



University of California
San Francisco

Striato-limbic Beta Power is Associated with Diurnal Variation and DBS-induced Arousal in Patients with Severe OCD

Bianca De^{1*} BS, Joline Fan^{2*} MD, Genevieve Basich-Pease³ BA, Andrew Krystal³ MD, A Moses Lee MD PhD³
School of Medicine¹, Department of Neurology², Department of Psychiatry and Behavioral Sciences³, University of California San Francisco, *contributed equally

Background

Deep brain stimulation (DBS) treats severe, refractory OCD using electrodes to deliver current to the anterior limb of the internal capsule (ALIC) and neighboring striato-limbic structures: caudate, bed nucleus of the stria terminalis (BNST), and hypothalamus. Transient hypomania is the most common side effect. Treatment can be activating and is associated with sleep disruption. New DBS systems can record local field potential (LFP) signals from implanted electrodes. Feedback algorithms in adaptive closed-loop DBS could use these signals to dynamically adjust stimulation parameters.

We aim to identify electrophysiological biomarkers of sleep-wake diurnal variation and arousal for development of closed-loop control systems that can minimize risk of hypomania, sleep disruption, and excessive activation. We hypothesized that biomarkers may be present in beta-band activity because it is associated with states of arousal on EEG.

Methods

Subjects: Four subjects with severe, refractory OCD treated with DBS targeting the ALIC and BNST (leads 3387 or 3391; Medtronic, Minneapolis, MN) using the Percept PC system (Medtronic, Minneapolis, MN), the first FDA HDE-approved DBS device that records LFP signals. Electrode localization was visualized using the open-access toolbox Lead-DBS for co-registration and normalization of pre- and post-operative MRI.

LFP Diurnal Regression: Bilateral LFP beta power was recorded in Brainsense Timeline mode, which averages the power in a 5Hz frequency band in 10-minute intervals. To minimize stimulation artifact, data from actively stimulating leads was not used. Outliers were removed, and the signal was smoothed and detrended by normalizing over 24-hour periods. All data for each lead was plotted against 24-hour clock time. Linear regression with sinusoidal time term was used to fit a sine curve with 24-hour period to the data.

$$\text{Normalized LFP Power} = A * \sin\left(\frac{24}{2\pi}(t - B)\right)$$

DBS Arousal Analysis: 2 subjects rated their energy (VAS-Energy) and sleepiness (Stanford Sleepiness Scale) every 3 minutes as stimulation was toggled between 5 and 6 mA. LFP signals from the stimulating and sensing electrode were recorded in Brainsense Streaming mode, which samples at 250Hz. The short-term Fourier Transform and Hilbert Transform were calculated, and spectral power was normalized to the baseline low-stimulation segment. Principal component analysis was used to determine the relationship of behavioral scores to stimulation and spectral power.

Results

-In long-term recordings from bilateral leads, striato-limbic beta power shows statistically significant diurnal variation, with daytime increase and nighttime decrease consistent with waking/sleeping hours. Sinusoidal regression coefficient $p < 0.0005$ in all leads (Fig 2)

-Increased arousal scores indexed by the VAS-energy and Stanford Sleepiness Scales were significantly associated with ALIC DBS and increased in beta power (Fig 3, Fig 4)

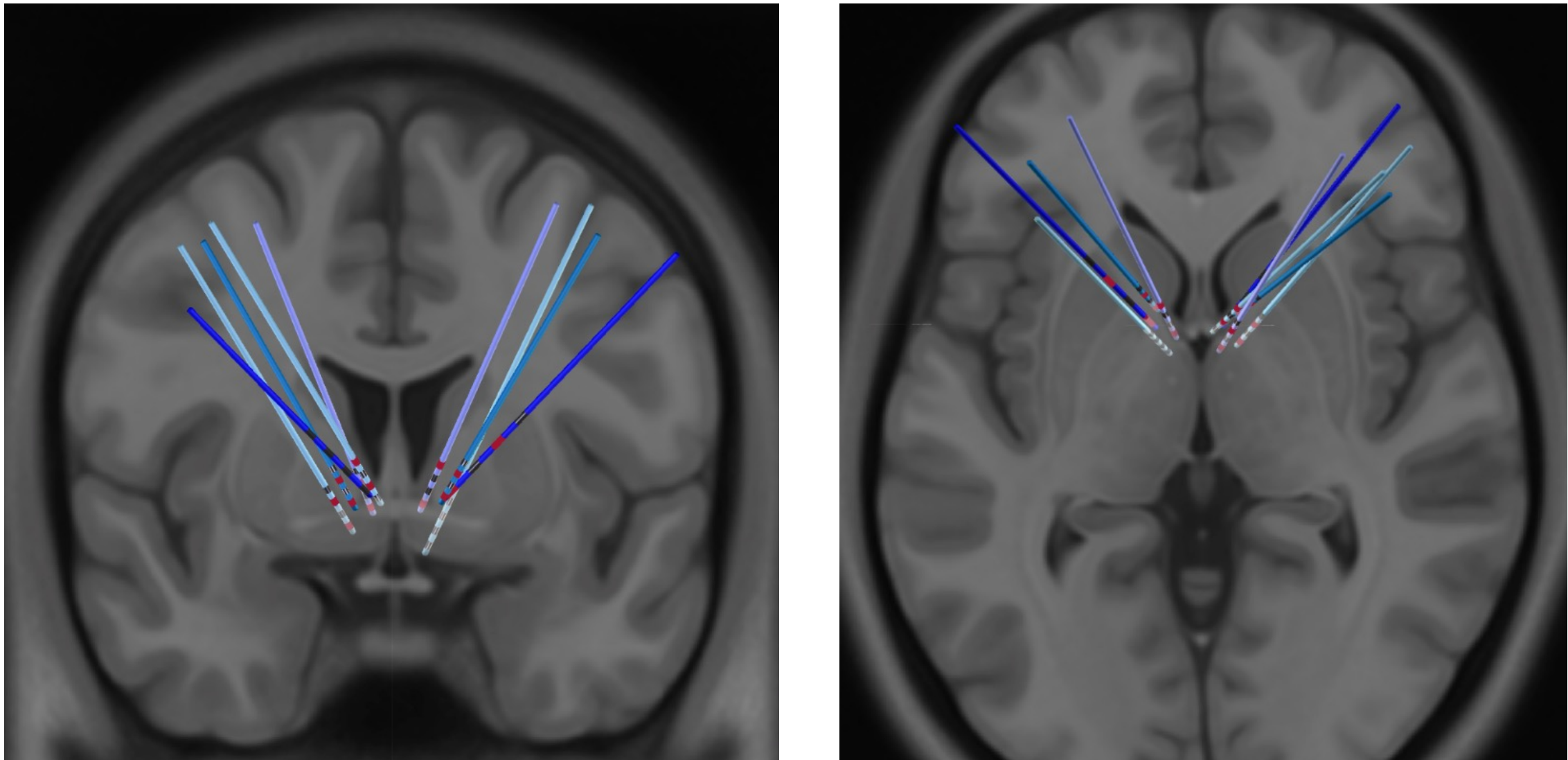


Figure 1. Location of DBS electrodes in 4 subjects across 7 bipolar recording sites in coronal (top) and axial (bottom).

Subject (Lead)	Center Frequency (Hz)	Recording Duration (days)	Electrode Type	Active Lead Stimulation (mA)	Sinusoidal Amplitude Coefficient A	Phase term B (hr)
OCD1 (R, pre*)	25.39	50.22	3387	6-7.5	0.62	-10.03
OCD1 (R, post*)	25.39	7.11	3387	0	0.58	-9.14
OCD2 (R)	25.39	60.88	3387	0, 7, 9	0.40	-5.33
OCD2 L)	25.39	35.98	3387	0	0.62	-5.48
OCD3 (R)	25.39	3.49	3387	0	0.55	-11.99
OCD3 (L)	25.39	3.49	3387	0	0.53	-10.42
OCD4 (L)	32.23	16.78	3391	6.5	0.69	-9.94

Table 1 Details of LFP Timeline recording and sinusoidal regression by subject. *OCD1 recordings before and after the right electrode was repositioned were analyzed separately

References

-Denys, D. et al. Efficacy of Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Refractory Obsessive-Compulsive Disorder: A Clinical Cohort of 70 Patients. Am. J. Psychiatry 177, 265–271 (2020).
-Greenberg BD, Gabriels LA, Malone DA Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry 2010; 15:64.
-Horn, A., Kühn, A. Lead-DBS: A Toolbox for Deep Brain Stimulation Electrode Localizations and Visualizations. NeuroImage (2014).

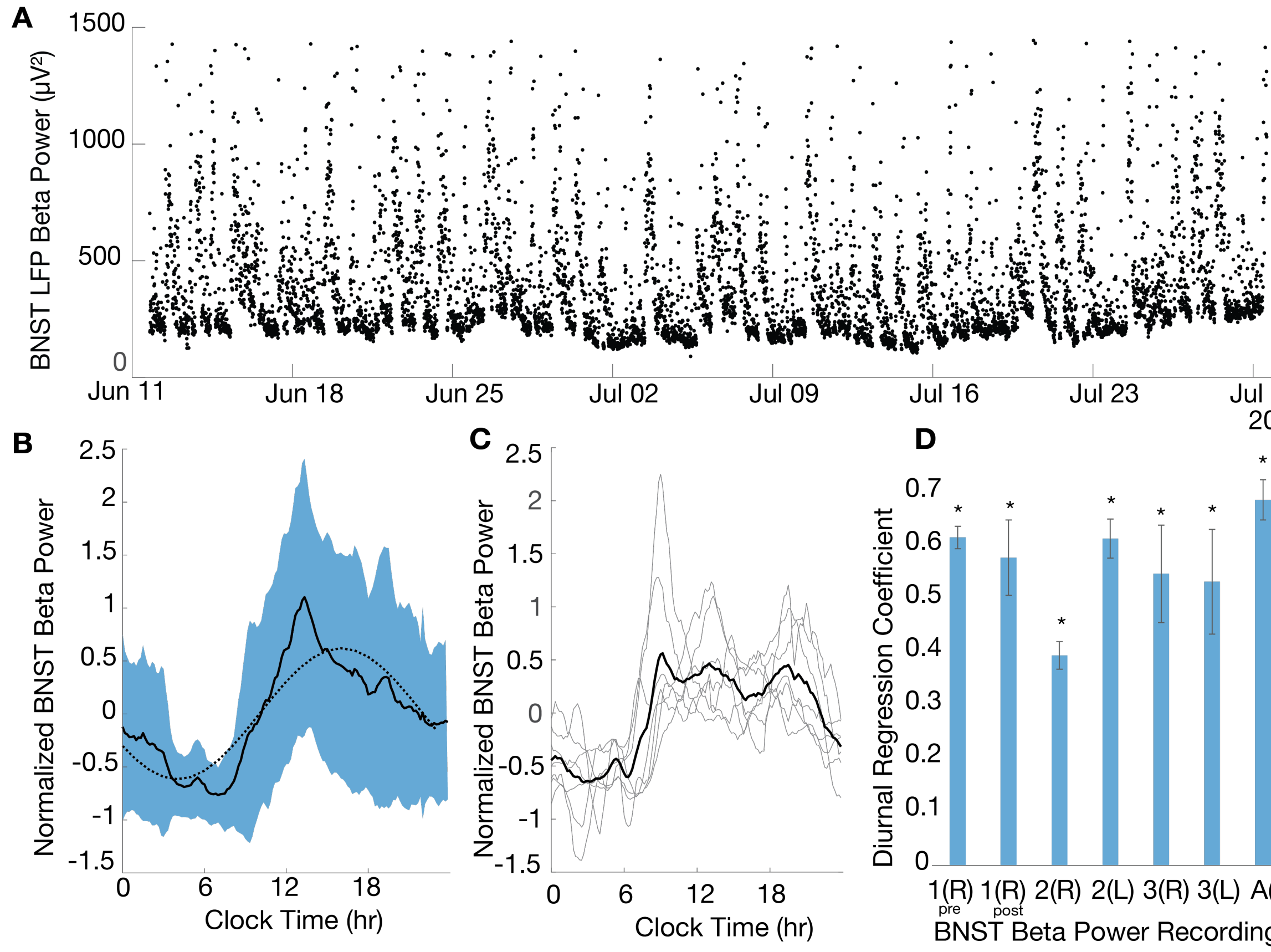


Figure 2. Striato-limbic Recordings Demonstrate Diurnal Variation in Beta Power: A) Example 7-week continuous timeline mode recording from subject OCD1 shows power in the $25.39 \pm 2.5\text{Hz}$ frequency band averaged over 10-minute intervals. B) Example OCD1 beta power vs. clock time. Solid line represents average z-scored power by clock. Shaded region represents $\pm$ std. Dotted line shows sinusoidal regression fit. C) Average striato-limbic beta power vs. clock time for each recording electrode (thin grey lines) and average beta power across recording electrodes (black line). D) Diurnal regression amplitude coefficients in each subject for mean striato-limbic beta power vs. clock time

Figure 3. Example of changes in arousal and striato-limbic activity with left ALIC DBS.

A) Changes in arousal over 40 minutes of continuous LVC stimulation at 130Hz for OCD1. Yellow boxes indicate high stim (6mA) vs low stim (5mA).

B) Spectrogram of L striato-limbic recording with L ALIC DBS. Spectral power is represented by the z-score to the initial baseline.

C) Spectrogram at R striato-limbic recording site with L ALIC DBS as in B.

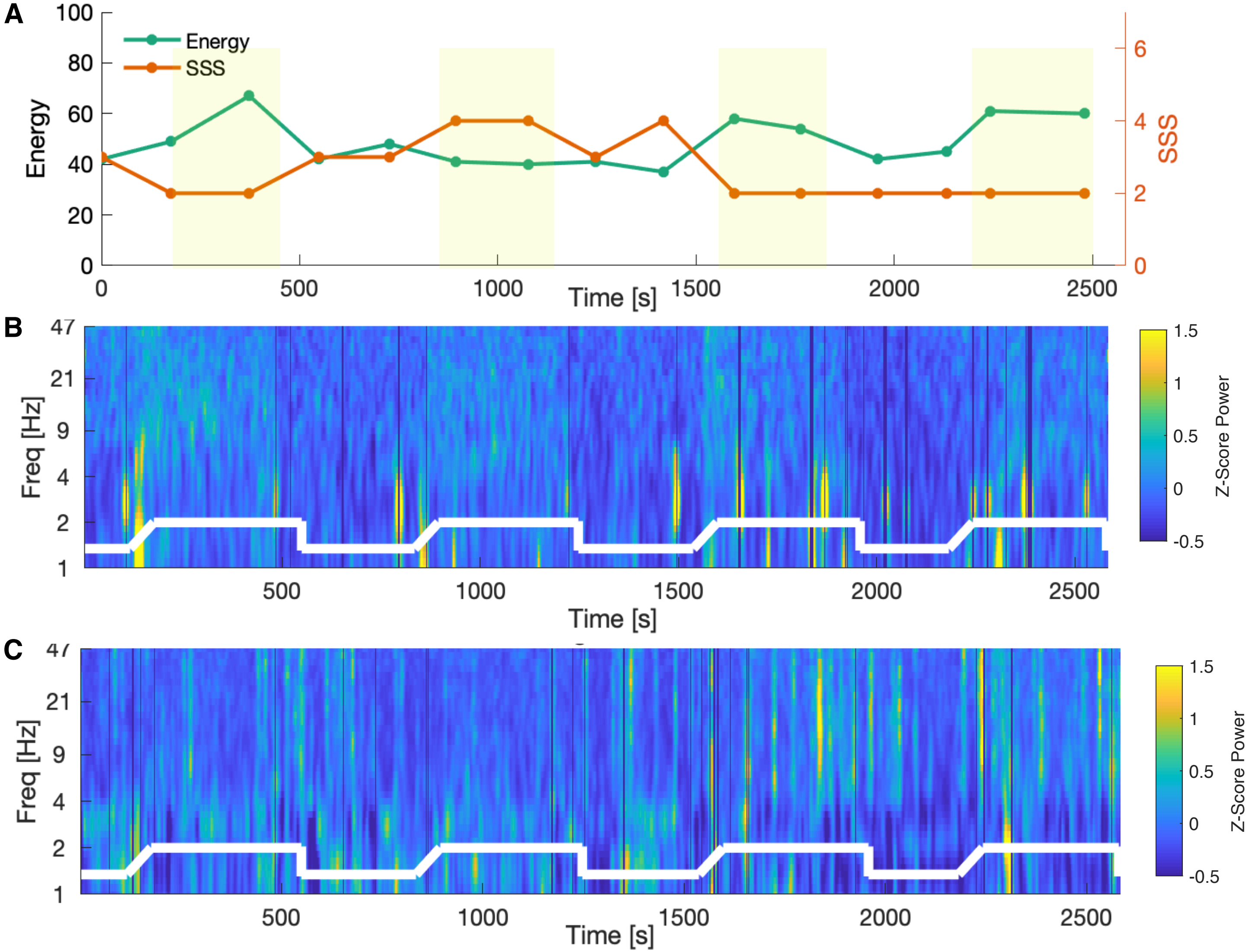
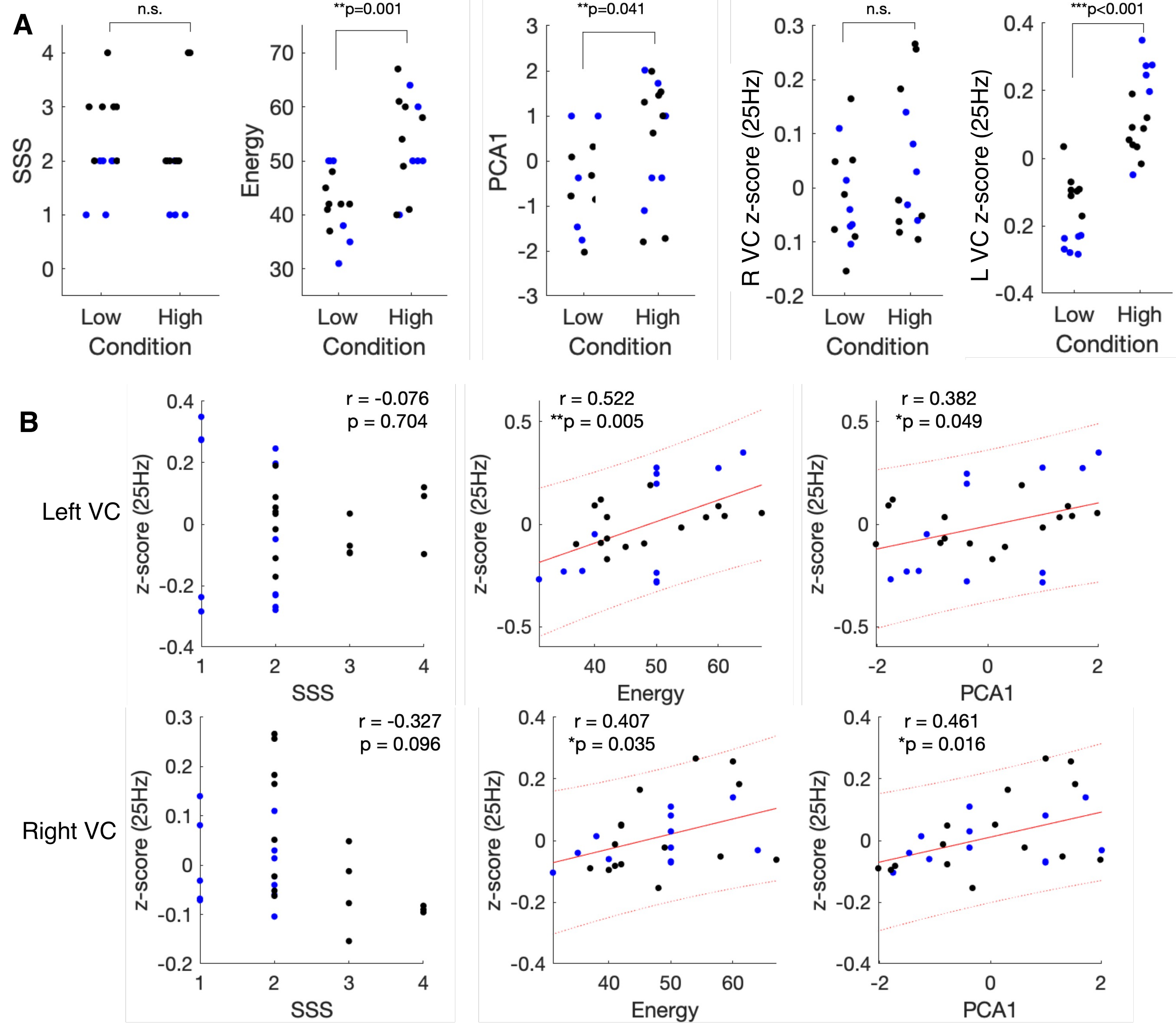


Figure 4. Stimulation, beta-band spectral power, and behavioral scores across two subjects.

A) Changes in SSS, VAS-E, PCA of SSS/VAS-E, and z-scored spectral power within the beta band in right and left lead relative to low and high L ALIC DBS across OCD1 (black dots) and OCDA (blue dots). Significance determined by Wilcoxon rank sum test.

B) Scatter plots demonstrating the relationship between z-scored beta band spectral power and behavioral scores (SSS, VAS-E, and PCA) across patients. Linear regression is performed across patients with Pearson's correlation denoted. Top panel is beta power from left striato-limbic recording site. Bottom panel is beta power from right striato-limbic recording site.



Discussion

-This study shows **significant diurnal fluctuation in striatolimbic beta power** and suggests that **it could be used as a biomarker for arousal and the sleep-wake cycle**.

-Closed-loop DBS algorithms that incorporate striato-limbic beta power fluctuations in development of feedforward and feedback systems may minimize risks of sleep disruption and mania, known adverse effects of DBS for OCD.

Future Directions

-Collect sleep, mood, and OCD symptom diaries and wearable data to study correlation with BNST beta power and characterize variation in individual patterns of diurnal fluctuation.

-Develop closed-loop methods to enforce circadian patterns of arousal with stimulation to help promote natural sleep-wake pattern.

-Investigate whether DBS can be used to treat other disorders of sleep-wake cycles such as excessive daytime sleepiness.