Neural Correlates of Eye Tracking Deficits in First-degree Relatives of Schizophrenic Patients

A Positron Emission Tomography Study

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Background: Schizophrenia is thought to arise from the interaction of genetically mediated and environmentally triggered abnormalities in brain function. Reduced frontal activation, reported in schizophrenic patients, may be one expression of genetic risk. The present study investigated whether frontal activation in relatives of schizophrenic patients would be related to eye tracking deficits (ETD), which are considered a behavioral marker of risk for schizophrenia.

Methods: Subjects were first-degree relatives of schizophrenic patients (n = 17) and controls (n = 11). Relatives were divided into those with normal and abnormal pursuit based on qualitative ratings. Subjects were scanned using positron emission tomography and the H₂¹⁵O bolus subtraction technique while performing smooth pursuit and fixation. Brain areas more active in pursuit than fixation were identified in the 3 groups. Correlations were used to investigate the relationship between activation of pursuit regions and pursuit gain in the relatives.

Results: Controls significantly activated frontal eye fields (FEFs) and posterior areas, including the motion processing area, V5, and cuneus. The 2 groups of relatives activated the same posterior regions as controls, but differed from each other in activation of FEFs. Relatives with normal tracking activated right dorsal FEFs while relatives with ETD did not. Individual subtractions revealed that 90% of controls and 100% of the relatives with normal tracking activated FEFs during pursuit compared with 42% of relatives with ETD (P = .009). Pursuit gain was significantly and selectively associated with percent activation of right dorsal FEFs (r = 0.74).

Conclusions: Subtle frontal dysfunction seems to be a pathophysiological substrate of ETD in relatives of schizophrenic patients, and may be one aspect of genetically mediated differences in brain function relevant to schizophrenia.

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Neurodevelopmental models of schizophrenia have postulated both a genetic and an environmental contribution to the development of the disorder. First-degree relatives of schizophrenic patients are at increased risk of developing schizophrenia, and can transmit the risk without having expressed the clinical syndrome. Several deficits in cognitive and motor tasks found in schizophrenic patients have been identified as well in healthy first-degree relatives of schizophrenic patients. Because they occur at elevated rates in the schizophrenic patients and their relatives but not in the relatives of patients with other psychiatric disorders, they are thought to represent behavioral markers of genetic risk (otherwise conceived of as alternative phenotypic expressions of the disease). Abnormalities in smooth pursuit eye tracking are one of the best-documented behavioral markers. Between 50% and 80% of schizophrenic patients have eye tracking deficits (ETD), compared with about 8% of the general population. Populations at high risk for schizophrenia, including first-degree relatives of schizophrenic patients and individuals with schizophrenia spectrum personality disorders, also have elevated rates of ETD; first-degree relatives of patients with other psychotic disorders do not.

Many schizophrenic patients show a pattern of reduced frontal activation during frontal tasks. Levin advanced the hypothesis that pursuit deficits in schizophrenia were related to abnormal function of the frontal eye fields (FEFs), a frontal region involved in smooth pursuit. Many authors have tested this hypothesis indirectly by evaluating the relationship between pursuit quality and performance on tasks thought to tap FEFs or adjacent frontal areas. Results generally support an association between measures of...
SUBJECTS AND METHODS

SUBJECTS

Thirty subjects, 17 first-degree relatives of schizophrenic patients and 13 controls who were similar in age, sex, IQ, and father’s socioeconomic status, participated in the study (Table 1). Relatives were recruited from family studies of schizophrenia at the Douglas Hospital, Verdun, Quebec, and by advertisement in local newspapers and family support newsletters. They met the following inclusion/exclusion criteria: between age 18 and 50 years, normal or corrected-to-normal vision, right-handed, no history of Axis I disorder ascertained in a semistructured interview (Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-IV]), no personal history of neurological disorder, estimated full-scale IQ above 80, and medication free. Relatives were required to have a first-degree relative who met DSM-IV criteria for schizophrenia, as determined by an interview with the proband or by review of the proband’s inpatient medical records. The control subjects were recruited by advertisement and met the same inclusion/exclusion criteria, except that they were required to have no first-degree relative with a psychotic disorder and to have normal pursuit (see below). Of the 13 consecutively recruited controls, 1 (8%) was excluded for ETD. All subjects passed a physical examination, had no medical contraindications for a magnetic resonance imaging (MRI) scan, and had not previously participated in a PET study. Subjects did not eat or smoke for 3 hours prior to the PET scans, and had abstained from alcohol for a minimum of 24 hours. They underwent a urine toxicology screen sensitive to drugs of abuse (Triage Panel for Drugs of Abuse; Biosite Diagnostics, San Diego, Calif) immediately prior to scanning. Each subject’s MRI scan was read blindly by a neuroradiologist; subjects were excluded if the MRI was clinically abnormal. One subject, a control, was excluded for this reason.

The groups did not differ significantly in demographic variables, and no demographic variable was significantly associated with pursuit performance (all $P>.10$) (Table 1).

The study was approved by the institutional review board at McGill University Medical School, Montreal, Quebec. Subjects gave written informed consent and were compensated for their participation.

PROCEDURES

Eye Movements

A high-speed (250-Hz) infrared video-based pupil tracker (Eyelink; SR Research, Mississauga, Ontario) recorded from the subject’s dominant eye (the right for all but 1 control and 1 relative). This system has a spatial resolution of about 0.25° of visual angle. Subjects were asked to track a target that was either moving (pursuit) or immobile (fixation).

Pursuit. The target was a square subtending one-half degree of visual angle. It moved horizontally at 0.4 Hz across 24° of visual angle, and had a sinusoidal velocity profile. At the center of the square, an X changed to an O and back at random intervals. Subjects indicated each change by pressing a button. Monitoring tasks such as this one improve pursuit, and do so equally in normal controls and schizophrenic patients. Subjects performed 24 cycles of pursuit in each scan.

Fixation. The same target remained at the center of the screen for the duration of the scan. This task was essentially pursuit at velocity zero: as with the pursuit task, the subjects kept their eyes on the target and indicated target changes with a button press.

MRI Scan

Each subject underwent a high-resolution MRI scan obtained with a 1.5-T Philips scanner (Philips, Eindhoven, the Netherlands) with 160 slices 1-mm thick. Each MRI was transformed using a 3-dimensional image cross-correlation algorithm where the MRI is resampled by a linear transform to match the target volume (a database of 305 MRIs transformed to Talairach space through identification of neuroanatomical landmarks).

Positron Emission Tomography

Subjects were positioned in a head scanner (Scanditronix 2048; Scanditronix, Uppsala, Sweden) that has an intrinsic resolution of $5 \times 5 \times 6$ mm. Laser beams were aligned at the orbitomeatal line and the subject’s head was stabilized using a molded foam support. An intravenous line was placed in the subject’s left arm. The video camera of the pupil tracker was mounted on the head-holder. The tracker controlled data acquisition and was linked to a computer controlling stimulus display.

A 17-in monitor was positioned 57 cm from the subject’s eyes. A 10-minute transmission scan was obtained using a rotating rod of $^{68}$Ge for attenuation correction. Subsequently, the PET scans (60 seconds long, separated by 10-minute intervals) were conducted using the $^{15}$O bolus method with averaged image subtraction.

During each scan, the room was darkened and an opaque black cloth was draped over the gantry. Eye position was calibrated across 24° of visual angle and validated prior to each scan. Eye position was represented linearly across this range. Each eye movement condition was performed twice; conditions were presented in palindromic order with the condition presented first counterbalanced across subjects. Between scans, the cloth was removed and the room was illuminated to prevent dark adaptation.

Fifteen contiguous brain slices were obtained for each subject with a 6.5-mm center-to-center distance (axial field = 97.5 mm) and an intrinsic axial resolution of 6.0-mm full-width half-maximum (FWHM). Image reconstruction was performed using a measured attenuation correction from transmission scans and a Hanning-weighted reconstruction filter to an in-plane resolution of 8.0-mm FWHM. The PET and brain anatomical data were

frontal integrity and smooth pursuit. The findings of a recent neuroimaging study are consistent with the hypothesis that ETD is related to reduced activity in the FEFs in schizophrenic patients. An alternative hypothesis is that abnormal smooth pursuit reflects an abnormality in motion processing, mediated by a region in the temporal lobe called V5. Recently, several studies have reported that schizophrenic
patients have impaired motion perception, and that this is also found in the first-degree relatives of schizophrenic patients. Nonetheless, the data on a role for V5 in ETD are conflicting. Studies of saccades to moving targets in schizophrenia have generally reported intact motion perception. One study of smooth pursuit found greater performance deficits when subjects had to predict the target movement (thought to compensate for the predicted movement) than when they had to predict a movement that they could not predict. Studies of saccades to moving targets in schizophrenia have generally reported intact motion perception. One study of smooth pursuit found greater performance deficits when subjects had to predict the target movement (thought to compensate for the predicted movement) than when they had to predict a movement that they could not predict.
To our knowledge, no study has used positron emission tomography (PET) to investigate the neural basis of pursuit deficits in populations at risk for schizophrenia. In the current article, we used PET and the $H^{15}O$ bolus subtraction technique to investigate the relationship between individual differences in pursuit quality and regional cerebral blood flow (rCBF) in healthy first-degree relatives of schizophrenic patients. Our specific hypothesis was that subjects with ETD would have reduced activation of FEFs during smooth pursuit.

**RESULTS**

**EYE MOVEMENTS**

**Smooth Pursuit Eye Tracking**

Ten relatives were rated blindly as having normal pursuit and 7 with abnormal pursuit (Table 1). Pursuit gain was highly correlated with qualitative ratings ($r = -0.86$, $P < .001$); relatives with ETD had lower gain than both comparison groups (Figure 1). Test-retest reliability was high: the subjects returned to the laboratory on average 1.1 years (SD, ±0.6 years) after their PET scan and the intraclass correlation coefficient between the pursuit gain in the scanner and the pursuit gain in the laboratory was 0.76 ($P < .001$). All relatives assigned to the ETD group based on pursuit during the PET scan also received a blind qualitative rating of abnormal pursuit in the laboratory. At the follow-up, it was found that 1 subject with ETD had developed her first psychotic symptoms 5 months after her scan. She was receiving neuroleptic medication; thus, her pursuit data were excluded from the reliability analyses.

**Fixation**

All subjects fixated the target for the duration of the scan. No subject in any group broke fixation to make a saccade of more than 2°.

**PURSUIT-RELATED CHANGES IN rCBF**

Smooth pursuit significantly activated visual and oculomotor areas in normal controls (Table 2). This included activation of a dorsal and ventral region in the FEFs bilaterally (location of highest FEF activation in controls is shown in Figure 2). The greatest activations were in the cuneus in area 18 and area 19, and in the medial occipitotemporal area. The next highest activations were in V5 bilaterally. Subthreshold activations (unadjusted $P < .001$, adjusted $P$ not significant) were found in the left supplementary eye fields, right superior parietal cortex, and left lateral occipitotemporal cortex.

Relatives of schizophrenic patients with normal pursuit activated the same region of FEFs that had the highest level of activation in controls. They also activated all posterior regions that were significantly activated by controls, including V5.
rCBF CORRELATIONS WITH PURSUIT GAIN

Of the pursuit regions, only activation in right dorsal FEFs was significantly correlated with pursuit gain in relatives ($r = 0.74$, $n = 17$, $P = .001$) (Figure 3). Activation in this area had the highest correlation with pursuit gain in the entire brain. The peak correlation was centered at $x = 28.1$, $y = -7.4$, $z = 58$, less than 1 resolution element from the center of highest FEF activation in controls, and 3 mm from the maximum FEF activation in relatives with normal tracking. The correlation was not attributable to subjects’ sex or smoking status (partial correlation between pursuit gain and activity in this region did not covary for smoking, $r = 0.39$, $P = .03$; partial correlation between FEF activation and gaining, covarying for smoking, $r = 0.79$, $P = .006$). The correlation between gain and activity in this region did not obtain in controls ($r<0.1$).

Percent activation in V5 did not significantly predict pursuit gain (left, $r = 0.31$, $P = .23$; right, $r = 0.22$, $P = .39$) with or without the covariates. Correlations between gain and activation in other posterior pursuit regions were also nonsignificant (all $r<0.13$, all $P>.60$).

INDIVIDUAL SUBTRACTIONS

Individual subtractions revealed that 90% of control subjects and 100% of the relatives with normal tracking had detectable activation of FEFs during pursuit. In contrast, only 42% of the relatives with ETD activated any region of FEFs. This difference was significant ($\chi^2 = 9.3$, $P = .009$). There were no significant differences between groups in the proportion of subjects activating V5 or any of the post hoc regions (all $P>.20$).

During smooth pursuit, control subjects significantly activated FEFs and V5 bilaterally, along with 2 regions in the cuneus and the medial occipitotemporal area. That FEFs and V5 play a role in pursuit is consistent with stimulation and single-unit data in the monkey, and with reports of pursuit abnormalities in patients with lesions to these regions. The large activation (10% ± 7.5%) in the dorsal cuneus in the region of the parieto-occipital sulcus is consistent with our previous results comparing pursuit with reflexive saccades.

Differences in pursuit-related activation in relatives were not distributed throughout the brain, but were focused in frontal oculomotor regions. Relatives with normal tracking activated right dorsal FEF and the same posterior regions as controls. Relatives with ETD did not significantly activate FEFs. They did activate the same posterior regions as the other 2 groups. Of the pursuit regions, only activation in the right dorsal FEF was significantly associated with pursuit gain in relatives. This was the highest correlation with pursuit gain in the entire brain.

Our findings are consistent with the hypothesis that smooth pursuit deficits in schizophrenic patients and their relatives reflect FEF dysfunction. Neural activity in the pursuit region of FEFs is correlated with pursuit eye velocity, and electrical stimulation of this region accelerates the eye smoothly, in proportion to the intensity of stimulation. Lesions of the FEFs produce pursuit deficits similar to those seen in schizophrenia. The region of FEFs, in the present study, that is best correlated with gain seems to be similar to the region activated by the antisaccade task, a test of saccade inhibition. Pursuit gain and the number of saccades made during pursuit are naturally negatively correlated since low-velocity smooth eye movements must be compensated for by catch-up saccades. Nonetheless, it is interesting to note

<table>
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<th>Brain Region</th>
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<th>Adjusted P</th>
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<td>&lt;.001</td>
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</table>

*FEF indicates frontal eye field.

**Table 2. Pursuit Minus Fixation in Normal Controls**

![Figure 2. Pursuit-related activation of frontal eye fields (FEFs) in normal controls (n = 10). Frontal eye fields were maximally activated (z = 3.6) in pursuit relative to fixation at Talairach coordinates x = 20.1, y = −10.8, and z = 57. Activation is bilateral in the slices below.](image)
that a recent study reported that neurons in the FEFs that can suppress saccades seem to be localized in the pursuit region. Thus activation of these overlapping regions could serve both to generate smooth eye movements and inhibit saccades during pursuit.

The fact that relatives with ETD did not significantly activate right dorsal FEF is unlikely to reflect a problem of statistical power since the effect size of activation in this region was 0.33 (compared with 1.1 for controls and 0.96 for normal relatives). With this effect size, 82 subjects with ETD would be required to reach a significance threshold of .05. That the relatives with ETD were activating a different region of FEF was also not supported. The 2 largest \( z \) scores in the region of the FEF were 1.9 (right ventral FEF) and 1.32 (left ventral FEF). These were the largest \( z \) values anywhere in the middle frontal and prefrontal gyri. Analysis of individual subtractions revealed that this was not attributable to the individual activations occurring at different locations. A significantly smaller proportion of subjects in the group with ETD activated any region of FEFs than in the other 2 groups. Significant V5 activation was observed in all 3 groups. Average V3 activation was not significantly correlated with gain in the relatives. Thus this area would seem to play less of a role in ETD than the FEFs. However, it is worth noting that, for V5, percent activation may not be the best measure of functional integrity because the activation reflects motion signal (increased firing of neurons sensitive to the target speed) and background noise (increased firing of neurons sensitive to other velocities).

Our interpretation of the data is constrained by the study's limitations. First, subjects with ETD generated lower gain pursuit and more saccades during the scan; therefore, it is possible that activation differences simply reflect a failure of these subjects to engage in the required task. We do not believe this to be the case because eye movement recordings indicated that all subjects tracked the target without attentional lapses, and that subjects with ETD generated smooth eye movements that were, on average, 90% of the target speed. However, subjects with low gain did generate more saccades during pursuit, and during these saccades (epochs of about 20 milliseconds) they may not have been activating the pursuit area of FEFs. Our study cannot differentiate between the possibility that lower FEF activation reflects less time spent in pursuit, and the possibility that lower FEF activation is the cause of low gain pursuit. It is also not possible to determine from our data whether reduced prefrontal activation in relatives with ETD was specific to schizophrenia or whether it would be found in any group with abnormal pursuit. The inclusion of a group of normal subjects with ETD, or another group of neuropsychiatric patients with ETD, would be necessary to address this question.

Finally, there is some overlap between the percent activation of frontal regions in the relatives with ETD and the group with normal tracking. This is common in neuroanatomical studies comparing schizophrenic subjects with control populations. Future studies might include siblings from the same family, one with a behavioral marker for schizophrenia and the other without. The ap-

### Table 3. Pursuit Minus Fixation in Relatives With Normal Tracking*

<table>
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<tr>
<th>Brain Region</th>
<th>Coordinates</th>
<th>( z ) Score</th>
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<th>Adjusted P</th>
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<td>A priori regions</td>
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<td>4.4</td>
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<td>V5 (left)</td>
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<tr>
<td>Medial occipitotemporal</td>
<td>10.7</td>
<td>−69.3</td>
<td>−6.0</td>
<td>6.4</td>
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</table>

*FEF indicates frontal eye field.

### Table 4. Pursuit Minus Fixation in Relatives With Abnormal Tracking*

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<th>( z ) Score</th>
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<td>6.3</td>
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</table>

*FEF indicates frontal eye field.†Maximum activation anywhere in FEF.
proach of using members of the same family or twins discordant for the disease has, in the past, strengthened the power of studies to detect subtle morphological changes related to the disease process. The same approach could be applied to detect subtle differences associated with behavioral markers of risk.

Some brain imaging data that support a role of genetic differences in brain development in risk for schizophrenia have already been provided by Cannon et al. This group showed that the size of the cortical sulci was a function of the degree of genetic vulnerability of the subject. Our data build on these observations by providing physiological evidence of reduced frontal cortical function in subjects who have markers of risk. We cannot say at this point whether relatives with ETD (or any other behavioral marker) are carrying genes involved in schizophrenia: a possible intermediate neurological phenotype. Further studies on this subject may show whether relatives with ETD will be at risk for developing psychotic symptoms.

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REFERENCES