Improving and Automating Sleep Study Interpretation

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Improving and Automating Sleep Study Interpretation

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Introduction

Sleep is core to mental health and has medical, psychological and societal impact. Sleep deprivation impairs performance, judgment, mood, and is a preventable contributor to accidents. We all experience sleep; yet why we sleep and how the brain generates sleep remain biological mysteries because we lack the tools and data needed to gain a comprehensive picture of sleep.

To fill this gap, the Stanford Center for Sleep Sciences and Medicine, with assistance from a multi-disciplinary team, is setting up the infrastructure for a large-scale project to develop and disseminate essential tools and data to the scientific community to advance the field of sleep medicine. These data and tools will be crucial for our understanding of the genetic architecture of sleep and will improve detection, treatment and prevention of sleep disorders. We aim at nothing less than being a catalyst for changing the sleep field.

Methods

The Stanford Technology Analytics and Genomics in Sleep (STAGES) study is a prospective cross-sectional, multi-site study which is outlined in Figure 1. The proposed aims will develop the critical infrastructure needed for sleep and sleep disorder research and will provide essential tools and data for sleep research.

Specific Aim 1: Collect and make available PSG, ASQ, neuropsychological testing data, biological samples, and DNA on 30,000 adult/adolescent patients evaluated for sleep disorders, creating a unique reference database for the field of sleep medicine.

Sleep clinic patients will be enrolled at 11 data collection sites from six centers including Stanford University (Stanford, CA), Bogan Sleep Consultants (Columbia, SC), Geisinger (3 locations in Pennsylvania, USA), Mayo Clinic (Rochester, MN), MedSleep (5 locations in Ontario, Canada), and St. Luke’s Hospital, Chesterfield, MO.

A comprehensive dataset will be collected, catalogued and stored using a robust data platform (see Figure 2), including:
- Alliance Sleep Questionnaire (ASQ) an on-line sleep/medical history questionnaire
- In lab nocturnal polysomnography data (one night PSG)
- Computerized Neurocognitive Battery (CNB) developed by UPenn
- Actigraphy with sleep diary (2 weeks)
- Genetics - Genome wide association data
- Stored biological samples (DNA, plasma, serum) for future biomarker research
- 3-D facial image
- Medical Record Data

Specific Aim 2: Develop and make available software that will streamline PSG analysis, extract meaningful sleep phenotypes, and standardize analysis in large samples. Validate this software in smaller, existing cohorts and use software in the large 30,000 sample in conjunction with GWAS to answer critical questions related to sleep and sleep disorders.

A wealth of data is collected daily by sleep clinics, but it is not stored or exploited digitally. The gold standard PSG is comprised of multiple digital signals (EEG, ECG,EOG, chin and leg EMG, breathing effort, and airflow) recorded over the night (see Figure 3). PSGs are currently scored by humans who evaluate a study in 30-second segments to extract simple features such as sleep/REM sleep latency, sleep stage proportions, number of sleep apnea events (Apnea-Hypopnea Index, AHI), and number of periodic leg movements (PLM). This is time consuming and variable based on individual scorers. In some centers, semi-automatic programs now assist scoring, but these programs try to mimic humans and do not go beyond what is accepted by a consensus of sleep experts. Machine learning and signal processing techniques will be used for this project to create software and algorithms that will be employed to streamline PSG analysis (see Figure 4), extract meaningful sleep phenotypes, and standardize analysis in large samples. All resources developed will be shared.

Specific Aim 3: Use GWAS in conjunction with machine learning and phenotype analysis in the 30,000 sample to discover genetic modifiers for sleep and sleep disorders focusing on genetic variants that control EEG traits and hypersomnia phenotypes. We anticipate that this approach will unravel novel molecular mechanisms underlying sleep and sleep disorders.

Genetic approaches are effective at opening biological black boxes, especially for traits that are objectively measured such as sleep. Genetic approaches have been applied successfully to many disorders and physiological measurements (notably circadian biology), but not sleep, with the exception of narcolepsy and restless legs syndrome, where it has been successful. This is surprising as sleep is a measurable biology with strong genetic effects so it should be tractable by genetic analysis, providing objective evaluation and adequate sample size (see Figure 5). Until now, there have been few sleep cohorts large enough to measure genetic effects.

Resource Sharing:
The project’s philosophy is to make all resources generated by the study available to the widest potential audience with the least number of restrictions. Therefore, all data, biological samples, and electronic products collected or developed under the STAGES project will be available for any interested researcher. Phenotypic data will be posted at the NIH Data Archive (NDA). Genotype data will be at dbGaP. Details regarding data content, format, and organization will be available for download from a Stanford Center for Sleep Sciences and Medicine project website and referenced in and any publications related to the project.

Results

Under Aim 2, we have been exploring machine learning as a new method for differentiating PSG characteristics. We have designed algorithms to automatically score sleep stages, detect EEG and autonomic arousals, sleep apnea, PLMs and other features. Table 1 summarizes our algorithms to date. These automated methods are more reliable and consistent than human annotations. For example, our machine learning models of sleep stage scoring are performing better than single scorers and can score by 5s segments instead of 30-s. More importantly, these algorithms are also revealing new features that have potential beyond classic PSG scoring. As an example, the output of our deep neural network (DNN) algorithms based on cross-correlation transformation of the EEG to classify sleep stages has found that in the sleep disorder narcolepsy, the probability of wake during REM sleep is abnormally high, which can be used as a diagnostic feature. Similarly, we found that subtypes of sleep apneas with differential effects on sleepiness and the cardiovascular system could be objectively found. Using these techniques, we believe many traits can be automatically generated and validated for usefulness in epidemiological samples.

Conclusion

We are creating a unique resource that will be shared with the scientific community. In parallel, we are developing analytical tools such as machine learning and new statistical methods that will assist in the interpretation of these data. Access to these data and tools will spark new research opportunities and genetic analysis, which will result in new diagnostic biomarkers for sleep disorders and a better molecular understanding of sleep regulation.

Support / Contact Information
This project is funded by the Klarmann Family Foundation
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Figure 1. Overarching Design of STAGES

Figure 2. Architecture of STAGES Data Platform

Table 1. PSG Algorithm Performance Measures

<table>
<thead>
<tr>
<th>Event type</th>
<th>Modalities</th>
<th>Performance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep stages</td>
<td>EEG, EOG, EMG</td>
<td>84% acc., 0.75 kappa</td>
<td>DOI: 10.1093/sleep/zsy061.315</td>
</tr>
<tr>
<td>EEG and autonomic arousals</td>
<td>EEG, EOG, EMG</td>
<td>79% F1 score</td>
<td>DOI: 10.1093/sleep/zsy061.141</td>
</tr>
<tr>
<td>Apnea events</td>
<td>EOG, EMG, ECG</td>
<td>75% F1 score</td>
<td>DOI: 10.1093/sleep/zsy060.327</td>
</tr>
<tr>
<td>Leg and PLM</td>
<td>Tibial EMG</td>
<td>85% F1 score</td>
<td>DOI: 10.1093/sleep/zsy061.322</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>EEG, EOG, ECG</td>
<td>91.9% sens/spec</td>
<td>arXiv:1710.02094</td>
</tr>
</tbody>
</table>

Figure 3. Example of Polysomnography (PSG)

Figure 4. Comparison of a Machine Learning Sleep Stage Scoring Algorithm to Human Consensus Data

Figure 5. Overarching Design of STAGES

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DOI: 10.1093/sleep/zsy061.327