Gene Expression Biomarkers for Identifying Vigilance Impairment from Total Sleep Deprivation

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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.

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PVT lapses increase with SD

- Control
- Sleep Deprived

Time

Baseline, Day 2
Experimental, Day 4 (hours 24-36 of SD)
Recovery, Day 6 (after 10 h in bed)
Clustering ~212 treatment effect genes by temporal expression in SD subjects

Cluster 1

Cluster 2

Cluster 3

Cluster Membership Score

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Functional enrichment of the 212 genes related to SD

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

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

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Diseases and functions for the 212 SD genes

Blue = inhibition. Orange = activation.

Z-score: <-3.32

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Mechanistic network of upstream regulators for SD genes

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
Functional enrichment of the 28 genes related to PVT scores

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<tbody>
<tr>
<td>1</td>
<td>1.65</td>
<td>9</td>
<td>cell motility; inflammatory response</td>
</tr>
<tr>
<td>2</td>
<td>1.37</td>
<td>9</td>
<td>vesicle-mediated transport; intracellular signaling cascade</td>
</tr>
<tr>
<td>3</td>
<td>1.37</td>
<td>19</td>
<td>membrane</td>
</tr>
<tr>
<td>4</td>
<td>1.35</td>
<td>5</td>
<td>calcium-binding EF-hand</td>
</tr>
</tbody>
</table>

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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

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