Target Engagement in Subcallosal Cingulate Deep Brain Stimulation

Vineet Tiruvadi, *Member, IEEE,* Allison Waters, Ashan Veerakumar, Andrea Crowell, *Fellow, OSA,* Patricio Riva-Posse, *Fellow, OSA,* Robert Gross, Robert Butera, *Fellow, OSA,* and Helen Mayberg, *Life Fellow, IEEE*

***Abstract*—Deep brain stimulation (DBS) of subcallosal cingulate white matter (SCCwm) alleviates symptoms of treatment resistant depression (TRD). SCCwm-DBS, when informed by individualized patient tractography, achieves more reliable efficacy, though the underlying therapeutic mechanism remains unclear. In this paper we characterize the mechanistic effects of SCCwm-DBS on whole-brain oscillations using a novel combination of clinical neural recordings of intracranial LFP and scalp EEG. *Local* changes at the SCC and *remote* changes in other measurable cortex are characterized under precise SCCwm-DBS (ONTarget) against nearby stimulation (OFFTarget). We then develop a non-invasive classifier that can be used to confirm adequate SCCwm stimulation. Our results demonstrate that SCCwm-DBS evokes specific responses only in cortical regions away from the target SCC, supporting the role of tractography-guided implantation. These results enable improved design of clinical trials and a preliminary control model for therapy optimization.**

***Index Terms*—IEEE, IEEEtran, journal, LATEX, paper, template.**

I. Introduction

Deep brain stimulation (DBS) in the subcallosal cingulate (SCC) has shown efficacy in alleviating symptoms of treatment resistant depression (TRD) []. Early studies implemented broad stimulation of the SCC [] but clinical trials failed to show a robust effect []. Newer work further refined the therapeutically critical target to be the four white matter tracts passing through the SCC: uncinate fasciculus, forceps minor, cingulum bundle, and thalamic projections []. Subsequent targeting of these tracts using patient-individualized tractography resulted in improved outcomes []. A clearer understanding of where and how SCCwm-DBS effects its influence is needed to improve antidepressant therapy.

DBS is thought to effect immediate modulation of a network of brain regions [] but it remains unclear whether the region immediately adjacent to the electrode is modulated (local), whether regions downstream of white matter tracts are modulated (remote), a combination of both, or neither. Recent investigations have demonstrated direct modulation of α under DBS in PD []. The mechanistic effects of SCCwm-DBS must be clarified in order to develop control strategies that evoke healthy brain states []. Understanding the therapeutic mechanism of action of SCCwm-DBS first requires a clearer model of its immediate mechanistic effects. Specifically, whether therapeutic DBS immediately engages *local* SCC activity, *remote* cortical activity, a combination of both, or neither.

In this report we characterize the immediate, direct effects of SCCwm-DBS using multimodal clinical neural recordings. We demonstrate that SCCwm-DBS evokes specific cortical oscillatory changes that are not evoked by broader SCC stimulation. We then develop a classifier capable of accurately confirming stimulation of the SCCwm using EEG recordings. This work provides preliminary models of the mechanistic effects of SCCwm-DBS and an open-source classifier for non-invasive confirmation of target engagement.

M. Shell was with the Department of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA, 30332 USA e-mail: (see http://www.michaelshell.org/contact.html).

J. Doe and J. Doe are with Anonymous University.

Manuscript received April 19, 2005; revised August 26, 2015.

II. Methods

A. Regulatory and patient enrollment

Patients were enrolled into a research protocol at Emory University testing the safety and efficacy of SCC DBS for TRD. (clinicaltrials.gov NCT00367003) (Table **??**). Four consecutive patients were analysed for this study. Written informed consent was provided by each patient to participate in the study and the study protocol was approved by the Emory University Institutional Review Board and US Food and Drug Administration under an investigational device exemption (G060028). The study was continuously monitored by the Emory University Department of Psychiatry and Behavioral Sciences Data and Safety Monitoring Board. Patients were recruited based on strict inclusion and exclusion critera (described in [**?**]).

B. Tractography and Implantation

The target brain structure is the subcallosal cingulate white matter (SCCwm) [] which is identified using individualized traactography [].

Two DBS leads (Medtronic 3387) were implanted, each with four $1.5\,\mathrm{mm}$ electrodes spaced $1.5\,\mathrm{mm}$ apart. One of the middle two electrodes on each lead was used to implant at bilateral SCCwm targets.

C. Experimental Setup and recordings

a) LFP recordings: Differentially recorded local field potentials (LFPs) are captured using the Activa PC+S system (Medtronic). Channels are recorded by measuring from two electrodes immediately adjacent to the stimulating electrode (Figure**??**). SCC-LFP recordings are sampled at 422Hz and hardware bandpassed at 0.5Hz - 100Hz.

b) EEG recordings: EEG was acquired using a 256-channel EGI system (DETAILS). Recordings were sampled at 1 kHz with a 100 Hz lowpass filter and a 2 Hz highpass filter. dEEG recordings are taken using (REFERENCING SCHEME) sampled at 1000Hz and digitally bandpassed at 1Hz - 50Hz. dEEG recordings are locally re-referenced to their neighbors (Supplementary A) to avoid global operations on data and keep our results as congruent with intraoperative limitations as possible.

c) Stimulation: Stimulation location was selected between *OnTarget* and *OffTarget*. OnTarget is defined as bilateral stimulation at the electrodes places closest to the SCCwm targets. OffTarget is defined as bilateral stimulation at the electrodes 3mm towards the center of the DBS electrode array. OffTarget is defined as such in order to allow for simultaneous recording and stimulation using the Activa PC+S DBS device. All other stimulation parameters are kept constant at 6 mA amplitude, 130 Hz frequency, 90 µs pulsewidth, monopolar. The effect of stimulation on both LFP and EEG recordings was assessed (Figure S**??**).

d) Experiment: Two epexier Experiments are done one month after surgical implantation. In this study, we performed a *targeting experiment* where two target combinations are implemented with simultaneous LFP and EEG recordings. A single recording session consisted of 16 min with three stimulation configurations. In this report, we focus only on the bilateral stimulation condition.

D. Preprocessing and Oscillatory Response

a) Filtering and Preprocessing: dLFP recordings are

Hardware filters on the dEEG recordings are set at 100 Hz low-pass filtering Further analytical filtering is done as a part of preprocessing. First, recordings are bandpass filtered at 1 Hz and 50 Hz.

dLFP is preprocessed to remove the effect of stimulation-related gain compression []. The oscillatory state is then extracted by identifying the median oscillatory power within adjusted oscillatory bands. EEG is preprocessed using a lowpass filter, automatic artifact removal [], and global re-referencing. Stimulation artifacts were sufficiently attenuated using hardware filters in the dEEG recordings. One recording... After both preprocessing pipelines, oscillatory state is extracted using fourier-based techniques. First, recordings are segmented into 2 second segments before each segment is tranformed into the frequency domain using a Welch estimator of the power spectral density (PSD). Oscillatory band power is extracted by computing the area under the curve of the PSD for each segment. Oscillatory states are then binned according to the stimulation condition. before the median state is computed for further analyses.

b) Oscillatory Response: Oscillatory states are calculated by finding the median PSD value within predefined oscillatory band ranges. Band ranges are adjusted to avoid device artifacts **??** and applied uniformly across LFP and dEEG measurements.

Oscillatory states are calculated for both pre-stimulation and peri-stimulation epochs. The oscillatory state change, or *reponse*, is calculated by subtracting the pre-stimulation state from the peri-stimulation state $\Delta\theta = \theta_{\text{peri}} - \theta_{\text{pre}}$.

c) Quality Assessment: The quality of the resulting data is assessed. Stimulation artifacts are strongly attenuated and the resulting signal in the low-frequency bands being analysed do not demonstrate distortions. ONTarget and OFFTarget response PSDs exhibit. Distributions of responses are pooled across channels to determine if OnTarget and OffTarget stimulations elicit the same response. A Kolmogorov-Smirnoff test is used to assess the difference in distributions.

E. Response Characterization

1) Observation Pooling: After responses are characterized within each patient's ONTarget and OFFTarget conditions. Median oscillatory responses in each channel are characterized across patient-pooled observations. An estimate of the oscillatory response is calculated using Jackknife resampling. The oscillatory response is calculated separately in each oscillatory band, yielding a final oscillatory response estimate $\theta_i \in R^{256}$ for both ONTarget and OFFTarget. The estimator distribution is compared between ONTarget and OFFTarget to establish specificity of the ONTarget response.

F. Target classifier

a) Training and Validation: We learn a linear support vector machine (SVM) that is capable of accurately identifying stimulation at the SCCwm using only EEG oscillatory responses. A binary classification is performed using the ONTarget and OFFTarget observations. Per-patient, per-session baseline-corrected responses are divided into 2 sec segments. Response segments are concatenated across all n=4 patients, yielding approximately o=600 observations. The total set of segments are split into training (20%) and testing (80%) sets. 10-fold CV was used to learn the SVM classifier within the training set and then applied over 1000 iterations to subsets of the testing set.

We developed a support vector classifier (sklearn.SVC) to perform a binary classification between ONTarget, and OFFTarget conditions. Each segment consisted of a $256x5$ feature vector. L1 regularization was used to promote sparsity in the learned model. Training curves were used to identify the optimal size for the training set. 100 SVC models are learned and the resulting model's performance is assessed in a *validation set* with the performance measure being accuracy. Errors are assessed through the confusion matrix. Model parameters are analysed using robust principal component analysis (rPCA), an approach that is robust to artifactual recordings in both time and in a particular channel.

b) Classifier Coefficients: Statistical validation of our coefficients is done in two ways. First, we use a cross-validation approach to the statistical significance of our coefficients. We assess performance of our model in all folds, and then report the final application of the classifier to the validation sets. Finally, we construct a simulated null hypothesis by randomly shuffling the stimulation labels with respect to their observed EEG states and report performance of our classifier. The coefficients of the learned SVM are then used to identify the

most informative EEG channels. Coefficient distributions for each oscillatory feature are computed and channels where at least one coefficient is in the upper 90% are labeled as *active* and included in the empirical mask.

G. Code and Data availability

Code is available opensource at github.com/virati/X. Clinical datasets can be made available upon request to corresponding author.

III. Results

A. Stimulation evokes only remote response

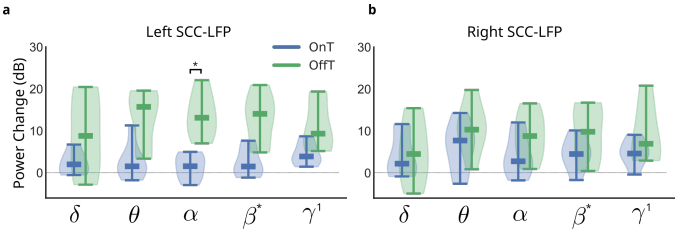

Fig. 1. **Stimulation response measured at SCC-LFP** across all n=6 patients. a, Average left SCC-LFP change from baseline under ONTarget (blue) and OFFTarget (green). b, Right SCC-LFP oscillatory changes. Statistical significance is defined as p¡0.005, signified with a star (*).

a) Local measurements at LFP: No significant oscillatory changes are measured under ONTarget stimulation (Figure1a,b blue). Significant changes are observed under OFFTarget stimulation (Figure1a,b green). The only statistically significant difference between ONTarget and OFFTarget stimulation occurred in the left α oscillatory band (p¡0.005).

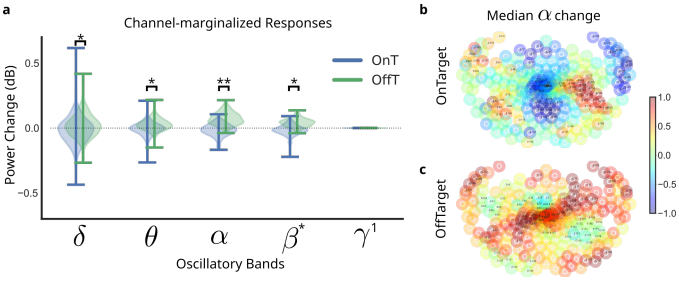

Fig. 2. **Stimulation response measured at scalp EEG** across all patients. a, Channel marginalized distribution of oscillatory changes under ONTarget (blue) and OFFTarget (green) stimulation. b, Spatial pattern of α changes under ONTarget and c, OFFTarget.

b) Remote measurements at EEG: EEG recordings measured significantly different responses between ONTarget and OFFTarget stimulation (Figure2 a). Channel-marginalized differences were significant for all oscillatory bands (p¡0.01) with the α band demonstrating the largest signal (Figure**??**).

c) α Response: The largest differential response between ONTarget and OFFTarget were found in α oscillations.

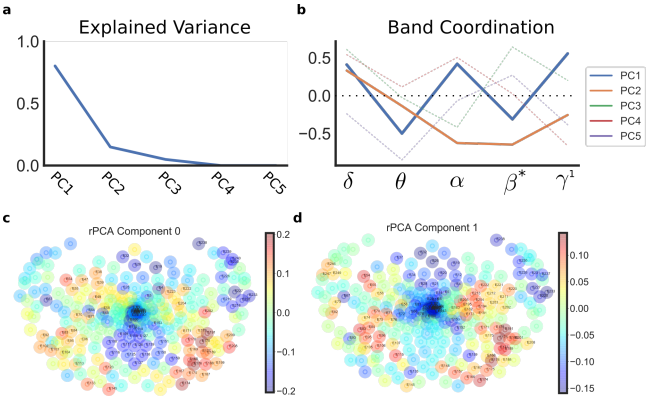

Fig. 3. **Cortical response modes** to SCCwm-DBS. a, rPCA identifies two significant correlation patterns in our data, called *response modes*. b, The top two PCA components exhibit patterns of oscillatory activity. c, The primary response mode exhibits asymmetrical activations in midline, right parietal, and right temporal channels. d, The secondary response mode exhibits symmetric activations about the midline in parietal, temporal, and frontal channels.

B. Stimulation effects two modes of control

a) Primary Mode: Robust dimensionality reduction on the full oscillatory response demonstrates two dominant control modes. The first mode accounts for 85% of the total variance. Oscillatory coordinations exhibit correlated δ, α and γ^1 activity. Anticorrelated to those oscillations is the θ and $\beta*$ activity. This pattern is found predominantly in the right hemisphere, with the positive pattern being found in EEG channels over the parietal cortex and negative pattern being found over the temporal and midline channels.

The second mode accounts for 10% of the total variance. This mode consists primarily of δ oscillations with anticorrelated θ, α, $\beta*$ and γ^1. This pattern is found symetrically about the midline, primarily in parietal and midline channels.

C. High accuracy classifier for SCCwm-DBS

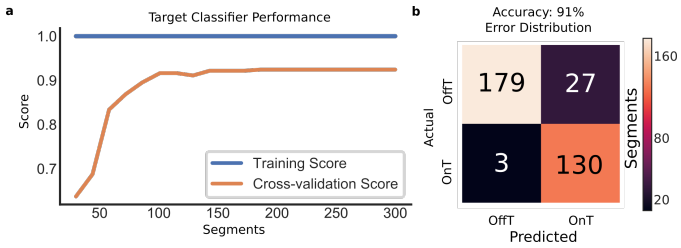

Fig. 4. **EEG-based Targeting Classifier** across all segments and patients. a, Training curve demonstrates plateau at approximately 30% of the training set. b, Example classifier prediction on validation set achieves high accuracy.

a) Classifier Training: A learning curve computed on the entire dataset demonstrated rapid learning up to approximately 30% of the dataset, achieving approximately 90% accuracy. Notably, the training score does not decrease, suggesting the utility of larger datasets. The set of all observations was split into five groups (o=45 observations per group). The first four groups were used to learn a cross-validated model M_{final} (Figure**??**).

b) Classifier Validation: Validation was done over 100 trials randomly subsampling with replacement from the validation set. The resulting accuracy was X%.

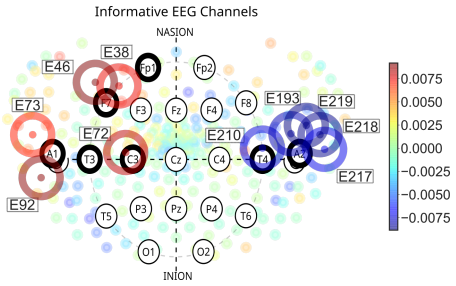

Fig. 5. **Most informative channels in EEG Classifier** Channels with the most energy in the coefficients of the SVM across all oscillatory bands. Laterality and asymmetry can be seen.

c) Key EEG channels: The most informative channels are in the right and left temporal and parietal regions.

The importance of channel-specific coefficients is assessed from our final model M_{final} The distribution of coefficient energies across channels demonstrates clustering (Figure**??** histogram of channel energies). The most informative EEG channels consisted of those in (Figure**??** EEG topomap of best channels)

IV. Discussion

We've provided the first quantitative characterization of the mechanistic effects of SCCwm-DBS. Using a combination of intracranial and scalp recordings we've identified oscillatory changes specific to SCCwm-DBS. This provides evidence that DBS precisely targeted at individualized tractography evokes specific changes to neural dynamics that may be necessary for long-term therapeutic response. Our observations are used to identify patterns of coordinated oscillatory responses and to train/validate an EEG classifier.

We first observe changes in the SCC-LFP under SCCwm-DBS. No significant oscillatory changes are observed across all four patients.

A major limitation of our study is the limited patient sample size. Our reliance on field potentials is another limitation as certain activity is not measurable using field potentials [].

A. SCCwm-DBS engages only remote, not local, elements

The immediate electrophysiologic effects of DBS remain poorly characterized. In particular, whether DBS directly modulates the gray matter adjacent to the stimulating electrode or whether it modulates white matter tracts passing by the electrode remains unclear. In this study we used a novel combination of clinical neural recordings to clarify the network action of SCCwm-DBS. We found that DBS at the SCCwm evoked a specific response characterized only by changes in *remote* measurements across scalp and not *local* measurements at the SCC. Hypermetabolic activity in the SCC that was correlated with depression were originally thought to be directly downregulated by DBS. Our results remain consistent with these observations. Immediate modulation of a network of brain regions is unlikely to alleviate depression. Instead, depression arises from network activity and network activity.

Our observations were consistent with previous demonstrations that DBS predominantly evokes changes in α oscillations []. We further characterized the interplay between oscillations using dimensionality reduction techniques and found several *control modes* evoked by SCCwm-DBS.

The metabolic activity of the SCC is known to change with depression state over months []. While we see no immediate changes in the SCC-LFP under SCCwm-DBS, this does not preclude long-term SCC-LFP changes. Depression is by definition a slow-changing disease and we did not assess the long-term changes in EEG responses. Chronic changes are likely mediated by plastic changes in multiple distributed brain networks, requiring more nuanced analytical approaches and recording hardware.

The universal lack of response under SCCwm-DBS was striking given the variable response evoked by stimulation just $1.5\,\text{mm}$ away.

B. SCCwm-DBS evokes spatial patterns of coordinated oscillatory changes

a) α modulation: DBS has been shown to modulate α oscillations [], which are anticorrelated with inputs into a measured brain region. Our observations support the hypothesis that DBS disrupts signaling and decreases the inputs into a brain region []. Consistent between ONTarget and OFFTarget stimulation is the presence of large α power changes []. The differential response is in the location of the α increases.

b) Coordinated Responses: α doesn't change alone, however, and DBS is found to evoke coordinated changes in oscillatory activity. ONTarget stimulation evokes coordinated changes across oscillatory bands (Figure**??**). Two coordination patterns, or *modes*, are effect by SCCwm-DBS.

We find that SCCwm-DBS evokes two distinct oscillatory patterns (Figure**??**). The first pattern accounts for a large portion of the evoked response (Figure**??**). The second pattern accounts for a smaller, but still significant, portion of the evoked response (Figure**??**). Our observation of these two patterns provides a clearer idea of how SCCwm-DBS influences the brain's oscillatory state and provides a clearer idea of the *control modes* SCCwm-DBS is capable of.

Computational investigations into DBS mechanism have identified synchronization changes as the primary effects of stimulation [**?**].

C. Target engagement classifier achieves high performance

EEG oscillations were significantly different between stimulation at the target SCCwm and stimulation just $1.5\,\text{mm}$ away. This suggests the specificity of

We learned a single classifier capable of differentiating recordings taken from all patients. This reflects the large signal-to-noise ratio of the cortical response to stimulation. It also reflects the strong consistency of this signal across patients with different tractography, different medications, and different backgrounds.

Importantly, we find that accurate classification can be achieved using just EEG measurements. While SCC-LFP has been shown to reflect depression state [] it's unlikely

D. Limitations

The study has several overall limitations. First, the functional connectivity map used to determine second-order nodes is based on a healthy subject set while studies have shown functional connectivity in depressed patients can be different [] and variable []. Second, the support models using simple euclidean distances to forward project the tractography-mediated EEG changes may be overly simplified. This could lead to EEG channels being included that should not be, reducing the effective difference between primary and secondary EEG channels. Third, while we were able to demonstrate strong generalizability of our classifier to unseen data, the model itself may still be overfit to the patients in this study. Generalizability to broader patient cohorts must be assessed and our code is provided open-source to facilitate this among the community. The heterogeneity of our patients suggests that the effect we are capturing is large and consistent if stimulation is delivered consistently to the SCCwm.

We observed large changes in SCC-LFP under OFFTarget stimulation which cannot be explained using the data in this study. Further work is needed to combine multimodal electrophysiology with precise tractography and stimulation volume modeling to determine the underlying.

V. Conclusion

In this study we demonstrated that SCCwm-DBS elicits a specific oscillatory response in whole-brain oscillations.

First, precise targeting of the SCCwm achieves a measurably different EEG response. This suggests that individualized connectomics can induce a specific state in the brain. Further study is needed to determine whether that specific state is associated with long-term therapeutic efficacy. Second, our development of a classifier is a first step towards achieving intraoperative parameter optimization using objective oscillatory measures of brain state. Third, our identification of the therapeutic mechanism of action as a desychronization mediated by white matter tracts suggests alternative targets and actuation directions. For example, direct transcranial α drive of parietal and right-temporal regions may elicit similar desynchronizations without the need for implanted electrodes.

Acknowledgment

The authors would like to thank Dr. Allison Waters for assistance in EEG collection. Sinead Quinn and Lydia Denison for assistance in.

VI. Supplementary

A.

B.

References

[1] H. Kopka and P. W. Daly, *A Guide to LaTeX*, 3rd ed. Harlow, England: Addison-Wesley, 1999.

Fig. 6. **Computed PSDs for EEG Segments** a, Median PSD across segments for each patient

PLACE PHOTO HERE

Michael Shell Biography text here.

John Doe Biography text here.

Jane Doe Biography text here.