general, the results showed that the externally (visually) triggered and externally (visually) guided saccades (gap and overlap saccades) are relatively unaffected in the patients. In contrast to the externally-triggered and -guided saccades, the anti-saccades, and, even more pronouncedly, the memory-guided saccades (as an example for guided saccades) showed increased latencies and reduced gains. Furthermore, the suppression of unwanted saccades under these conditions were disturbed in the patients. While treatment had no effect on the ability to suppress unwanted saccades, neuroleptics significantly improved psychopathological status as evaluated by the BPRS score and SANS scale. The treatment caused only a small to moderate reduction in the latencies of the anti-saccades and only a small increase in the primary hypometric gain of the memory-guided saccades, which were still hypometric compared with that of the controls. The treatment did not improve the performance of sequences of memory-guided saccades. The relationship between the SANS subscales Alogia and Blunted affect, and the Memory, Sequential memory, and Anti-task saccades in the medicated patients indicate that some of the schizophrenia- negative symptoms may influence the saccades. It was interesting that no relationship to the subscale Attention was found. This suggests that the increased error rates are not a result of an attentional deficit in schizophrenics. Since the initial examination was performed with patients who had been admitted to the hospital due to an acute exacerbation of the disorder, positive symptoms were predominantly seen in these unmedicated patients. This may explain why a relation between saccades and schizophrenia-negative symptoms was found only at the reexamination. Angst et al. (1989) reported that negative symptoms are often covered by positive symptoms and (re)appear after improvement of the positive symptoms.

Most studies have also reported increased suppression of errors and increased latencies, especially in the anti-saccades of schizophrenic patients (Fukushima et al. 1988; Fukushima et al. 1990a, b; Sereno and Holzman 1995; Fukushima et al. 1994). Since patients with prefrontal lesions also make more suppression errors, this finding is assumed to support hypofrontality in schizophrenic patients (Fukushima et al. 1994). Studies that also investigated memory-guided saccades (Everling et al. 1996; Park et al. 1995) generally reported more hypometric saccades in patients than in healthy controls. We found a similar hypometria of the memory-guided saccades. This finding can be explained either by the spatial working memory deficit of schizophrenic patients (spatial working memory is anatomically located in the dorsolateral prefrontal cortex (Park et al. 1995), or by a generally reduced gain of the internally guided saccades. Furthermore, the performance of sequences of memory-guided saccades were dramatically impaired to the same extent in both unmedicated and medicated schizophrenics. This impairment of the sequences of memory-guided saccades is thought to be topographically connected with a dysfunction of the supplementary eye field in the prefrontal cortex (Pierrot-Deseilligny et al. 1995; Gaymard et al. 1990). Thus, our results agree with findings on saccadic eye movements in schizophrenics and suggest that there is a functional disturbance of frontal cortical circuits. We questioned whether this is due to disturbed input to the frontal cortex from the basal ganglia, which is interconnected with the frontal cortex by recurrent loops (Alexander et al. 1986; Alexander et al. 1990). To answer this question, we discuss our results in relation to the current model of saccade generation.

According to the model of saccade generation proposed by Pierrot-Deseilligny (1994) several types of saccades can be distinguished: (a) reflexive saccades, which are either visually or acoustically guided (these saccades are mostly controlled by pathways from the parietal eye field to the brainstem); (b) intentional saccades, which are either internally (scanning saccades) or externally triggered (e.g., anti-saccades) and otherwise externally (e.g., scanning saccades) or internally guided (e.g., memory saccades). Intentional saccades are believed to depend more on the integrity of the frontal eye field, the prefrontal and dorsolateral frontal cortex, and the oculomotor pathway through the basal ganglia to the brainstem, since this type of saccade is affected by disorders involving the basal ganglia, e.g., Parkinson's syndrome (Crawford et al. 1989; Kennard and Lueck 1989). Animal experiments (Hikosaka and Wurtz, 1989) support this view and show that neurons in the substantia nigra pars reticulata are primarily active in internally triggered and guided saccades.

Whereas reflexive visually guided saccades (tested by the gap and overlap paradigms) are relatively unaffected in both medicated and unmedicated schizophrenic patients, intentional saccades, e.g., anti-saccades and memory-guided saccades, are strongly affected in medicated and unmedicated schizophrenic patients. For this reason, our discussion concentrates on the pathways involved in the generation of intentional saccades.

In several papers Alexander and colleagues have described various different pathways through the basal ganglia (Alexander et al. 1986; Alexander et al. 1990; Alexander and Crutcher 1990). They also mention an oculomotor loop which is analogous to the skeletal motor pathway through the basal ganglia. All these loops are constituted by a direct and an indirect pathway. In the case of the oculomotor pathway, the cortical, excitatory projec-

tions from the frontal eye field, and the supplementary eye fields to the caput nuclei caudatus, are divided into topographically distinct inhibitory pathways. It is thought that the direct pathway is responsible for initiating internally guided saccades by disinhibiting the neurons in the superior colliculus (Hikosaka and Wurtz 1983), whereas the indirect pathway is responsible for the suppression of unwanted saccades (Hikosaka et al. 1993; Hikosaka et al. 1995). Functional electrical stimulation of the posteroventral pallidum had shown that not only the performance of internally triggered limb movements of the somato-motoric system is improved, but also that of internally guided saccades in Parkinson's disease (Straube et al. 1998).

In this context, we propose that both the direct and the indirect pathways are disturbed in schizophrenic patients, since the initiation of internally guided saccades as well as the suppression of unwanted saccades are disturbed.

Effect of neuroleptics on suppression errors

One of the major deficits of saccadic eye movements in schizophrenic patients is the increase in suppression errors in the anti-saccades (Fukushima et al. 1990a, b; Sereno and Holzman 1995). The differential effect of treatment on the different parameters suggests that the alterations in the saccadic eye movements are an effect of the schizophrenic disorder and not of the treatment with neuroleptics. Especially with the anti-task (anti-gap, anti-overlap) saccades, neuroleptic effects may be involved in the suppression error rate (Fukushima et al. 1988; Fukushima et al. 1990b; Thaker et al. 1989). Our study included 24 neuroleptic-naive patients, most of whom also showed a statistically significant higher rate of suppression errors than the controls, who had a percentage of misdirected saccades in the range of the values previously published (Pierrot-Deseilligny et al. 1991). Our results

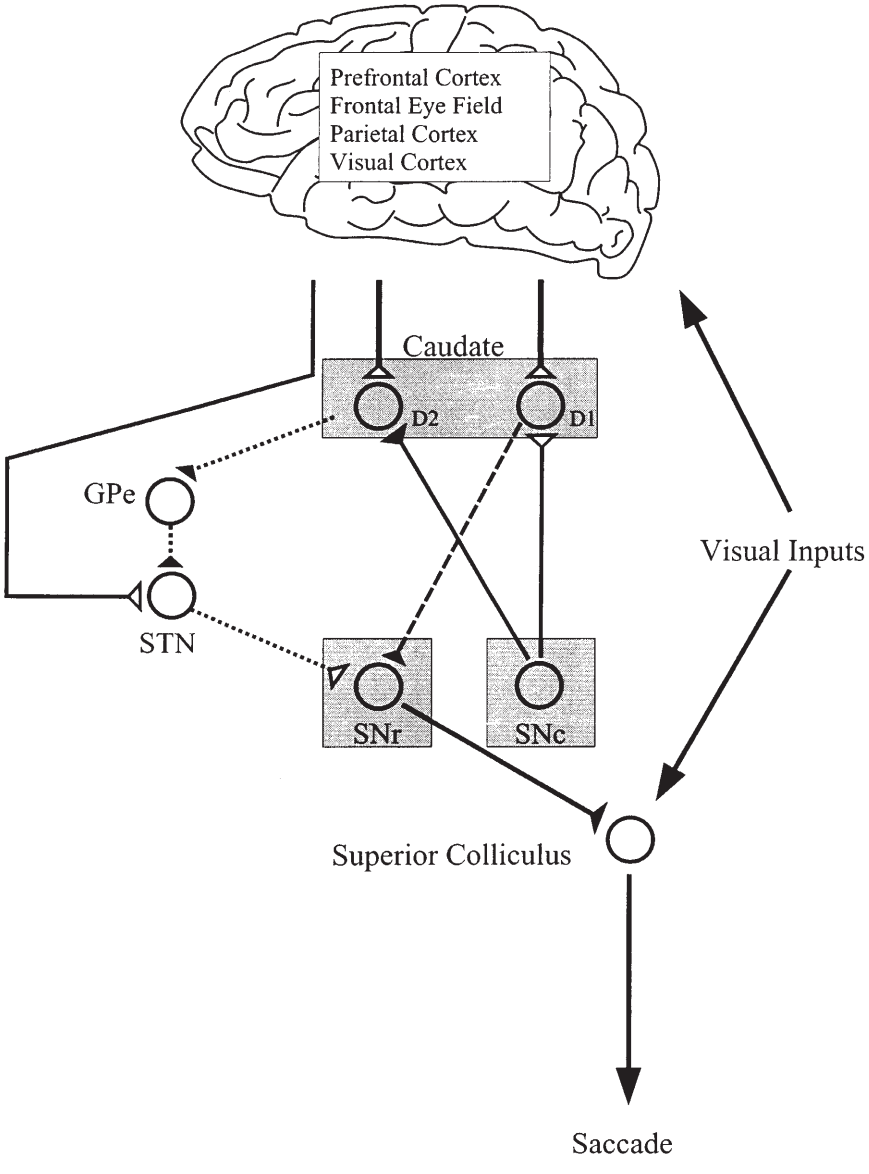

Fig. 5 Drawing of the hypothesized pathways within the oculomotor loop through the basal ganglia. The direct pathway from the caudate nucleus over the substantia nigra pars reticulata *(SNR)* is indicated by the *dotted line* (note that the stimulation of the D1 receptors activates the neurons), the indirect pathway with the connection to the subthalamic nucleus *(STN)* and globus pallidus externus *(GPE)*, by the *dotted line*. *Filled triangles* indicate inhibitory synapsis and *open triangles* excitatory

also indicate that the high rate or errors is a basic effect of the disorder and not a side effect of the neuroleptics as mentioned previously (Thaker et al. 1989). Moreover, during medication, the suppression error rate decreases only insignificantly, and the close, statistically significant relationship of the error rate and the negative symptomatology shows that the error rate correlates with the schizophrenia-negative symptoms, especially Alogia and Blunted affect, and not with the medication. Two other investigators also did not find a significant effect of neuroleptic medication on the suppression error rate (Mackert and Flechtner 1989; Arolt et al. 1993). Since clinical observations and experimental results have found increased error rates in dysfunctions of the frontal lobe (Guitton et al. 1985; Braun et al. 1992; Pierrot-Deseilligny 1994; Pierrot-Deseilligny et al. 1995) and an involvement of frontal lobe dysfunction is also suggested in the negative symptomatology of schizophrenia (Andreasen and Olsen 1982), our finding of a correlation between an increased error rate in the anti-task paradigms and negative symptoms in the psychometric tests agrees with a dysfunction of the frontal lobe in these patients.

An alternative explanation would be that the indirect oculomotor pathway through the basal ganglia is disturbed. This assumption, however, does not explain why neuroleptics do not substantially improve the suppression and only moderately decrease the latencies. The direct pathway to the substantia nigra pars reticulata is controlled by striato-nigral neurons, which express dopamine (D)1 receptors, substance P, and dynorphin. In contrast, the indirect pathway is controlled by striato-pallidal neurons, which express D2 receptors and enkephalin (Gerfen et al. 1990). Activation of the direct pathway by stimulating the D1 receptors of neurons in the caudate finally causes via the increased inhibition of the tonic inhibition (by the substantia nigra pars reticulata neurons) a disinhibition of the cells in the intermediate layer of the superior colliculus (SC, Hikosaka et al. 1995). The SC must be activated before a saccade can be made (Fuchs et al. 1985; Wurtz 1996). Thus, we would expect neuroleptics to reduce such activation and consequently prolong initiation of internally guided saccades; however, this is not what we observed. The latencies in the anti-saccades were significantly shorter during neuroleptic treatment and the gain of the memory saccades was larger.

Activation of the D2 receptors of the indirect pathway is followed by a decrease in the inhibition of the globus pallidum externum, which causes an increased inhibition of the SC neurons. Hikosaka et al. (1995) proposed that the indirect pathway is more active during the active suppression of saccades; it is switched off only after the direct pathway is activated by a cue triggering a new saccade. Thus, neuroleptics should as D2-antagonists cause a decreased inhibition of the superior colliculus and therefore more unwanted saccades. We did not observe a significant increase in suppression errors under medication with neuroleptics.

Our findings do not support the concept of a primary disturbance of the dopaminergic input in the basal ganglia oculomotor loop. The results do, however, indicate that the cortical input to this loop may be abnormal (Fig. 5).

In conclusion, our findings suggest that there is a hypoactivity of the direct (prolonged latencies of the anti-saccades and memory-guided saccades) and the indirect loops (increased suppression errors) as they pass through the basal ganglia. Our finding that neuroleptics have no significant effect on these saccades supports the idea of a primary abnormal cortical input to the basal ganglia oculomotor loop, but does not support the alternative explanation of a primary dysfunction within the basal ganglia oculomotor loop. As regards the effect of neuroleptics, it is doubtful whether a primary disorder of the D2 receptors in the indirect pathway can account for the observed abnormalities in suppression of unwanted saccades. Moreover, a disturbance of the D1 receptors cannot explain the increased latencies of intentional saccades.

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