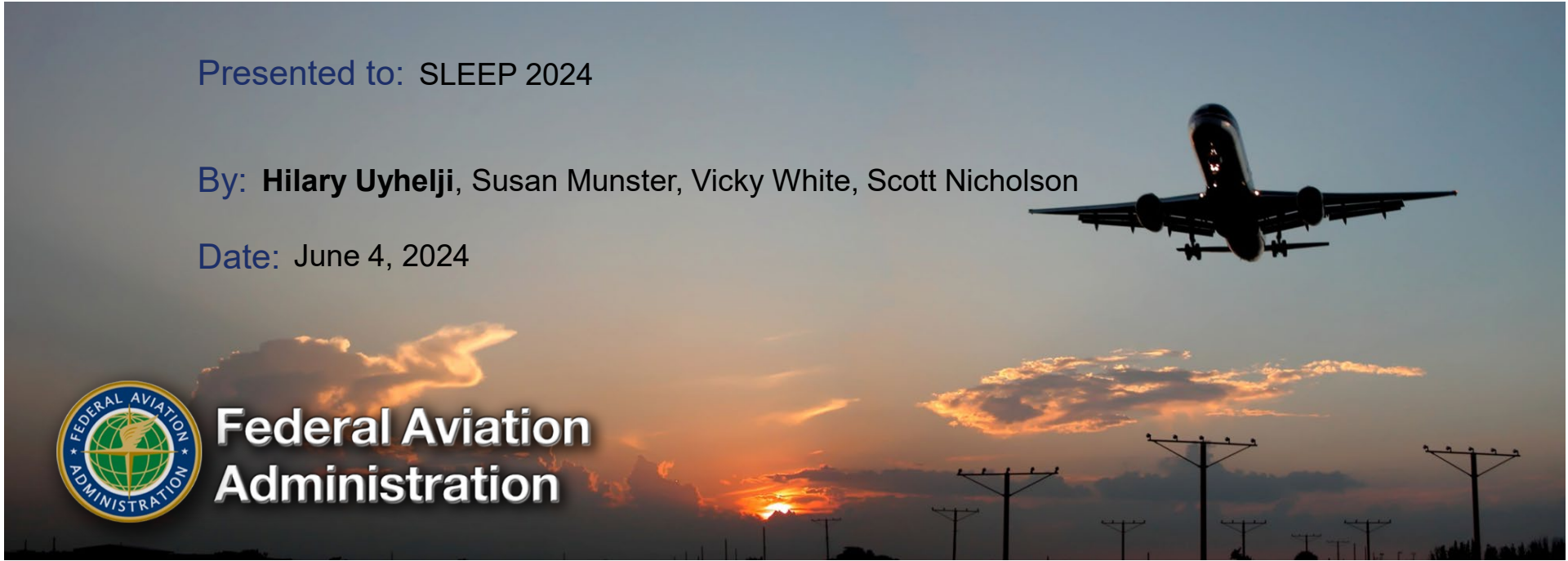
Gene Expression and Attention Lapses with a Countermeasure for Sleep Loss



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By: **Hilary Uyhelji**, Susan Munster, Vicky White, Scott Nicholson

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Federal Aviation Administration

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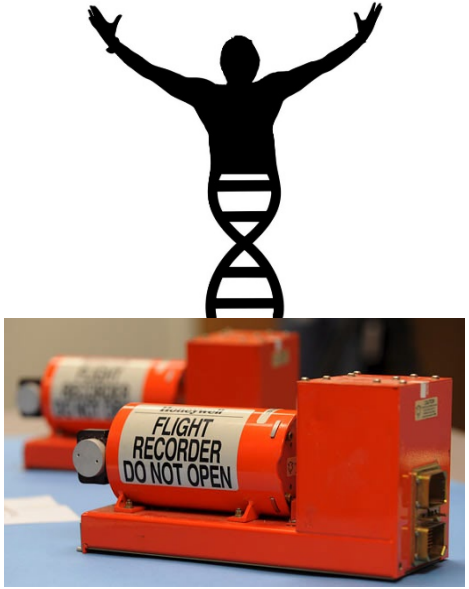
Fatigue as a safety risk

- **14 CFR 117.3**
  - "Fatigue means a physiological state of **reduced mental or physical performance** capability resulting **from lack of sleep or increased physical activity** that can reduce a flightcrew member's alertness and ability to safely operate an aircraft or perform safety-related duties."

Accident investigation biomarkers

- **Utilize FAA biorepository of blood from autopsies of fatal aviation accidents**
- **Goal: develop and test molecular *human* "flight recorder" biomarkers to assess safety risks**

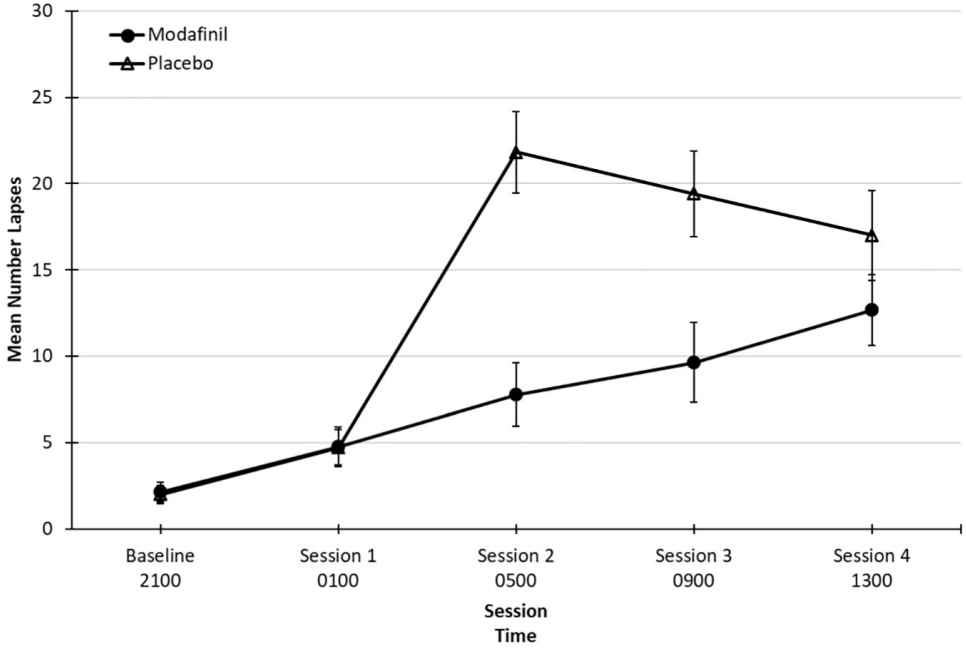


Total sleep disruption study

- **Collaboration with NAMRU-D** (Caldwell et al.)
- **19 persons x 2 study runs, ~36 hr wake**
  - Total sleep deprivation + placebo OR modafinil
- **Neurobehavioral performance**
- **Gene expression in blood**
  - Biomarkers for performance impairment, with & without modafinil

Performance worsens with sleep loss, mitigated by modafinil

- **Phenotype**
  - Impacts on Psychomotor Vigilance Test, Match to Sample, Rapid Decision Making, and POMS fatigue



Caldwell et al. 2018 *Pharmacology Biochemistry and behavior*
https://doi.org/10.1016/j.pbb.2020.172968

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Large changes in gene expression with sleep loss

- **Gene expression influenced by time awake, circadian rhythms, modafinil use, and performance test assayed**
- **Positive correlation of time awake to attention impairment**

Hundreds of biomarker candidates

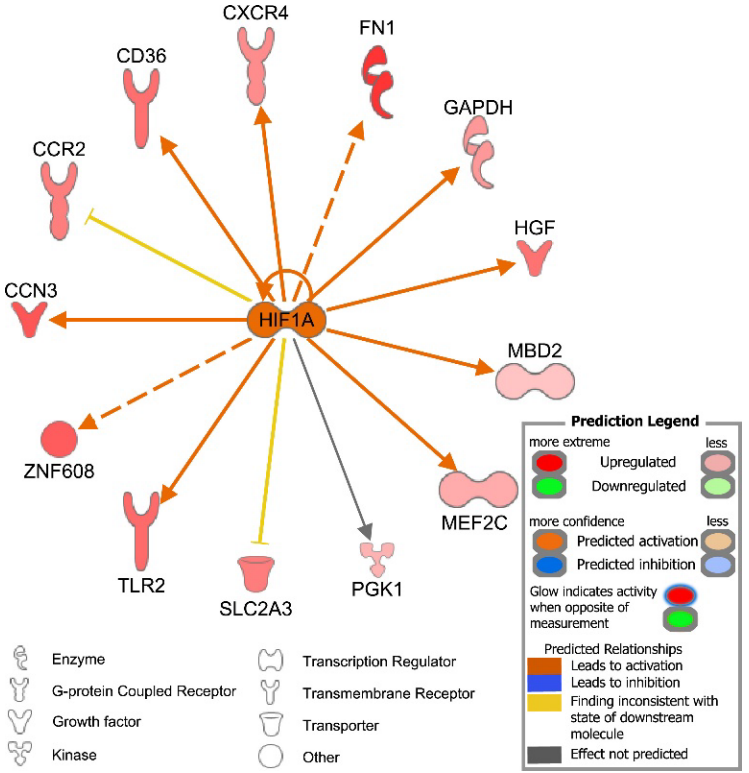
Assay	Circadian Rhythms modeled?	Diff. Expr. Genes: Placebo	Diff. Expr. Genes: Modafinil
PVT	Yes	232	0
PVT	No	1169	0
MTS	No	1	596
RDM	No	0	0
POMS fatigue	No	3	418

Limited overlap across assays

- **Placebo run**
  - *CXCR4* and *DDIT4* with FDR<0.05 for PVT and POMS fatigue
- **Modafinil run**
  - 87 genes with FDR<0.05 for MTS and POMS fatigue, including *CXCR4*
  - *DDIT4* with FDR<0.05 for POMS fatigue only

Activation of hypoxia pathway

- **Inferred upregulation of molecular pathway regulated by *Hypoxia Inducible Factor 1 (HIF1A)***



Synopsis

- **Biomarker candidates identified for neurobehavioral performance impairment during total sleep loss**
- **Biomarker utility is impacted by modafinil**
- **Different biomarker genes may apply pending the performance outcome of interest**

Acknowledgments

- **Functional Genomics Research Team at FAA/AVS/CAMI**
- **External collaborators**
  - Naval Medical Research Unit – Dayton
  - Baylor College of Medicine