Quantitative Assessment of Smooth Pursuit Gain and Catch-up Saccades in Schizophrenia and Affective Disorders

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The smooth pursuit responses to 5° and 20°/sec constant-velocity stimuli were recorded from 23 patients with schizophrenia, 16 affective disorder patients, and 21 normals using low-noise infrared oculography. Pursuit gain, catch-up saccade (CUS) rate and amplitude, and their interrelationships were examined. Gain in the schizophrenic patients was reduced only at 20°/sec, but for both patient groups, CUS rate at 5°/sec was significantly lower than in normals. Using CUS rate at 20°/sec, the patient groups could be distinguished from each other (the rate for schizophrenic patients being highest, and the rate for affectives the lowest) but neither differed significantly from normals. The diagnostic groups did not differ significantly in mean CUS amplitude, although there was a trend for patients to have larger saccades. Gain–CUS rate correlation was strong in normals but reduced or absent in both patient groups. These results indicate that the ocular motor systems of patients with schizophrenia and affective disorders process eye position error abnormally.

Introduction

Although abnormal performance on smooth pursuit tasks has frequently been reported in schizophrenic patients, the exact nature of the defects has not been well established. Still unresolved is whether the abnormalities seen during pursuit are those of the smooth pursuit system itself (i.e., low pursuit gain with resultant catch-up saccades) or, instead, are some form of saccadic intrusion. Here, gain refers to the ratio of eye velocity to target velocity; this is the generally accepted measure of how well the smooth pursuit system is performing. Saccadic intrusions are, collectively, the several types of inappropriate fast eye movements that can occur during execution of a tracking task. They are functionally independent of the pursuit system itself. The most common saccadic intrusions are square-wave jerks (SWJs), which are small pairs of saccades in opposite directions, separated by a normal saccadic latency of 200–450 msec. During SWJs, pursuit continues virtually uninterrupted. Also seen are anticipatory saccades (ASs), which are much larger (>5°), have a longer intersaccadic interval, and take the eyes to a new location well

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ahead of the pursuit target. After an AS, pursuit virtually ceases. These saccadic intrusions must be distinguished from catch-up saccades (CUSs), which are elicited whenever a pursuit gain of less than one causes the eyes to gradually fall behind the target. CUSs are not intrusions into pursuit; rather, their presence is attributable to inadequate performance on the part of the pursuit system. They do, however, give a "staircase" or "cogwheel" appearance to a pursuit recording.

The uncertainty over the origins of defective tracking in schizophrenia persists because most studies in this area have used one of several global measures of pursuit quality, identifying the extent to which a patient's tracking deviates from ideal without specifying the nature of the deviation (Abel and Ziegler 1988). These measures include rating scales, good–bad judgments, root-mean-square error and the logarithm of the signal-to-noise ratio (ln|S/N|) (Lindsey et al 1978; Holzman et al 1984; Holzman 1985; Ross et al 1988; Mather and Putchat 1982–1983). This uncertainty has left the type and extent of defective tracking poorly understood.

In recent years, however, a number of papers have applied the quantitative techniques used in other areas of ocular motor research to psychiatric populations. Low pursuit gain was noted by several groups (Levin et al 1982, 1988; Schmid-Burgk et al 1982; Yee et al 1987; Litman et al 1989); this could also be inferred from another study that noted cogwheel pursuit (Matsue et al 1986). Several studies found increased saccade frequencies in schizophrenic patients in comparison with normals (Cegalis and Sweeney 1979; Mialet and Pichot 1981; Cegalis et al 1983; Mather 1985); they did not discriminate among CUS, SWJ, and AS, however, thus leaving it unclear whether the abnormality lay in the saccadic system, pursuit system, or both. SWJs were specifically noted in one study (Levin et al 1981) and found to be absent in another (Levin et al 1988).

Thus, the existing body of literature has provided evidence that schizophrenic patients perform differently from normals on smooth pursuit tasks, but without clearly indicating the origins of this difference. Clarification of the nature of the ocular motor defect or defects present is a prerequisite for a study of their etiology.

A number of studies of smooth pursuit in affective disorder patients using global assessment techniques found abnormal performance in this population as well (Holzman 1985). The only quantitative data available on the performance of affective disorder patients on these tasks found their responses to resemble those of schizophrenic patients (Yee et al 1987), thus failing to support the specificity of any defect for schizophrenic patients.

The present study presents a detailed analysis of the eye movements generated by schizophrenic patients, affective disorder patients, and controls while tracking constant velocity pursuit stimuli. It examines in detail the smooth pursuit gain, the rate of catch-up saccade generation, and the relationship between the two. Patients with lower gain would be expected to have a higher CUS rate, since position errors would grow more quickly, provided that the position error threshold at which a CUS is elicited remains constant. This possible correlation between gain and CUS rate has not been previously examined in either normal or psychiatric populations. Saccadic abnormalities will be reported separately (Friedman et al, in preparation).

Methods

All patients in this study were recruited from the research wards of the Psychiatry Service of the Cleveland Veterans Administration Medical Center. There were 23 schizophrenic patients (8 chronic paranoid, 5 chronic undifferentiated, 2 chronic residual, 2 chronic

disorganized, 1 chronic catatonic, and 5 schizoaffective–depressed–chronic, mainly schizophrenic), 16 affective disorder patients (10 major depression–unipolar–nonpsychotic, 4 major depression–bipolar–nonpsychotic, 1 major depression–unipolar–psychotic, and 1 schizoaffective disorder, mainly affective), and 21 normal controls. Normal controls were recruited by advertisement, primarily from hospital staff. Prospective controls were excluded if they had a history of psychiatric or neurological disease, if they had a first-degree relative with psychiatric illness, or if they had a significant ophthalmologic condition (not including myopia or hyperopia). Mean ages and standard deviations for the three groups were 37.5 ± 10.9 for controls, 37.4 ± 9.0 for schizophrenic patients, and 48.4 ± 12.4 for affective disorder patients. All subjects were male. All patients were assigned a primary diagnosis using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L) (Endicott and Spitzer 1978; Spitzer and Endicott 1978). The diagnosis was reached by consensus by a multidisciplinary team that was familiar with the patient, after a review of the SADS-L. Each patient was also assigned a secondary diagnosis for past (6 months or more) or current episodes of alcohol abuse using the Research Diagnostic Criteria (Spitzer et al 1978). This assessment was based on the results of the Alcohol Abuse section of the Diagnostic Interview Schedule (Robbins et al 1981). Four schizophrenic patients had a secondary diagnosis of past and current alcohol abuse, six had a diagnosis of past abuse, four had a diagnosis of current abuse, and nine had no diagnosis of abuse. Seven affective disorder patients had a secondary diagnosis of past abuse and nine had no diagnosis of abuse. Eleven schizophrenic and 12 affective disorder patients were unmedicated; the remainder received conventional doses of typical neuroleptics or antidepressants. None was receiving lithium, since this has previously been reported to impair smooth pursuit performance (Iacono et al 1982; Levy et al 1985); five patients had previously been exposed to lithium, however. None of the patients had received benzodiazepines in the 24 hr before recording, since these drugs have been shown to affect smooth pursuit (Abel and Hertle 1988). Several additional subjects were recorded but were excluded from analysis because of the presence of nystagmus (one patient), patient self-reporting of extreme drowsiness during the recording (two patients), or inability to obtain calibration (one patient).

After the testing protocol was explained, written informed consent was obtained. The subjects' eye movements were recorded with infrared oculography as they followed constant-velocity stimuli moving horizontally at 5° and then 20°/sec between ± 15°. The target (a He–Ne laser spot) paused at the extremes of travel for 1.8 sec. Ten cycles were presented; the first was omitted from the analysis. Target position, eye position, and eye velocity were recorded on a rectilinear chart recorder for subsequent analysis. Recording system bandwidth was DC-100 Hz. Saccades down to at least 0.2° could readily be detected. The eye position data were entered into the computer from the chart recording with a graphics tablet by selecting those portions of the pursuit record demarcated by saccades and recording their beginning and ending positions. Eye movements identified as pursuit segments were periods of continuous tracking, uninterrupted by blinks or saccades, occurring while the target was moving. The gain of each segment was found by dividing its slope by that of the target tracing. Time-weighted average gain (TWAG) and the CUS rate were calculated. TWAG was computed by multiplying the gain of each pursuit segment by its duration, summing the products, and then dividing by the sum of the durations. This yielded an estimate of average pursuit performance, rather than a peak measure. This was felt both to provide a better estimate of how well the subjects were carrying out the task as a whole and to be more readily related to the global performance measures widely used in the literature. CUSs were defined as saccades

occurring during pursuit, in the direction of target motion, that take the eyes from a position behind the target to one on or near the target. We required that a CUS be preceded by a clear period of pursuit, thus omitting saccades that were the initial response to target motion. Interrater reliability for eight randomly selected records for the three scorers at 5°/sec was 0.93 for CUS rate, 0.98 for CUS amplitude, and 0.88 for TWAG; at 20°/sec it was 0.93, 0.99, and 0.95, respectively. CUS amplitude was measured from the chart recordings using a 7X magnifying reticle calibrated in 0.1-mm increments.

The correlation between CUS rate and smooth pursuit gain was calculated for all groups, as was a similar correlation of gain with the number of SWJs plus the number of CUSs. Each subject was represented by his TWAG and CUS rate (or CUS + SWJ count). Our preliminary analyses had suggested that gain and CUS rate were inversely correlated in some subject groups (Abel et al 1988, 1989), but with different relationships, as reflected by their differing slopes. The combination of SWJs and CUSs was made to see if the sum, which included virtually all saccades made during tracking (other than the far less frequent ASs), was related to gain. Adding SWJ and CUS counts corresponds to the technique of counting all saccades; this sum could reflect pursuit performance if the return saccade of an SWJ brought the eyes back on target, thus serving the dual role of completing the SWJ and acting as a CUS. Correlations between CUS rate and amplitude were also examined.

Statistical analyses were performed using SPSS/PC+ version 3.0. To test the differences between the three groups on four measures (TWAG and CUS rate at 5° and 20°/sec) a multivariate analysis of variance (MANCOVA) was employed. The test statistic employed for the MANCOVA was Pillai's trace. Since the patients with affective disorders were significantly older than the other two groups, and since pursuit measures have been reported to be correlated with age (Kuechenmeister et al 1977; Sharpe and Sylvester 1978; Hutton et al 1983; Kaufman and Abel 1986), age was a covariate in the analyses. A statistically significant result of the MANCOVA was followed by inspection of the univariate ANOVA tests. In cases where the univariate ANOVA was statistically significant, Duncan's multiple range tests were performed to allow post hoc multiple comparisons among group means. The relationship between TWAG and CUS rate at each target speed for each group was assessed with multiple regression analysis, with CUS rate as the dependent measure and TWAG as the independent measure. An analogous test was done with CUS rate as the dependent and CUS amplitude as the independent measure.

The complete analysis was repeated after removal of all outliers. The algorithm for outlier detection was as follows: First determine the 25th percentile score and the 75th percentile score. Second, compute the interquartile range, which is the difference between these two percentile scores. The upper threshold for classifying a point as an outlier equals the 75th percentile score $+(1.5 \times$ interquartile range); the lower threshold for classifying a point as an outlier is the 25th percentile score $-$ (1.5 $\times$ interquartile range).

Results

Age

As mentioned above, the affective disorders group was significantly older than both the normals and the schizophrenic patients ($F = 8.08$, df = 2,57, $p < 0.001$; Duncan's test $p < 0.05$). Schizophrenic patients did not differ in age from controls. Age was a

Table 1. Time-Weighted Average Gains[a]

Target velocity	Normals	Schizophrenic patients	Affective disorder patients
5°/sec	0.93 ± 0.05	0.89 ± 0.08	0.91 ± 0.08
20°/sec	0.87 ± 0.06	0.77 ± 0.11[b]	0.85 ± 0.10

[a]Data reported as mean ± SD.
[b]$p < 0.05$, Duncan's test, versus normals.

Table 2. Catch-up Saccade Rates (saccades/sec)[a]

Target velocity	Normals	Schizophrenic patients	Affective disorder patients
5°/sec	0.85 ± 0.30	0.65 ± 0.32[b]	0.55 ± 0.22[b]
20°/sec	2.29 ± 0.87	2.75 ± 0.77[c]	2.06 ± 0.74[c]

[a]Data reported as mean ± SD.
[b]$p < 0.05$, Duncan's test, versus normals.
[c]$p < 0.05$, Duncan's test, between patient groups.

Table 3. Mean Catch-up Saccade Amplitude (degree of visual angle)[a]

Target velocity	Normals	Schizophrenic patients	Affective disorder patients
5°/sec	0.52 ± 0.15	0.62 ± 0.17	0.67 ± 0.26
20°/sec	1.47 ± 0.31	1.77 ± 0.43	1.79 ± 0.56

[a]Data reported as mean ± SD.

Table 4. TWAG–CUS Rate Correlations, 5°/sec Targets

	Normals	Schizophrenic patients	Affective disorder patients
r	−0.66 ($p < 0.001$)	−0.42 ($p < 0.05$)	−0.11 ($p = 0.35$)
Slope	−4.07 (−6.31 to 1.82)	−1.68 (−3.34 to −0.01)	—
Intercept	4.63 (2.54 to 6.73)	2.14 (0.65 to 3.63)	—

Table 5. TWAG–CUS Rate Correlations, 20°/sec Targets

	Normals	Schizophrenic patients	Affective disorder patients
r	−0.57 ($p = 0.005$)	−0.24 ($p = 0.13$)	−0.31 ($p = 0.13$)
Slope	−7.93 (−13.45 to −2.42)	—	—
Intercept	9.21 (4.39 to 14.03)	—	—

statistically significant covariate in the MANCOVA ($F = 2.54$, df = 6,51, $p < 0.05$). All measures presented subsequently are for age-corrected data.

Diagnosis as a Main Effect

The MANCOVA revealed a statistically significant difference among the three groups ($F = 2.56$, df = 12,104, $p < 0.01$). TWAG and CUS rates and mean CUS amplitudes are given in Tables 1, 2, and 3, respectively. Inspection of the univariate F tests revealed statistically significant differences among the three groups on CUS rate at 5°/sec ($F = 4.45$, df = 2,56, $p < 0.02$) and 20°/sec ($F = 3.35$, $p < 0.05$) and on TWAG at 20°/sec ($F = 6.01$, $p < 0.01$), but not on TWAG at 5°/sec ($F = 1.89$, $p = 0.16$) (Table 4) and not on mean CUS amplitude at 5°/sec ($F = 1.89$, $p = 0.10$) or 20°/sec ($F = 2.74$, $p = 0.07$).

Gain Differences Between Groups

No gain differences were noted at 5°/sec (Table 1). For 20°/sec targets, TWAG was higher in the control group than in the schizophrenic group. Differences between affective disorder patients and the other groups were not statistically significant.

CUS Rate Differences Between Groups

During tracking of 5°/sec targets, both patient groups had a statistically significant reduction in CUS rate at 5°/sec when compared with controls (Table 2). In both cases, the patients made fewer CUSs than the controls, even though their gains were virtually identical. At 20°/sec, the age-corrected mean for CUS rate for schizophrenic patients was larger than for controls, and that for patients with affective disorders was smaller than for controls. Only the difference between the patient groups was significant.

Mean CUS Amplitude Differences Between Groups

The two patient groups had larger mean CUS amplitudes at both target speeds (Table 3). As noted above, the univariate ANCOVAs were not significant, although they may be considered trends. Post hoc tests were not performed.

Gain–CUS Rate Correlation

At 5°/sec, CUS rate was significantly negatively correlated with gain for both normals and schizophrenic patients (more strongly in normals), but with a lower slope and intercept for the latter group. Schizophrenic patients' slopes and intercepts both lay outside the 95% confidence limits of the normal group (Table 5). In contrast, affective disorder patients showed no relationship between CUS rate and gain. At 20°/sec only normals showed a significant TWAG/CUS rate correlation (Table 5). The results of the gain–CUS + SWJ correlation exactly paralleled these findings and are not presented separately.

Effects of Removing Outliers

To remove concern that our results may be seriously affected by outlying data points, outliers were identified as follows: one normal subject with an elevated CUS rate at 20°/sec, two schizophrenic patients with a low TWAG at 5°/sec, one schizophrenic patient with an elevated CUS rate at 5°/sec, one affective disorder patient with an elevated CUS rate at 5°/sec, one affective disorder patient with a reduced CUS rate at 5°/sec, and one affective disorder patient with a reduced TWAG at 20°/sec. Subjects with outlying values for any variable were removed, and the entire analysis repeated to determine if any substantive changes would occur. Only two such changes were found. First, the univariate ANCOVA test for the effect of diagnosis on mean CUS amplitude, which was borderline nonsignificant with outliers in, became borderline statistically significant ($F = 3.19$, df $= 2,48$, $p = 0.05$) and post hoc tests now revealed that patients with schizophrenia now had a significantly increased mean CUS amplitude compared to normals. Second, the correlation between CUS rate and TWAG at 5°/sec in schizophrenic patients went from borderline significance to nonsignificance.

Discussion

The results of the present study are complex, since a different pattern emerged with respect to group differences for each ocular motor measure. At 5°/sec, there were no gain differences among the groups, indicating that the patient groups showed no global inability to carry out a pursuit task. At 20°/sec, schizophrenics had a significantly reduced gain compared with normals, but not compared with affectives, who were intermediate. Significantly reduced gain at high target speeds in schizophrenics is in agreement with other reports (Levin et al 1982, 1988; Schmid-Burgk et al 1982; Yee et al 1987; Ross et al 1988; Litman et al 1989). Our finding that patients with affective disorders do not have significantly reduced gain is not consistent with the report of Yee et al (1987), although their nonschizophrenic patient group was more heterogeneous than ours, both in terms of diagnosis and medication status. The rate of CUS per se has not been addressed in other reports, so earlier studies are not directly comparable. Other workers have reported an elevated saccade rate, but have not distinguished between corrective saccades and saccadic intrusions. Our patient groups had a significantly reduced CUS rate at 5°/sec, and this is the first report of a decrease in saccade activity at any speed in the literature. At 20°/sec, the highest CUS rate was found in schizophrenics, the lowest was found for patients with affective disorders, and normals were intermediate—only the two patient groups differed significantly. An increase in saccade rate during tracking has been reported in schizophrenics (Cegalis and Sweeney 1979; May 1979; Mialet and Pichot 1981; Cegalis et al 1983; Mather 1985; Hommer et al 1987; Mather et al 1989), although several studies report no effect (Iacono and Koenig 1983; Thaker et al 1989). The diagnostic groups did not differ significantly in terms of mean CUS amplitude at 5°/sec, although means for both patient groups were higher than for controls. At 20°/sec, patient means were again higher and, with outliers removed, patients with schizophrenia had a significantly elevated mean amplitude. The trend is thus at 5°/sec for both patient groups to produce fewer but larger CUSs in response to position error, although gains were nearly the same for all three groups. At 20°/sec the picture is less clear because of gain differences, but patients and controls continue to correct for error in different ways. Thus, each of our ocular motor measures, taken separately, bears a different relationship to psychiatric diagnosis.

Smooth pursuit gain and CUS rate are not uncorrelated variables; hence, their interrelationship bears close examination. Since CUSs are corrective, a significant inverse relationship between CUS rate and gain might be expected, as we indeed observed in normals (Table 5). This was also true to a much weaker extent for schizophrenic patients at 5°/sec, and, indeed, if outliers are removed, this relationship is no longer significant. Schizophrenic patients exhibited no TWAG–CUS rate correlation at 20°/sec, and affective disorder patients showed none at either target speed. Thus, for these predictable targets both patient groups tended to generate corrective saccades at a fixed rate, regardless of the increasing position error accumulating during tracking. One possible explanation for this finding is that patients have a different threshold for position error. In other words, patients may make smaller or larger CUSs, dependent upon how far behind the target they allow themselves to fall before correcting. We found evidence consistent with this in the present study: both patient groups tended to make larger CUSs, but the finding was only statistically significant for patients with schizophrenia during tracking at 20°/sec, after outlier removal. CUS rate and amplitude were uncorrelated for any subject group at either target speed, suggesting that the process of error correction may vary idiosyncratically among subjects. Thus, the precise relationship among gain, CUS rate, and CUS amplitude in psychiatric patients remains to be clarified in future studies.

The relationship between pursuit and saccades was studied in detail in normals by Puckett and Steinman (1969), who found that two highly trained subjects could switch between purely smooth tracking with considerable position error or tracking that remained closer to the target but that included significantly more saccades. Since it seems highly unlikely that any of our experimentally naive subjects were intentionally manipulating their CUS rates, this is not a probable explanation for the intergroup differences.

The site where the interaction between the pursuit and saccadic systems might be occurring remains unknown, although a possible location would be the frontal eye fields (FEF), since this region is known to be involved in the control of both saccadic and smooth pursuit systems (Ferrier 1874; Goldberg and Bushnell 1981; Bruce and Goldberg 1984; Levin 1984; Guitton et al 1985; Lynch 1987; Hommer and Radant 1989). Lynch (1989) recently reported that as gain recovered in monkeys with bilateral ablations of pursuit-related regions of the FEF, the amplitude of CUSs remained constant.

It is the precise identification and quantification of the saccadic and pursuit components of subjects' tracking that enables us to build upon prior reports of abnormal pursuit in schizophrenic patients and to describe what it is that makes it abnormal. The most striking difference between patients and normals lay not in the defective function of either their pursuit or saccadic systems, but rather in how these two mechanisms interacted. We can now attempt to identify potential neural mechanisms that underlie these defects and relate them to those implicated in other aspects of the symptomatology of schizophrenia.

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