Saccadic eye movements in schizophrenic patients

Bouchaib Karoumia,*, Jocelyne Ventre-Domineyb, Alain Vighetto, Jean Dalerya, Thierry d'Amatoa

aInstitut de Psychopathologie Cognitive et Neurobiologique, Jeune Equipe 1882 (Université Lyon I), Hôpital du Vinatier, 95 Boulevard Pinel, 69677 Lyon-Bron Cedex, France
bINSERM, Unité 94 (Vision et Motricité), 16 Avenue du Doyen Lepine, 69500 Lyon-Bron, France
Service de Neuro-Ophthalmologie, Hôpital Neurologique, 59 Boulevard Pinel, 69003 Lyon, France

Received 26 February 1996; revised 3 February 1997; accepted 10 April 1997

Abstract

The nature of saccadic abnormalities in schizophrenia was investigated in three different paradigms: (1) the visually guided saccade; (2) the antisaccade; and (3) the remembered saccade paradigm. Subjects comprised 14 schizophrenic patients and 14 normal volunteers. Deficits in the schizophrenic group were observed in the antisaccade and remembered saccade tasks, both of which were characterized by increased latency and reduced gain. Moreover, in the antisaccade task, schizophrenic patients showed an increased number of errors compared with control subjects. Saccadic abnormalities in the patients were correlated with impaired performance on the Wisconsin Card Sorting Test. These data suggest that schizophrenic patients have difficulty in inhibiting reflexive saccades and in producing voluntary saccades. The implications of these findings for a prefrontal cortex dysfunction involved in oculomotor control in schizophrenia are discussed. © 1998 Elsevier Science Ireland Ltd.

Keywords: Antisaccades; Remembered saccades; Oculomotor control; Prefrontal cortex

1. Introduction

Many hypotheses have been proposed to explain the pathophysiology and the diversity of clinical facets of schizophrenia. One of the most widely studied involves a dysfunction of the frontal lobe, especially the prefrontal cortex. Some schizophrenic symptoms are similar to those of patients with frontal lobe lesions; for example, avolition, blunted affect and impoverished thought (Matsushima et al., 1992). Furthermore, there are clusters of schizophrenic symptoms — psychomo-
tor poverty, disorganisation of thought and affect, and reality distortion — have been linked, respectively, to the dorso-lateral prefrontal cortex, the orbito-frontal cortex, and the temporal lobe (Liddle et al., 1989). Schizophrenic patients perform poorly on cognitive tasks sensitive to frontal cortex dysfunction, as do patients with frontal lobe lesions (Kolb and Wishaw, 1983). Functional cerebral imaging studies have demonstrated low cerebral blood flow or metabolic activity in frontal cortex of schizophrenic patients (Ingvar and Franzén, 1974; Weinberger et al., 1986; Buchsbaum et al., 1990). However, despite considerable effort, no reliable biological marker of this disorder has yet been identified.

The exploration of eye movements in schizophrenic patients has revealed an oculomotor dysfunction. Several studies have reported smooth pursuit eye movement (SPEM) abnormalities in 50–80% of schizophrenic patients and in 45% of their first-degree relatives (Holzman et al., 1973, 1984, 1988; Abel et al., 1992; Campion et al., 1992). These findings suggest that smooth pursuit abnormalities might be a biological marker of vulnerability to schizophrenia (Holzman et al., 1984, 1988; Clementz and Sweeney, 1990). Even though a frontal lobe dysfunction has been proposed as a pathophysiological explanation of the SPEM disorders in schizophrenia (Levin, 1984; Gerdsen et al., 1996), neither the anatomical site nor the precise pathophysiological mechanism of this oculomotor dysfunction has been identified.

Saccadic eye movements have not been investigated as extensively as SPEM in schizophrenic patients. Behavioral and functional imaging studies have demonstrated that cerebral control of saccadic eye movements involves several cortical and subcortical regions, especially the posterior parietal cortex (PPC), the frontal eye field (FEF), the prefrontal cortex (PFC), the supplementary motor area (SMA), the basal ganglia, and the superior colliculus (SC) (Fox et al., 1985; Leigh and Zee, 1991; Fischer et al., 1993; Petit et al., 1993; Andersen et al., 1994; Lang et al., 1994; Pierrot-Deseilligny et al., 1995). Reflexive saccades in response to visual stimuli are under cortical control, mainly of the PPC and the FEF, where neurons discharge during the presaccadic period and the execution of saccades (Schall, 1991; Segraves and Park, 1993; Pierrot-Deseilligny et al., 1995). Voluntary saccades, like antisaccades and remembered saccades, involve complex cortico-subcortical processes. In an antisaccade task, subjects are requested to move their eyes in the mirror position of a visual target. An antisaccade is generated by inhibition of a reflexive saccade and by production of a voluntary saccade. The PFC and the basal ganglia play an important role in the generation of antisaccades (Guitton et al., 1985; Fukushima et al., 1994; Pierrot-Deseilligny et al., 1995). Remembered saccades are voluntary saccades in response to the memorized location of a previously presented visual target. Different cortical areas (e.g. the PPC, FEF, PFC and SMA) might be involved in controlling the production of remembered saccades (Gaymard et al., 1990; Pierrot-Deseilligny et al., 1991a, 1993).

In schizophrenia, the most frequent saccadic abnormality is found in antisaccades, with an increased number of errors, i.e. the number of reflexive saccades to the visual target, and prolonged antisaccadic latency (Fukushima et al., 1988, 1990b; Thaker et al., 1989; Sereno and Holzman, 1995). Likewise, deficits in remembered saccades (delayed latency) are reported in schizophrenic patients (Fukushima et al., 1990a; Park and Holzman, 1992). It is noteworthy that similar saccadic disorders are observed in patients with lesions of the frontal lobe (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991b; Fukushima et al., 1994) and basal ganglia such as occur in Huntington’s disease (Lasker et al., 1987) and, less consistently, in Parkinson’s disease (White et al., 1983). These observations lead to the idea of a possible dysfunction of the fronto-striatal system in schizophrenia.

To investigate further the possible role of a frontal cortex dysfunction in schizophrenia, we studied the ability to perform different forms of saccades: (1) visually guided saccades and (2) voluntary saccades, namely antisaccades and remembered saccades, in schizophrenic patients and age-matched normal volunteers. In addition, we correlated the subjects’ performance of two neuropsychological measures that rely on PFC activation (Pardo et al., 1990; Marenco et al.,
1993): the Wisconsin Card Sorting Test (WCST) and the Stroop Test.

2. Methods

2.1. Subjects

We studied 14 patients (seven males and seven females; mean age, 30 years; range, 20–45 years) who fulfilled DSM-III-R criteria (American Psychiatric Association, 1987) for schizophrenic disorders (eight disorganised, four paranoid and two residual); nine were in-patients at the CHS Le Vinatier (Lyon-Bron), and five were out-patients. All but three patients had been treated with stable doses (for at least a month) of neuroleptic medication (Table 1); eight of them were receiving anticholinergic medication (Simpson-Angus Scale score < 6). The 14 patients were compared with a group of 14 age-matched normal volunteers (eight males and six females; mean age, 33 years; range, 27–49) recruited from the hospital staff. Subjects who met DSM-III-R criteria for past or present substance abuse or dependence or who had low intelligence levels were excluded. Neither the patients nor the normal volunteers showed any signs of neurologic, ophthalmologic or vestibular disorders, and none had received benzodiazepine (for at least 1 month) or lithium medication. Interviews with the normal subjects gave no indication of personal or familial psychiatric history as determined by the Family History Research Diagnostic Criteria (Andreasen et al., 1986). Table 1 presents the demographic characteristics of the study group.

2.2. Clinical and neuropsychological assessment

Patients were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) (Table 1). Before eye-movement testing, all subjects performed a modified version of the WCST (Nelson, 1976) and the color word Stroop Test.

2.3. Eye-movement recordings

Subjects were seated in darkness in front of an arc (radius = 114 cm) supporting light-emitting diodes (LED). The target lights were located at 10, 20 and 30 degrees, right and left from the center (0 degrees). Horizontal saccades were recorded by direct current electro-oculography (EOG) with surface electrodes placed on the outer canthi. The head was immobilized against a headrest and held in place by a frontal strap. Eye blinks were monitored by vertical eye-movement recordings. EOG signals were amplified and filtered with a low-pass analogue filter (40 Hz) and digitized at a rate of 250 Hz by computer and saved for off-line analysis.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30</td>
<td>6.9</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>7/7</td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td>6.1</td>
<td>4.5</td>
</tr>
<tr>
<td>BPRS, total score</td>
<td>56.7</td>
<td>13.8</td>
</tr>
<tr>
<td>PANSS, positive score</td>
<td>25.7</td>
<td>6.8</td>
</tr>
<tr>
<td>PANSS, negative score</td>
<td>23.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Neuroleptic medication (CPZ equivalent, mg)</td>
<td>258</td>
<td>184</td>
</tr>
</tbody>
</table>

NS, not significant.
2.4. Paradigms

Saccades were tested in three behavioural paradigms. The subjects were clearly instructed about the task and had to repeat the instructions before starting the paradigm. In each paradigm, the trial began with a fixation of the center point (fixation point). At a random time (1400–2400 ms), a target appeared at a random location (10, 20, 30 degrees, on the right and on the left). The center offset coupled with a beep sound cued the subject to bring his or her eyes towards a target. A total of 60 trials was run for each paradigm.

2.4.1. Visually guided saccades

Simultaneous with the prearranged signal (central point offset and beep), a target was illuminated. The subject had to look at the target as quickly as possible. This paradigm tested the ability to initiate a visually triggered saccade.

2.4.2. Antisaccades

As in the previous paradigm, the fixation point disappeared and the beep sounded at the same time that a target was illuminated. The subject was instructed not to look at the target but to make a saccade in the mirror position opposite to the illuminated target. After 750 ms, the target was extinguished and the one located in the mirror position was illuminated to make the subject correct for any error of eye position with respect to the second target. This paradigm tested the ability of the subject to suppress a saccade to a suddenly appearing visual stimulus and to initiate a voluntary saccade.

2.4.3. Remembered saccades

While the fixation point was illuminated, the target was switched on for 1500 ms and then extinguished. After 1000–2000 ms from the target offset, the cue signal occurred and the subject had to look at the remembered location of the previous target. After 750 ms from the cue's occurrence, the target was illuminated again to make the subject correct for any error of eye position with respect to the target. This paradigm tested the ability to suppress a visually triggered saccade and to produce an internally generated saccade to the remembered location of a visual target.

2.5. Data analysis

Interactive software was used for saccade analysis. Saccade detection was automatically performed on the basis of the velocity signals and then was subsequently verified by visual inspection of each trial. Saccades were calibrated based on the known location of targets during visual fixation, using a linear voltage-to-degree transformation. For each paradigm, the oculomotor performance was quantified by measuring the latency and the amplitude (measured from the starting position of the eyes) of the first saccade of each correct trial. Gain was calculated by the ratio of the saccade amplitude to the target eccentricity. In the antisaccade paradigm, the number of errors was defined as the number of trials with reflexive saccades in response to the visual target. Data were analyzed by a three-way multifactor analysis of variance (ANOVA). The between-group factor was Group (normal and schizophrenic), and the within-subject factors were Side (left and right) and Eccentricity (10, 20, 30 degrees right and left). Multivariate analysis of variance (MANOVA) was performed to assess group differences in neuropsychological performance (WCST and Stroop). All correlations between saccadic abnormalities and scores on the clinical scales (BPRS, PANSS) and neuropsychological measures (WCST, Stroop) were assessed by Spearman's rank correlation analysis.

To examine the effects of neuroleptic medication (converted to chlorpromazine (CPZ) equivalents) on saccadic abnormalities, we analyzed the relation between medication dosage and antisaccades and remembered saccades (latency, gain and errors) by Spearman's correlation analysis.

3. Results

3.1. Neuropsychological performance

Compared with the normal subjects, the schizophrenic patients showed significantly poorer
Table 2
Neuropsychological data of the schizophrenic and of the control groups

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categories</td>
<td>5.07 (1.3)</td>
<td>5.85 (0.3)</td>
</tr>
<tr>
<td>% Perseverative errors</td>
<td>30.37 (19.3)</td>
<td>4.58 (9.4)</td>
</tr>
<tr>
<td>Total errors</td>
<td>6.35 (3.4)</td>
<td>2.42 (2.7)</td>
</tr>
<tr>
<td>STROOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (s)</td>
<td>124 (24)</td>
<td>93 (15)</td>
</tr>
<tr>
<td>Errors</td>
<td>4.2 (3.6)</td>
<td>1.8 (1.2)</td>
</tr>
</tbody>
</table>

NS, not significant.

Performance on the WCST, with higher perseverative and error indices. Likewise, the patients were slower in the execution of the Stroop Test and made more errors than the normal subjects (Table 2).

3.2. Visually guided saccades (VGS)

VGS latency did not differ significantly in the schizophrenic compared with the normal group (main group effect: $F = 0.40$, df = 1,154, $P = 0.52$).

![Saccade Latency Graph](image)

Fig. 1. Mean saccadic latency in control group and in schizophrenic group. VGS, visually guided saccade; RS, remembered saccades; and AS, antisaccades. Standard deviation (S.D.) is represented by bar deviation.
The mean VGS latency was 247 ms (S.D. = 41) in the normal group versus 252 ms (S.D. = 46) in the schizophrenic group (Fig. 1). In either direction of saccades, VGS gain was normal (main group effect: $F = 0.95$, df = 1,154, $P = 0.32$; group $\times$ side interaction: $F = 0.33$, df = 1,154, $P = 0.56$) (Fig. 2).

### 3.3. Antisaccades

A significant increase in antisaccade latency was observed in the schizophrenic group (420 ± 70 ms) compared with the control group (369 ± 72 ms) (group effect: $F = 19.11$, df = 1,141, $P < 0.0001$) (Fig. 1). This increase in latency was independent of the direction of the antisaccades (group $\times$ side interaction: $F = 0.68$, df = 1,141, $P = 0.41$).

Mean antisaccade gain was decreased in the schizophrenic group (0.83 ± 0.36) with respect to the control group (0.95 ± 0.35) (Fig. 2). This reduction was highly significant (main group effect: $F = 8.02$, df = 1,141, $P = 0.005$), independent of the saccadic direction (group $\times$ side interaction: $F = 0.52$, df = 1,141, $P = 0.46$).

As shown in Fig. 3, the number of errors (number of reflexive saccades towards the visual target) was strongly increased in the schizophrenic group (52%, S.D. = 21) compared with the control group (19%, S.D. = 10). This difference in the number of errors in the antisaccade task was highly significant (main group effect: $F = 25.44$, df = 1,26, $P < 0.0001$).

### 3.4. Remembered saccades

As shown in Fig. 1, remembered saccade latency was significantly increased in the schizophrenic group (346 ± 74 ms) compared with the control group (294 ± 49 ms; main group ef-
Fig. 3. Percentage of errors in antisaccades paradigm in control group and in schizophrenic group. Errors are counted as the number of reflexive saccades.

\[ F = 26.26, \text{ df } = 1,150, \ P < 0.0001 \] independent of the side of remembered saccades (group \( \times \) side interaction: \( F = 0.01, \text{ df } = 1,150, \ P = 0.90 \)).

The mean remembered saccade gain of the schizophrenic group (0.86 ± 0.14) was significantly reduced with respect to that of the control group (0.91 ± 0.13), in either direction of saccades (main group effect: \( F = 7.91, \text{ df } = 1,150, \ P = 0.005 \); group \( \times \) side interaction: \( F = 0.18, \text{ df } = 1,150, \ P = 0.66 \)) (Fig. 2).

### 3.5. Correlation between saccadic abnormalities and clinical and neuropsychological ratings

Oculomotor abnormalities were correlated to some of the neuropsychological deficits and to clinical ratings. We found (1) a significant negative correlation between remembered saccade latency and BPRS score \( (r = -0.79, \ P = 0.008) \), (2) a significant positive correlation between antisaccadic errors and WCST errors \( (r = 0.58, \ P = 0.04) \) and (3) between antisaccadic gain and WCST categories \( (r = 0.82, \ P = 0.006) \). In the control group, no significant correlation was found between saccadic parameters and neuropsychological performances.

### 3.6. Medication effects

No relation was found between the amount of medication and any parameter of antisaccades and remembered saccades (Spearman’s rank analysis, \( P > 0.05 \)).

### 4. Discussion

Although visually guided saccades were normal in schizophrenic patients, voluntary saccades, antisaccades and remembered saccades were impaired mainly in the movement initiation.
4.1. Antisaccadic abnormalities and frontal hypothesis

The generation of antisaccades implies the integrity of the frontal lobe. Schizophrenic patients are unable to produce normal antisaccades as indicated in this study by the increase in the number of errors, the increased latency and the reduced gain of antisaccades. These oculomotor disorders suggest that schizophrenic patients are impaired in suppressing reflexive saccades to a visual target and in initiating correct voluntary saccades. These findings are in agreement with previous studies in schizophrenic patients (Fukushima et al., 1988, 1990a,b, 1994; Thaker et al., 1989; Matsue et al., 1994; Clementz et al., 1994; Sereno and Holzman, 1995), in patients with frontal lesions (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991b; Fukushima et al., 1994), and in patients with Huntington’s disease (Lasker et al., 1987) or progressive supranuclear palsy (Pierrot-Deseilligny et al., 1989).

Behavioral studies in schizophrenic patients have shown that antisaccade abnormalities are correlated to frontal cortex atrophy visualized on computed tomography (Fukushima et al., 1990a). It is known that the frontal cortex, mainly the prefrontal cortex, plays a crucial role in inhibiting unwanted reflexive saccades by a reinforcement of the inhibiting input on the superior colliculus (SC), either through direct prefrontal projections or through striatal projections (Guitton et al., 1985; Hikosaka and Wurtz, 1985; Pierrot-Deseilligny et al., 1991b). It seems reasonable to argue that the production of inappropriate saccades and the distraction towards any visual stimuli observed in schizophrenic patients arise from a prefrontal dysfunction. In agreement with this hypothesis, we observed a significant positive correlation between the abnormalities in the antisaccades (error rate, gain) and in the WCST: as WCST performance worsened, the rate of antisaccade errors further increased. Direct evidence for a correlation between WCST performance and prefrontal cortex (PFC) activation has been established by positron emission tomography: regional cerebral blood flow does not increase in the dorsolateral PFC of schizophrenic patients as it does in control subjects during WCST performance (Weinberger et al., 1986). We suggest that the alteration in programming and executing antisaccades is the consequence of the involvement of the PFC as described in schizophrenia.

4.2. Remembered saccades and mnesic processes

Our schizophrenic patients showed abnormalities in remembered saccades, mainly an increased latency. The same disorders have been previously reported in a few studies in schizophrenia (Fukushima et al., 1990b; Park and Holzman, 1992) and frontal lobe lesions (Pierrot-Deseilligny et al., 1993). The generation of remembered saccades requires an internal representation of the visual target location and a short-term memorization of this location. Thus, the impairment of remembered saccades might be related to deficits either in movement initiation or in internal representation and memorization of the visual target location (Kori et al., 1995). Based on our data, the first hypothesis can be excluded; indeed, as the latency of visually guided saccades was normal in our schizophrenic patients, it is likely that the prolonged latency of remembered saccades does not rely only on a motor initiation deficit. Alternatively, the inability of schizophrenic patients to maintain and memorize an internal representation of target location cannot be excluded. Very few studies have investigated this last hypothesis in schizophrenic patients. Interestingly, Park and Holzman (1992) demonstrated that schizophrenic patients are impaired in an oculomotor delayed-response task, as monkeys with prefrontal lesions are in a similar task (Funahashi et al., 1993). These authors suggest a deficit in spatial working memory in schizophrenic patients. Goldman-Rakic (1987, 1994) proposed that the delayed-response tasks measure working memory capacity performed by PFC. Similarly, we propose that our deficits in remembered saccades of our schizophrenic patients might arise from disorders in memory capacity related to a prefrontal dysfunction. Based on our data and those of the literature, it is difficult to dissociate the deficits related to mnesic processes from those related to the internal representation of space, both in-
volved in the generation of remembered saccades. Even if not excluded, an alteration of spatial processes is likely less implicated in our deficits in remembered saccades than an alteration in mnesic processes.

4.3. Medication effects

While several studies did provide evidence that neuroleptic medication does not affect pursuit eye movements (Siever et al., 1986; Campion et al., 1992), few studies have explored the effects of antipsychotic drugs on saccadic eye movements in schizophrenic patients. Previous works indicate that neuroleptic medication does not seem to significantly affect the saccade latency and the antisaccade error rates (Fukushima et al., 1990a; Clementz et al., 1994; Sereno and Holzman, 1995; Crawford et al., 1995). Our study provides further arguments in favor of this last observation. Firstly, in our schizophrenic group, three patients had not received any psychotropic medication for more than 4 months before the study and demonstrated the same saccadic abnormalities as medicated patients. In addition, we did not find any significant relation between the amount of medication and the saccadic abnormalities. Based on these observations, we can reasonably argue that medication did not interfere significantly with oculomotor disorders observed in our schizophrenic patients.

4.4. Saccadic abnormalities and attentional deficits

In schizophrenia, the role of attention in oculomotor deficits remains a controversial question. Abnormalities in smooth pursuit eye movement (SPEM) in these patients have been attributed by some authors to a deficit in attentional mechanism (Holzman et al., 1976; Brezinova and Kendell, 1977), whereas others maintain that these abnormalities are primarily of oculomotor origin (Lipton et al., 1980; Mather et al., 1989). Although our patients performed poorly during the Stroop test compared with control subjects, there was no correlation between the antisaccade and the remembered saccade abnormalities and Stroop test performance. Mather et al. (1989) concluded that attentional deficits did not explain the saccadic abnormalities that characterize schizophrenic patients. Based on these observations, we suggest that the attentional deficit usually described in schizophrenic patients cannot account for all the impaired saccadic performance, especially in the antisaccade and the remembered saccade tasks. However, the role of attention in the saccadic disorders reported in schizophrenia merits further studies of the oculomotor system that use more specific paradigms.

5. Conclusion

Schizophrenic patients exhibit oculomotor abnormalities that are revealed in paradigms that require inhibition of reflexive saccades and internal programming of voluntary and memorized saccades. The saccadic disorders, as well as their association with neuropsychological deficits, are consistent with a frontal lobe dysfunction, especially of the prefrontal cortex in schizophrenia.

Acknowledgements

This research was supported by grant number 951097 from Université Claude Bernard, Lyon (Jeune Equipe Universitaire 1882, Psychopathologie Cognitive et Neurobiologique). We are grateful to Françoise Comte, Armelle Hours, Genevieve Bernard and Edmond Derrington for their assistance and patient recruitment. We also thank INSERM, Vision et Motricité Laboratory, for technical assistance, in providing the EOG registration lab and the photography assistance.

References

B. Karoumi et al. / Psychiatry Research 77 (1998) 9–19


