Saccadic hypometria in drug-naïve and drug-treated schizophrenic patients: A working memory deficit?


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Abstract

In certain conditions patients with schizophrenia make markedly smaller (hypometric) saccades than controls. This hypometria has been thought to reflect dopaminergic blockade as a result of antipsychotic medication. We tested this hypothesis by comparing the performance of an antipsychotic-naïve group and an antipsychotic-treated group of first-episode schizophrenic patients on a predictive saccade paradigm. We explored the possibility that hypometria reflects a spatial working memory deficit by correlating performance on neuropsychological tests of mnemonic function with saccadic accuracy. Both the drug-naïve and treated schizophrenic patients made hypometric saccades when compared with a group of matched controls. Primary saccade amplitude also correlated significantly with performance on some of the neuropsychological tests. These results are discussed in terms of the roles of cortical dopamine and working memory deficits in schizophrenic patients.

Descriptors: Predictive saccades, Schizophrenia, Working memory, Drug-naïve, Hypometria, First-episode

Most research into oculomotor abnormalities in schizophrenic patients has focused on smooth pursuit eye tracking (see Hutton & Kennard, 1998, for a review). Until recently, saccadic eye movements were considered to be normal in this population (Iacono, 1988). Several studies have indeed shown that in simple reflexive saccade paradigms, in which an eye movement is made toward a visual stimulus in the periphery, metrics such as the latency and amplitude of the primary saccade, and the final eye position after corrective saccades, are normal in both chronic and first-episode schizophrenic patients (Crawford, Haeger, Kennard, Reveley, & Henderson, 1995a; Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Hutton et al., 1998a).

Recently, however, patients with schizophrenia have been assessed on a number of more complex saccadic paradigms, and abnormal performance has been observed. For example, in the antisaccade paradigm subjects are instructed on presentation of a target to make a saccade in the opposite direction to a mirror-image location. In general, schizophrenic patients make more errors (a reflexive saccade toward the target) on this task than controls, and also take longer to initiate correct antisaccades (Crawford et al., 1995a; Fukushima et al., 1994; Hutton et al., 1998a). Correct performance on the antisaccade task requires both the inhibition of a habitual response (the reflexive saccade toward the target), and the initiation of a nonreflex response (a saccade away from the target). Both the inhibition of habitual responses and initiation of nonreflex responses are sensitive to damage of the prefrontal cortex (Burgess & Shallice, 1996). Indeed, patients with lesions of the dorsolateral prefrontal cortex (DLPFC) have been shown to make significantly more errors than controls on an antisaccade paradigm (Guiton, Buchtal, & Douglas, 1985; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991), leading to the hypothesis that poor performance on the antisaccade task in schizophrenic patients also reflects DLPFC dysfunction (Crawford et al., 1995a; Fukushima et al., 1994; Hutton et al., 1998a; Sereno & Holzman, 1995). Although one neuroimaging study found activation in the frontal eye fields (FEF) rather than the DLPFC during performance of the antisaccade task (O’Driscoll et al., 1995), others confirmed the relative importance of the DLPFC over the FEF in performing the antisaccade task (Muri et al., 1996; Sweeney et al., 1996). In addition, discrete lesions to the FEF in humans do not cause an increase in antisaccade error rates (Paus et al., 1991; Pierrot-Deseilligny et al., 1991; Rivaud, Muri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994).

Schizophrenic patients also show abnormalities on a predictive saccade paradigm (Clementz, McDowell, & Zisook, 1994; Crawford, Haeger, Kennard, Reveley, & Henderson, 1995b; Hommer, Clem, Litman, & Pickar, 1991; Karoumi, Ventre-Dominey, & Dalery, 1998; McDowell, Clementz, & Wixted, 1996). In its simplest form,
two targets equidistant from an initial central fixation point are illuminated alternately at a regular fixed frequency. In this “square wave tracking” task, subjects are instructed to move their eyes in time with the light to maximize fixation time on the target. Healthy individuals rapidly reduce their saccadic latencies over the first few trials and develop anticipatory or predictive saccades that precede the target movement (Ross & Ross, 1987).

In one variation of this paradigm, after predictive behavior has been established over the first block of trials, the target is switched off and the subject is required to continue to initiate saccadic movements in time with an auditory signal. Patients with Parkinson’s disease make primary predictive saccades of reduced amplitude (hypometria) when performing this test, when compared with healthy controls, particularly in the “no-vision” condition (Crawford, Henderson, & Kennard, 1989; O’Sullivan et al., 1997). Primary saccade hypometria in a predictive paradigm has also been observed in schizophrenic patients (Crawford et al., 1995b; Hommer et al., 1991; Karoumi et al., 1998; McDowell et al., 1996). Because patients with Parkinson’s disease have reduced striatal dopamine activity, the hypometria in schizophrenic patients has been ascribed to the extrapyramidal effects of antipsychotic medication, rather than to the schizophrenic illness itself. This hypothesis has received additional support from studies that have found that primary saccade hypometria is more severe in patients receiving antipsychotic medication than in those who have had their medication withdrawn (Crawford et al., 1995b; Hommer et al., 1991).

An alternative hypothesis is that the saccadic hypometria observed in schizophrenic patients performing this paradigm is intrinsic to the disorder itself, and reflects dysfunction of the DLPCF. In a series of saccadic eye movement studies in nonhuman primates, Goldman-Rakic and colleagues (1996) demonstrated that the integrity of the DLPCF is essential for accurate performance on a delayed response task, in which saccadic eye movements are guided by the internal representation of a spatial location of a target that has been recently extinguished. As predictive saccades are initiated before the target has moved, it has been argued that they are guided by an internal representation rather than an external stimulus, thus providing a parallel with the above nonhuman primate studies (Hommer et al., 1991). In support of this contention, Park and Holzman (1992), in an oculomotor delayed response task directly analogous to that used in nonhuman primates, found that patients with schizophrenia made more incorrect responses than bipolar patients. Because both groups were taking antipsychotic medication, Park and Holzman ascribed this working memory deficit to schizophrenia itself rather than to the effects of drug treatment.

However, the extent to which a behavior that is nonexternally guided can be assumed to be guided by representations held in working memory is a matter of debate. It could be argued, for example, that predictive saccades are based on motor learning, which occurs rapidly over the first few target movements. Because the cognitive demands of the predictive saccade paradigm differ markedly from the delayed response paradigm commonly used to assess spatial working memory (e.g., Goldman-Rakic, 1996; Park & Holzman, 1992), predictive saccades are perhaps better described as being “nonvisually guided.” This definition emphasizes that predictive saccades are generated internally in some way, but makes no assumptions concerning the nature of the underlying mechanism or representation. One key aim of this study was to assess the relationship between working memory and predictive saccade generation.

In addition to primary saccade gain, another measure that can be used to explore the pathophysiological basis of oculomotor abnormalities in schizophrenia is saccadic latency. Healthy individuals learn to predict the timing of the target alternation over the first few trials and saccadic latencies diminish rapidly (Ross & Ross, 1987). This function is thought to reflect the integrity of the FEF. Nonhuman primates with FEF lesions do not show the normal reduction in saccadic reaction times (Bruce & Borden, 1986), and FEF lesions in humans lead to an increase in saccadic reaction times (but not errors) in the antisaccade task (Rivaud et al., 1994).

The results of studies that have assessed saccadic latencies in a predictive paradigm in schizophrenic patients are conflicting (Clementz et al., 1994; Crawford et al., 1995a; Hommer et al., 1991; Karoumi et al., 1998; McDowell et al., 1996). Hommer et al. (1991) found that a small proportion of patients failed to develop any anticipatory latencies whereas McDowell et al. (1996) found that schizophrenic patients made as many predictive saccades as controls, and that these saccades had significantly lower latencies (i.e., were more anticipatory) than controls. Karoumi et al. (1998) found that schizophrenic patients made more predictive saccades than controls, and that these saccades were more anticipatory. The other studies did not find any differences.

To further examine the hypothesis that predictive saccade hypometria is secondary to medication effects, we tested patients with first-episode schizophrenia, a proportion of whom had never received antipsychotic medication. To examine the hypothesis that hypometria reflects a specific failure of spatial working memory, we measured the performance of the same group of patients on a number of mnemonic tests that placed varying demands on spatial working memory, and related this performance to predictive oculomotor function. Finally, to look for further evidence of a prefrontal deficit in schizophrenia, we measured saccadic latencies and the development of predictive saccades in the early phase of the task. To determine whether any deficits observed in the schizophrenic patients were specific to the predictive paradigm, or simply reflected a general dysfunction of the oculomotor system, subjects also performed a reflexive saccade paradigm.

Method

Subjects

Subject details are summarized in Table 1. The patient sample consisted of 63 patients experiencing their first psychotic episode who later received a diagnosis of DSM-IV schizophrenia. These patients were recruited during the first 4 years of an ongoing longitudinal study of first-episode schizophrenia being conducted in London. All patients provided written informed consent. Thirteen of the patients were completely drug naïve (DN) at the time

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (years)</th>
<th>Gender (M/F)</th>
<th>SAPS</th>
<th>SANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>40</td>
<td>25.3 (4.8)</td>
<td>30/10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Drug treated</td>
<td>50</td>
<td>24.3 (5.9)</td>
<td>41/9</td>
<td>50.3 (21.7)</td>
<td>33.46 (23.0)</td>
</tr>
<tr>
<td>Drug naive</td>
<td>13</td>
<td>29.15 (9.1)</td>
<td>10/3</td>
<td>45.69 (18.8)</td>
<td>43.00 (32.5)</td>
</tr>
</tbody>
</table>

Note: Mean age (SD) and total scores for Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS).
of testing. The remaining 50 patients had been receiving anti-psychotic drug treatment (DT) for a short time; the median duration of treatment in 40 subjects for whom reliable data were available was 44 days (range 1–147 days). Their mean daily dosage in chlorpromazine equivalent units was 389 mg (SD = 174, reliable data available on 47 subjects). Clinical assessments were performed on recruitment into the study, and included the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984b). The two patient groups (DN and DT) did not differ on total positive or negative symptoms at presentation, both ts(61) < 1.5, ps > .2. The patients were compared with a group of 40 healthy controls, living in the same community area and matched for gender (chi-square = 0.674, p = .71). An analysis of variance (ANOVA) revealed that the groups were not completely matched for age, F(2,100) = 3.38, p < .05. Post hoc tests (Bonferroni) revealed that the DN group was slightly, but significantly, older than the DT group (mean difference = 4.58 years, p = .03). All other comparisons were nonsignificant.

**Apparatus**

Subjects were seated 1.5 m from a semiopaque screen with a buzzer located behind their head. Head movements were restrained using an adjustable headrest. All sessions were conducted in the dark. Eye movements were recorded using a Skalar IRIS infrared limbus reflection device. A hardware anti-aliasing filter (cut-off frequency 200 Hz) was used to filter eye position and the sampling rate was 500 Hz. Stimulus display and data sampling were controlled by a PDP 11/73 computer. Each paradigm was preceded by a calibration trial in which nine equally spaced LED targets with known horizontal positions were illuminated sequentially, and the subjects were required to fixate each target in turn.

**Procedures**

These tests were performed as part of a large battery of oculomotor and neuropsychological tests given to all patients entering into the West London First Episode Schizophrenia Study.

*Predictive paradigm.* Two targets positioned 11.25° to the left and right of the midline were illuminated alternately at a frequency of 1 Hz (each light remained illuminated for 1,000 ms, and the onset of one target occurred at the same time as the offset of the other). On each trial a buzzer, situated directly behind the subject’s head, provided an audible cue synchronous with each target step. Subjects performed three blocks, each of 12 target steps, the blocks being run as a continuous sequence. Two blocks with presentation of the visual targets (V1 and V2) were separated by a block in which no visual target was presented (NV) but the buzzer continued, as before, to supply timing information. Subjects were informed about the unvarying regularity of the target alternation and were asked to move their eyes in time with the stepping of the target. Subjects were also informed about the sudden withdrawal of the target at the commencement of the NV block, and were requested to continue executing saccades back and forth, exactly as if the target was present. This block arrangement allowed us to measure latency data in block V1 to examine the build up of predictive behavior, and compare primary saccade amplitude and final eye position in blocks NV and V2, when predictive behavior had been well established.

*Reflexive paradigm.* Each trial consisted of the following sequence: First, a central fixation LED was illuminated at the beginning of each trial. Then after 800 ms the fixation LED was extinguished and simultaneously a peripheral target LED was illuminated for 1,000 ms and a 200-ms buzzer signal was initiated. Subjects were asked to direct their gaze as quickly and as accurately as possible to the newly illuminated target LED and then return to the central fixation point. Targets were presented at ±3.75°, 7.5°, 11.25°, and 15°. The order of targets was varied pseudorandomly to prevent predictive behavior. Each subject completed 24 trials.

**Neuropsychological Tests**

These tests have been described previously in detail (Hutton et al., 1998b). Briefly, the tests consisted of the spatial working memory, spatial and pattern recognition memory, and spatial span subtests of the CANTAB automated neuropsychological battery (Sahakian & Owen, 1992).

*Spatial working memory.* In this test subjects were required to search through a number of boxes displayed on the screen for hidden tokens. On each trial, only one box contained a token and the subjects were required to search through the boxes until they found it, at which point the next token was hidden and the search continued. Subjects searched at their own pace. The essential instruction was that once a token had been found in a box, that box would never be used again to hide a token. There were four levels of difficulty: three-, four-, six-, and eight-box problems. Subjects performed four trials at each level. Errors were made when a subject returned to open a box in which a token had already been found. These errors reflect the inability to remember, across searches, which boxes had contained tokens, while at the same time conducting a new search. The measure taken was the total number of errors at the more difficult six- and eight-box problems.

*Spatial span.* In this computerized version of Corsi’s block tapping task, spatial span was determined from the ability of subjects to remember the order in which a sequence of squares was highlighted on the screen. Each square was illuminated for 3 s, with an interval of 500 ms in between squares. After the sequence had been presented there was a 1-s delay before recall of the sequence was attempted. Spatial span was calculated as the highest number of squares successfully recalled on at least one sequence.

*Spatial recognition memory.* In the learning phase a series of five identical squares (the targets) were presented, one at a time, each in a different location on the screen. Each square was present for 3 s. In the recognition phase (which occurred 5 s after the last square had been presented) two squares were displayed on screen at the same time, one square in a target location and one in a novel location. Subjects were asked to press the square at the location they recognized from the learning phase. This sequence of five target presentations followed by five recognition trials was repeated three further times, for a total of 20 trials. Performance was measured by the number of correct spatial locations remembered by each subject.

*Pattern recognition memory.* In the learning phase 12 abstract visual stimuli were presented sequentially on the screen. Each stimulus was present for 3 s. In the recognition phase (which followed a 5-s delay) each stimulus was then represented together with a novel stimulus and the subject was asked to touch the familiar stimulus. This sequence was repeated, for a total of 24
trials. Performance was measured by the number of stimuli correctly recognized.

**Oculomotor Data Analysis**

Saccades were analyzed using interactive computer programs (one written locally using ASYST, Asyst Software Technology, Rochester, NY and a commercial program EYEMAP, Antech GmbH, Heidelberg, Germany). The amplitude of the primary saccade (defined as the first saccade occurring prior to or just after a target step in the appropriate direction, with an amplitude of greater than 4°) and the final eye position (FEP, defined as the longest stable fixation period after secondary and corrective saccades had been made) were measured. Amplitudes were measured as the distance from the eye position at the initiation of the saccade to the eye position at the end of the saccade. In the reflexive saccade paradigm, saccades were excluded if they occurred less than 100 ms after the target’s appearance. In addition, the latency of each saccade in respect to its target step was recorded. In the predictive paradigm, the first step in each block was not analyzed as in block V1 it was a half step, and in the other two blocks it marked a transitory period.

**Results**

**Reflexive Paradigm**

The metrics for the reflexive saccades are shown in Table 2. There were no significant differences between the groups, primary saccade gain: $F(2,100) = 2.108, p = .13$; FEP: $F(2,100) = .61, p = .55$; latency: $F(2,100) = 1.84, p = .16$.

**Predictive Paradigm**

Latencies. Latency data from block V1 were used to analyze the build up of predictive behavior. The mean latencies of Trials 1–11 for the three groups are presented in Figure 1. All groups showed a reduction in latency across the first four trials, followed by relatively stable latencies for the remaining trials. Inspection of the data suggested a difference in the build up and maintenance of predictive latencies between the DN group on the one hand, and the control and DT groups on the other. An ANOVA with group as the between-subjects variable and condition as the within-subjects factor revealed significant main effects of group, $F(2,100) = 17.87, p < .001$, and condition, $F(1,100) = 12.05, p < .001$. The Condition × Group interaction just failed to reach significance, $F(2,100) = 2.64, p = .08$. The main effect of condition reflected the fact that latencies were generally greater in the NV condition. The main effect of groups was explored further by collapsing the data across condition. Across conditions both the DT and DN groups had significantly lower primary saccade latencies than controls, $t(88) = -5.92$ and $t(51) = -3.60$ (both $p < .01$), and did not differ significantly from each other, $t(61) = 0.67, p = .5$.

**Final eye position.** The FEPs are presented in Figure 3. A mixed $2 × 2$ ANOVA revealed significant main effects of group, $F(2,100) = 13.54, p < .001$, and condition, $F(1,100) = 40.42, p < .001$. The Group × Condition interaction was also significant, $F(2,100) = 5.94, p < .005$, reflecting the fact that the difference between the schizophrenic groups and controls was greater in the NV condition than in the V2 condition. The main effect of condition was due to FEP being generally greater in the NV condition compared with the V2 condition. In the NV condition, as with the primary saccade amplitude, FEP was significantly lower than controls in both the DT, $t(88) = -4.64, p < .001$, and DN groups, $t(51) = -3.41, p < .001$, who did not differ from each other, $t(61) = 0.02, p = .98$. This pattern of results was confirmed in the V2 condition—again, FEP was significantly lower than controls in both the DT, $t(88) = -2.67, p < .01$, and DN groups, $t(51) = -2.94, p < .01$, who did not differ from each other, $t(61) = -0.77, p = .45$.

**FEP hypometria.** In the NV condition, in which no targets were present, FEP is presumably based on an internal representation of the target’s location. However, in the V2 condition the FEP is generally assumed to reflect accurate corrective saccades made in the presence of the target (Crawford et al., 1995a; O’Sullivan et al., 1997). Thus the FEP hypometria we observed in both groups of schizophrenic patients in the V2 condition requires further explanation.

One possibility is that FEP in these patients is in fact accurate, but inaccurate calibration or head movements in the schizophrenic patients while performing the task leads to a consistent underestimation of eye position. To explore this possibility we examined the eye movement data from the same patients on a number of different saccadic paradigms, and found no evidence of hypometric FEPs, nor any evidence of a systematic calibration bias or head movements (Hutton et al., 1998a). In addition, we carried out tests

<table>
<thead>
<tr>
<th>Group</th>
<th>Primary saccade gain</th>
<th>Final eye position gain</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0.93 (0.09)</td>
<td>1.00 (0.09)</td>
<td>189.69 (20.8)</td>
</tr>
<tr>
<td>Drug treated</td>
<td>0.89 (0.11)</td>
<td>0.98 (0.1)</td>
<td>199.95 (41.5)</td>
</tr>
<tr>
<td>Drug naïve</td>
<td>0.91 (0.13)</td>
<td>1.00 (0.11)</td>
<td>210.04 (48.4)</td>
</tr>
</tbody>
</table>

Note: Standard deviations in parentheses. Due to the different target amplitudes used in this paradigm, amplitude and final eye position data are presented as gain values (eye position/target position).
in our eye movement laboratory on 5 healthy volunteers, instructing them to move their heads side to side while performing the predictive saccade paradigm. The small head movements possible while the head is supported in the head rest did not result in hypometric FEPs. Large head movements (which have to be made by moving the head out of the head rest) did result in hypometric FEPs, but the eye position trace reveals a large vestibulo-ocular response component that we did not observe in the traces analyzed for this study. However, as we felt that the nature of the predictive paradigm is more likely to elicit side-to-side head movements, we did not assess the influence of vertical (nodding) head movements.

Another possible explanation of FEP hypometria is that it occurs because schizophrenic patients make fewer corrective saccades than controls during the predictive saccade paradigm. Henderson, Crawford, and Kennard (1997) argued that a general lack of motivation may be a parsimonious explanation of hypometria in schizophrenic patients. To explore this possibility, the number of all nonprimary saccades generated by subjects in the V2 condition was quantified. The results, as displayed in Table 3, show that both groups of schizophrenic patients in fact made significantly more secondary saccades than controls, presumably as a consequence of the greater hypometria of their primary saccades. A significant proportion of these secondary saccades cannot, however, be described as “corrective” as they were initiated before the appearance of the target. Based on normative data from the reflexive paradigm, we chose to define truly corrective saccades as those

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**Figure 1.** Group mean primary saccade latencies in the first block of visually presented targets (V1) for controls (filled squares), drug-treated patients (filled circles), and drug-naïve patients (open circles). Bars represent standard error. The dotted line at 0 ms represents the time at which the target moved.

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**Figure 2.** Mean primary saccade amplitude in the no visual target (NV) and second visual target (V2) blocks for controls (filled squares), drug-treated patients (filled circles), and drug-naïve patients (open circles). Bars represent standard error.

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**Figure 3.** Mean final eye position in the no visual target (NV) and second visual target (V2) blocks for controls (filled squares), drug-treated patients (filled circles), and drug-naïve patients (open circles). Bars represent standard error.
occurring at least 150 ms after appearance of the target. Using these criteria, the schizophrenic patients made more truly corrective saccades than controls, main effect of group, $F(2,100) = 5.43$, $p < .01$, and post hoc comparisons (Tukey’s LSD) with the control group reveal significant differences for both the DT ($p < .005$) and DN ($p < .05$) groups. The FEP hypometria is therefore unlikely to reflect a failure to try to correct retinal error, and therefore cannot be explained purely in terms of a lack of “effort” on behalf of the patients. Also, an increase in corrective saccades would not be expected if subjects were moving their heads.

To ensure that the differences in primary saccade gain between the groups were not due to differences in FEP, we reanalyzed the gain data with V2 FEP as a covariate. The main effect of group remained highly significant, $F(2,99) = 12.66$, $p < .001$, again reflecting the fact that primary saccade amplitude in both the DN and DT schizophrenic patients was lower than that of controls.

**Table 3. Average Number (SD) of Secondary Saccades Generated for Each Target Step in the V2 Condition**

<table>
<thead>
<tr>
<th>Group</th>
<th>All secondary saccades</th>
<th>Secondary saccades $&gt;150$ ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0.64 (0.32)</td>
<td>0.28 (0.24)</td>
</tr>
<tr>
<td>Drug-treated</td>
<td>0.96 (0.42)</td>
<td>0.46 (0.34)</td>
</tr>
<tr>
<td>Drug naïve</td>
<td>0.87 (0.23)</td>
<td>0.52 (0.11)</td>
</tr>
</tbody>
</table>

*Note: Both schizophrenic groups made significantly more secondary saccades than controls.*

measures. As the above analyses had revealed there were no significant differences in either primary saccade amplitude or FEP between the two patient groups, data from these groups were combined. Two patients from the DT group did not have any neuro psychological data and were excluded from the analysis, leaving a total group of 61 subjects.

Correlations were performed between primary saccade amplitude and FEP in the NV condition, and the four neuropsychological measures—spatial span, spatial working memory errors, spatial recognition memory, and pattern recognition memory. Primary saccade amplitude correlated with spatial recognition memory ($r = .28, p < .05$), pattern recognition memory ($r = .29, p < .05$), and spatial working memory errors ($r = -.34, p < .01$), but not with spatial span ($r = .004, p = .97$). Each significant correlation indicated that superior neuropsychological performance was related to fewer hypometric primary saccades. There were no significant correlations between the FEP and any of the neuropsychological measures.

**Discussion**

In this study of predictive saccades in first-episode schizophrenic patients there were two novel findings that help to resolve the question of whether the abnormalities found in previous studies reflect antipsychotic drug effects or intrinsic cortical dysfunction. The first finding was that, in a predictive saccade paradigm, primary saccade amplitude and FEP are hypometric in both antipsychotic-treated and antipsychotic-naïve first-episode schizophrenic patients. The finding of hypometric predictive saccades in chronic schizophrenic patients is well documented (Crawford et al., 1995b; Hommer et al., 1991; Karoumi et al., 1998; McDowell et al., 1996). However, this is the first demonstration of this phenomenon in schizophrenic patients who have never received antipsychotic medication. Other evidence that saccadic abnormalities, including spatial inaccuracy, can be observed in the absence of neuroleptic medication comes from studies that examined saccadic performance in the unmedicated relatives of schizophrenic patients (Clementz et al., 1994; Ross et al., 1998).

These findings argue against an interpretation of hypometric predictive saccades in schizophrenic patients purely in terms of the extrapyramidal action of antipsychotic medication. In particular, our results demonstrate that this phenomenon is intrinsic to the disorder and is present early in the course of the illness. Further, the fact that the magnitude of the effect was equivalent in DN and DT patients suggests that, at least in the early stages of treatment, antipsychotic drugs do not appear to significantly influence this phenomenon.

These findings seem difficult to reconcile with previous studies that addressed the role of neuroleptic medication in predictive saccade performance (Crawford et al., 1995a; Hommer et al., 1991). If, as our result suggests, hypometria can be intrinsic to schizophrenia, the question remains as to why both these studies found no significant differences in saccade amplitudes between drug-free patients and controls. In the paper by Crawford and colleagues, both the amplitudes and FEPs of saccades in the drug-free group were in fact hypometric compared with controls, but statistically the difference was significant only at the trend level ($p > .05$, $< .10$). The paper by Hommer and colleagues had only a relatively small number of patients and controls, and it remains possible that in a larger sample, significant differences may have emerged.

In addition, our finding does not negate a possible detrimental effect of long-term antipsychotic treatment in chronic patients. In both papers that addressed this issue, predictive saccades were found to be more hypometric in chronic schizophrenic patients who were maintained on antipsychotic medication than in those whose medication had been withdrawn (Crawford et al., 1995b; Hommer et al., 1991). Our DT patients were tested a median of 44 days following initiation of antipsychotic treatment, possibly before any significant long-term effects of chronic striatal dopamine receptor blockade (such as those leading to tardive dyskinesia) had become established. Further, because these were first-episode patients who are known to respond more favorably to drug treatment than chronic patients (e.g., Lieberman et al., 1993), it is likely that they were receiving lower doses of medication than the chronic patients. Indeed, the drug-treated group in the Crawford et al. (1995b) study were receiving a mean of 1,637 chlorpromazine equivalent units, and the treated patients in the Hommer et al. (1991) study were receiving a mean daily dose of fluphenazine of 26.25 mg (1,313 chlorpromazine equivalent units), both of which are substantially higher than the mean of 389 mg in our DT group. Finally, because of the recency of our study, more than 40% of our patients were receiving atypical antipsychotics. All of these factors suggest that any striatal influence of dopamine receptor blockade on eye movements is much more likely to be apparent in chronic medicated patients, as reported in previous studies, than in our group of recently treated first-episode patients.

Although clearly inconsistent with an explanation based only on the effects of antipsychotic medication, to what extent can saccadic hypometria be explained by a dysfunction of spatial working memory intrinsic to the schizophrenic illness (Goldman-Rakic, 1994; Hommer et al., 1991)? Some support for this hypothesis is
provided by the results of the correlational analyses. In all schizophrenic patients, primary saccade amplitude during an NV condition correlated significantly with performance on a test of spatial recognition memory, which arguably shares some cognitive characteristics with the predictive saccade task in that the subject is required to hold in mind the spatial location of a previously presented target. Further, predictive saccade amplitude during NV also correlated with another test of spatial working memory in which subjects need to hold in mind the spatial location of targets previously identified while searching for new ones. However, primary saccade amplitude also correlated with a nonspatial recognition memory task, and failed to correlate with spatial span. In addition, FEP in the NV condition, also presumably based on an internal representation of spatial location, did not correlate with any neuropsychological measure.

Another potential obstacle for a working memory account is the FEP hypometria observed during the V2 condition. Although primary saccades in the V2 condition are typically initiated before the target has moved, and are therefore based on an internal representation, the analysis of secondary saccades indicated that the FEP in V2 is often the result of saccades initiated in the presence of the target, and ought therefore to be based on current visual information. This makes the FEP hypometria observed in the V2 condition difficult to explain in terms of a working memory dysfunction. It should be emphasized that the hypometria in the schizophrenic groups cannot be ascribed to nonspecific performance deficits. Both groups of schizophrenic patients had normal primary saccades and FEP in the reflexive saccade paradigm, and the schizophrenic patients in fact made more corrective saccades in V2 than controls.

The FEP hypometria observed in this study remains difficult to interpret. We are currently systematically exploring the conditions under which it occurs. For example, under the relatively fast-paced nature of the predictive saccade task, secondary saccades, even when initiated more than 150 ms after the targets appearance, may not be the same as corrective saccades initiated in the reflexive saccade paradigm, and therefore could be considered as part of a sequence of planned saccades. In these terms, it would not be surprising that these secondary saccades are also hypometric.

The second novel finding of this study was that first-episode schizophrenic patients learned to predict the timing of target alternation and developed anticipatory saccades over the initial trials, but that the development of this behavior differed between DT and DN subgroups. Normal controls and DT patients showed a fast reduction in latencies from a mean of around +180 ms to around –250 ms across the first four trials. This was followed by a stable series of latencies across the remaining trials that varied between –150 and –250 ms. The DN group showed a less steep reduction in latencies, followed by a series of latencies that were consistently, but not significantly, less predictive than those in the control and DT groups.

Previous studies that measured the latencies of predictive saccades in chronic schizophrenic patients have produced conflicting results. One reported that 20% of a group of mixed drug-treated and drug-free patients failed to consistently generate anticipatory saccades, a result that the authors argued reflects a dysfunction of the oculomotor corticostriatal loop originating in the frontal eye fields (Hommer et al., 1991). Other studies have found no impairment in a group of antipsychotic-treated schizophrenic patients (Clementz et al., 1994; Crawford et al., 1995a), whereas still others have actually found faster anticipatory saccades in schizophrenic patients than in a control group, a result inconsistent with dys-functional frontal eye fields (Karoumi et al., 1998; McDowell et al., 1996). Karoumi et al. and McDowell et al. argued that their finding of faster latencies in schizophrenic patients was not a medication effect because the existing evidence predicted that dopamine antagonism would prolong reaction times not shorten them. Specifically, they cited that haloperidol injected directly into prefrontal cortex of nonhuman primates produces slower saccadic reaction times as well as more spatially inaccurate responses in an oculomotor spatial working memory task (Sawaguchi & Goldman-Rakic, 1994). However, more recent research (Williams & Goldman-Rakic, 1995) demonstrated that spatial working memory performance can be disrupted by either too much or too little dopamine. Indeed, on the basis of these findings it has been proposed that in acute schizophrenia there may be a functional over-activity of prefrontal dopamine, which gives rise to disrupted prefrontal cognitive function (Arntsen, 1997). Accordingly, dopamine receptor blockade would improve cognitive function. In this context, our latency data could be interpreted in terms of antipsychotic medication normalizing saccadic latencies in schizophrenic patients as a result of an action on prefrontal cortical dopamine receptors. Interestingly we have also observed normal saccadic latencies in an antisaccade paradigm in an antipsychotic-treated group of schizophrenic patients, but not in an antipsychotic-naive group (Hutton et al., 1998a).

We did not replicate the finding of faster predictive saccade latencies in medicated schizophrenic patients compared with controls (Karoumi et al., 1998; McDowell et al., 1994). However, this finding may reflect the particular timing characteristics of the predictive saccade paradigms used in those studies. In both instances, the target alternated at relatively slow speeds (0.4 and 0.5 Hz, respectively). At these slow speeds, control subjects appear to move their eyes at almost exactly the same time as the target step (i.e., mean latencies tend to be around 0). Under these conditions, schizophrenic patients may make predictive saccades earlier than controls, a behavior that may reflect the same saccadic disinhibition, which leads to their increased errors on the antisaccade task. In this study, as in the previous papers published by this laboratory on chronic schizophrenic patients (Crawford et al., 1995a, 1995b) the target alternated at 1 Hz, and at this comparatively fast speed it appears that controls also initiate saccades that precede the target step. In future studies we intend to systematically explore the effects of varying the timing of the predictive saccade paradigm on saccadic latencies and amplitudes.

The most significant finding of this study is that abnormalities of predictive saccades, both in terms of spatial accuracy and latency, can be observed in antipsychotic-naive first-episode schizophrenic patients. This finding demonstrates that these abnormalities are intrinsic to the disorder and are not artifacts of antipsychotic medication as previously suggested. This finding adds to the saccadic eye movement abnormalities observed in the antisaccade paradigm in schizophrenic patients (Crawford et al., 1995a; Fukushima et al., 1994; Hutton et al., 1998a). The most likely explanation is that this finding represents a dysfunction of prefrontal cortical mechanisms, especially within FEF, known to be responsible for the control of certain nonreflexive saccadic eye movements (Paus, 1996). Although some of our findings are consistent with a hypothetical functional overactivity of dopamine in the prefrontal cortex of acute schizophrenic patients leading to deficits in spatial working memory (e.g., Goldman-Rakic & Selemon, 1997), others do not support this view. In particular, there is no significant selective disadvantage of performance in the absence of a visual target compared to performance in the presence of a visual target, and
although dopamine antagonism by antipsychotic medication appears to normalize latencies, it has no effect on spatial accuracy. The interpretation that dopamine blockade normalizes saccadic latencies is compatible with the hypothesis that there is a functional overactivity of dopamine in the prefrontal cortex of schizophrenic patients, but it would appear that this overactivity leads to nonspecific deficits in what could perhaps be described as information processing speed, rather than spatial working memory.

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