Gene Expression Biomarkers for Identifying Vigilance Impairment from Total Sleep Deprivation

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Presented to: 10th International Conference on Managing Fatigue

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Date: 22 March 2017

Federal Aviation Administration

Fatigue is a concern in transportation safety, and health in general. Yet how do we objectively measure fatigue?

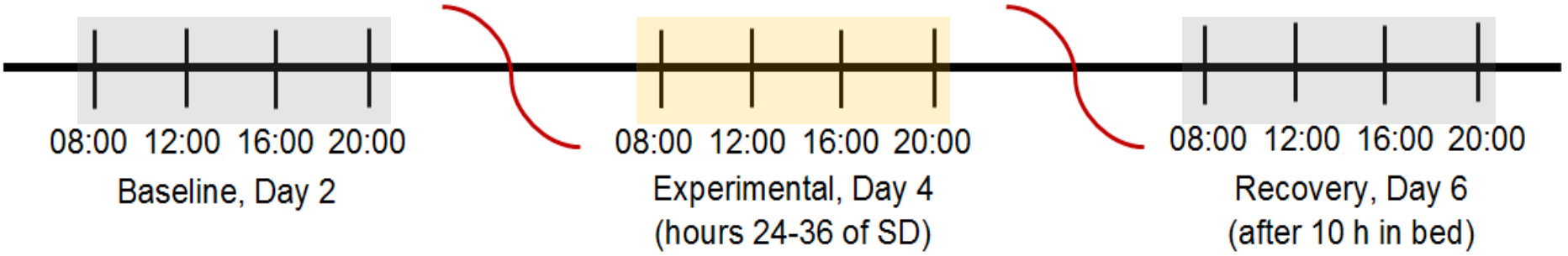
Experimentally impose acute sleep deprivation

- **Wash. State Univ. sleep lab for 7 days**
  - 6 Control persons: 10 h in bed each night
  - 11 Sleep Deprived persons (SD): 62 h wakefulness
- **Data collection**
  - Blood for gene expression microarrays
  - Psychomotor Vigilance Test (PVT) for cognition
- **Test for differential gene expression**
  - Treatment effect: Control vs. SD individuals
  - Cognitive performance: PVT lapses

For cognition measurements and overview of study design, see Whitney et al. 2015 (http://dx.doi.org/10.5665/sleep.4668)

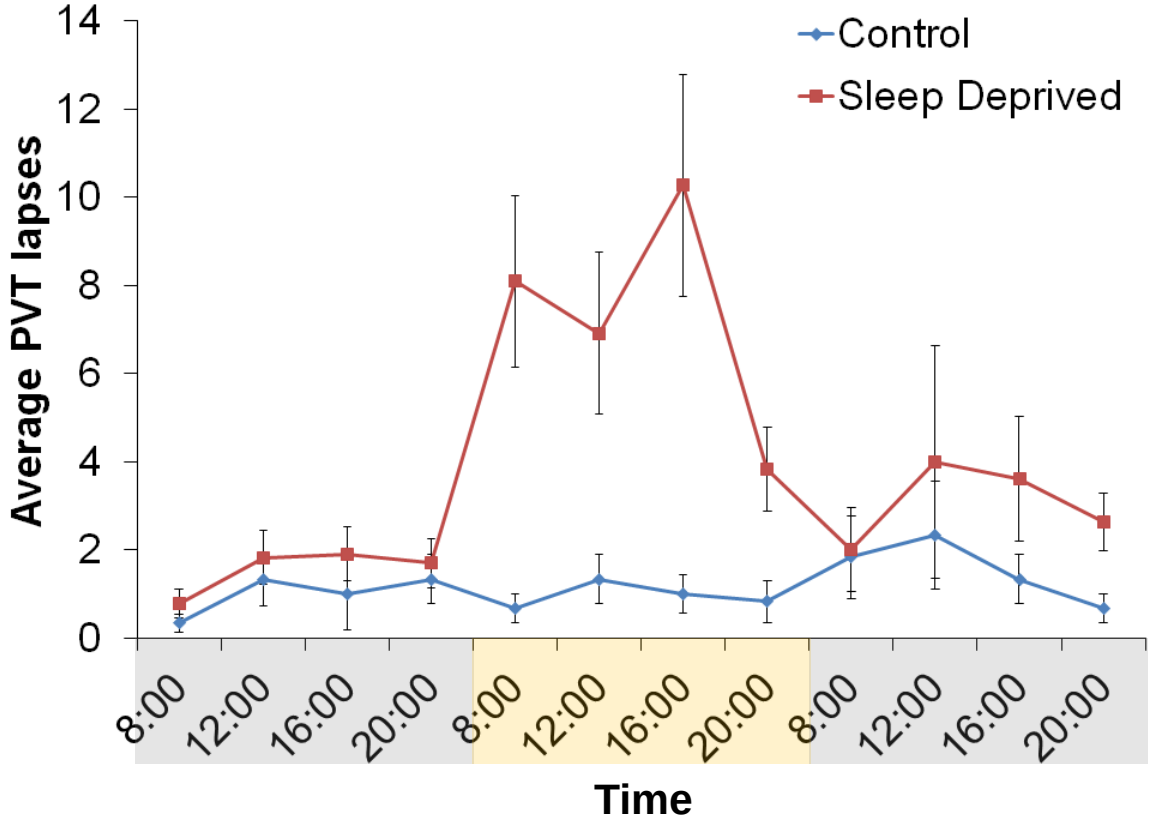
Blood draws for gene expression every other day

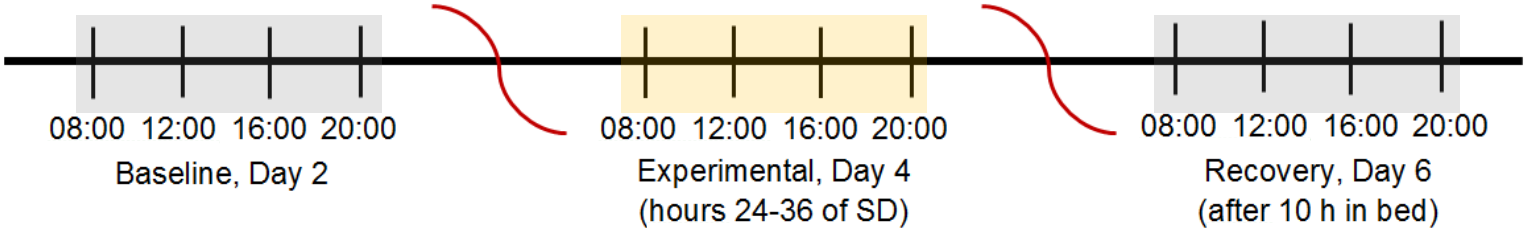
- **Control: 10 h in bed every night**
- **Sleep Deprived: no sleep from 08:00 Day 3, until 22:00 Day 5**



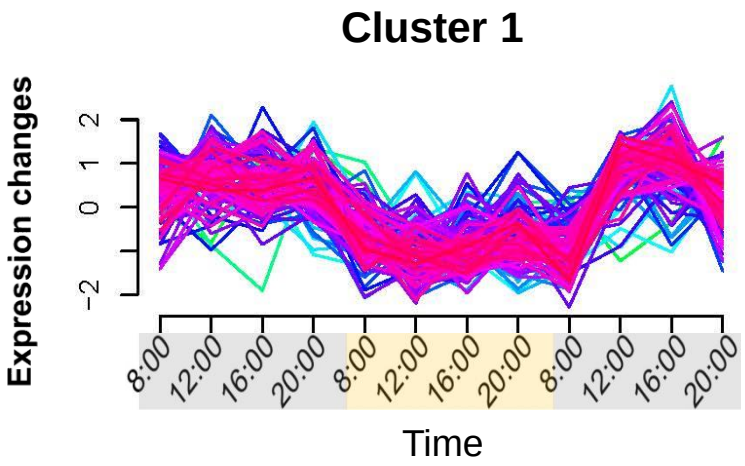
Informed consent and IRB approval were obtained for this research.

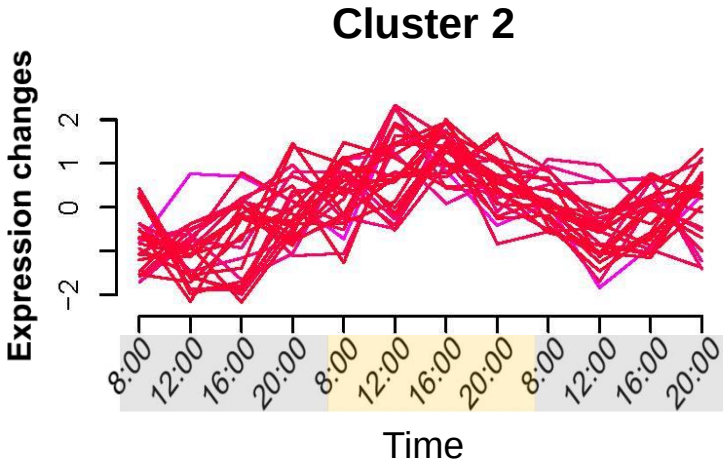
PVT lapses increase with SD

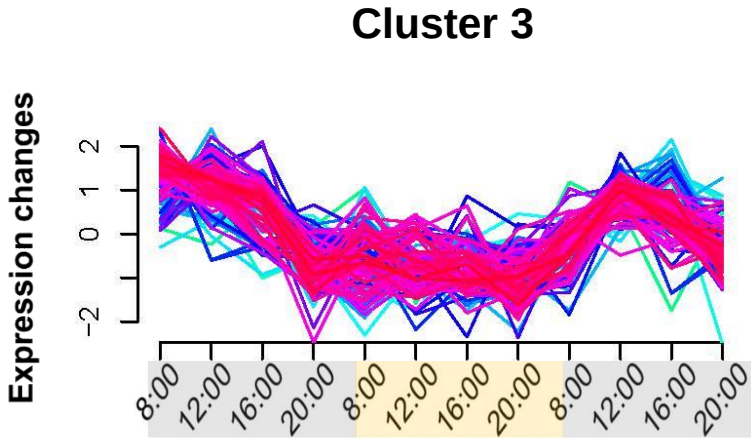


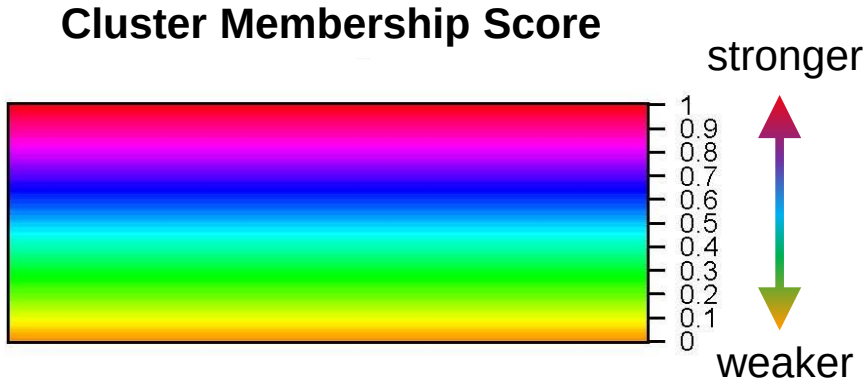


Clustering ~212 treatment effect genes by temporal expression in SD subjects







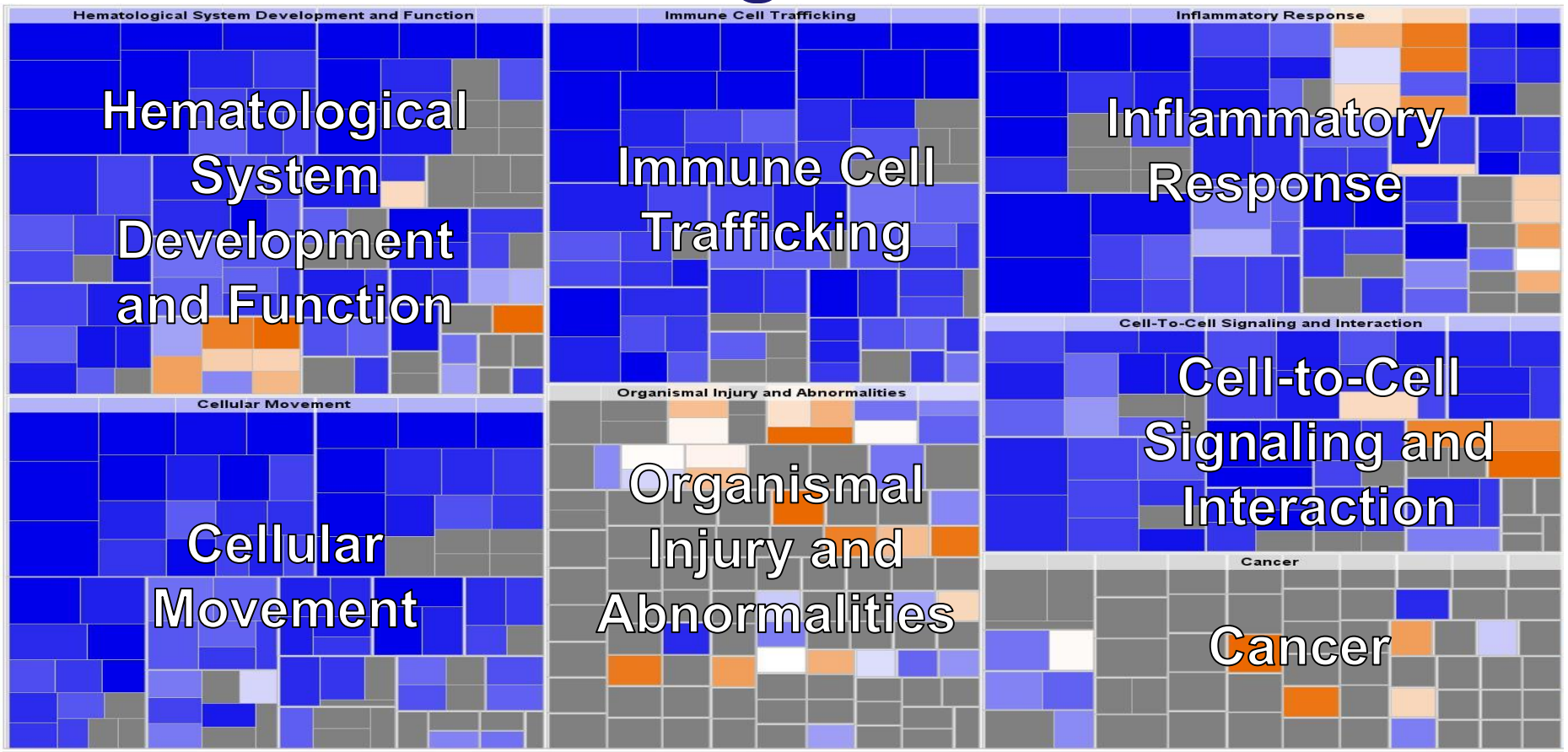


Functional enrichment of the 212 genes related to SD

Functional Group	Enrichment Score	Number of Genes	Description
1	4.43	99	membrane
2	2.82	14	immunoglobulin
3	2.74	16	cell adhesion
4	2.34	38	cell motility; inflammatory response
5	2.24	13	cell junction
6	2.03	12	coagulation
7	1.96	21	cell fraction
8	1.76	3	metal ion-binding site:calcium
9	1.44	15	vesicle
10	1.43	3	sushi; complement control module
11	1.33	13	lipoprotein

Functional analysis performed with the DAVID bioinformatics tool at https://david.ncifcrf.gov

Diseases and functions for the 212 SD genes



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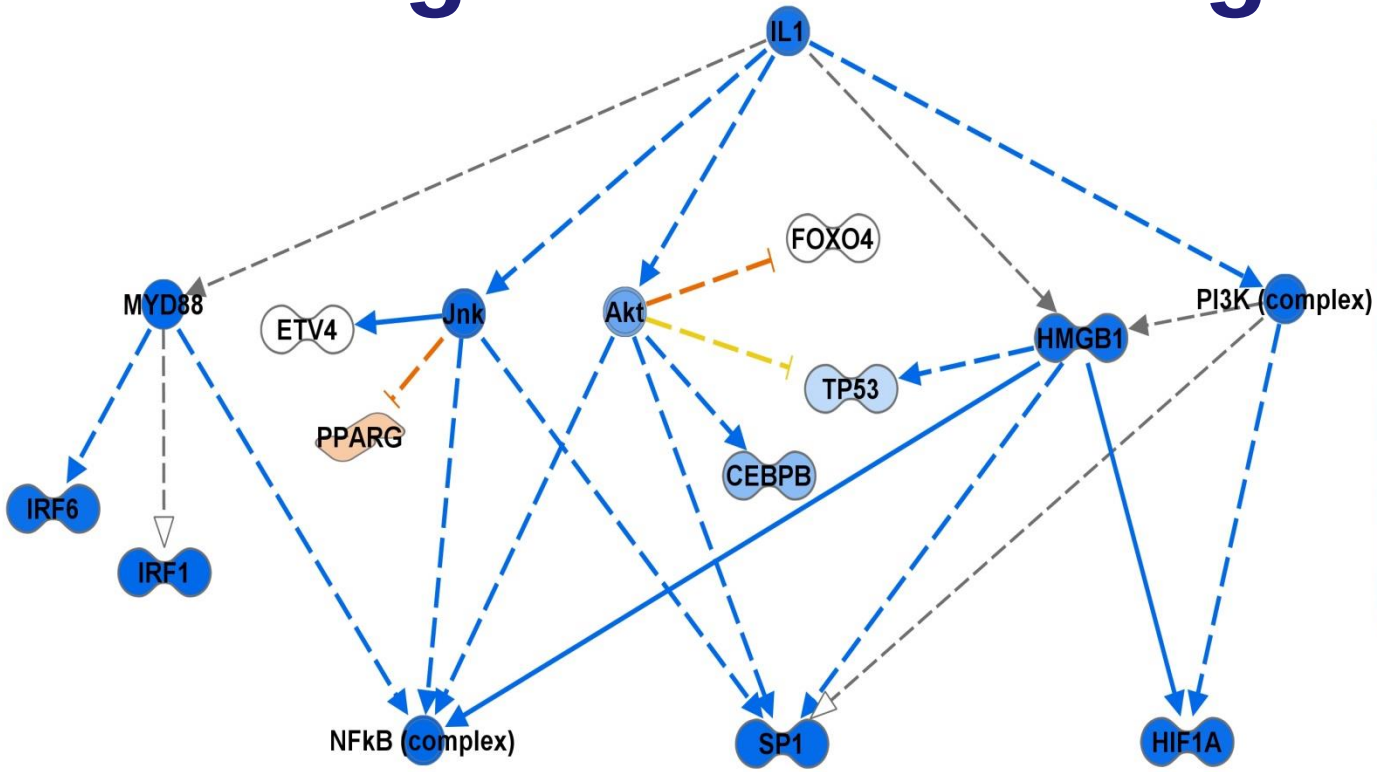
Blue = inhibition. Orange = activation.

Z-score: <-3.32 1.52

Mechanistic network of upstream regulators for SD genes



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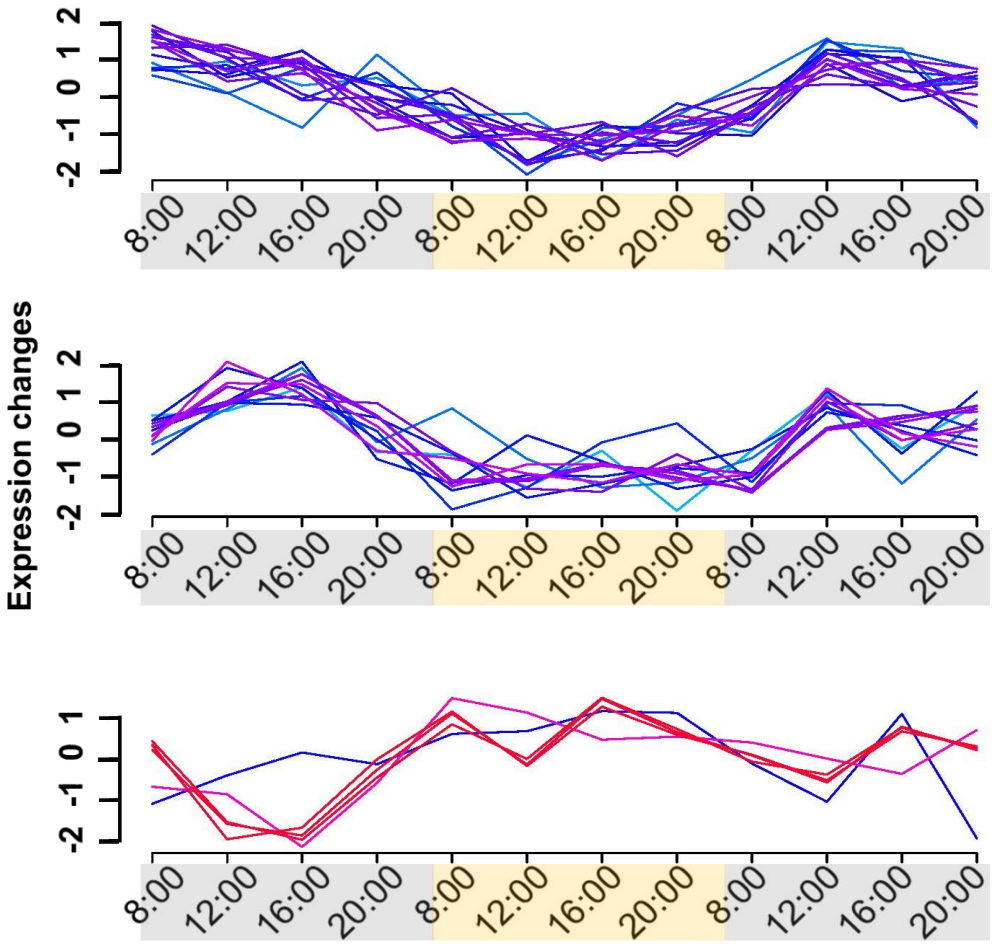
59 downstream SD genes used to predict this network
(all but 4 of which are down-regulated by SD)

Clustering 28 PVT cognition genes by their temporal expression in SD subjects



Cluster 1

Cluster2

Cluster 3

Functional enrichment of the 28 genes related to PVT scores

Functional Group	Enrichment Score	Number of Genes	Description
1	1.65	9	cell motility; inflammatory response
2	1.37	9	vesicle-mediated transport; intracellular signaling cascade
3	1.37	19	membrane
4	1.35	5	calcium-binding EF-hand

Functional analysis performed with the DAVID bioinformatics tool at https://david.ncifcrf.gov

Summary of findings

- **Measurable effects on cognition and gene expression (e.g., cytokines) with one night of sleep deprivation**
- **Overall, we see a reduction in gene expression with sleep deprivation**
- **Future needs:**
  - Fine-tune cognitive measures
  - Increase sample size
  - Assess circadian component

Acknowledgments

- **FAA: grant DTFAAC-11-A-00003**
- **NIH: grant R01HL105768**