Neuropsychological and Eye Movement Abnormalities in First-Episode and Chronic Schizophrenia

by John A. Sweeney, Gretchen L. Haas, and Shuhua Li

Abstract

It is well known that neurobehavioral deficits are associated with schizophrenia. Little is known, however, about whether these disturbances become more severe over the course of the illness. In the present study, 101 patients with schizophrenia, of whom 45 were first-episode cases, performed pursuit eye tracking tasks. A subset of 60 of these patients, including 27 first-episode cases, were administered a battery of neuropsychological tests. Patients with a history of prior psychotic episodes demonstrated more severe pursuit eye movement dysfunction than first-episode patients and more severe disturbances on neuropsychological tests sensitive to prefrontal and left temporal cortical dysfunction. Longitudinal studies of patients ascertained close to the point of illness onset are needed to determine whether these findings reflect a progressive deterioration in neurobehavioral functioning over the course of schizophrenia.

The classic Kraepelinian notion of dementia praecox (Kraepelin 1896) proposed that a progressive deterioration in brain function was an integral part of the illness. This notion is compatible with clinical studies demonstrating that some patients show serious deterioration in role functioning over the course of schizophrenia (Bleuler 1978). This longstanding view of a progressive disease process affecting brain function was challenged to some extent by computed tomography (CT) studies of brain conducted in the early and mid-1980s (Weinberger et al. 1982; Schulz et al. 1983; Williams et al. 1985; Illowsky et al. 1988). These CT studies failed to identify greater cerebral ventricular enlargement in older chronic patients than in young patients assessed near the point of illness onset. This led to speculation that structural brain changes associated with schizophrenia were static in nature, perhaps resulting from a neurodevelopmental failure. However, recent findings from magnetic resonance imaging (Bogerts et al. 1990) and $^{31}$P (phosphorous) magnetic resonance spectroscopy studies (Pettegrew et al. 1991) suggests that there may indeed be progressive brain changes that begin early in the course of the illness.

Surprisingly, very few longitudinal studies of neurobehavioral deficits in schizophrenia have been conducted to determine whether disturbances in brain-behavior systems associated with the illness are progressive in nature. Few studies have even addressed the question of whether deficits are more severe in chronic cases than in patients assessed early in the course of their illness.

One approach to addressing the question of whether a progressive deterioration in neurobehavioral functions is associated with schizophrenia is to compare first-episode cases with patients who have had multiple exacerbations of illness. There are three reasons to conduct such an investigation. First, if chronic cases do not have more severe impairments in particular functions than patients assessed at illness onset, there would be little point in undertaking difficult longitudinal studies attempting to identify progressive changes in those impairments. Second, in planning a longitu-
dinal study of neurobehavioral deficits in schizophrenia, it is important to be able to selectively assess specific domains of function, identified in cross-sectional studies, where deterioration is expected. Identifying neurobehavioral deficits that are more severe in patients with multiple, as opposed to single, episodes of illness would provide one source of direction for selecting measures for longitudinal studies. Third, establishing whether neurobehavioral deficits occur in first-episode cases of schizophrenia is important in its own right. In these cases, several potentially confounding effects on cognitive functioning, such as institutionalization, exposure to social and occupational challenges, and neuroleptic treatment, are minimized. As a result, primary impairments associated with the disorder may be more clearly evident early in the course of illness.

Studies of neuropsychological functioning and eye movement activity are two of the most common approaches used to assess neurobehavioral deficits in schizophrenia. Multiple studies confirm the presence of impaired neuropsychological competence in schizophrenia (Klonoff et al. 1970; Bilder et al. 1988). Eye tracking abnormalities are one of the most robust findings in schizophrenia research (Holzman et al. 1974; Cegalis and Sweeney 1979; Abel et al. 1991; Iacono et al. 1992). Studies of oculomotor (Leigh and Zee 1983; Johnston and Pirozzolo 1988) and neuropsychological (Walsh 1978) functioning have been useful in tracking the progression of many neurological diseases and may have similar value in schizophrenia research.

While standardized procedures exist for administering and scoring neuropsychological tests, many studies of eye movement dysfunction in schizophrenia employed global measures of visual tracking performance—visual inspection, Root Mean Square (RMS) error, and Log of the Signal-to-Noise Ratio (Ln[S/N])—that are not capable of identifying specific eye movement disturbances (Abel and Ziegler 1988; Clementz and Sweeney 1990). Partly as a result of these measurement limitations, the specific disturbances in brain systems causing eye tracking dysfunction in schizophrenia remain to be clarified. For the same reason, little is known about clinical correlations with disturbances of oculomotor functioning in schizophrenia.

Iacono and colleagues (1992) conducted a study of visual tracking in first-episode psychosis and demonstrated increased global tracking impairment (RMS error) relative to control subjects. The present study replicates and extends that investigation by studying specific components of eye movement activity during pursuit tracking and by comparing the severity of impairments in first-episode and multiple-episode cases. To our knowledge, no large neuropsychological studies of first-episode cases have yet been published (other than abstracts from a symposium at the 1990 meeting of the American College of Neuropsychopharmacology [DeLisi and Lieberman 1991]), although such studies are now ongoing in several laboratories.

Method

All admissions to the 108-bed inpatient psychiatric service of the New York Hospital-Cornell University Medical College, a metropolitan teaching hospital, were screened to determine whether psychotic symptoms were suspected or known to be present. Identified cases with suspected or definite psychotic symptoms were approached to obtain informed consent, and diagnostic interviewing was conducted within 1 week of admission. Diagnoses were determined using a structured clinical interview procedure, the Structured Clinical Interview for DSM-III-R diagnoses (SCID; Spitzer et al. 1987); additional data were obtained from family members and treating clinicians about symptoms and course of illness. All subjects were between 18 and 50 years of age and had no known systemic or neurologic illness, no history of head trauma or substance dependence, and no substance abuse within the month prior to testing. Patients had no prior treatment with electroconvulsive therapy, and had not taken lithium within 2 months or benzodiazepines within 2 weeks before eye movement testing.

Eye movement testing and ratings of clinical symptom severity using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), the Scales for the Assessment of Negative and Positive Symptoms (SANS; Andreasen 1983; SAPS; Andreasen 1984), and the Global Assessment Scale (GAS; Endicott et al. 1976) were performed within 1 week of hospital admission (see table 1). Diagnostic interviews and clinical ratings were performed by clinicians without knowledge of the results of eye movement or neuropsychological studies.

To limit the potentially confounding influence of psychotic disorganization on complex task performance, the more lengthy and difficult neuropsychological assessment was performed near the time of hospital discharge. The time from hospital admission to neuropsychological assessment was similar for first-episode (43.5 ± 33.6 days) and multiple-episode (38.1 ± 25.8 days) cases.
Table 1. Demographic and clinical history data, and clinical symptom ratings, from first- and multiple-episode patients with schizophrenia, schizoaffective and schizophreniform disorders, and normal controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal controls (n = 55)</th>
<th>First-episode schizophrenia (n = 45)</th>
<th>Multiple-episode schizophrenia (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td>31.4 (7.0)</td>
<td>27.9 (6.6)</td>
<td>31.1 (6.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>34 male/21 female</td>
<td>30 male/15 female</td>
<td>34 male/22 female</td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
<td>25.8 (8.1)</td>
<td>22.7 (5.1)</td>
</tr>
<tr>
<td>Cumulative hospitalizations</td>
<td></td>
<td>0</td>
<td>3.7 (2.6)</td>
</tr>
<tr>
<td>Cumulative hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAS</td>
<td>25.5 (6.5)</td>
<td>54.2 (12.2)</td>
<td>52.5 (9.3)</td>
</tr>
<tr>
<td>BPRS (total score)</td>
<td></td>
<td>14.1 (3.5)</td>
<td>14.7 (3.8)</td>
</tr>
<tr>
<td>SANS (total of global scores)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS (total of global scores)</td>
<td></td>
<td>11.5 (4.0)</td>
<td>10.4 (3.7)</td>
</tr>
</tbody>
</table>

Note.—Data are means and standard deviations unless otherwise specified. GAS = Global Assessment Scale (Endicott et al. 1976); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); SANS = Schedule for the Assessment of Negative Symptoms (Andreasen 1983); SAPS = Schedule for the Assessment of Positive Symptoms (Andreasen 1984).

Mann-Whitney U = 692.5, not significant (NS). Overall, there was considerable clinical improvement from the time of hospital admission to the time of neuropsychological assessment, reflected in a significant decrease in BPRS scores (51.8 ± 11.1 to 36.6 ± 10.4; t = 10.0; df = 58; p < 0.001).

The patient population was ethnically and socioeconomically diverse, broadly representing the New York City population. The final sample included 101 cases with schizophrenia-spectrum psychotic disorders with the following diagnoses: schizophrenia (n = 82), schizoaffective disorder (n = 12), and schizophreniform disorder (n = 7). Forty-five of these patients had never been hospitalized for psychiatric reasons, nor had they met criteria for a schizophrenia-spectrum psychotic disorder before their current episode. The remaining 56 patients had at least one prior hospitalization. There was no difference between first-episode and multiple-episode cases in neuroleptic dose (t = 1.52; df = 99; NS) or dose of anticholinergic medication (t = 0.53; df = 99; NS). The multiple-episode cases had, on average, been treated for several years with antipsychotic medication (60 ± 61 months). The control subjects for the eye movement studies consisted of hospital staff and individuals recruited from community advertise-ments. These control cases denied any history of psychotic symptoms personally and in first-degree relatives.

Eye Movement Testing Procedures. Subjects were tested in a quiet, darkened room. Targets were presented on a computer monitor at a distance of 51 cm. The target subtended 0.7 degrees of visual angle and moved in the horizontal plane at 0.4 Hertz (Hz) across ± 10 degrees of visual angle. Three tasks were performed, each taking 30 seconds. Subjects were told simply to keep their eyes focused on slowly moving targets. During two trials, the letter X oscillated across the screen with a sinusoidal (pendular) velocity. During a third trial, the target oscillated at a constant velocity (a triangular waveform moving at 16 degrees/second). A brief rest period followed each trial. Subjects were actively encouraged to focus their attention on the moving target, and performance was monitored on-line so that subjects could be immediately realerted if they stopped tracking the target. Chin, forehead, and head supports were used to minimize head movement.

Eye movement recordings were obtained using infrared (IR) scleral-reflection sensors mounted on spectacle frames (Applied Science Laboratories, Inc.). Sensor signals were low pass filtered, digitized at 250 Hz using a Techmar Labmaster A/D board, and stored for off-line analysis with custom software. Calibration data from fixations of points ± 3, 6, 9, and 12 degrees of visual angle from central fixation were used to convert the digitized recording of each subject's IR sensor data (in millivolts) to excursion of eye movement in degrees of visual angle.
Measurement of Eye Movement Activity.

Pursuit gain. The primary function of pursuit eye movements is to match the angular velocity of the eyes to that of slowly moving objects. The accuracy of this velocity match is referred to as the "gain" of pursuit eye movements and is calculated as the ratio of average pursuit eye movement velocity over target velocity. In most normal subjects, pursuit of slowly moving targets has a gain approaching 1.0 (Leigh and Zee 1983), reflecting a reasonably close match of pursuit and target velocities. The extent to which gain drops below 1.0 indicates the severity of pursuit eye movement disturbance.

In this study, pursuit gain was calculated using data obtained during pursuit of the constant velocity target. In this condition, eye velocity can be directly compared to the constant velocity of the target on a sample-by-sample basis. Pursuit of the first and last target oscillation was excluded, yielding 6,250 samples of visual tracking for analysis (25 seconds of pursuit sampled at 250 Hz). The recordings were subjected to a 5-point moving average (smoothing) before quantitative analyses. Before calculating pursuit gain, saccades (identified as periods where eye acceleration increased above 600 degrees/second²) were identified and deleted. Recordings were manually edited for blinks and pauses after anticipatory saccades.

The constant velocity task with an oscillating target is useful for calculating pursuit gain for reasons described above. Sinusoidal targets, by contrast, have the limitation that they require an abrupt reversal of pursuit direction at the point of target reversal as the target sweeps back and forth across the display screen. The eyes cannot abruptly reverse pursuit direction. As a result, pursuit velocity needs to slow and then accelerate in the opposite direction when the target reverses direction.

Very slow pursuit activity at the point of target reversal reduces the overall average pursuit velocity. Therefore, when this slow activity is included in the pursuit gain calculation, it causes an underestimation of the functional capacity of the pursuit system in terms of its ability to maintain the focus of vision on steadily moving targets. Further, the amount of time the eyes move at a very low velocity near the point of target reversal can vary depending on how well subjects anticipate where the spatially and temporally predictable target reversal will occur. To reduce the impact of slow pursuit at the endpoint of target reversal on pursuit gain calculations, velocity samples were not included in gain calculations when eye velocity dropped below 20 percent of target velocity (3.2 degrees/second) as the eyes reversed direction of pursuit.

More low velocity activity was dropped from patients than controls (268 msec ± 48 vs. 124 msec ± 48 per target reversal; t = 7.57; df = 155; p < 0.001), indicating that dropping low velocity activity around the point of target reversal made the patient versus control comparisons more conservative than they would otherwise have been. The amount of slow pursuit activity as the eyes reversed direction around the point of target reversal did not differ between first-episode and multiple-episode cases (t = 1.37; df = 99; NS).

Saccadic eye movements. An evaluation of saccadic eye movements during pursuit provides further information about visual tracking performance. Corrective saccades (rapid eye movements) compensate for pursuit error by abruptly shifting the eyes toward the target. The frequency and size of corrective saccades typically increase as pursuit gain decreases, reflecting the need for more frequent and larger corrections for pursuit tracking error.

Intrusive saccades disrupt pursuit by shifting the focus of the eyes away from the target. The most common intrusive saccades are called square wave jerks. During pursuit, square wave jerks divert the eyes away from the target for up to 450 msec, during which time pursuit continues until a second saccade refocuses on the target (Abel et al. 1991). Another type of intrusive saccade is anticipatory saccades (Whicker et al. 1985), wherein a saccade moves the eyes ahead of the target after which pursuit velocity is immediately and markedly reduced. These movements are considered anticipatory because the eyes appear to suddenly move ahead to where the target is expected and then wait for it to arrive at the anticipated location.

The abrupt reversal in direction at the maximum lateral excursion of triangle waveforms often leads to large corrective saccades that can be difficult to differentiate from intrusive saccades. Further, these large corrective saccades are not really catchup saccades in the sense of compensating for pursuit lag during ongoing pursuit. For these reasons, intrusive and corrective saccades...
were tabulated only during trials where subjects tracked targets moving at a sinusoidal or pendular velocity, where the target gradually slows to zero velocity before reversing direction.

Neuropsychological Testing. A battery of neuropsychological tests was administered to a subset of 60 patients who participated in pursuit eye movement studies. Twenty-seven of these patients presented with their first episode of psychotic symptoms. Tests were selected to assess psychomotor speed and attention (Finger Tapping, Trail Making, Digit Span and Digit Symbol [Reitan and Davison 1974; Wechsler 1958]), verbal skills (Verbal Fluency and Rey list learning [Benton et al. 1983; Rey 1964]), visual-spatial skills (Judgment of Line Orientation, Block Design, Wechsler Memory Scale designs [WMS; Wechsler 1945, 1958; Benton et al. 1983]), and IQ (Ammons and Iman 1962).

Data Analysis. Patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder did not differ significantly on any demographic, eye movement, or neuropsychological measure. The lack of such differences permitted pooling patients with schizophrenia-spectrum psychotic disorders as initially planned. However, it is important to note that the samples of schizophreniform and schizoaffective cases were not sufficiently large to exclude the existence of such differences. Because of skewed distributions of intrusive saccade frequencies, rank transformations were performed before parametric statistical analyses of these data (Conover and Iman 1981), and Spearman's rho correlations were computed to assess correlations between intrusive saccade frequencies and clinical/demographic variables. Tukey post-hoc tests were used to identify pairwise group differences in order to follow up on significant findings in analyses of variance (ANOVA).

Results

Demographic and Clinical Comparisons. Data pertaining to clinical and demographic descriptions of the subject groups are presented in table 1. There was a significant difference in age among the three groups (F = 3.49; df = 2,155; p < 0.05). Post-hoc pairwise group comparisons revealed that the first-episode group was younger than both the multiple-episode patients and the healthy control group, although the differences were both less than 4 years. The groups did not differ in gender ratios (χ² = 0.41; df = 2; NS). The two patient groups did not differ significantly on any clinical rating instrument (p > 0.10).

Group Comparisons on Eye Movement Measures. The means and standard deviations of the measures of eye movement activity in the first-episode and multiple-episode schizophrenic patients and in the normal control subjects are presented in table 2.

Pursuit gain. An ANOVA comparing pursuit gain of the two patient groups and control subjects demonstrated that the groups differed significantly (F = 31.93; df = 2,153; p < 0.0001). Post-hoc tests revealed that both schizophrenic groups were impaired relative to normal controls and that the first-episode cases had a less severe reduction in pursuit velocity than multiple-episode cases.

Table 2. Pursuit gain, size and frequency of catchup saccades, and frequency of square wave jerks and anticipatory saccades during visual pursuit tracking by patients with schizophrenia, schizophreniform and schizoaffective disorders, and normal controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal controls (n = 55)</th>
<th>First-episode schizophrenia (n = 45)</th>
<th>Multiple-episode schizophrenia (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pursuit gain</td>
<td>0.89 (0.06)</td>
<td>0.80 (0.09)</td>
<td>0.75 (0.13)</td>
</tr>
<tr>
<td>Number of catchup saccades</td>
<td>61.95 (22.63)</td>
<td>80.53 (32.92)</td>
<td>80.68 (32.25)</td>
</tr>
<tr>
<td>Mean size of catchup saccades</td>
<td>1.53 (0.38)</td>
<td>1.72 (0.43)</td>
<td>1.95 (0.50)</td>
</tr>
<tr>
<td>Anticipatory saccades</td>
<td>1.60 (2.77)</td>
<td>2.38 (4.05)</td>
<td>4.45 (7.09)</td>
</tr>
<tr>
<td>Square wave jerks</td>
<td>5.16 (0.38)</td>
<td>3.38 (4.24)</td>
<td>2.38 (3.09)</td>
</tr>
</tbody>
</table>

Note.—Data are means and standard deviations. The number of catchup saccades, anticipatory saccades, and square wave jerks are presented in terms of their frequency per minute of visual tracking.

1Different from controls, p < 0.05.
2Different from first-episode cases, p < 0.05.
Corrective saccades. The subject groups differed in the number of catchup saccades during pursuit ($F = 7.16$; $df = 2,153$; $p < 0.01$). Post-hoc group comparisons revealed that both patient groups differed from controls but that the first- and multiple-episode patient groups did not differ.

There were also significant group differences in the mean size of catchup saccades during pursuit ($F = 12.91$; $df = 2,153$; $p < 0.0001$). Post-hoc group comparisons revealed that the multiple-episode cases had significantly larger saccades than controls and first-episode cases, with first-episode cases between the two groups and significantly different from both.

Intrusive saccades. The three subject groups differed in rates of anticipatory saccades ($F = 3.15$; $df = 2,153$; $p < 0.05$). Although the multiple-episode cases had more anticipatory saccades than the other groups, post-hoc tests failed to identify any significant pairwise differences. The subject groups also differed in frequency of square wave jerk intrusions during pursuit ($F = 10.94$; $df = 2,153$; $p < 0.0001$). Post-hoc tests revealed that both schizophrenic groups had fewer square wave intrusions than control subjects and that the two schizophrenic groups did not differ significantly.

Correlations of deviant pursuit tracking with demographic and clinical factors. To determine associations between pursuit performance and clinical status, eye movement measures from the schizophrenic patients were correlated with scores on the clinical symptom rating instruments. No correlations with any eye movement measures were significant for the first-episode group. In the multiple-episode group, severity of negative symptoms (SANS scores) was correlated with anticipatory saccade frequency ($r = 0.27$; $p < 0.05$), and there were trends for SANS scores to be associated with pursuit gain ($rho = -0.22$; $p < 0.05$) and catchup saccade size ($r = 0.33$; $p < 0.05$). Also GAS scores (indexing global clinical/functional status) were correlated with pursuit gain ($r = 0.23$; $p < 0.05$). These associations suggest a modest association between visual tracking impairments and the severity of functional deficits in multiple-episode cases.

Acute symptom severity, as indexed by total scores from the BPRS and the SAPS, was not significantly correlated with any eye movement measure in either patient group. Duration of illness (time since onset of psychotic symptoms) was significantly correlated with pursuit gain ($r = -0.22$; $p < 0.05$), frequency of anticipatory saccades ($r = 0.29$; $p < 0.01$), and number of corrective catchup saccades ($r = 0.23$; $p < 0.05$).

Group Differences in Neuropsychological Functioning. Neuropsychological test scores of the first- and multiple-episode cases are presented in table 3. Significant group differences were observed on a psychomotor test emphasizing visual search and flexibility in shifting cognitive set (Trails B), verbal fluency (FAS word production), verbal learning/memory (Rey list learning test), and complex problem-solving and the ability to shift cognitive set (WCST). First- and multiple-episode schizophrenic patients did not differ in IQ, basic psychomotor speed (e.g., Finger Tapping, Trails A, and Digit Symbol), visual/spatial analysis (Judgment of Line Orientation and Block Design), or in visual memory (visual designs from the WMS-R).

Discussion

Results of the present study, which used a large-sample consecutive-admission sampling strategy, indicate that impairments of pursuit eye movements and some neuropsychological impairments are less severe in first-episode cases than in more chronic multiple-episode cases. Eye movement impairments were present in both first-episode and multiple-episode patients. Multiple-episode cases, however, demonstrated a lower gain of pursuit eye movements and larger catchup saccades during visual pursuit than first-episode cases.

The number of catchup saccades did not differ between first-episode and multiple-episode groups, suggesting that factors influencing catchup saccade size (such as lower pursuit gain) may lead to different compensations by saccadic eye movements later in the course of the illness. One possible explanation for the difference in observed saccade size and saccade frequency is that an increase in the number of catchup saccades may be a first adaptation to low-gain pursuit but, with larger reductions in pursuit gain, compensation for pursuit lag begins to be made by larger, rather than more frequent catchup saccades. This might explain why both schizophrenic groups demonstrated a similar increase in the number of catchup saccades, while multiple-episode cases who had the lowest pursuit gain demonstrated larger catchup saccades than both first-episode cases and controls.

A second unanticipated observation in the eye movement data was that the rate of square wave jerks, rather than being increased, was actually lower in schizophrenic patients than in normal controls. The observation of lower rates of square wave
Table 3. Neuropsychological functioning in first-episode and multiple-episode schizophrenic patients

<table>
<thead>
<tr>
<th>Functional area and test</th>
<th>First-episode schizophrenia (n = 27)</th>
<th>Multiple-episode schizophrenia (n = 33)</th>
<th>t-test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychomotor/attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger Tapping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand</td>
<td>46.0 (9.3)</td>
<td>45.0 (6.5)</td>
<td>0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Nondominant hand</td>
<td>42.7 (8.9)</td>
<td>41.7 (5.6)</td>
<td>0.52</td>
<td>NS</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form A</td>
<td>34.6 (15.7)</td>
<td>40.9 (18.8)</td>
<td>1.48</td>
<td>NS</td>
</tr>
<tr>
<td>Form B</td>
<td>78.4 (43.8)</td>
<td>112.8 (60.0)</td>
<td>2.48</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>WAIS-R Digit Span</td>
<td>15.9 (3.9)</td>
<td>13.9 (3.7)</td>
<td>1.96</td>
<td>NS</td>
</tr>
<tr>
<td>WAIS-R Digit Symbol</td>
<td>48.3 (15.2)</td>
<td>43.9 (13.2)</td>
<td>1.15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Verbal skills</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>42.0 (14.1)</td>
<td>33.9 (15.0)</td>
<td>2.07</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Rey list learning</td>
<td>47.1 (10.5)</td>
<td>39.9 (12.1)</td>
<td>2.36</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td><strong>Visual/spatial skills</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Judgment of line orientation</td>
<td>23.1 (5.3)</td>
<td>21.3 (6.2)</td>
<td>1.22</td>
<td>NS</td>
</tr>
<tr>
<td>WMS-R designs (memory)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>35.9 (4.8)</td>
<td>32.0 (7.1)</td>
<td>1.99</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed</td>
<td>31.7 (7.3)</td>
<td>27.8 (9.1)</td>
<td>1.45</td>
<td>NS</td>
</tr>
<tr>
<td>WAIS-R block design</td>
<td>29.7 (11.6)</td>
<td>27.4 (10.4)</td>
<td>0.69</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
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<tr>
<td>Wisconsin Card Sort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverative errors</td>
<td>14.2 (11.3)</td>
<td>21.7 (13.9)</td>
<td>2.14</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Categories</td>
<td>5.4 (1.2)</td>
<td>4.2 (2.0)</td>
<td>2.68</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>IQ</td>
<td>104.8 (15.7)</td>
<td>102.9 (10.0)</td>
<td>0.53</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—Data are means and standard deviations. WAIS-R = Wechsler Adult Intelligence Scale-Revised (raw scores) (Wechsler 1958); WMS-R = Wechsler Memory Scale-Revised (raw scores) (Wechsler 1945); IQ was assessed using the Ammons' Quick Test, a recognition test of vocabulary knowledge (Ammons and Ammons 1962).

Jabberwocky in the schizophrenic patients was surprising because increased rates of square wave jerks is a non-specific finding in many neurologic disorders (Leigh and Zee 1983). One possibility is that the control group in this study was atypical in some way. Some evidence to the contrary is that the rates of square wave jerks observed in the control subjects in the present study were similar to those reported by Shallo-Hoffmann and colleagues (1990) in normal subjects of a similar age during a visual fixation task (6.1 ± 4.8). A second possibility is that the difficulty level of the specific tasks used was greater for schizophrenic patients, which might have engaged their attention more effectively and thereby suppressed intrusive saccades. Replication of this effect is needed, particularly with assessment of square wave jerk frequency during pursuit of targets moving at several different velocities. This may be important because Levin and colleagues (1982), in a small-sample study (n = 6), reported that schizophrenic patients demonstrated far more frequent slow wave jerk-like intrusions only when tracking targets moved much more slowly than the targets used in the present study.

The findings with regard to visual tracking abnormalities are generally consistent with early studies of eye tracking impairments in schizophrenia. Holzman and colleagues (1974) and Cegalis and Sweeney (1979) reported that chronic schizophrenic cases performed more poorly...
than acute cases. However, these older studies failed to characterize the basic oculomotor disturbances that contributed to the observed visual tracking impairment. Further, as was common practice at the time those studies were conducted, the acute/chronic distinction was determined by duration of episode or hospitalization, rather than where patients were in the course of their illness. Thus, the results of the present study extend older findings by demonstrating that patients show less severe pursuit eye movement impairments (rather than just more deviant visual tracking) early in the course of their illness.

The multiple-episode schizophrenic cases also demonstrated more severe impairments on several neuropsychological tests. These included performance in verbal fluency, verbal memory, and complex problem-solving in tasks requiring the ability to flexibly shift cognitive set. There were no significant differences on tests of motor speed, visual analysis, visual or verbal memory, or IQ. The specific differences in neuropsychological functioning observed in the present study suggest that more severe impairments of prefrontal and left temporal cortical functioning may be the primary neuropsychological factors that discriminate first-episode and chronic schizophrenic patients.

In Katsanis and Iacono’s (1991) recent study of associations between RMS eye tracking error and neuropsychological test performance in chronic schizophrenic patients, they reported a specific association between neuropsychological deficits on tests of prefrontal cortical functioning and disturbed visual tracking performance. This is consistent with several lines of evidence suggesting that pursuit impairments may result from prefrontal cortical dysfunction (Levin 1984). Katsanis and Iacono (1991) observed the highest associations between visual tracking impairment and neuropsychological impairment on the WCST, Verbal Fluency testing, and the Trail Making Test, tests sensitive to impairments of prefrontal cortical functions. These specific tests differentiated first- and multiple-episode cases in the present study. Therefore, the eye movement and neuropsychological findings from the present study converge in suggesting that increased disturbances in prefrontal cortical functions may be a specific characteristic of schizophrenic patients who have had more than one psychotic episode and that some progressive disturbance in cognitive processes mediated by prefrontal cortex may occur in at least a subgroup of schizophrenic patients. The findings with the Rey verbal list learning test indicate that progressive impairments may also be observed in left temporal cortex.

Cross-sectional studies such as the one we report here are limited in their ability to address questions of disease progression. The group differences we observed could result from either of two factors. First, the first-episode cases could have less severe eye movement and neuropsychological impairments because they were evaluated early in the course of what ultimately may prove to be progressive neuropathology. Alternatively, neurobehavioral impairments might be nonprogressive (or static) impairments associated with a chronic recurrent course of illness. In this case, selection of multiple-episode cases would result in an increased representation of patients with more serious neurobehavioral impairments.

In the case of eye movement studies, few longitudinal data are available to evaluate whether disturbance of the pursuit system might deteriorate over the course of the illness. Similarly, few studies have longitudinally followed neuropsychological functioning over the course of illness. Three neuropsychological studies followed schizophrenic cases after stabilization for at least 1 year after an acute episode of illness. Sweeney and colleagues (1991a) followed a mixed group of first-episode and chronic cases, Bilder and colleagues (1991) followed first-episode cases, and Kolb and Whishaw (1983) did not report the number of first-episode cases among the 16 they followed. The pattern of findings from all three studies indicates a general improvement rather than deterioration in neuropsychological test scores over the followup interval. These data suggest that antipsychotic medications may play a significant role in preserving neuropsychological functions in schizophrenia.

The finding of overall improvement in neuropsychological test performance may appear to contradict the pattern of poorer performance by multiple-episode patients in the study. However, acute episodes of illness and the adverse effects of medication on neuropsychological test performance may impair neuropsychological functioning for some time after an acute episode of illness (Sweeney et al. 1991a, 1991b). Thus, decline in test performance in patients tested near the time of acute episodes of illness might be expected, with some degree of recovery over the postpsychotic period occurring in many patients.

Somewhat consistent with the observations of the present study, Bilder and colleagues (1991) reported preliminary longitudinal data from first-episode cases suggesting deterioration in attentional control with in-
creased set maintenance difficulty in some patients, suggesting that even in the context of a general pattern of improvement in neuropsychological functioning over the course of periods of clinical remission, there may be declines in some areas of functioning.

A programmatic research strategy is needed to resolve the important question of whether disturbances in brain-behavior systems are progressive over the course of schizophrenia. One stepwise research strategy for addressing such questions is (1) to demonstrate and replicate the presence of a particular neurobehavioral deficit in schizophrenic patients; (2) to demonstrate that first-episode cases have less severe manifestations of the deficit than chronic cases; and (3) to study the deficit longitudinally in first-episode cases to determine whether progressive dysfunction of brain systems can be identified. In this framework, the results of the present study suggest that the second criterion is met for both pursuit eye movement and some neuropsychological dysfunctions.

As in many neurological disorders, longitudinal neurobehavioral studies can provide a useful strategy for localizing brain disturbances and monitoring progression of disease processes. Given significant differences in the severity of neurobehavioral deficits between first- and multiple-episode cases, longitudinal studies of these impairments have the potential to generate important findings. One possible outcome of longitudinal studies would be the demonstration of neurobehavioral deterioration, perhaps only in a subgroup of patients. This observation would have a powerful impact on conceptualization of the disease processes underlying schizophrenia. Longitudinal clinical studies would also provide the data needed to determine whether patients manifesting relatively static neurobehavioral deficits early in the course of illness are more likely to have a poor course of illness. If progressive deterioration of functioning is demonstrated, it would focus attention on determining whether there is an at-risk subgroup and on development of treatments to prevent a progressive dementia. The results of the present study suggest that prefrontal cortex, and perhaps left temporal cortex, may be promising areas in which to begin to search for progressive changes in brain function.

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