CHRONIC DECODING OF DEPRESSION STATE

A PREPRINT

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December 16, 2019

ABSTRACT

***K*eywords** Deep brain stimulation · depression · decoding · feedback model

1 Introduction

Treatment resistant depression (TRD) is a life-threatening mood disorder that arises from pathological activity across a brain network []. The subcallosal cingulate cortex (SCC) is one region of this network with metabolic activity correlated with depression severity []. Stimulation

Metabolic hyperactivity in the SCC has been shown to correlate with depression symptom severity [] and reductions in metabolic activity are seen in successful antidepressant pharmacotherapy [] and deep brain stimulation []. Patient-individualized stimulation of subcallosal cingulate white matter (SCCwm) has been shown to lead to reliable antidepressant response [].

Efforts to make DBS for depression more adaptive are growing [] but require a reliable measure of depression state derived from physiologic measurements []. MDD is known to be a network disease and efforts to identify depression encoding oscillatory activity across networks have had early success []. However, recovery from depression requires weeks to months of therapy and chronic recordings are needed to identify and validate a depression readout. Recent DBS hardware enables long-term recording of LFP

In this study we find that oscillatory activity in the SCC can be used to predict the depression state. This work enables the growing field of adaptive DBS in depression by providing a candidate feedback signal from SCC recordings.

[*]Use footnote for providing further information about author (webpage, alternative address)—*not* for acknowledging funding agencies.

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2 Methods

2.1 Regulatory, Patients, and Clinical

Six consecutive patients were enrolled into an Emory IRB approved study into the safety and efficacy of SCCwm-DBS (s). Inclusion and exclusion criteria are identical to those previously published []. Multiple recordings a day were measured in bilateral SCC using the Activa PC+S.

Various clinical scales are administered to patients during weekly visits with study psychiatrists. The primary outcome measure used in this study is the Hamilton Depression Rating Scale (HDRS). The HDRS is a set of 17 questions that ask about the severity of various depression-associated symptoms over the past seven days. Half of the pre-implantation HDRS is the *response threshold* for each patient. Patients who are at or below this threshold at six months post-implantation are considered responders to therapy.

2.2 DBS Implantation

Two DBS leads (Medtronic 3387) are stereotactically implanted into bilateral SCC []. The target is the subcallosal cingulate white matter [] which is targeted using patient individualized tractography []. The DBS electrode is implanted such that one of the center two electrodes is placed at the individualized SCCwm target, bilaterally. This enables differential LFP recordings on the two electrodes

2.3 Neural Recordings

Local field potentials (LFPs) are recorded using the Activa PC+S []. Recordings are sampled at $422\,\mathrm{Hz}$. Hardware filters are set at. Recording channels are chosen to be the two electrodes immediately adjacent to the therapeutic stimulation electrode (Figure**??**).

2.4 Preprocessing and Analysis

Oscillatory state Oscillatory states are computed for each available recording. First, recordings are transformed into power spectral densities (PSDs) using the Welch estimate algorithm []. We use a Blackman-harris window of 2 with 0% overlap and an NFFT of $2^{10} = 1024$. The PSD is then corrected to account for mismatch compression[]. The oscillatory power is then calculated through the median value of the corrected PSD within the adjusted oscillatory within each adjusted oscillatory window.

Artifact corrections The Activa PC+S contains several device-related artifacts. We first take a conservative approach to correcting these artifacts using methods previously published []. Briefly, we take a conservative approach to remove features that are affected by impedance mismatches.

Behavioral and Disease state The behavioral state of each patient at each week in the study is derived from the HDRS17. For each patient, the HDRS17 is normalized to the Within each patient, a linear detrend is done across the HDRS17 to eliminate the large difference between the pre-therapy and end-therapy HDRS17 changes that The resulting value is used for further regression analysis.

The disease state of each patient at each week is a binary value that is derived from thresholding the behavioral state. A value below the response threshold is considered not-depressed, while a value above is defined to be depressed.

Weekly Analysis We assume that both the depression state and the brain state are stationary within any given seven-day period []. State measurements taken in the seven days before each available HDRS are associated with that HDRS measurement. Only measurements taken during daytime hours are used for further analysis to maximize our assumption of stationarity. The weekly state is calculated by finding the feature-wise median across the available recordings. This process yields a single state-HDRS pairing for each patient at each clinical visit.

2.5 Regression Model

Elastic Net We use an elastic net regression approach to learn a linear model linking oscillatory state to depression state []. Nested cross-validation is used, with the two layers corresponding to weekly observations and patients respectively (Figure**??**). Training-set accuracy is reported. The final model is taken from the median coefficient in each of the features.

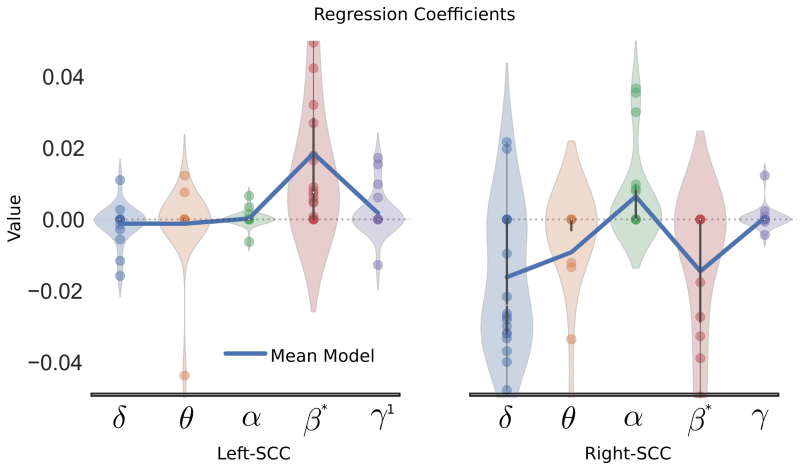

Figure 1: **Cross-validated models learned across SCC oscillations**

Accuracy Validation The accuracy of our model is assessed by computing the Spearman Rank Correlation between our candidate readout and the empirical HDRS17 []. Accuracy is assessed in a non-overlapping validation set of neural recordings taken within the same patients over the same seven months of the study.

Binary Classification Finally, we assess our readouts performance in predicting the binarized depression state. Normalized scores above 0 are labeled 'depressed' while those below are labeled 'not-depressed'. The entire validation set is subsampled (with replacement) 100 times to generate an ensemble of ROC curves.

3 Results

3.1 Oscillatory patterns in SCC correlate with depression

In our training set we learn a set of m=20 models using leave-three-out cross-validation across patients. The final model M_{final} was calculated by taking the mean of each feature's coefficient across folds (Figure**??**). The final model M_{readout} demonstrates that θ and β correlate with depression severity, while α decorrelates with depression severity. While δ and γ coefficients were large in some learned models, their correlation with the data was inconsistent.

Across folds the training-set correlation exhibited bimodality. Low correlations were driven by the inclusion of one particular patient (FigureS**??**).

3.2 Oscillations predict depression state

The final model was validated in a held-out set of recordings from the same patients over the same time period. Validation was done across 100 randomly sampled subsets taken from validation set observations. In each validation trial a Spearman Correlation was computed between predicted depression state and the normalized HDRS17 (Figure**??**a). The same data, when plotted within each patient across their study timeline, visually demonstrates the prediction accuracy (Figure**??**b).

The median prediction accuracy across 100 validation trials was 0.35 (Figure**??**c). The final model M_{readout} was then applied to a held-out validation set of recording. The validation set recordings (r=2000) were randomly subsampled over 1000 times. Prediction was assessed by.

Visual inspection of model predictions demonstrates

3.3 Classification Performance

For each trial of the validation procedure an ROC was computed.

A threshold-based classifier achieves significant performance in classifying 'depressed' vs 'not-depressed'. ROC curves demonstrate performance above chance (Figure**??**). The distribution of AUCs centers at 0.68 (p<?) (Figure**??**).

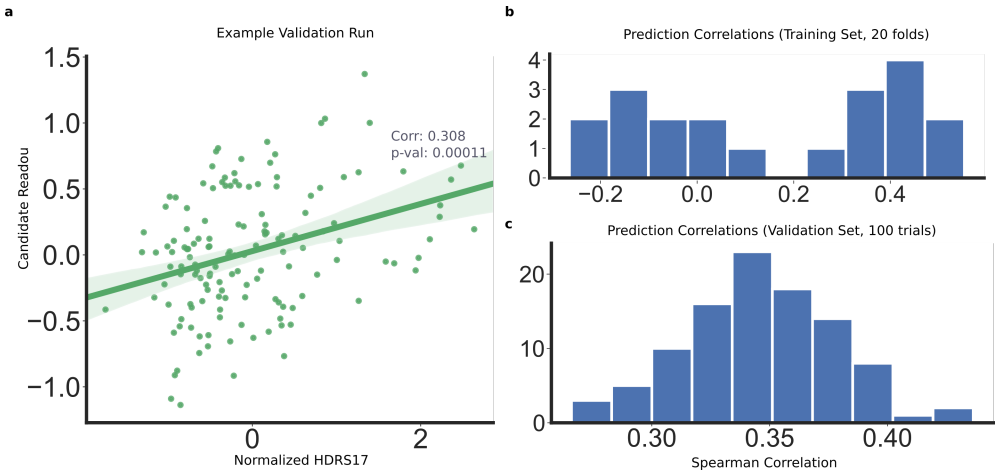

Figure 2: **Prediction Validation** a,

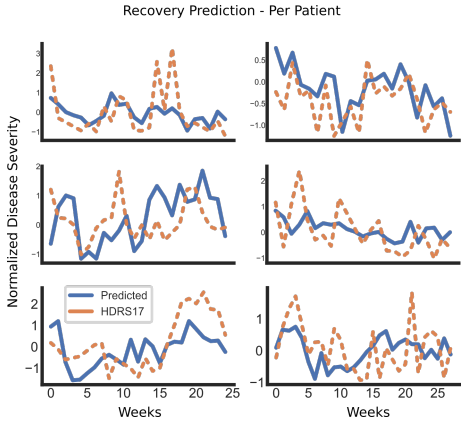

Figure 3: **Example Prediction Trajectories** Predicted vs actual HDRS17 for each of six patients (subpanels).

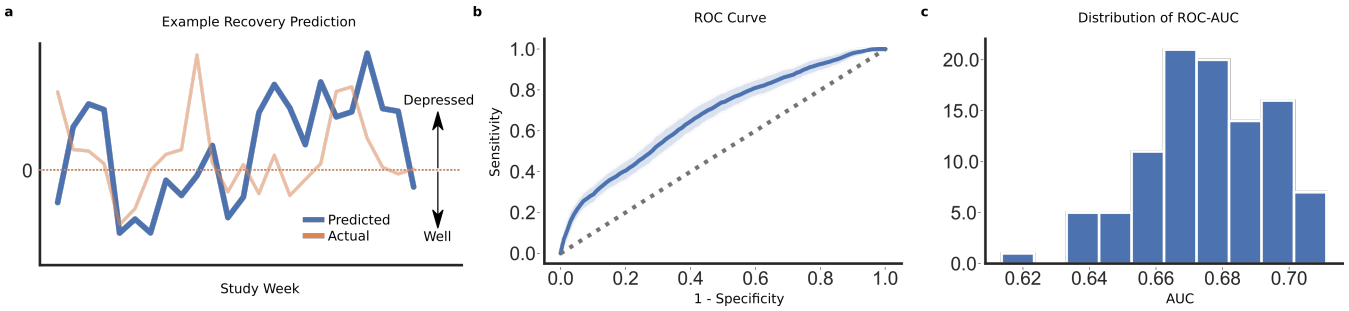

Figure 4: **Receiver-Operator Curves for Threshold Classifier** - a, Example of a prediction trial of patient recovery over 28 weeks. b,

4 Discussion

Long-term monitoring of depression state is critical to rational DBS parameter adjustment and adaptive DBS strategies. In this study we use a novel dataset consisting of clinical LFPs measured in TRD patients treated with SCCwm-DBS. We take a machine-learning approach to learn correlated oscillatory activity and then validate it in a non-overlapping set of observations. The resulting readout model enables an objective readout to monitor treatment efficacy and a preliminary model for aDBS strategies.

4.1 SCC oscillations encode depression

We observed chronic SCC oscillations that correlated with depression state. In training our model we achieved a high training accuracy **??**.

Our candidate readout is able to achieve significant prediction of the depression state when compared to the HDRS17. In the context of a simple threshold classifier, we achieve significant classification accuracy as reflected by AUC-ROC measures. While the correlation is low (35%) this is determined to be reasonable given we are only measuring from bilateral SCC. More probes are needed to measure from other regions known to be a part of the depression brain network []. Additionally, single-week spikes in the HDRS17 may not represent a true return to depression state. Further work is needed to determine whether our readout tracks with newer mood measures that may be more specific to depression symptoms [].

4.2 Important Oscillations

Patterned activity between θ, α, and β dominate our.

Additionally, we found an asymmetry in our model that prioritized oscillatory features from the right SCC. This asymmetry further corroborates previous demonstrations of asymmetryic response to DBS [].

4.3 Limitations

The study has several limitations. One limitation to our ability to predict the depression state to more accuracy may be in the limited recording coverage. Depression is known to involve activity across a distributed set of regions extending beyond the SCC []. Our readout achieved a prediction accuracy of 25%. This is in line with recent demonstrations of semi-chronic recordings across a network of brain regions []. Improving on this prediction performance likely requires chronic recordings across a distributed set of brain regions []. An alternative approach requires improved computational models of the brain network being modulated in order to infer the state of unmeasured brain regions [].

Our study was focused on primary TRD patients with minimal comorbidities. This resulted in a smaller cohort size where heterogeneities introduce challenges in identifying a consistent readout. We observed that the inclusion of certain patients in the training set yielded significantly poorer model prediction (Supplementary Figure**??**). The ultimate model, however, achieved a significant prediction accuracy in this patient, suggesting that individual patients may

5 Conclusion

In this study we identified oscillatory patterns in the SCC that predicted depression state. We use machine learning approaches on a novel set of intracranial recordings dataset spanning seven months of SCCwm DBS for TRD. We found that an asymmetric.

This work provides the first candidate readout signal for a closed-loop DBS device for antidepressant depression.

Further work is needed to improve the ability to predict behavioral states from neural recordings. One important approach relies on recording activity from more of the brain regions known to be a part of the depression network []. Another important step is to develop next-generation recording devices that have better noise profiles, enabling us to record more subtle oscillations that may be missed in our analysis.