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# Oculometric Assessment of Mild Neural Impairment

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# Why eye movements?

## Diagnostic

For over 100 years, neurologists have used eye movements to identify brain injuries and impairments. Prior to the age of modern imaging (1980 onward), qualitative assessment of eye movements were a critical component of diagnoses and remains a routine law-enforcement tool to detect the use of drugs and alcohol.



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# Why eye movements?

## Quantitative

Eye movements and associated ocular responses (e.g., Pupillary Light Reflex) can provide a highly quantitative window into neural processing from the retina to the brainstem, cerebellum, and cortex, and into human performance from reflexive autonomic responses to the perceptual/cognitive processing within extra-striate and frontal cortex that guides operationally relevant sensorimotor behavior.



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# Why eye movements?

## Efficient

Standard psychophysical or survey testing takes a long-time (i.e., by design, each 2AFC response after a ~1-2s trial provides a single bit of information), but the associated oculomotor data provides orders of magnitude more information (many bits of azimuth and elevation data in each 4-ms frame).



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# Why eye movements?

## Difficult to Game

Although driven by neural pathways from low-level reflex loops to higher-order perceptual/cognitive processing, most parametric factors of the oculomotor responses are outside of voluntary control and thus not gameable. One can decide not to track, but the dozens of fine details of task performance are not under voluntary control and gross attempts at gaming are easily detected.

# Key System Features:

**To optimize S/N of oculomotor measurements, our existing data-collection and analysis system has the following features:**

- High spatio-temporal resolution eye tracking (250 Hz sampling rate with HD spatial resolution)<sup>1</sup>.
- High spatio-temporal resolution display (144 Hz LCD display of HD images)<sup>1</sup>.
- Robust and automated saccade detection to properly separate pursuit from saccades (reliably identifies small saccades down to ~0.15 deg of amplitude)<sup>2</sup>.
- Efficient (~5-min) radial tracking task with spatial, temporal, directional, and speed randomization (high uncertainty) to minimize anticipatory responses and to assess direction and speed tuning of visual motion processing<sup>3,4,5</sup>.

1. Liston, Simpson, Wong, Rich, & Stone. Design and validation of a simple eye-tracking system. In: *Proceedings of the Ninth Biennial ACM Symposium on Eye Tracking Research & Applications*, pp. 221-224. ACM, (2016).

2. Liston, Krukowski, & Stone. Saccade detection during smooth tracking. *Displays*, 34, 171–176 (2013).

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

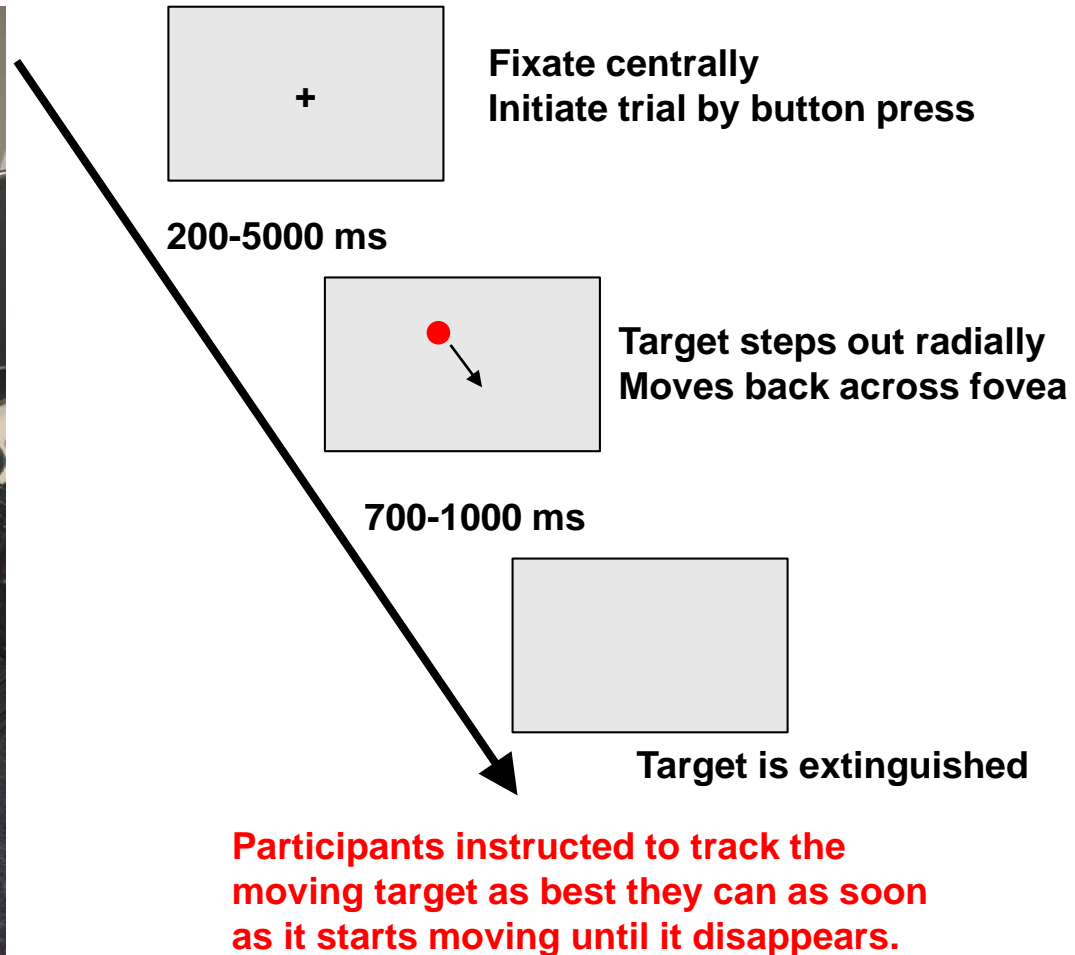
4. Krukowski & Stone Expansion of direction space around the cardinal axes revealed by smooth pursuit eye movements. *Neuron*, 45, 315-23 (2005).

5. Liston & Stone. Oculometric assessment of dynamic visual processing. *J. Vision*, 14:12, 1-17 (2014).

# Methods:

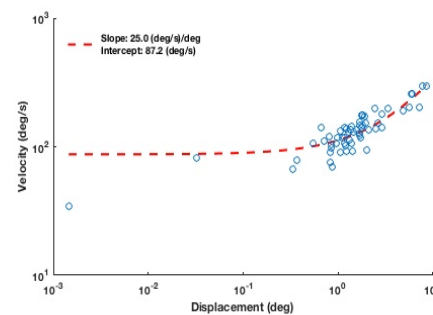
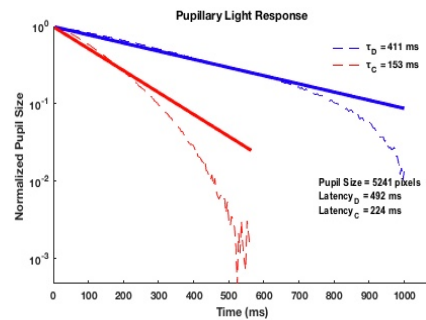
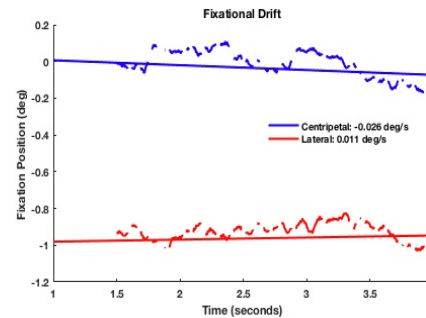
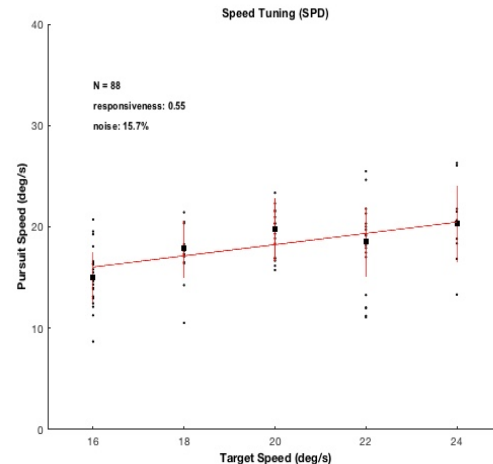
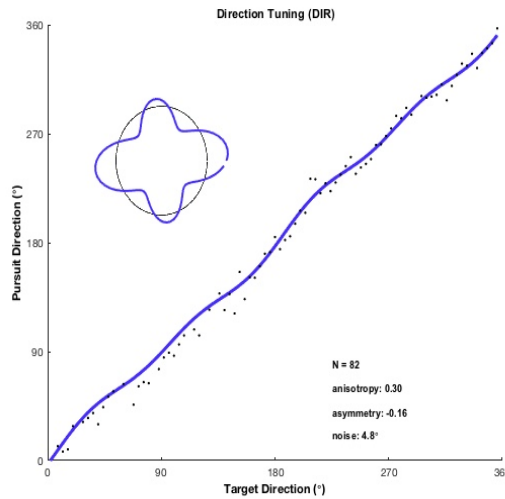
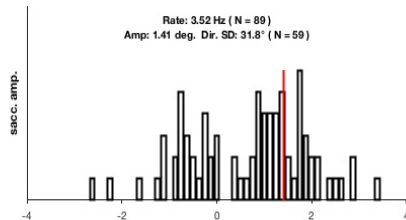
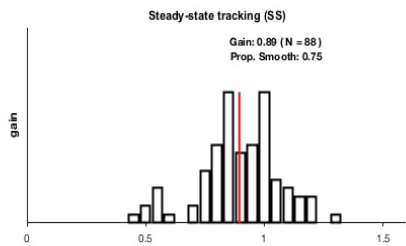
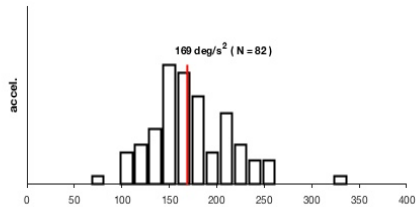
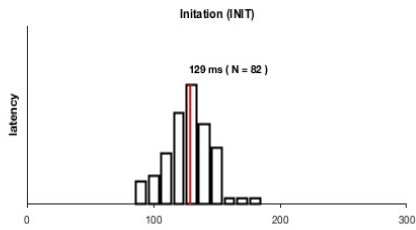


Video-based tracker & gaming display



Radial step-ramps (90-180 directions)

# Oculometric summary chart:



## Pursuit System

- Latency
- Initial acceleration
- Steady-State Gain
- Proportion smooth

## Saccade System

- Rate
- Amplitude
- Direction dispersion
- Peak Velocity - slope
- Peak Velocity - Intercept

## Direction Tuning

- Anisotropy (oblique effect)
- Hor/Vert Asymmetry
- Noise

## Speed Tuning

- Responsiveness
- Noise

## Fixational Drift

- Centripetal
- Lateral

## Pupil Light Reflex

- Contraction tau
- Dilation tau
- Contraction latency
- Dilation latency
- Mean pupil size



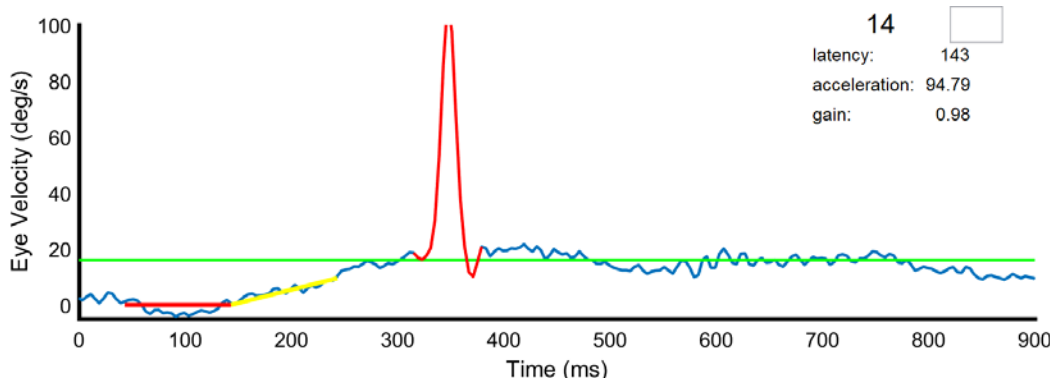
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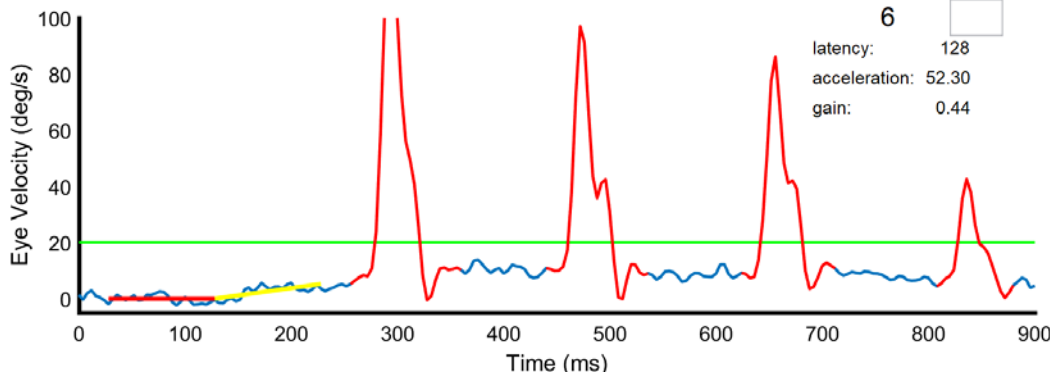
# Effect of low-dose EtOH



# Raw Data: Two individual trials



BAC: 0.00%

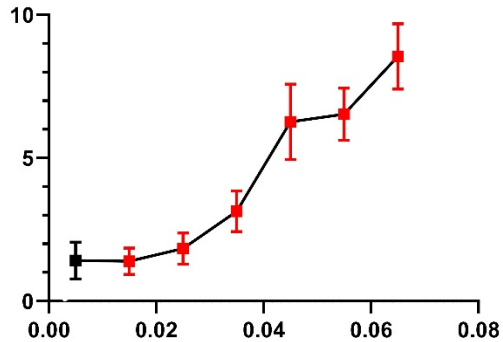


BAC: 0.06%

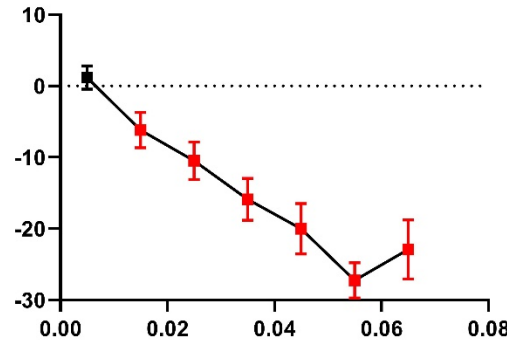
- Alcohol generates: 1) decreased steady-state eye velocity (blue trace) that does not match target speed (green) & 2) increased number/size of compensatory saccades.
- While the participant continues to try to catch up to the moving target with saccades, there is no smooth acceleration response despite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

## Pursuit Behavior

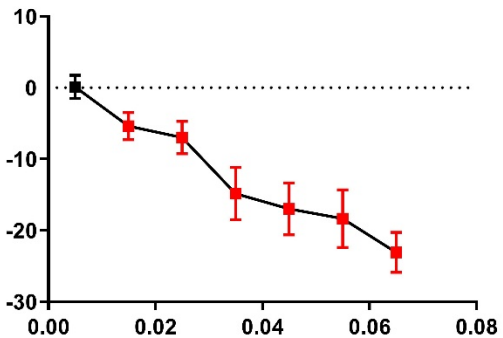
Latency



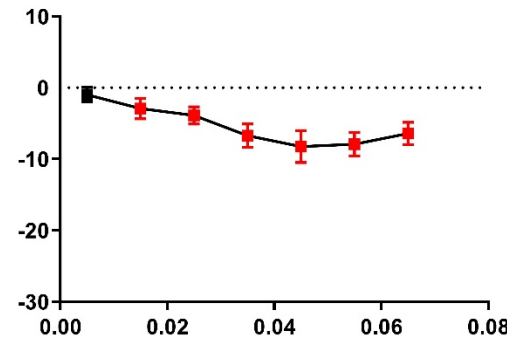
Acceleration



Steady-State Gain



Proportion Smooth



Blood Alcohol Concentration (%)

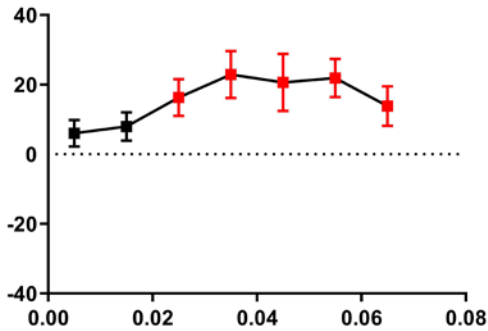
Data points here, and elsewhere, are turned red if Bonferroni-Holms corrected *post-hoc* t-tests are significant (only after a primary finding of a significant ( $p < 0.05$ ) trend using linear regression).

*Tyson, Feick, Cravalho, Tran, Flynn-Evans, & Stone, Impairment of Human Ocular Tracking with Low-Dose Alcohol, Neural Control of Movement abstract (2018)*

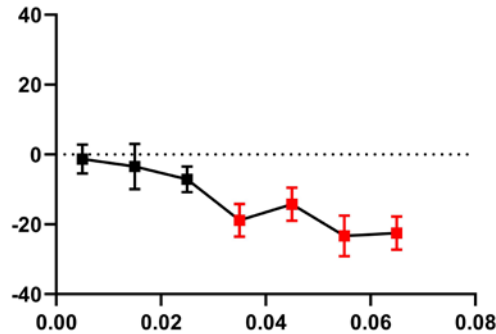
- All four pursuit parameters are significantly impaired (significant linear trend), starting at ~0.01% BAC (lowest significant Bonferroni-Holms corrected, *post-hoc* t-test).
- Open-loop (acceleration) and closed-loop (gain) responses are reduced by ~25% at ~0.06%, leading to 1.1 deg of lost ground in the steady-state analysis window.

## Saccade Behavior

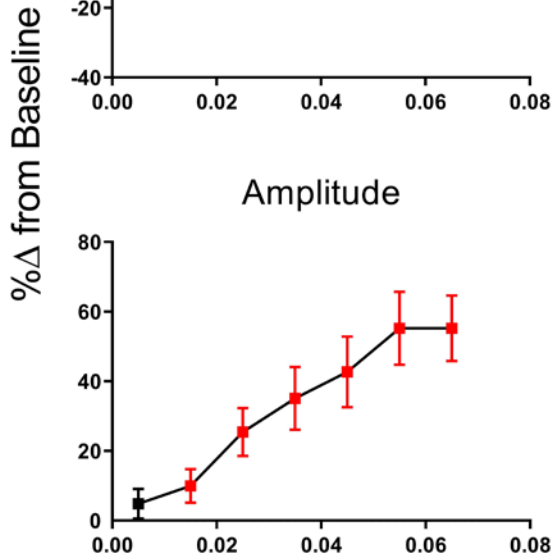
Rate



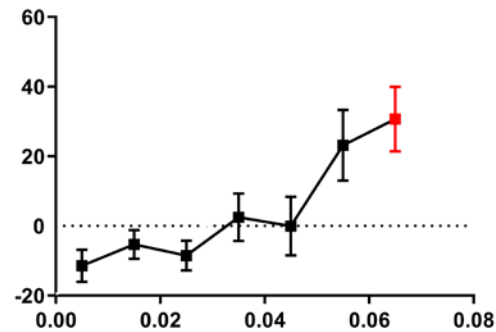
Peak Velocity: Slope



Amplitude



Peak Velocity: Intercept



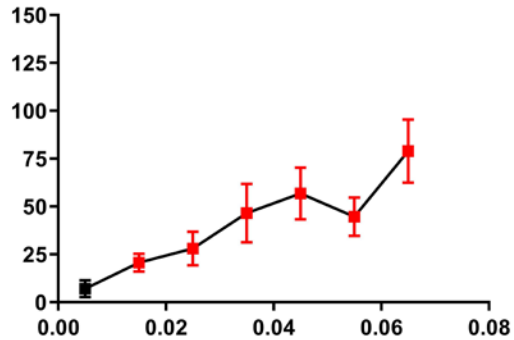
Blood Alcohol Concentration (%)

Tyson, Feick, Cravalho, Tran, Flynn-Evans, & Stone, *Increased Dependence on Saccades for Ocular Tracking with Low-Dose Alcohol*, *Neurosci. Abstr.* (2018).

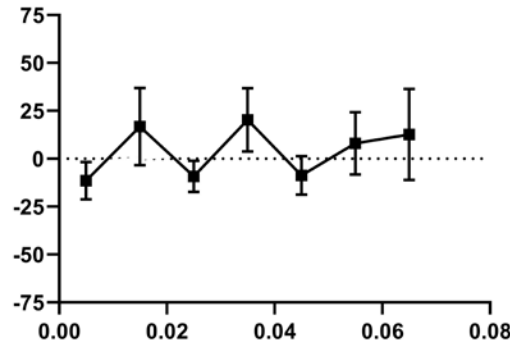
- Saccadic amplitude increases significantly starting at ~0.015% BAC plus a weak rate increase, recouping 1.1 deg of ground (near complete compensation) for pursuit loss.
- Saccadic dynamics (main sequence) show significant trends with clear impairment at 0.035%, suggesting impact on the brainstem saccadic generator at moderate BACs.

## Motion Processing

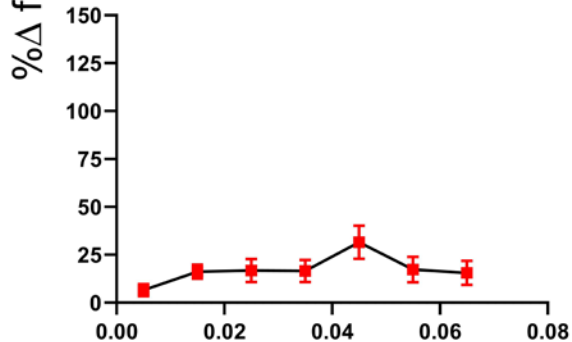
Direction Noise



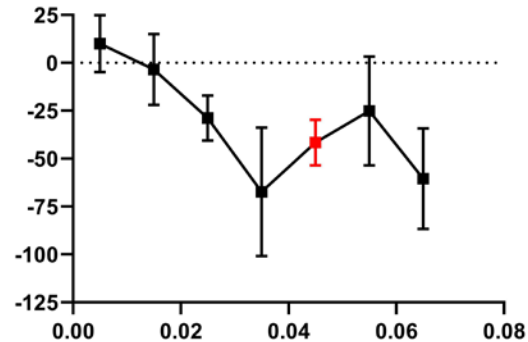
Direction Anisotropy



Speed Noise



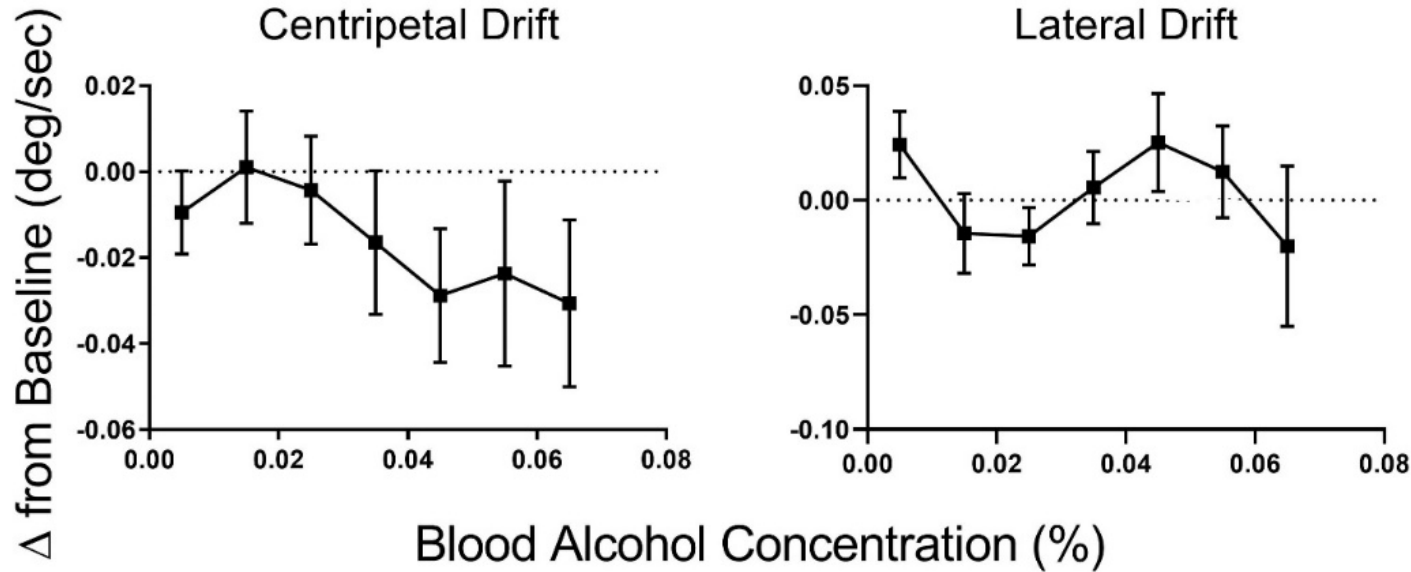
Speed Slope



Blood Alcohol Concentration (%)

- The precision of motion processing is significantly impaired starting at ~0.01% BAC (direction by ~80% at ~0.065% with speed precision effect weaker at ~25%).
- No change in direction tuning (anisotropy/asymmetry); decreased speed response.

## Eccentric Gaze Holding



- As expected, centripetal drift (gaze-evoked nystagmus with fixation at  $\pm 25$ deg) shows a significant linear trend with BAC, consistent with cerebellar involvement, yet there is no clear impairment threshold below 0.07% due to inter-subject variability.
- No systematic lateral drift, suggesting balanced cortical motion inputs.

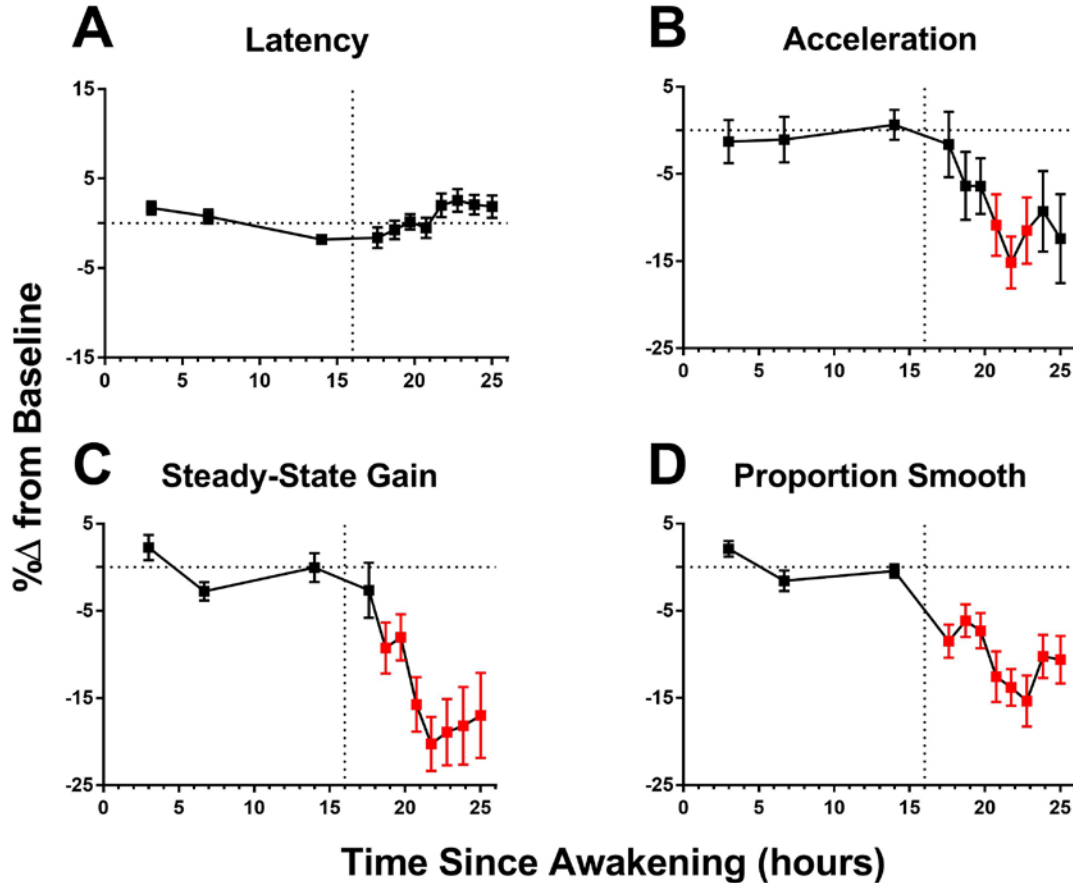


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# **Effect of 24-hr Acute Sleep Deprivation and Circadian Misalignment**

## Pursuit Behavior

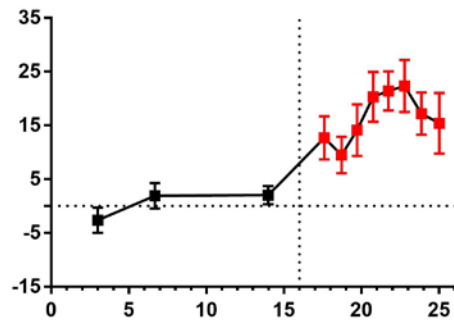


Stone, Tyson, Cravalho, Feick, & Flynn-Evans. Distinct pattern of oculomotor impairment associated with acute sleep loss and circadian misalignment. *Journal of Physiology (London)*, 597(17):4643-4660 (2019)

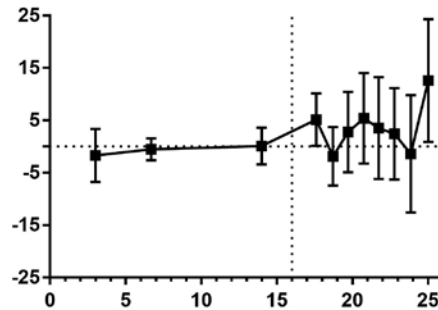
- Smooth pursuit behavior is significantly impaired starting 2-4 hours after bedtime, but latency is not systematically affected (unlike with alcohol).
- Open-loop (initial acceleration) and closed-loop (steady-state gain) responses are reduced by ~15-20% by ~21hrs of being awake, leading to ~0.9 deg of lost ground.

## Saccade Behavior

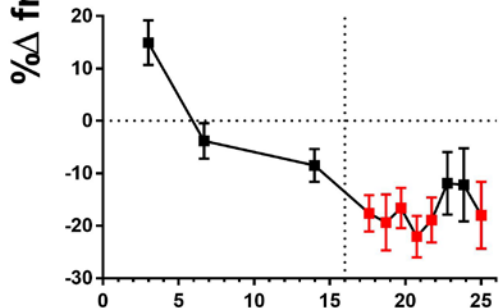
**A** Saccadic Rate



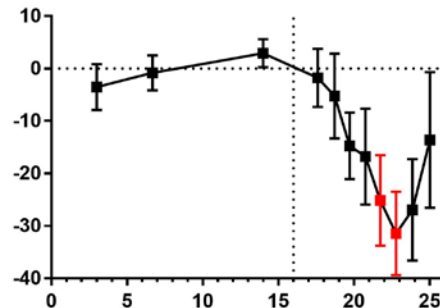
**B** Saccadic Amplitude



**C** Saccadic Peak Velocity - Slope



**D** Saccadic Peak Velocity - Intercept



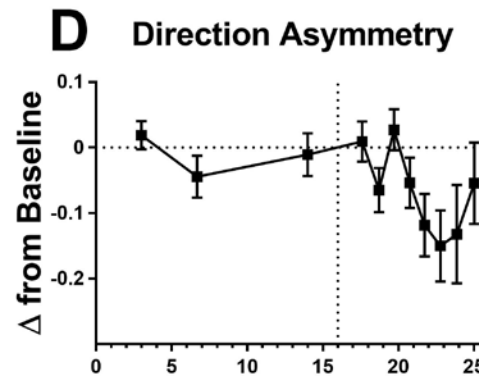
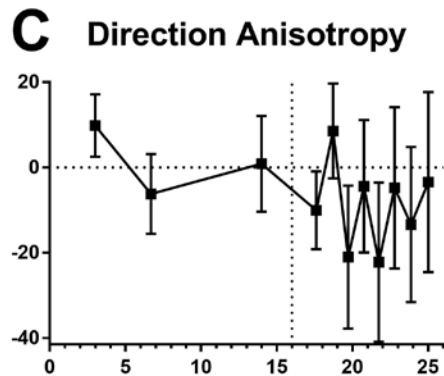
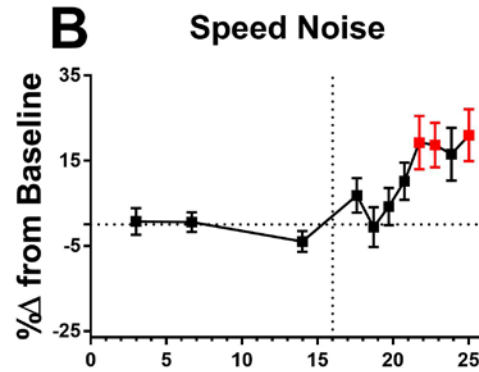
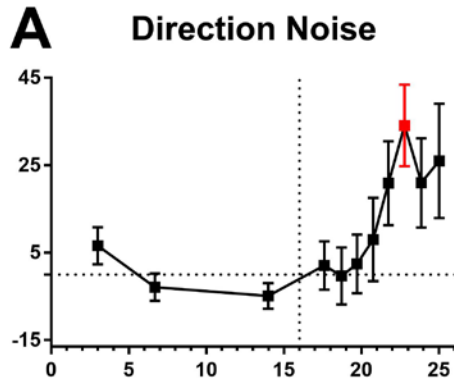
Time Since Awakening (hours)

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)

- Saccadic rate increases peaking at ~20% (with no change in amplitude unlike with alcohol) recouping ~0.45 deg of lost ground, or ~50% compensation for pursuit loss.
- Saccadic dynamics show impairment, suggesting brainstem saccadic generator involvement, but intercept change is in opposite direction as for alcohol consumption.



## Motion Processing



Time Since Awakening (hours)

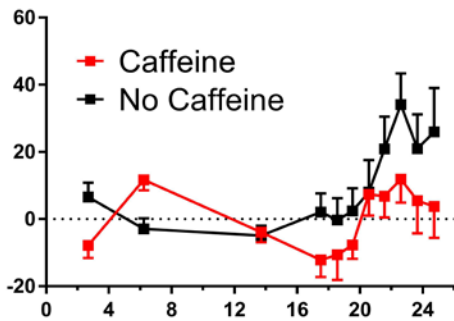
Stone, Tyson, Cravalho, Feick, & Flynn-Evans. Distinct pattern of oculomotor impairment associated with acute sleep loss and circadian misalignment. *Journal of Physiology (London)*, 597(17):4643-4660 (2019)

- The precision of motion processing is significantly impaired (15-30% after 22 hrs awake) suggesting (extrastriate and/or frontal) cortical involvement.
- No change in oblique effect (anisotropy) or speed tuning, but reduced H/V asymmetry.

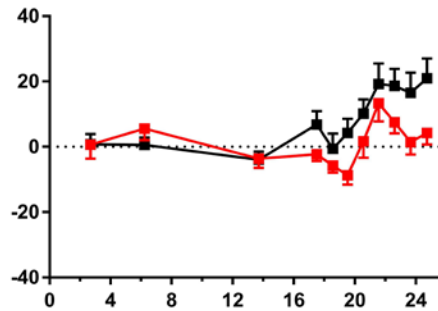
# Assessing countermeasure efficacy

## Motion Processing

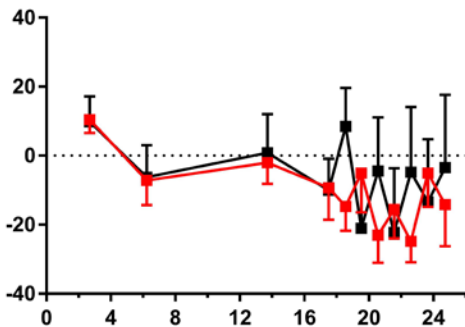
Direction Noise



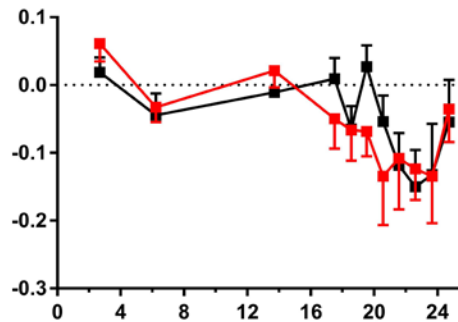
Speed Noise



Direction Anisotropy



Direction Asymmetry



Time Since Awakening (Hours)

*Flynn-Evans, Tyson, Cravalho, Feick, & Stone, Low-Dose Caffeine Administration During Acute Sleep Deprivation Eliminates Visual Motion Processing Impairment, but Does Not Improve Saccadic Rate. Annual SLEEP conference (2019).*

- Caffeine protects the precision of motion processing (no residual linear trends).
- Caffeine does not alter direction tuning; oblique effect & H/V asymmetry unchanged.



# Leveraging multi-dimensionality

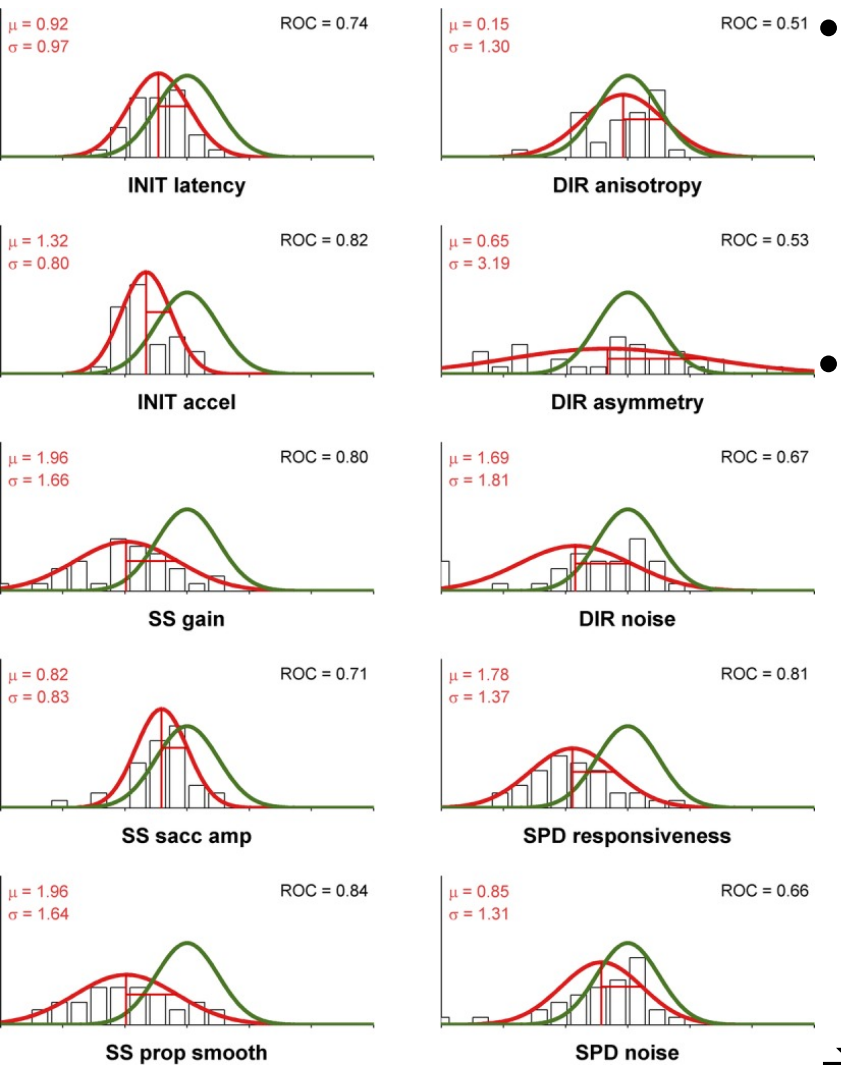
- **Sensitivity**: Increasing the set of largely independent metrics increases overall detectability by (on the order of)  $\sqrt{N}$  (with  $N$ , the number of largely independent metrics).  
By projecting an individual's "performance vector" onto a candidate "impairment vector" for a given suspected condition, one can compute an overall "impairment index" with greater sensitivity.
- **Specificity**: The pattern of effects across metrics allows us to characterize the deficit (and to assist in diagnosis).  
By comparing impairment indices for multiple potential causes (e.g., TBI, sleep deprivation, alcohol, etc. with non-colinear impairment vectors), one can estimate the relative probabilities across a set of suspected causes.



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# **Increased Sensitivity: Effect of Traumatic Brain Injury (TBI)**



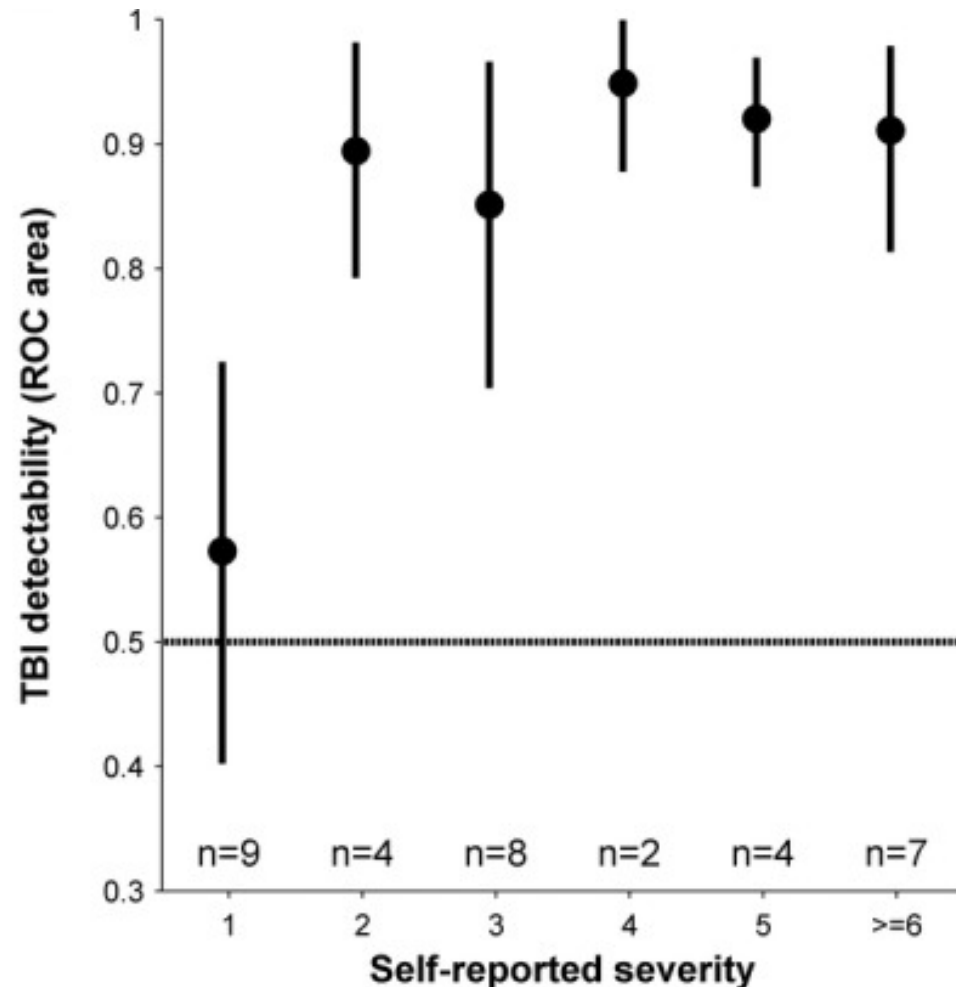
● 34 recovered/ing TBI patients (red Gaussian and histogram) were compared to a separate population of 41 normal (green Gaussian) using z-scored oculometrics.

● Many TBI population metrics (red) were found to be significantly ( $p < 0.05$ ) worse than normal (green):

- Latency (ROC area: 74%)
- Initial Acceleration (82%)
- Gain (80%)
- Saccadic Amplitude (71%)
- Proportion smooth (84%)
- Speed tuning/slope (81%)
- Speed precision unchanged (66%) (unlike with either alcohol or sleep loss)

➔ Individual metric sensitivity: ~71-84%

## Enhanced sensitivity through combined metrics:



- We combined oculometric measures into a single TBI impairment index and sub-divided TBI population by residual severity (1 'little to no residual injury' to 10 'completely disabled')
- Plot shows overall detectability using TBI impairment index (90% confidence interval).
- Detectability of those with severity of 1 was 59% (not significant).
- Detectability for 25 subjects reporting meaningful residual impairment (severity > 1) was 85% to 95%.

- Combining multiple oculometric measures allows for greater sensitivity to detect mild neural impairments → **overall TBI index sensitivity: ~91%**

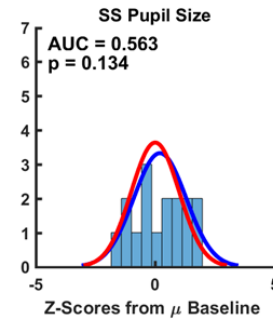
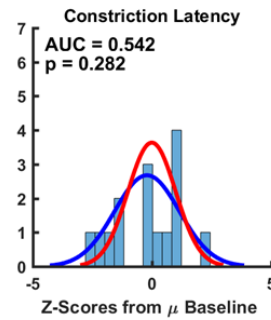
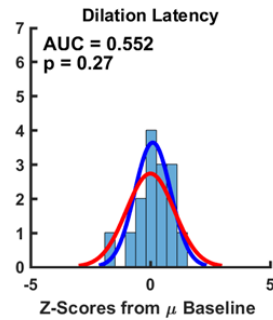
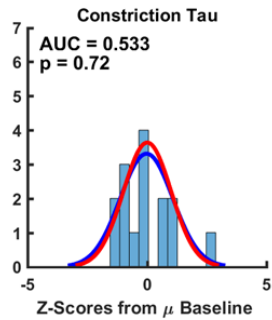
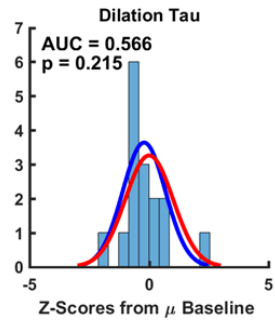


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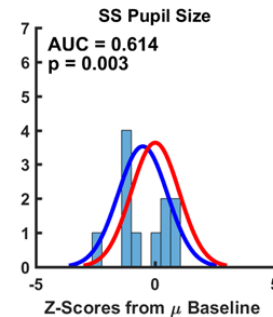
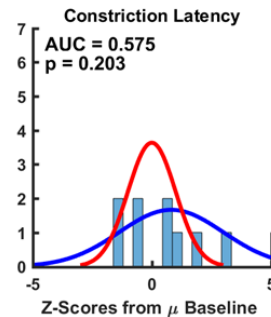
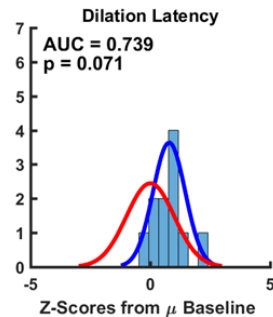
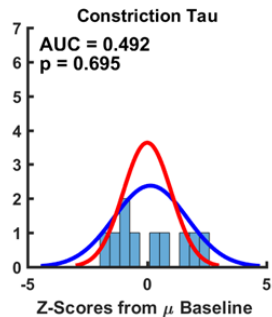
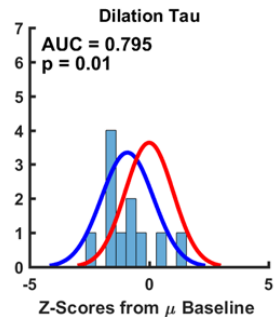
# **Enhanced specificity: Differential effects of alcohol and acute sleep deprivation on the Pupillary Light Reflex (PLR)**

# Different response pattern across set of measures



BAC 0.07%  
vs. baseline

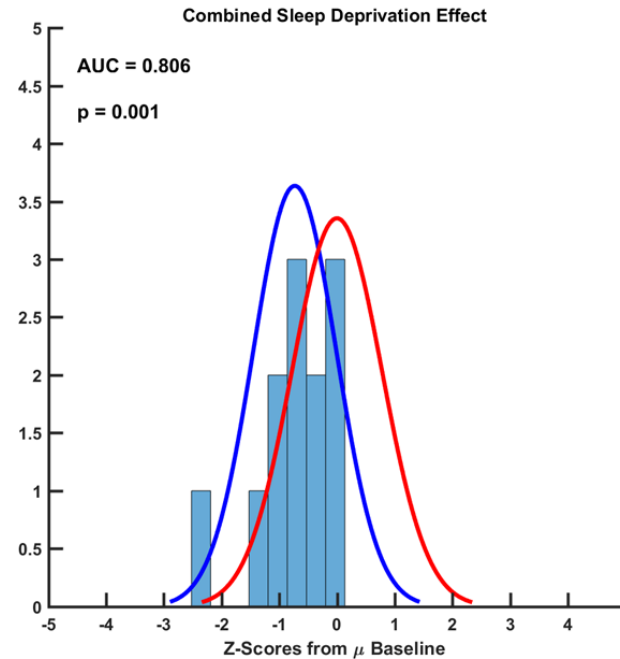
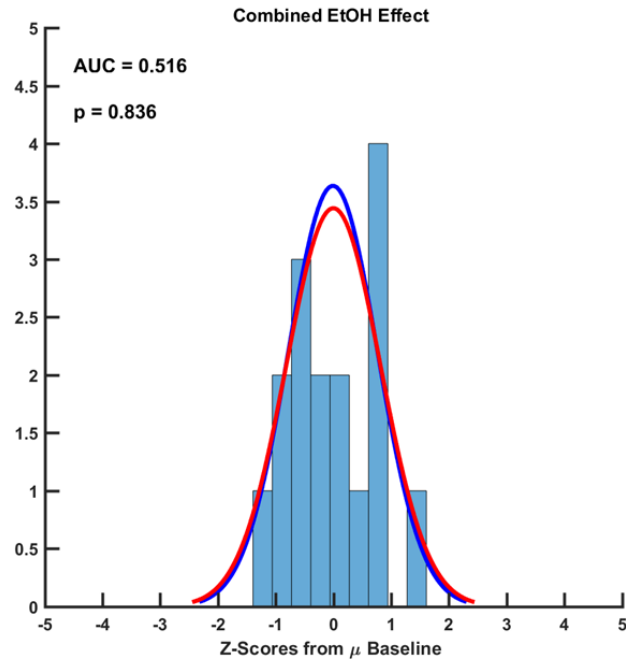
Effect Histogram  
Effect Gaussian  
Baseline Gaussian



23 hrs awake  
vs. baseline

- Sleep deprivation systematically decreases dilation time constant & mean pupil size.
- Low-dose alcohol does not alter any of our five measured PLR parameters.

# Creating a specific biomarker (preliminary demo)



*Tyson, Feick, Cravalho, Flynn-Evans, & Stone. Differential Effects of Low-Dose Alcohol versus Acute Sleep Deprivation on Light-Evoked Pupil Response Dynamics. Journal of Vision 19(10):73a (2019).*

- By combining across a judiciously selected subspace of oculometric measures one can craft a biomarker with sensitivity to detect mild alcohol intoxication (right-hand panel) yet specificity to reject effects from other causes (no shift in left-hand panel)  
→ Sleep-loss detectability: ~81% (with no alcohol confound).



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# Conclusion

We used a set of nearly two dozen oculometric measurements during a 5-min behavioral task to examine a range of visual and visuomotor deficits associated with alcohol consumption, sleep loss, and traumatic brain injury. We found different patterns of impairment from these stressors across our metrics.

Our approach provides a sensitive and specific method:

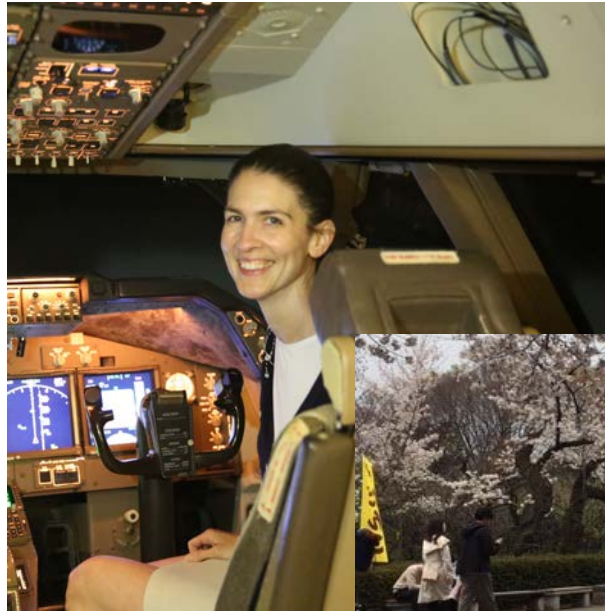
- to detect sub-clinical impairment of neural function, and
- to distinguish between suspected potential causes.



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# Acknowledgments



**Dr. Erin Flynn-Evans, Principal Investigator  
Fatigue Countermeasures Laboratory**



**Terence Tyson, General Engineer  
Visuomotor Control Laboratory**

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Dr. Dorion Liston  
and Lily Wong**