The association between lithium carbonate and smooth pursuit eye tracking among first-episode patients with psychotic affective disorders

DIANE C. GOODING, WILLIAM G. IACONO, JOANNA KATSANIS, MORTON BEISER, AND WILLIAM M. GROVE

Abstract

The association between treatment with lithium carbonate and smooth pursuit eye tracking performance was investigated in first-episode patients with psychotic affective disorders. The horizontal pursuit performance of patients with major depression and bipolar disorder who were receiving lithium carbonate was contrasted with that of patients not receiving lithium carbonate. In addition, the accuracy and quality of pursuit eye tracking was examined in bipolar patients whose lithium status changed from the time of initial testing to the time of restest 10 months later. For the combined group of depressed and bipolar patients, treatment with lithium carbonate was not associated with worse pursuit performance. Bipolar disordered patients on lithium did not differ in tracking proficiency from those not on lithium; bipolar patients whose lithium status changed from intake to restest also did not display a significant change in pursuit performance.

Descriptors: Smooth pursuit eye movements, Bipolar mood disorder, Lithium carbonate

Smooth pursuit eye tracking dysfunction has generated much interest as a potential marker of vulnerability to schizophrenia (Holzman et al., 1974; Iacono, 1985, 1988). However, investigators have questioned the specificity of pursuit dysfunction to schizophrenia because impaired smooth pursuit eye tracking has appeared in affective disorder patients as well as in schizophrenics (Holzman, Solomon, Levin, & Wateraux, 1984; Iacono, Pelouquin, Lumry, Valentine, & Tuason, 1982; Lipton, Levin, & Holzman, 1980; Salzam, Klein, & Strauss, 1978; Shagass, Amadeo, & Overton, 1974). Impaired smooth pursuit eye movements among schizophrenic patients are not likely to be a consequence of neuroleptic treatment (Holzman et al., 1984; Levy, Lipton, Holzman, & Davis, 1983; Saletu, Kufferle, Grunberger, & Anderer, 1986; but see Rea, Sweeney, Solomon, Walsh, & Frances, 1989), a finding that buttresses the hypothesis that eye tracking dysfunction is a stable trait independent of psychotropic medication effects in patients with this disorder. In contrast, there have been indications that the tracking abnormality observed among affective disorder patients may be dependent upon state-related phenomena, such as treatment with lithium (Holzman, O’Brian, & Wateraux, 1991; Iacono et al., 1982; Levy et al., 1984, 1985).

Only a few studies have examined the relationship between lithium carbonate treatment and smooth pursuit tracking performance (Holzman et al., 1991; Iacono et al., 1982; Levy et al., 1985). All three studies concluded that the smooth pursuit system may be adversely affected by lithium. Iacono et al. (1982) compared the tracking performance of 31 affective patients taking lithium carbonate with that of 18 affective patients who were not taking lithium and 46 control subjects. Because pharmacologic treatment was randomly assigned, the greater impairment displayed by the group on lithium was attributed to drug effects. However, these researchers also observed that although 52% of the unipolar patients were receiving lithium treatment, some of them actually displayed better tracking performance than the control subjects. This finding suggests that some lithium-treated patients are good trackers, despite their medication status, and raises the question of a possible interaction between lithium carbonate and diagnosis.

In another study of lithium’s effect on smooth pursuit, Levy et al. (1983) observed that 14 of 15 bipolar inpatients had impaired pursuit while taking lithium carbonate and seven of the eight previously good trackers showed signs of tracking impairment following lithium administration. Among remitted pa-
tients on lithium, 56% were classified as bad trackers. Despite lithium treatment, the remaining 44% were good trackers, a finding that is consistent with the Iacono et al. (1982) results, indicating that treatment with lithium is not invariably accompanied by bad tracking. Similar results were obtained by Holzman et al. (1991), who examined the pursuit eye movements of 11 bipolar patients before and after lithium therapy. Two of the patients showed deviant tracking while off lithium, and 64% were impaired while receiving this medication. The patients also showed a trend indicating that pursuit gain was diminished while on lithium, and they generated more saccades while on the drug. The findings from these three reports together suggest that earlier reports of eye tracking dysfunction among bipolar patients (Lipton et al., 1980; Slagter et al., 1974) may have reflected a drug artifact. In a recent report documenting impaired smooth pursuit eye tracking in 41% of a sample of bipolar patients, all 46 of the patients were taking lithium (Holzman et al., 1984).

Most of the patients in the studies that indicated an association between lithium treatment and impairment of smooth pursuit eye tracking were chronically ill and had had many prior episodes of disorder; inclusion of such patients raises the issue of possible confounds, such as treatment duration and other effects of prior antipsychotic medication use and/or chronic illness. The present analysis was undertaken to complement this line of research by examining the relation between lithium treatment and tracking performance in affective disorder patients experiencing their first psychotic episode. Studying first-episode psychiatric patients eliminates the confounding effects of prior antipsychotic medication use and/or chronic illness. The possible relation between treatment with lithium carbonate and eye tracking dysfunction was explored in two ways: we compared patients receiving lithium with those not receiving lithium treatment, and in a subsample of these subjects we evaluated their tracking proficiency on and off lithium.

### Method

### Subjects

Subjects in the present investigation were drawn from a comprehensive study of 158 patients experiencing their first lifetime episode of psychosis (Beiser, Fleming, Iacono, & Lin, 1988; Erickson, Beiser, Iacono, Fleming, & Lin, 1989; Iacono & Beiser, 1989). A recruitment strategy that extended beyond the mental health care system was used in an effort to recruit every case of first-episode psychosis between the ages of 16 and 54 in the major metropolitan area of Vancouver, Canada. This recruitment effort yielded a community-based sample. However, the subjects in this report were all inpatients referred from psychiatric hospitals and psychiatric services of general hospitals. Exclusion criteria were the following: known ocular motor dysfunction; organic cerebral illness; prior treatment with antipsychotics, antidepressants, or lithium carbonate; severe mental retardation; chronic physical disorder; and/or chemical dependence.

Sixty psychotic patients with mood disorders met the inclusion criteria and completed the eye tracking assessment. These patients were receiving benzodiazepine treatment. However, because benzodiazepines may affect pursuit eye tracking (Abel & Hertle, 1988), these three patients were dropped from this study.

<table>
<thead>
<tr>
<th>Lithium status</th>
<th>Other medications*</th>
<th>Major depression (n = 26)</th>
<th>Bipolar disorder (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On lithium</td>
<td>None</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>N, AP</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AD, AP, N</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not on lithium</td>
<td>None</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>N, AD</td>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>N, AP</td>
<td></td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>N, AD, AP</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*None = no other drugs; N = neuroleptic; AD = antidepressant; AP = anti-Parkinson agent.

Only the 57 remaining individuals who satisfied DSM III criteria for bipolar disorder or major depression were included in this report; 26 patients had major depression and 31 patients had bipolar disorder. Table 1 provides the medication status of the subjects at the time of the initial oculomotor testing. Briefly, five of the patients with major depression were medication free, and one patient with major depression was receiving lithium carbonate. Only two of the patients with bipolar affective disorder were medication free. Fifteen bipolar patients were receiving lithium treatment. No patients received MAO inhibitors, carbamazepine, or barbiturates. As indicated in Table 1, most of the sample was receiving neuroleptics, which is not surprising given their psychotic status. None of these first-episode patients showed any signs of tardive dyskinesia.

All subjects were tested after their clinical status and medication status had been stabilized. Most patients were tested close to discharge to assure that they were not in acute psychiatric distress. Medications for these patients must have been stabilized for at least 7 days prior to psychophysiological testing. Eye tracking performance and clinical status were reassessed in a subsample of 10 bipolar subjects approximately 10 months following initial testing (mean, 10.3 months; range, 5-15 months). The length of time the patients had been lithium free prior to the second assessment varied from 4 months to 12 months.

Psychiatric diagnoses were assigned based on agreement between at least two experienced diagnosticians who used DSM-III (1980) criteria and data derived from an interview with the Present State Examination (Wing, Cooper, & Sartorius, 1974), a thorough chart review, and an interview with a friend or relative of the patient. Kappa coefficients for Axis I psychiatric diagnoses among pairs of clinicians varied from .74 to .97.

### Apparatus and Procedure

A more detailed description of the apparatus and procedure has been published previously (Iacono, Moreau, Beiser, Fleming, & Lin, 1992). Briefly, each subject watched a 5-mm luminous spot with a dot in its center. The target traversed 20 degrees of visual arc and was displayed approximately 30 cm from the sub-
ject on a cathode ray oscilloscope screen. The target was driven sinusoidally by a waveform generator and moved horizontally for approximately 50 s at a frequency of 0.4 Hz. An adjustable head-and-chin rest that included temporal bone supports was employed to position the subject’s head and help keep it stationary during the task. Subjects were instructed to relax, remain still, refrain from blinking, and follow the spot of light as closely as possible by focusing their gaze on the dot in the center of the circle.

Recording Techniques
Amplified eye and target movements were fed into a Beckman Type R-612 Dynograph and recorded on FM tape. Eye movements were recorded binocularly using horizontal electro-oculography (EOG); AC coupling with a 3-s time constant was used. Beckman Ag-AgCl electrodes were placed at the outer canthi. An earclip electrode served as the ground.

Eye Movement Analysis
Eye tracking was assessed using four variables: root-mean-square error, qualitative ratings, anticipatory saccades, and total number of intrusive saccades. The root-mean-square (RMS) error (Iacono & Lykken, 1979a, 1979b) indicates the degree to which the subject’s tracking record can be superimposed on the target waveform. To obtain this estimate, the subject’s pursuit and the target waveforms were converted to digital form using a 12-bit A-D converter at a sampling rate of 240 Hz. A computer was programmed to compute the RMS error deviation between the two channels after aligning them to eliminate phase differences. To eliminate the effect of occasional cycles of unusually poor tracking performance, the median (rather than mean) RMS error of 16 consecutively tracked cycles was calculated. The median RMS error score is logarithmically transformed to reduce the skewness of the data. Lower RMS error scores indicate more accurate pursuit performance.

RMS error is a robust index of tracking proficiency; it can differentiate both schizophrenics (including those in remission) and their relatives from normal subjects (e.g., Clementz, Sweeney, Hirt, & Haas, 1990; Iacono, Tuason, & Johnson, 1981). It is under genetic influence (Iacono, 1982), and it has high temporal stability over periods as long as 2 years (Iacono & Lykken, 1981). It also correlates highly with raters’ judgments of tracking proficiency in normal subjects (n = 64; r = .91, Iacono & Lykken, 1979b) and with oculomotor gain in schizophrenics (n = 38; r = .88, Clementz, Grove, Iacono, & Sweeney, 1991).

In the figure published with their article, Levy et al. (1985) illustrated the EOG tracing of a patient before and after lithium treatment. After taking lithium, the patient’s EOG had a “spiky” appearance. Spiky tracking probably reflects leakage of EEG activity, especially the alpha rhythm, into the EOG (Iacono & Lykken, 1981). Levy et al.‘s figure thus raises the possibility that the lithium effect was due in part to lithium’s influence on the EEG. Lithium increases EEG amplitude, including the amplitude of alpha (Johnson, Maccario, Gershon, & Korein, 1970), and increases alpha anteriorization (Ulrich, Frick, Stiegitz, & Muller-Oerlinghausen, 1987). Both of these EEG effects could contribute to the development of spiky EOGs following lithium therapy. To assess this possibility, we rated eye tracking on a 4-point spikiness scale that was the equivalent of the 5-point spikiness scale illustrated in Iacono and Koenig (1983, Figure 1) with scale points 4 and 5 collapsed into a single rating. Two raters blindly evaluated all the EOG tracings. Interrater reliability was high (intraclass correlation = .93). Discrepancies in ratings never exceeded 1 scale point; averaged ratings were employed in those cases where the two raters’ judgments were not identical.

Commenting on the studies of Levy et al. (1985) and Iacono et al. (1982), Abel and Hertle (1988) noted that the use of global measures of pursuit performance made it difficult to determine the specific nature of the effect. Abel and Hertle (1988) suggested that it would be informative to determine whether saccadic interruptions, specifically square wave jerks and anticipatory saccades, accounted for the lithium effect. To assess this possibility, we measured these saccadic events using off-line visual inspection of digitized records. These analyses were performed using Assistant’s (Asyst Software Technologies, Inc.) interactive waveform analysis program. The eye tracking trials were displayed on a 14-in. color monitor screen, equipped with 640 x 480 pixel resolution graphics. An ASYST program with scroll windows allowed expansion of each eye tracking cycle so that it filled an entire screen. The resulting resolution was adequate to detect and measure saccadic intrusions. Anticipatory saccades were defined as singular saccadic events greater than 5 degrees in amplitude and moving in the same direction as the target, followed by a decrease in pursuit velocity (Abel & Ziegler, 1988). Three types of square wave jerks were examined. Square wave jerks were defined as pairs of back-to-back saccades ranging from 1 to 5 degrees in amplitude, with an intersaccadic interval of approximately 200–500 ms, during which pursuit continued parafoveally. Large square wave jerks were square wave jerks greater than 5 degrees in amplitude with intersaccadic intervals of approximately 200 ms. Macro-square wave jerks were greater than 10 degrees in amplitude with considerably shorter intersaccadic intervals, typically 100–120 ms. The operational definitions for anticipatory saccades and square wave jerks are consistent with those commonly employed in the oculomotor literature (Abel & Ziegler, 1988; Clementz & Sweeney, 1990; Clementz et al., 1990; Elidan, Gav, & Lev, 1984; Leigh & Zee, 1983). Illustrations of these types of intrusive saccadic events can be found in Clementz, Sweeney, Hirt, and Haas (1991, Figure 1).

The number of saccadic intrusions was independently determined by two raters who were blind to subject identity, group membership, and medication status. Interrater reliability for the presence of anticipatory saccades was .96 (intraclass correlation). The various types of square wave jerks appeared so infrequently in some of the records that an intraclass correlation for each type of square wave jerk could not be computed; instead, an intraclass correlation for total number of intrusive saccades was computed. Despite the relative infrequency of saccadic events in some records, the two raters always agreed (within 1) in their tally of square wave jerks. The overall interrater reliability for the presence of intrusive saccades was .90 (intraclass correlation). Because the frequency of anticipatory saccades was strongly correlated (r = .99) with the total number of saccadic events in this sample, we used only the total number of intrusive saccades in the data analyses.

To test the association between lithium carbonate and impaired smooth pursuit and to maximize power for our sample size, we employed one-tailed significance tests. On the basis of previous findings, we predicted that patients on lithium carbonate would display poorer tracking than those who were not receiving lithium.
Table 2. The Association Between Lithium Carbonate and Tracking Performance

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Age (years)</th>
<th>log RMS</th>
<th>Ratings</th>
<th>Intrusive saccades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Total</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Affective patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On lithium</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td>27.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Not on lithium</td>
<td>15</td>
<td>26</td>
<td>41</td>
<td>25.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Bipolar only*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On lithium</td>
<td>8</td>
<td>7</td>
<td>15</td>
<td>28.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Not on lithium</td>
<td>7</td>
<td>9</td>
<td>16</td>
<td>25.6</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Note: The log RMS (root-mean-square) error is a quantitative assessment of tracking; lower scores are associated with more accurate eye tracking. Eye tracking records were rated on a scale of 1-4; higher scores indicate pursuit characterized by excessive spikiness. The total number of intrusive saccades (including anticipatory saccades and various types of square wave jerks) was also tabulated.

*These 31 "bipolar only" patients are a subgroup of the 57 "affective" patients (above).

Results

Relationships Among Dependent Variables

The correlation between the spikiness ratings and computer-derived quantitative scores (RMS error) was moderate ($r = .60$, $p < .01$). RMS error scores were significantly correlated with the frequency of anticipatory saccades and with the total number of intrusive saccades, $r = .66$ and .69, respectively (both $p < .01$). Spikiness ratings were not significantly associated with the total number of intrusive saccades. Overall, these results indicate that these dependent variables were tapping somewhat different aspects of oculomotor functioning.

Lithium Treatment in Affective Disorder Patients

The sample group not on lithium consisted of 25 patients with major depression and 16 patients with bipolar disorder; 7 of these patients were unmedicated. The group receiving lithium included 1 patient with major depression and 15 patients with bipolar disorder (Table 2). Patients receiving lithium did not differ from patients who were not taking lithium in age, $t(55) = -1.24$, n.s., or sex, $\chi^2(1) = .35$, n.s. Although the comparison groups did not differ in terms of these demographic characteristics, they were clinically heterogeneous; the group not on lithium was comprised of affective patients, whereas almost all of the patients on lithium had bipolar disorder. A multivariate analysis of variance (MANOVA) was calculated to determine if the affective disorder patients on lithium and those not on lithium differed in RMS error scores, spikiness ratings, or frequency of intrusive saccades. The MANOVA failed to indicate a significant lithium effect, $F(3, 53) = .67$. Univariate tests computed for each variable were similarly nonsignificant at the .05 level (one-tailed).

Our comparison of patients on and off lithium could be compromised if the other medications these patients were receiving affected oculomotor function. To investigate this possibility, we compared the smooth pursuit of subjects on and off neuroleptics, antidepressants, and anti-Parkinson agents; none of these drugs were significantly associated with eye tracking impairment.

Lithium Treatment in Bipolar Patients

A lithium effect on eye tracking could have been obscured in the above analysis on all affective disorder patients if the drug effect was specific to bipolar disorder. Therefore, we compared the pursuit performance of the bipolar patients on lithium with that of bipolar patients not receiving lithium. Because RMS error, spikiness ratings, and frequency of intrusive saccades did not differ significantly between bipolar patients who received lithium and neuroleptic treatment ($n = 5$) and those who received lithium only ($n = 9$), all bipolar patients on lithium were grouped together for the remaining analyses.

The demographic and smooth pursuit performance characteristics of the 16 bipolar patients not on lithium and 15 patients who received lithium are summarized in Table 2. The two groups of bipolar patients did not differ significantly in terms of age or gender. Other than lithium, the two groups of bipolar patients did not differ in terms of the relative percentages that were receiving other types of medications, Fisher's exact test, $p = .28$, one-tailed. A MANOVA applied to the measures of smooth pursuit performance yielded a nonsignificant multivariate $F(3, 27) = .83$. The results of univariate analyses carried out on the same variables also failed to reveal a significant medication effect.

All the bipolar subjects in this study, whether receiving lithium or not, may have been deviant trackers. If such were the case, any lithium effect could be masked by the overall poor performance of these patients. To evaluate this possibility, we compared the RMS errors of the bipolar patients off lithium and those on lithium with the RMS errors of 121 normal subjects who were recruited as part of a comparison sample for the larger study of which these bipolar patients were a part (see Incono et al., 1992). Neither bipolar group differed from this normal sample, both $t < 1.27$.

Lithium Status and Test-Retest Performance

We also examined the pursuit performance of bipolar patients whose lithium status changed from the time of intake to the time of follow-up data collection. Lithium status changed for 10 subjects of whom we had both intake and retest data. Table 3 provides the RMS error scores, spikiness ratings, and numbers of saccades for each of the subjects on both testing occasions. Among the bipolar patients whose lithium status changed, four patients were not on lithium during the initial testing, whereas in six cases, lithium treatment was discontinued by the time of the 9-month follow-up.
Table 3. Bipolar Patients Whose Lithium Status Changed From Intake to Resi

<table>
<thead>
<tr>
<th>Subject number</th>
<th>On lithium</th>
<th></th>
<th>Total saccades</th>
<th>Off lithium</th>
<th></th>
<th>Total saccades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Other drugs</td>
<td>RMS</td>
<td>Ratings</td>
<td>Other drugs</td>
<td>RMS</td>
<td>Ratings</td>
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<tr>
<td>1</td>
<td>None</td>
<td>2.21</td>
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</tr>
<tr>
<td>2</td>
<td>None</td>
<td>1.81</td>
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<td>None</td>
<td>1.78</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>N, AD</td>
<td>1.88</td>
<td>4.0</td>
<td>N, AP</td>
<td>1.95</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>N, AP</td>
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<td>3.0</td>
<td>None</td>
<td>1.87</td>
<td>1.0</td>
</tr>
<tr>
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<td>3.5</td>
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<td>2.44</td>
<td>3.5</td>
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<td>6</td>
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<td>7</td>
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<td>8</td>
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<tr>
<td>9</td>
<td>N</td>
<td>2.30</td>
<td>3.0</td>
<td>N</td>
<td>2.37</td>
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</tr>
<tr>
<td>10</td>
<td>AD</td>
<td>1.83</td>
<td>4.0</td>
<td>None</td>
<td>1.77</td>
<td>1.0</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>2.11</td>
<td>2.8</td>
<td></td>
<td>2.14</td>
<td>2.4</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>0.28</td>
<td>1.1</td>
<td></td>
<td>0.31</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Note. The log RMS (root-mean-square) error is a quantitative measure of tracking; lower scores are associated with more accurate eye tracking. Eye tracking records were rated on a scale of 1-4; higher scores indicate pursuit characterized by excessive spikiness. Frequency of total number of intrusive saccades (including anticipatory saccades and various types of square wave jerks) was also tabulated.

None = no other drugs; N = neuroleptic; AD = antidepressant; AP = anti-Parkinson agent.

The mean values for each of the dependent variables on and off lithium are shown in Table 3. A repeated measures MANOVA using RMS error scores, spikiness ratings, and frequency of intrusive saccades showed no significant difference in tracking performance while on lithium or off lithium, F(3, 7) = 1.59. Similarly, one-tailed, paired-sample t tests (on vs. off lithium) computed for each of these variables was not significant.

Discussion

Our results clearly indicate no association between lithium therapy and smooth pursuit impairment and suggest that patients receiving lithium do not necessarily show eye tracking dysfunction. Iacono et al. (1982), Levy et al. (1985), and Holzman et al. (1991) also found lithium treated patients who were not bad trackers. For example, 7 of 16 outpatients and 5 of 15 inpatients on lithium were good trackers in the study of Levy et al. (1985). These findings complement those of Opdenoorte, Kral, and Wolf (1986), who found no differences in saccadic eye movement latency or velocity between patients receiving long-term lithium prophylaxis (average 5.6 years) and healthy controls.

Because bipolar disorder appears to be a distinctly different illness from schizophrenia, bipolar patients are a desirable psychiatric control group. However, the usefulness of these patients as controls would be limited if only lithium-free patients could be studied. Neither the bipolar patients on lithium nor those off this drug differed significantly from 121 psychiatrically healthy, normal subjects. Because schizophrenics consistently have significantly poorer tracking than normal controls, this finding provides additional evidence that smooth pursuit dysfunction is specific to schizophrenia. Because our sample is epidemiologically based, our results may be more generalizable than those derived from patients recruited through a single source.

This study is not a systematic investigation of lithium effects on eye tracking; patients were not randomly assigned to medications. Thus, when the patients on lithium were compared with those off lithium, these groups may have differed in ways other than medication status. Although these unidentified group differences may have obscured observation of a lithium effect, this possibility is unlikely, considering the consistent results of our within-subject assessment of eye tracking performance when patients were on and off lithium.

Many of our patients were receiving more than one medication at the time of study, and types of medications were allowed to vary naturally. Although there are limitations inherent in an uncontrolled study like this one, the advantage of enhanced external validity should not be overlooked. In clinical management, patients are often given combinations of psychotropic drugs not seen in most controlled studies. The epidemiologically based sample employed in this study may better reflect the medication status of typical patients than do subjects of the treatment regimes administered in a systematic drug study.

Serum lithium levels were not recorded in this study; therefore, we cannot be certain that patients took lithium as prescribed. However, because the analyses were based on the data derived from inpatients stabilized on their medications for at least 1 week and because medications were therefore supervised, we have no reason to suspect that subjects were either noncompliant or at subtherapeutic levels. Of the 10 subjects who were evaluated twice, 6 were inpatients on lithium, and the 4 outpatients stated that they were medication compliant during a follow-up interview. When these subjects were assessed while off lithium, 4 had never taken lithium and the remainder had been lithium free for at least 4 months.

Our failure to find a lithium effect may have been because the subjects were taking other drugs besides lithium. However, among affective subjects, we found no impact of other drugs on pursuit tracking. There also were no significant differences between bipolar patients on and off lithium in terms of the proportion taking other medications. For the retes group, only 2 of the off-lithium subjects were receiving any other drugs. RMS...
errors of these two subjects were essentially identical on and off lithium. Thus, there is no evidence that other medications obscured a lithium effect.

Negative findings such as these often have low statistical power. To determine the power of our study, we estimated effect sizes from studies by Levy et al. (1985), Iacono et al. (1982), and Holzman et al. (1991). Levy et al. measured signal-to-noise ratio, a global measure related to RMS error (Iacono & Lykken, 1983; Lykken, Iacono, & Lykken, 1981). Using the effect size calculated from Levy et al. (1985), 1.09 SD, and applying it to our RMS error data, our power would have been .99 ($\alpha = .05$, one-tailed). The RMS error effect size from the correlational data reported by Iacono et al. (1982), 0.63 SD, would give power at the one-tailed .05 level of significance of .66, moderate power with which to detect significant differences (Kraemer & Thiemann, 1987). We have distinctly higher power to detect group differences between our normal subjects and our bipolar patient groups using RMS error. There are no data on effect sizes associated with spikiness ratings available in the literature. However, on the basis of the between-subjects analysis provided in the Holzman et al. (1991) report, the effect size for the saccade measure can be estimated at 0.92 SD. If we assume that the true effect size lies between 0.63 and 1.09 SD for the spikiness rating measure, that the other measures have effect sizes as indicated above, and that these variables all intercorrelate at about .6 (as we found in this report), then our MANOVA based on RMS error, spikiness ratings, and intrusive saccades would have had a power in excess of .90 ($\alpha = .05$, two-tailed). Furthermore, the effect size from the within-subject analysis reported by Levy et al. (1985), 1.09 SD, corresponding to our paired-sample t-tests, would give power at the one-tailed .05 level of significance of .90. Our findings thus are not likely due to low statistical power.

The data in Table 3 show no hint of a trend in the predicted direction. In terms of RMS error, 5 patients were worse on lithium and 4 were worse off lithium. Seven of 10 patients had identical spikiness ratings on the two testing occasions, 1 was better on lithium, and 2 were worse. The intrusive saccade count identified 4 subjects with more saccades on lithium, 5 with more off lithium, and 1 with no saccades either way.

It is unclear why our results differ from those of previous studies. Differences in the clinical condition of the subjects probably cannot account for the results. Iacono et al. (1982) found the effect in remitted affective patients and Levy et al. (1985) found it in both remitted and acutely ill subjects. In the Holzman et al. (1991) sample, pursuit performance appeared to be independent of clinical status. A possible contributing factor is that our subjects were about 10 years younger than those in Iacono et al. (1982) and Levy et al. (1985) and were approximately 5 years younger than those in Holzman et al. (1991). Perhaps even more importantly, our subjects were experiencing their first illness episode. The bipolar patients in Iacono et al. (1982) had all been medicated previously and had an average of 11 prior episodes, whereas 80% of the inpatients of Levy et al. (1985) had been medicated before. Although Holzman et al. (1991) did not provide a detailed history of their patients, none of their subjects were first-episode patients and many if not all of these patients had a prior history of psychotropic medications other than lithium. Perhaps age, history of prior episodes, and/or medications interact with lithium status in a way that can influence eye tracking performance.

Short- and long-term administration of lithium may also affect pursuit differently (Levy et al., 1985), and this effect can influence electroencephalographic activity (Dimitrakoudis & Jennett, 1975; Johnson et al., 1970). Levy et al. observed that among remitted bipolar patients those with more impaired tracking had had longer lithium therapy. The timing of such a lithium effect is unknown, and the factors that influence individual differences in sensitivity to lithium are also unknown. Although we hypothesized that the lithium effect could occur by augmenting EEG activity that is picked up by the EOG, we lack of a lithium effect leaves us with nothing to explain. Because lithium influences EEG, which in turn may affect the EOG, future studies should evaluate the lithium effect using infrareye movement recordings that are not contaminated by EEG. It is interesting that Holzman et al. (1991) found some evidence of a lithium effect when using infrared recording.

Further research could determine the circumstances that would mandate exclusion of eye tracking data from patients on lithium. Future studies should include never-medicated and previously medicated subjects as well as first-episode and chronic cases. The optimal design would involve the multivariate assessment of pursuit in affective disordered patients before, during, and after receiving lithium. All the samples of bipolar patients receiving lithium have been relatively small; larger samples of bipolar patients are necessary to provide more conclusive evidence. Large samples of depressive patients on lithium would also be useful to address more definitively the possibility of a diagnosis × Lithium interaction.

REFERENCES


Effects of lithium on eye tracking


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