ORIGINAL ARTICLE

Smooth Pursuit Eye Movements to Extraretinal Motion Signals

Deficits in Relatives of Patients With Schizophrenia

Gunvant K. Thaker, MD; David E. Ross, MD; Shawn L. Cassady, MD; Helene M. Adami, MSW; David LaPorte, PhD; Deborah R. Medoff, PhD; Adrienne Lahti, MD

Background: Although mounting evidence supports the idea that smooth pursuit abnormality marks the genetic liability to schizophrenia, the precise ocular motor mechanism underlying the abnormality remains unknown. Based on recent findings in schizophrenia, we hypothesize that subtle deficits in the ability to hold online and/or use extraretinal motion information underlie the pursuit abnormality in vulnerable individuals.

Methods: The hypothesis was tested in 69 first-degree, biological relatives of probands with schizophrenia; 26 relatives had schizophrenia spectrum personalities (SSP). Subjects recruited from the community (n=71; 29 with SSP), without a known family history of psychosis, constituted the comparison groups. The traditional smooth pursuit gain measure, which is a ratio of smooth pursuit eye velocity in response to both retinal and extraretinal motion signals and the target velocity, was obtained. In addition, newly developed measures of predictive smooth pursuit (ie, in the presence of only extraretinal motion signals) were obtained. The latter measures were evaluated after the current retinal motion signals were made unavailable by briefly making the target invisible.

Results: Relatives, particularly those with SSP, showed significantly poorer predictive pursuit response to extraretinal motion signals ($F_{2,130}$=6.51, $P<.005$), compared with the community subjects. However, the traditional smooth pursuit gain in response to both retinal and extraretinal motion signals was not different between groups.

Conclusions: These results suggest that relatives of patients with schizophrenia, particularly those with SSP, have specific deficits in predictive pursuit based on only extraretinal motion signals. Normal smooth pursuit gain in response to both retinal and extraretinal motion signals is likely due to compensation based on retinal motion information. The latter suggests normal retinal motion processing and smooth pursuit motor output.

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From the Maryland Psychiatric Research Center, Baltimore (Drs Thaker, Ross, Cassady, Medoff, and Lahti and Ms Adami), and the Department of Psychology, Indiana University of Pennsylvania, Indiana (Dr LaPorte).

A WEALTH of evidence, including a preliminary report of linkage of the pursuit abnormality to chromosome 6p21 in relatives of patients with schizophrenia, suggests that the smooth pursuit defect marks the genetic liability to schizophrenia.[1,2] Despite these rich data, fundamental aspects of smooth pursuit function remain unexamined in these disorders. Toward this goal of determining the precise mechanism underlying the abnormality, individual components of smooth pursuit need to be evaluated. The smooth pursuit system, which is dependent on motion information to generate smooth eye movements, initiates smooth pursuit based on the slippage of the image of the target on the retina (henceforth called *retinal motion*). Once the moving image is captured onto the fovea and the eye approximates the target motion, smooth pursuit is maintained mostly on the basis of information from sources other than the retina.[3] There are potentially 2 sources of extraretinal motion information—the memory of the motor command (so-called efference copy) and the memory of previous retinal motion.[3-5]

Evidence suggests that subjects with schizophrenia spectrum disorders have deficits in generating smooth pursuit in response to extraretinal motion signals. This hypothesis is based on the findings of poor smooth pursuit during pursuit maintenance, a phase when extraretinal motion signals play a major role in driving the system. Patients with schizophrenia show poor response to extraretinal motion.[6,7] We hypothesized that a similar deficit in predictive pursuit (ie, in response to only extraretinal motion signals) would occur in their relatives. Since most studies,[8-10] but not all,[11] noted an association between schizophrenia spectrum personality (SSP) symptoms and abnormalities in smooth pursuit eye movements, we further hypothesized that the deficit would occur mostly in relatives with SSP symptoms. Be-

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SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited from first-degree, biological relatives of 54 patients with *DSM-III-R*–defined schizophrenia,[19] and from the community; none had participated in a previous study.[8] The community subjects were recruited by newspaper advertisements. Some of the advertisements listed schizotypal symptoms,[8] one half of which listed only negative symptoms. Subjects responding to the advertisements were screened using a 15-minute telephone interview, and eligible subjects were invited for participation.

All subjects gave informed written consent. Subjects were paid $10 an hour. The Structured Clinical Interview for *DSM-III-R* (SCID)[20] and Structured Interview for *DSM-III-R* Personality Disorders (SIDP-R)[21] were administered. Questions probing magical thinking and perceptual distortions from the Structured Interview for Schizotypy,[22] and deficit symptoms from the Schedule for the Deficit Syndrome[23] were added to the SIDP-R. Community subjects had no known family history of psychosis as confirmed by a family history interview (Family History Research Diagnostic Criteria).[24] The interrater reliabilities were above 0.81 (κ) on these instruments. All available information was reviewed in a diagnostic meeting to reach *DSM-III-R* Axis I diagnoses. In addition, subjects were assigned to SSP groups if they had 3 or more paranoid, 3 or more schizoid, or 4 or more schizotypal traits (ie, 1 less than necessary to meet the *DSM-III-R* criteria of these personality disorders). This threshold for SSP was lowered to match the study design of a previous study,[8] and to increase the sensitivity of the instrument to identify affected individuals. This would generally reduce the specificity, which was not a concern because the experimental group was recruited from the relatives in whom even mild symptoms are likely to be related to schizophrenia. Relatives and subjects responding to the advertisements for normal subjects were assigned to the non-SSP groups if they had less than the threshold number of SSP symptoms. Individuals without SSP symptoms but with other personality disorders were excluded.

Participants with current or lifetime Axis I diagnosis (except those with a single, past episode of major depression that did not require biological treatment, or those with a history of substance abuse ending at least 6 months before the study) were excluded in the studies. Random drug screens were performed. Individuals with neuro-ophthalmological conditions and neurological disorders were excluded. None took prescriptions or over-the-counter drugs other than multivitamins and analgesics (eg, aspirin).

Subjects were divided into the following 4 subgroups: community subjects with SSP (n=29) and without SSP (n=42); and relatives with SSP (n=26) and without SSP (n=43). Clinical and demographic information on these groups is given in **Table 1**. The respective age range and 25th, 50th, and 75th percentile ages in years were as follows: 18-48, 31.7, 35, and 43.2 in the SSP relatives; 18-50, 27, 35, and 40 in the non-SSP relatives; 20-51, 25.5, 30, and 39.5 in the community subjects with SSP; and 20-48, 27, 33.5, and 43 in the community subjects without SSP.

LABORATORY PROCEDURES

Ramp-Mask-Ramp Task

A fovea-petal step-ramp with unpredictable onset was presented, followed by 3 to 4 cycles (±12°) of triangular waveform target motion. In this task, a target moved smoothly at a constant velocity, back and forth between 2 extreme points of 12° to the left and right of the center of the visual field. The excursion of the target at a constant velocity from one extreme to another (henceforth called "ramp") constitutes a half-cycle and after 4 to 6 such half cycles, the target was unpredictably blanked out (masked) for 500 milliseconds. The subjects were instructed to "... follow the target as it moves. Occasionally, the target will become invisible for very brief periods. During these periods the target will keep on moving, so continue moving your eyes to follow the invisible but moving target." One half of the trials had the mask at the beginning of a ramp and in the other half of the trials, the mask varied sometime during the ramp. Three constant target velocities of 9.4°, 14.0°, and 18.7° per second were presented for trials with the mask during the ramp, and 14.0° and 18.7° per second for trials with the mask at the beginning of the ramp. A total of 25 trials were presented in 2 blocks of 12 and 13 trials each.

Continued on next page

cause subjects with SSP are known to have subtle cognitive impairments[12] that can affect smooth pursuit performance, independent of a family history of schizophrenia, the present study recruited individuals with SSP without a known family history of psychosis as a comparison group. In this context, note that cases of SSP when encountered in the community are likely to be heterogeneous in their origins and not necessarily related to schizophrenia.[13-18]

RESULTS

CLINICAL AND DEMOGRAPHIC VARIABLES

Table 1 shows mean values for clinical and demographic variables. The 4 groups were not different in their mean age and female-male ratio. The 2 SSP groups had significantly worse socioeconomic status[27] scores than the 2 non-SSP subject groups ($F_{1,136}$=13.58, P<.001) Community subjects with SSP had significantly more schizotypal symptoms and higher cognitive-perceptual dimensional scores than the relatives with SSP ($F_{1,54}$ >4.41, P<.05).

OCULOMOTOR MEASURES

Table 2 shows the measures of predictive pursuit in response to only extraretinal signs.

Closed-Loop Pursuit Gain

A main effect of target velocity on pursuit gain was found ($F_{2,135}$=23.56, P<.001); no other significant main effects or interactions were noted. In contrast, the root mean square error was significantly larger in the relatives than in the community subjects ($F_{1,136}$=4.19, P<.05).

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Analysis

Eye movement data were obtained using an infrared technique (sampling rate of 333 Hz with a time constant of 4 milliseconds) filtered at 75-Hz low-pass filter and converted to digital signals using 16-bit A-D converter.

Analysis of the eye movement data used interactive software. After saccades, blinks, and slow compensatory pursuit after rare anticipatory saccades were removed, 3 sets of eye movement measures were obtained: (1) Response when the target was visible: *Closed-loop gain* (ie, gain of pursuit in response to both retinal and extraretinal motion signals) was measured from the ramp that preceded the ramp with the mask. Gain was calculated by dividing mean eye velocity by target velocity. Root mean square error was obtained by first finding the position error (ie, eye minus target position in degrees) for each 3-millisecond datum point. These values were squared and then averaged for each trial. The square root of this mean value gave the mean square root value for each trial. (2) Response when the mask occurred at the beginning of the ramp: The latency of the change in direction of eye velocity from the time of the expected change in direction of the target was obtained. Absolute latency values were used because our interest was mainly in the timing of change, because all nonzero latency values indicate mistiming. *Change in direction latency* conceptually corresponds to the phase lag. We measured peak predictive eye velocity within the mask, in the direction of expected ramp. The corresponding gain (ie, *peak predictive gain*) was calculated by dividing the peak predictive eye velocity by the expected target speed. (3) Response when the mask occurred during the ramp: *Mean predictive pursuit gain* was obtained from 101 to 400 milliseconds of the mask. The last 2 measures were selected because in our pilot studies we found that (1) they are highly correlated with previous target velocity, explaining 40% to 72% of the variance; (2) each independently contributes to the variance in the traditional measure of smooth pursuit gain, and together they explain 80% to 82% variance in the pursuit gain in normal and schizophrenic patients; and (3) both significantly differentiate schizophrenic patients from normal subjects.[6]

As noted previously by other investigators,[25] when the mask occurred during the ramp, the eye would continue to move at the same velocity as before the mask for about 130 to 170 milliseconds (**Figure**), presumably still a closed-loop response. After this initial period, there was a 35% to 50% decline in the eye velocity. From this point backward, the algorithm identified the local "peak" eye velocity value by analyzing the smoothed first and second derivatives; this point in time is marked as a transition point from closed-loop to predictive pursuit (Figure 1). The velocity following this period, which is called *residual predictive pursuit*, is thought to be the response to only extraretinal signals. We measured *residual predictive pursuit latency* (time between the beginning of the mask to the beginning of residual predictive pursuit) and *residual predictive pursuit gain*. Eye data filtered by a 20-Hz low-pass filter were used in these analyses.

DATA ANALYSIS

For each subject, the data were collapsed across trials to obtain mean values, which were averaged to get the group means. Previous analyses showed no significant effects of ramp direction and number of cycles before the occurrence of the mask and their interactions with group membership. Thus, the data were collapsed across these factors. Separate repeated-measures analysis of variance (multivariate analog; subject source and SSP as 2 between-subjects factors and 2 or 3 target velocities as a within-subjects factor) were performed for each of the dependent measures. In the presence of interactions, the analyses focused on the highest level of interaction, ignoring the lower-level interactions and the main effects involving the same factors. The number of symptoms for each *DSM-III-R* SSP diagnosis were summed for each individual in each personality category. Within the schizotypal category, separate dimensional scores for cognitive-perceptual, interpersonal, and oddness dimensions were calculated on the basis of 3 factor solutions noted by recent studies.[26] For the statistical significance, the α level was set at .05. Post hoc comparisons used Tukey honestly significant difference (HSD) tests. Spearman correlations were conducted between the dimensional scores and mean and peak predictive gain in relatives and community subjects separately; the α level was adjusted to .01 (0.05/6) for the number of correlations. Results are presented as mean ± SD.

Mask at the Beginning of the Ramp

Examination of change in direction latency showed a significant effect of subject source ($F_{1,129}$=7.51, P<.008); the change in eye direction better coincided with that of expected target direction in the community subjects (81 ± 36 milliseconds) compared with the relatives (100 ± 43 milliseconds). After the change in the direction of pursuit, peak predictive gain was significantly lower in relatives (0.48 ± 0.20) than in the community subjects (0.55 ± 0.19) ($F_{1,129}$=3.85, P=.05).

Mask During the Ramp

Comparison of the mean mask pursuit gain during the ramp suggested a subject source × SSP group × target velocity interaction ($F_{2,130}$=6.51, P<.005). To analyze the interactions, effects of subject source and SSP were separately examined at 3 levels of target velocity by analyses of variance. Results showed that at a target velocity of 9.4° per second, there was a main effect of SSP group on mean predictive gain ($F_{1,131}$=5.79, P<.02). No significant effects were noted at a target velocity of 14.0° per second. At a target velocity of 18.7° per second, there was a significant subject source × SSP interaction ($F_{1,131}$=15.23, P<.001). Post hoc comparisons showed that relatives with SSP had significantly lower mean predictive gain compared with the relatives without SSP and both community subject groups (P<.05, Tukey HSD test).

There was a main effect of target velocity, but no significant main effects or interactions involving subject source or SSP on residual predictive pursuit latency. Examination of residual predictive pursuit gain showed a subject source × SSP group × target velocity interaction ($F_{2,130}$=4.33, P<.02). Analysis of the interaction showed no significant effects at target velocities

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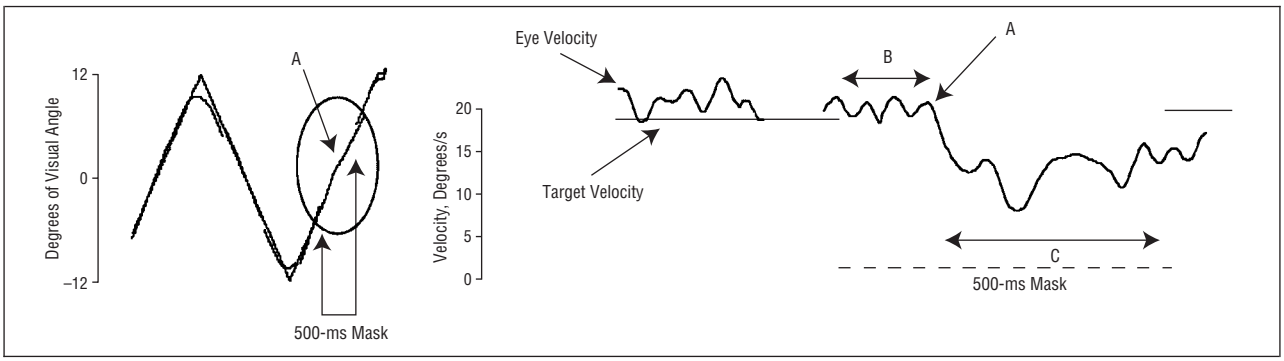
Table 1. Clinical and Demographic Information*

Clinical Variables	Community Subjects		First-degree Relatives of Patients With Schizophrenia	
	Non-SSP (n = 42)	SSP (n = 29)	Non-SSP (n = 43)	SSP (n = 26)
Age, y	34.5 (8.6)	32.4 (8.7)	34.5 (8.0)	36.8 (8.0)
Sex, F/M	20/22	11/18	26/17	12/14
SES score†	2.71 (0.94)	3.41 (0.87)‡	2.98 (0.91)	3.46 (0.99)‡
No. of personality symptoms§				
Schizotypal	0.38 (0.73)	4.31 (1.44)‖	0.49 (0.80)	3.56 (1.56)
Paranoid	0.12 (0.40)	1.62 (1.52)	0.42 (0.76)	1.46 (1.73)
Schizoid	0.14 (0.42)	2.90 (1.99)	0.23 (0.43)	2.73 (2.20)
Schizotypal dimensional scores§				
Cognitive-perceptual	0.26 (0.54)	2.34 (1.26)¶	0.33 (0.61)	1.35 (1.20)¶
Interpersonal	0.00 (0.00)	1.00 (0.65)	0.12 (0.32)	1.04 (0.77)
Oddness	0.12 (0.40)	0.97 (0.78)	0.05 (0.21)	1.08 (0.93)

*Mean (± SD) values are shown, except for sex. SSP indicates schizophrenia spectrum personalities.
†Socioeconomic status (SES) score using the Hollingshead scale.[27] The scores in the scale range from 1 (best educational and occupational functioning) to 5 (worst functioning).
‡There was a significant main effect of SSP ($F_{1,136}$ = 13.52, P<.001).
§One-way analyses of variance were conducted comparing the 2 SSP groups. The 3-dimensional scores were based on the 3 factors proposed by Battaglia et al.[26]
‖Community subjects with SSP greater than relatives with SSP; $F_{1,54}$ = 4.41, P<.05.
¶Community subjects with SSP greater than relatives with SSP; $F_{1,54}$ = 9.01, P<.005.



The left panel of the figure graphs target and eye position data from a single trial of the ramp-mask-ramp task (the whole trial is not shown). The pursuit section marked by the oval is shown in the right panel, which graphs the eye and target velocity data. The eye velocity did not change during the initial part of the mask. At point A, which marks the transition point from closed-loop to predictive pursuit, the eye abruptly slowed down and stabilized to a new level. Residual predictive pursuit latency, marked as B, is the duration between the beginning of the mask and the transition point (A), which is about 150 milliseconds in the illustration. Mean eye velocity is calculated from the transition point to the end of the mask (this duration is marked as C). The ratio of this mean eye velocity to target velocity before the mask gives the residual predictive pursuit gain.

of 9.4° and 14.0° per second, and a significant subject source × SSP group interaction at a target velocity of 18.7° per second ($F_{1,131}$=6.49, P<.02). Post hoc Tukey HSD test showed that relatives with SSP were significantly different from the 2 community subject groups on this measure. The relatives without SSP were not statistically different from any group on this measure.

The above findings did not change when age was used as a covariate in the analyses. **Table 3** gives correlations among measures of predictive gain and clinical symptoms within the relatives and the community subjects.

COMMENT

These results suggest that nonill, first-degree relatives of schizophrenic probands have subtle deficits in holding online extraretinal motion information (or using such information for smooth pursuit response). This deficit was noted mostly in relatives with SSP in trials with mask during a ramp. However, when the mask occurred at the beginning of a ramp, relatives with and without SSP were not different, both groups performing worse than the community subjects. Similarly, on most measures, subjects with SSP who did not have a family history of psychosis performed normally. However, at low target velocity, individuals with SSP, regardless of family history, showed lower mean predictive gain than individuals without SSP. These findings suggest that individuals who were most likely to have the genetic vulnerability to schizophrenia, as evidenced by their blood relationship with a patient and the presence of a clinical phenotypic marker (ie, SSP), showed the most pronounced deficit in their response to the extraretinal motion.

Consistent with a recent report by Keefe and colleagues,[11] overall or closed-loop pursuit gain did not differentiate relatives from the community subjects even though the response to extraretinal signals was abnormal. In the presence of defective extraretinal signals, the smooth pursuit system can still follow a target by in-

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Table 2. Measures of Predictive Pursuit in Response to Only Extraretinal Signals*

Target Velocity, Degrees/s	Community Subjects		First-degree Relatives of Patients With Schizophrenia	
	Non-SSP (n = 42)	SSP (n = 29)	Non-SSP (n = 43)	SSP (n = 26)
Closed-Loop Condition				
Pursuit gain†				
9.4	0.88 (0.09)	0.88 (0.11)	0.87 (0.14)	0.84 (0.15)
14.0	0.86 (0.13)	0.85 (0.16)	0.85 (0.15)	0.80 (0.22)
18.7	0.81 (0.14)	0.82 (0.16)	0.76 (0.18)	0.76 (0.17)
Root mean square error†‡				
9.4	1.40 (0.53)	1.29 (0.60)	1.44 (0.63)	1.45 (0.70)
14.0	1.73 (0.64)	1.57 (0.71)	1.83 (0.92)	2.02 (0.90)
18.7	1.85 (0.60)	1.68 (0.61)	1.94 (0.57)	2.10 (0.90)
Mask During the Ramp				
Mean predictive gain§				
9.4	0.65 (0.15)	0.59 (0.13)	0.65 (0.17)	0.58 (0.15)
14.0	0.60 (0.14)	0.58 (0.17)	0.61 (0.14)	0.57 (0.18)
18.7	0.60 (0.15)	0.64 (0.14)	0.65 (0.13)	0.49 (0.18)
Residual predictive latency†				
9.4	152 (45)	149 (26)	149 (48)	143 (44)
14.0	182 (58)	176 (39)	170 (55)	173 (47)
18.7	177 (85)	168 (45)	181 (68)	174 (43)
Residual predictive gain§				
9.4	0.76 (0.18)	0.73 (0.20)	0.75 (0.21)	0.77 (0.15)
14.0	0.60 (0.12)	0.60 (0.14)	0.57 (0.15)	0.57 (0.21)
18.7	0.59 (0.17)	0.64 (0.21)	0.56 (0.18)	0.45 (0.13)
Mask at the Beginning of the Ramp				
Change in the direction latency, ms‖				
14.0	85 (37)	81 (56)	105 (79)	109 (44)
18.7	81 (37)	75 (38)	94 (38)	92 (48)
Peak predictive gain†¶				
14.0	0.54 (0.21)	0.45 (0.28)	0.42 (0.23)	0.47 (0.38)
18.7	0.61 (0.24)	0.60 (0.23)	0.53 (0.18)	0.49 (0.18)

*Mean (± SD) values are shown. SSP indicates schizophrenia spectrum personalities.
†There was a significant effect of target velocity ($F_{2,130} > 12.69$, $P < .001$).
‡Relatives had significantly worse root mean square error than community subjects ($F_{1,136} = 4.19$, $P < .05$).
§There was a significant target velocity × subject source × SSP interaction ($F_{2,130} > 4.32$, $P < .02$).
‖Relatives had significantly longer latency than community subjects ($F_{1,128} = 7.51$, $P < .008$).
¶Relatives had significantly lower peak gain than community subjects ($F_{1,129} = 3.85$, $P = .05$).

Table 3. Spearman Correlation Coefficients for Measures of Predictive Smooth Pursuit

Schizotypal Dimensional Scores	First-degree Relatives of Patients With Schizophrenia		Community Subjects	
	Mean Predictive Gain	Peak Predictive Gain	Mean Predictive Gain	Peak Predictive Gain
Cognitive-perceptual	−0.43*	−0.14	0.16	−0.16
Interpersonal	−0.22	−0.23	0.22	−0.14
Oddness	−0.36*	−0.01	0.19	−0.19

*$P < .01$.

creasing the gain to the retinal motion signal. This would result in an inefficient tracking because the retinal motion signals, which inversely vary with eye velocity, are not constant. The high and low eye velocities are averaged out when overall pursuit gain is calculated, therefore explaining a normal mean gain. However, other global measures such as qualitative score or root mean square error, which examine how far apart the eye position is from that of the target, would be sensitive to such abnormalities. Indeed, Keefe et al[11] noted that their qualitative score was able to differentiate relatives from the comparison group even though pursuit gain did not. Consistent with these findings, the root mean square error was significantly higher in the relatives compared with the community subjects in the present study.

Functionally specific neurophysiological measures are more informative than the global or overall measures of pursuit function at the level of information processing and the mediating neural circuitry. For eye movement responses, retinal motion information is processed in middle temporal and medial-superior temporal areas in monkeys,[28] although motion perception can occur in the temporal stream when motion defines object attributes.[29-31] While performing an eye tracking task, individuals with schizophrenia are able to process motion normally as indicated by normal saccadic responses to a moving target.[7,32,33] Processing of extraretinal motion information occurs early in the so-called dorsal stream of visual processing in the medial-superior temporal area

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in monkeys.[34,35] This region receives projections from the brainstem area and is thought to process the efference copy.[36,37] Posterior parietal cortex in monkeys is shown to carry the information regarding previous retinal slip velocity independent of the efference copy.[38] Frontal cortical areas, including the frontal eye fields, are thought to integrate the extraretinal motion signals to generate predictive smooth pursuit.[39-41] Abnormality in predictive mechanism could explain findings of abnormal pursuit initiation in the schizophrenia spectrum[42,43] since it plays a critical role in the initial phase of pursuit by generating anticipatory pursuit.[40,41] MacAvoy and colleagues[40] reported persistent deficits in anticipatory initiation of pursuit and predictive continuation of pursuit after target extinction in monkeys with frontal eye field lesions. The deficits observed in the present study would implicate abnormalities in circuits that involve parietal and/or frontal cortical ocular motor regions in individuals who have genetic liability for schizophrenia.[44]

There are several limitations to this study. The 2 groups of subjects with SSP are not likely to be representative of the respective populations from which they were selected. The community subjects with SSP may not adequately control for the effects of SSP symptoms on the eye movement measures since their symptoms may qualitatively differ from those of the relatives with SSP. In addition, the presence or absence of SSP symptoms was determined on the basis of subjects' own reports wherein a systematic bias cannot be ruled out.

In conclusion, we found deficits in smooth pursuit response to extraretinal motion signals in the relatives of patients with schizophrenia, particularly those with SSP, compared with the community subjects. The inability to hold online extraretinal motion information may represent a specific type of more general deficits in working memory,[45,46] a construct similar to the construct of extraretinal motion. Examination of the relationship between working memory deficits and the traditional measures of smooth pursuit have generally revealed significant correlations.[46,47]

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Reprints: Gunvant K. Thaker, MD, Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228 (e-mail: gthaker@MPRC.umaryland.edu).

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