



National Aeronautics and
Space Administration



Efficient Oculometric Assessment of Altered Neural Function

Lee Stone

**Visuomotor Control Laboratory
NASA Ames Research Center**

Key Contributors:

- NASA/ARC Visuomotor Control Lab: Terence Tyson, Rahul Goel, Mark Anderson, Kenji Kato
- NASA/ARC Fatigue Countermeasures Lab: Erin Flynn-Evans, Patrick Cravalho, Nathan Feick
- Stanford Univ. School of Medicine, Byers Eye Institute: Loh-Shan Leung, Andrew Berneshawi
- NASA/JSC Research Operation and Integration Lab: Kimia Seyedmadani
- Z3VR: Josh Ruben, Roberto Pena
- AdHawk: Nino Zahirovik



National Aeronautics and
Space Administration



BLUF:

- Most astronauts who spend extended time in space are affected by Spaceflight Associated Neuro-Ocular Syndrome (SANS), which manifests itself primarily as changes in the thickness of the retina (as revealed by OCT) and of the shape of the eye (leading to acuity changes).
- SANS studies have been hampered by a lack of tools capable of gathering reliable functional measures of mild visual impairment because of the severe limitation on data collection time and sample size.
- NASA-patented Comprehensive Oculomotor Behavioral Response Assessment (COBRA) technologies are designed to overcome these challenges so are well suited contribute to our understanding of the visual and neural impacts of spaceflight.
- They have been validated for earth-based clinical and research applications and we are working to develop and validate a head-mounted system suitable for in-flight use.

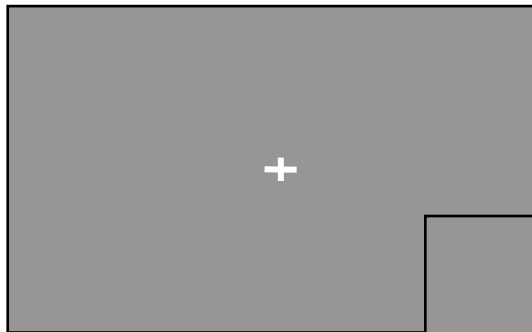


National Aeronautics and
Space Administration



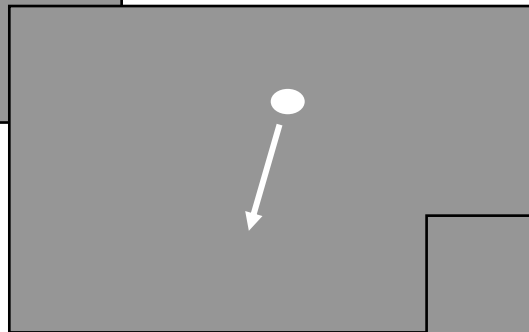
Prologue on perceptual/cognitive testing: The Forced-Choice **Gold** Standard

Fixation:



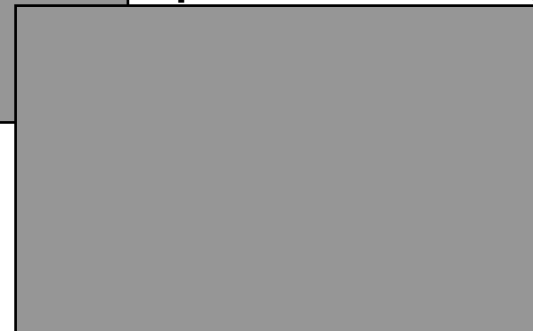
Visual Stimulus (or two):

target motion constant within trial
direction (or speed or ...) varies slightly trial by trial

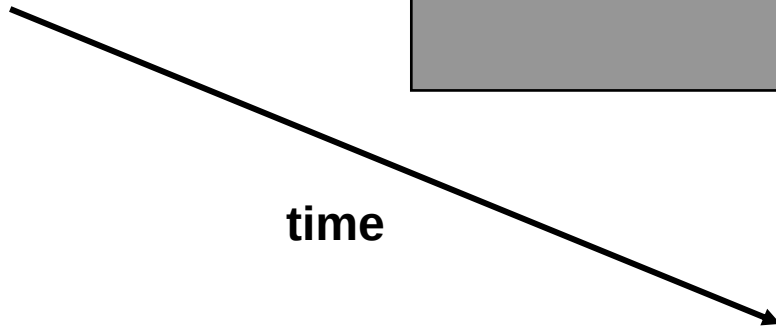


Binary Decision:

Faster/Slower
Up/Down or Left/Right



time



button press

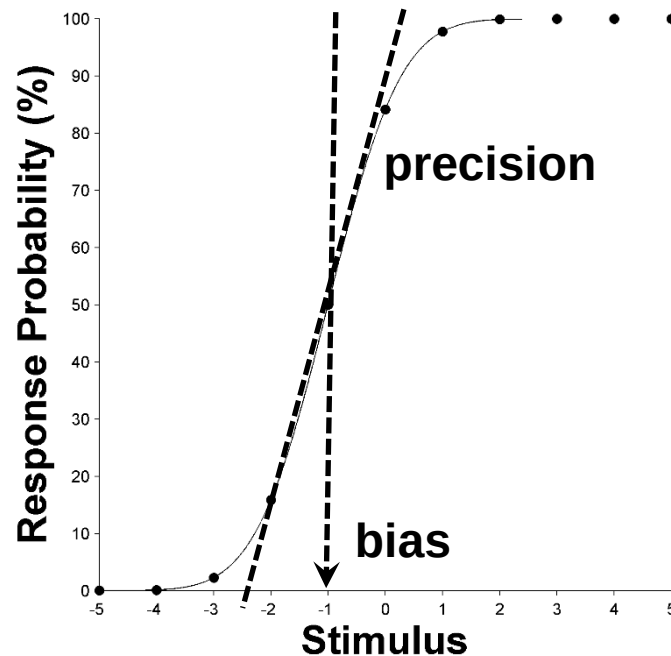
→ 1 single bit of button-press data for each 1-3 s trial



National Aeronautics and
Space Administration



Psychometric curve: coin of the realm



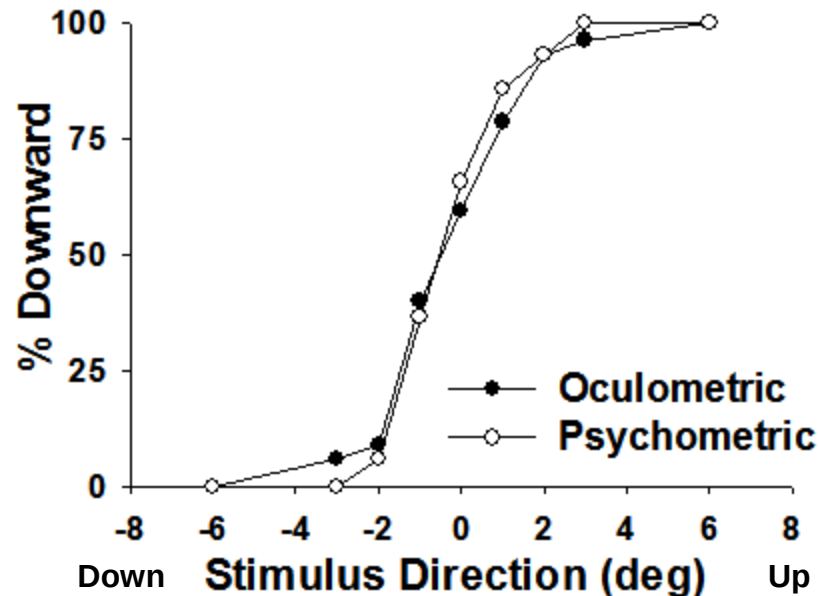
- ➔ Binary responses from 2AFC/yes-no perceptual/cognitive tasks are then used to compute response probabilities to measure performance bias (offset) & precision (slope) rigorously.
- ➔ Inefficient - typically takes hours to collect full set of data per observer



National Aeronautics and
Space Administration



Psychometric vs. Oculometric Curves



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

- Collate binary ocular “decisions” to compute “oculometric” curves
- Oculometric and psychometric curves typically superimpose.
- The responses correlate on a trial-by-trial basis.
- ➔ Each oculometric trial collects hundreds of bits of information.
- ➔ Oculometrics collect data on visual function much more efficiently.



National Aeronautics and
Space Administration



Introduction

- Eye movements have long been known to explain gross deficits in sensorimotor function due to tumors or other serious brain pathologies (Leigh and Zee's *The Neurology of Eye Movements*, 2015).
- COBRA generates a validated set of reliable and sensitive eye-movement biomarkers of neural function for the detection and characterization of a wide array of mild (pre-clinical) impairment.
 - Intra-Class Correlation (ICC) analysis indicates that most COBRA oculometrics have good to excellent (> 0.7) reliability scores even for single measures,
 - Most also exhibit no significant run-by-run learning effects and, even for those that do, this potential artifact is small ($\sim 2\%$ improvement/run).



National Aeronautics and
Space Administration

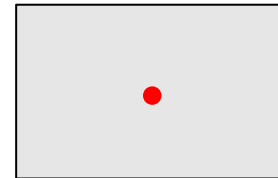


Methods



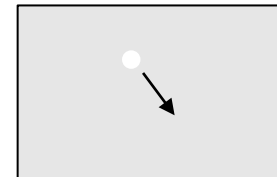
Radial step-ramp stimuli:

- 90 or 180 randomized directions (5 or 10 min)
- 5 randomized speeds



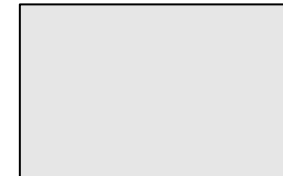
Fixate centrally
Initiate trial by button press

200-5000 ms (randomized delay)



Target appears perifoveally
Moves back across fovea

700-1000 ms (randomized duration)



Target is extinguished

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

Video-based tracker & gaming display

(Krukowski & Stone, Neuron 2005)



National Aeronautics and
Space Administration



We compute 20 oculometrics:

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 (τ)
- Dilation time constant (τ)
- Mean pupil diameter



National Aeronautics and
Space Administration



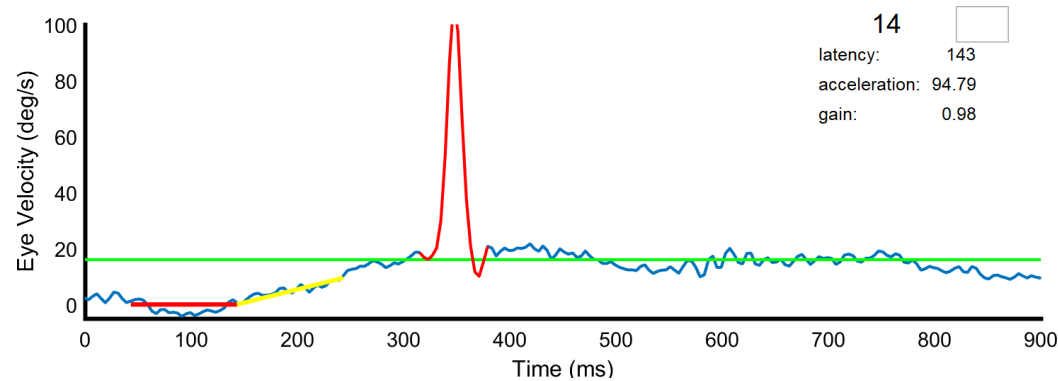
Effect of low-dose EtOH



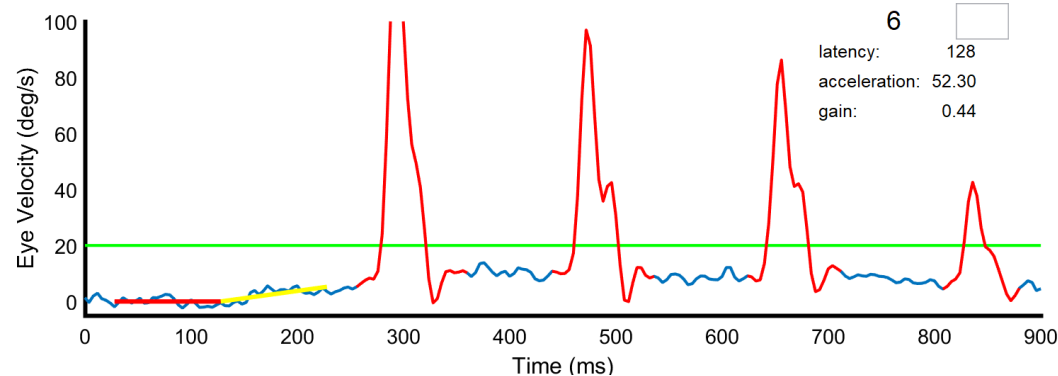
National Aeronautics and
Space Administration



Raw Data: Two individual trials



BAC: 0.00%



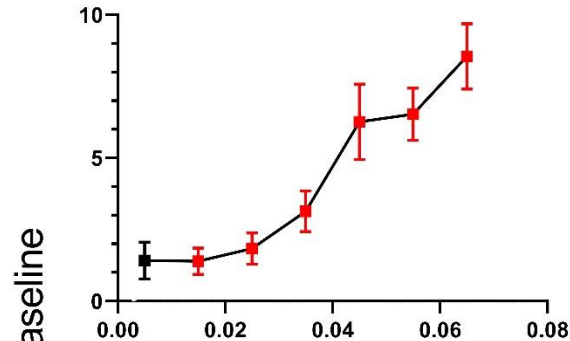
BAC: 0.06%

- 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.

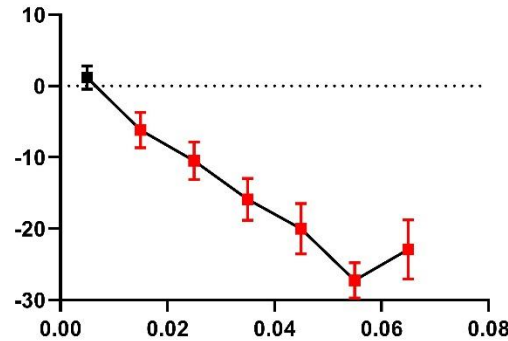


Pursuit Behavior

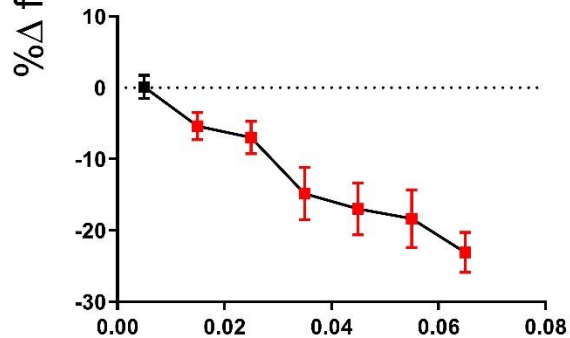
Latency



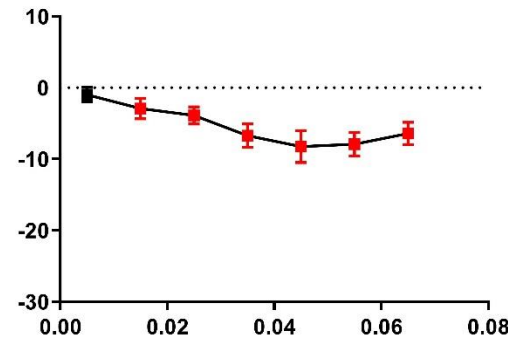
Acceleration



Steady-State Gain



Proportion Smooth



Blood Alcohol Concentration (%)

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%.



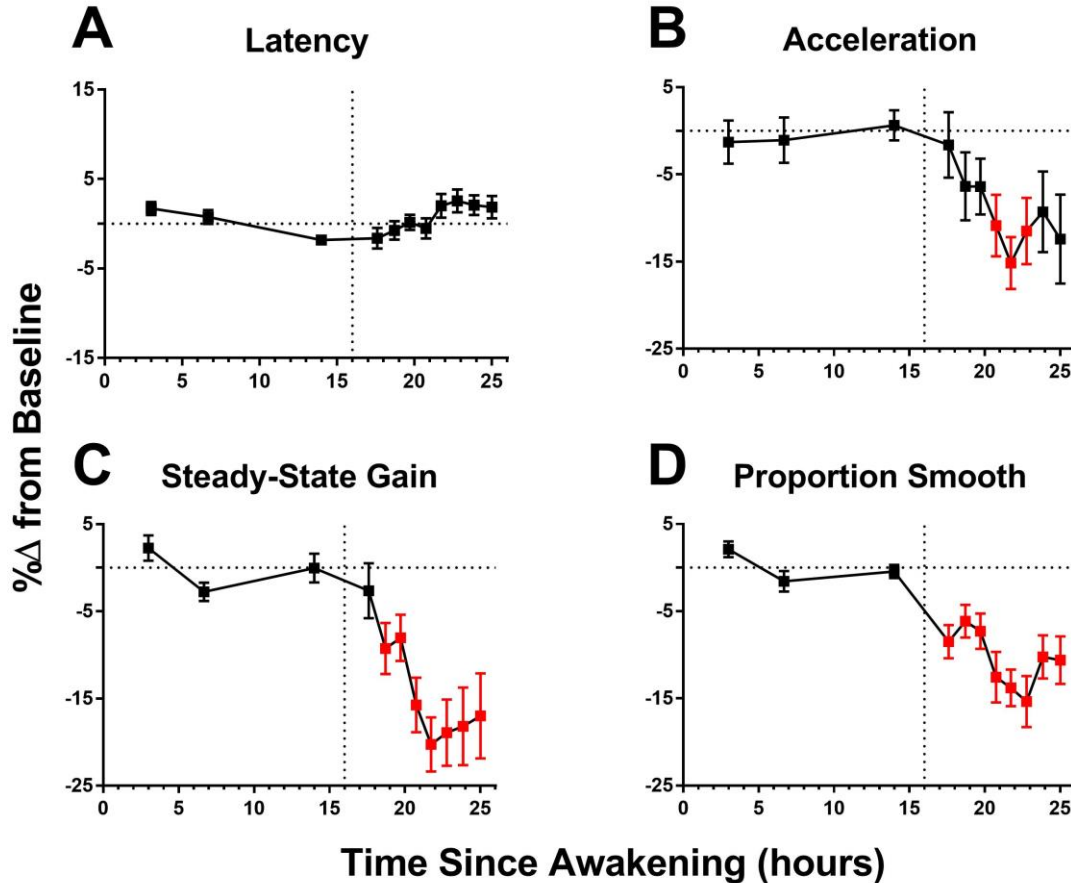
National Aeronautics and
Space Administration



Effect of 24-hr Acute Sleep Deprivation and Circadian Misalignment



Pursuit Behavior



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.



National Aeronautics and
Space Administration



Assessing countermeasure efficacy

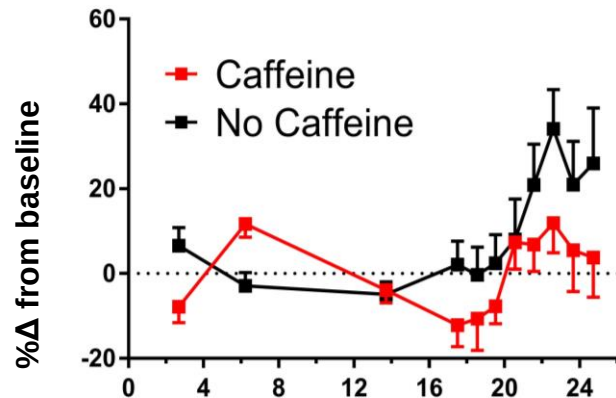


National Aeronautics and
Space Administration

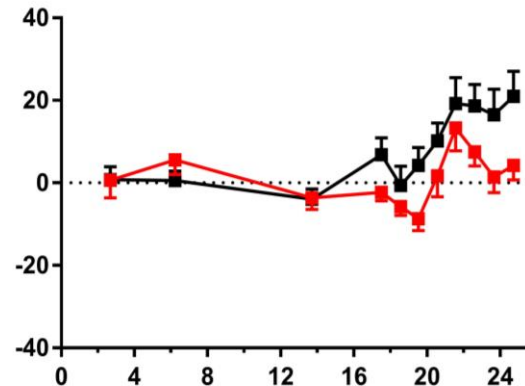


Motion Processing

Direction Noise



Speed Noise



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 from 24-hrs of ASL (no residual linear trend).
- However, the circadian modulation remains.



National Aeronautics and
Space Administration



Clinical surveillance:

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

Berneshawi, Seyedmadani, Goel, Anderson, Tyson, Akay, Akay, Leung, & Stone. Oculometric biomarkers of visuomotor deficits in clinically asymptomatic patients with systemic lupus erythematosus undergoing long-term hydroxychloroquine treatment. Frontiers in Ophthalmology, in press (2024).

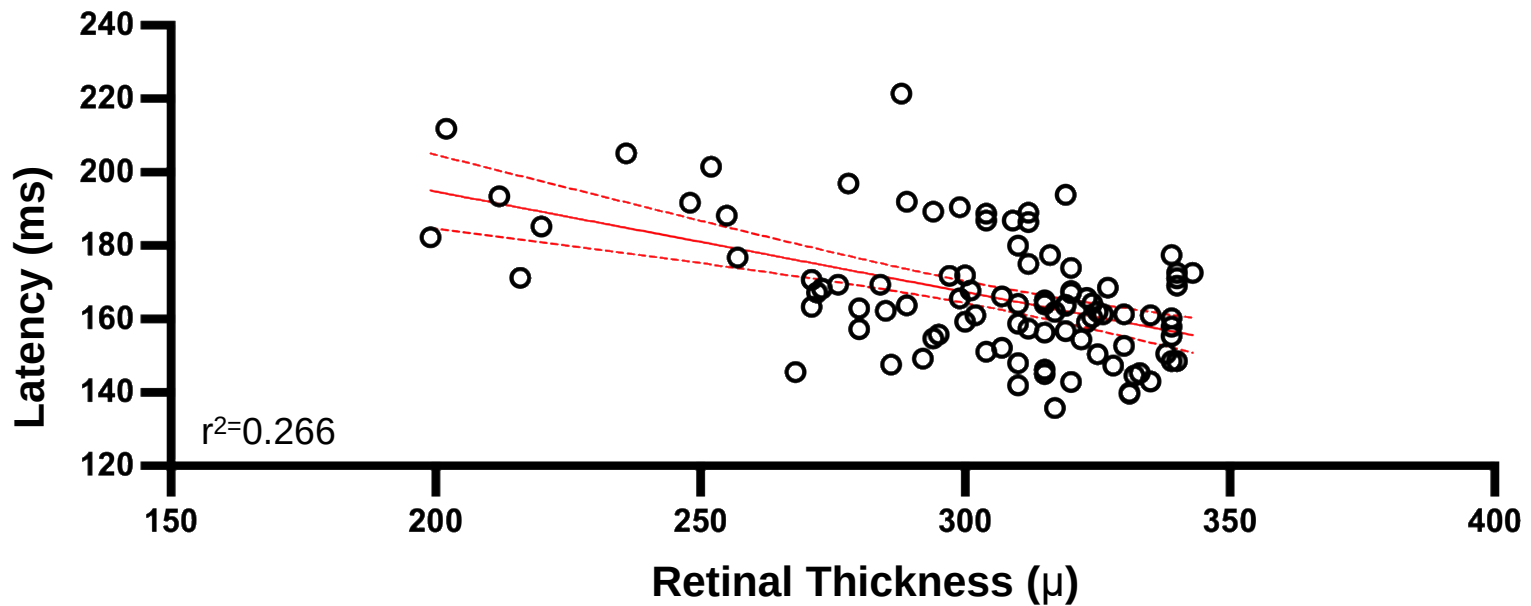
- We compared 10 visually asymptomatic lupus patients on hydroxychloroquine without clinical toxicity with 17 age-matched healthy controls.
 - Patients showed significantly impaired pursuit (lower acceleration, steady-state gain, and speed responsiveness) and saccadic compensation (larger catch-up saccades).
- ➔ Across-subject oculometric testing detected several components of altered visual function although standard clinical tests [Optical Coherence Tomography (OCT) and perimetry] did not, suggesting a potential future role in ophthalmological and neurological surveillance, even in the absence of a baseline measure.



National Aeronautics and
Space Administration



Examining structure-function correlations using oculometrics



Leung, Hwang, Berneshawi, Goel, Tyson, Chang, & Stone. *Correlated Changes in Retinal Thickness and Visuomotor Function in Asymptomatic Hydroxychloroquine Toxicity Patients*. NASA IWS (2023).

- 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 performance variation (function) associated with variation in retinal thickness (structure).



National Aeronautics and
Space Administration

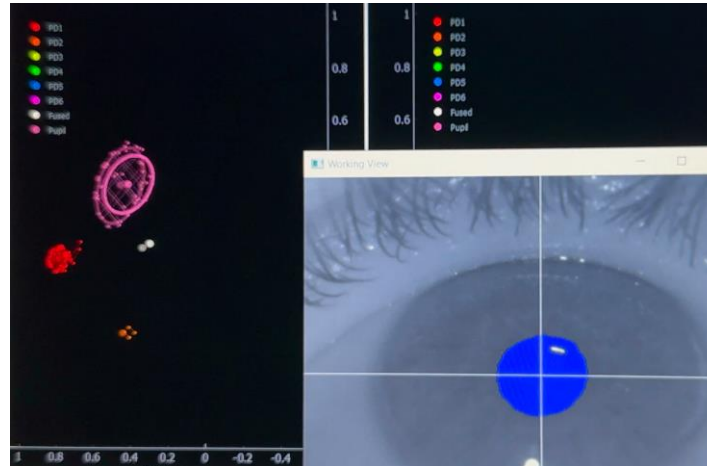


Development and validation of a VR COBRA system (ongoing)

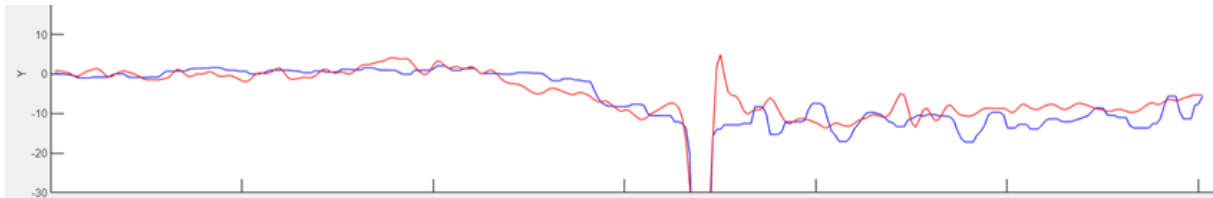




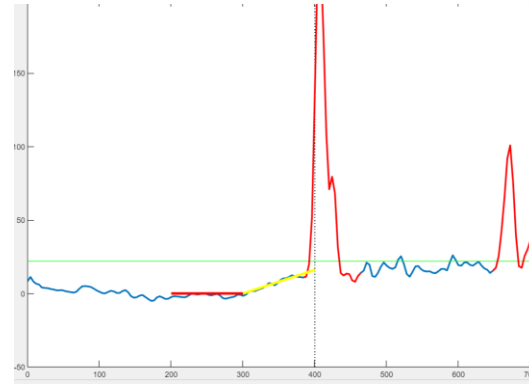
National Aeronautics and
Space Administration



Dual tracker test set-up. We simultaneously used a gold-standard pupil tracker (NASA high-speed camera system) and AdHawk's MEMS system (glasses).



Dual eye-tracker traces (NASA red, AdHawk blue). The plot shows eye velocity (in deg/s) vs time (tics represent 100 ms). Shared variance (r^2) between these traces is ~90%.



AdHawk eye-tracker ring inserts for Oculus (Left) and a COBRA trial from that VR system (Right). We are working to optimize and validate VR-collected COBRA data with the goal of enabling easy and reliable in-flight testing.



National Aeronautics and
Space Administration



Take-home message

- Astronauts who spend extended time on ISS are affected by Spaceflight Associated Neuro-Ocular Syndrome (SANS), but the stressors driving SANS and sensorimotor adaptation may have immediate manifestations detectable by oculometrics.
- The COBRA laboratory set-up at JSC has been validated in the Stanford Ophthalmology Clinic and in multiple scientific studies (so is ready for earth-based clinical or research uses). It is available NOW for crew visual/visuomotor testing pre/post-flight.
- We are developing and validating a VR-based system to allow for reliable in-flight oculometric testing in the near future.



National Aeronautics and
Space Administration



Acknowledgments

NASA/ARC Visuomotor Control Lab:

Terence Tyson (UC Berkeley doctoral student)

Dr. Rahul Goel
Mark Anderson
Kenji Kato

NASA/ARC Fatigue Countermeasures Lab:

Dr. Erin Flynn-Evans, Principal Investigator
Dr. Patrick Cravalho
Nathan Feick
Greg Costedoat

Byers Clinic- Stanford University Medical School

Dr. Loh-Shan Leung, Clinical Assistant Professor of Ophthalmology
Andrew Berneshawi (Stanford University medical student)

NASA/JSC Research Operation and Integration Lab:

Kimia Seyedmadani (University of Houston doctoral student)
Keith Tucker

Z3VR

Josh Ruben
Robert Pena

AdHawk

Nino Zahirovik

Supported by:

- *Ames Research Center Innovation Fund (Stone)*
- *ONR Force Health Protection Program (Stone)*
- *NASA Human Research Program TRISH grant (Ruben/Stone)*
- *National Eye Institute (P30-026877) (Leung)*
- *Research to Prevent Blindness (Leung)*
- *NASA Grant 80NSSC19M0186 (Seyedmadani)*
- *NASA Ames Graduate Fellowship Award (Tyson)*