ORIGINAL ARTICLE

Dependence of Impaired Eye Tracking on Deficient Velocity Discrimination in Schizophrenia

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Background: Abnormal smooth pursuit eye movements have been found in many schizophrenic patients and in about 40% of their first-degree biological relatives. A velocity discrimination deficit has also been demonstrated in schizophrenic patients. In this study, we address the relation between deficient velocity discrimination and impaired smooth pursuit eye movements, inasmuch as the brain regions responsible for processing velocity signals are implicated in generating and maintaining smooth pursuit.

Methods: Horizontal eye movements of 15 schizophrenic patients and 8 normal controls were recorded in response to sine wave (predictable) and step-ramp (nonpredictable) targets. Smooth pursuit eye movements were assessed during both the initiation and maintenance periods. Correlations were computed between measures of smooth pursuit (qualitative rating, peak gain, saccade frequency, and initial acceleration) and contrast sensitivity for velocity discrimination.

Results: Contrast sensitivity for fine velocity discrimination was significantly correlated both with initial acceleration of smooth pursuit and with peak gain, but was not significantly correlated with saccade frequency and qualitative ratings of pursuit integrity. No significant correlations were found within the normal control group.

Conclusion: Deficient processing of velocity information seems to be one component that contributes to a dysfunction in the initiation and maintenance of smooth pursuit in schizophrenia.

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PREVIOUSLY,[1] we reported that about 40% of schizophrenic patients had significantly raised thresholds for fine velocity discrimination compared with normal controls. Here we address the relation between raised thresholds in motion perception and abnormal smooth pursuit eye movements (SPEM), or eye tracking dysfunction (ETD), which has been stable in a significant proportion of schizophrenic patients and their first-degree biological relatives.[2-6] This study was undertaken to explore the processes that underlie ETD.

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Eye tracking dysfunction in schizophrenia comprises irregularities in tracking that reflect at least low steady-state gain, low open-loop acceleration (OLA) (eye acceleration after the first 120 milliseconds following target movement), and increased frequency of saccades during eye tracking.[7-9] A comprehensive review may be found in Levy et al.[10]

Smooth pursuit eye movements are complex oculomotor activities, and consist of processes that initiate pursuit and maintain pursuit.[11,12] Both processes depend on the presence of motion signals from a stimulus, intact pathways in the brain for processing the motion signals, and an intact motor apparatus for executing eye movements. When any of these component processes is compromised, SPEM becomes abnormal. Motor control over eye movements seems to be normal in schizophrenic patients. They are able to generate slow and fast eye movements (such as nystagmus) in response to vestibular stimulation.[13] Full-field optokinetic responses,[14] as well as the oculocephalic reflex,[15] are intact; and both latency and accuracy of voluntary saccades are essentially normal.[16,17] Only SPEM, generated when pursuing a moving target, are impaired in schizophrenic patients.

Our earlier study of motion perception[1] was undertaken to investigate the component processes assumed to be implicated in ETD. We proposed that impaired motion processing is a major factor in these abnormalities. An underlying motion processing

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SUBJECTS AND METHODS

SUBJECTS

Fifteen patients with chronic schizophrenia and 8 normal control subjects who had participated in the motion perception tasks[1] took part in the current study. Diagnostic procedures are described in Chen et al.[1] All patients met *DSM-III-R* criteria for schizophrenia (n=5) or schizoaffective disorder (n=10), based on the Structured Clinical Interview for *DSM-III-R*[20] administered by trained interviewers and reviewed, together with all hospital records, by a team of experienced clinicians, all of whom were blind to the experimental data. Subjects had no concurrent substance abuse or dependence for at least 6 months and no diagnosed central nervous system abnormalities. Eleven patients were receiving antipsychotic pharmacologic treatment. All participants gave written informed consent and were paid a modest honorarium. Normal controls were also clinically screened with the Structured Clinical Interview for *DSM-III-R;* none met criteria for any *DSM-III-R* Axis I psychotic condition.

PROCEDURES

Previous Motion Perception Experiments

A full description of the procedures used to obtain thresholds for velocity discrimination is contained in Chen et al.[1] In brief, we obtained contrast sensitivities for velocity discrimination (which of 2 targets moves faster), contrast detection, and orientation discrimination. We used the standard psychophysical "staircase" method, which increases the task difficulty by 1 step after 3 consecutive correct responses, and decreases the task difficulty by 1 step after 1 incorrect response. This procedure identifies for each individual the threshold of a psychometric function at which all subjects, patients and controls alike, perform at 79.4% accuracy.[21] Thus, the dependent variable in all of these threshold measurements was the amount of target contrast necessary to achieve an accurate perceptual judgment of 79.4% correct.

SPEM Tasks

All subjects were asked to follow a small circle of light that subtended a visual angle of 1.25°, presented on a computer screen 56 cm in front of the subject. There were 2 eye movement tasks. In the first, the target moved horizontally and sinusoidally at a temporal frequency of 0.4 Hz. The amplitude of the excursion was 28° peak to peak; maximum velocity was 35.2° per second. The color of the circle changed unpredictably and the subject was asked to count silently the number of times the color changed. This manipulation enhances attention to the task and minimizes anticipatory saccades.[22]

The second target presentation employed a subset of the step-ramp introduced by Rashbass.[23] The target, located straight ahead, remained stationary for a short period that varied quasirandomly from 1 to 3 seconds, and then jumped either right or left of the central fixation point (the "step"). After a pause (200 milliseconds), the target began to move slowly in a horizontal direction opposite to that of the jump (the "ramp"), crossing the midline 200 milliseconds later. The ramp velocities were 5°, 10°, and 20° per second. Both the directions and velocities were unpredictable from trial to trial. There were 4 trials at each of the 3 velocities and, for each direction of movement, for a total of 24 trials. Because the normal initial smooth pursuit response, which occurs within about the first 100 milliseconds, is to the perceived target movement alone and does not yet involve any corrective feedback from target position or from an efference copy of an eye movement, it is termed "open-loop." Sustained smooth pursuit then follows. This phase of eye tracking, during which corrections are based on the feedback of retinal slip, is usually measured by closed-loop gain.

deficit seemed plausible because SPEM is impaired when the motion-sensitive areas of the brain—the middle temporal (MT) area and the medial superior temporal (MST) area—suffer lesions, either experimentally produced in monkeys[18] or naturally occurring in humans.[19] We demonstrated that schizophrenic patients had impaired motion perception, as measured by the contrast required to detect small differences in velocity, but that they did not show impairments in nonmotion tasks. These features of motion perception were stable over time in both normal controls and schizophrenic patients, and thus represent trait characteristics.

In this article, we examine whether and how performance on smooth pursuit tasks and on velocity discrimination tasks are related in schizophrenic patients. We hypothesized that relative insensitivity in velocity discrimination is associated with both low OLA and closed-loop gain in SPEM.

RESULTS

VELOCITY DISCRIMINATION

The previous study of motion perception[1] established that the contrast sensitivities for velocity discrimination were significantly lower in schizophrenic patients, as compared with normal controls, when the velocities to be compared differed by 20% (11° per second vs 9° per second) (**Table**). Contrast sensitivities for contrast detection and orientation discrimination and for judging 2 velocities that differed by 100% (15° per second vs 5° per second), however, were similar for both groups.

SMOOTH PURSUIT

Figure 1 shows representative responses of a normal control and a schizophrenic subject to the sine wave target. Compared with the normal control, the patient's sustained eye tracking appears to have lower gain and is consistently accompanied by saccades. **Figure 2** shows representative responses of a normal control and a schizophrenic patient to the 20° per second step-ramp target. The normal control initiates a clearly accelerating pursuit eye movement about 150 milliseconds after the target begins to move in its ramp trajectory. In contrast, the patient's eye movement shows a very low initial acceleration.

Eye Movement Apparatus and Recording

The apparatus for recording eye movements was a fully computerized limbus tracker (Eye and Brain Technologies Inc, Thessaloniki, Greece). It consisted of photodiodes, sensors that receive infrared reflections from the eyes, an amplifier, and a digitizer. The sensors were placed on spectacle frames that the subject wore during the eye movement recordings. The sampling rate for eye position was 1000 Hz. Eye position was calibrated to ±12°. Eye position signals were recorded by a computer that also controlled the presentation of the moving targets. Each subject's head was immobilized by use of a custom-fitted bite bar made of dental compound.

Principal Measures

The data were analyzed both qualitatively and quantitatively using custom-designed software. For data obtained from sinusoidal tracking, a 5-point qualitative rating system,[7] modified from the scale of Benitez,[24] was used to characterize the integrity of the eye tracking. A score of 1 indicated very good eye tracking, and a score of 5 indicated very impaired eye tracking. The qualitative ratings mainly take account of the frequency of intrusive and corrective saccades as well as the peak gain.[10] Two judges, highly experienced in rating SPEM, independently rated each sinusoidal recording; interrater agreement was more than 95%.

Data from the pursuit records were also analyzed quantitatively. For the sinusoidal targets, we computed peak gain and frequency of saccades. After excluding saccades (defined as eye movements faster than 60° per second, or 1.7 times the maximum velocity of the target), blinks, and square wave jerks,[10] we calculated peak gain, defined as the ratio of eye velocity to target velocity, both averaged across a range of ±200 milliseconds around the maximum velocity of the target for every cycle of target movement. The number of saccadic events during 30 seconds of tracking was another quantitative index of eye tracking performance. For the step-ramp target we computed OLA, defined as the mean acceleration of initial pursuit, beginning 130 milliseconds after the onset of the ramp component of each of the 24 step-ramp trials and lasting 100 milliseconds.[12] Eye acceleration was obtained by computing the second derivative of eye position signals after filtering by a second-order Butterworth low-pass filter (cutoff frequency, 50 Hz); trials containing saccades during this open-loop period were excluded.

In summary, 4 eye movement measures were used to evaluate smooth pursuit: a qualitative rating, peak gain, saccade frequency (all for the sinusoidal target), and OLA (for the step-ramp target).

Data Analysis

Using Pearson product-moment correlations separately within the schizophrenia group and the 8 normal controls, we examined the association between velocity discrimination and each of the 4 measures of smooth pursuit. We also analyzed the differences between the patients and normal controls with respect to OLA at the 3 ramp velocities by a repeated-measures analysis of variance. To determine whether our version of the step-ramp procedure was equivalent to the standard Rashbass presentation (no delay between step and ramp),[23] we tested 20 additional subjects (approximately equal numbers of patients and controls) on both paradigms; the correlation between OLA on both procedures was 0.69 ($P<.005$), with no outliers. The 2 paradigms thus give similar OLA data. The effects of medication status and the differences between schizophrenic and schizoaffective patients on each of the measures were assessed by t tests, with significance fixed at an α level of .05, 2 tailed. There were no significant differences between these 2 patient groups on any of the measures used in this study. The 11 patients receiving antipsychotic medications did not differ from the 4 patients receiving no antipsychotic medications with respect to open-loop and peak gain, saccade frequency, qualitative score, and motion sensitivity.

RELATION OF VELOCITY DISCRIMINATION TO INITIATION OF SMOOTH PURSUIT

We calculated the mean initial acceleration for all subjects during the open-loop period for the step-ramp targets. These values are plotted as a function of the 3 ramp velocities in **Figure 3**. In both the schizophrenic patients and the normal controls, initial acceleration progressively increased as ramp velocity increased. However, the initial acceleration of the schizophrenic patients was significantly lower than that of the normal controls for all 3 ramp velocities ($F_{1,21}=5.49$, $P=.03$ at 5° per second; $F_{1,21}=4.78$, $P=.04$ at 10° per second; $F_{1,21}=9.39$, $P=.006$ at 20° per second). These data agree with previous reports of low initial acceleration in schizophrenic patients.[8,9,25]

The Pearson correlation coefficient between OLA for the ramp at 10° per second and velocity discrimination is 0.70 ($P<.01$), which indicates that about 50% of the variance in OLA can be accounted for by contrast sensitivity for velocity discrimination. The observed correlation suggests a strong relationship between velocity discrimination and OLA, but the confidence intervals (CIs) are necessarily wide because of the limited sample size (90% CI, 0.38-0.87). Therefore, a weaker but still a nonzero effect cannot be definitely ruled out. Both measurements (velocity discrimination and OLA) were obtained with the target moving at or around 10° per second,

Velocity Discrimination and Eye Tracking Measurements

	Mean (SD)	
	Schizophrenic Patients	Normal Controls
Velocity discrimination (contrast sensitivities)		
15° vs 5° per second	430 (191)	417 (174)
11° vs 9° per second	173 (106)	71 (39)
Eye tracking		
Qualitative rating (1-5)*	2.87 (1.3)	1.44 (0.7)
Initial acceleration, degrees per second²	48.5 (26.7)	75.0 (29.8)
Peak gain	0.75 (0.1)	0.80 (0.04)
Saccade frequency	13.8 (5.6)	10.7 (3.4)

**1 indicates normal eye tracking; 5, abnormal eye tracking.*

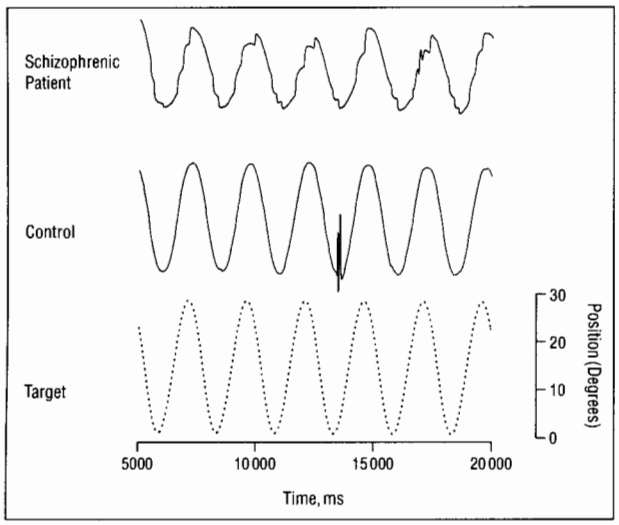

Figure 1. *Sample tracings of smooth pursuit eye movements of a schizophrenic patient (top) and a normal control (middle) following a 0.4-Hz sine wave (bottom, dashed line). Note that the normal control record is smooth except for a blink at about 12 seconds into the record. The record of the schizophrenic patient shows a very irregular pattern, suggestive of low gain pursuit with frequent saccadic eye movements.*

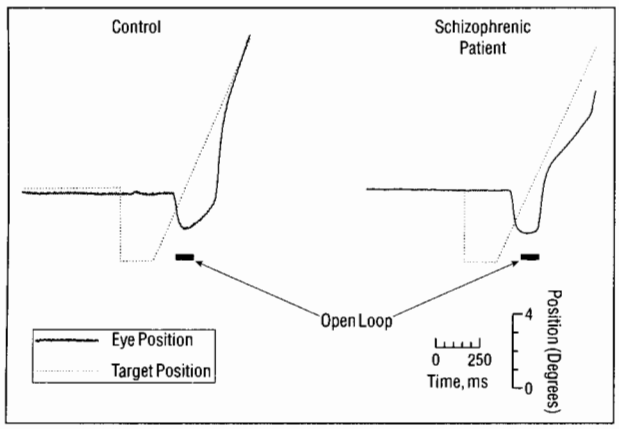

Figure 2. *Step-ramp pursuit of a normal control (left) and a schizophrenic patient (right). The target, illustrated by the dotted line, steps abruptly to the left and remains stationary for 200 milliseconds before beginning a 20° per second ramp trajectory to the right. The open-loop period is denoted by the black bars, which begin at 130 milliseconds after the target starts its ramp and continue for 100 milliseconds. In response, at about 150 milliseconds after the start of the ramp, the normal control begins a smooth eye movement that accelerates at a rate that is discernibly faster than that of the schizophrenic patient, whose initial eye movement barely accelerates.*

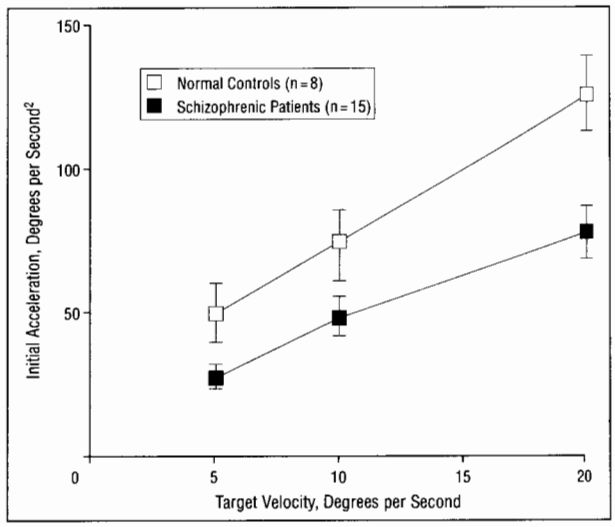

Figure 3. *The relation between target ramp velocity and initial acceleration. In contrast to the higher accelerations by normal control subjects, the schizophrenic patients show initial accelerations that are considerably lower in magnitude at all 3 target velocities.*

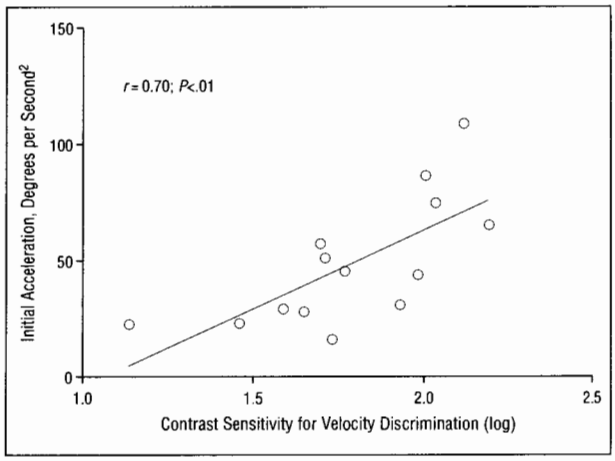

Figure 4. *Scatter diagram of the relationship within the schizophrenia group (n=15) between open-loop acceleration for the 10° per second target and velocity discrimination between 2 targets (11° per second vs 9° per second).*

presumably within the optimal range for motion processing. Correlation coefficients with similar magnitudes were obtained between velocity discrimination and OLA for ramp targets of 5° per second (r=0.59, P<.05) and 20° per second (r=0.65, P<.01). Those schizophrenic patients with low contrast sensitivity for velocity discrimination show low initial acceleration, as seen in the scatter diagram of that relationship (**Figure 4**). For the 8 normal controls, none of the correlations between OLA and velocity discrimination were statistically significant.

We also tested motion discrimination around a base velocity of 20° per second.[1] These faster-moving targets resulted in higher thresholds for both groups of participants. Schizophrenic patients, however, were again significantly less sensitive than the normal controls. The correlations between OLA and velocity discrimination between velocities of 18° per second and 22° per second followed the same pattern, with the same regression slopes as those around the 10° per second base.

RELATION OF VELOCITY DISCRIMINATION TO MAINTENANCE OF PURSUIT

Qualitative Rating

Five (33%) of the 15 patients had qualitative ratings of 4 or 5, indicating ETD. The correlation between the qualitative ratings of SPEM and the contrast sensitivities for discrimination of the 20% velocity differences was 0.25 (P=.37; 90% CI, −0.22 to 0.62). Thus, overall sustained eye tracking, as measured by global qualitative ratings,

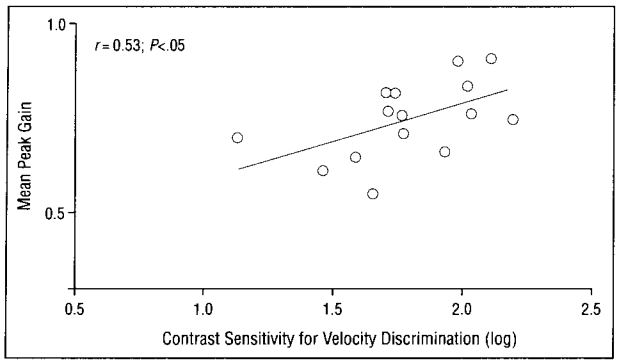

Figure 5. *Scatter diagram of the relationship within the schizophrenia group (n=15) between peak gain for the 0.4-Hz sine wave and velocity discrimination between 2 targets (11° per second vs 9° per second).*

seems not to be significantly related to sensitivity in detecting small velocity changes.

Peak Gain

For the schizophrenia group and the normal control group, the mean (±SD) peak gain for the 0.4 Hz sine wave target was 0.75 (±0.10) and 0.80 (±0.04), respectively. The 5 patients with qualitative ratings of 4 or 5 had a mean peak gain score of 0.73 (±0.07), which was significantly lower than that of the normal controls (t=2.62, P<.05). The scatter diagram (**Figure 5**) of the relationship between mean peak gain and contrast sensitivities for velocity discrimination shows that patients with low contrast sensitivities for velocity discrimination tended to have low peak gain. The correlation between velocity discrimination and peak gain for the sine wave was 0.53 (P<.05; 90% CI, 0.12-0.79).

Saccade Frequency

The correlation between saccade frequency and velocity discrimination in the schizophrenic patients was −0.39 (P=.15; 90% CI, −0.71 to 0.06). Although not reaching a statistically significant level, the negativity of the correlation is consistent with the relation described above between peak gain and velocity discrimination. That is, patients with low contrast sensitivity for velocity discrimination tended to make more saccades to compensate for low gain pursuit.

COMMENT

We report that velocity discrimination, previously shown to be impaired in schizophrenic patients,[1] is associated with lowered OLA and closed-loop gain. This association contributes to our understanding of the origin of ETD in schizophrenia.

MOTION DISCRIMINATION DEFICIT: A COMPONENT OF ETD

Both OLA and closed-loop gain involve detection of motion signals. To initiate a normal pursuit movement in response to a visual stimulus that has begun to move, the viewer must first be aware that the target is moving. Open-loop acceleration, which appears to be a pure response to motion signals from the sensory system, is reduced when motion detection is impaired. During this period of open loop, no feedback is available from the effects of a previous eye movement response to the target, since none has yet been made. Cognitive factors such as anticipation of target movement may also influence pursuit initiation, a factor that merits separate study. Steady state or peak gain, which is involved in maintaining smooth pursuit, is also associated with impairments in velocity discrimination, and is affected by previous eye movements, such as the feedback when retinal slip occurs. It has been suggested that the position of a moving target drives sustained eye tracking.[26,27] It is, therefore, possible that schizophrenic patients with impaired velocity discrimination partially compensate for their motion perception deficit by reliance on position cues to keep the fovea on a moving target, particularly when target velocity is relatively slow and when target movement is predictable. This interpretation may partially explain why the qualitative ratings of sustained tracking target are poorly related to velocity discrimination, whereas measures of OLA and closed-loop gain are significantly related to velocity discrimination. The qualitative rating reflects more than the velocity match between eye and target movement. It no doubt includes position match and some extraretinal events (such as predictive tracking), which appear as irregularities in the record and which are not taken into account in the acceleration and gain measurements. We note here that correlations between OLA and orientation discrimination (r=0.17, P=.56) and contrast sensitivity (r = 0.40, P = .08) are not significant, indicating that the results of this study do not reflect impaired motivation and generalized deficit performance frequently found in schizophrenia.

ARE MOTION-SENSITIVE AREAS OF THE BRAIN IMPLICATED IN ETD?

The processing of visual signals in the brain is carried out in many different areas of the visual system. These areas respond to different attributes of a visual stimulus, such as color, form, slant, and motion.[28] It is now known that the MT and MST areas have a large population of cells devoted to visual motion processing, including detection of changes in velocity.[29,30] Moreover, these same areas play a principal role in the adaptive control of eye movements, including SPEM.[31] Wurtz et al,[32] for example, reported that a punctate chemical lesion in monkey MT produced a deficit in motion perception tasks and in the onset of smooth pursuit. These deficits are quite similar to those seen in the present experiment in the initial eye tracking responses of schizophrenic patients with compromised motion discrimination. Studies also show that the lateral dorsal area of MST is involved in the regulation of the maintenance of pursuit.[32] The cells in this region respond to both retinal and extraretinal signals, the latter perhaps representing a proprioceptive input that is relevant to pursuit maintenance.

Because MT and MST are involved in both motion perception and smooth pursuit, any irregularity in the neural responses of these 2 areas should affect performance on both types of tasks. This indeed was the out-

come of the present experiment, which showed that schizophrenic patients whose velocity discrimination was poor had lowered open-loop and peak gains.[33] Stuve et al[34] had earlier reported that responses to the direction of motion in a coherent motion task and performance on a smooth pursuit task are significantly correlated in schizophrenic patients. Our present findings show that sensitivity to perception of velocity is implicated. Both studies suggest that impaired functioning of motion-sensitive areas such as MT and MST may be causally implicated in the ETD found in schizophrenic patients.

INVOLVEMENT OF OTHER BRAIN AREAS IN ETD

Smooth pursuit eye movements, including planning and executing them, are complex processes. They involve many brain areas, as has been shown in numerous physiological and brain-lesion studies. Those areas involved in the generation of smooth pursuit include both cortical regions—such as MT and MST and frontal eye fields (FEF)—and subcortical regions such as the basilar pons and cerebellum. It is conceivable, however, that after the motion signals are processed and relayed, other brain areas, such as those in the frontal lobes, play important roles in executing and maintaining smooth pursuit based both on current eye movements and on target movement. Information from eye velocity and eye position are also used adaptively to control on-line smooth pursuit, which may not solely be registered in MT and MST. Information about target movement may be conveyed not only from updated sensory signals but also from memory of, or extrapolation from, previously retained knowledge about the target motion; the latter would implicate neuronal activity in the frontal lobes. Indeed, Bruce et al[35] found so-called "pursuit neurons" in FEF. Other reports[36,37] showed clear activity of neurons in several areas of the frontal lobes while monkeys tracked a small target. Smooth pursuit to a target with predictable movement is usually spared when lesions occur in other brain areas but impairments were observed in a patient with damage to the FEF.[38]

With respect to schizophrenia, it has been shown that the behavioral impairment in at least 2 independent tasks is related to functional integrity in the frontal lobe. First, spatial working memory, which is associated with neural responses of area 46 in the frontal lobe,[39] was found to be impaired in schizophrenic patients.[40] Second, endogenous (sustained), but not exogenous (transient), attention engagement, in which prefrontal cortex may be involved,[41] was compromised in schizophrenia.[42] These considerations suggest that smooth pursuit impairment in schizophrenia may reflect contributions from nonsensory components, particularly during pursuit maintenance.

Many of the brain areas mentioned are, of course, interconnected with each other. Area MT is located within the occipitoparietal cortex of the rhesus monkey. Maunsell and Van Essen[43] traced projections from the striate cortex to MT via the striate areas V2 and V3, and from there to the superior temporal sulcus and parietal cortex, which includes MST and the inferior parietal lobule. These areas contain neurons that project to the FEF,[44] which also discharge during SPEM. Lesions to FEF and MT and MST all cause very profound impairment of SPEM.[45] Similarly, after comprehensively reviewing the effects on SPEM of various diseases and specific lesions, Sharpe and Morrow[46] conclude that MT, MST, inferior parietal lobule, and the FEF are critically implicated in specific abnormalities of SPEM, including lowered gain. The existence of the network linking these brain areas makes it difficult to be certain, when one brain area (such as MT) is damaged, whether the resulting SPEM impairment is caused by damage to this area or by the effects of such damage on other connected areas of the network, such as the MST or FEF.

In the case of schizophrenia, several previous eye tracking studies attribute the dysfunction to prefrontal involvement.[47] The neural activities of the frontal and prefrontal lobes in SPEM of schizophrenic patients should be considered in the context that these brain areas also receive inputs from, or provide feedback to, the posterior parietal lobe, where motion information is primarily processed (but also see Nawrot and Rizzo[48] for a role of the cerebellum in visual motion processing). Two studies of schizophrenic patients[25,49] reported that patients' initial saccades to a step-ramp target were similar to those of the normal controls. The authors concluded that the patients' generation of unimpaired saccades to a moving target indicated that motion processing was intact, because an earlier study of monkeys with lesions in the motion-sensitive MT area[50] showed impaired saccades to moving targets. However, we must point out that generating saccades to moving or stationary visual targets may rely on position as well as motion information. Therefore a direct assessment of motion discrimination, as was done in our earlier study,[1] is required to decide the issue of whether motion processing is impaired in schizophrenia. It is noteworthy, moreover, that Newsome et al[50] reported that a decrease in initial eye velocity in smooth pursuit accompanied damage to area MT, and Clementz,[25] in a study of saccades to moving targets in schizophrenia, also reported low OLA. In this article, we show that low OLA is significantly related to raised motion discrimination thresholds. We therefore suggest that whereas MT and MST are functionally involved in abnormal generation of smooth pursuit, the impairment in the maintenance of smooth pursuit in schizophrenia probably also implicates frontal and prefrontal areas.[36,37] Our finding of a significant functional relation between impaired velocity discrimination and reduced OLA and closed-loop gain in schizophrenic patients represents only the beginning phase of unraveling these complex processes.

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