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Role of Anticipation in Schizophrenia-Related Pursuit Initiation Deficits

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Avila, Matthew T., L. Elliot Hong, Amanda Moates, Kathleen A. Turano, and Guntav K. Thaker. Role of anticipation in schizophrenia-related pursuit initiation deficits. *J Neurophysiol* 95: 593–601, 2006. First published November 2, 2005; doi:10.1152/jn.00369.2005. Schizophrenia patients exhibit several smooth pursuit abnormalities including poor pursuit initiation. Velocity discrimination is also impaired and is correlated with pursuit initiation performance—suggesting that pursuit deficits are related to impairments in processing velocity information. Studies suggest that pursuit initiation is influenced by prior target motion information and/or expectations and that this is likely caused by expectation-based changes in the perceptual inputs to the pursuit system. We examined whether poor pursuit initiation in schizophrenia results from inaccurate encoding of immediate velocity signals, or whether these deficits reflect a failure to use prior target motion information to “optimize” the response. Twenty-eight patients and 24 controls performed an adapted version of a “remembered pursuit task.” Trials consisted of a series of target motions, the first of which occurred unexpectedly, followed by four to seven identical targets each preceded by an auditory cue and a “catch target” in which a cue was given followed by target extinction. Initiation eye velocity in response to unexpected, first targets was similar in the patient and control groups. In contrast, patients showed lower eye velocity in response to repeated, cued targets compared with controls. Patients also showed reduced eye velocity in response to catch targets. Reduction in pursuit latency across repeated targets was less robust in patients. Results suggest that processing of immediate velocity information is unaffected in schizophrenia and that pursuit initiation deficits reflect an inability to accurately generate, store, and/or access “remembered” velocity signals.

INTRODUCTION

Smooth pursuit eye movements are an important means by which humans interact visually with their environment. They allow us to maintain the image of a moving object of interest on the fovea so that it can be analyzed with a high degree of accuracy. Significant progress has been made in characterizing how the CNS accomplishes this complex behavior. In turn, theoretical and experimental advances in the basic visual neurosciences have given clinical investigators powerful tools with which to study disease-related abnormalities in oculomotor behavior and visual motion processing. Here we describe the results of experiments, adapted from the work of Barnes (Barnes and Donelan 1999; Barnes et al. 2000) and others (e.g., Kowler et al. 1984; Krauzlis and Adler 2001; Takagi et al.

2000), showing that the abnormalities in smooth pursuit initiation seen in patients with schizophrenia involve a deficit in the anticipatory component of motion processing.

Converging lines of evidence suggest that the neural circuits responsible for processing motion provide the primary inputs needed to execute an oculomotor response to a moving stimulus (Ilg 2002). Earlier studies extensively characterized the initiation of the smooth pursuit eye movement response in primates (Keller and Khan 1986; Krauzlis and Lisberger 1994). Neurons in the mediotemporal (MT) cortex encode retinal motion information critical to the initiation response. MT neurons show selectivity for both the direction and speed of target motion (Lisberger et al. 1987). Lesions in area MT cause deficits in pursuit initiation but do not seem to affect steady-state pursuit (Newsome et al. 1985). Similarly, microstimulation of these neurons alters the speed and direction of the pursuit response 20–60 ms after the onset of target motion; the effect lasts ~100 ms (Groh et al. 1997).

Although pursuit initiation is considered an “open-loop” response in that it is not influenced by immediate feedback (Lisberger et al. 1987), there is growing evidence that retinal motion processing and the corresponding oculomotor response can be influenced by prior motion information leading to adaptive changes under conditions of predictable target motion (see Barnes and Schmid 2002 for a review). Several investigators have shown adaptive change in initial eye acceleration and velocity consistent with the subject’s expectations based on their previous experience (Kahlon and Lisberger 1996; Krauzlis and Adler 2001; Takagi et al. 2000). Barnes and colleagues have observed a similar phenomenon using a “remembered pursuit task.” Human volunteers were presented with a series of repeated sinusoid target motions, the first of which occurred unexpectedly in the absence of a cue; subsequent targets were preceded by an auditory cue with a predictable premotion time interval (see METHODS). Under these conditions, significant reductions in response latency and increases in initial eye velocity were evident as early as the second target presentation in a series; subsequent changes in performance tended to be modest, with most subjects achieving peak performance within three target presentations (Barnes et al. 2000). Barnes et al. and others have suggested that these anticipatory pursuit eye movements are based on the short-term storage and timed release of a velocity-coded premotor drive (Barnes and

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Donelan 1999), the neural origins of which likely involve frontal eye fields (FEFs), supplementary eye fields (SEFs), striatum, medio-superior temporal cortical neurons (MSTs) (Ilg 2003), and perhaps dorso-lateral prefrontal cortex (Barnes et al. 1995, 2000; Ono et al. 2005) and ventrolateral thalamus (Tanaka 2005). This is supported by both neurophysiological studies in monkeys and human imaging studies (Heinen 1995; Hong et al. 2005; Keating 1991; Lencer et al. 2004; Newsome and Pare 1988; Schmid et al. 2001; Tanaka and Fukushima 1998). Human subjects with known lesions in these regions show smooth pursuit deficits particularly in predictive pursuit (Braun et al. 1996; Heide et al. 1996; Lekwuwa and Barnes 1996; Rivaud et al. 1994).

The purpose of this study was to determine if a similar phenomenon can explain previous reports of reduced open-loop acceleration among individuals with schizophrenia. Schizophrenia patients exhibit a number of pursuit abnormalities including reduced steady-state or closed-loop gain (e.g., Levy et al. 2000; Sweeney et al. 1999), which is thought to reflect problems with the predictive component of sustained visual tracking (Thaker et al. 1999, 2003), and an increase in intrusive saccades, particular anticipatory saccades, (Avila et al. 2002; Ross et al. 2000), which may reflect a loss of cortical inhibitory control over saccades during pursuit (Avila et al. 2003). Interestingly, there are aspects of the pursuit system that are not affected in schizophrenia. Patients are able to inhibit the optokinetic reflex during smooth pursuit (Hutton et al. 2000) and make equally accurate saccades to a moving target during initiation as normal control subjects (Clementz 1996; Thaker et al. 1996).

In addition, a number of studies have found that schizophrenia patients show lower open-loop eye velocity and acceleration compared with healthy individuals (Clementz and McDowell 1994; Clementz et al. 1995; Farber et al. 1997; Hong et al. 2003; Radant et al. 1997; Ross et al. 1996; Sweeney et al. 1998). Thus far, studies of open-loop impairments in schizophrenia have been primarily descriptive, and hypotheses regarding its cause(s) have been general—suggesting only that a problem exists in the cortical circuitry responsible for processing motion [e.g., MT, MST, posterior parietal cortex (PPC), and FEFs]. However, Chen et al. (1999a) have shown that schizophrenia patients have higher speed discrimination thresholds compared with healthy controls at intermediate base speeds suggesting an impairment that is specific to the processing of velocity-based signals. They have also shown that this motion perception deficit is significantly correlated with open-loop acceleration in patients. In addition, shifts of visual attention may play an important role in initiation and may partly explain the observed differences in smooth pursuit initiation between schizophrenia and control subjects (Knox et al. 1999).

Thus it is possible that impaired pursuit initiation results from inaccurate encoding of velocity signals implicating primarily cortical regions MT and MST. Some investigators have argued against this explanation based on studies showing that patients produce accurate saccades to moving targets during initiation (Clementz 1996; Kim et al. 1997; Sweeney et al. 1999). Alternatively, the problem could involve the adaptive control of the initiation response based on short-term storage of velocity information, which might involve MT and MST and/or frontal cortical areas such as the FEFs, SEFs, and PFC.

In this case, increased speed discrimination thresholds would reflect difficulty holding velocity information “on-line” to make a comparative perceptual judgment for sequentially presented targets. Similarly, anticipatory responding may contribute to the open-loop response in step-ramp target paradigms, which have been the primary means of examining pursuit initiation in schizophrenia. The duration of pretrial fixation is typically varied only within a small range (≤ 1 s), and although speed and target direction are usually varied, the step-size is fixed such that the target crosses 0° after some constant duration—raising the possibility that over repeated trials, the step-size could become a cue for the speed of subsequent target motion.

In this study, we adapted the “remembered pursuit task” developed by Barnes et al. (2000), adding intertrial random step sequences to further reduce anticipation to initial targets, and tested a group of patients with schizophrenia and a group of healthy controls (Barnes et al. 2000). We hypothesized that in response to uncued first targets (where the contribution of anticipatory pursuit is minimal), patients and controls would exhibit similar response latencies and initial eye velocities; however, we expected patients to perform poorly compared with controls in response to repeated targets (i.e., where anticipation plays a more prominent role).

METHODS

Research participants

Twenty-eight patients with schizophrenia (24 males) were recruited from inpatient and outpatient programs at the Maryland Psychiatric Research Center (MPRC). The diagnosis of schizophrenia was confirmed using the Structured Clinical Interview for DSM-IV diagnosis (SCID-IV) (First et al. 1997). Twenty-four healthy controls (15 males) were recruited from the greater Baltimore-Washington area using newspaper advertisements. All subjects signed an informed consent after an explanation of the study procedures and risks. The study was approved by the University of Maryland Institutional Review Committee. The SCID-IV, Structured Interview for DSM-IV Personality Disorders (SID-P) (Pfohl et al. 1989), and Family History Research Diagnostic Criteria (FH-RDC) (Andreasen et al. 1986) were used to screen and exclude community volunteers with a family history of psychotic illness, current or lifetime Axis-I or Axis-II disorders, or a history of substance abuse in the 6 months before the study. Clinical interviews were conducted by trained masters and doctoral level clinicians. Kappa (κ) interrater reliability estimates for these assessments were >0.85 . Patient and control groups did not differ in age (39 ± 11 vs. 41 ± 12 yr; $P > 0.05$), or racial makeup (white vs. African American vs. other in the 2 groups was 15:13:0 and 11:11:2, respectively; $P > 0.05$). All but three patients received antipsychotic medications—eight received olanzapine [21.0 ± 10.5 (SD) mg/d], nine received risperidone (3.9 ± 2.1 mg/d), seven received clozapine (461 ± 245 mg/d), and one was taking aripiprazole (15 mg/d). In addition, four patients receiving risperidone were also taking benztropine (1.5 ± 0.6 mg/d).

Laboratory procedures

OCULOMOTOR DATA ACQUISITION. Eye movements were recorded using infrared oculography (Applied Sciences Model 210 Eye-Tracker) at a sampling rate of 330 Hz. Analog data were digitized using a 16-bit analog to digital converter and stored for off-line analysis. Visual stimuli were presented on a 43-cm VGA monitor (resolution of 640×480 with refresh rate of 60 Hz) positioned ~ 71

cm from the subject's eyes, for a screen size of 33.7°. The head was stabilized using a chin rest and head abutments. The target consisted of a crosshair positioned in a 0.25 × 0.25° box that was displayed with a target to background photometric contrast of 2.1 log units.

REMEMBERED PURSUIT TASK. The task was adapted from the remembered pursuit task described by Barnes et al. (2000). The target remained visible throughout the testing period. The first presentation consisted of an uncued target motion, followed by four to seven identical targets each preceded by an 80-ms audio cue (500-Hz sine wave audio tone at 63 decibels) and a "catch target" in which a cue was given followed by target extinction (a sample trial is depicted in Fig. 1, top). Trials were separated by a sequence of random left/right target steps lasting 10–25 s. This procedure was added to ensure that onset of the first, uncued target motion was unexpected. The target moved in a horizontal plane, rightward from the center position (0°) to 9.4° before returning to center. Two different target trajectories, one with a peak velocity of 30°/s (Pk30) and the other with a peak velocity of 20°/s (Pk20), were used (Fig. 1). The same target trajectory was repeated within a trial, but the presentation of the target trajectories were randomized across trials. Each trial lasted ~3–4.5 min. A brief rest period was given between testing blocks. During the Pk30 target trajectory, the target moved at 2.2°/s for the first 100 ms, and the velocity gradually increased in small steps (see Figs. 1 and 3). One target presentation (i.e., the target moving from the center to 9.4° to right and back) took 1.89 s. Target motion in the Pk20 target trajectory lasted 2.46 s, beginning at 2.2°/s velocity for the first 150 ms, followed by gradual increases (Figs. 1–3). Increases in the target velocity in both types of targets were in small steps in the beginning to avoid creating a large position error and eliciting a saccadic eye movement (Figs. 1 and 2). The time between the offset of the auditory cue and the onset of target motion was a constant 330 ms. However, the time interval between the end of a target motion and the subse-

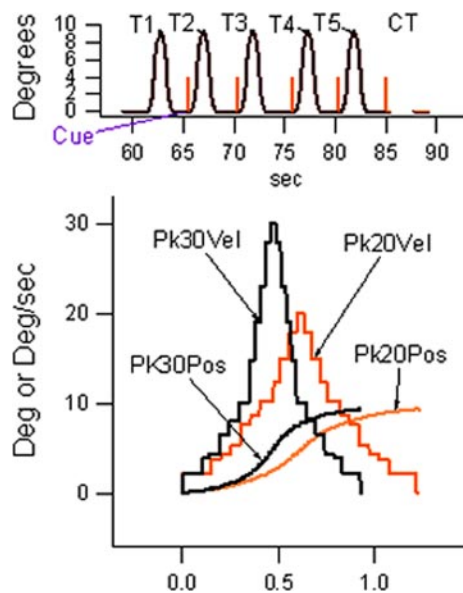


FIG. 1. Top: example of a trial from remembered pursuit task. First target presentation in a trial occurred unexpectedly after 10–25 s of random target steps. Each trial consisted of initial target presentation without a cue, followed by 4–7 repetitions of the same target each preceded by an auditory cue 330 ms before target motion onset. Number of repeated targets was varied to elicit catch target responses, although all trials had ≥4 repetitions (labeled T2–T5). Catch target (CT) presentation, 330 ms after an auditory cue, is denoted by a gap in the target line, in this example occurring after 5 target presentations. Target trajectory was varied across trials to present 2 different target types: 1 with peak velocity 20°/s and the other 30°/s. Target trajectory was from center to right 9.4° for both target types. Bottom: position (Pk20Pos and Pk30Pos) and velocity (Pk20Vel and Pk30Vel).

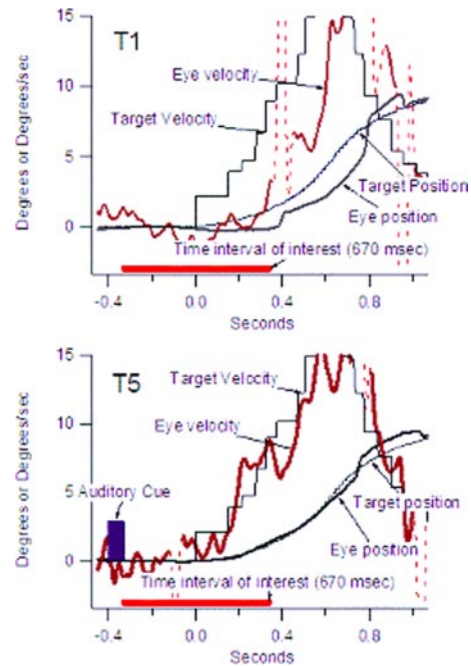


FIG. 2. Response to T1 (top) and T5 (bottom) in a healthy subject for Pk20 target trajectory. There was a reduction of tracking error during T5 compared with T1. There were significantly more saccades during T1 than T5 in both groups. Saccades were removed and shown as dotted lines in the velocity tracing.

quent target's auditory cue was varied from 1 to 2.5 s in a pseudo-random fashion (200-ms intervals). Sixteen trials were presented in four blocks of four trials each.

REMEMBERED STEP TASK (CONTROL TASK). A control task was used in a subgroup of the participants (11 patients and 12 comparison subjects). The task was similar to the repeated pursuit task in all aspects except that 10° right target steps were presented instead of the target motion described above. Thus the first presentation consisted of an uncued right 10° target step, fixation at that location for a second, and a target step back to the center. This was followed by four to seven such target step presentations, each preceded by an 80-ms audio cue and a "catch target" in which a cue was given followed by target extinction. Trials were separated by a sequence of random left/right target steps lasting 10–25 s.

Statistical analyses

EYE MOVEMENT ANALYSIS. Linear eye position data were filtered using a 75-Hz low-pass filter (Aqcknowledge). Eye position data were differentiated to obtain velocity and acceleration data (Igor, Wave-metrics). Eye position was calibrated before each trial using flanking target steps of 10° left and right of center. Before analysis, saccades were identified based on velocity (>35°/s) and acceleration (>600°/s²) criteria and removed. The onset of pursuit initiation was identified using eye velocity data filtered by a 20-Hz low-pass filter (finite impulse response filter; transition band = 20–30 Hz; attenuation in reject band = 80 dB). Before application of the 20-Hz low-pass filter, saccades were replaced in the eye velocity waveform using linear interpolation. Pursuit in the direction of target motion was detected in the velocity waveform using a 3°/s threshold criterion. From this point, the algorithm searched for the last preceding point at which eye velocity was equal to zero. The algorithm sought a trained scorer's approval before proceeding, and the scorer was able to overrule the algorithm's identification of the beginning of pursuit. This time-point was marked as the onset of pursuit and was used to calculate pursuit latency. Similar to Barnes et al. (2000), we analyzed initial eye

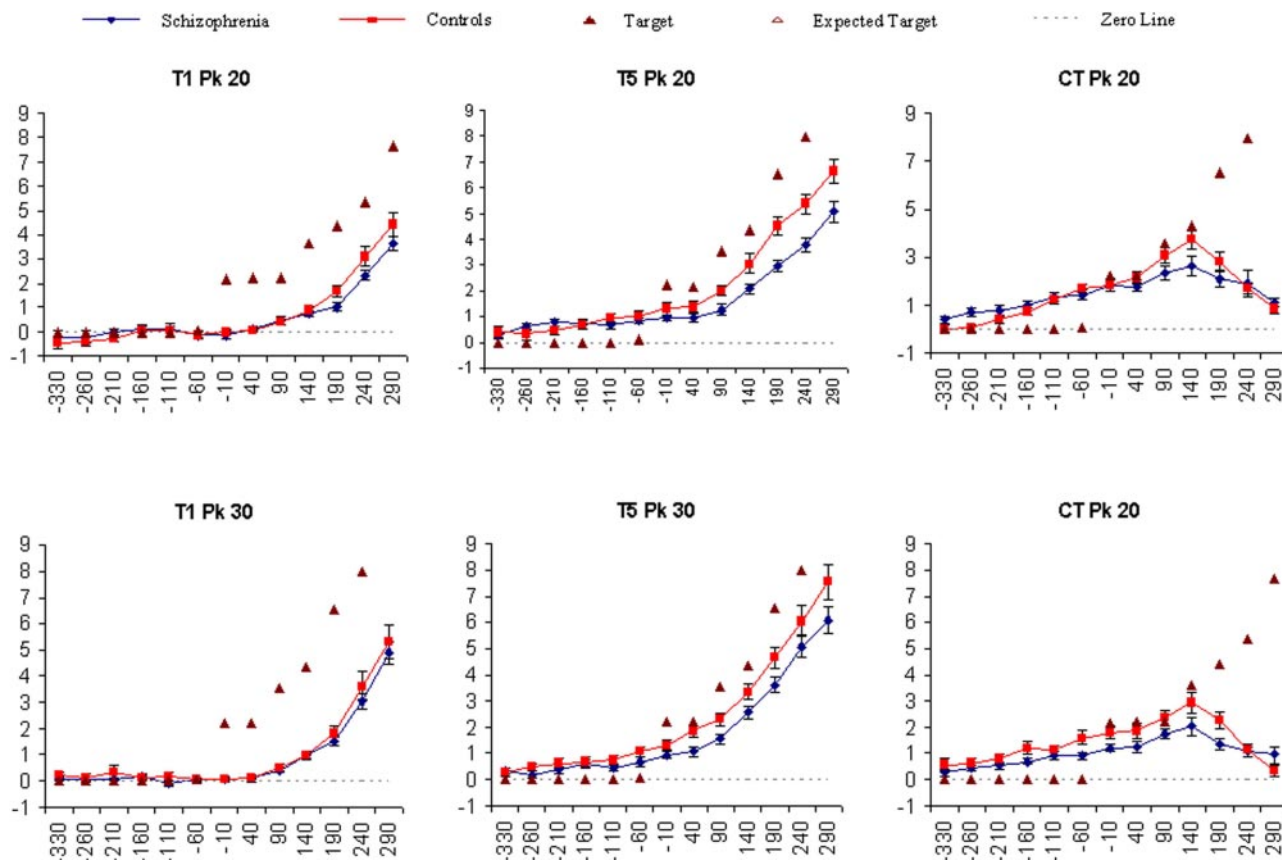


FIG. 3. Patient and control responses to the 1st, uncued target in the series (T1), cued 5th target (T5), and cued catch target (CT). Each graph shows average eye velocity (\pm SE) for 13 intervals of 50 ms each (except the 1st, which was 70 ms). These spanned the period 330 ms before target motion onset to \leq 340 ms after target motion onset. *Top*: results for Pk20 target trials. *Bottom*: results for Pk30 target trials. Note that the target was not visible during CT and the open triangles in the 2 rightmost panels are showing mean expected target velocities. There were no significant differences between the 2 groups during T1; the 2 groups differed in responses during T5 and CT.

velocity in 50-ms intervals starting with the offset of the auditory cue and continuing \leq 340 ms after target motion onset. Similar procedures were used to identify the onset and latency of pursuit responses to catch targets. The percentage of catch targets in which a pursuit response was observed was calculated. Duration of the pursuit response was also calculated from pursuit onset to the point at which eye velocity returned to zero.

ANALYSIS OF GROUPS AND TIME INTERVALS. Comparisons of mean eye velocity were carried out using mixed design ANOVA with subject group (patients vs. controls) entered as a between-subjects factor and interval entered as a within-subjects factor. A Greenhouse-Geisser correction was applied to tests of models where the assumption of sphericity was violated. Analysis of simple effects was used to compare group performance within individual intervals after significant group or group by interval interaction effects (Levine 1991). Target velocity conditions were analyzed separately. Latency was compared using mixed design ANOVAs with group entered as a between-subjects factor and target sequence entered as a within-subjects factor [all trials contained \geq 5 targets in a sequence: an uncued first target (T1) and 4 cued, repeated targets (T2–T5)]. ANOVAs were used to compare the number of pursuit responses to catch targets and the latency and duration of the response.

RESULTS

Pursuit initiation eye velocity

UNEXPECTED TARGETS (T1). Statistical comparisons of mean eye velocity for patients and controls in response to the first,

uncued target (T1) showed no significant effects of group or group by interval interactions in either target speed condition (F -statistics for the effect of group in the Pk20 and Pk30 conditions were $F_{(1,50)} < 1.00$, $P = 0.44$ and $F_{(1,50)} = 1.39$, $P = 0.24$, respectively; tests of the interaction terms were $F_{(12,600)} = 1.92$, $P = 0.12$ and $F_{(12,600)} < 1.00$, $P = 0.68$). Figure 3 shows average eye velocities for intervals 330 ms before onset of target motion to \leq 340 ms after the onset of target motion in the two groups. From the figures, it is clear that patients and controls performed similarly in response to unexpected target motion.

REPEATED TARGETS. In contrast, analysis of eye velocity in response to the second target (T2) revealed significant main effects of group and group by interval interactions for Pk20 and Pk30 trials ($F_{(12,600)} = 3.91$, $P = 0.007$ and $F_{(12,600)} = 3.77$, $P = 0.03$, respectively). In the Pk20 condition, patients exhibited significantly lower eye velocities in intervals that included the time period—10–290 ms after the target motion onset. In the Pk30 condition, significant differences were observed for 140–290 ms after target motion onset; intervals –10 to 40 and 290–340 ms yielded marginally nonsignificant differences ($P = 0.085$ and 0.059 , respectively).

Patient control differences in eye velocity continued to persist after additional target presentations. Recall that the number of repeated targets varied from four to seven; thus all participants viewed at least four cued targets after the uncued

first target. Analysis of the last of these repeated targets, the fifth in the series (T5), yielded similar results to those obtained for T2. A main effect of group and a group by interval interaction was observed in the Pk20 condition ($F_{(1,50)} = 7.94$, $P = 0.007$ and $F_{(12,600)} = 5.86$, $P < 0.001$, respectively). For time intervals between 91 and 270 ms after the target motion onset, patients exhibited significantly lower eye velocities compared with controls ($P < 0.05$; the difference for interval 40–90 ms failed to reach statistical significance, $P = 0.09$). Simple effects analysis following a significant main effect of group ($F_{(1,50)} = 5.95$, $P = 0.02$) in the Pk30 condition yielded significant differences for intervals 41–240 ms after the target motion onset. Results for targets 3 and 4 (T3 and T4) in the series were similar to those reported for T2 and T5. For the sake of brevity and figure clarity, the data for these targets are not shown. Adaptation across repeated targets in both groups (i.e., improvement across repeated targets T1, T2, and T5) occurred; however, the initial adaptive response is more robust in healthy controls and comes to more closely approximate the expected target velocity after repeated target presentations.

Pursuit latency

Group by target (T1–T5) analysis of pursuit latency produced significant main effects of group and group by interval interactions for both target speed conditions ($F_{(4,200)} = 3.78$, $P = 0.005$ and $F_{(4,200)} = 2.58$, $P = 0.03$). Timing of the pursuit response became more anticipatory in both groups as evidenced by significant tests for the quadratic trend in each group ($P < 0.0005$). However, the magnitude of initial improvement was reduced in schizophrenia patients, and their performance failed to reach levels comparable with controls across repeated targets. This was confirmed by simple effects analysis of pursuit latency for targets T1–T5. In both target speed conditions, patients and controls exhibited similar T1 pursuit latencies ($P = 0.83$ and 0.14 for Pk20 and Pk30, respectively); however, patients had significantly longer T2, T3, T4, and T5 latencies compared with healthy controls ($P < 0.03$). These data are shown in Fig. 4.

Catch targets

For catch targets, we first compared the number of trials in which patients and healthy controls made a pursuit response. In both target speed conditions, the percentage of pursuit responses was significantly higher among controls (76 vs. 64% for Pk20 targets, $F_{(1,49)} = 5.15$, $P = 0.03$ and 82 vs. 70% for Pk30 targets, $F_{(1,48)} = 4.80$, $P = 0.03$). Analysis of pursuit latency and duration for catch targets where a response was observed showed no differences between patients and controls

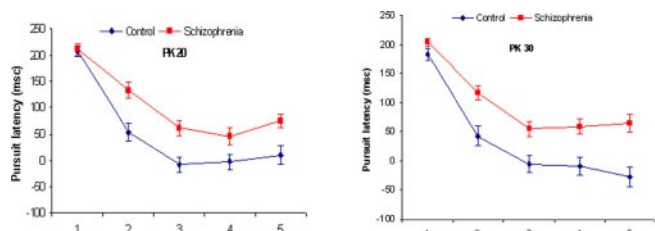


FIG. 4. Average pursuit latency (\pm SE) for the 1st 5 targets in the series (T1–T5). Bars depict SD above and below the mean. A and B: data for Pk20 and Pk30 conditions, respectively.

TABLE 1. Characteristics of catch target responses in patients and controls

Speed	Group	Percent Response	Response Latency, ms	Response Duration, ms
Pk20*	Patient	63 \pm 20%	-50 \pm 85	309 \pm 84
	Control	76 \pm 17%	-79 \pm 79	359 \pm 106
Pk30†	Patient	70 \pm 18%	-52 \pm 86	349 \pm 95
	Control	82 \pm 20%	-58 \pm 61	391 \pm 93

Values are mean \pm SD. *Inferential statistics for Pk20 percent response, latency, and duration were $F_{(1,49)} = 5.15$, $P = 0.03$, $F_{(1,49)} = 1.65$, $P = 0.21$, and $F_{(1,49)} = 3.39$, $P = 0.07$, respectively. †Inferential statistics for Pk30 percent response; latency, and duration were $F_{(1,49)} = 4.80$, $P = 0.03$, $F_{(1,49)} < 1.0$, $P = 0.78$, and $F_{(1,49)} = 2.58$, $P = 0.12$, respectively.

(Table 1). However, Fig. 3 shows that patients failed to achieve eye velocities comparable with healthy controls over the course of the response. Mixed design ANOVAs yielded significant group by interval interactions for both target speed conditions ($F_{(12,588)} = 2.25$, $P = 0.05$ and $F_{(12,576)} = 3.01$, $P < 0.03$). Simple effects analysis of individual intervals revealed significant differences for the periods -10 to 40 and 190–240 ms after the expected onset of target motion in the Pk20 target condition ($P < 0.05$) and a trend toward significance in the intermediate period ($P < 0.09$). Differences for individual intervals in the Pk30 condition did not achieve statistical significance ($P < 0.09$ for intervals 91–140 and 141–190 ms). The figure shows that the catch response was adapted to the expected target velocity in both groups but that this adaptation was less accurate within and across target speed conditions in schizophrenia patients.

Saccadic eye movements

There were significantly more saccades during T1 than T5 presentation; saccades during initiation (i.e., within -330 to 340 ms of target onset, the time interval of interest) occurred in 72 \pm 23% of first target presentations compared with only 47 \pm 26% of fifth target for 20°/s peak velocity targets (Fig. 5). Significantly more saccades occurred in trials with Pk30 velocity -76 \pm 24% for T1 and 54 \pm 27% for T5. These findings were confirmed by a repeated-measure ANOVA (target velocity and presentation as repeated, and subject group as between-

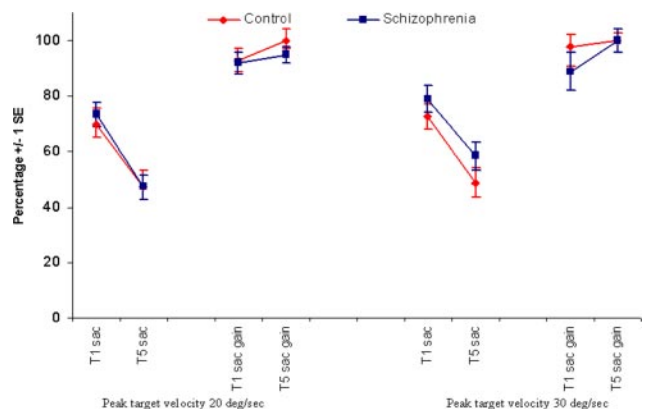


FIG. 5. Percentage of trials with saccades during initiation for T1 (T1 no sac) and T5 (T5 no sac). A larger proportion of trials showed saccades (72 \pm 23%) for T1 than for T5 (47 \pm 26%). However, these proportions were not different between groups. Saccadic gains were also similar between groups. Right panel gives the same data for Pk30 targets.

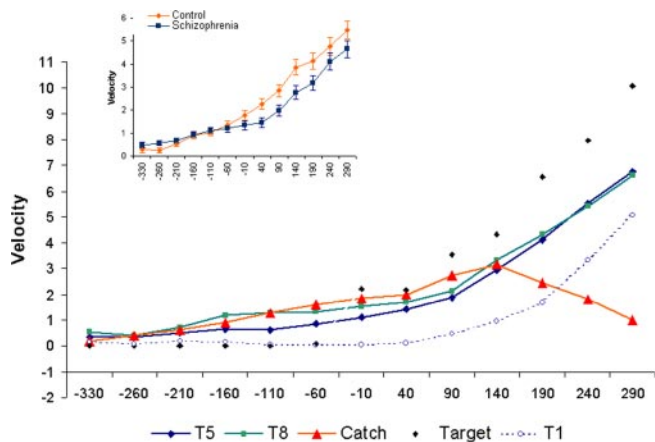


FIG. 6. Data from PK30 targets showing that subjects showed increased anticipation and were able to better match the target velocity for ~90 ms after expected target motion onset during T8 and catch targets than T5. Data from T1 were not used in this analysis but are plotted to show that most improvement occurred early. Healthy control subjects showed significantly higher average eye velocities collapsed across T5, T8, and catch targets than patients (inset).

subjects factor). There were main effects of target velocity ($F_{(1,50)} = 4.5, P < 0.05$) and target presentation ($F_{(1,50)} = 38.7, P < 0.001$). There were no other significant effects or main effect or interactions involving subject group ($P > 0.15$). Saccades were more accurate with the higher target velocity (saccadic gain = 1.0 ± 0.14) than with Pk20 target condition ($0.95 \pm 0.15; F_{(1,50)} = 7.4, P < 0.005$). Reanalyses of the smooth pursuit eye velocity data for T1 and T5 that included data only from target presentations without saccades did not change the original findings (these analyses were possible in 14 patients and 13 control subjects). For Pk20 and Pk30 T1 targets, there were significant effects of time interval ($P < 0.001$), but no group effects or group by interval interactions ($P > 0.25$). However for the T5 targets, there were significant

group by time interval interactions ($P < 0.01$); control subjects showed significantly higher eye velocity within 190- to 340-ms time intervals for Pk20 targets and within 140- to 290-ms time intervals for Pk30 targets than the patients (all $P < 0.05$).

Secondary exploratory analyses

As can be seen in Fig. 3, there appeared to be better performance during the first 90–140 ms of target onset in the catch target than in T5. This could be a cumulative learning effect of further repetitions of the target after T5. Note that all trials had a minimum of four repetitions, whereas some had five to seven repetitions of target presentation before the catch target. Analyses of data from T5, T8, and catch targets suggested that, for Pk30 targets, there was a significant target repetition by time interval interaction ($F_{(24,984)} = 42.6, P < 0.001$; see Fig. 6) and a significant diagnosis by time interval interaction ($F_{(12,984)} = 3.4, P < 0.01$; see Fig. 6, inset). Post hoc comparisons showed that both subject groups had significantly better performance in CT than T5 during the period -60 to 90 ms of target motion onset. Similar findings were observed for the Pk20 targets but only in healthy subjects. There was a significant group by target repetition by time interval interaction ($F_{(24,1008)} = 3.36, P < 0.005$). Healthy subjects, but not patients, showed significantly higher eye velocity in CT than T5 during time intervals between -10 and 90 ms of the expected target motion onset ($P \leq 0.05$).

There were no significant differences in performance among patients on risperidone, olanzapine, or clozapine. Similarly patients not receiving antipsychotic medications performed similarly compared with patients on antipsychotic medications (Fig. 7).

Repeated step task

There was a significant decrease in saccadic latencies in both patient and healthy control subjects on repeated target presen-

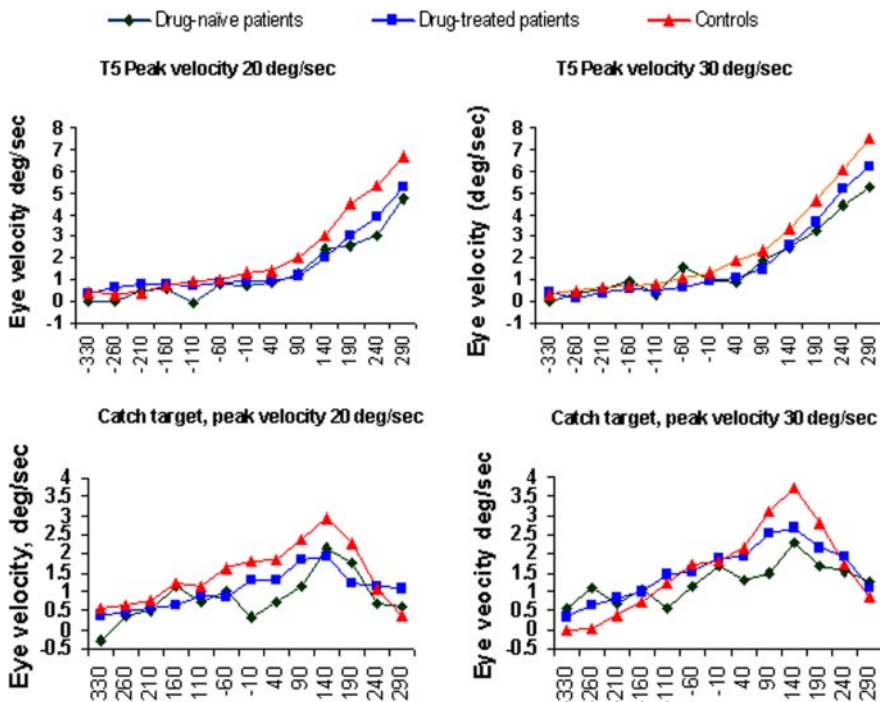


FIG. 7. Lower eye velocities on repeated target presentation (T5) and catch target in schizophrenia compared with healthy control subjects were not caused by medication effects. Patients never treated with antipsychotic medications also showed similar (or slightly lower) eye velocities as treated patients.

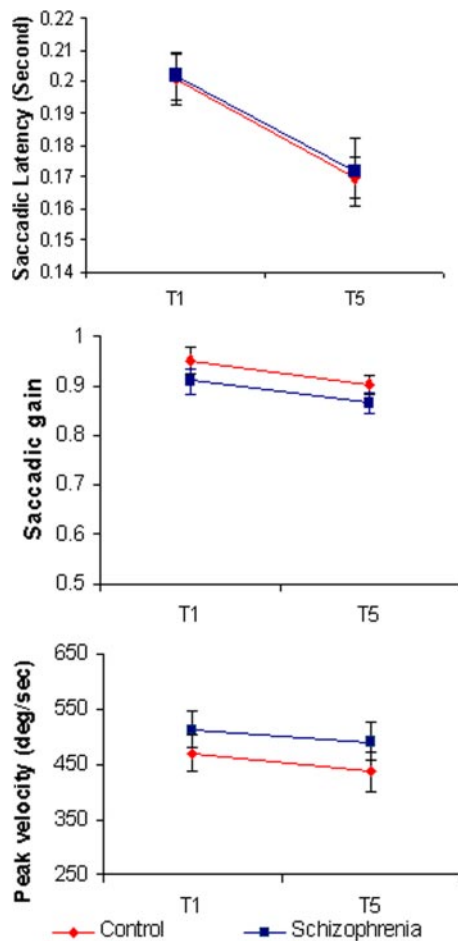


FIG. 8. There was a significant shortening in saccadic latencies in both patients and healthy control subjects from T1 to T5. However, there was a response latency by accuracy trade-off such that there was a significant decrease in saccadic accuracy (i.e., saccadic gain). Peak saccadic velocity also significantly decreased. There were no significant group effects or group by repeated presentation interactions on any of the measures.

tations (T1 vs. T5; $F_{(1,21)} = 33.2$, $P < 0.001$; Fig. 8). These effects were not different between groups (i.e., no group by repeat target presentation interaction, $P > 0.8$), and the two groups were also not different ($P > 0.7$). As one would have expected, there was a speed by accuracy trade-off in both groups such that the saccadic accuracy (i.e., gain) was less on repeated presentation ($F_{(1,21)} = 8.34$, $P < 0.01$; Fig. 8). As above, there was no significant group effect or group by repeated target presentation interaction ($P > 0.2$).

Similar findings were observed with the peak saccadic velocity after controlling for saccadic amplitude. There was a main effect of repeated presentation ($F_{(1,21)} = 4.8$, $P < 0.05$) but no significant group by repeated target presentation interaction or a group effect (Fig. 8).

DISCUSSION

A number of investigators have shown that predictable target motion leads to adaptive changes in pursuit latency and eye velocity during pursuit initiation (Barnes and Donelan 1999; Barnes et al. 2000; Kowler et al. 1984; Krauzlis and Adler 2001; Takagi et al. 2000). Therefore, although pursuit initiation can be considered an “open-loop” response in that it is not

influenced by immediate feedback, it does seem to be influenced by expectations based on previous target motion conditions. According to Barnes, this predictive or anticipatory component is based on the short-term storage and timed release of a velocity-coded premotor drive (Barnes and Donelan 1999). In this study, we tested the hypothesis that schizophrenia-related pursuit initiation deficits reflect an inability to accurately generate, store, and/or access these “remembered” velocity signals. This was done by comparing pursuit eye movements where the speed and timing of target motion were unexpected to responses in which these parameters were predictable.

Similar to previous reports, we observed increases in eye velocity and decreases in pursuit latency among healthy volunteers in response to expected target motion such that the average response came to more accurately reflect the speed and timing of target motion over repeated presentations. Consistent with what Barnes et al. (2000) have reported previously, changes in eye velocity seemed to be “tuned” specifically to the expected target speed. This is shown most clearly in Fig. 3 for catch target responses. Note that the peak average eye velocity (220 ms after expected target motion) approximated the expected target speed—i.e., was tuned to the appropriate target speed based on the specific condition (Fig. 3, Pk20 in the *top panel* and Pk30 in the *bottom panel*).

Consistent with our hypothesis, when the pursuit response was based primarily on immediate visual information, as was the case for T1 targets, no significant differences were observed between patients and controls. In contrast to the pattern of results observed in controls, schizophrenia patients showed only modest improvements in initiation over repeated targets (see Fig. 3). Figure 3 shows that, although patients were able to generate a predictive open-loop response, the average eye velocity was significantly lower than that of controls—falling short of the expected target speed.

A similar pattern of results was observed for pursuit latency. In response to unexpected targets (T1), patients and controls generated a pursuit response ~ 200 ms after target motion onset. In response to repeated targets (T2–T5), patients and controls exhibited shortened latencies; however, this improvement was more marked among control subjects (see Fig. 3). The differential effects of repeated and cued target presentations on the two groups cannot be attributed to the differential processing of the auditory cue. This is because the effects of the cue during the repeated target presentations in the control tasks were similar between groups.

Our results expand on previous studies of pursuit initiation in schizophrenia by suggesting what specific aspects of visual motion processing are likely to be affected by the disease and what brain regions are likely to be involved. Our results show that when the contribution of prediction/anticipation to the pursuit response is minimized, patients do not show deficits in initiation performance. However, when the response is based, in part, on previous target motion information, schizophrenia patients perform significantly worse than healthy individuals. This suggests that schizophrenia-related pursuit initiation deficits are not caused by errors in the processing of immediate retinal velocity signals and are therefore not likely to involve MT lesions (Newsome and Pare 1988). Instead, higher cortical areas such as FEFs, SEFs, PPC, and perhaps PFC that appear to modulate retinal motion signals and the corresponding

oculomotor response (Assad and Maunsell 1995; Haarmeier et al. 1997; Heinen 1995; Keating 1991; Tanaka and Fukushima 1998) should be considered as likely candidates for the location of disease-related abnormalities. This is consistent with the results of brain imaging studies that have reported reduced FEF activation during closed loop pursuit in patients with schizophrenia and in relatives of affected probands with poor closed loop gain (O'Driscoll et al. 1999; Ross et al. 1995; Tregellas et al. 2004). We also observed significant reductions in brain activation in these regions when patients are following a predictable target (Hong et al. 2005). It is interesting to note that previous target masking experiments in our laboratory have suggested that deficits in sustained visual tracking (closed loop) also involve predictive components of the pursuit response (Thaker et al. 1998, 1999, 2003)—raising the possibility that both open- and closed-loop impairments have a similar or even a common cause.

Nonspecific deficits and medication effects

Schizophrenia can be associated with attentional impairments and low motivation (Brown and Pluck 2000; Cornblatt and Malhotra 2001). Results are not likely caused by nonspecific or generalized deficits in motivation or attention because the percentage of catch targets in which a pursuit response occurred, although somewhat less than for controls, was still substantial—64 and 70% for Pk20 and Pk30 target trials, respectively. In addition, average duration of catch target responses was similar in the patient and control groups (Table 1), as was the time-course to peak eye velocity (Fig. 5). The fact that patients performed similarly to controls under unexpected target conditions also argues against the presence of motivational and/or attentional confounds. The observed deficits are also not likely to be caused by the effects of antipsychotic medications or overt psychotic symptoms. Previous studies have found that abnormalities in smooth pursuit initiation, maintenance, and predictive pursuit are independent of antipsychotic medication and occur in at-risk individuals or patients with recent onset illness never treated with these drugs (e.g., Chen et al. 1999b; Clementz and McDowell 1994; Clementz et al. 1995; Thaker et al. 1998, 1999). In addition, pursuit deficits have been observed in neuroleptic-naïve, first-episode patients, who on 2-year follow-up continued to show deficits despite improvement in clinical state and the introduction of antipsychotic medication (Sweeney et al. 1998).

Implications and conclusions

Results of this study have a number of implications. Although a number of important studies have contributed to a basic description of pursuit initiation deficits in schizophrenia, ours is the first to show under what conditions this deficit is or is not present and what the likely mechanisms underlying the deficit are. Our results implicate a number of specific brain regions and are therefore important for future studies of schizophrenia pathophysiology. Many of the pursuit abnormalities observed among patients are present in a proportion of their unaffected relatives, suggesting that they are associated with genetic risk for the disease. A number of authors have suggested that pursuit measures can be used as alternative phenotypes in molecular genetic studies (Calkins and Iacono 2000;

Gottesman and Gould 2003). We argued that the success of this strategy depends on how accurately the measure of interest reflects the presence of a particular genetic variation and that the more specific a measure is to the underlying biological mechanism the more likely this is to be the case (Avila et al. 2002). Thus our results are very important to ongoing efforts to identify genetic risk factors for the disease.

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