Automated sleep stage classification with ECoG

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# Initial Proposal (for BDGN Training Grant)

In summary, this proposal is motivated by the need for predictive models that can classify functionally distinct brain states in order to (1) connect these distinct brain states to behavior and (2) determine what brain states are most conducive to plasticity and stimulation-based interventions. Sleep staging was selected due to its already well-known and documented changes in neural oscillations, which can already be used as features for automated classification. In addition, sleep is closely tied to memory consolidation, and I believe that once we build an automated classifier, we can introduce stimulation interventions to see whether stimulation at different sleep stages produces differing outcomes – specifically with neural plasticity. This research will help us better understand how these functionally distinct brain states cause different results with stimulation intervention and ideally discover which brain states are most conducive to stimulation.

Aim 1: Feature finding for sleep

* Use current known features used for sleep staging
* Functional connectivity measures
* Using DMD to look for spindles or other features
* Include EOG, EKG, video?

Aim 2: Build sleep classifier with features

* First classification: sleep vs. wake
* Then REM vs. NREM (using video – **this is what set me apart**)
* Then different sleep stages

For sleep staging, we have learned that it is not possible to have a ground truth measure with our data, so we will perform unsupervised clustering and set the number of clusters (3-5). While this is not ideal in terms of validating our sleep classifier, we can still identify distinct functional brain states during sleep, which is the ultimate goal. Additionally, we can take a look at the spectrogram of the clusters and determine whether it makes sense based on what we know about sleep stages. In the future, we would need simultaneous ECoG and EEG in order to properly validate the sleep stages.

Aim 3: Measure neural excitability with different sleep stages

* Single-site stimulation during different sleep stages – measure neural excitability
* Would potentially need to make an IRB modification – get started on this with Jeff

*Side note:* I submitted this proposal with the intent of having 2 years of funding, so it’s TOTALLY FINE AND ACTUALLY EXPECTED for me not to get to this by the end of the first year. I can alternatively just spend time evaluating the classifier and seeing how generalizable it is between patients.

Towards brain state-dependent stimulation: classification of sleep stages using electrocorticography

**Background:** With the development of new stimulation protocols for neuromodulation, it has become evident that the existing brain state has a significant effect on stimulation outcome. Stimulation-based protocols, including stimulation to induce neural plasticity for neurorehabilitation or providing stimulation as a feedback mechanism for brain-computer interfaces, have produced varying outcomes given the exact same stimulation parameters. Previous work has shown brain state dependency on changes of neural behavior when given stimulation, and some studies have been able to predict those changes based on the prior state of the brain1.

Establishing that this prior state is non-trivial in influencing the outcome of stimulation, current efforts have been focused on creating predictive models able to characterize the effects of stimulation given a known prior state. To build this predictive model, we would need methods of classifying different functional brain states from neural recordings, reflective of when a person is moving, at rest, or sleeping. In doing so, we would be able to explore how to best optimize stimulation parameters in congruency with these underlying neural states towards an intended outcome. Research in this area has mostly been in awake human subjects, but stimulation research during sleep has been largely unexplored. Sleep is particularly interesting due to its intricate relationship with memory consolidation; however, these studies rely on polysomnography technicians to spend hours scoring sleep into different sleep stages. Sleep staging follows a standardized set of rules, making it an ideal candidate for automation. Sleep stage classification has been done mostly with non-invasive recording technologies using electroencephalography (EEG), but due to the poor spatial resolution and high noise that comes with EEG, it limits the ability to detect more subtle changes that may better classify sleep and additionally add to our understanding of sleep2. **With the improved spatial resolution and signal quality of electrocorticography (ECoG), I propose to design a sleep stage classifier towards automation of functional brain state classification and state-dependent stimulation.**

**Preliminary work**: Previous work in our lab has examined neural properties of brain states and begun to classify how natural behavioral states manifest in the brain. In resting-state ECoG, specific features and measures of functional network connectivity have been explored and summarized, including phase-locking across frequency bands and coherence3. We can similarly build upon this existing work to identify features for different stages of sleep. In addition, a comprehensive dataset of naturalistic human behavior coupled with ECoG, audio, and video recordings has previously been collected and well annotated4. Using unsupervised machine learning on power spectral features, the neural dataset was successfully classified into behaviors of the subject moving, speaking, and resting, and we plan to leverage these machine learning techniques towards building a sleep classifier.

Another computational approach called dynamic mode decomposition (DMD) has been used to process and analyze neural signals, due to its unique ability to characterize large datasets into its fundamental spatiotemporal characteristics. For example, DMD is capable of identifying sleep spindles, or sudden bursts of 12-14 Hz oscillations that occur during NREM sleep, which is commonly used for manual sleep staging5. This demonstrates the ability for DMD to extract spatiotemporal features that change with different sleep stages.

**Proposed Work:**

*Our first aim is to identify unique neural features indicative of different sleep stages.* Our lab has worked with Harborview Medical Center in conducting research on patients with intractable epilepsy, where week-long ECoG data is recorded for the purpose of localizing seizure foci. As a result, we have access to hours of sleep data from many patients, which will be used for feature identification. Prior known information about different sleep stages and how they present in terms of neural synchrony and frequency bands of interest will be used. For instance, slow-wave sleep (SWS) is characterized by high synchrony and low firing rates, and the delta frequency band is deeply linked with sleep. We can additionally take advantage of the gold standard sleep staging rules to inform which features could be of interest. Using computational methods such as measures of functional connectivity and DMD will help establish an investigative feature set and help identify which brain regions are most informative for sleep stage classification.

*Our second aim is to build a sleep classifier based on these identified features.* Our goal is to specifically distinguish between sleep vs. wake, and then the different stages of sleep, including light sleep, slow-wave sleep, and REM sleep. Previous classification attempts using ECoG were unsuccessful with REM classification due to its neural features being markedly similar to the awake stage6. To address this, we plan to use video recordings of patients to help classify between awake versus asleep. A previous dataset of ECoG paired with video has been used to detect when a patient is at rest versus moving, and we plan to build on the methods used for this classifier. This dataset has been well annotated, serving as partial validation for classification of sleep vs. wake. For further classification into different subcategories of sleep, different machine learning methods will be explored, using the previously identified features to classify between REM versus NREM and subsequently between different stages of NREM. Some methods of interest include unsupervised clustering and cascade classification. Testing of classification outcome will include statistical analysis of accuracy, sensitivity, and specificity. For complete validation, a certified polysomnography technician will manually score the ECoG data, and proper statistical comparisons will be performed.

*Our third aim is to examine differences in cortical excitability between different sleep stages*. Using this sleep stage classifier, we plan to conduct stimulation experiments and investigate how cortical excitability varies between awake state and different stages of sleep. Single-site direct electrical stimulation will be performed using electrodes in regions that are non-contributive towards sleep stage classification and are not near seizure foci. Stimulation will be timed based on when the classifier has confidently determined the sleep stage. We hypothesize that differences in underlying neural activity will change stimulation outcome, measured by changes in the stimulation evoked response. These findings will contribute towards an effort to automate brain state classification in addition to understanding the interplay between stimulation and underlying neural activity. Future efforts will be made to build predictive models that inform the design of stimulation parameters to reach specific desired neural outcomes.

**References:**

1. Keller CJ, et al. Induction and Quantification of Excitability Changes in Human Cortical Networks. *J Neurosci*. 2018

2. Hamida ST Ben, et al. Computer based sleep staging: Challenges for the future. *2013 7th IEEE GCC Conf Exhib GCC*

3. Casimo K, et al. Directional patterns of cross frequency phase and amplitude coupling within the resting state mimic patterns of fMRI functional connectivity. *Neuroimage*. 2016

4. Wang NXR, et al. Unsupervised Decoding of Long-Term, Naturalistic Human Neural Recordings with Automated Video and Audio Annotations. *Front Hum Neurosci*. 2016;

5. Brunton BW, et al. Extracting spatial–temporal coherent patterns in large-scale neural recordings using dynamic mode decomposition. *J Neurosci Methods*. 2016

6. Kremen V, et al. Automated unsupervised behavioral state classification using intracranial electrophysiology. *J Neural Eng*. 2019

# Documentation of work

## Aim 1: Identifying neural features

**Frequency power bands**

<bar chart>

<frequency power across electrodes heat map>

**Sleep-staging features**

**Other features**

* Using DMD, spindle detection, other methods
* EKG, EOG, video

## Aim 2: Building and evaluating sleep classifier

### Aim 2.1: Classifying between sleep vs. wake

**Classifying sleep vs. wake**

* Using only frequency power, able to classify with high accuracy
* Which electrodes has the most predictive power? What region of the brain?

**Evaluation of sleep vs. wake classifier**

* Use multiple days’ worth of annotated data

### Aim 2.2: Classifying between different sleep stages

**Unsupervised clustering of**

### Aim 2.3: Classifier generalizability

**Generalizability to multiple patients**

* Test classifier as-is on other patients
* Use first 2 nights of patient sleep as training data + re-test on subsequent nights
* Optional: build a huge ass classifier with TONS of data + see how generalizable it is to new patients (similar to the EEG massive study)

## Aim 3: Stimulation studies