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RESEARCH ARTICLES

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The relationship of saccadic peak velocity to latency: evidence for a new prosaccadic abnormality in schizophrenia

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Abstract Antisaccades have not only longer latencies but also lower peak velocities than prosaccades. It is not known whether these latency and velocity differences are related. Studies of non-human primates suggest that prosaccade peak velocity declines as latency from target appearance increases. We examined whether a similar relationship between peak velocity and latency existed in human saccades, whether it accounted for the difference in peak velocity between antisaccades and prosaccades, and whether it was affected by schizophrenia, a condition that affects antisaccade performance. Sixteen control and 21 schizophrenia subjects performed prosaccade and antisaccade trials in the same test session. In both groups antisaccades had lower peak velocities than prosaccades. Latency did not influence the peak velocities of antisaccades in either subject group. At short latencies, the peak velocities of prosaccades were also similar in the two groups. However, while prosaccade peak velocities declined minimally with increasing latency in control subjects, those in the schizophrenia group declined significantly until they reached a value similar to antisaccade peak velocities. We conclude that, in normal subjects, the effect of latency on prosaccade peak velocity is minimal and cannot account for the lower velocity of antisaccades. In schizophrenia, we hypothesize that the latency-related decline in prosaccade peak velocity may reflect either an increased rate of decay of the effect of the transient visual signal at the saccadic goal, or a failure of the continuing presence of the target to sustain neural activity in the saccadic system.

Keywords Saccade · Antisaccade · Schizophrenia · Peak velocity · Latency · Visual transient

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Introduction

When a target suddenly appears, the usual response of subjects is to shift their gaze to it with a saccadic eye movement, a prosaccade. However, subjects can also choose to look away from it, making an antisaccade. Antisaccades are an example of a controlled response, requiring inhibition of the reflexive prosaccades and substitution of a novel act. Many studies have shown that, compared with prosaccades, antisaccades have greater error rates and longer latencies. Another consistent finding is that antisaccades have lower peak velocities than prosaccades (Hallett 1978; Hallett and Adams 1980; Fischer and Weber 1992; van Gelder et al. 1997).

Why are antisaccade velocities lower than those of prosaccades? One possibility is that velocity is influenced by the transient visual activity occurring at the goal of prosaccades (but not antisaccades) when the target appears. A potential influence of 'visual transients' on saccadic velocity is suggested by a study of prosaccades in non-human primates. Delaying prosaccades—and hence increasing their latency and the time elapsed since the visual transient—resulted in lower peak velocities and decreased neural activity in the superior colliculus (Edel-

man and Goldberg 2001). Such a relation between latency, peak velocity and neural activity had also been suggested in prior studies. Neural activity in the superior colliculus correlates with prosaccadic peak velocity (Berthoz et al. 1986; Sparks and Hartwich-Young 1989), and neural activity in the frontal eye fields and superior colliculus correlates inversely with saccadic latency (Goldberg and Segraves 1989; Dorris et al. 1997; Everling and Munoz 2000; Munoz et al. 2000). From this result, Edelman and Goldberg (2001) hypothesized that a visual target at the saccadic goal boosts saccade-related neural activity transiently, reflected in an increase in peak velocity. If increasing the time between the visual target and saccade onset decreases neural activity and peak velocity, then the lack of any suddenly appearing target at the goal, as in antisaccades, may also be associated with less neural activity and low peak velocities, as well as increased latency. Likewise, this finding could also account for the reduced peak velocities of saccades to remembered target locations and saccades made in anticipation of a target (Körner 1975; Smit and van Gisbergen 1989).

Whether prosaccadic peak velocity is related to latency in a similar manner in humans is unknown. Empirically, at least four models of the relationship between peak velocity and latency in prosaccades and antisaccades can be envisaged (Fig. 1). Determining which of these models best describes the human data would clarify the hypothesized role of the visual transient upon saccadic peak velocity.

In model 1, the peak velocities of prosaccades, but not antisaccades, decline with increasing latency. This is the result expected if the visual transient at the saccadic goal is the source of the latency effect on peak velocity. Since antisaccades lack this visual transient, their velocity would not change with latency. Given a long-enough latency for the effect of the visual transient to disappear, the velocities of prosaccades would approach that of antisaccades.

In model 2, the peak velocities of prosaccades and antisaccades are not related to latency. The difference between prosaccadic and antisaccadic peak velocities is due to a factor that does not vary with latency. This factor could still be an effect on neural activity of a visual transient located at prosaccadic, but not antisaccadic, goals, but only if the effect of this transient was long-lasting, unlike the effect hypothesized by Edelman and Goldberg (2001). Alternatively, it might be related to non-visual factors, such as the additional cognitive control functions needed for antisaccades.

In model 3, the peak velocities of both antisaccades and prosaccades decline with increasing latency, but the lines are not superimposed. The decline with latency of not only prosaccadic but also antisaccadic velocities would imply

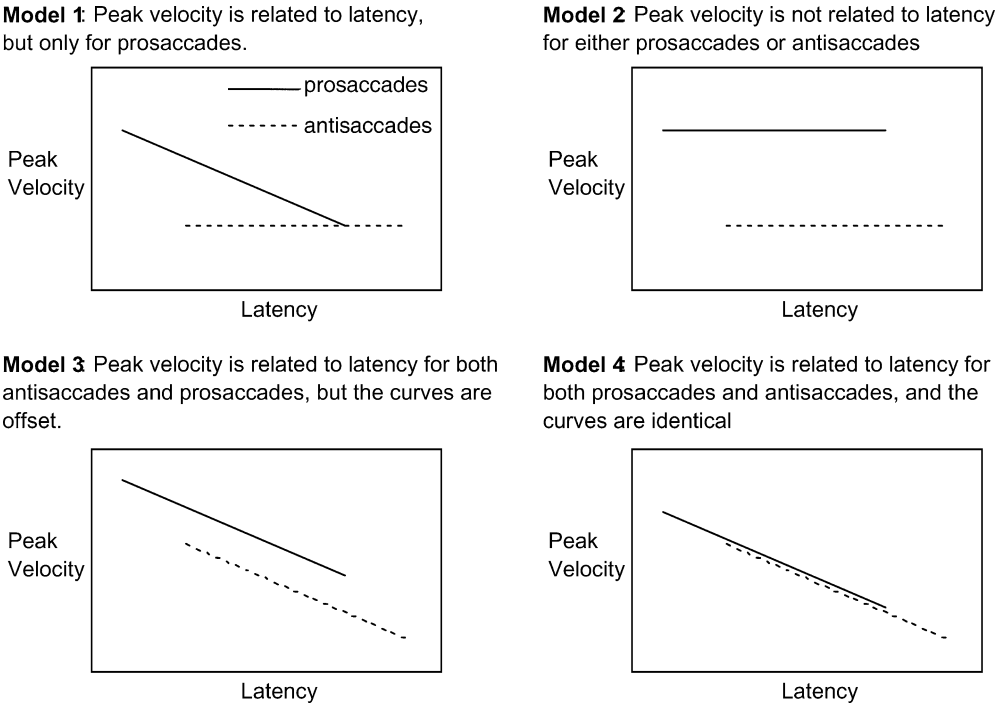

Fig. 1 Possible relationships between saccadic peak velocity and latency for prosaccades and antisaccades. *Model 1*: peak velocity is related to latency, but only for prosaccades. Thus, some prosaccade-related factor (like a visual transient) generates the latency effect. Lack of this prosaccade-related factor may contribute to the lower peak velocity of antisaccades, which is similar to the peak velocity of long-latency prosaccades. *Model 2*: a prosaccade-related factor creates the difference in peak velocity between prosaccades and antisaccades in a manner that does not depend upon latency. *Model 3*: peak velocity is related to latency but this relationship does not depend upon a prosaccade-related factor since it occurs for both antisaccades and prosaccades. However, a prosaccade-related factor creates an additional difference in peak velocity between prosaccades and antisaccades since the lines are offset. *Model 4*: peak velocity is related to latency but this relationship does not depend upon a prosaccade-related factor, and there is no prosaccade-specific effect on latency. The lower mean peak velocity of antisaccades is simply due to the fact that antisaccades sample from further right on the line than prosaccades do

that visual transients at saccadic goals do not generate the relationship between peak velocity and latency. Also, the difference between the antisaccadic and prosaccadic lines would imply that there must be another latency-independent factor causing the difference between prosaccadic and antisaccadic peak velocities, as in model 2.

In model 4, the peak velocities of both antisaccades and prosaccades decline with increasing latency and the lines are superimposed, with the same slopes and intercepts. Again, as in model 3, because antisaccadic peak velocities decline with increasing latency, the latency/peak velocity relationship is not related to visual transients at the saccadic goal. Since the lines are identical for prosaccades and antisaccades, there is no other latency-independent factor creating the difference in prosaccadic and antisaccadic peak velocities. Rather, the mean peak velocity of antisaccades is lower merely because, since antisaccades have longer latencies than prosaccades, they sample from further to the right of the same line that prosaccades lie upon.

Our main goal was to determine which of these models best characterized the variation of peak velocity with respect to saccadic latency, for both antisaccades and prosaccades, in healthy subjects. We also investigated this relationship in schizophrenia, a disorder characterized by abnormal antisaccadic performance. On antisaccadic tasks schizophrenia patients make more errors (looking towards, rather than away from the target) and are frequently found to have longer latencies for correct responses (Fukushima et al. 1990b, 1994; Manoach et al. 2002). Deficient antisaccade performance is a consistent finding across numerous studies (for review see Levy et al. 1998) and has been reported in both medicated and neuroleptic-naïve patients, schizophrenia patients in remission, healthy first-degree biological relatives, and in individuals with schizotypy. This suggests that antisaccadic deficits may index a genetic liability for schizophrenia (Clementz et al. 1994; Crawford et al. 1998; Hutton et al. 1998; O'Driscoll et al. 1998; McDowell et al. 1999; Curtis et al. 2001). These abnormalities have been attributed to dysfunction of the prefrontal cortex (Fukushima et al. 1990a; Nakashima et al. 1994; McDowell et al. 2002), although the evidence for this is inconsistent (Crawford et al. 1996; Raemaekers et al. 2002). Given the neurophysiologic evidence that both saccadic latency and peak velocity reflect neural activity in a saccadic control network, components of which may be abnormal in schizophrenia (Raemaekers et al. 2002), we hypothesized that the peak velocity–latency relationship for prosaccades and/or antisaccades may be abnormal in this condition.

Methods

Details of subject information, symptom ratings, and data collection methods have been published previously (Manoach et al. 2002). Schizophrenia outpatients were recruited from an urban mental health center. They had been maintained on stable doses of antipsychotic medications for at least 6 weeks: 15 subjects on atypical agents and six on conventional ones. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al. 1997). Healthy control subjects, without a history of psychiatric illness, were recruited from the hospital community. All subjects were screened to exclude substance abuse or dependence within the past 6 months and any independent conditions that might affect brain function. Two schizophrenia subjects and four control subjects did not complete the protocol because they could not tolerate the

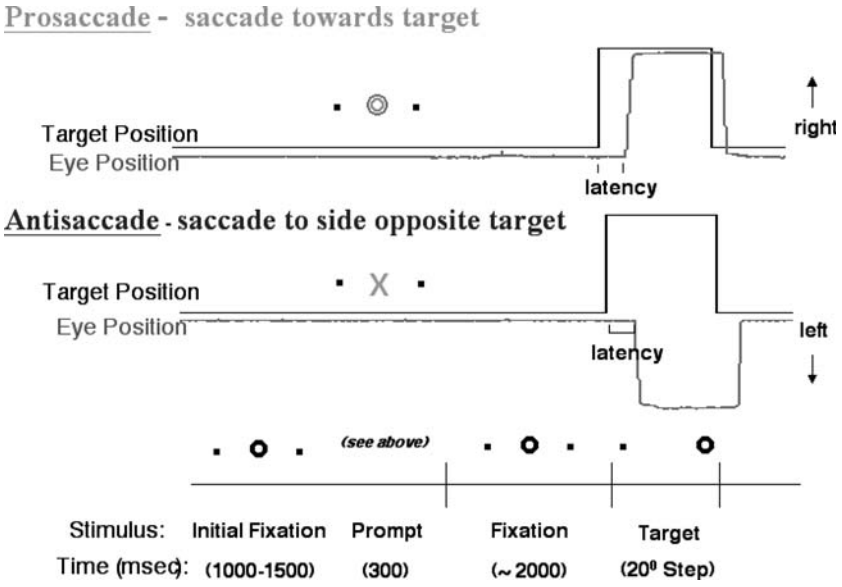

Fig. 2 Explanation of saccadic tasks for the experimental protocol. Progress over time (*bottom scheme*) is from left to right. A simulation of the screen during a prosaccade trial (*top*) and an antisaccade trial (*middle*) is illustrated. When eye position is within 3° of screen center, marked by the fixation ring, a trial begins with a fixation period. Following this, a prompt appears for 300 ms, either a yellow double ring for a prosaccade or a blue 'X' for an antisaccade. After the prompt disappears the fixation ring reappears for another 2000 ms. The fixation ring is then shifted to either the right or left markers at 20° eccentricity to become the target. The subject makes a saccade (indicated by *arrow*), with the latency being the time between onset of the target and onset of the saccade. The trial is terminated when eye position is within 3° of the correct location for that trial

contact lens. The data from one schizophrenia subject who completed the protocol were excluded due to a greater than 50% error rate on antisaccade trials, which limited the data available to calculate latency effects. The final sample size was 21 schizophrenia subjects and 16 control subjects. Seventeen schizophrenic and 11 control subjects were strongly right-handed, with a laterality score of 70 or above on the modified Edinburgh Handedness Inventory (White and Ashton 1976). Subject groups did not differ in age (mean ages 40.3 years for control, 43.7 years for schizophrenia), sex (11:5 male:female for control, 17:4 male:female for schizophrenia), or parental socio-economic status (SES) as determined by the Hollingshead Index (Hollingshead 1965) (mean parental SES 2.1 for control, 2.8 for schizophrenia). Control subjects had significantly more years of education and higher verbal IQ estimates based on a test of single-word reading (American National Adult Reading Test; Blair and Spreen 1989). The protocol was approved by the institutional review board of the Beth Israel Deaconess Medical Center and conformed to the ethical standards in the 1964 Declaration of Helsinki. All subjects gave informed consent prior to inclusion in the study.

Eye movement apparatus and protocol

We recorded eye movements using a magnetic search coil technique, with a scleral contact lens and a 3-foot field coil (Crist Instruments, Bethesda, MD, USA). The subject's head was secured in a chin rest with the cornea 87 cm away from a tangent screen. Displays were generated by a Power Macintosh 9600/233 computer, using programs written in C++ on the Vision Shell programming platform (www.kagi.com/visionshell), and back-projected with an Eiki LC-7000U LCD-projector. The lens was placed in the left eye. The system was calibrated by having the subject sequentially fixate nine targets in a square grid spanning 50°. Twelve data points were collected at each of the target locations, and a regression method was used to find the best linear fit. Eye position was digitized at 500 samples/s. A five-point central difference algorithm (Bahill and McDonald 1983) was used to derive velocity from eye position.

The initial display was a dark background with a central white fixation ring of 0.4° diameter and luminance of 20 cd/m^2 (Fig. 2) The fixation ring was flanked by two dots of 0.2° diameter and the same luminance placed 20° right and left of center. These two peripheral dots were visible in each trial unless obscured by a target. The subject was required to look at the central fixation point and each trial began when a subject's eye fell within 3° of the fixation point. After a period randomly varying between 1 and 1.5 s, the fixation point was replaced by one of two symbols. A yellow 'O' with a surrounding ring of 0.8° diameter was the prompt for a prosaccade and a blue 'X' spanning 0.8° was the prompt for an antisaccade. Prompts lasted 300 ms and were then replaced by the white fixation ring. After a mean interval of 2 s, the fixation ring disappeared and a similar ring appeared around one of the two peripheral dots, the side it appeared being randomly determined. This was the cue for the subject to make their saccade as quickly and accurately as possible. The white ring remained in the peripheral location until either the subject's eye had fallen within 3° of the desired end position or 10 s had passed, at which time it returned to the central fixation point for the next trial.

Prior to testing, the tasks were explained to each subject and they were informed that they would receive a monetary bonus for each correct response. The incentive was intended to mitigate potential motivational deficits in the schizophrenia subjects. Subjects performed three practice blocks of 20 trials each. In the experiment, saccadic trials were given as both single-task blocks, in which 26 trials were all prosaccades or all antisaccades, and mixed-task blocks, in which 52 trials of prosaccades and antisaccades were mixed. Blocks were repeated with short rest periods intervening, until subjects had performed 416 saccadic trials. Since analysis failed to show any significant effect of block type upon the variables of peak velocity and amplitude, the data will be presented for all blocks combined. Practice blocks and the first trial of experimental blocks were omitted from analysis.

Scoring of eye movement protocols

We identified saccades as eye movements with velocities exceeding 47°/s. The onset of a saccade was defined as the point at which the velocity of the eye first exceeded 31°/s, and the end of a saccade was the point where the eye's velocity fell below this baseline. For each saccade, we recorded directional accuracy with respect to the required response. Only directionally correct responses are reported in this study. For these saccades, we recorded latency (the time from target onset to saccade onset), amplitude (the distance traveled between the onset and end of a saccade), and peak velocity (the greatest velocity attained during the saccade). Saccades were included for further analysis if their amplitudes were between 15° and 25° and their latencies between 130 and 800 ms. The cutoff of 130 ms excluded anticipatory saccades (Fischer and Breitmeyer 1987; Doricchi et al. 1997; Straube et al. 1999), which are not true responses to the appearance of the visual target. About 100–200 prosaccades and 60–200 antisaccades per subject met these criteria. The overall database consisted of 2,879 prosaccades and 2,536 antisaccades for control subjects, and 3,452 prosaccades and 2,451 antisaccades for schizophrenia subjects.

Data analysis

Analysis was performed using JMP statistical software (version 4.0 SAS Institute, Cary, NC, USA). Prosaccades and antisaccades were separated for each subject group (schizophrenia vs control), giving four saccadic sub-groups: schizophrenic prosaccades, schizophrenic antisaccades, control prosaccades, and control antisaccades.

We first examined the variables of peak velocity, latency, and amplitude of our prosaccades and antisaccades in the two subject groups. We used randomized block analysis of variance (ANOVA), with subjects nested within group as a random effect and group (schizophrenia vs control) and task (prosaccade vs antisaccade) as the main factors, to confirm that our data on latency and peak velocity were similar to those reported by others.

To characterize the relationship of peak velocity to latency in each saccadic sub-group, we performed linear regressions of peak velocity by latency for the pooled data separated by both saccadic type (prosaccades vs antisaccades) and subject group (schizophrenia vs healthy). To determine whether peak velocity-latency relationships differed among the sub-groups, we used a randomized block analysis of covariance (ANCOVA) with subjects nested within group as a random effect. We initially examined the peak velocity data of all subjects with the main effects of group (schizophrenia vs control) and task (antisaccade vs prosaccade), and latency as the covariates. We also performed two secondary ANCOVA analyses. First, we analyzed peak velocity data to determine whether the effects of latency differed for prosaccades and antisaccades within each group. These ANCOVAs had task as a main effect and latency as covariate, and were conducted separately for each group. Second, we investigated whether the effects of latency on peak velocity differed between the two subject groups for each type of saccade. These ANCOVAs had group as a main effect and latency as covariate, and were conducted separately for prosaccades and antisaccades.

To graphically portray the variation of peak velocity with latency, we calculated the average peak velocity for all saccades with the same latency value (spaced 2 ms apart). Where there were less than ten saccades per latency value, as occurred at longer latencies, we grouped the closest ten saccades, calculated their mean peak velocity, and their mean latency. The resulting values were then smoothed with a gaussian weighting of the six neighboring points.

A potential limitation is that the findings from pooled data might be an artifact of merging data from subjects with different saccadic characteristics. For example, if data from a subject with short

latencies and high velocities were pooled with that of a subject with long latencies and low velocities, this would generate the appearance of a declining relationship of peak velocity against latency in the pooled data, even if no such relationship existed within each subject's individual data. To guard against this, we also analyzed the peak-velocity–latency relationship within each subject. We obtained slopes for the linear regressions of peak velocity against latency for each subject's antisaccades and prosaccades separately. The means and standard deviations of these slopes were calculated for each of the four saccadic sub-groups (schizophrenic prosaccades, schizophrenic antisaccades, control prosaccades, and control antisaccades). For each sub-group we used *t*-tests to determine whether the slopes were significantly different from zero. To compare the slopes of the regression lines of the different subject groups and saccadic types, we performed a randomized block ANOVA with subjects nested within group as a random effect and group (schizophrenia vs control) and task (prosaccades vs antisaccades) as the main factors.

Although our chief interest was the relationship of latency to peak velocity, we also examined for a potential relationship between latency and amplitude. Peak velocity increases in a non-linear fashion with amplitude, an empiric observation that has been termed the 'main sequence' (Bahill et al. 1975; Becker 1989). If latency alters amplitude, changes in peak velocity may be merely a secondary effect from the peak-velocity–amplitude relationship. Therefore parallel statistical analyses were done with amplitude in place of peak velocity.

Results

Saccadic parameters

Our findings regarding saccadic parameters (Fig. 3) were similar to others reported in the literature for saccades and schizophrenia (for review, see Hutton and Kennard 1998). For peak velocity, there was a main effect of task (prosaccades vs antisaccades, $F_{(1,35)}$=1010, p<0.0001), with antisaccades having lower peak velocities. The main effect of group (schizophrenia vs control) was not significant ($F_{(1,35)}$=1.91, p<0.18), but there was a significant interaction between group and task ($F_{(1,35)}$=20.75, p<0.0001). Peak velocities of antisaccades were significantly slower (p<0.0001) than those of prosaccades, slightly more so for schizophrenia patients (mean difference 43°/s) than for control subjects (mean difference 32°/s).

Mean saccadic amplitudes of each group–task subset were all between 18.5 and 20°. There was a main effect of task on amplitude, with antisaccades being slightly smaller than prosaccades, by 0.2° ($F_{(1,35)}$=11.1, p<0.001). The group effect and group-by-task interactions were not significant.

We previously reported the latency data of this study (Manoach et al. 2002). There was no significant main effect of group. Antisacccades had longer latencies than prosaccades, with a significant main effect of task ($F_{(1,35)}$=1899, p<0.0001). There was a significant interaction between task and group ($F_{(1,35)}$=108, p<0.0001): while both subject groups had similar latencies for prosaccades, schizophrenia patients had latencies for antisaccades about 30 ms longer than those of the controls.

Thus, these data reproduce the observations that antisaccades have longer latencies and lower peak velocities, with only slightly reduced amplitudes, compared to prosaccades. They also confirm that schizophrenia patients have abnormal antisaccades, with lower peak velocities and longer latencies.

The relationship of peak velocity to latency

There was a significant main effect of task (prosaccades vs antisaccades, $F_{(1,35)}$=148, p<0.0001), with prosaccades faster than antisaccades, but no significant main effect of group. There was no significant interaction between group and latency, but there was an interaction between task and latency ($F_{(1,35)}$=5.07, p<0.03). More importantly, ANCOVA showed a significant three-way interaction between group (schizophrenia vs control), task (prosaccades vs antisaccades) and latency ($F_{(1,35)}$=25.78, p<0.0001). The nature of this interaction was clarified in the secondary ANCOVA analyses. These showed that, when schizophrenia data was analyzed alone, there was an interaction between latency and task ($F_{(1,20)}$=64.46, p<0.0001). This indicated that the effects of latency on peak velocity

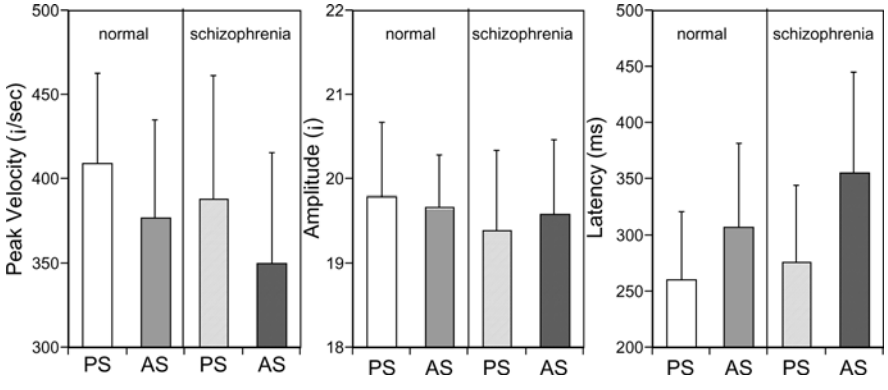

Fig. 3 Saccadic parameters in the two subject groups (normal, schizophrenia) for the two tasks (*PS* prosaccades, *AS* antisaccades). Peak velocities were reduced for antisaccades compared with those for prosaccades, in both subject groups. Schizophrenia patients also had lower peak velocities than the controls in general. Mean saccadic amplitudes were all very similar, between 19–20°. The latencies of antisaccades were longer than those of prosaccades. While prosaccadic latencies were similar in controls and schizophrenics, antisaccade latencies were longer in the schizophrenia group

differed between prosaccades and antisaccades in this group of subjects. However, no such interaction was seen in the analysis that was restricted to control subjects. When prosaccade data was considered alone, there was an interaction between group and task ($F_{(1,35)}$=10.98, p<0.0009). This indicated that the effects of latency on peak velocity differed between controls and schizophrenia subjects for prosaccades. In contrast, no such interaction was seen in the analysis that was restricted to antisaccades.

Figure 4a shows the origins of these effects. Peak velocity declined with increasing latency for prosaccades in schizophrenia subjects, but not in any other saccadic subgroup. Linear regressions confirmed a significant decrease in peak velocity with increasing latency only for schizophrenic prosaccades (slope =−0.23, r=−0.17, p<0.0001). Linear regressions for schizophrenic antisaccades, healthy antisaccades, and healthy prosaccades were not significant, even when performed on log-transformed latency data (to correct for the possibility of a non-linear relationship between latency and peak velocity).

The within-subject slope analysis confirmed these findings (Fig. 5). The mean slopes for antisaccades in both the schizophrenic and control subjects did not differ significantly from zero. The mean slope of the regression lines for prosaccades in schizophrenia subjects showed a significant decrease in peak velocity with increasing latency (slope =−0.11, SD =0.09, $t_{(20)}$=5.53, p<0.0001). The peak velocities for prosaccades in control subjects also declined slightly with increasing latency (slope = −0.03, SD =0.06, $t_{(15)}$=2.36, p<0.04) but linear contrasts demonstrated that the decline in schizophrenia was significantly greater than that in the control subjects (p<0.03).

The relationship of amplitude to latency

Could the findings for peak velocity be explained by a change in amplitude with latency? Unlike the data for peak velocity, ANCOVA did not demonstrate a significant three-way interaction of group-by-task-by-latency for amplitude ($F_{(1,35)}$=1.20, not significant). While linear regressions of amplitude by latency for pooled data showed a slight decrease in amplitude with increasing latency for antisaccades in schizophrenia (slope = −0.00063, p<0.04) and control subjects (slope =−0.0011, p<0.003), this was not confirmed by the within-subject slope analysis (Fig. 5). In this analysis the mean slopes of the regressions of amplitude upon latency did not differ from zero for any saccadic subgroup. Inspection of Fig. 4b further suggests that if there is any slight decline for prosaccadic peak velocities with increasing latency, it appears to be confined to saccades with latencies greater than 400 ms, well beyond the period where schizophrenia peak velocities decline as a function of latency. Furthermore, data on the relationship between peak velocity and amplitude (Becker 1989) indicate that, for a 20° saccade, amplitude would have to be reduced by 4–5° to account for the 80°/s decrease in peak velocity evident in schizophrenic prosaccades. This is clearly not the case in Fig. 4b. Thus, we conclude that changes in prosaccadic amplitude do not account for the changes in peak velocity with latency in schizophrenia subjects.

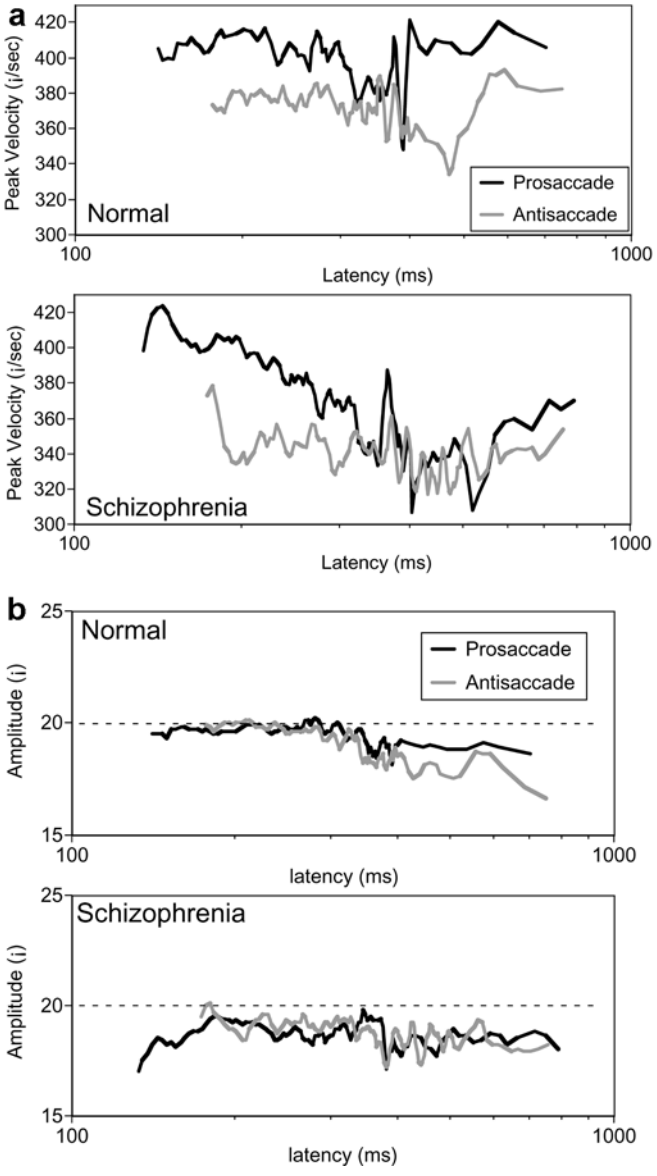

Fig. 4a,b Relationship of peak velocity and amplitude to latency. **a** Peak velocity declined with increasing latency for prosaccades in schizophrenia subjects. This was not seen for antisaccades in either subject group, or for the prosaccades of control (normal) subjects. **b** Amplitude did not vary significantly with latency for either prosaccades or antisaccades, in either subject group

Discussion

We found that the peak velocity of prosaccades declined with increasing latency in the schizophrenia group, while that of antisaccades did not. Schizophrenia subjects differed significantly from healthy subjects in the relationship of peak velocity to latency for prosaccades. In healthy subjects the evidence for a decline of prosaccadic peak

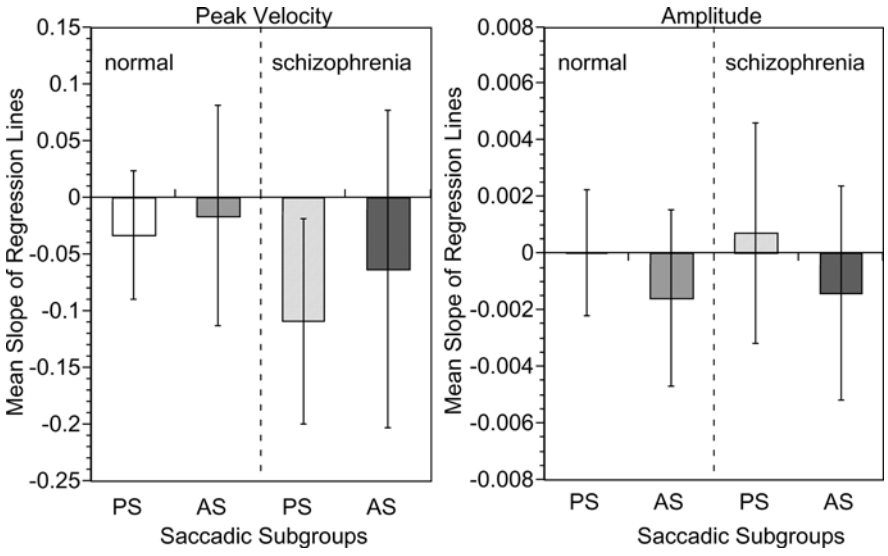

Fig. 5 Within-subject slope analysis of peak velocity and amplitude of saccade against latency for the two subject groups (normal, schizophrenia) in the two tasks (*PS* prosaccades, *AS* antisaccades). For prosaccades, the mean slope of the regression of peak velocity against latency was significantly negative for both schizophrenia and control subjects, with the decreasing slope being more significant for schizophrenia subjects. The mean slopes of peak velocity vs latency regression lines for antisaccades were not significantly different from zero. The mean slopes of amplitude vs latency regression lines were not significantly different from zero for any of the saccadic subgroups. (*error bars* = 1 SD)

velocity against latency was equivocal. A weak, but significant relation was found in the within-subject analysis with linear regression, but not in the group ANCOVA analysis. Importantly, there was little relationship between prosaccadic amplitude and latency. Hence, the effect of latency on peak velocity is not a trivial secondary effect of a progressive undershoot of the target.

Model 1 outlined in the Introduction (Fig. 1) proposed a latency effect on peak velocity that is related to some factor specific to prosaccades and not antisaccades. This model fits the schizophrenia data well. The peak velocities of schizophrenic prosaccades at short latencies are indistinguishable from those of control prosaccades at short latencies, both being about 400°/s. However, the peak velocities of schizophrenic prosaccades decline with increasing latency. At latencies of more than 300 ms, they are indistinguishable from those of schizophrenic antisaccades, which are not affected by latency.

It is less clear which model best describes the control data. The within-subject slope analysis suggested that increasing latency was associated with a slight decline in the peak velocities of prosaccades but not of antisaccades. If so, model 1 may also apply to control subjects, but with a much longer time-constant (a measure of the rate of decay of activity) for the decline of the influence of the prosaccade-specific factor than for that in schizophrenia. That is, an effect that boosts prosaccadic but not antisaccadic peak velocity may dissipate more rapidly in schizophrenia than it does in healthy subjects. Alternatively, there may be no real relationship between peak velocity and latency in control subjects, and hence model 2 (Fig. 1) would be more appropriate. This model postulates that the factor that generates the difference between antisaccadic and prosaccadic peak velocities does not vary with latency.

One candidate for the prosaccade-specific factor generating the latency effect on peak velocity is the visual transient at the saccadic goal, as suggested by data from non-human primates (Edelman and Goldberg 2001). That study examined the effect of prosaccadic latency on velocity and neural activity. They used a ‘visual delay’ task in which the fixation point did not disappear until 750–1000 ms after the appearance of the target, at which point the animal was to make a prosaccade. This was contrasted with standard tasks in which the monkey made a saccade as soon as the target appeared. The neural activity of some superior colliculus neurons was higher for prosaccades made without delay than for those made after a visual delay. Likewise, the mean peak velocity for prosaccades without delay was greater than that of delayed prosaccades. Additional mechanisms such as cortical inputs from the frontal eye field may have contributed to the effect on peak velocity since the decline in peak velocity with increasing latency was more than that predicted from the analysis of superior colliculus activity. By inference from these data, the authors of the study postulated that the lower peak velocities of antisaccades and memory-guided saccades might be due to the lack of a visual transient at the saccadic goal. The fact that prosaccades with long latencies in our schizophrenia group have peak velocities similar to their antisaccades is consistent with this proposal. (Our control data, on the other hand, neither confirm nor refute their hypothesis.)

Why is the decline in prosaccadic peak velocity with latency present (or at least much more evident) in schizophrenia patients but not in control subjects? Although both groups were within the average range, the

estimate of IQ for schizophrenia patients was 10 points lower. While IQ may affect antisaccade performance, there is no evidence that it affects prosaccade parameters. There are at least two possible explanations for the group difference. If there is indeed a slight decline in control prosaccadic peak velocity with latency, as in model 1, the difference between the two groups may be quantitative, rather than qualitative. This would be a reduction of the time-constant of the decay of the influence of the prosaccade-specific factor, which we hypothesize to be the visual transient at the saccadic goal.

The other possibility is that schizophrenia patients lack a second factor that maintains prosaccadic peak velocity independent of latency. In this scenario, the decline of peak velocity with latency in schizophrenia is the normal control effect of the visual transient at the saccadic goal, which is masked in control subjects by the operation of this second factor to create a model 2 effect. One candidate for this second factor is the continued presence in our protocol of the saccadic target after its appearance. The persistence of a visual target increases neural activity in the superior colliculus, compared to targets that appear then disappear (Edelman and Goldberg 2001). It may be that activity from the continued presence of the target sustains saccadic peak velocity across a wide range of latencies in control subjects, but fails to do so in schizophrenia patients.

Our findings may be related to a large body of research on perceptual dysfunction in schizophrenia. The time-course of our effects are measured in hundreds of milliseconds, which is similar to the time-course of the effects in studies of visual persistence and visual backward masking in these patients (Schwartz et al. 2001). Some of this work has suggested a reduced persistence of the visual image of high spatial frequency targets, which has been interpreted as a "..premature termination or decay of sustained (e.g. pattern) information" (Schwartz and Winstead 1988). Other studies suggest ineffective temporal integration of visual signals (Schwartz et al. 1983). Either of these findings may be relevant to our second possible explanation, which proposes that the target's continued presence over time fails to sustain saccadic neural activity in schizophrenia subjects. However, the bulk of the work on masking has led to a conclusion that there is dysfunctional processing in transient visual channels, manifest in masking studies as a failure to inhibit activity of sustained channels (Schwartz et al. 2001). It may be that this failure of inhibition reflects weaker or unstable neural activity related to visual transients in general, rather than just their inhibitory outputs. If so, this instability may be reflected in our study in a more rapid loss of the effect of visual transients in boosting peak velocity. This would thus provide a physiologic basis for the first possible explanation, which proposes a shorter time-constant for the decay of the effect of the visual transient on saccadic neural activity in schizophrenia. Studies that contrast prosaccades made to targets that persist with those to targets that disappear would be helpful in determining whether the abnormal peak-velocity/latency relationship in schizophrenia is linked more to the target's visual transient or to its continued presence.

Whether antipsychotic medications may contribute to the findings in schizophrenia patients is unclear. Some studies show no effect of antipsychotic drugs on latencies of antisaccades or prosaccades (Crawford 1995) whereas others find increased latency for antisaccades but not prosaccades (Green and King. 1998; Muller et al. 1999). Regarding peak velocity, some find that medication reduced the peak velocities of antisaccades more than prosaccades (Straube et al. 1999) whereas others report the opposite result (Green and King, 1998). In addition, another study suggested that peak velocities were decreased and latencies prolonged by some antipsychotic drugs but not others (Sweeney et al. 1997). Given these variable results, it is not possible to either exclude or claim an influence of medication upon our findings.

In conclusion, we found that saccadic peak velocity for prosaccades declines with increasing latency to a greater degree in schizophrenia subjects than in controls. To our knowledge, this prosaccadic abnormality has not been described in schizophrenia, and stands in contrast to a number of claims that prosaccades are normal in this condition. Replication of this unexpected finding in future studies would be important. In both controls and schizophrenia patients, we hypothesize that the relationship between peak velocity and latency is due to the effect of a visual transient at the saccadic goal, and that this may also explain, at least in part, the lower peak velocities of antisaccades. The greater latency effect on prosaccadic peak velocity in schizophrenia may reflect either a more rapid decay of the activity from the visual transient that boosts peak velocity, or a failure of continuing target presence to sustain saccade-related neural activity.

References

Bahill T, McDonald J (1983) Frequency limitations and optimal step size for the two-point central difference derivative algorithm with applications to human eye movement data. IEEE Trans Biomed Eng 30:191–194

Bahill AT, Clark MR, Stark L (1975) The main sequence, a tool for studying human eye movements. Math Biosci 24:191–204

Becker W (1989) Metrics. In: Wurtz RH, Goldberg ME (eds) The Neurobiology of saccadic eye movements. Elsevier Science, Amsterdam, pp 13–68

Berthoz A, Grantyn A, Droulez J (1986) Some colliculur efferent neurons code saccadic eye velocity. Neurosci Lett 72:289–294

Blair J, Spreen O (1989) Predicting premorbid IQ: a revision of the national adult reading test. Clin Neuropsychologist 3:129–136

Clementz BA, McDowell JE, Zisook S (1994) Saccadic system functioning among schizophrenia patients and their first-degree biological relatives. J Abnorm Psychol 103:277–287

Crawford TJ (1995) Saccadic abnormalities in psychotic patients. II. The role of neuroleptic treatment. Psychol Med 25:473–483

Crawford TJ, Puri BK, Nijran KS, Jones B, Kennard C, Lewis SW (1996) Abnormal saccadic distractibility in patients with schizophrenia: a 99mTc-HMPAO SPET study. PsycholMed 26:265–277

Crawford TJ, Sharma T, Puri BK, Murray RM, Berridge DM, Lewis SW (1998) Saccadic eye movements in families multiply affected with schizophrenia: the Maudsley Family Study. Am J Psychiatry 155:1703–10

Curtis CE, Calkins ME, Grove WM, Feil KJ, Iacono WG (2001) Saccadic disinhibition in patients with acute and remitted schizophrenia and their first-degree biological relatives. Am J Psychiatry 158:100–6

Doricchi F, Perani D, Incoccia C, Grassi F, Cappa SF, Bettinardi V, Galati G, Pizzamiglio L, Fazio F (1997) Neural control of fast-regular saccades and antisaccade: an investigation using positron emission tomography. Exp Brain Res 116:50–62

Dorris MC, Pare M, Munoz DP (1997) Neuronal activity in monkey superior colliculus related to the initiation of saccadic eye movements. J Neurosci 17:8566–8579

Edelman JA, Goldberg ME (2001) Dependence of saccade-related activity in the primate superior colliculus on visual target presence. J Neurophysiol 86:676–691

Everling S, Munoz DP (2000) Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. J Neurosci 20:387–400

First M, Spitzer R, Gibbon M, Williams J (1997) Structured clinical interview for DSM-IV axis I disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/P W/PSY SCREEN). Biometrics Research, New York State Psychiatric Institute, New York

Fischer B, Breitmeyer B (1987) Mechanisms of visual attention revealed by saccadic eye movements. Neuropsychologia 25:73–83

Fischer B, Weber H (1992) Characteristics of “anti” saccades in man. Exp. Brain Res. 89:415–424

Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I (1990a) Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. J Psychiatr Res 24:9–24

Fukushima J, Fukushima K, Morita N, Yamashita I (1990b) Further analysis of the control of voluntary saccadic eye movements in schizophrenic patients. Biol Psychiatry 28:943–958

Fukushima J, Fukushima K, Miyasaka K, Yamashita I (1994) Voluntary control saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. Biol Psychiatry 36:21–30

Goldberg ME, Segraves MA (1989) The visual and frontal cortices. In: Wurtz RH, Goldberg ME (eds) The neurobiology of saccadic eye movements. Elsevier Science, Amsterdam, pp 283–314

Green J, King, DJ (1998) The effects of chlorpromazine and lorazepam on abnormal antisaccade and no-saccade distractibility. Biol Psychiatry 44:709–715

Hallett PE (1978) Primary and secondary saccades to goals defined by instructions. Vision Res 18:1279–1296

Hallett PE, Adams BD (1980) The predictability of saccadic latency in a novel voluntary oculomotor task. Vision Res 20:329–339

Hollingshead A (1965) Two factor index of social position. Yale University Press, New Haven CT

Hutton S, Kennard C (1998) Oculomotor abnormalities in schizophrenia. A critical review. Neurology 50:604–609

Hutton SB, Crawford TJ, Puri BK, Duncan LJ, Chapman M, Kennard C, Barnes TR, Joyce EM (1998) Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. Psychol Med 28:685–92

Körner F (1975) Non-visual control of human saccadic eye movements. In: Lennerstrand G, Bach-y-Rita P (eds) Basic mechanisms of ocular motility and their clinical implications. Pergamon Press, Oxford, pp 565–569

Levy DL, Mendell NR, LaVancher CA, Brownstein J, Krastoshevsky O, Teraspulsky L, McManus KS, Lo Y, Bloom R, Matthysse S, Holzman PS (1998) Disinhibition in antisaccade performance in schizophrenia. In: Lenzenweger MF, Dworkin RH (eds) Origins and development of schizophrenia. American Psychological Association, Washington DC, pp 185–210

Manoach DS, Lindgren KA, Cherkasova MV, Goff DC, Halpern EF, Intriligator J, Barton JJS (2002) Schizophrenic subjects show deficient inhibition but intact task-switching on saccadic tasks. Biol Psychiatry 51:816–825

McDowell JE, Myles-Worsley M, Coon H, Byerley W, Clementz BA (1999) Measuring liability for schizophrenia using optimized antisaccade stimulus parameters. Psychophysiology 36:138–141

McDowell JE, Brown GG, Paulus M, Martinez A, Stewart SE, Dubowitz DJ, Braff DL (2002) Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. Biol Psychiatry 51:216–223

Muller N, Riedel M, Eggert T, Straube A (1999) Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part II. Saccadic latency, gain, and fixation suppression errors. Eur Arch Psychiatry Clin Neurosci 249:7–14

Munoz DP, Dorris MC, Pare M, Everling S (2000) On your mark, get set: brainstem circuitry underlying saccadic initiation. Can J Physiol Pharmacol 78:934–944

Nakashima Y, Momose T, Sano I, Katayama S, Nakajima T, Niwa S, Matsushita M (1994) Cortical control of saccade in normal and schizophrenic subjects: a PET study using a task-evoked rCBF paradigm. Schizophr Res 12:259–264

O’Driscoll GA, Lenzenweger MF, Holzman PS (1998) Antisaccades and smooth pursuit eye tracking and schizotypy. Arch Gen Psychiatry 55:837–843

Raemaekers M, Jansma J, Cahn W, Van der Geest J, van der Linden J, Kahn R, Ramsey N (2002) Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch Gen Psychiatry 59:313–320

Schwartz B, Winstead D (1988) Visible persistence in paranoid schizophrenics. Biol Psychiatry 23:3–12

Schwartz B, Wiknstead D, Adinoff B (1983) Temporal integration deficit in visual information processing by chronic schizophrenics. Biol Psychiatry 18:1311–1320

Schwartz B, Tomlin H, Evans W, Ross K (2001) Neurophysiologic mechanisms of attention: a selective review of early information processing in schizophrenics. Front Biosci 6:d120–d134

Smit A, van Gisbergen J (1989) A short-latency transition insaccade dynamics during square-wave tracking and its significance for the differentiation of visually guided and predictive saccades. Exp Brain Res 76:64–74

Sparks DL, Hartwich-Young (1989) The deep layers of the superior colliculus. In: Wurtz RH, Goldberg ME (eds) The neurobiology of saccadic eye movements. Elsevier Science, Amsterdam, pp 213–256

Straube A, Riedel M, Eggert T, Muller N (1999) Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part I. Saccadic velocity. Eur Arch Psychiatry Clin Neurosci 249:1–6

Sweeney J, Bauer K, Keshavan M, Haas G, Schooler N, Kroboth P (1997) Adverse effects of risperidone on eye movement activity: a comparison of risperidone and haloperidol in antipsychotic-naive schizophrenic patients. Neuropsychopharmacology 16:217–228

van Gelder P, Lebedev S, Tsui WH (1997) Peak velocities of visual and nonvisually guided saccades in smooth-pursuit and saccadic tasks. Exp Brain Res 116:201–215

White K, Ashton R (1976) Handedness assessment inventory. Neuropsychologia 14:261–264