

2-1-2021

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Terence L. Tyson
NASA Ames Research Center

Nathan H. Feick
San Jose State University, nathan.feick@sjsu.edu

Patrick F. Cravalho
San Jose State University, patrick.cravalho@sjsu.edu

Erin E. Flynn-Evans
NASA Ames Research Center

Leland S. Stone
NASA Ames Research Center




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Recommended Citation

Terence L. Tyson, Nathan H. Feick, Patrick F. Cravalho, Erin E. Flynn-Evans, and Leland S. Stone. "Dose-dependent sensorimotor impairment in human ocular tracking after acute low-dose alcohol administration" *Journal of Physiology* (2021): 1225-1242. <https://doi.org/10.1113/JP280395>

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Dose-dependent sensorimotor impairment in human ocular tracking after acute low-dose alcohol administration

Terence L. Tyson¹ , Nathan H. Feick³, Patrick F. Cravalho³ , Erin E. Flynn-Evans² and Leland S. Stone¹ 

¹Visuomotor Control Laboratory, Human Systems Integration Division, NASA Ames Research Center, Moffett Field, CA, USA

²Fatigue Countermeasures Laboratory, Human Systems Integration Division, NASA Ames Research Center, Moffett Field, CA, USA

³San José State University, San José, CA, USA

Edited by: Richard Carson & William Taylor

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Key points

- Oculomotor behaviours are commonly used to evaluate sensorimotor disruption due to ethanol (EtOH).
- The current study demonstrates the dose-dependent impairment in oculomotor and ocular behaviours across a range of ultra-low BACs (<0.035%).
- Processing of target speed and direction, as well as pursuit eye movements, are significantly impaired at 0.015% BAC, suggesting impaired neural activity within brain regions associated with the visual processing of motion.
- Catch-up saccades during steady visual tracking of the moving target compensate for the reduced vigour of smooth eye movements that occurs with the ingestion of low-dose alcohol.
- Saccade dynamics start to become 'sluggish' at as low as 0.035% BAC.
- Pupillary light responses appear unaffected at BAC levels up to 0.065%.

Abstract Changes in oculomotor behaviours are often used as metrics of sensorimotor disruption due to ethanol (EtOH); however, previous studies have focused on deficits at blood-alcohol concentrations (BACs) above about 0.04%. We investigated the dose dependence of the impairment in oculomotor and ocular behaviours caused by EtOH administration across a range of ultra-low BACs ($\leq 0.035\%$). We took repeated measures of oculomotor and ocular performance from sixteen participants, both pre- and post-EtOH administration. To assess the neurological impacts across a wide range of brain areas and pathways, our protocol measured 21 largely independent performance metrics extracted from a range of behavioural responses ranging from ocular tracking of radial step-ramp stimuli, to eccentric gaze holding, to pupillary responses evoked by light flashes. Our results show significant impairment of pursuit and visual motion processing at 0.015% BAC, reflecting degraded neural processing within extrastriate cortical pathways. However, catch-up

Terence L. Tyson is a General Engineer and Research Aerospace Technologist within the Human Systems Integration Division at the NASA Ames Research Center. He is a member of several human factors teams at NASA, where he contributes to the research and development of complex human-centered aerospace systems and human performance monitoring tools. He received a BS in Psychology with an emphasis in Mathematics from the University of California, Davis and an MS in Human Factors and Ergonomics from the College of Engineering at San José State University.



Leland S. Stone is the senior author of this report.

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saccades largely compensate for the tracking displacement shortfall caused by low pursuit gain, although there still is significant residual retinal slip and thus degraded dynamic acuity. Furthermore, although saccades are more frequent, their dynamics are more sluggish (i.e. show lower peak velocities) starting at BAC levels as low as 0.035%. Small effects in eccentric gaze holding and no effect in pupillary response dynamics were observed at levels below 0.07%, showing the higher sensitivity of the pursuit response to very low levels of blood alcohol, under the conditions of our study.

(Received 24 June 2020; accepted after revision 13 October 2020; first published online 17 December 2020)

Corresponding author T. L. Tyson: NASA Ames Research Center, MS 262-2, Moffett Field, CA 94035-1000, USA.

Email: terence.l.tyson@nasa.gov

Introduction

The consumption of ethyl alcohol (EtOH) is associated with approximately 29% of the vehicular-related fatalities in the United States in 2017 (Traffic Safety Facts Annual Report Tables, 2017), diminished effectiveness in the workplace (Blum *et al.* 1993; Mangione *et al.* 1999), and even medical errors by surgeons (Oreskovich *et al.* 2012). EtOH has a range of effects on the central nervous system (CNS) related to its non-specific disruption of cell membranes and other mechanisms (McIntosh & Chick, 2004; Zoethout *et al.* 2011). For example, EtOH has a general effect on the depolarization phase of action potentials by interfering with the influx of Na⁺ ions (Treisman *et al.* 1991; Mullikin-Kilpatrick & Treisman, 1994). EtOH also affects voltage-gated Ca²⁺ channels in CNS neurons at concentrations as low as 10 mM (the equivalent of 0.046% BAC) (Treisman *et al.* 1991; Mullikin-Kilpatrick & Treisman, 1994; Solem *et al.* 1997; Dopico *et al.* 1999). Additionally, EtOH acts as a non-competitive agonist of γ -aminobutyric acid A (GABA_A) receptors (Mihic, 1999) and as a non-competitive antagonist of *N*-methyl-D-aspartic acid (NMDA) receptors (Hoffman *et al.* 1989; Lovinger *et al.* 1989; Nagy, 2008), which decreases glutamate activity and depresses neuronal activity (Vengeliene *et al.* 2008). In rodent models, EtOH affects GABA receptors at levels as low as 0.01% BAC (Pati *et al.* 2016). The conjunction of these and other examples of altered physiological responses at the cellular and molecular levels are likely to underlie the known effects on sensorimotor performance in general (Sullivan *et al.* 2010; Bjork & Gilman, 2014) and oculomotor performance in particular (Wilson & Mitchell, 1983; Zoethout *et al.* 2011; Maurage *et al.* 2020), but, typically, such functional effects have been described for BAC levels above 0.035%. Little information is known about how lower doses of EtOH might influence oculomotor and other ocular behaviours.

The impairment of eye movements by EtOH has been previously described across the entire gamut of voluntary and reflexive human oculomotor behaviours: saccades (Vorstius *et al.* 2008; Roche & King, 2010; Silva *et al.* 2017), smooth pursuit (Lehtinen *et al.* 1982; Blekher *et al.* 1997; Fransson *et al.* 2010), vergence (Miller *et al.* 1986;

Miller, 1991), eccentric fixation (Romano *et al.* 2017), the vestibulo-ocular reflex (Takahashi *et al.* 1989; Post *et al.* 1994; Roth *et al.* 2014) and optokinetic nystagmus (Mizoi *et al.* 1969). Previous studies showed that steady-state, closed-loop pursuit gain during tracking of sinusoidal or step-ramp target motion was significantly decreased at levels ranging from 0.04 to 0.10% BAC (Fransson *et al.* 2010; Roche & King, 2010). Similarly, for saccades, EtOH has been shown to decrease peak velocity and increase latency at levels in the 0.04–0.10% BAC range (Vorstius *et al.* 2008; Fransson *et al.* 2010; Roche & King, 2010). However, another study did not find an effect on saccadic latency at BACs up to 0.12% (Lehtinen *et al.* 1979). During steady-state tracking, saccadic rate has been shown to increase at levels ranging from ~0.08 to 0.14% BAC (Lehtinen *et al.* 1982) suggesting a compensatory role for saccades when pursuit is impaired by alcohol. Gaze-evoked nystagmus (GEN), associated with cerebellar dysfunction, can typically be observed when attempting to hold eccentric gaze at BACs ~0.06%, with a persistent centripetal ocular drift followed by corrective centrifugal saccades (Goding & Dobie, 1986; Whyte *et al.* 2010; Romano *et al.* 2017). GEN invoked by alcohol intoxication is a key behaviour assessed during the NHTSA-administered standard field sobriety test (Tharp *et al.* 1981) and is used by law enforcement when a motor vehicle driver is suspected of driving under the influence. The pupillary light reflex (PLR) has also previously shown some degree of modulation from EtOH administration, but only at BAC levels \geq 0.05% (Skoglund, 1943; Lobato-Rincon *et al.* 2013; Amodio *et al.* 2019).

In this study, we measured a wide range of largely independent ocular and oculomotor parameters using a radial step-ramp ocular tracking task with high stimulus uncertainty, i.e. randomized target speed, direction, initial position and motion onset (Liston & Stone, 2014). This protocol has previously been demonstrated to provide a sensitive measure of impaired neural function (Liston *et al.* 2017; Stone *et al.* 2019). Our approach allowed us to examine pursuit and saccades and their coordination, as well as dynamic visual processing along extrastriate and frontal cortical pathways (Krauzlis, 2004), during the initiation and maintenance of voluntary tracking to unpredictable target motion. We also investigated

Table 1. Demographics of study participants (mean \pm SD)

	Female	Male
<i>n</i>	8	8
Age (years)	25.1 \pm 2.0	26.0 \pm 4.1
Weight (kg)	63.6 \pm 6.6	74.2 \pm 8.2
Height (cm)	162.9 \pm 8.4	176.5 \pm 5.6
Body mass index	24.0 \pm 2.0	23.8 \pm 2.3

eccentric gaze holding (EGH), a standard measure of cerebellar function, and the dynamics of the pupillary light reflex (PLR), a measure of subcortical non-image-forming visual pathways (Takahashi *et al.* 1984; Lucas *et al.* 2001; Münch *et al.* 2012). The simultaneous examination of this large suite of oculomotor and ocular measures in the current study yielded a comprehensive evaluation of visual and visuomotor processing, and of other associated ocular responses, with reliable effects at ultra-low BAC levels ($<0.02\%$ BAC), well below levels where effects have been previously reported. Additionally, our data allowed us to directly compare the pattern of effects observed after low-dose alcohol consumption with that caused by other neural stressors (Liston *et al.* 2017; Stone *et al.* 2019).

Methods

Ethics approval

Sixteen participants (age: 25.6 ± 3.1 years (mean \pm SD); eight females) completed the study. Their demographics are presented in Table 1. All participants voluntarily read and signed a consent form approved by the Human Research Institutional Review Board (HRIRB) under protocols HRI-336 and HRI-349, conducted at the National Aeronautics and Space Administration (NASA) Ames Research Center. The study complied with the ethical principles established in the *Declaration of Helsinki*, except for registration in a database. De-identified summary data may be made available, as appropriate, upon request to the senior author.

Exclusionary criteria

Binocular static visual acuity was measured in all participants using the Freiburg vision test (Bach, 1996). Individuals were excluded if their corrected binocular visual acuity was worse than 20/40 (>0.30 logMAR). Potential participants completed a phone or in-person interview and a set of surveys prior to their participation. Participants were also screened for traumatic brain injury (TBI) using the Ohio State University TBI identification method (all included participants did not report any past events that led to a loss of consciousness) and for

post-traumatic stress disorder (PTSD) using the civilian PTSD checklist (version PCL-C) (PTSD severity score: 20.2 ± 4.5). Individuals were also excluded if they reported heavy drinking habits (>7 standard drinks/week for females and >14 standard drinks/week for males) or had no previous experience drinking alcohol. For included participants, the average (\pm SD) of self-reported habitual alcohol consumption for female and male participants was 1.7 ± 1.7 and 2.2 ± 1.8 standard drinks/week, respectively. Individuals who travelled outside the time zone in the three months prior to the study were also excluded. All participants completed a general medical interview with the NASA Ames Chief Medical Officer (CMO) and provided a letter confirming their good health from their primary care physician prior to study participation.

Experimental procedure

The study was separated into two phases in the following sequence: an at-home study phase and a laboratory study phase. Alcohol and caffeine consumption were prohibited during the entirety of the study, with the exception of the lab-administered alcohol dosages. During the 3-day at-home phase, participants were asked to maintain a sleep schedule that reflected their approximate habitual sleep-wake cycle. During this phase, participants maintained a sleep-wake journal and call-in journal to verify approximate times of their sleep and wake periods. An actigraphy sensor (Actiwatch Spectrum, Respironics Inc., Bend, OR, USA) was worn on the non-dominant wrist, which recorded levels of activity throughout the 24-h day and provides a quantitative estimate of sleep-wake compliance.

After the completion of the at-home study phase, participants were asked to visit NASA Ames Research Center to complete two days of a laboratory study in which they were given a daily single-dose administration of an alcoholic beverage and performed pre- and post-dose measurements using our ocular tracking task, returning home between the two daytime test sessions. The alcoholic beverage consisted of a mixture of Smirnoff vodka (40% alcohol by volume) and juice. All participants were given a 300 ml beverage, but the ratio of juice was tailored to each participant and was different for the two dosing conditions. Alcohol dosages were computed using a variant of the Widmark model (Widmark, 1932; Searle, 2015), using weight (1-h preceding the start of alcohol administration), sex and target peak BAC as the input parameters.

A single pre-dose BAC measurement (approximately 2 h after awakening) and hourly post-dose measurements of BAC were made using an Alco-Sensor IV breathalyzer (Intoximeters Inc., St Louis, MO, USA). On a given day, participants were randomly assigned either the lower-dose or higher-dose alcohol administration with

Table 2. Alcohol administration profile of study participants (mean \pm SD)

	Lower initial dose (0.02% BAC target)		Higher initial dose (0.06% BAC target)	
	Female	Male	Female	Male
<i>n</i>	8	8	8	8
Standard drinks	0.91 \pm 0.10	1.26 \pm 0.14	2.16 \pm 0.23	2.97 \pm 0.33
40% EtOH volume (ml)	41 \pm 4	56 \pm 6	96 \pm 10	132 \pm 15
Juice volume (ml)	259 \pm 4	244 \pm 6	204 \pm 10	168 \pm 15
EtOH:juice ratio	1:6.4	1:4.4	1:2.1	1:1.3

Abbreviations: EtOH: ethanol.

target peak BACs of 0.02% and 0.06% BAC, respectively. Neither the participant, nor the experimenter running the oculomotor testing, was aware of which dosage would be given on any given day. The experiment was counterbalanced for dose-condition order separately by sex (see Fig. 1). For the lower-dose administration, male and female participants were given 0.24 and 0.20 g/kg, respectively, and for the higher dose, 0.56 and 0.48 g/kg, respectively (see Table 2 for summary of EtOH dosage). The dose administration occurred approximately 2.6 h after the pre-dose BAC measurement and 1 h before the initial post-dose BAC measurement. Sleep instructions between lab visits mimicked the at-home phase of the study.

Oculometrics

During the laboratory phase, participants performed a radial Rashbass-like ocular tracking task (Rashbass, 1961;

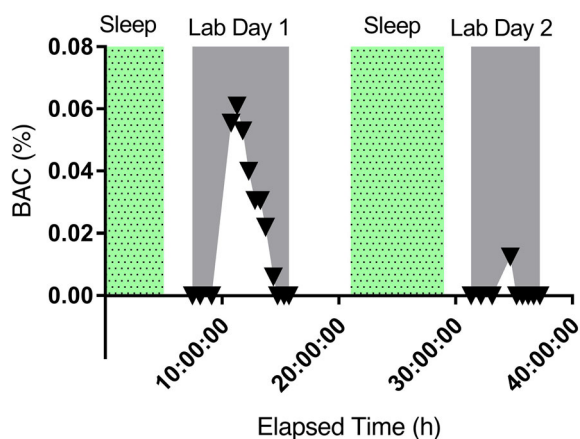


Figure 1. Time course of BACs during the 2-day lab procedure for a single participant

The diagram shows the first and second days with the higher and lower initial doses, respectively. Sleep (in green) was defined by the data collected from actigraphy. The inverted black triangles represent repeated BAC measurements from an individual participant across the two sequential days of testing.

Krukowski & Stone, 2005) before (three pre-dose runs) and after (5–13 post-dose runs) alcohol administration. The task encompassed a high degree of spatiotemporal uncertainty across a multitude of task parameters (see Fig. 2) in order to mitigate anticipation and to maximize performance based on the processing of visual stimulus information, as opposed to prior expectation or prediction (e.g. Barnes, 2008). The motion stimuli and task have been explained in detail previously (Liston & Stone, 2014); however, each run was shortened to 90 trials (as opposed to 180 trials in previous studies, i.e. Liston & Stone, 2014, Liston *et al.* 2017; Stone *et al.* 2019), with random directional sampling in 4° increments around the circle [0, 4, ..., 356°]. The core oculometric analyses were performed in the same manner as in the Stone *et al.* (2019) study. Stimuli were presented on a BenQ XL2420Z monitor (1920 \times 1080 resolution; BenQ Corp., Taipei, Taiwan) at a 144-Hz refresh rate using in-house developed code based on the open-source PsychoPy library (www.pavlovia.org) graphically driven by a GeForce GTX 750 Ti GPU (Nvidia Corp., Santa Clara, CA, USA). Task scripts and executables were launched on an Ubuntu Linux_x86_64 operating system (Canonical Ltd, London, UK).

As in our previous study (Stone *et al.* 2019), we present 14 core oculometric measures in three categories. First, pursuit metrics documenting its latency, initial (open-loop) acceleration, and (closed-loop) gain and proportion smooth in the 400–700 ms post-motion-onset steady-state interval. Second, saccade metrics documenting saccadic rate, amplitude, directional dispersion and dynamics (the slope and intercept of the peak velocity *versus* amplitude ‘main sequence’ curve, corrected for concurrent pursuit displacement and velocity, as per de Brouwer *et al.* 2002). Third, motion-processing metrics documenting direction accuracy (oblique-effect anisotropy and horizontal-vertical asymmetry) and precision (noise), as well as speed accuracy (responsiveness) and precision (noise).

In addition to these core oculometric measurements and analyses described in detail previously (Stone *et al.* 2019), two new classes of oculometrics were also included

here: (1) eccentric gaze holding (EGH) and (2) pupillary light reflex (PLR). EGH was performed by having the subject fixate on a stationary spot for 5 s at ± 25 deg eccentricity in lower-left and lower-right positions of the monitor display, during the calibration prior to each run of tracking trials. To characterize the eccentric holding of gaze, we computed the drift by fitting a simple linear regression model over the change in horizontal gaze position with respect to time. Weighted averages of linear regression estimates of the slopes of the inter-saccadic pieces (≥ 160 ms) of the smooth drift were computed using the left-side (L) and right-side (R) 25-deg eccentric fixations to yield our measures of centripetal, $(L - R)/2$, and lateral drift, $(L + R)/2$.

To invoke the pupil response to light, we used two cycles of a square-wave pulse of background white light

($L_{\text{white}} = 94 \text{ cd/m}^2$, $L_{\text{black}} = 4 \text{ cd/m}^2$, chromaticity_{white}(x, y): 0.309, 0.363, chromaticity_{black}(x, y): 0.307, 0.335) throughout a 7.6-s fixation of the central spot during the calibration prior to each tracking run. Dynamic descriptors of the PLR covered the time constants (τ) of both the dilatation and constriction responses, their corresponding response latencies after the luminance change and the average 'steady-state' pupil size during the second full luminance cycle (Tyson, 2018).

Statistical analysis

All data processing routines were performed using MATLAB (versions R2017a and R2020a, MathWorks, Natick, MA, USA) and statistical analyses were performed

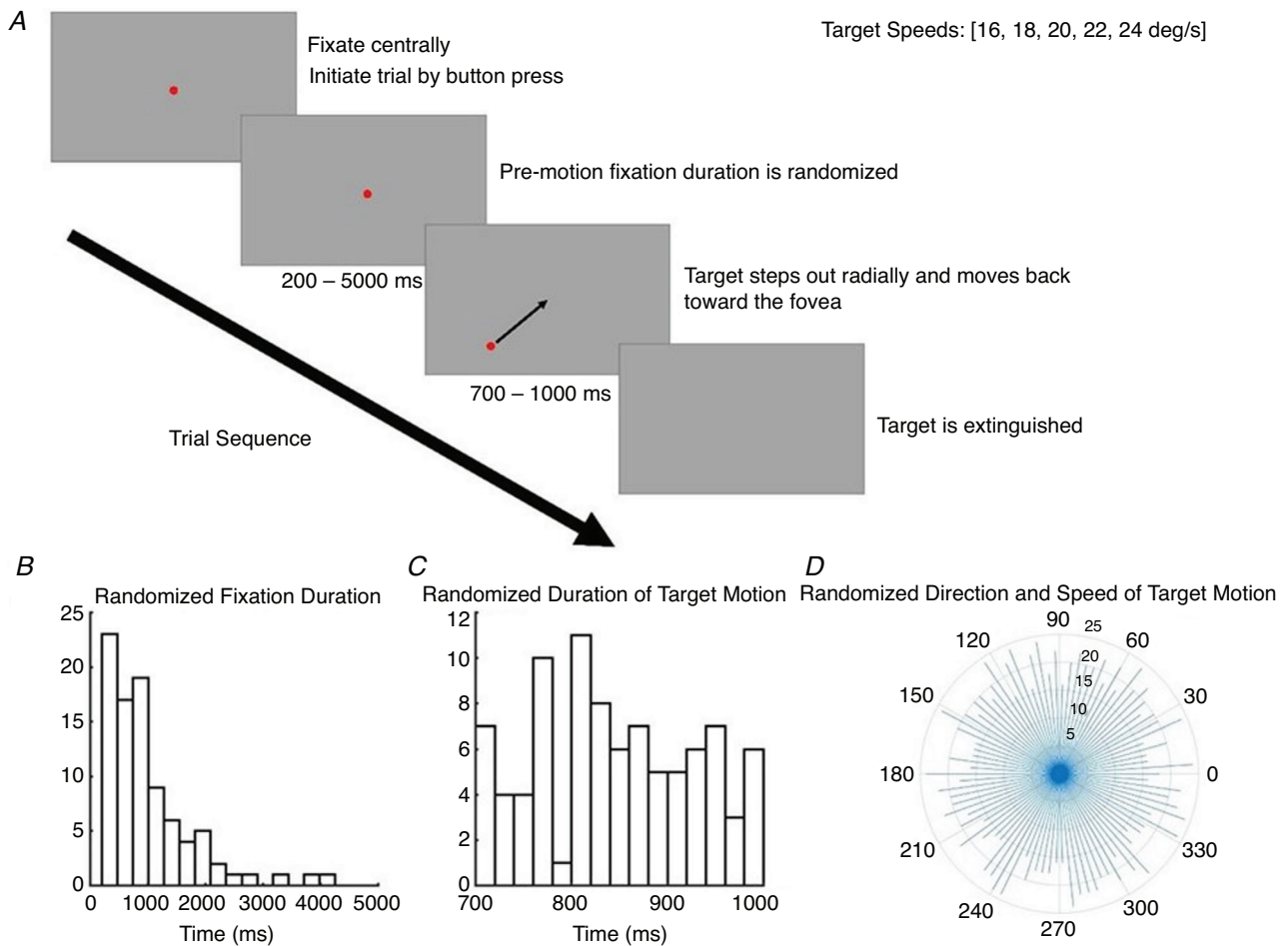


Figure 2. Example stimulus data set from a single participant
 Data set of randomly selected spatial and temporal parameters for a given 90-trial test run of the step-ramp ocular tracking task for a single participant. *A*, the timeline of trial events for the step-ramp ocular tracking task. *B*, the histogram of the pre-motion fixation durations, randomly sampled from an exponential probability density function ranging from 200 to 5000 ms. *C*, the histogram of the target motion durations, randomly sampled from a uniform probability density function ranging from 700 to 1000 ms. *D*, a polar plot showing the 90 radial trajectories of target motion in blue. The randomly chosen target speed (16, 18, 20, 22, or 24 deg/s) is reflected in the trajectory length of the radial lines.

using GraphPad Prism (versions 7 and 8, GraphPad Software, San Diego, CA, USA), MATLAB and Excel (Microsoft Corp., Redmond, WA, USA). All data were transformed to normalized unitless measures of percentage change relative to a within-subject baseline (except for direction asymmetry for which we analysed absolute change because percentage change could not be reliably computed given the near-zero baseline). Specifically, a within-subject baseline for each participant was computed by averaging their three pre-dose baseline runs. Post-dose measurements were then converted to percentage change from baseline by subtracting the baseline from all the post-dose measurements, dividing the resulting difference by the baseline, and multiplying by 100. The within-subject data were then binned into 0.01% BAC intervals and we computed medians across participants for each of the seven bins covering the intervals centred from 0.005 to 0.065% BAC (n from lowest to highest BAC bin: 14, 15, 16, 14, 15, 10 and 11 subjects). A putative bin centred at 0.075% BAC was excluded from the regression analysis because it would only have included data from four participants who overshoot their target BAC. We used simple linear regression across the binned values (occasionally across the full set of unbinned values for greater statistical power) to estimate the dose-dependent effects of BAC separately on each of the oculometric parameters measured. We then performed non-parametric Bonferroni-Holm corrected *post-hoc* tests of the significance of their expected signed change (Wilcoxon signed-rank test, one-tailed, $P < 0.05$) for each of the individual binned values.

Control

To assess the potential psychological effects of anticipation and subjective sense of intoxication with perceived alcohol consumption, we had participants report their level of subjective drunkenness using a slider scale. A simple linear regression model was fitted across all data points of reported drunkenness for each dose condition. The estimated slope and intercept regressors for the two dose conditions were fitted then compared using an ANCOVA to quantify any psychological (i.e. non-BAC related) effect of dose condition. The same analysis was performed on each of the objective oculometrics.

Results

Control for subjective drunkenness

On two consecutive days, participants were given a higher ($BAC_{\text{target}} = 0.06\%$ BAC) or lower initial dose ($BAC_{\text{target}} = 0.02\%$ BAC) in random order using individually tailored dosing (Table 2), which elicited significantly ($t_{15} = 25.03$, $P < 0.01$) different actual peak

BACs in the two conditions ($0.067 \pm 0.010\%$ BAC_{actual} and $0.015 \pm 0.007\%$ BAC_{actual} , respectively).

To assess the potential psychological effects of anticipated drunkenness and subjective sense of intoxication with perceived alcohol consumption, we had participants subjectively report their level of drunkenness. We found that, in the BAC region of overlap across the two dosage levels (0–0.025%), as expected, linear regression revealed a large and highly significant elevation in the y -intercept estimate for the lower-dose condition ($\Delta = +15.6\%$, $F_{1,23} = 12.67$, $P = 0.0017$). This is consistent with the known ‘placebo’ effect on the *subjective* sense of drunkenness (see Fig. 3). In stark contrast, we found that only three of the 21 *objective* oculometric measures showed significant y -intercept offsets (Fig. 4) and only one of these (saccadic peak velocity slope) showed a small offset in the correct direction for a placebo effect ($\Delta = +4.3\%$, $F_{1,69} = 7.17$, $P = 0.0092$, uncorrected for 21 multiple tests). A fourth metric (latency) showed no significant regression slope for either dosing condition, yet nonetheless showed a small, but significant, positive simple offset between the two dosing conditions ($\Delta = +2.5\%$, $t_{70} = 4.06$, $P = 0.0001$).

Baseline (pre-dose) measures

For pursuit behaviour during the initiation (open-loop) phase of ocular tracking, the average (\pm SD across subjects) baseline latency and acceleration were 149 ± 12 ms and 123 ± 32 deg/s², respectively, consistent with our previous studies using high directional uncertainty (159 ms and 104 deg/s², respectively, in Stone *et al.* 2019; 159 ms latency for Expt 5 in Krukowski & Stone, 2005). For

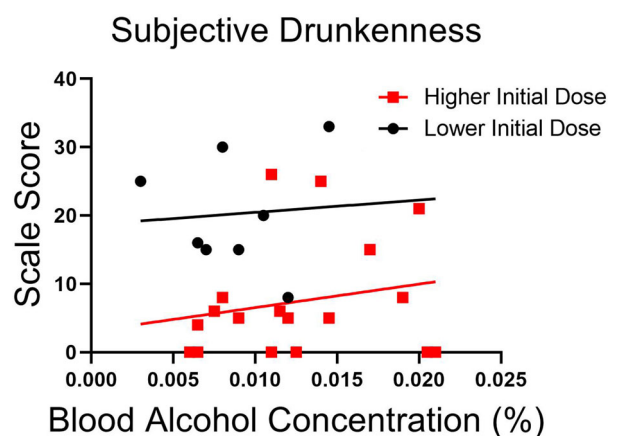


Figure 3. Dose effect on subjective drunkenness

Control data from all participants associated with BACs below 0.025% showing a systematic vertical shift in the subjective experience of drunkenness between the two initial dose conditions. The figure plots scores using a slider scale ranging from 0 to 100, with 0 indicating ‘sober’ and 100 indicating ‘extremely drunk’.

pursuit behaviour during the steady-state (closed-loop) phase of ocular tracking, the average gain and proportion smooth were 0.81 ± 0.14 and 0.77 ± 0.06 , respectively, consistent with our previous findings (0.76 and 0.76, respectively, in Stone *et al.* 2019). For saccadic behaviour, the average rate, amplitude and directional dispersion were 3.2 ± 0.6 Hz, 1.5 ± 0.7 deg, and $17.8 \pm 4.3^\circ$, respectively, consistent with our previous findings (3.8 Hz, 2.0 deg and 17.2 deg, respectively, in Stone *et al.* 2019). The saccadic peak velocity slope and intercept parameters from the ‘main sequence’ fit yielded $34.7 \pm 8.5/s$ and 47.4 ± 17.8 deg/s, consistent with previous findings (30/s and 49 deg/s, respectively, in Stone *et al.* 2019). The average direction noise, (oblique effect) anisotropy, and (horizontal-vertical) asymmetry were $7.6^\circ \pm 2.4^\circ$, 0.35 ± 0.07 and 0.002 ± 0.158 , respectively, consistent with our previous results (9.4, 0.31 and 0.09, respectively, in Stone *et al.* 2019). Speed noise and responsiveness

were, on average, $15.3 \pm 5.0\%$ and 0.52 ± 0.20 , respectively, consistent with our previous results (19.6%, and 0.37, respectively, in Stone *et al.* 2019). The mean gaze drift in the eccentric and lateral directions during eccentric gaze fixation were 0.06 ± 0.06 deg/s (centripetal) and 0.04 ± 0.07 deg/s (leftward), respectively. The mean estimated time constants (τ) of the light-evoked constriction and dilatation responses of the pupil were 186 ± 21 ms and 542 ± 69 ms, respectively. The mean response latencies for constriction and dilatation were 236 ± 39 ms and 377 ± 61 ms, respectively. The mean pupil diameter during the calibration was 5.0 ± 2.2 mm.

Effect of BAC

Figures 5A and 5B show a pair of example eye-velocity traces (in blue) in trials from pre- and post-dose runs of the same participant. The green horizontal line

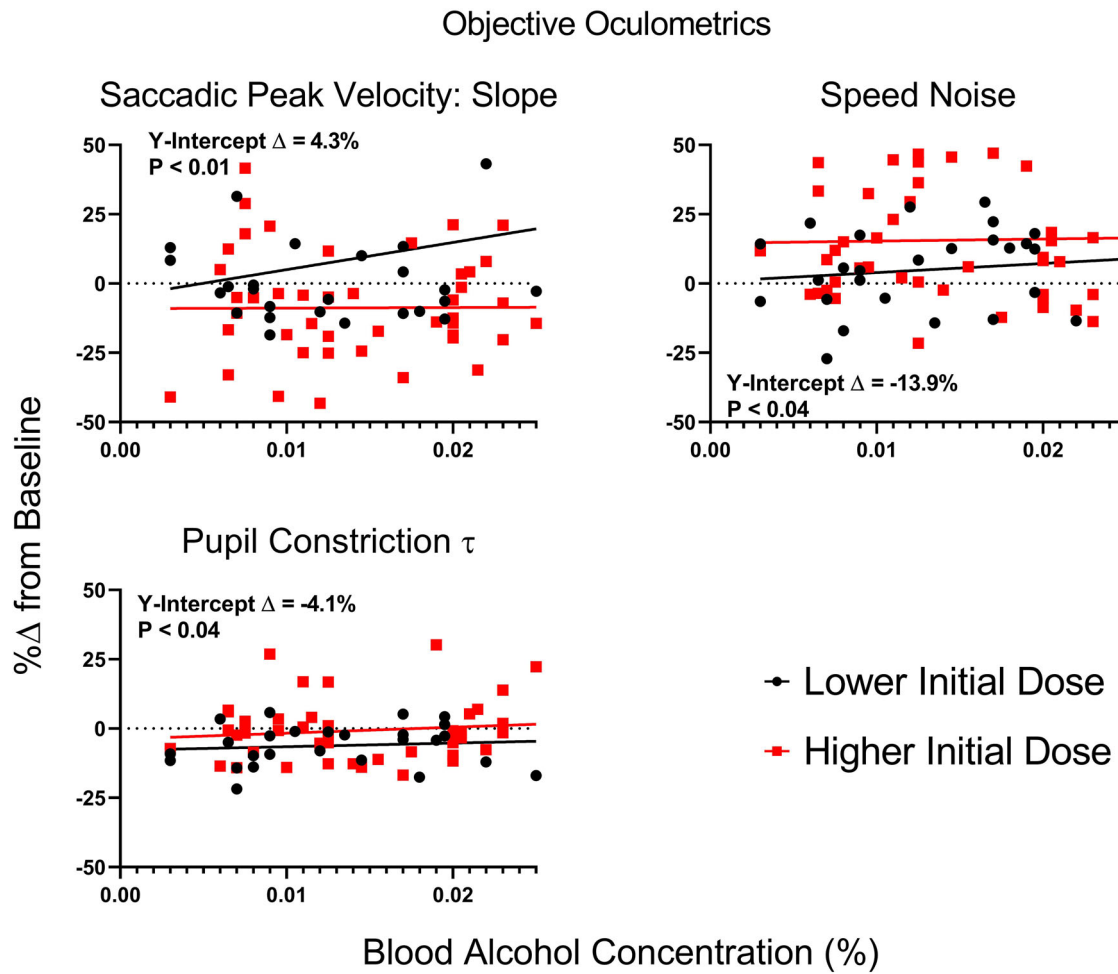


Figure 4. Dose effect on objective oculometrics
Objective oculometric data from all participants associated with BACs below 0.025% generally shows a lack of clear differences in performance between dose conditions. Only four of the 21 oculometrics showed a significant difference ($P < 0.05$) between the dose conditions and only two (latency not shown) were in the same direction as in the subjective data in Fig. 3.

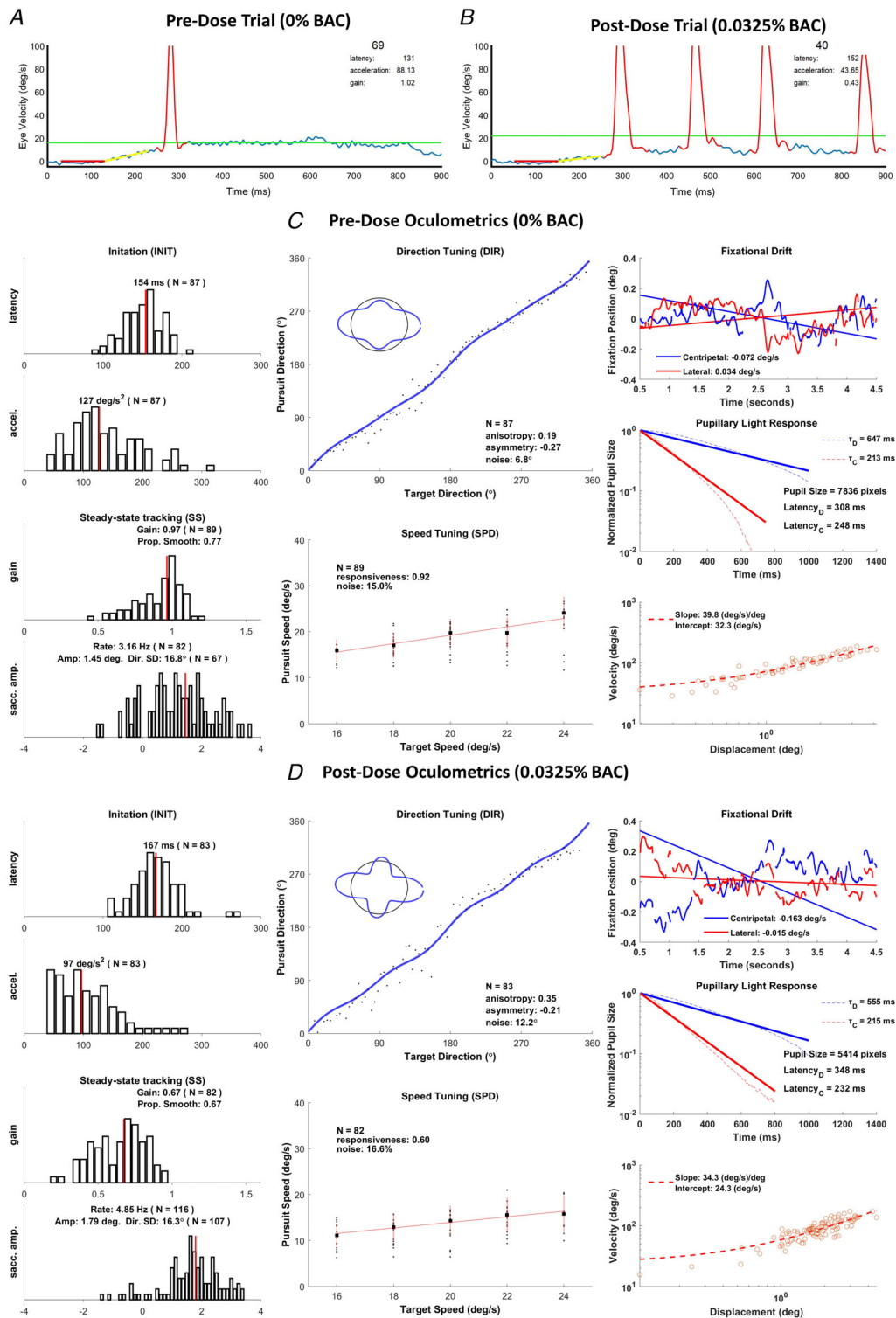


Figure 5. Example response data from an individual participant

A, an example trial from a pre-dosing run. The blue trace shows the smooth eye velocity over the entire trial. The green horizontal line indicates the constant target speed (16 deg/s in this trial). Our steady-state analysis interval spans from 400 to 700 ms (sloped yellow line) of tracking, after an initial fixation baseline (red horizontal line) marking the latency (131 ms), represents the open-loop acceleration (88.1 deg/s²) of smooth pursuit (Lisberger & Westbrook, 1985; Tychsen & Lisberger, 1986). Note the single initial saccade (in red) and high steady-state pursuit gain with no catch-up saccades during near-perfect steady-state tracking (gain

of 1.02). *B*, an example post-dosing trial at a measured BAC of 0.0325% for the same participant. Note the longer latency (152 ms), lower open-loop acceleration (43.7 deg/s²), and multiple catch-up saccades during steady-state tracking to compensate for the attenuated pursuit gain (0.43), with no indication of a smooth corrective acceleration associated with the sustained steady-state retinal slip. *C*, the oculometric summary chart of the computed oculometrics before dose administration for the same participant. *D*, the oculometric summary chart after dose administration for the same participant. Note the systematic impairment of visual and sensorimotor performance with gaze-holding and saccade dynamics mildly compromised and with the PLR largely unaffected.

represents the constant velocity profile of the pursued target. Note the absence of catch-up saccades (in red) in our 400–700 ms analysis window associated with vigorous steady-state smooth tracking in the pre-dose trial. In contrast, the post-dose trial (i.e. one from a run after alcohol administration) shows large and frequent catch-up saccades and diminished pursuit gain, indicating compromised pursuit associated with low-dose alcohol

and concomitant compensation by the saccadic system to maintain foveation (or near foveation) of the moving target.

Pursuit initiation was systematically impaired by alcohol administration across the range tested. Pursuit latency increased significantly as a function of BAC ($F_{1,5} = 39.9$, $r^2 = 0.89$, $P = 0.0015$) but rising only by 9% at 0.065% BAC (Fig. 6A). Initial (open-loop) acceleration

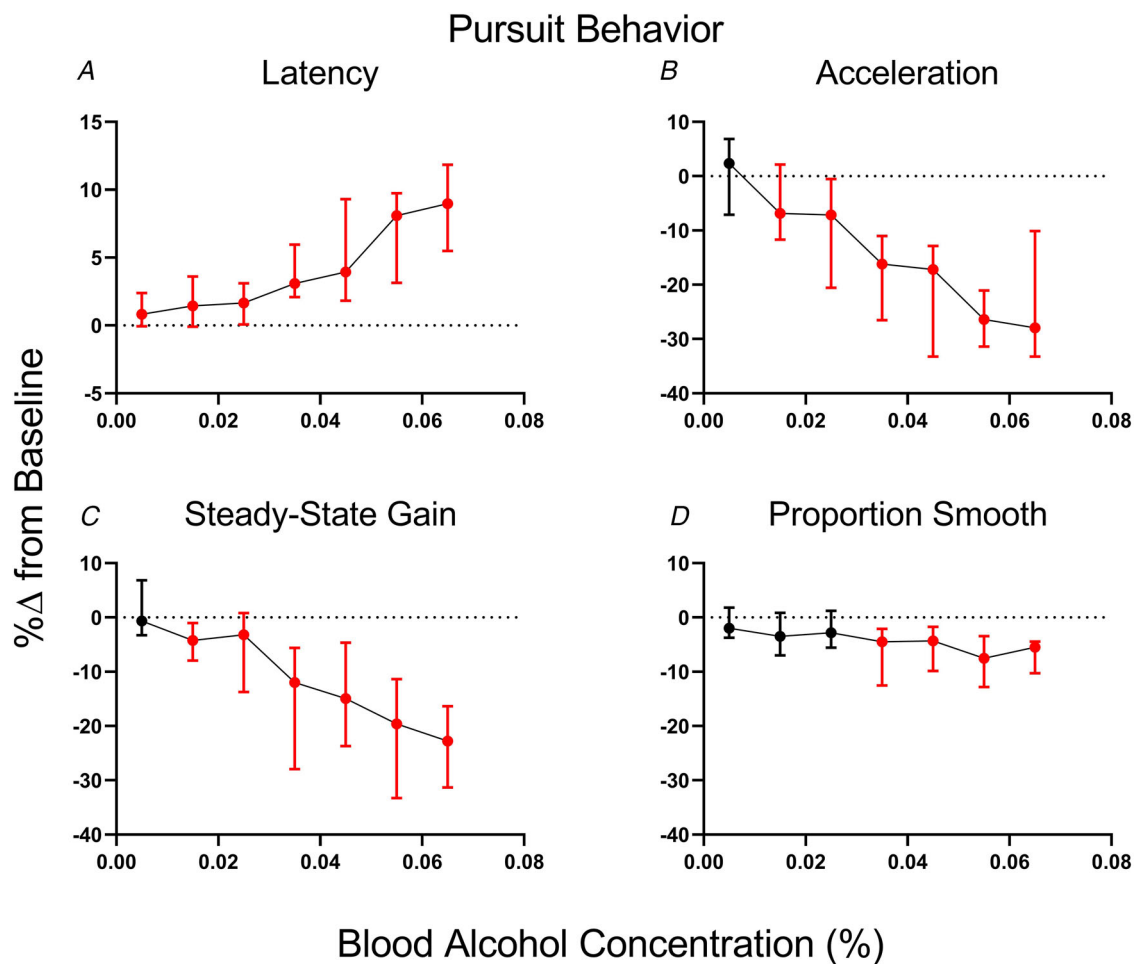


Figure 6. Pursuit behaviour

Dose-response curves of pursuit behaviour as a function of BAC. Panels show plots of median percentage change from within-subject baseline (error bars representing interquartile range across subjects) across both dose conditions for latency (*A*), acceleration (*B*), gain (*C*) and proportion smooth (*D*) as a function of BAC. Points in red are significantly different than baseline as indicated by the horizontal dotted line (Wilcoxon signed-rank, Bonferroni-Holm corrected, one-tailed, $P < 0.05$). On average, steady-state gain was reduced by ~16% and ~22% at 0.035% and 0.055% BAC, respectively, resulting in an ~69% and ~91% increase, respectively, in the average ground lost due to inadequate pursuit during the steady-state tracking interval compared to that during baseline performance. Note the scale difference in *A*.

decreased significantly as a function of BAC ($F_{1,5} = 124.8$, $r^2 = 0.96$, $P = 0.0001$), with the reduction reaching 16% by 0.035% BAC (Fig. 6B). Steady-state pursuit also showed declining performance as a function of BAC. Both (closed-loop) gain ($F_{1,5} = 107.1$, $r^2 = 0.96$, $P = 0.0001$) and proportion smooth ($F_{1,5} = 12.5$, $r^2 = 0.71$, $P = 0.0167$) showed significantly decreasing trends with performance decrements from baseline reaching approximately 12% and 4%, respectively, by 0.035% BAC (Fig. 6C and D).

Saccadic behaviour was also systematically altered by alcohol administration across the range tested (see Fig. 7). Saccadic amplitude showed a robust increase as a function of BAC ($F_{1,5} = 50.42$, $r^2 = 0.91$, $P = 0.0009$) reaching 27% by 0.035% BAC, whereas saccadic rate showed a smaller, but systematic increase, reaching significance

only for the regression across the full, unbinned data set ($F_{1,143} = 6.76$, $r^2 = 0.045$, $P = 0.0103$). Saccadic direction dispersion (not shown) decreased with BAC ($F_{1,5} = 9.23$, $r^2 = 0.65$, $P = 0.0288$), but this result could be an artifactual consequence of the large increase in saccadic amplitude in the presence of fixed tracker position noise. The slope and intercept parameters of the 'main sequence' linearly decreased ($F_{1,5} = 20.32$, $r^2 = 0.80$, $P = 0.0064$) and increased ($F_{1,5} = 14.39$, $r^2 = 0.74$, $P = 0.0127$), respectively, as a function of BAC, reaching approximately 21% below and 9% (not significant) above baseline, respectively, by 0.035% BAC.

Visual motion processing also showed systematic effects of alcohol administration across the range tested (see Fig. 8). Direction noise ($F_{1,5} = 27.14$, $r^2 = 0.84$,

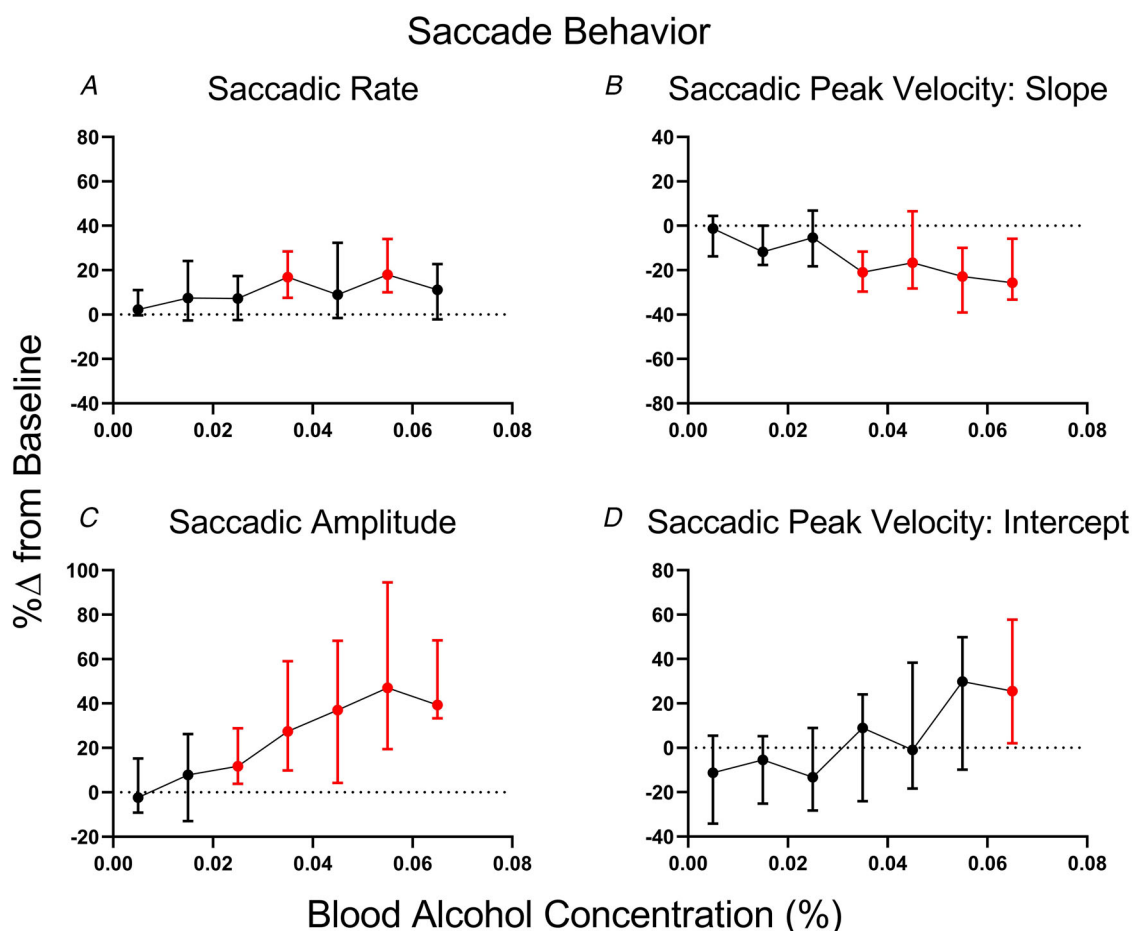


Figure 7. Saccade behaviour

Dose-response curves of saccadic behaviour as a function of BAC. Panels show plots of the median percentage change from within-subject baseline (error bars representing interquartile range across subjects) across both dose conditions for rate (A), amplitude (C), peak velocity: slope (B) and intercept (D) as a function of BAC. Points in red are significantly different than baseline as indicated by the horizontal dotted line (Wilcoxon signed-rank, Bonferroni-Holm corrected, one-tailed, $P < 0.05$). On average, saccadic amplitude and rate were both increased at 0.035% BAC, by 37% and 24% respectively, resulting in a ~70% mean increase in the amount of ground recouped by saccades above that during baseline performance (i.e. complete compensation for the 69% decrease in ground lost from impaired pursuit). At 0.055% BAC, on average, the ground recouped was ~94% in response to the ~91% lost.

$P = 0.0034$) showed a significant increase as a function of BAC, reaching 30% above baseline by 0.035% BAC and 73% by 0.065% BAC. Direction tuning showed no significant change ($P = 0.1291$) in the (oblique effect) anisotropy (not shown), but did show a significant reduction in the (horizontal-vertical) asymmetry ($F_{1,5} = 9.50, r^2 = 0.66, P = 0.0274$). Speed responsiveness (slope) showed a systematic decrease with increasing BAC ($F_{1,5} = 53.35, r^2 = 0.91, P = 0.0008$), reaching 28% by 0.035% BAC. Speed noise showed a weak increasing trend that reached significance across the full, unbinned data set ($F_{1,143} = 6.22, r^2 = 0.042, P = 0.0137$).

As expected, gaze holding was impaired by alcohol consumption, with eccentric gaze showing a dose-dependent increase in centripetal drift ($F_{1,5} = 18.29, r^2 = 0.79, P = 0.0079$) (Fig. 9A), but there was no systematic effect on lateral drift ($P = 0.20$), even for a regression across the full, unbinned data set ($P = 0.095$)

(Fig. 9B). The pupillary light reflex (PLR) showed no consistent effect of low-dose alcohol (Fig. 10) in either the constriction or dilatation time constants ($P > 0.11$ for both the binned and unbinned regressions) as well as in either the constriction or dilatation response latencies ($P > 0.11$ for both the binned and unbinned regressions). Pupil size showed no significant trend with BAC ($P > 0.15$ for both the binned and unbinned regressions).

Table 3 summarizes our results and shows that most of the parameters of visual motion processing and oculomotor control that we measured show significant linear trends with increasing BAC. The first column reports the slopes of the linear regression as a measure of the sensitivity to BAC while the second column shows the lowest BAC level at which we were able to detect significant effects using *post-hoc* Wilcoxon signed-rank tests. Note that: (1) both pursuit and saccades show systematic changes across the range tested with

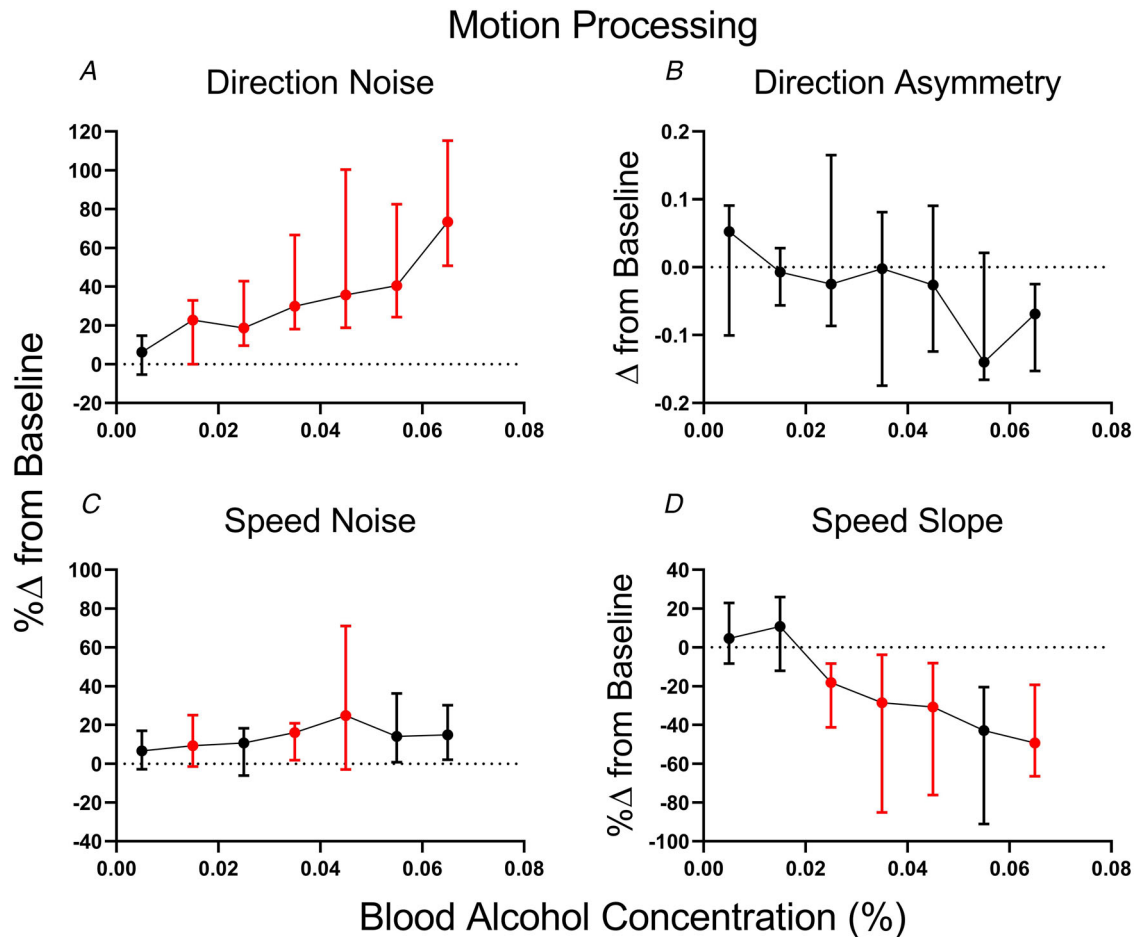


Figure 8. Visual motion processing
Dose-response curves of visual motion processing as a function of BAC. Panels show plots of the median percentage change from within-subject baseline (error bars representing interquartile range across subjects) across both dose conditions for direction noise (A) and asymmetry (B), and speed noise (C) and slope (D) as a function of BAC. Points in red are significantly different than baseline as indicated by the horizontal dotted line (Wilcoxon signed-rank, Bonferroni-Holm corrected, one-tailed, $P < 0.05$).

decreasing pursuit performance and increased reliance on saccades at BAC levels as low as 0.015%, (2) visual motion processing is impaired, with direction uncertainty particularly sensitive, and (3) the PLR shows little or no effect of BAC in the range tested.

For those measures for which there were significant effects of BAC, we found that none showed significant residual 'hangover' effects once BAC returned to 0% (Wilcoxon signed-rank test, two-tailed, $P > 0.11$), except for speed noise, which was borderline significant ($P = 0.0833$).

Discussion

We systematically examined the effects of low-dose ethanol (leading to BAC levels up to $\sim 0.07\%$) on a wide variety of oculometric measures during voluntary tracking of unpredictable target motion with randomized directions, speeds, temporal onsets and initial spatial locations (including open-loop measures that capture effects occurring prior to any possible visual information being available from the negative feedback control loop). We document for the first time that pursuit and saccadic behaviour, as well as the underlying visual motion processing (Stone & Krauzlis, 2003), were significantly altered at BAC levels as low as 0.015%. We also found that the precision of both direction and speed discrimination was reduced (i.e. noise increased) and that accuracy of speed processing was impaired, consistent with a systematic underestimation of target speed. The

pursuit response was slightly delayed (by ~ 15 ms at 0.065%) with pursuit gain (both open and closed loop) significantly reduced starting at 0.015% BAC, reaching reductions of 25% or more by 0.065% BAC. We also found that saccadic amplitude increases dramatically to compensate, accompanied by a modest increase in saccadic rate, such that overall tracking effectively covers the same target displacement at least up to 0.055% BAC, albeit less smoothly. Specifically, the $\sim 22\%$ reduction in closed-loop gain at 0.055% BAC resulted in $\sim 91\%$ increase in lost ground of the eye with respect to the moving target compared to baseline performance, but the lost eye displacement was fully recouped by saccadic compensation ($\sim 94\%$ increase in ground gained). Note, however, that while the saccadic compensation places the image of the target at or near the fovea, it does not actually stabilize the target image on the retina as healthy pursuit does. Thus, despite the fact that the combined pursuit and saccadic tracking keeps up with the target, low-dose alcohol probably results in a significant reduction in dynamic visual acuity due to the uncorrected residual retinal slip, i.e. the repeatedly re-foveated target is not actually fully stabilized, so legibility or other perceptual judgments requiring good dynamic acuity may be impaired when residual slip exceeds about 3 deg/s (Westheimer & McKee, 1975). Previous studies have found similar pursuit deficits and saccadic compensation, but they examined higher BAC levels (at and above 0.05%) and used predictable target motion allowing them to focus on the motor output component of the pursuit deficits as opposed to the sensory/perceptual input drive (Barnes,

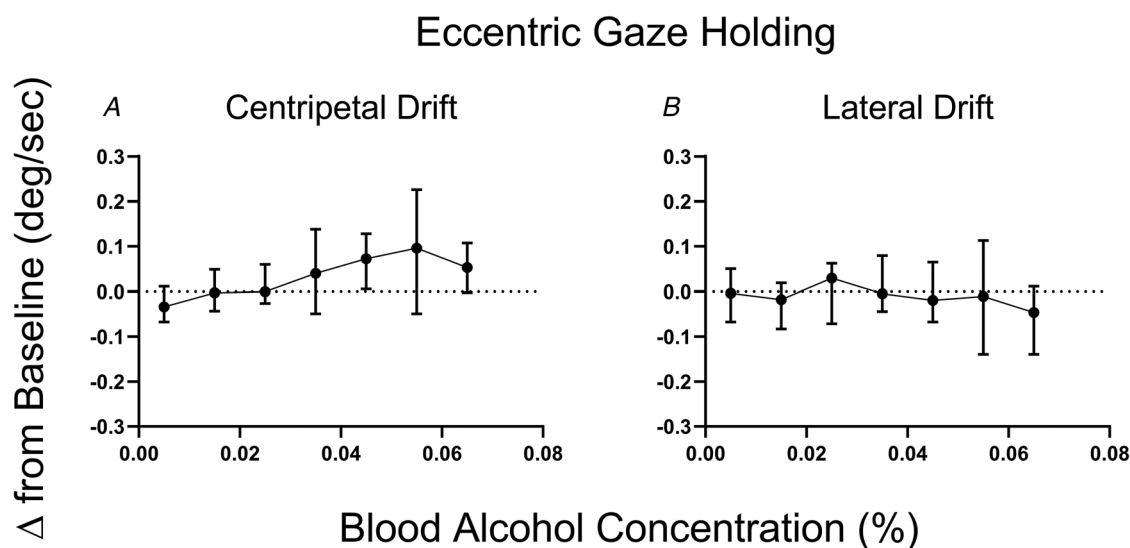


Figure 9. Eccentric gaze holding

Dose-response curves of gaze holding behaviour as a function of BAC. Panels show plots of the median percentage change from within-subject baseline (error bars representing interquartile range across subjects) across both dose conditions for centripetal (A) and lateral (B) drift. Although there was a significant linear increase in centripetal drift with increasing BAC, no individual points were found to be significantly different than baseline as indicated by the horizontal dotted line (Wilcoxon signed-rank, Bonferroni-Holm corrected, one-tailed, $P > 0.14$).

1984; Lehtinen *et al.* 1982; Moser *et al.* 1998; Roche & King, 2010). The largely successful ability of saccades to mitigate lost ground suggests that ultra-low-dose alcohol (<0.065% BAC) has only a negligible adverse impact on the saccadic system. This is not the case, for instance, with acute sleep deprivation (Stone *et al.* 2019), as performance in the middle of a sleepless night (i.e. ~23 h after habitual awakening) shows a similar decrease in pursuit gain (resulting in ~60% increase pursuit lost ground) that is only partially compensated for by catch-up saccades (~25% increase in ground gained), suggesting a different mechanism(s) is (are) at play whereby both saccades and pursuit are functionally impaired.

In addition to our novel findings of altered visual motion processing and open-loop pursuit gain at ultra-low BAC levels, our results confirmed the previously observed impairment of the so-called 'main sequence' of saccadic dynamics with decreased peak velocity, reaching

significance at higher BAC levels (~0.065%) (Lehtinen *et al.* 1979; Moser *et al.* 1998; King & Byars, 2004; Fransson *et al.* 2010; Roche & King, 2010). We also confirmed that eccentric gaze holding appears to show impairment with BAC but, because inter-subject variability was high and we only examined two 5-s eccentric fixations per run, none of the individual data points reached significance below 0.07%. Lastly, we found no adverse effects on the PLR at BAC levels below 0.07%.

Physiological implications

The above assortment of findings indicate that cortical processing of visual motion signals and the associated pursuit response is exquisitely sensitive to ultra-low-dose alcohol with deficits as large as 23% observed at a BAC level of only 0.015%, up to 30% at a BAC level

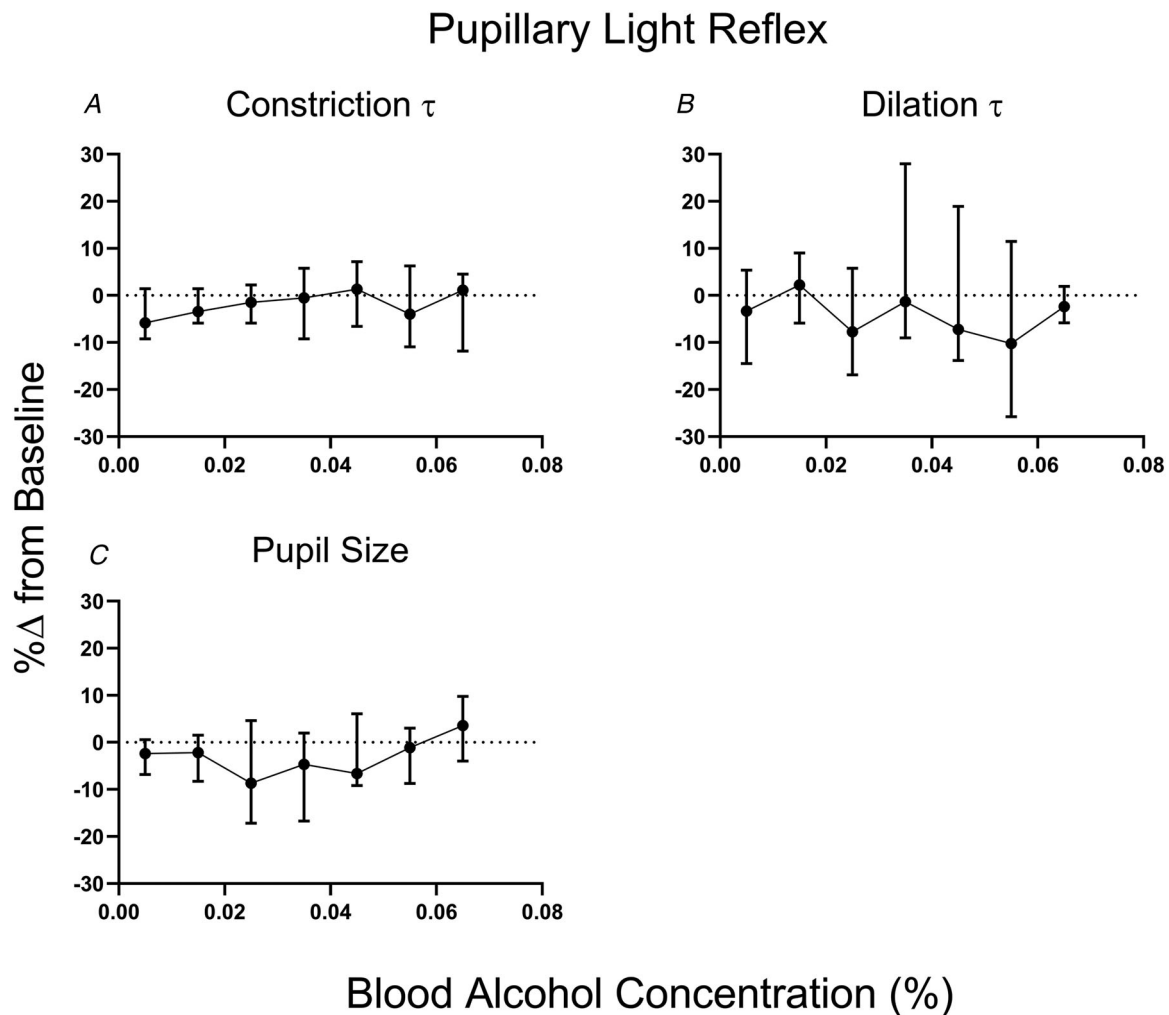


Figure 10. Pupillary light reflex

Dose-response curves of the pupillary light reflex as a function of BAC. Panels show plots of the median percentage change from within-subject baseline (error bars representing interquartile range across subjects) across both dose conditions of the constriction (A) and dilatation (B) time constants as well as of the average pupil size (C).

Table 3. Oculometric sensitivity to blood alcohol concentration

	BAC slope (%/0.01% BAC)	BAC threshold (% BAC)
Pursuit latency	1.43	0.005
Open-loop acceleration	-5.00	0.015
Steady-state gain	-3.89	0.015
Proportion smooth	-0.72	0.035
Saccadic amplitude	8.17	0.025
Saccadic dispersion	-4.24	0.065
Saccadic rate	2.67	0.035
Saccadic velocity (slope)	-3.81	0.035
Saccadic velocity (Int)	6.90	0.065
Direction noise	9.08	0.015
Direction anisotropy	*	*
Direction asymmetry	-2.26 [†]	> 0.065
Speed noise	2.60	0.015
Speed responsiveness	-10.06	0.025
Centripetal drift	1.90 [‡]	> 0.065
Lateral drift	*	*
Steady-state pupil size	*	*
Constriction τ	*	*
Dilatation τ	*	*
Constriction latency	*	*
Dilatation latency	*	*

The first column reports the regression slopes across seven binned BAC levels, except for the values for saccadic rate and speed noise, which are the regression slopes across 145 unbinned measurements. The second column reports the lowest BAC value for which the effect for a single BAC bin was significant by a *post-hoc* one-tailed, Bonferroni-Holm corrected, Wilcoxon signed-rank test across subjects.

*Not significant ($P \geq 0.05$);

[†] units are 1/0.01% BAC;

[‡] units are deg/s/0.01% BAC.

of 0.035%, and reaching 73% at a BAC of 0.065%. These dose-dependent alcohol-related deficits, which are evident even in individual trials (Fig. 5B), illustrates the striking fact that, even in the steady-state, there is no correction of the tracking velocity error with a smooth acceleration, despite the strong negative feedback drive to do so. Our observation is reminiscent of pursuit deficits observed with lesions of the medial superior temporal (MST) or frontal pursuit area (FPA) (Newsome *et al.* 1985; Dürsteler *et al.* 1987; Dürsteler & Wurtz, 1988; Newsome & Paré, 1988; Keating, 1991; Morrow & Sharpe, 1993, 1995; Heide *et al.* 1996; Shi *et al.* 1998), consistent with a systematic misperception of target speed and with physiological recordings in these two areas (Chou & Lisberger, 2004; Newsome *et al.* 1985; Dürsteler & Wurtz, 1988; Newsome & Paré, 1988; Mahaffy & Krauzlis, 2011). These physiological and psychophysical findings (Steinbach, 1976; Kowler & McKee, 1987; Beutter

& Stone, 1998; Stone *et al.* 2000; Stone & Krauzlis, 2003; Krukowski & Stone, 2005), as well as our current findings, strongly suggest that pursuit eye movements are driven by a cortically reconstructed representation of target motion, shared with visual perception (Stone *et al.* 2009) and saccades (Orban de Xivry & Lefèvre, 2007), and not by the raw retinal slip that is experienced, uncorrected, during steady-state tracking under low-dose alcohol and MST or FPA lesions (see, however, Krauzlis & Lisberger, 1989; Gegenfurtner *et al.* 2003). That said, our data do not rule out a role for alcohol effects earlier in visual motion processing pathways as well. Indeed, our findings of increased pursuit latency and reduced precision in open-loop direction signals are consistent with the involvement of the middle temporal (MT) area (Maunsell & Van Essen, 1983; Albright, 1984; Felleman & Kaas, 1984; Lisberger & Movshon, 1999) and perhaps even earlier visual processing (Hubel, 1959; Churchland *et al.* 2005; Gur *et al.* 2005; Li *et al.* 2008; Elstrott & Feller, 2009), given the role of these areas in the processing of direction signals. The fact that similar alcohol-related deficits have recently been found in perceptual direction thresholds and direction repulsion (Wang *et al.* 2018), albeit at a higher BAC level of $\sim 0.07\%$, also suggests that early cortical motion processing pathways feeding into the posterior parietal cortex are affected by low-dose alcohol.

Our findings also indicate that the well-known effects of alcohol on cerebellar and brainstem function (oculomotor output pathways), captured by deficits in eccentric gaze holding (Goding & Dobie, 1986; Whyte *et al.* 2010; Romano *et al.* 2017) and decreased peak saccadic velocity (Lehtinen *et al.* 1979; Moser *et al.* 1998; King & Byars, 2004; Fransson *et al.* 2010; Roche & King, 2010) respectively, only become significant at higher BAC levels, at and above 0.035%, consistent with previous findings and with altered responses of Purkinje cells (Sinclair *et al.* 1980; Franklin & Gruol, 1987; Idrus & Napper, 2012) and brainstem burst-neurons (Henn *et al.* 1984). Lastly, our findings indicate that the non-image-forming pathways of the PLR (Kelbsch *et al.* 2019) appear unaffected by BAC levels below 0.07%. However, previous studies have found mixed results of PLR dynamics influenced by acute alcohol administration at doses around or above 0.05% BAC (Skoglund, 1943; Brown *et al.* 1977; Lobato-Rincon *et al.* 2013; Amodio *et al.* 2019), but discrepancies across studies (and our failure to detect a dose-dependent effect) may be due to experimental limitations in the control of circadian or homeostatic processes that could have otherwise been harnessed to amplify PLR disruption (Münch *et al.* 2012).

Caveats

Given that our procedures involved taking multiple measurements during the recovery from a peak alcohol dosing, it is possible that some of our measurements at

low BAC levels were affected by previously experienced higher BAC levels (a 'hangover' effect). Comparison of our initial lower (0.02% target) and higher (0.06% target) dosing levels allowed us to control for this possibility. We found no difference between the BAC effects under these two dosing conditions in all but four cases. In two cases, the constriction time constant and speed noise, we found higher BAC responses (either a higher slope or offset) after the higher initial dosing (Fig. 4), such that some 'hangover' effect was possible when the residual BAC level is still above zero (despite our finding of no significant hangover effects for these metrics after fully returning to 0% BAC). However, for constriction tau, this control finding is largely irrelevant as we found no dose-dependent effect of BAC anyway, and for speed noise, the amplitude of the observed difference between the two dosing conditions (13.9%) cannot fully account for the observed overall BAC effects reported in Fig. 8 and Table 3 (up to 24.8%). In the other two cases, the observed higher effect for the lower initial dosing for pursuit latency and the slope of the saccadic 'main sequence' curve suggests the possibility of a psychological 'placebo' effect but, again, the small amplitudes (2.5% and 4.3%, respectively) cannot account for the observed overall BAC effects, reported in Figs 6 and 7 and Table 3 (up to 9.0% and 25.5%, respectively). In addition, it is possible that the observation of a small increase in pursuit latency (Fig. 6A) could have been an artifactual consequence of the large decrease in initial acceleration, given our least-square estimation of latency in the presence of fixed eye-tracker noise. Similarly, the decrease in saccadic dispersion may have been an artifactual consequence of the increase in saccadic amplitude. Lastly, the increase in direction and speed noise probably compromised to some degree our measurements of direction and speed accuracy.

Conclusions

Our data demonstrate that pursuit and the underlying visual motion processing during the tracking of a moving target are significantly impaired at BAC levels as low as 0.015%. However, the saccadic system responds by increasing the size and frequency of catch-up saccades during steady-state tracking and effectively recoups the lost ground associated with reduced pursuit gain at least up to BAC levels of 0.055%, masking the tracking deficit of the pursuit loss. Although effective overall ocular tracking (measured as the ratio of eye to target displacement) is still possible at levels at least up to 0.055%, the profound deficits in visual motion processing at BACs as low as 0.015% reduce the quality (precision and accuracy) of the visual motion information used for visual perception/cognition/attention, as well as any visuomotor coordination. Furthermore, the unsmooth nature of the tracking may lead to a functionally relevant decrement

in the dynamic visual spatial acuity available for the performance of any concurrent perceptual, cognitive and motor control tasks requiring proper stabilization of the moving retinal image, even though the overall tracking displacement gain is close to normal.

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Additional information

Data availability statement

De-identified summary data presented in this article may be made available, as appropriate, upon request to the Senior Author (leland.s.stone@nasa.gov), pending NASA review and ethical approval for secondary use of the data.

Competing interests

There are no competing interests. The last author is listed as an inventor on three related NASA-held US patents Nos 9,730,582/10,420,465/10,463,249 awarded 8/2017, 9/2019, and 10/2019, respectively, but he has no direct role in any commercialization.

Author contributions

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

This work was supported by the Force Health Protection Program of the Office of Naval Research (SAA2 402925-1, Contract Award no. N0001418IP00050) and in part by NASA cooperative agreement NNX17AE07A. We also thank NASA's Human Research Program for support during the writing of this article.

Acknowledgements

We acknowledge the invaluable comments on an earlier draft from Drs Brent Beutter, Joel Lachter and Shu-Chieh Wu and the excellent technical support from Mark Anderson.

Keywords

alcohol, saccades, smooth pursuit, visual motion processing

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Statistical Summary Document