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Oculometric detection and characterization of sub-clinical visual/visuomotor impairment

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Background

- Eye movements have long been known to provide insight into human sensorimotor brain function and pathology (for a review see Leigh and Zee's *The Neurology of Eye Movements*, 2015), with a strong tradition of applying linear system theory to explain gross deficits in oculomotor or visual-vestibular function.
- Kowler & McKee, in their 1987 study of motion perception, applied the principles of forced-choice psychophysics to the analysis of eye movements, coining the term oculometrics and using eye movements to quantify the precision of speed perception, heralding the assessment of subtler aspects of visual and cognitive function[e.g.,1,2,3].
- Oculometrics can be <u>reliable biomarkers</u> of visual function. For the set we use:
  - Within-subject test-retest variability across 18 months is smaller than across-subject variability,[4]
  - Intra-Class Correlation (ICC) analysis indicates that, for 12 oculometrics in our set, single measures have good to excellent (> 0.7) reliability scores,[5]
  - Most show no significant run-by-run learning effects and, even when they do, any potential artifact is small (~ 2% improvement/run).[5]

1. Stone & Krauzlis. Shared motion signals for human perceptual decisions and oculomotor actions. J. Vision, 3:725-36 (2003)

2. Beutter & Stone. Human motion perception and smooth eye movements show similar directional biases for elongated apertures. Vision Research, 38:1273-1286 (1998)

3. Stone, Beutter, & Lorenceau, J. Visual motion integration for perception and pursuit. PerceptIon, 29:771-787 (2000)

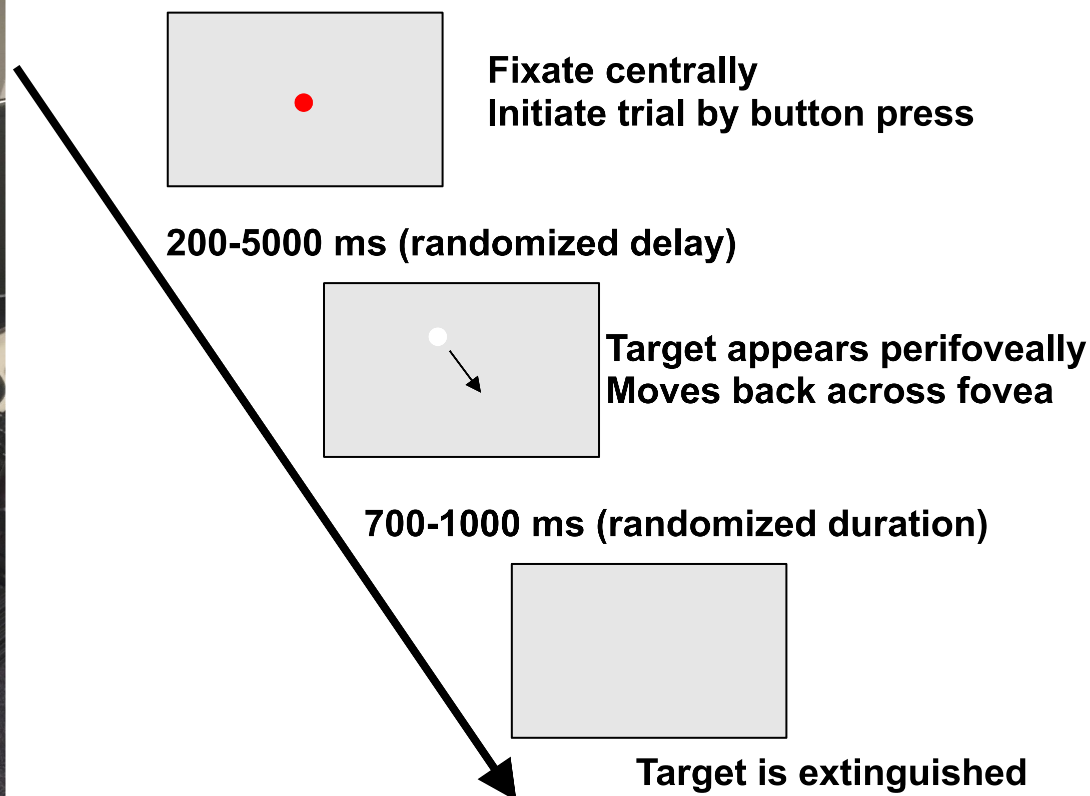
4. Liston & Stone. Oculometric assessment of dynamic visual processing. J. Vision, 14:1-17 (2014)

5. Stone et al. Normative Baseline Oculomotor Performance. NASA HRP Annual Investigators Workshop (2022)

Methods

Radial step-ramp stimuli:
- 90 or 180 randomized directions (5 or 10 min)
- 5 randomized speeds

Video-based tracker & gaming display



Participants instructed to track the moving target as best they can as soon as it starts moving until it disappears.

(Krukowski & Stone, Neuron 2005)

The 20 oculometrics we compute

From the step-ramp trials

Pursuit System

- Latency
- Initial acceleration
- Steady-state gain
- Proportion smooth

Saccade System

- Rate
- Amplitude
- Direction dispersion
- Peak velocity vs. Amplitude - slope
- Peak velocity vs. Amplitude - Intercept

Direction Tuning

- Anisotropy (oblique effect)
- Horizontal/Vertical asymmetry
- Direction noise

Speed Tuning

- Responsiveness
- Speed noise

From the calibration session

Fixation Control

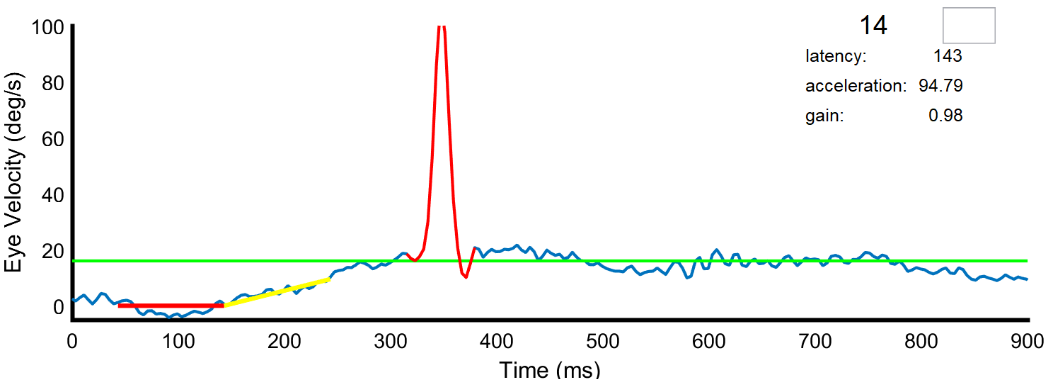
- Centripetal drift
- Lateral drift
- Fixation accuracy

Pupil Light Reflex

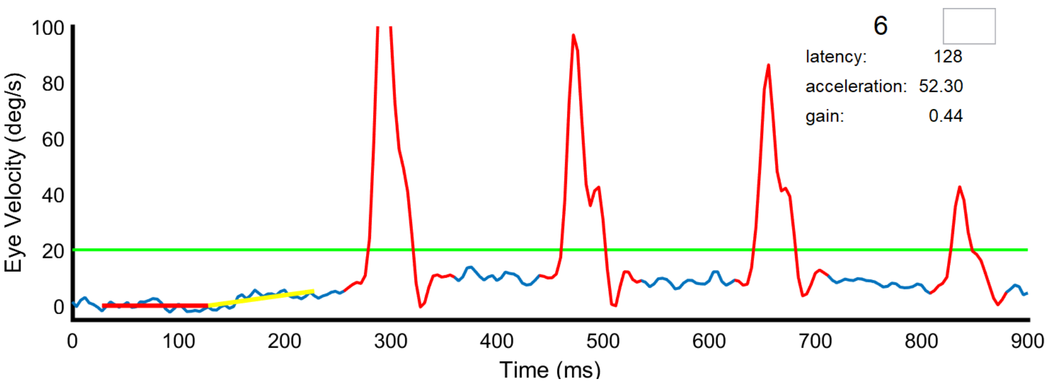
- Contraction time constant (tau)
- Dilation time constant (tau)
- Mean pupil diameter

Effect of low-dose EtOH

Raw Data: Two individual trials

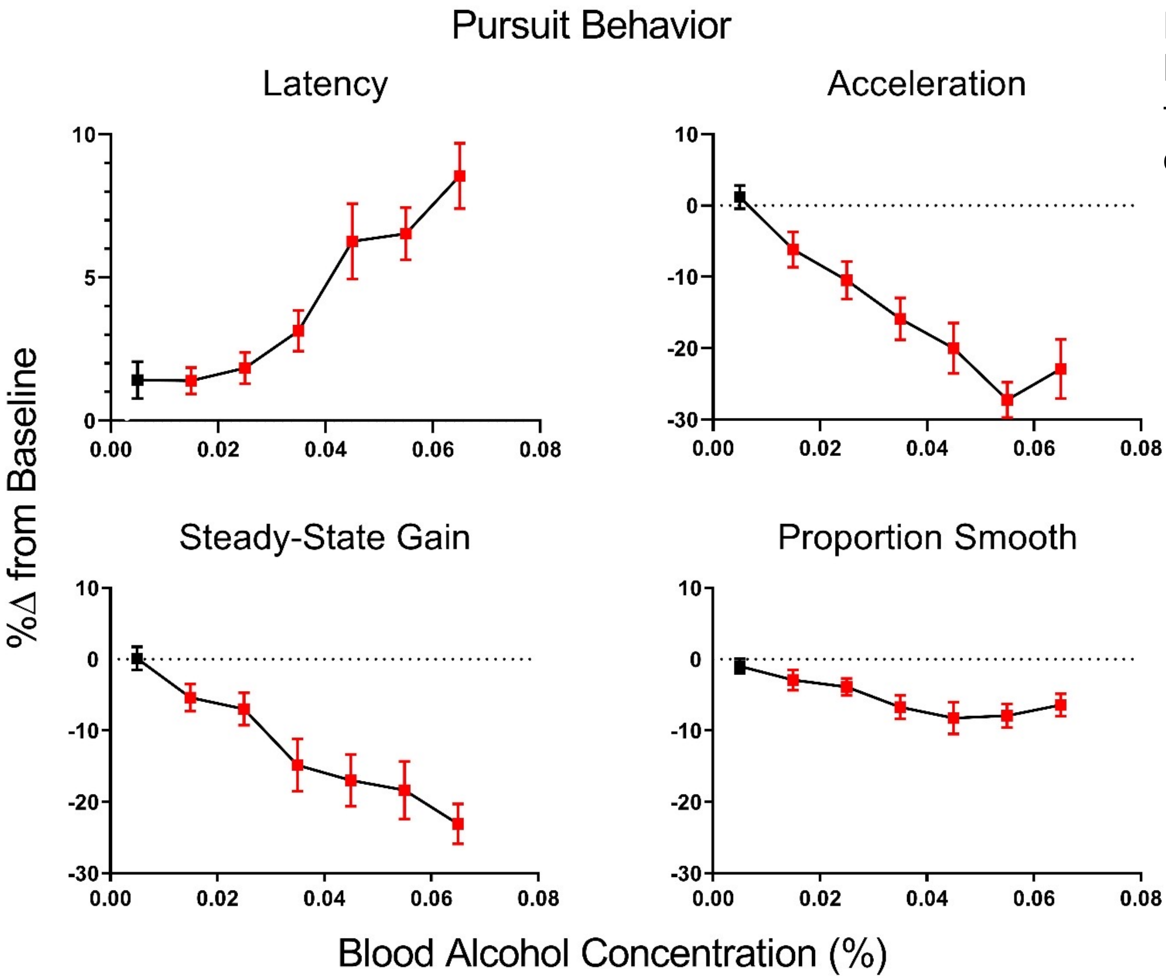


BAC: 0.00%



BAC: 0.06%

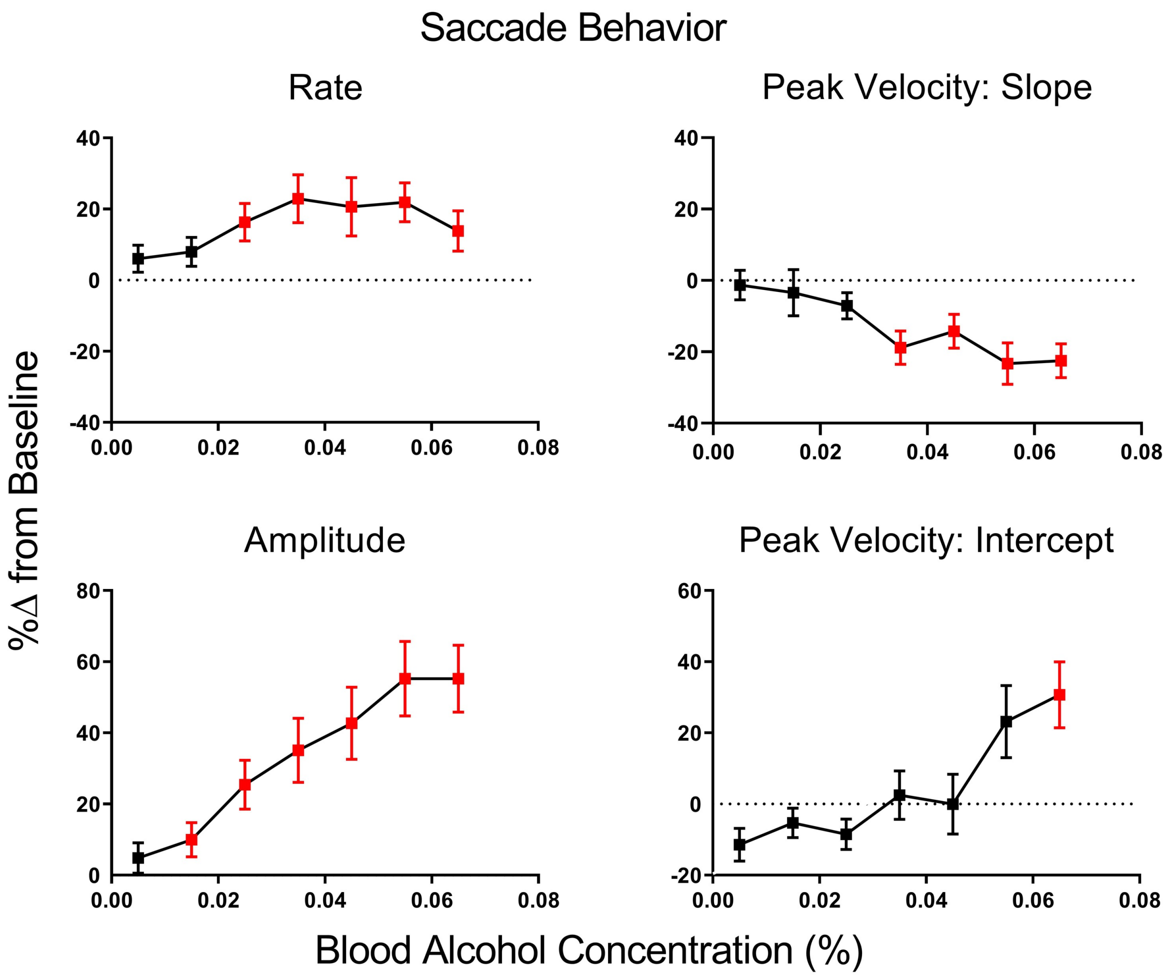
- EtOH generates: 1) decreased steady-state eye velocity (blue trace) that does not match target speed (green) & 2) increased number/size of compensatory saccades.
- While the participant continues to try to catch up to the moving target with saccades, there is no smooth acceleration response despite the large residual retinal slip.



Data points here, and elsewhere, are red if Bonferroni-Holms corrected *post-hoc t*-tests are significant (after a primary finding of a significant ($p < 0.05$) linear trend).

Tyson, Feick, Cravalho, Flynn-Evans, & Stone, Dose-dependent sensorimotor impairment in human ocular tracking after acute low-dose alcohol administration, J. Physiol. (London) 599(4):1225–1242 (2021)

- Pursuit metrics are significantly impaired (significant linear trends), starting at 0.015% BAC (lowest BAC w/ significant Bonferroni-Holms corrected *post-hoc t*-test).
- Pursuit responses are delayed by up to ~10 ms and reduced by up to ~25%.



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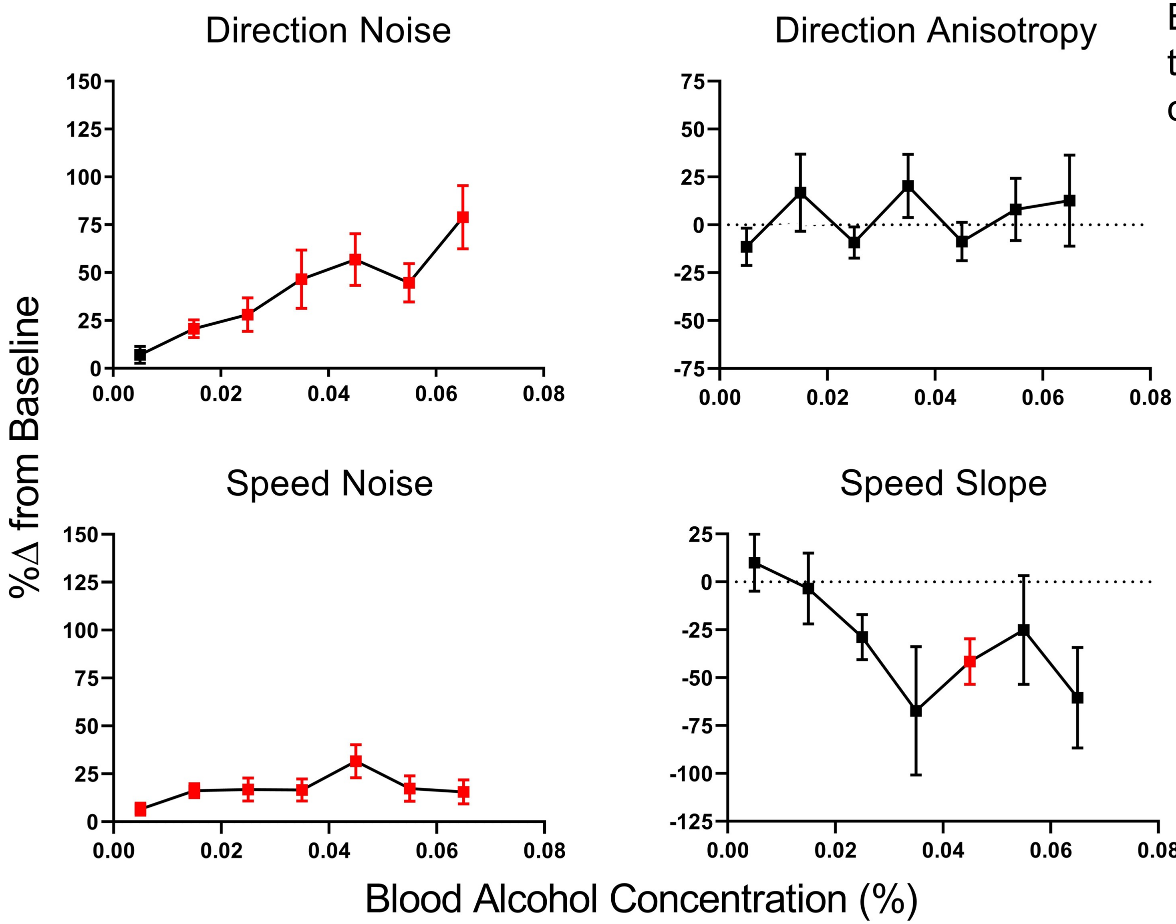
- Saccade rate/amplitude increase at 0.015-0.025% and compensate for pursuit loss.
- Saccade dynamics (main sequence) show significant changes at 0.035-0.065% consistent with impairment of the brainstem saccade generator.

Motion Processing



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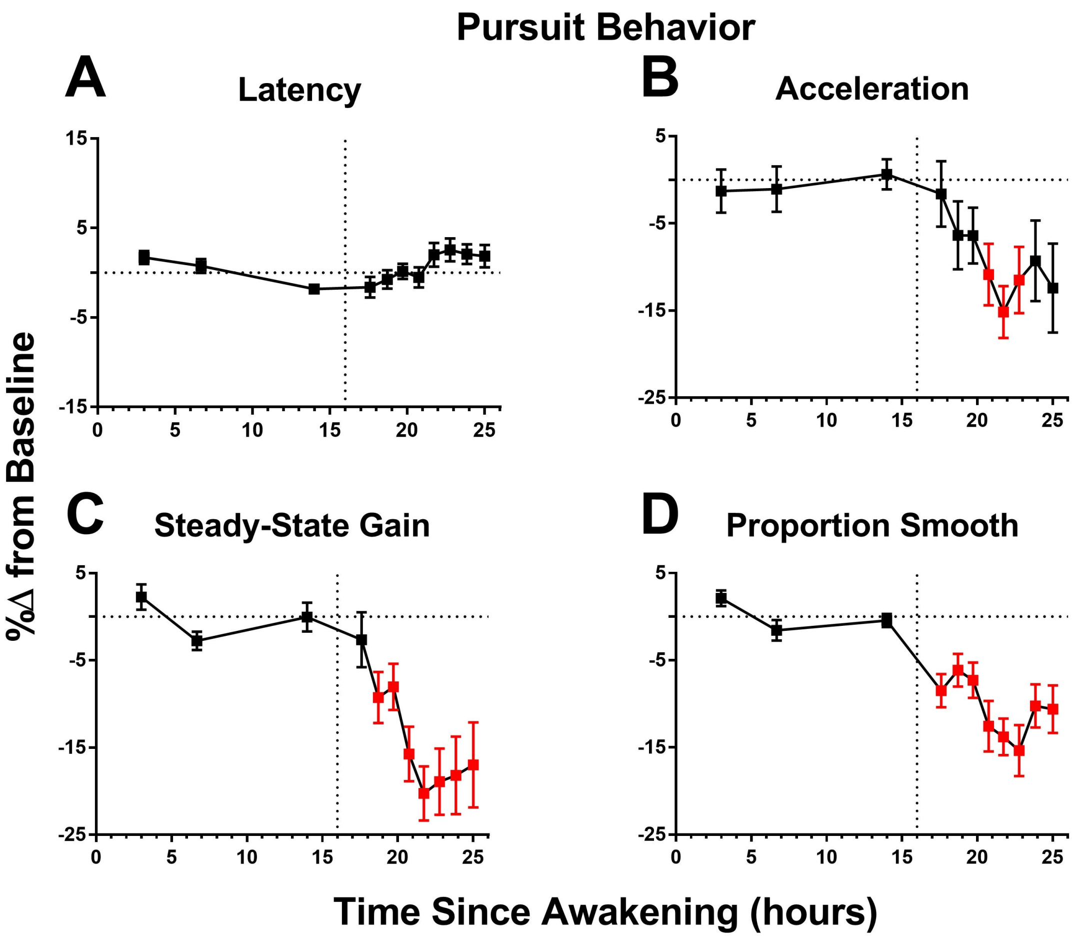
Tyson, Feick, Cravalho, Flynn-Evans, & Stone, Dose-dependent sensorimotor impairment in human ocular tracking after acute low-dose alcohol administration, J. Physiol. (London) 599(4):1225–1242 (2021)

- Motion processing is significantly impaired starting at ~0.01% BAC (direction precision reduced by up to ~75% and speed precision by up to ~25%).

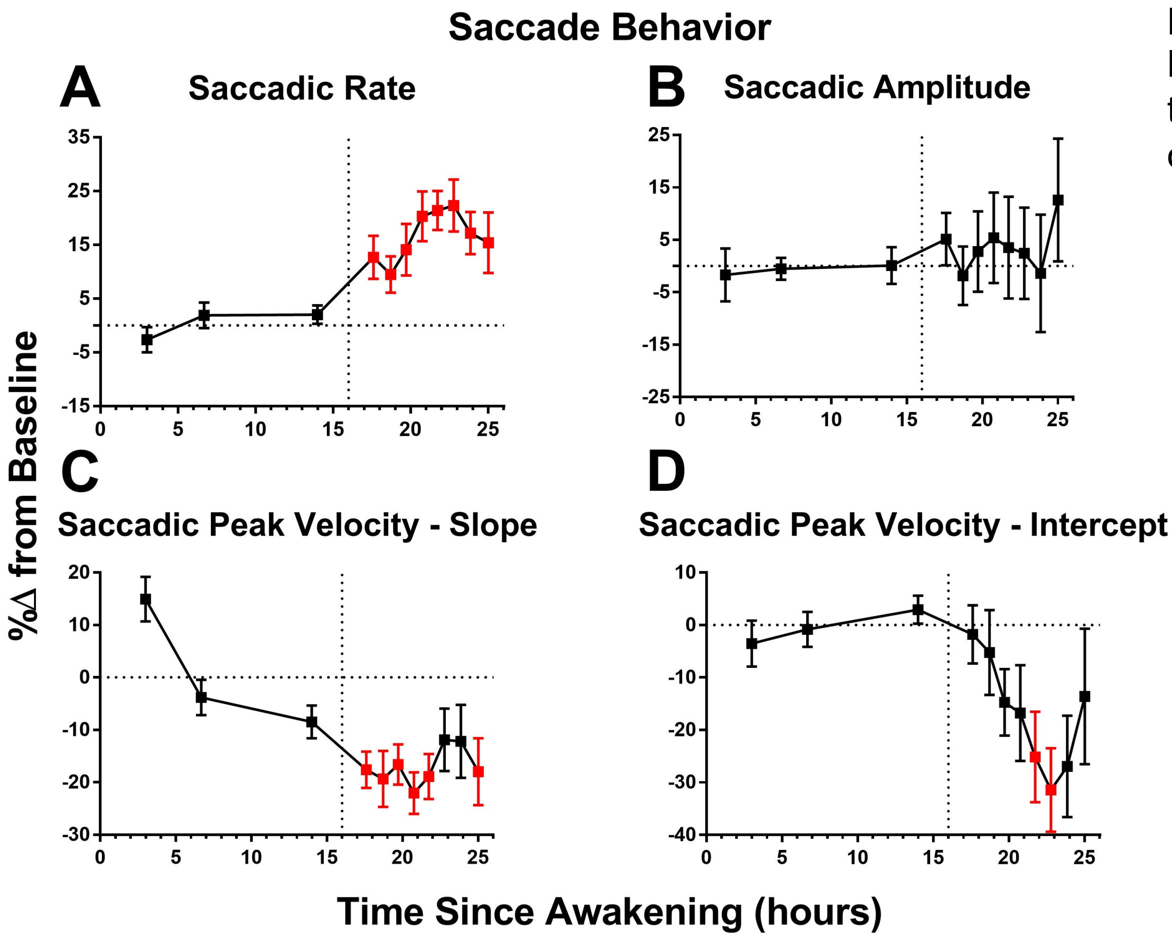
Effect of 24-hr Acute Sleep Deprivation and Circadian Misalignment



Data points here, and elsewhere, are red if Bonferroni-Holms corrected *post-hoc t*-tests are significant (after a primary finding of a significant ($p < 0.05$) linear trend).

Stone, Tyson, Cravalho, Feick, & Flynn-Evans. Distinct pattern of oculomotor impairment associated with acute sleep loss and circadian misalignment. Journal of Physiology (London), 597(17):4643-4660 (2019)

- Pursuit is significantly impaired starting ~2 hours of being awake past bedtime but, surprisingly, latency is not systematically affected (unlike with EtOH).
- Pursuit responses are reduced by up to ~20% by ~21hrs of being awake.



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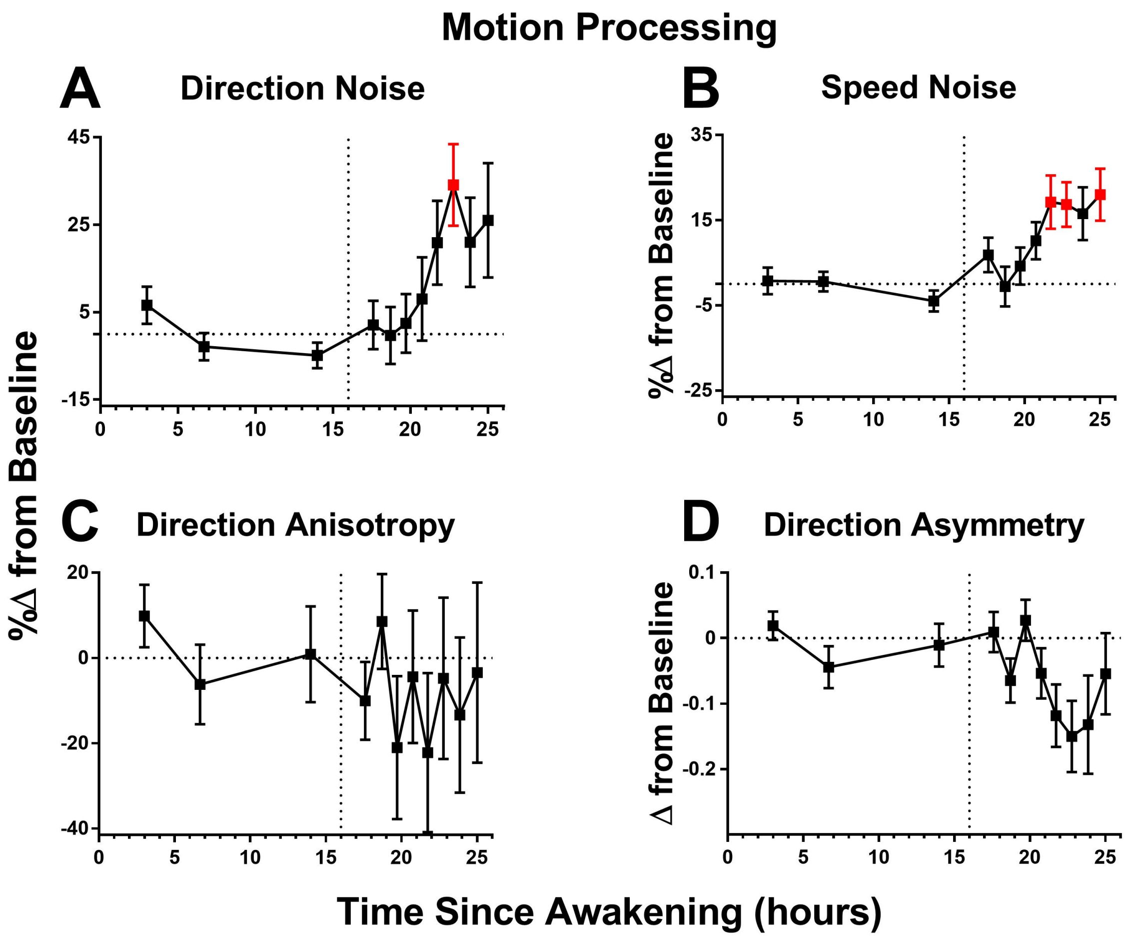
- Saccadic rate increases by up to ~20% with no change in amplitude (unlike EtOH).
- Saccadic dynamics are more sluggish by up to ~30%, suggesting brainstem saccadic generator involvement (note: intercept change is opposite that with EtOH).



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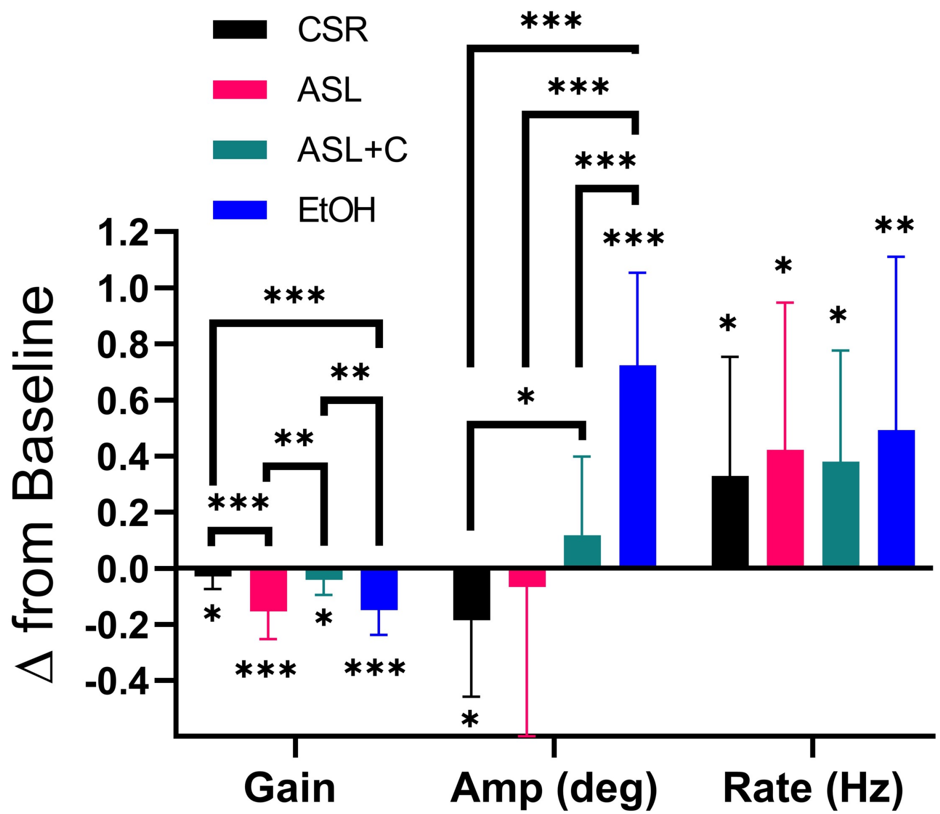
Stone, Tyson, Cravalho, Feick, & Flynn-Evans. Distinct pattern of oculomotor impairment associated with acute sleep loss and circadian misalignment. Journal of Physiology (London), 597(17):4643-4660 (2019)

- The precision of motion processing is significantly impaired by up to ~30% after 22 hrs of being awake.

Differential Pattern Across Metrics for Different Stressors



Tyson, Flynn-Evans, & Stone. Differential Saccade-Pursuit Coordination under sleep loss and low-dose alcohol. Frontiers in Neuroscience 16:1067722 (2023).

ASL: 23 hours awake
ASL+C : 23 hours awake with 0.3 mg/kg hourly caffeine
CSR: 5-hr/night sleep restriction for 2 weeks
EtOH: BAC of 0.065%

- Low-dose ethanol and sleep loss (acute ASL w/ or w/o caffeine and chronic CSR) cause significant decreases in pursuit gain and increases in catch-up saccade rate.
- Saccadic <u>amplitude</u> compensation is large for EtOH yet ineffective for ASL.

➔ The pattern above reveals <u>qualitative</u> differences across stressors (insight into cause) and suggests collicular/brainstem effects in ASL, but not EtOH (insight into locus).

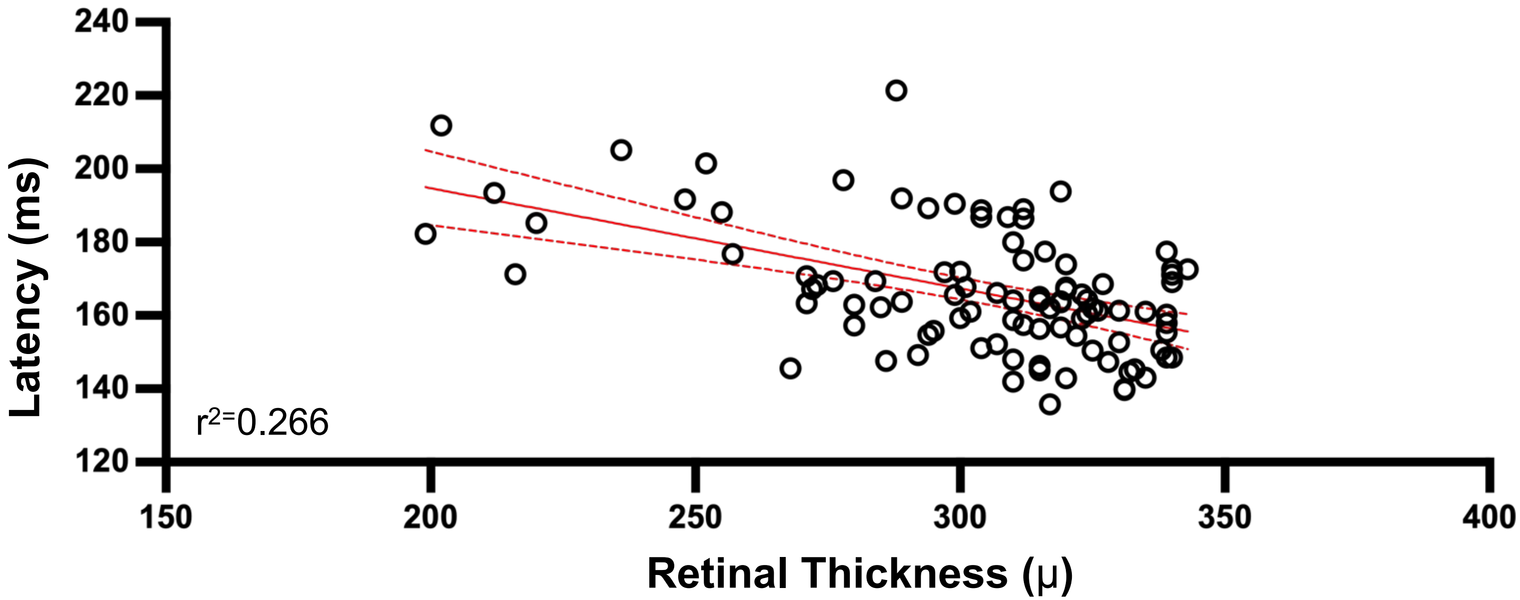
Monitoring patients with lupus at risk of retinal damage from drug toxicity

Functional Effects	Early Perifoveal Vision		Late Foveal Vision	Visual Motion Precision		Visual Motion Accuracy			Subcortical Visuomotor Response		Localization
	Latency (ms)	Acceleration (deg/s^2)	Gain	Direction Noise (°)	Speed Noise (%)	Direction Anisotropy	Direction Asymmetry	Speed Slope	Saccade Rate (Hz)	Saccade Amplitude (deg)	Fixation Error (deg)
Patient Average (N = 10)	162	92.2	0.80	9.0	16.2	0.27	-0.02	0.33	3.53	2.14	0.70
Control Average (N = 17)	165	116.7	0.87	9.5	15.6	0.26	0.05	0.53	3.49	1.48	0.57
p	N.S.	0.0004	0.02	N.S.	N.S.	N.S.	N.S.	0.02	N.S.	0.0008	0.059

- We compared 10 visually asymptomatic lupus patients on hydroxychloroquine who had no clinical signs of toxicity with 17 age-matched healthy controls.
- Patients showed significantly impaired pursuit (lower initial acceleration, steady-state gain, and speed responsiveness) and apparent saccadic compensation (larger catch-up saccade amplitude).
- Patients also showed lower fixation accuracy that nearly reached significance.

➔ Eye-movement metrics detected several components of altered visual function although standard clinical tests [Optical Coherence Tomography (OCT) and perimetry], did not, suggesting a potential future role for oculometrics in both ophthalmological and neurological surveillance.

Examining structure-function correlations using oculometrics



- The above figure plots the correlation between a functional oculometric (Latency) and a structural OCT metric (retinal thickness) across 96 local sectors (4 sectors/retina) of 12 visually asymptomatic lupus patients on hydroxychloroquine.
- Latency showed a significant correlation with sector retinal thickness across the mild range thickness changes observed ($p = 0.043$).

➔ Pursuit latency is capturing subclinical performance variation (function) associated with variation in <u>local</u> retinal thickness (structure).

Summary and Conclusions

We used a set of up to 20 largely independent oculometric measurements collected during a 5-min behavioral test to examine visual/visuomotor impairment associated with alcohol consumption, sleep loss, and drug toxicity.

A recent collaboration between NASA and Stanford University Medical School suggests that oculometrics may detect mild yet significant functional deficits before current state-of-the-art clinical measures indicate structural or functional impairment.

Oculometrics provide a sensitive method to track sub-clinical variation in visual/visuomotor function and to provide insight into potential causes and neural loci.

Acknowledgments

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Keith Tucker

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