Smooth Pursuit in Twins Before and After Alcohol Ingestion

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Purpose. The influence of genetic factors on characteristics of smooth pursuit were evaluated in young adult monozygotic (MZ) and dizygotic (DZ) twins before and after the administration of a single dose of ethanol.

Methods. Sinusoidal pursuit was recorded using a scleral search coil at frequencies of 0.25 and 0.5 Hz before and after alcohol consumption. Pursuit gain, interval between saccades, saccadic accuracy, and saccadic amplitude were quantified.

Results. Alcohol consumption reduced pursuit gain and saccadic accuracy and increased the rate and amplitude of saccades. Before and after alcohol consumption, the intraclass correlations for MZ twins (rMZ) were highly significant for pursuit gain, interval between saccades, and saccade amplitude. Corresponding correlations for DZ twins (rDZ) were not significant. Heritability values were similar before and after alcohol ingestion.

Conclusions. The disparity between rMZ and rDZ suggests either multiple gene interactions or common environmental influences for MZ twins, greater than those for DZ twins. Invest Ophthalmol Vis Sci. 1997;38:1768–1773.

Pursuit eye movements are normally made to track an object moving smoothly in the visual environment. Tests of smooth pursuit are commonly used to evaluate patients with neurologic, ophthalmologic, and psychiatric disorders, as well as to evaluate the effect of drugs.[1–4] Abnormalities in smooth pursuit have been reported in patients with schizophrenia and their first-degree relatives, suggesting that abnormal tracking may serve as a biological marker[5] or an indicator of genetic liability[6] for schizophrenia. Iacono and Lykken[7] have shown that normal monozygotic (MZ) twins have similar patterns of eye movements. Iacono[8] examined smooth pursuit in healthy MZ and dizygotic (DZ) twins and found that intraclass correlation averaged over all pursuit tasks was 0.68 and 0.35 for identical and fraternal twins, respectively. He showed that there was a relatively strong genetic influence over the global accuracy of smooth-pursuit tracking, measured by root mean square error, and a much weaker influence for phase lag. Pursuit gain was not assessed. Results obtained in our laboratory showed an intraclass correlation for pursuit gain of 0.91 in MZ twins.[9] The possible heritability of parameters of smooth pursuit is of interest both for a general understanding of the pathways controlling underlying eye movements and as a basis for determining possible genetic influences on specific disorders.

Alcohol has been found to impair smooth-pursuit performance when administered acutely and in chronic alcohol abusers.[4,10,11] There is considerable evidence for genetic influence[12] on alcoholism, but debate continues about the identity of specific genes.[13] Cowley et al[14] found that diazepam administration caused significantly less reduction in peak saccadic velocity and pursuit gain in the sons of alcoholics than in control subjects. This observation suggested that the susceptibility of the ocular motor system to alcohol may be linked to the factors responsible for alcoholism. In a previous article,[15] we evaluated possible genetic influences on the control of saccadic eye movements both before and after alcohol consumption, comparing MZ and DZ twins. We found that saccadic tracking is at least in part genetically determined. In

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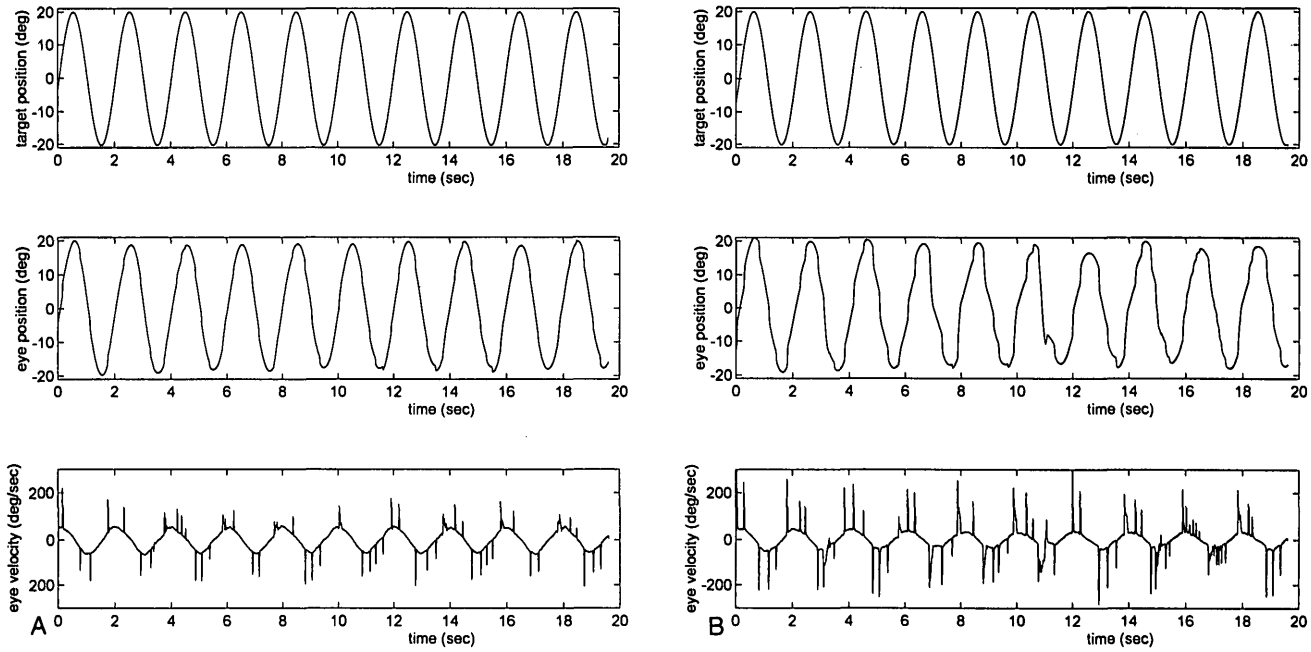

FIGURE 1. Examples of typical pursuit records (target position and eye position) and calculated eye velocity. Frequency of target was 0.5 HZ. (**A**) Before and (**B**) after alcohol consumption. After alcohol administration, pursuit gain and intersaccadic interval decreased and saccadic amplitude increased.

this investigation, we examined pursuit tracking and corrective, or catch-up, saccades in the same MZ and DZ twins to evaluate the genetic influence on pursuit eye movements both before and after alcohol consumption. Corrective, or catch-up, saccades during pursuit tracking reduce the position errors between the retinal image of the target and the fovea when pursuit eye velocity is less than the target velocity and the eye falls behind the target. A typical example of recordings before and after alcohol consumption is shown in Figure 1.

METHODS

Twenty-four pairs of MZ twins were tested (mean age, 33.6 ± 8.3 years; 10 male and 14 female) and 23 pairs of same-gender DZ twins (mean age, 32.4 ± 7.7 years; 14 male and 9 female). All subjects were social drinkers who had no known neurologic or ophthalmologic disorders. The research was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from subjects after the procedures were explained to them. The methods were the same as described in our previous article.[15] Two hours after a standard light breakfast, the subjects drank 0.44 ml/kg (for male twins) or 0.41 ml/kg (for female twins) of ethanol in an 11.88% solution with caffeine-free diet soda. These dosages were selected to bring the subject's blood alcohol concentration to ~0.05%. Breath alcohol was measured using a breath analyzer (Datamaster Breath Alcohol Analyzer, National Patent Analytical System, Mansfield, OH). Blood alcohol concentrations, estimated from breath analysis, were 0.061% (SE = 0.003%) and 0.051% (SE = 0.003%) before and after measurement of the eye movements, respectively.

Subjects were seated 1 m from a screen onto which a red, helium-neon laser spot (0.25° in diameter) was rear-projected by a computer-controlled mirror galvanometer. A head restraint was used to minimize head movements. Horizontal eye movements were recorded monocularly using the scleral search coil technique[16,17] and digitized at 1000 Hz for later analysis. Viewing was binocular. Pursuit tests consisted of 10 cycles of sinusoidal tracking at 0.25 and 0.50 Hz over ±20°. For data analyses and graphic presentation of results, interactive programs were written using Matlab and Microsoft Visual C++. The digitized eye position signal was differentiated. The desaccading algorithm was based on a combination of the Kalman filter algorithm[18] and an algorithm for defining the saccade threshold. Pursuit gain, the interval between catch-up saccades during pursuit, saccadic amplitude, and saccadic accuracy were calculated. Blinks were removed from the record. Pursuit gain was calculated as the mean of the ratio (eye velocity to target velocity) for all points of smooth pursuit, except where target velocity was near 0. The mean interval between saccades and the mean amplitude of saccades were calcu-

lated for all catch-up saccades. The accuracy of catch-up saccades was defined as the mean of target position minus eye position at the end of the saccade.

To obtain unbiased estimates of heritability using the twin model, several assumptions were required. These five assumptions and their potential effect on results, discussed in our previous article,[15] are that the data are normally distributed within zygosities, that the twins are a random sample of population twins, that the total variances of MZ and DZ twins are equal, that there is a random mating within the population, and that the environmental covariance of MZ twins equals the environmental covariance of DZ twins.

The correctness of the first three assumptions for our data was tested. The departure from normality (first assumption) was tested by the Kolmogorov–Smirnov test, and saccadic amplitude and intersaccadic interval were normalized by logarithmic transformation. Although there was also violation from normality in the accuracy of catch-up saccades, no suitable data transformation could be found. The means of the MZ and DZ twins (second assumption) were tested, and the variances of MZ and DZ twins (third assumption) were compared using an F′ test.[19] There were no significant differences between the two groups of twins in means and, typically, in total variances. The only exception was saccadic amplitude (before alcohol) for frequency 0.5 HZ, where MZ variances were significantly greater than DZ variances.

Data analyses followed the method (see Appendix) detailed by Christian et al.[20] This method allowed the evaluation of the fraction of total variance resulting from additive population genetic factors (A), interaction of two genetic factors (D), interaction of three or more genetic factors (I), and environmental covariance of MZ and DZ twins (C). The heritability (H^2) was obtained by summing the estimates of A, D, and I. MZ and DZ interclass correlations (rMZ and rDZ) were calculated from the among-pair mean squares (AMS) and within-pair mean squares (WMS) for each zygosity, using the formula:

$$\text{intraclass correlation} = \frac{(\text{AMS} - \text{WMS})}{(\text{AMS} + \text{WMS})} \quad (1)$$

The null hypotheses that rMZ and rDZ = 0 were tested using one-tailed F-ratios (AMS/WMS). The hypothesis that rMZ = rDZ (that is, A + D + I = 0) was tested by one-tailed comparison of Z transformations that rMZ > rDZ. The rationale for this test is described by Snedecor and Cochran.[21]

RESULTS

Tables 1, 2, 3, and 4 summarize the results obtained for pursuit gain, intersaccadic interval, saccadic amplitude, and saccadic accuracy at 0.25 and 0.5 Hz before and after alcohol administration. Table 1 presents MZ and DZ means, intraclass correlations (rMZ and rDZ), variance fractions C, A, D, and I, and H^2 for pursuit gain before and after alcohol consumption. There was no significant difference in pursuit gain between MZ and DZ twins. After alcohol administration, pursuit gain strongly decreased. However, rMZ, rDZ, and H^2 were almost the same for both frequencies before and after alcohol ingestion. All four rMZ, but no rDZ, reached statistical significance ($P < 0.05$). Additive genetic variance (A) and interaction of two genetic factors (D) were the main components of heritability. All four heritability values were statistically significant.

Tables 2 and 3 present the same measures (means of original data for MZ and DZ, rMZ, rDZ, C, A, D, I, and H^2) for intersaccadic interval and saccadic amplitude during pursuit. Results showed the same pattern as for pursuit gain. There were no significant differences between means for MZ and DZ for both parameters. Alcohol consumption changed the interval between saccades as well as their amplitude. All rMZ, but only one rDZ, were significant. A and D were the main components of heritability. Table 4 shows the same characteristics for accuracy of saccades during smooth pursuit. For this parameter only, rMZ reached a statistically significant level at three experiments. H^2 did not reach a statistically significant level.

To evaluate the pure effect of alcohol on pursuit tracking, each twin pair was separated into two independent groups. In both groups, pursuit gain, intersaccadic interval, saccadic amplitude, and saccadic accuracy were compared before and after alcohol administration (*t*-test for paired comparison, $P < 0.05$). In both groups, after alcohol administration, pursuit gain and intersaccadic interval decreased and saccadic amplitude increased significantly for both frequencies (0.25 and 0.5 Hz).

DISCUSSION

The effects of alcohol on pursuit gain seen in this study are consistent with those reported in the literature.[4,11,12] The changes seen in the programming of corrective saccades, which have not previously been examined in detail, are those that might be expected consequent to reduced pursuit gain—that is, catch-up saccades became both larger and slightly more frequent. One might have anticipated that alcohol would interfere with compensation for position error during tracking by making corrective saccade programming less accurate, but this does not appear to be the case, as evidenced by the modest changes seen in saccadic accuracy after alcohol ingestion.

The results of this study of genetic influences and alcohol effects on smooth pursuit and corrective sac-

TABLE 1. Pursuit Gain*

Frequency (Hz)	*Mean MZ*	*rMZ*	*Mean DZ*	*rDZ*	*C*	*A*	*D*	*I*	H^2
Before alcohol									
0.25	0.92	0.703†	0.91	0.22	0	0.17	0.53	0	0.70‡
0.5	0.84	0.701†	0.83	0.17	0	0	0.69	0.01	0.70‡
After alcohol									
0.25	0.83	0.695†	0.83	0.26	0	0.35	0.35	0	0.70‡
0.5	0.68	0.704†	0.67	0.20	0	0.10	0.60	0	0.70‡

* Pursuit gain was calculated as the mean of the ratio (eye velocity/target velocity) for all points of smooth pursuit, except where target velocity was near 0 degrees/second.
† $P < 0.01$.
‡ $P < 0.05$.

TABLE 2. Interval Between Saccades During Smooth Pursuit*

Frequency (Hz)	*Mean MZ*	*rMZ*	*Mean DZ*	*rDZ*	*C*	*A*	*D*	*I*	H^2
Before alcohol									
0.25	0.45	0.82†	0.39	0.11	0	0	0.06	0.76	0.82†
0.5	0.30	0.71†	0.28	0.23	0	0.19	0.52	0	0.71‡
After alcohol									
0.25	0.37	0.71†	0.35	0.17	0	0	0.66	0.05	0.71‡
0.5	0.27	0.73†	0.26	0.36‡	0	0.70	0.03	0	0.73

* The mean interval between saccades (in seconds) was calculated for all catch-up saccades.
† $P < 0.01$.
‡ $P < 0.05$.

TABLE 3. Amplitude of Saccades During Smooth Pursuit*

Frequency (Hz)	*Mean MZ*	*rMZ*	*Mean DZ*	*rDZ*	*C*	*A*	*D*	*I*	H^2
Before alcohol									
0.25	2.27	0.75†	2.42	0.30	0	0.44	0.32	0	0.75‡
0.5	4.33	0.78†	4.49	0.19	0	0	0.70	0.07	0.78†
After alcohol									
0.25	2.97	0.89†	3.04	0.28	0	0.21	0.68	0	0.89†
0.5	6.04	0.73†	5.46	0.23	0	0.17	0.56	0	0.73‡

* The mean amplitude of saccades (in degrees) was calculated for all catch-up saccades.
† $P < 0.01$.
‡ $P < 0.05$.

TABLE 4. Accuracy of Saccades During Smooth Pursuit*

Frequency (Hz)	*Mean MZ*	*rMZ*	*Mean DZ*	*rDZ*	*C*	*A*	*D*	*I*	H^2
Before alcohol									
0.25	−0.44	0.48†	−0.32	0.17	0	0.21	0.27	0	0.48
0.5	−0.62	0.54†	−0.47	0.25	0	0.45	0.09	0	0.54
After alcohol									
0.25	−0.50	0.55‡	−0.41	0.12	0	0	0.44	0.11	0.55
0.5	−0.60	0.28	−0.46	0.20	0.13	0.15	0	0	0.15

* The accuracy of catch-up saccades was defined as the mean of target position minus eye position (in degrees) at the end of saccade.
† $P < 0.01$.
‡ $P < 0.05$.
Mean MZ and mean DZ = mean of original data for monozygotic and dizygotic twins; rMZ and rDZ = intraclass correlations of monozygotic and dizygotic twins; A = fraction of total variance caused by additive genetic effects; D = caused by interaction of two genetic factors; I = caused by interaction of three or more genetic factors; C = caused by environmental effects common to cotwins; H^2 = heritability or fraction of total variance caused by the sum of genetic components.

cades parallel in some ways our results from the study of reflexive saccades in the same sample of twins.[15] In all but one instance, rMZs were significant for all four measures of pursuit tracking at both target frequencies both before and after ingesting alcohol. Conversely, only one rDZ reached significance, and rDZ values were almost always much lower than would be expected from the additive genetic model. H^2 measures were significant.

Grove et al[22] proposed a single gene for ocular motor dysfunction that, they suggested, may be a risk factor for schizophrenia. Our results suggest a relatively strong genetic influence over pursuit gain, intersaccadic interval, and saccade amplitude and point to interactions of two or more genetic factors as an important component. The same pattern was previously noted in event-related potential and electroencephalographic studies.[23,24] An alternative explanation could be that the assumption of the twin model about equality of environmental covariance of MZ and DZ twins does not hold. Inequalities in these environmental terms would bias all estimates of genetic variance; hence, greater MZ than DZ environmental similarities (e.g., because of in utero differences) could provide a false appearance of gene interactions. Thus, further studies examining these possible environmental effects are necessary to determine the relative importance of inheritance and environment on normal eye movement control.

Key Words

alcohol, genetics, pursuit eye movements

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APPENDIX

The expected values for rMZ and rDZ are:

$$rMZ = \frac{2(\sigma^2A + \sigma^2D + \sigma^2I + CMZ)}{2(\sigma^2A + \sigma^2D + \sigma^2I + \sigma^2E)} \quad (2)$$

$$rDZ = \frac{2(\frac{1}{2}\sigma^2A + \frac{1}{4}\sigma^2D + \frac{1}{8}\sigma^2I + CMZ)}{2(\sigma^2A + \sigma^2D + \sigma^2I + \sigma^2E)} \quad (3)$$

where σ^2A is the additive population genetic variance, σ^2D is the variance due to the interactions of two genetic factors (dominance or two-factor epistasis), σ^2I is the variance due to the interactions of three or more genetic factors, CMZ and CDZ are the environmental covariance of MZ and DZ twins, respectively, and σ^2E is the variance due to environmental factors unique to individual twins. CMZ and CDZ were assumed to be equal: C = CMZ = CDZ. The expected value of the difference of (rMZ − rDZ) is proportional to:

$$(rMZ - rDZ) \sim (\frac{1}{2}\sigma^2A + \frac{3}{4}\sigma_2D + \frac{7}{8}\sigma^2I) \quad (4)$$

The fraction of population genetic variance was partitioned into estimates of C, A, D, and I based on (rMZ − rDZ)/rMZ, (rMZ − rDZ) (equation 4), and rMZ (equation 2). For example, if (rMZ − rDZ)/rMZ equals 0, 0.5, 0.75, or 0.875, all the (rMZ − rDZ) (equation 4) may be attributed to either C, σ^2A, σ^2D, or σ^2I. Between any two of these four points (rMZ − rDZ)/rMZ were assumed to be weighted linear combinations of C and σ^2A, σ^2A and σ^2D, or σ^2D and σ^2I. Ratios greater than $\frac{7}{8}$ were assumed to be owing to I alone. Substituting this linear combination into the difference of (rMZ − rDZ) (equation 4) gives the fractions of these components (C, A, D, and I) in population variance.