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Alcohol impairment of saccadic and smooth pursuit eye movements: impact of risk factors for alcohol dependence

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Abstract

Rationale—While persons at risk for alcohol dependence by virtue of heavy drinking patterns or family history (FH) of alcohol use disorders have exhibited differential alcohol responses on a variety of measures, few studies have examined alcohol's effects on eye movements in these subgroups.

Objectives—The purpose of this study was to (1) conduct a placebo-controlled, dose-ranging study of alcohol's effects on eye movements and (2) examine the impact of these risk factors on oculomotor response to alcohol.

Methods—A within-subject, double-blind laboratory study was conducted in $N=138$ heavy (HD; $n=78$) and light social drinkers (LD; $n=60$) with self-reported positive (FH+) or negative (FH−) family history. Subjects participated in three laboratory sessions in which they consumed a beverage containing a high (0.8 g/kg) or low (0.4 g/kg) dose of alcohol or placebo. Smooth pursuit, pro-saccadic, and anti-saccadic eye movements were recorded before and at two intervals after alcohol consumption.

Results—Alcohol significantly impaired smooth pursuit gain and pro- and anti-saccade latency, velocity, and accuracy in a dose and time specific manner. HD and LD showed similar impairment on smooth pursuit gain and anti-saccade measures, but HD were less impaired in pro-saccade latency, velocity, and accuracy. FH+ and FH− subjects were equally impaired in nearly all pro- and anti-saccade measures, but FH+ were less impaired in smooth pursuit gain.

Conclusions—In sum, alcohol produced systematic impairment on oculomotor functioning, even at a non-intoxicating dose. Furthermore, high- and low-risk drinkers may be vulnerable to select performance deficits relative to eye movement task.

Keywords

Alcohol; Pro-saccade; Anti-saccade; Smooth pursuit; Family history of alcohol use disorders; Binge drinking

Introduction

Impairment of oculomotor function may play a role in alcohol-related accidents and injury. Therefore, studying how alcohol acutely affects this neurophysiological system and who may be at greatest risk for such impairment is of vital importance. Acute alcohol consumption has been shown to impair both saccadic (i.e., short, rapid eye movements performed to align a stimulus with the fovea) and smooth pursuit eye movements (i.e., maintaining a slow-moving visual stimulus centered on the fovea) (Flom et al. 1976; Gale et al. 1996; Holdstock and de Wit 1999; King and Byars 2004; Levy et al. 1981; Moser et al. 1998; Vorstius et al. 2008; Wilkinson et al. 1974). Saccades are generally measured using paradigms that elicit either reflexive movement toward a visual target (pro-saccade tasks) or a volitional response, after initial inhibition of a reflexive saccade, away from a target (anti-saccade tasks). Both saccades and smooth pursuit are highly heritable, with little intra-subject variability across sessions (Blekher et al. 1997, 1998; Iacono and Lykken 1981; Katsanis et al. 2000, 2002; Malone and Iacono 2002), and are sensitive to genetic influence on drug response (Cowley et al. 1994; Iwata et al. 1999). The combination of reliability, heritability, and sensitivity makes the tracking of eye movements an ideal method of examining the impact of intermediate endophenotypes on response to alcohol.

While alcohol has been routinely reported to impair smooth pursuit performance (Blekher et al. 1997; Holdstock and de Wit 1999; King and Byars 2004; Levy et al. 1981; Moser et al. 1998), its effects on saccades have been less clear. Most studies have shown that alcohol increases the latency to initiate and decreases the peak velocity of a pro-saccade (Blekher et al. 2002a, b; Gale et al. 1996; King and Byars 2004; Moser et al. 1998; Vorstius et al. 2008; Wegner and Fahle 1999), without impairing its accuracy, i.e., how close to a target a saccade brings the eye's fixation point (Blekher et al. 2002a, b; Lehtinen et al. 1979; Moser et al. 1998; Vassallo and Abel 2002; Vorstius et al. 2008). However, some studies have failed to find alcohol-induced impairment on pro-saccade latency (Holdstock and de Wit 1999; Jantti et al. 1983; Lehtinen et al. 1979; Nyberg et al. 2004) or have shown that alcohol degrades pro-saccade accuracy (Gale et al. 1996; Nyberg et al. 2004). Relatively few studies have used anti-saccade paradigms to examine the effect of alcohol on volitional saccades; most, but not all (Vassallo and Abel 2002), have found that alcohol impairs latency and velocity, with mixed results on accuracy (Blekher et al. 2002a, b; Khan et al. 2003; Ramchandani et al. 1999; Vorstius et al. 2008).

Discrepant findings among the aforementioned studies may relate to methodological differences. For example, some studies used only one type of eye movement task (i.e., smooth pursuit, pro- or anti-saccade) and/or reported only one or two descriptive measurements of eye movements (i.e., velocity, latency, or accuracy), both of which limit meaningful comparisons across studies. Many studies failed to include a placebo to control

for alcohol expectancies (Blekher et al. 1997; Gale et al. 1996; Levy et al. 1981; Moser et al. 1998; Vassallo and Abel 2002) or administered only one dose of alcohol (Blekher et al. 1997; Gale et al. 1996; Lehtinen et al. 1979; Moser et al. 1998; Vassallo and Abel 2002; Vorstius et al. 2008; Wegner and Fahle 1999; Wilkinson et al. 1974). Furthermore, most single-dose studies administered a moderate amount of alcohol (e.g., producing 0.05–0.06 breath alcohol concentration (BrAC)), limiting assessment of the effects of light (~2 standard drinks) or heavy alcohol consumption, such as at the legal limit for impaired driving (0.08 BrAC).

Given the small sample sizes in most studies to date, there is a paucity of information on the impact of risk factors for development of alcohol use disorders (AUDs) on alcohol-induced eye movement impairment. In contrast, risk factors for AUDs have been more thoroughly investigated for other alcohol responses, such as subjective effects (King et al. 2002; Pollock 1992; Schuckit 1984b, 1994), neuroendocrine response (Gianoulakis et al. 1996; King et al. 2006; Schuckit 1984a), EEG (Padmanabhapillai et al. 2006), and heart rate (Conrod et al. 1997). Family history (FH) of AUD and heavy/binge drinking patterns of alcohol use are the two risk factors studied thus far for sensitivity to alcohol impairment of eye movements. One study showed that FH– subjects (vs. FH+) display greater alcohol-induced impairment in the latency of anti-saccades, but not in pro-saccades (Blekher et al. 2002b). Another reported that FH+ subjects (vs. FH–) show a greater *initial* impairment of anti-saccade latencies, but also exhibit acute tolerance during a steady exposure to alcohol, i.e., a faster recovery to alcohol's impairing effects (Ramchandani et al. 1999). Heavy social drinkers (HD) (vs. lighter drinkers (LD)) have been shown to exhibit less smooth pursuit impairment but more pro-saccade latency impairment (King and Byars 2004). The variability in findings suggests that larger sample sizes are required for drawing firm conclusions on the nature of the impairments associated with each risk factor and if the risk factors might be synergistic in their influence.

The first goal of our experiment was to conduct a placebo-controlled, dose-ranging study of alcohol effects on a comprehensive battery of eye movement responses before and after alcohol consumption. We hypothesized that a high dose of alcohol (0.8 g/kg) would impair smooth pursuit and pro- and anti-saccade latency, velocity, and accuracy at both the peak and the declining limb of the BrAC curve. Given data showing oculomotor sensitivity to low levels of alcohol (Blekher et al. 1997; Gale et al. 1996; Holdstock and de Wit 1999; Vassallo and Abel 2002), we also hypothesized that a low dose of alcohol (0.4 g/kg) may result in an intermediate level of impairment. Our second goal was to examine the role of risk factors for the development of AUD (i.e., heavy drinking patterns and FH) on sensitivity to alcohol-induced oculomotor impairment.

Method

Participants

The study sample consisted of a subset of $n=138$ nonalcoholic social drinkers (aged 21–35) extracted from the larger Chicago Social Drinking Project (CSDP; $N=190$), a longitudinal study examining alcohol responses and drinking patterns in heavy and light social drinkers. The subset of 138 subjects was examined because they could be classified as either FH+ or

FH– and had complete eye movement data. The study was approved by The University of Chicago Institutional Review Board and performed in accordance with the Declaration of Helsinki. Candidates interested in the CSDP study were initially screened on the telephone and those meeting general eligibility requirements were invited for an in-person screening session. At the screening session, the participant provided informed consent and then underwent extensive screening procedures to assess eligibility and obtain demographic information (including FH of AUD). Diagnostic interviews, including the Structured Clinical Interview for the DSM IV-Patient Version (SCID; First et al. 1995) and the Short Michigan Alcoholism Screening Test (SMAST; Selzer et al. 1975), and a medical assessment by a nurse or physician were employed to exclude those with past or current psychiatric disorders or major medical conditions. Negative drug and pregnancy test results and within normal limits liver enzyme levels were required for participation in each session. For further details on the screening measures, see Brumback et al. (2007).

Risk factors

Heavy vs. light drinking—Participants in the CSPD were HD and LD. Based on established guidelines (SAMHSA 2007; Dawson 2000), criteria for HD was non-dependent drinkers who consume ten to 40 drinks per week with regular weekly binge episodes, defined as 5+ drinks per occasion (4+ for females) one to five times per week for 2 years or longer. LD consume less than six drinks per week with few or rare binge episodes in the past (i.e., less than six times per year and at most one past interval, lasting a maximum of 6 months, with no more than twice weekly binge drinking).

Family history of alcohol use disorders—Subjects were enrolled regardless of FH, but the majority of participants (138 of 190, 73%) could be classified as either FH+ or FH–, as determined at screening by family tree for all primary and secondary biological relatives. If a subject identified a biological family member as having an AUD, follow-up questions were asked that were consistent with FH-RDC for drinking consequences (Andreassen et al. 1977). Subjects with FH+ ($n=72$) were those who reported having at least one primary (parent or sibling) or two or more secondary relatives with history of AUD. Subjects with FH– ($n=66$) were those who reported at least two generations of primary family without AUD and were able to identify >50% of secondary relatives' negative AUD history.

Procedure

Each of three laboratory sessions began between 3 and 5 PM, lasted approximately 5 h, and was separated by at least 48 h. All sessions were identical except for beverage content. The subject consumed a beverage containing placebo (1% ethanol as taste mask), a low alcohol dose (0.4 g/kg; approximately two to three drinks equivalent), or a high alcohol dose (0.8 g/kg; approximately four to five drinks equivalent), with the order randomized across sessions. To reduce the possible confound of alcohol expectancy, the subject was told the beverages might contain alcohol, stimulant, sedative, placebo, or any combination thereof. All beverages consisted of a mixture of Kool-Aid, water, Splenda® and 190-proof ethanol. Women received an appropriate 85% dose of alcohol compared to men due to differences in

total body water affecting blood/breath alcohol concentrations (Frezza et al. 1990; Sutker et al. 1983).

Each participant was instructed to abstain from recreational drug use (including alcohol) for 48 h before each session, as well as food, caffeine, and cigarettes for 3 h before each session. Upon arrival, the participant consumed a low-fat snack (15% daily calories), provided a baseline BrAC via breathalyzer and a urine sample for psychoactive drug and pregnancy testing. If the subject tested positive for alcohol, illicit drugs, or pregnancy, he or she was not allowed to participate in the session. Thirty minutes after arrival, the subject completed baseline (BL) eye-tracking tasks as well as several objective and subjective measures as part of the larger CSDP—results of which have been reported elsewhere: (Brumback et al. 2007; Epstein et al. 2007; King et al. 2006; Rueger et al. 2009). Shortly thereafter, the subject consumed the beverage over a 15-min period (two 5-min periods of drinking with a 5-min rest in between). Our lab has previously used a similar protocol and demonstrated a consistent, sharp rising phase of the BrAC within 1 h and a longer, slower declining phase across participants (Brumback et al. 2007; King et al. 2002, 2006; King and Epstein 2005). At 60 min (T1) and 180 min (T2) after the initiation of beverage consumption, participants repeated the eye-tracking tasks. These time points were chosen to both capture the time course of peak BrAC and the latter stage of the declining limb of the BrAC curve (Brumback et al. 2007; Holdstock and de Wit 1999; King and Byars 2004; King and Epstein 2005; King et al. 2002). Between time points, the participant was allowed to watch television or movies, read, and relax in a comfortable setting. At the end of each session, the participant was driven home by a car service. After the third session, the subject was debriefed and compensated \$150 plus a \$50 bonus for study completion.

Dependent variables: eye movement tasks

Eye movements were measured and analyzed using the VisualEyes™ VNG system (Micromedical Technologies, Chatham, IL), a non-invasive oculographic device. The subject was seated in a dimly lighted room, 1 m from a horizontal digital light bar that subtended 30° of the total visual angle (15° to the left and right of midline), and was fitted with goggles containing a monocular camera designed to center and track the pupil of the right eye. At each timepoint, the subject tracked random horizontal and vertical targets to calibrate eye position. The targets used during calibration and testing were red light emitting diodes that subtended to $0.29^\circ \times 0.58^\circ$ of the visual field. Performance was monitored live during testing and the subject was given instructions to refocus if any drowsiness or inattentiveness was observed. The eye movement protocol generally lasted ~10 min at each timepoint, which included calibration and three tasks. The order of testing was fixed within each block (i.e., smooth pursuit, pro-saccade, then anti-saccade).

Smooth pursuit eye movements—For smooth pursuit, the target traveled horizontally across the display (15° to the right and left of midline) in a predictable, oscillating sinusoidal waveform for 75 s. The target initially moved at 1 Hz for four cycles (one cycle=one oscillation), then increased to 2 Hz for four cycles, and finally to 4 Hz for six cycles. The subject was instructed to follow the target as closely and accurately as possible. Smooth pursuit is described by a measure of *gain*, which is the ratio of the velocity of the subject's

eyes to the velocity of the stimulus. The eye-tracking software filtered and excluded deviations from the target (e.g., blinks) or saccades made during pursuit tasks. For four subjects ($n=4$ of 138; 3% of sample), data were unavailable for smooth pursuit gain due to technical difficulties resulting in smooth pursuit analyses being conducted on $n=134$ subjects.

Saccadic eye movements—For the pro-saccade task, 30 separate, successive targets were randomly presented along the light bar with regard to both location (anywhere within a 15° horizontal angle from the center) and duration of presentation (1–3 s). There were no intervals of darkness between targets. The subject was instructed to locate and fixate on each illuminated target and then rapidly readjust his/her gaze to the location of the next light stimulus. For the anti-saccade task, the target presentation was identical to the pro-saccade task. However, the subject was instructed to not look directly at each light stimulus, but to instead redirect their gaze to the mirror position of the target on the opposite side of the midline. The subject maintained fixation on the location of the perceived target (opposite the actual target) until the next stimulus appeared and then immediately performed the next anti-saccade. The subject did not return their gaze to center between targets.

For both tasks, measures of latency, velocity, and accuracy were automatically calculated by the eye-tracking software for all correct saccades (i.e., those made toward the target in pro-saccade tasks and away from the target in anti-saccade tasks). Directionally incorrect saccades were filtered out and not used in any subsequent analyses, along with saccades that were 50% below and 133% above each subject's mean. *Percent Accepted* refers to the number of correct saccades accepted by the software, divided by the number of target presentations ($n=30$). *Latency* represents the interval in milliseconds (ms) between target presentation and initiation of the saccadic eye movement. *Velocity* describes the peak rate (degrees per second) at which the saccadic eye movement travels. *Accuracy* is the ratio of the amplitude of the initial saccade to the amplitude of target [(initial eye deflection/target deflection) $\times 100$]; “undershoots” of the target result in accuracy <100 and “overshoots” >100 . One subject's data were unavailable for pro- and anti-saccades due to technical difficulties, resulting in saccade analyses being conducted on $n=137$ subjects.

Statistical analysis

To examine the effects of alcohol on eye movements, separate repeated measures analyses of variance (ANOVAs) were conducted for each eye-tracking measurement. For pro- and anti-saccade tasks, saccade measurement (latency, velocity, and accuracy), dose (placebo, low, and high dose) and time (Baseline, T1, T2) were entered as three level, within-subject factors. For analysis of smooth pursuit gain, dose, time, and temporal frequency of sinusoidal stimuli (1, 2 and 4 Hz), were entered as three level, within-subject factors.

For risk factor analyses, the drinking and FH groups were first compared on background characteristics and on BrAC levels at BL, T1, and T2 by ANOVAs and/or Chi-square tests, as appropriate. Any variable that significantly differed between groups were included as covariates in subsequent analyses comparing the risk groups. A multivariate General Linear Model analysis was separately performed for each eye movement measure with both FH and

current drinking group entered as between-subject variables and dose and time entered as within-subject factors, respectively. For analysis of smooth pursuit gain, Hz level was also entered into the multivariate model as an additional within-subject factor. Only interactions (risk factor×dose or risk factor×dose×time) that remained significant after the addition of covariates are reported. Significant interactions were further examined using Tukey's post hoc test.

Results

Effects of alcohol dose on eye movement response

Demographic variables and breath alcohol concentration—The study sample was primarily Caucasian ($n=95$; 69%), with an average age of 25.5 ± 3.3 (mean±SD) years, 16.1 ± 1.8 years of education, and a BMI of 24.7 ± 3.0 kg/m². The sample included similar ratios of men ($n=78$; 57%) and women ($n=60$; 43%). In the sessions, as expected, the high dose of alcohol produced higher BrACs than the low dose (high dose: 0.089 ± 0.017 % at T1, 0.057 ± 0.015 % at T2; low dose: 0.037 ± 0.008 and 0.006 ± 0.015 , respectively).

Smooth pursuit

Gain: Alcohol impaired smooth pursuit gain in a dose-dependent fashion (Fig. 1; dose×time: $F(4,532)=32.40$, $p<0.0001$). The high dose decreased gain at both T1 and T2, with peak impairment at T1 (Tukey's: high dose: T1<T2<BL, $p<0.0001$; T1: high dose<low dose<placebo, $p<0.0001$; T2: high dose<low dose=placebo, $p<0.0001$). The low dose of alcohol significantly decreased gain at T1, but not T2 (low dose: T1<BL=T2, $p<0.001$; T1: low dose<placebo, $p<0.001$). There was no effect of Hz on smooth pursuit performance

Pro-saccades

Percent accepted: At baseline, $81\%\pm0.08$ (mean±SD) of pro-saccades were accepted, which increased over time to $83\%\pm0.09$ ($p<0.001$) but was not affected by alcohol.

Latency: Alcohol significantly increased the latency of prosaccades in a dose-dependent manner (Fig. 2a; dose×time: $F(4,544)=35.2$, $p<0.0001$). The high dose of alcohol impaired latency at both T1 and T2 (T1: high dose>low dose>placebo, $p<0.0001$; T2: high dose>low dose=placebo, $p<0.001$), with peak impairment observed at T1 (high dose: T1>T2>BL, $p<0.001$). The low dose of alcohol significantly increased latency at T1, but not at T2 (low dose: T1>BL, $p<0.05$; T1: low dose>placebo, $p<0.0001$).

Velocity: Alcohol slowed peak velocity only at the high dose (Fig. 2b; dose×time: $F(4,544)=10.03$, $p<0.0001$), which was evident at both T1 and T2 (T1: high dose<low dose=placebo, $p<0.0001$; T2: high dose<low dose=placebo $p<0.001$). During all sessions, saccade velocity decreased from BL to T1 ($p<0.0001$), but remained stable from T1 to T2.

Accuracy: Similar to saccade velocity, only the high dose of alcohol had a significant effect on the accuracy of prosaccades (Fig. 2c; dose×time: $F(4, 544)=2.44$, $p<0.05$). At T1 and T2, the high dose lowered accuracy compared to placebo and low dose (T1: high

dose<placebo=low dose, $p<0.05$; T2: high dose<placebo, $p<0.01$; T2: high dose<low dose, $p=0.05$). Placebo and the low alcohol dose did not differ over time.

Anti-saccades

Percent accepted: At baseline, $64\% \pm 0.1$ (mean $\pm$ SD) of anti-saccades were accepted, which increased over time to $67\% \pm 0.1$ ($p<0.0001$) and was slightly increased by alcohol ($p<0.05$; 66% at placebo and low dose to $67\% \pm 0.1$ at high dose).

Latency: Alcohol dose-dependently increased the latency to initiate anti-saccades (Fig. 2d; dose $\times$ time: $F(4, 544)=18.49$, $p<0.0001$). The high dose impaired performance to the greatest extent at T1 (high dose: T1>T2=BL $p<0.001$; T1: high dose>low dose>placebo, $p<0.001$), with continued impairment at T2 (high dose>low dose=placebo, $p<0.0001$). The low dose of alcohol significantly increased latency at T1 compared to placebo ($p<0.0001$), but not at T2. During low dose and placebo sessions, latency decreased over time (placebo and low dose: BL>T2, $p<0.0001$).

Velocity: Alcohol decreased anti-saccade velocity (Fig. 2e; dose $\times$ time: $F(4,544)=6.31$, $p<0.0001$). The high dose impaired velocity at T1 compared to placebo (high dose<placebo, $p<0.05$) and at T2 compared to both placebo and the low dose (high dose < placebo, $p<0.0001$; high dose<low dose, $p<0.001$), the latter time point being the point of peak impairment. The low dose did not differ from placebo, with peak velocity significantly increasing over time for both (placebo: T2>BL, $p<0.01$; low dose: T2>T1, $p<0.05$).

Accuracy: Alcohol had a significant, dose-dependent effect on the accuracy of anti-saccades (Fig. 2f; dose $\times$ time: $F(4,544)=4.31$, $p<0.01$). The high dose trended toward increasing accuracy compared to placebo at T1 (Tukey's: $p=0.06$). However, the initial increase was followed by a significant decrease to a level comparable to placebo and low dose at T2 (high dose: BL>T2, $p<0.001$; T1>T2, $p<0.0001$).

Risk factors and response to alcohol

No interactions were observed between risk groups (e.g., FH $\times$ drinking group effects) on any eye movement task or BrAC level. Therefore, all reported significant effects were only found within each risk group (e.g., FH $\times$ dose or drinking group $\times$ dose). Additionally, there were no differences in the percent of accepted saccades within or between risk groups on either saccade task.

Risk group comparisons on demographic variables and breath alcohol concentration

—Background characteristics and BrAC readings for the study sample based on HD/LD and FH+/FH– groups are presented in Table 1. FH– LD had more years of education than all other groups (drinking group $\times$ FH: $F(1,134)=15.23$, $p<0.001$; Tukey's: $p<0.0001$). FH groups did not differ in BrAC across time points at any dose, but HD had greater BrAC in response to the high dose at T1 in comparison to LD (drinking group $\times$ dose $\times$ time: $F(1,134)=7.02$, $p<0.01$; Tukey's: $p<0.05$). Therefore, BrAC at T1 and years of education were included in all risk group analyses as covariates. Finally, the FH groups did not differ in drinking characteristics.

Heavy drinkers vs. light drinkers

Smooth pursuit: No significant drinking group by dose interactions were observed.

Pro-saccades: LD were more sensitive to the impairing effects of alcohol than HD on measures of latency, velocity, and accuracy. *Latency:* While both LD and HD showed impairment in pro-saccade latency after consuming the high dose of alcohol (Fig. 3a; dose×drinking group: $F(2,262)=4.35$, $p<0.05$; Tukey's: LD & HD, high dose>placebo, $p<0.0001$; high dose>low dose: LD, $p<0.05$; HD, $p<0.0001$), LD exhibited significantly greater impairment than HD (high dose: LD>HD $p<0.05$). Low dose alcohol impaired latency in only in LD (low dose>placebo, $p<0.05$). *Velocity:* Overall, LD had slower peak velocity of anti-saccades than HD (drinking group: $F(1,132)=9.27$, $p<0.01$), a main effect that may be driven by a marginally significant group difference in response to alcohol (Fig. 3b; dose×drinking group: $F(2,264)=2.58$, $p=0.08$; Tukeys: LD: high dose<low dose=placebo, $p<0.0001$). Furthermore, the peak level of alcohol-induced impairment was significantly greater in LD than in HD (high dose: LD<HD, $p<0.01$). *Accuracy:* In comparison to placebo, the high dose of alcohol significantly impaired accuracy in LD but not in HD (Fig. 3c; dose×drinking group: $F(2,262)=3.24$, $p<0.05$; Tukey's: LD, high dose<placebo, $p<0.01$; high dose<low dose, $p<0.001$).

Anti-saccades: No significant drinking group by dose interactions were observed.

FH±/FH–

Smooth pursuit: While alcohol impaired both FH+ and FH– subjects on smooth pursuit gain, FH– subjects showed significantly greater overall impairment (Fig. 4a; dose×FH×time: $F(4,516)=5.27$, $p<0.001$). Compared to placebo, the high dose significantly impaired gain for both FH groups at T1 (high dose<placebo, $p<0.0001$) but only for FH– at T2 (high dose<placebo, $p<0.0001$). Additionally, compared to FH+, FH– subjects demonstrated a trend toward greater impairment in response to the high dose of alcohol at T1 (high dose: FH–<FH+ $p=0.07$).

Pro-saccades: No significant FH by dose interactions were observed.

Anti-saccades: *Latency:* Alcohol-induced impairment of anti-saccade latency did not differ between FH+ and FH– subjects. *Velocity:* Alcohol differentially impaired anti-saccade velocity in FH+ and FH– subjects (Fig. 4b; dose×FH×time: $F(4,524)=2.80$, $p<0.05$). The high dose impaired FH+ subjects at both T1 and T2 (T1: high dose<placebo, $p<0.001$; T2: high dose<placebo, $p<0.05$), but FH– subjects were only impaired by the high dose at T2 (high dose<low dose, $p<0.001$). In the placebo session, velocity increased over time in FH+, but not FH– subjects. *Accuracy:* Alcohol did not differentially impair accuracy between FH+ and FH– subjects.

Discussion

The current study was the first to examine the effect of multiple doses of alcohol on social drinkers' eye movements in smooth pursuit, pro-saccade, and anti-saccade tasks. We found

that a high dose of alcohol (0.8 g/kg) induced impairment in all eye movement measurements, while a moderate dose of alcohol (0.4 g/kg) produced a lesser impairment that was only apparent at peak BrAC. Additionally, we found evidence for differential impairment in response to the high dose of alcohol based on current heavy drinking and FH status on some, but not all, eye movement measures. Therefore, potential tolerance to alcohol's effects in more experienced drinkers or those at risk by virtue of FH does not appear to be widespread. Combined, these results suggest that alcohol impairs smooth pursuit and saccadic eye movements and this impairment may differ based on individual risk factors for the development of AUD.

The high dose of alcohol impaired eye movement performance on smooth pursuit gain and on pro- and anti-saccade latency, velocity, and accuracy. High dose-induced impairment was highest at peak BrAC, with a sustained, but slightly reduced impairment observed on the falling limb of the BrAC curve. Impairment of smooth pursuit gain and pro- and anti-saccade latency and velocity are in agreement with the majority of studies with blood alcohol content (BAC)/BrACs of 0.08 or higher (King and Byars 2004; Moser et al. 1998; Wegner and Fahle 1999; Wilkinson et al. 1974) or using a slightly lower dose, i.e., with a BAC/BrAC of .05–.07; (Blekher et al. 2002a; Gale et al. 1996; King and Byars 2004; Vorstius et al. 2008). However, in contrast to several studies (Blekher et al. 2002a, b; Lehtinen et al. 1979; Moser et al. 1998; Vassallo and Abel 2002; Vorstius et al. 2008), we found that alcohol significantly affected both pro- and anti-saccade accuracy.

The high dose of alcohol decreased pro-saccade accuracy relative to performance at baseline and placebo. This decrease in accuracy may be due to a decrease in the saccade amplitude (i.e., length), resulting in an “undershoot” of the target (Gale et al. 1996; Nyberg et al. 2004). In contrast, the high dose of alcohol increased anti-saccade accuracy at peak BrAC relative to placebo, similar to findings by other groups (Blekher et al. 2002a; Vorstius et al. 2008). As hypothesized by Vorstius and colleagues (2008), we infer these results to mean that alcohol is increasing the amplitude of an anti-saccade relative to performance under normal conditions and not that alcohol is “improving” anti-saccade functioning. Taken together, these results imply that a high dose of alcohol may alter the functioning of the neurocircuitry required for the rapid processing of visuospatial information.

The low dose of alcohol impaired performance on smooth pursuit gain and pro- and anti-saccade latency, with effects apparent at peak BrAC and recovering to baseline levels during the descending limb. In a previous study that included many of the same subjects as the current sample (Brumback et al. 2007), the low dose of alcohol did not produce impairments on psychomotor or cognitive tasks (Pegboard and Digit Symbol Substitution) and other studies in social drinkers have also failed to find behavioral impairment at BrACs <0.05 (for review, see Mitchell 1985). Therefore, in contrast to systems regulating psychomotor ability and short-term memory (Brumback et al. 2007; King and Byars 2004), the oculomotor system appears to be more sensitive to a moderate-to-low dose of alcohol. Overall, differences in response relative to the alcohol dose and to the timing of measures demonstrate the importance of multiple dosing and capturing time points throughout the BrAC curve to accurately determine alcohol's effects on oculomotor function.

In terms of the role of drinking phenotype on sensitivity to alcohol-induced impairment, we found mixed results. HD and LD demonstrated similar impairment in smooth pursuit gain and anti-saccade latency, velocity, and accuracy, which is consistent with our prior finding in cognitive and psychomotor tasks (Brumback et al. 2007). Despite showing similar impairment in performance, HDs report less perceived impairment from alcohol than LDs (Brumback et al. 2007). When combined with the current findings (i.e., acute behavioral tolerance in some, but not all, measures), this lack of self-awareness may put HD at greater risk for serious injury than LD. However, results in the current study do suggest that HD (vs. LD) may show tolerance to alcohol's effects on select eye movement variables, such as prosaccade latency, velocity, and accuracy. Repeated exposure to heavy or binge drinking may produce behavioral tolerance to certain aspects of response to alcohol (Fillmore and Vogel-Sprott 1995, 1996; Gabrielli et al. 1991; Goodwin et al. 1971; Mendelson and Mello 1966). Neuroimaging studies (Calhoun et al. 2004; Meda et al. 2009) have indicated that alcohol affects activity in areas involved in saccade accuracy [e.g., anterior cingulate cortex (ACC); frontal eye fields (FEF)] and latency [FEF and parietal eye fields; ACC; (McDowell et al. 2008; Muri and Nyffeler 2008)], but it remains to be determined whether those areas are susceptible to the effects of repeated alcohol exposure over time that results in behavioral tolerance.

Regarding the other main risk factor, positive biological FH of AUD, results were also mixed. Subjects with FH+ (vs. FH-), demonstrated less alcohol impairment in smooth pursuit gain, but not in pro- or anti-saccade measures. A characteristic low level of response to alcohol in FH+ (Pollock 1992; Schuckit 1998; Schuckit and Smith 1996) was observed in smooth pursuit performance, which may be due to differences between FH+ and FH- in GABA-A-(Cowley et al. 1994; Iwata et al. 1999; Petrakis et al. 2004) and NMDA-receptor function (Avila et al. 2002; Krystal et al. 2003; Petrakis et al. 2004). In contrast, FH+ subjects also demonstrated heightened alcohol-induced impairment of anti-saccade velocity compared to FH-. This finding warrants further investigation, as it varies from the results of other studies reporting either less anti-saccade velocity impairment in FH+ (Ramchandani et al. 1999) or no differences between FH+ and FH- groups (Blekher et al. 2002b).

Though the present study had several strengths, such as a placebo control, multi-level dosing, and a within-subjects design, a few caveats are worth mentioning. First, the anti-saccade task was somewhat atypical compared to other studies in that subjects did not return their gaze to center before presentation of the next target. Second, while administration of oral alcohol increases ecological validity, it also increases risks of potential confounds of both expectancy effects, given potent olfactory and gustatory cues, and the heterogeneity across individuals in BrAC curves.

In conclusion, the current study presented evidence that alcohol impairs smooth pursuit gain and the latency, velocity, and accuracy of pro- and anti-saccades in a dose and time dependent manner. Additionally, we demonstrated that risk factors related to the development of AUD may impact eye movement response to alcohol in some eye-tracking measures, but not others. As there were no significant interactions between FH and heavy drinking on alcohol-induced eye movement impairment, our results suggest that these factors are independent, and not additive, on the oculomotor effects of alcohol. Therefore,

smooth pursuit and saccade tasks appear to be differentially influenced by risk status and both high- and low-risk drinkers may be vulnerable to select alcohol-induced performance deficits.

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The experiments in this study comply with the current US laws and were in compliance with the Declaration of Helsinki for human subjects.

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Fig. 1.

Alcohol significantly impaired smooth pursuit gain (dose $\times$ time, $p<0.0001$). Gain is reported as mean $\pm$ SEM. Comparisons are high or low dose relative to placebo. (Tukey's: $\#p<0.0001$)

Fig. 2.

Alcohol significantly impaired all measures of pro- and anti-saccade tasks. Measures are reported as mean±SEM. Comparisons are high or low dose relative to placebo. (Tukey's: † $p=0.06$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, # $p<0.0001$). **a–c Pro-saccade measures:** **a** Latency (dose×time, $p<0.0001$): #high dose>placebo at T1 and T2; #low dose>placebo at T1. **b** Velocity (dose×time, $p<0.0001$): #high dose<placebo at T1; ***high dose<placebo at T2. **c** Accuracy (dose×time, $p<0.05$): *high dose<placebo at T1; **high dose<placebo at T2 **d–f Anti-saccade measures:** **d** Latency (dose×time, $p<0.0001$): #high dose>placebo at T1 and T2; #low dose>placebo at T1 **e** Velocity (dose×time, $p<0.0001$): *high dose<placebo at T1; #high dose<placebo at T2 **f** Accuracy (dose×time, $p<0.01$): †high dose>placebo at T1

Fig. 3.

Alcohol differentially impaired LD and HD in pro- and anti-saccade tasks. Measures are reported as mean $\pm$ SEM. **a Latency** (dose $\times$ drinking group, $p<0.05$): The high dose significantly increased pro-saccade latency in both LD and HD (Tukey's: LD and HD, high dose $>$ placebo, $p<0.0001$; high dose $>$ low dose: LD, $p<0.05$; HD, $p<0.0001$). LD were significantly more impaired by the high dose than HD (high dose, LD $>$ HD $p<0.05$). Low dose alcohol only impaired latency in LD (Tukey's: LD, low dose $>$ placebo, $p<0.05$). **b Velocity** (dose $\times$ drinking group, $p=0.08$): The high dose of alcohol significantly impaired velocity in LD, but not in HD (Tukey's: LD, high dose $<$ low dose=placebo, $p<0.0001$; LD $<$ HD, $p<0.01$). **c Accuracy** (dose $\times$ drinking group, $p<0.05$): The high dose of alcohol significantly impaired accuracy in LD but not in HD (Tukey's: LD, high dose $<$ placebo, $p<0.01$; high dose $<$ low dose, $p<0.001$).

Fig. 4.

Alcohol differentially impaired FH+ and FH- on smooth pursuit gain and anti-saccade velocity. Measures are reported as mean $\pm$ SEM. (Tukey's: † $p=0.06$, * $p<0.05$, *** $p<0.001$, # $p<0.0001$) **a** Smooth pursuit gain (dose $\times$ FH $\times$ time, $p<0.001$). FH+: #high dose<placebo at T1. FH-: #high dose<placebo at T1; #high dose<placebo at T2; †FH- at T1<FH+ at T1. **b** Anti-saccade velocity (dose $\times$ FH $\times$ time, $p<0.05$). FH+: ***high dose<placebo at T1; *high dose<placebo at T2. FH-: **high dose<low dose at T2

Table 1

Background characteristics and BrAC by risk group

	HD		LD		Notes
	FH+ (n=42)	FH- (n=36)	FH+ (n=30)	FH- (n=30)	
General characteristics					
Age (years)	24.9 (0.51)	25.4 (0.55)	25.7 (0.60)	26.6 (0.60)	
Education (yrs)	15.8 (0.24)	15.8 (0.26)	15.6 (0.29)	17.7 (0.29) ****	LD FH- ^a
Sex (% male)	24 (57%)	22 (61%)	12 (40%)	20 (67%)	
BMI	24.8 (0.46)	24.7 (0.49)	25.2 (0.54)	24.2 (0.54)	
Race (% White)	33 (79%)	23 (64%)	18 (60%)	21 (70%)	
Drinking characteristics ^b					
Drinking occasions per week	3.8 (0.17)	3.4 (0.19)	1.5 (0.21)	1.6 (0.21)	HD>LD ***
Drinks per occasion	5.2 (0.41)	5.8 (0.44)	1.8 (0.49)	1.5 (0.49)	HD>LD ***
Binges per month ^c	8.6 (0.40)	7.1 (0.43)	0.2 (0.47)	0.1 (0.47)	HD>LD ***
BrAC (mg/dl)					
Low dose					
T1	0.036 (0.001)	0.037 (0.001)	0.037 (0.002)	0.036 (0.002)	
T2	0.003 (0.001)	0.005 (0.001)	0.007 (0.001)	0.008 (0.001)	
High dose					
T1	0.093 (0.003)	0.093 (0.003)	0.085 (0.003)	0.085 (0.003)	HD>LD *
T2	0.055 (0.002)	0.058 (0.002)	0.055 (0.003)	0.060 (0.003)	

Data are mean (±SD) or n (%)

*
 $p < 0.05$,***
 $p < 0.001$,****
 $p < 0.0001$ ^aLD FH- had more years of education than all other groups (Tukey's $p < 0.0001$)^bDrinking data presented are obtained from a TLFB interview^cBinge drinking=5+ drinks per occasion for men, 4+ for women

T1=60 min and T2=180 min after initiation of beverage consumption