

# **First in Human Evidence of Ibogaine's Effects on Neural Oscillations and Complexity in Veterans with Traumatic Brain Injury**

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## Abstract

Traumatic brain injury (TBI) can lead to chronic psychiatric and cognitive symptoms, coupled with changes to the nature of cortical oscillations and neural complexity. Treatment with ibogaine was recently found to improve the sequelae of TBI, yet the effects of ibogaine on human cortical oscillations and complexity are unknown. Resting-state electroencephalography (EEG) was performed prospectively before, 3.5 days after, and one month after ibogaine treatment in an observational, open-label study of 30 combat veterans. We assessed the effects of ibogaine on cortical oscillations and complexity, and how these neurophysiological effects relate to psychiatric and cognitive outcomes of ibogaine treatment. After treatment, slower oscillations (theta-alpha) increased in power, and power at higher frequencies (beta-gamma) decreased. Accordingly, theta/beta ratio increased post-treatment, which correlated with improved cognitive inhibition. Peak alpha frequency and neural complexity were lower after treatment, which persisted at one-month follow-up. These neurophysiological markers correlated with improved executive function, PTSD, and anxiety after ibogaine. Altogether these findings suggest reduced spatiotemporal complexity of brain activity and ‘slowing’ of cortical oscillations in the brain at rest after ibogaine treatment, which may relate to psychiatric and cognitive improvements after ibogaine, thus providing key insight into the effects of ibogaine on brain function in humans. Follow-up controlled clinical trials are needed to confirm the findings from this initial single-arm trial.

Traumatic brain injury (TBI) can lead to a host of psychopathologies, including but not limited to post-traumatic stress disorder (PTSD), depression, anxiety, and cognitive impairment<sup>1,2</sup>. First-line treatments are ineffective for many individuals who suffer from TBI-related symptoms<sup>3,4</sup>. Ibogaine, an oneirogen derived from the *Tabernanthe iboga* shrub, is a promising alternative treatment for the psychiatric and cognitive sequelae of TBI. Improvements in day-to-day function, cognitive function, and PTSD, depression and anxiety symptoms were recently observed after a single ibogaine treatment in veterans with a history of TBI, with effects persisting for at least one month<sup>5,6</sup>. Despite its therapeutic potential, the effects of ibogaine on human brain function remain largely unknown.

Cortical oscillations and neural complexity are important dimensions of brain function that appear to be perturbed after TBI<sup>7-12</sup>. Neural activity commonly manifests as changes in brain rhythms, i.e. cortical oscillations, that represent the large-scale interactions among many neurons. Cortical oscillations and the complexity of cortical activity serve as markers of different brain states, such as high or low arousal/alertness<sup>13-17</sup>. Electroencephalography (EEG) studies have identified an association between TBI and diffuse slowing of cortical oscillations, including findings of elevated low-frequency (delta and theta) power and theta/beta ratio, and reduced alpha power<sup>7-11</sup>, as well as reduced neural complexity<sup>12</sup>. Similarly, common sequelae of TBI, such as symptoms of PTSD, depression and anxiety, have been associated with abnormal cortical oscillations and neural complexity<sup>18-21</sup>.

Understanding how cortical oscillations and neural complexity are engaged alongside improving TBI-related symptoms after ibogaine treatment is important for establishing the neurophysiological mechanisms of this promising rapid treatment. Preliminary evidence from rodent studies suggests that the administration of ibogaine can acutely decrease neural complexity and influence oscillations across delta to gamma frequency bands<sup>22-24</sup>, for example increasing theta and gamma power. However, the effects of ibogaine on human cortical oscillations and complexity have not yet been quantified. Classic psychedelic drugs, such as psilocybin, lysergic acid diethylamide (LSD), and N,N-Dimethyltryptamine (DMT), have shown utility in treating psychiatric disorders like depression<sup>25</sup>, and have also shown acute effects on cortical oscillations and complexity in healthy adults, such as increases in global Lempel-Ziv

complexity and reductions in broadband power, which correlated with functional network integrity and subjective experiences (e.g., ego-dissolution or intensity of the experience)<sup>26–33</sup>. Nevertheless, ibogaine differs from these psychedelic substances in clinically and biologically meaningful ways. For example, in contrast to hallucinogenic, empathogenic, and dissociative psychedelic drugs, ibogaine’s distinct subjective effects are classified as oneirogenic, involving a ‘dreamlike’ experience with an extensive period of self reflection. This experience includes unpleasant physical effects, enhanced memory retrieval, dreamlike visions and auditory phenomena, and a wide range of emotional and spiritual experiences (see Brown et al.<sup>34</sup> and Schenberg et al.<sup>35</sup> for more information). Additionally, ibogaine has a uniquely wide range of binding targets, including *N*-methyl-d-aspartate, kappa and mu opioid, and nicotinic acetylcholine receptors, and serotonin and dopamine transporters<sup>36,37</sup>. How changes in cortical oscillations and neural complexity relate to the psychiatric and cognitive outcomes of treatment with ibogaine are not yet known.

Pre-treatment cortical dynamics may also be useful for predicting psychiatric outcomes after ibogaine treatment. EEG is a promising tool for establishing indices of cortical dynamics as clinically deployable biomarkers due to its accessibility, affordability, and sub-millisecond temporal precision. For example, pre-treatment resting-state alpha power has been identified as a robust predictor of depressive symptom improvement after antidepressant pharmacotherapy<sup>38</sup>. EEG predictors of ibogaine treatment outcomes have not yet been identified.

Here, as part of the first prospective, single-arm study of ‘Magnesium–Ibogaine: the Stanford Traumatic Injury to the CNS protocol’ (MISTIC) that found striking psychiatric and cognitive improvements in Special Operations Forces veterans (SOVs) with a history of TBI, we used high-density resting-state EEG to measure the effects of ibogaine treatment on cortical oscillations and neural complexity. We then sought to relate these neurophysiological mechanisms to ibogaine treatment outcomes. We hypothesized that (1) EEG measures of cortical oscillations spanning delta to gamma frequencies and Lempel-Ziv complexity would be modulated 3.5 days and one month after ibogaine treatment, (2) treatment-modulated brain rhythms would correlate with symptom improvement, and (3) pre-treatment EEG markers would correlate with symptom improvement.

## **METHODS**

### **Participants**

Thirty-four participants were screened, and 30 participants were eligible for the study and completed pre- and post-treatment assessments. All participants were male SOVs with a history of TBI resulting from blast exposure, head trauma, or combat (mean  $\pm$  SD age =  $44.9 \pm 7.5$ ). The mean  $\pm$  SD number of prior TBIs was  $38.6 \pm 52.4$ , ranging in severity from mild (n=28) to moderate (n=1) and moderately severe (n=1), as determined by the Ohio State University Screening for TBI exposure<sup>39</sup>. The gender and racial/ethnic identity of participants were determined by self-report using provided classification terms. Twenty-six of the participants identified as white, one as Hispanic, one as Native American, and two as biracial (white and Native American). Diagnosed psychiatric disorders at entry into the study based on the Mini International Neuropsychiatric Interview included PTSD (n = 23), major depression (n = 15), anxiety disorder (n = 14), and alcohol use disorder (n = 15). In accordance with treatment protocols, participants discontinued medications with the potential to cause drug-drug interactions, including psychiatric medications and benzodiazepines<sup>5</sup>.

Participant characteristics and study methods are described in further detail in Table S1 and in prior work<sup>5</sup>. The study was approved by the Stanford University Institutional Review Board, and all participants provided written informed consent.

### **Treatment**

All participants were referred by the nonprofit Veterans Exploring Treatment Solutions (VETS), Inc. and independently scheduled for treatment with ibogaine at Ambio Life Sciences, in Mexico. MISTIC treatment involved the co-administration of oral ibogaine (mean  $\pm$  SD total dose =  $12.1 \pm 1.2$  mg/kg) with intravenous magnesium sulfate to protect against the cardiovascular effects of the drug, particularly Q-T interval prolongation<sup>5,40</sup>. Participants were medically evaluated and received preparatory coaching about the ibogaine experience from a licensed therapist before treatment. Integration resources were also made available to participants after treatment. No psychotherapy was delivered during treatment. The effects of ibogaine can

last 24 to 72 hours or longer<sup>41</sup>, therefore participants underwent continued monitoring for 72 hours after dosing.

### **Clinical and Neuropsychological Measures**

Depressive symptoms were assessed using the clinician-administered Montgomery–Åsberg Depression Rating Scale (MADRS)<sup>42</sup>, PTSD symptoms using the clinician-administered PTSD Scale (CAPS-5)<sup>43</sup>, and anxiety symptoms using the Hamilton Anxiety Rating Scale (HAM-A)<sup>44</sup>. A battery of neuropsychological tests was also performed at all study visits. In the current work, we focused on three neuropsychological measures that were substantially improved after ibogaine treatment<sup>5</sup> and have previously been shown to relate to spectral power: (1) processing speed (Wechsler Adult Intelligence Scale - Fourth Edition, Processing Speed Index)<sup>45</sup>, (2) cognitive inhibition (Delis Kaplan Executive Function System, Color-Word Inhibition)<sup>46</sup>, and sustained attention (Conners' Continuous Performance Test - Third Edition / CPT3)<sup>47</sup>. One participant was excluded from analyses of neurophysiological relationships with psychiatric outcomes as their baseline MADRS, CAPS, and HAM-A scores were not consistent with the presence of psychiatric symptoms<sup>5</sup>. Six participants did not complete the CPT3 (sustained attention) at baseline.

### **EEG Recording and Preprocessing**

See Figure 1 for an overview of EEG procedures. Participants underwent resting-state EEG 2-3 days before ibogaine treatment (n=30), 3.5 days post-ibogaine (n=30), and 1-month post-ibogaine (n=27). Three participants did not complete EEG recordings at the 1-month follow-up for logistical reasons. A total of six minutes of eyes-open EEG were recorded in two 3-minute segments with a short break in between recordings to promote wakefulness; this recording length has been shown previously to achieve high test-retest reliability<sup>48–51</sup>. Recordings were performed with eyes open to further promote wakefulness, and because eyes-open EEG spectral measures have previously been identified as robust predictors of psychiatric treatment outcomes<sup>38</sup>. Participants were seated upright and instructed to fixate on a centrally presented crosshair, stay still, and let their minds wander naturally without focusing on anything particular. Data were sampled at 10kHz using 64 Ag-AgCl channels (actiCAP slim EEG cap; Brain Products GmbH, Germany) with an acti64CHamp Amplifier, and referenced to Cz during recording. Channels

were arranged according to the 10-10 system. Impedance was maintained at  $< 10\text{k}\Omega$  in  $> 80\%$  of channels and  $< 25\text{k}\Omega$  in  $> 99\%$  of channels.

EEG data preprocessing was performed offline using a combination of the EEGLAB toolbox<sup>52</sup> and ARTIST code in MATLAB, which is an automated EEG artifact rejection algorithm<sup>53</sup>. The preprocessing pipeline consisted of the following steps: 1) Data were downsampled to 1kHz. 2) A notch filter was applied for 60 Hz line noise and harmonics, and high-pass (1Hz) and low-pass (50Hz) filters were applied using windowed-sinc finite impulse response filters. 3) The beginning and end of each recording were trimmed to eliminate filter edge effects. 4) Bad channel rejection was performed using a semi-automated method, including rejection based on impedance  $> 25\text{k}\Omega$ , detection of bridging, or persistent noise identified automatically<sup>53</sup> then visually inspected by an experienced rater ( $< 15\%$  of channels were rejected). For four recordings, an impedance threshold of  $50\text{k}\Omega$  was applied to maintain the channel rejection limit; however visual inspection of the data indicated good quality signal in all remaining channels. Sensitivity analyses were performed, excluding recordings in which  $> 10\%$  of channels showed impedance  $> 25\text{k}\Omega$  (Supplement). Spherical interpolation of missing channels was performed. 5) Data were binned into 2-second epochs, and epochs containing excessive noise were discarded (mean  $\pm$  SD % epochs rejected =  $6.1 \pm 2.6\%$ ; range: 1.7-13.9%). 6) Data were re-referenced to the average. 7) Independent component analysis was performed using the Infomax algorithm<sup>54</sup> with principal component analysis (PCA) dimension reduction (determined as the fewest principal components that explain  $> 99.9\%$  of the variance<sup>53</sup>; average principal components:  $50.2 \pm 4.7$ ; range=35-59), and components reflecting ocular and muscle artifacts were removed. 8) Data were re-referenced to the average. All steps were performed by an experienced rater who was blind to the visit number and clinical scores associated with each recording.

## **MRI**

A T1-weighted anatomical MRI scan was also performed for coregistration with EEG. MRI scans were performed using a 3T MRI scanner equipped with a 32-channel head coil (GE Discovery MR750). A T1-weighted anatomical MRI scan was acquired using the GE BRAVO

sequence (TR = 6.39ms; TE = 2.62 ms; flip angle = 12°; voxel size = 0.9 × 0.9 × 0.9 mm). Two participants did not undergo an MRI due to the presence of metal fragments in the eyes.

## Spectral Measures

In order to reduce the dimensionality of the data in our primary analyses, two regions of interest (ROIs) were defined a priori: a medial frontal ROI (AFz, F1, Fz, F2) and a medial posterior ROI (CP1, CPz, CP2, P1, Pz, P2, POz) approximating sensor-space ROIs previously found to show acute changes in oscillatory power after the administration of classic psychedelics<sup>29</sup>. Power spectral density (uV<sup>2</sup>/Hz) was calculated for all channels using Welch's method with 2-second Hamming windows and 50% overlap. Mean broadband power (1-50Hz) for each epoch was z-scored with respect to all epochs, and outlier epochs were excluded ( $z > 1.96$ ; <7% of epochs rejected). The average final recording length was 336s (range: 310-356s). The total percentage of epochs rejected did not differ significantly between study time points (baseline vs. post-ibogaine:  $t_{29} = 0.11$ ,  $p = 0.92$ ; baseline vs. 1-month follow-up:  $t_{26} = 0.78$ ,  $p = 0.44$ ). Power was calculated in predefined canonical frequency bands related to different neurophysiological mechanisms: delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz) and gamma (30-50Hz). Power values were normalized to broadband power by dividing the Riemann sum of power within a predefined band by the Riemann sum of power across all frequencies (1-50Hz), using the equation below:

$$\text{Normalized power}_{a-b\text{Hz}} = \frac{\sum_a^b P(f) * \Delta x(f)}{\sum_1^{50} P(f) * \Delta x(f)} \times 100\%$$

where  $a$  and  $b$  indicate the lower and upper bounds of the frequency range of interest,  $P(f)$  represents absolute power at frequency  $f$  (mcV<sup>2</sup>/Hz), and  $\Delta x$  represents the frequency bin width (Hz). Normalized power for each band therefore reflects that band's percentage of total power. The ratio of slow vs. fast oscillations was captured using theta/beta ratio, which is a putative marker of executive control<sup>55</sup>. Theta/beta ratio was calculated by dividing absolute theta power by absolute beta power. For each ROI, normalized power and theta/beta ratio were averaged across ROI channels.

Peak alpha frequency (PAF) was calculated for each channel using custom MATLAB scripts that identified the frequency with local maximum power within the 7-14Hz frequency range<sup>56-58</sup>. All spectra were reviewed to verify the accuracy of PAF estimates. PAF was estimated globally by

averaging across all channels, and the regional specificity of any PAF effects was explored by averaging channels within each predefined ROI. Channels in which no peak could be identified were excluded from the PAF estimate, and participants were excluded if no peak was identified in >20% of channels (n = 4 excluded; in accordance with prior reports that 10-15% of individuals do not show a dominant alpha rhythm<sup>59</sup>).

To explore the effects of ibogaine on aperiodic components of the EEG signal, the “Fitting Oscillations & One Over F” (FOOOF) toolbox<sup>60</sup> was used to compute the ROI aperiodic exponent and offset parameters (frequency range = 1-50Hz; peak width = 1-12Hz; max peaks = infinite; peak threshold = 2 stdev; aperiodic mode = fixed). The aperiodic offset and exponent are non-oscillatory features of the power spectra; the offset reflects uniform shifts in broadband power and the exponent reflects the steepness of the 1/f slope of power across frequencies. The potential influence of the aperiodic components on the primary results was explored by subtracting the aperiodic component from the power spectrum, and recomputing normalized power using the flattened spectrum.

Source localization was performed using the Brainstorm toolbox<sup>61</sup> to identify where changes in spectral power at the sensor level were localized in brain space. Source localization to the cortical surface was performed using minimum norm estimates and a boundary element model of the head using individual T1 images, or the ICBM152 standard MRI brain template when no individual MRI was available (n=2; see Supplement for sensitivity analyses excluding these two participants). Unconstrained dipole orientations<sup>62</sup> were generated at 15,000 cortical vertices. Inverse modeling was performed using L2-minimum norm estimation with depth weighting, and using the diagonal noise covariance. After transformation into source space, power spectral density was computed using the Welch method. Power was extracted for predefined frequency bands, normalized to total power (1-50Hz), and projected onto the cortical surface of a template brain for group analysis. Regions showing a significant change in power were identified using Desikan-Killiany and Schaeffer 100 parcel 7 network atlases (Table S2).

Considering the lack of a placebo control group in the current study, the publicly available EMBARC dataset was used to explore potential placebo effects on resting-state EEG measures

of spectral power<sup>63</sup>. In an age-matched subset of participants with depression (n=30), a total of four minutes of resting-state EEG data were collected before and after 1 week of placebo intervention. Source-space changes in spectral power were compared between baseline and 1-week timepoints using permutation tests (5000 permutations,  $p < 0.05$  threshold). See Supplement for further details.

### **Lempel-Ziv Complexity**

Lempel-Ziv complexity quantifies the number of unique patterns in the EEG signal, which reflects the diversity of activity patterns in both time and space. The Lempel-Ziv-Welch algorithm described by Schartner et al.<sup>64</sup> was applied to 2-second epochs at a 1kHz sampling rate. Lempel-Ziv complexity was also computed using 10-second epochs to verify that the results were not sensitive to epoch length (Supplement). A 30Hz low-pass filter was applied to the data to ensure that complexity measures were not impacted by muscle activity. Complexity was computed on the mean binarized envelope of the signal which was obtained via Hilbert Transform. Greater Lempel-Ziv complexity values reflect a larger number of non-redundant sub-sequences in the data, and therefore more randomness in the signal.

Two variants of Lempel-Ziv complexity were computed, in line with prior studies<sup>33,64</sup>: LZc captures complexity within and across channels, thus capturing both temporal and spatial signal diversity, whereas LZs captures the complexity of each channel separately, later averaged, thus capturing only temporal signal diversity. LZc and LZs were normalized to the number of patterns in the temporally shuffled binarized signal (range = 0 - 1, where 1 = maximum diversity). As an additional control to account for changes in the spectral profile of the data, raw values were also normalized using a phase-shuffled signal. Surrogate data were generated by phase randomization<sup>65,66</sup>, where phase values obtained by Fourier transform are randomized, then projected back into the time domain via Inverse Fourier Transform, which retains the spectral properties of the original signal while increasing overall diversity. For *phase-randomized* normalization, the raw LZc or LZs value was divided by the number of patterns in the phase-shuffled signal.

### **Statistics**

Primary analyses consisted of linear mixed-effects models testing for the effect of time on spectral measures in predefined ROIs. Linear mixed-effects models included time point as a categorical fixed effect (baseline, post-treatment and one-month follow-up) and participant as a random effect. Age, combat exposure and number of TBIs were included as covariates, given prior evidence that these factors might influence spectral power<sup>67–69</sup>. For 3 participants, the number of TBIs was too high to estimate (e.g. several hundred lifetime TBIs), therefore these values were imputed as 5 SD above the mean. The distributions of model residuals were checked using histograms and quantile–quantile (Q–Q) plots. Skew present due to outliers was addressed by excluding band-specific power outliers from each ROI (z-score > 3; 1.4% of observations removed; see Supplement for sensitivity analyses including these outliers). All models were corrected for multiple comparisons using FDR correction (accounting for all frequency bands and ROIs). Post hoc comparisons of spectral power at baseline vs. post-treatment and one-month follow-up were performed using Dunnett’s test to account for multiple comparisons<sup>70</sup>. Correlations with predefined psychiatric and cognitive outcomes were calculated using FDR-corrected Spearman’s rho. The primary aims were pre-registered at osf.io (<https://osf.io/24trc/>).

In order to explore changes in normalized power from pre- to post-ibogaine across the cortex for EEG measures that showed significant changes at the ROI level, nonparametric permutation tests were also performed in sensor and source space. Controlling for the Type 1 error rate, cluster-based permutation tests were performed in sensor space using 5000 permutations and a cluster-forming threshold of  $p < 0.05$  (two-tailed)<sup>71</sup>. Similarly, permutation tests using 5000 permutations and a  $p < 0.05$  threshold were performed to identify where significant changes in spectral power occurred in source space. Cluster-based permutation tests were similarly performed exploring pre- to post-treatment changes in power across all frequencies (1–50Hz) and 64 channels.

## RESULTS

### **Ibogaine treatment enhances theta-alpha (4–13Hz) and reduces beta-gamma (13–50Hz) power**

Ibogaine treatment had a significant effect on theta power in both ROIs (posterior:  $F_{2,52} = 4.11$ ,  $p_{FDR} = 0.033$ ; frontal:  $F_{2,52} = 5.78$ ,  $p_{FDR} = 0.027$ ) and alpha power in the posterior ROI ( $F_{2,54} = 4.08$ ,  $p_{FDR} = 0.033$ ; Fig.2A). Specifically, theta and alpha power increased significantly post-ibogaine (posterior theta:  $p = 0.014$ , Cohen's  $d = 0.47$ ; frontal theta:  $p = 0.0041$ , Cohen's  $d = 0.61$ ; posterior alpha:  $p = 0.021$ , Cohen's  $d = 0.45$ ). The significance of effects did not persist at one-month follow-up ( $p > 0.05$ ).

Accordingly, in channel-wide cluster-based permutation analyses, widespread increases in theta and posterior increases in alpha power were observed post-ibogaine compared to baseline (theta cluster:  $p = 0.0004$ , alpha cluster:  $p = 0.023$ ; Fig.2B). No significant clusters were identified for theta or alpha power at one-month follow-up compared to baseline (Fig.S1). Source estimation revealed that increases in theta power post-ibogaine were localized to bilateral fronto-central and temporal cortical regions, including regions associated with the default mode network, such as the precuneus and superior frontal cortex. Increases in alpha power were localized to parietal and occipital cortical regions, including regions associated with visual and default mode networks (Fig.2C, Fig.S2, Table S2).

Ibogaine treatment also had a significant effect on beta power in the frontal ROI ( $F_{2,54} = 9.82$ ,  $p_{FDR} = 0.0023$ ) and gamma power in both ROIs (posterior:  $F_{2,55} = 4.16$ ,  $p_{FDR} = 0.033$ ; frontal:  $F_{2,55} = 4.05$ ,  $p_{FDR} = 0.033$ ). In particular, frontal beta power was significantly reduced post-ibogaine ( $p = 0.0001$ , Cohen's  $d = 0.73$ ), but not at one-month follow-up ( $p > 0.4$ ). Gamma power was significantly reduced post-ibogaine (posterior:  $p = 0.025$ , Cohen's  $d = 0.70$ ; frontal:  $p = 0.016$ , Cohen's  $d = 0.50$ ), which persisted at one month in the posterior ROI, although with a lower effect size ( $p = 0.039$ , Cohen's  $d = 0.37$ ).

Congruent with the ROI-level results, channel-wide permutation analyses showed significant reductions in beta ( $p = 0.002$ ) and gamma power (cluster 1:  $p = 0.001$ , cluster 2:  $p = 0.035$ ) post-ibogaine compared to baseline, which did not persist at one-month follow-up (Fig.S1). This effect of increased power in slower frequencies (in the theta to alpha range) and decreased power in faster frequencies (in the beta to gamma range) post-ibogaine was similarly observed in cluster-based permutation analyses of all frequencies and channels (Extended Data Fig.1A), with

similar but mostly non-significant effects observed one month after treatment (Extended Data Fig.1B). Source estimation revealed that decreases in beta and gamma power post-ibogaine were localized to bilateral frontal and temporal cortical regions, including right frontal pole and bilateral superior frontal cortex. Reductions in gamma power were additionally localized to bilateral precuneus and superior parietal cortex (Fig.2C, Fig.S2, Table S2). Additionally, the observed effects on theta, beta, and gamma power were not found in an age-matched subset of EMBARC participants after one week of placebo intervention. A significant increase in left parietal alpha power was observed after placebo intervention, however (see Supplement and Extended Data Fig.2 for further details).

Theta/beta ratio in both ROIs was significantly changed after ibogaine treatment (posterior:  $F_{2,52} = 5.87$ ,  $p_{FDR} = 0.010$ ; frontal:  $F_{2,52} = 4.69$ ,  $p_{FDR} = 0.013$ ). Specifically, theta/beta ratio increased significantly post-ibogaine compared to baseline (posterior:  $p = 0.0033$ , Cohen's  $d = 0.54$ ; frontal:  $p = 0.0094$ , Cohen's  $d = 0.48$ ), which did not persist at one-month follow-up (Fig.3A).

Significant decreases in delta power were also observed one-month post-ibogaine as compared to baseline (see Supplement and Extended Data Fig.3 for further details). See Supplement for changes in absolute power after ibogaine treatment. No significant correlations were found between total ibogaine dose or time since ibogaine administration and changes in EEG measures post-ibogaine.

Overall, the observed effects were robust in a number of sensitivity analyses, including analyses that: account for the potential effects of preprocessing steps, exclude participants without an MRI scan for coregistration, exclude participants with a history of moderate to moderately severe TBI, and include alcohol consumption as a covariate (see Supplement). Of note, in exploratory analyses of changes in power at the online reference electrode (Cz), increased Cz theta power was observed post-ibogaine, which could have influenced the observed ROI increases in theta power post-ibogaine (see Supplement for further details). Importantly, most ROI EEG measures also showed excellent test-retest reliability between the two within-session EEG recordings (see Supplement and Table S3).

## **Ibogaine treatment lowers peak alpha frequency and complexity**

Global PAF was significantly lowered after ibogaine ( $F_{2,47}= 7.38$ ,  $p_{\text{FDR}}= 0.0024$ ), both post-ibogaine ( $p= 0.00090$ , Cohen's  $d= 1.05$ ) and at one-month follow-up ( $p= 0.036$ , Cohen's  $d= 0.41$ ), as compared to baseline (Fig.4). The effect of ibogaine on PAF was specific to the posterior ROI ( $F_{2,47}= 8.78$ ,  $p_{\text{FDR}}= 0.0017$ ), and not the frontal ROI ( $F_{2,47}= 1.69$ ,  $p_{\text{FDR}}= 0.19$ ). Posterior PAF was significantly reduced both post-ibogaine ( $p= 0.0010$ , Cohen's  $d= 1.00$ ) and at one-month follow-up ( $p= 0.0023$ , Cohen's  $d= 0.56$ ) (Fig.4B).

Similarly, global LZc was significantly reduced after ibogaine compared to baseline ( $F_{2,55}= 4.14$ ,  $p= 0.021$ ), both post-ibogaine ( $p= 0.023$ , Cohen's  $d= 0.55$ ) and at one-month follow-up ( $p= 0.044$ , Cohen's  $d= 0.41$ ) (Fig.5A). These effects remained significant when LZc was normalized to LZc of phase-randomized surrogate data (see Supplement). LZs was also significantly modulated after ibogaine, however these effects were not significant when the phase-randomized normalization was applied (see Supplement).

## **Effects on aperiodic components of the signal**

In exploratory analyses of changes in the non-oscillatory background spectral decay, we found significant increases in the frontal and posterior ROI exponents (frontal:  $F_{2,55}= 3.93$ ,  $p= 0.025$ ; posterior:  $F_{2,55}= 4.25$ ,  $p= 0.019$ ), reflecting a significantly steeper  $1/f$  slope post-ibogaine compared to baseline (frontal:  $p= 0.020$ , Cohen's  $d= 0.46$ ; posterior:  $p= 0.0072$ , Cohen's  $d= 0.66$ ), but not at one-month follow-up (Extended Data Fig.4). The ROI offsets did not change significantly after treatment compared to baseline.

Changes in band power after ibogaine treatment were also analyzed with the aperiodic component subtracted from the power spectrum (see Extended Data Fig.4). In cluster-based permutation tests using the flattened power spectrum, most findings persisted: theta ( $p=0.00020$ ) and alpha power ( $p=0.034$ ) increased significantly post-ibogaine, and delta ( $p=0.020$ ) and gamma power ( $p=0.0068$ ) decreased significantly at one-month follow-up. Similarly, significant increases in theta/beta ratio post-ibogaine compared to baseline persisted after removal of the aperiodic exponent from the spectrum (posterior:  $p= 0.0032$ , Cohen's  $d= 0.56$ ; frontal:  $p=$

0.000042, Cohen's  $d=0.80$ ). However, decreases in beta and gamma power post-ibogaine were not significant using the flattened power spectrum. Additionally, with the aperiodic exponent removed, increases in theta ( $p=0.019$ ) and alpha power ( $p=0.0086$ ) were also significant at one-month follow-up in cluster-based permutation tests.

### **Changes in cortical oscillations after ibogaine treatment correlate with improvements in executive function and PTSD symptoms**

Increased theta/beta ratio post-ibogaine correlated significantly with improved cognitive inhibition post-ibogaine in both frontal ( $\rho=0.54$ ,  $p_{FDR}=0.0026$ ) and posterior ROIs ( $\rho=0.59$ ,  $p_{FDR}=0.0015$ ) (Fig.3B). This relationship was specific to cognitive inhibition, as changes in theta/beta ratio did not correlate significantly with changes in processing speed or sustained attention post-ibogaine. Changes in power, PAF, LZc, and aperiodic components post-ibogaine did not correlate significantly with cognitive outcomes after FDR correction. Notably however, increased posterior theta power and decreased posterior beta power post-ibogaine showed moderate correlations with improved cognitive inhibition post-ibogaine, which were non-significant after FDR correction (theta:  $\rho=0.50$ ,  $p_{FDR}=0.052$ ,  $p_{uncorrected}=0.0052$ ; beta:  $\rho=-0.45$ ,  $p_{FDR}=0.067$ ,  $p_{uncorrected}=0.013$ ).

Lowered posterior PAF post-ibogaine was significantly correlated with greater percentage improvement in PTSD symptoms at one month ( $\rho=0.54$ ,  $p_{FDR}=0.011$ ) (Fig.4D). A similar relationship was observed between lowered posterior PAF post-ibogaine and one-month percentage improvement in anxiety symptoms ( $\rho=0.44$ ,  $p_{FDR}=0.058$ ), however the correlation was non-significant after FDR correction. Given prior evidence of a relationship between PAF and arousal/alertness in particular<sup>14,72,73</sup>, the relationship between lowered posterior PAF post-ibogaine and percentage improvement in the CAPS subscale for arousal and reactivity symptoms was also explored, and a similar relationship was observed ( $\rho=0.53$ ,  $p=0.0050$ ) (Fig.4D). A significant correlation was also observed between changes in the posterior ROI aperiodic exponent and percentage reduction in PTSD symptoms at one month ( $\rho=0.53$ ,  $p_{FDR}=0.015$ ). Changes in normalized power, theta/beta ratio, LZc, and other aperiodic components post-ibogaine did not correlate significantly with 1-month psychiatric outcomes after FDR correction.

## **Pretreatment EEG measures correlate with improvements in executive function, PTSD and anxiety**

Greater improvement in cognitive inhibition post-ibogaine was significantly correlated with lower PAF pre-treatment (global:  $\rho = -0.54$ ,  $p_{\text{FDR}} = 0.0045$ ; posterior:  $\rho = -0.63$ ,  $p_{\text{FDR}} = 0.0012$ ) (Fig.4C) and lower LZc pre-treatment ( $\rho = -0.51$ ,  $p = 0.0038$ ) (Fig.5B). Baseline PAF and LZc were not significantly correlated with improved processing speed or sustained attention. In exploratory correlations between baseline measures, lower baseline PAF also correlated with lower baseline cognitive inhibition (see Supplement and Extended Data Fig.5 for details).

See Fig.6 and Fig.S3 for a summary of channel-wide relationships between baseline normalized power and improvement in CAPS and HAM-A scores one month after ibogaine. After FDR correction, improvement in PTSD symptoms at one-month follow-up correlated significantly with lower baseline alpha power, and higher baseline delta and gamma power. Similarly, improvement in anxiety symptoms at one-month follow-up correlated significantly with lower baseline alpha power, and higher baseline beta and gamma power. Similar associations were observed in ROI-specific correlations (Supplement). Channel-wide correlations with depressive symptom improvement at one-month follow-up were non-significant after FDR correction (Fig.S4).

## **DISCUSSION**

This study was, to our knowledge, the first quantitative investigation of the effects of ibogaine on human cortical dynamics. Cortical oscillations and complexity were measured prospectively in SOVs with a history of TBI who suffered from marked disability, including PTSD, depression, anxiety, and cognitive dysfunction, and who demonstrated striking improvements in these symptoms after ibogaine treatment<sup>5</sup>. We identified post-acute changes in cortical oscillations after ibogaine treatment across most EEG measures, including enhanced theta and alpha power, reduced beta and gamma power, increased theta/beta ratio, reduced global Lempel-Ziv complexity, and lowered PAF. PAF slowing was most prominent in the posterior cortex and sustained one month after treatment. Of note, when non-oscillatory components of the signal were removed, increases in theta and alpha power also persisted one month after treatment.

Taken together, these findings suggest an overall slowing of spontaneous cortical oscillations and a shift to a more stable spatiotemporal pattern of cortical activity after ibogaine treatment. Changes in cortical oscillations showed moderate relationships with improved executive function and PTSD symptoms after treatment. In addition to being engaged by ibogaine treatment, baseline measures of cortical oscillations and neural complexity were associated with individual differences in executive function, PTSD, and anxiety symptom improvements after MISTIC. To our knowledge, this is the first study to identify neurophysiological mechanisms and pre-treatment EEG measures that relate to the therapeutic outcomes of treatment with ibogaine.

### **Post-Acute Drug Effects of Ibogaine**

The observed transient changes in theta to gamma power and the complexity of spontaneous brain activity provide novel evidence of the post-acute drug effects of ibogaine. These initial effects of ibogaine on oscillations in theta, alpha, beta, and gamma bands were localized to a range of frontal, parietal, and temporal cortical regions, including substantial overlap with hubs of the default mode network. Effects localized to frontal and temporal cortices are particularly interesting to treating TBI neuropathology, since TBI has been found to primarily affect frontal and temporal gray matter, regardless of the site of impact<sup>74</sup>. Interestingly, this shift towards theta and alpha power and reduction in spatiotemporal complexity after ibogaine treatment differs from many of the acute changes identified immediately after the administration of other psychedelic substances in healthy adults, such as broadband reductions in power<sup>26–31</sup>, increases in delta power<sup>75,76</sup>, and increases in complexity<sup>31–33,77,78</sup>. As such, the observed post-acute effects might be unique to the pharmacological mechanisms of ibogaine. The aperiodic slope of the power spectrum was also found to be post-acutely increased after ibogaine, potentially reflecting a shift in the excitation-inhibition balance in favor of inhibitory GABA synaptic currents<sup>60,79</sup>. Importantly, these EEG measures of ibogaine's post-acute effects on neural function may be useful for personalizing ibogaine treatment; current ibogaine dosing techniques rely on subjective reports of ibogaine-induced symptoms rather than biological indicators of neural engagement. EEG measures of cortical oscillations are relatively low-cost to acquire and may therefore be useful as objective markers of optimal ibogaine dosing. For example, EEG monitoring is used to optimize the dosing of anesthetic drugs and can lead to lower rates of

under- and over-dosing<sup>80,81</sup>. Future studies on the real-time effects of ibogaine on cortical activity are needed to further explore these potential biomarkers of optimal ibogaine dosing.

The observed post-acute reduction in complexity 3.5 days after the administration of ibogaine may be in line with a neural annealing model of psychedelic treatments<sup>82</sup>. According to this model, psychedelics may acutely increase entropy during administration, followed post-acutely by a return to a rebalanced, potentially lower entropy state. A similar pattern has been described for meditation; for example, complexity increases acutely during the meditative state, but baseline complexity decreases with long-term meditation practice<sup>83</sup>.

### **Neurophysiological Correlates of Ibogaine Treatment Outcomes**

Additionally, our findings offer novel insight into the neural mechanisms through which ibogaine may exert its therapeutic effects in TBI populations. Specifically, an increase in the relative dominance of theta rhythms (4-8Hz) post-ibogaine, captured as an increased theta/beta ratio, showed a moderate relationship with improved executive function post-ibogaine. Of note, although potentially conflicting findings exist linking higher theta/beta ratios to worse cognitive control over emotional information<sup>84</sup>, a similar relationship between higher theta/beta ratio at rest and greater inhibitory control has been observed previously in healthy adults<sup>85</sup>, and increased frontal theta power has repeatedly been shown to be a mechanism for cognitive control<sup>86,87</sup>. Additionally, we report a specific relationship between post-acute within-subject *changes* in theta/beta ratio and *changes* in cognitive inhibition after treatment, therefore this finding is distinct from prior cross-sectional studies examining theta/beta ratio as a between-subjects marker of cognitive control. A potentially related reduction in PAF<sup>88</sup> after treatment was also moderately associated with better PTSD outcomes. Future work should additionally assess whether these EEG changes relate to the real-time subjective intensity of the ibogaine experience.

It is possible that these changes in cortical oscillations associated with cognitive and psychiatric outcomes relate to the neuroplastic effects of ibogaine<sup>89</sup>. Nardou et al. recently showed in rodents that ibogaine can reopen critical learning periods in part through the induction of metaplasticity<sup>90</sup>. Although speculative, the neuroplastic effects of ibogaine may facilitate

cognitive flexibility, thus enabling some of the observed therapeutic effects. In line with this idea, theta rhythms are associated with long-term potentiation<sup>91</sup>, and our work suggests that ibogaine may promote theta rhythms and executive function concurrently. Accordingly, other types of interventions that are thought to promote both neuroplasticity and executive function, such as neuromodulation<sup>92–95</sup> and meditation<sup>58,96–98</sup>, have shown similar effects on cortical activity to those reported here, including enhanced theta power<sup>99–101</sup> and decreased complexity<sup>83</sup>. By contrast, advancing age is associated with reductions in metaplasticity, executive function, and resting-state theta power<sup>68,102</sup>, and higher theta power has been linked to better executive function in older adults<sup>68,103</sup>. Additionally, improvements in executive function have been shown to mediate the therapeutic effects of psychedelic substances, including ibogaine<sup>104</sup>. Although further work is needed to identify causal relationships between ibogaine, theta oscillations, neuroplasticity, and executive function, these lines of evidence suggest that the enhancement of theta oscillations after ibogaine treatment might reflect a transition into a more malleable brain state, which could allow some of the marked changes in mental state observed after ibogaine treatment.

Moreover, persisting reductions in PAF and neural complexity might relate to a reduction in hyperarousal after ibogaine treatment. TBI and PTSD have been linked to states of hyperarousal<sup>105,106</sup>, which is associated with poorer executive function<sup>107</sup>. Elevated PAF has been observed in PTSD<sup>18</sup>, elevated Lempel-Ziv complexity has been observed in individuals with chronic stress<sup>108</sup>, and elevated PAF and complexity are both putative markers of higher arousal/alertness<sup>14,17,72,73,109</sup>. Exploring this relationship, we found that PAF slowing post-ibogaine was associated with reduced arousal symptoms one month after treatment. The observed reductions of PAF and complexity that persisted one month after ibogaine treatment may therefore reflect a lasting reduction in hyperarousal at rest. There is evidence that reducing hyperarousal in treatment can mediate improvement in other PTSD symptom clusters<sup>110</sup>.

### **Pre-Treatment EEG Measures Related to Ibogaine Treatment Outcomes**

EEG measures of PAF, neural complexity, and spectral power collected prior to treatment may also be valuable for predicting individual ibogaine treatment outcomes. In particular, lower baseline PAF and complexity were related to greater improvement in cognitive inhibition post-

ibogaine. Accordingly, emerging evidence supports PAF as a biomarker for stratifying patients to different psychiatric interventions; for example, low baseline PAF has been shown to predict better response to specific types of antidepressant treatment<sup>111</sup>. Additionally, we found that the relative dominance of alpha versus delta, beta, and gamma rhythms at baseline was related to improvement in PTSD and anxiety symptoms one month after ibogaine treatment. These results are similarly in line with a growing body of evidence showing that pre-treatment EEG measures of spectral power can be used to predict psychiatric treatment outcomes<sup>38,112</sup>. Further work is needed to assess the specificity of these potential biomarkers to ibogaine treatment, in order to validate their potential use in the stratification of patients to different types of interventions.

### **Potential Biological Significance of Changes in Cortical Oscillations**

Findings of increased posterior alpha power and reduced delta power (Supplement) after ibogaine treatment might reflect the normalization of abnormally low alpha and high delta power previously reported after TBI<sup>7-11</sup>. Accordingly, higher baseline delta power was associated with greater combat exposure (Supplement). Increased theta power and theta/beta ratio, and lower PAF and complexity after ibogaine treatment, on the other hand, are not in line with the normalization of TBI-related neurophysiological impairments. These changes may instead index an alternative mechanism of the recovery process, such as neuroplasticity, or reflect the normalization of impairments related to specific symptom dimensions, such as hyperarousal. Future work with an age-matched healthy control comparison group is needed to clarify whether changes in neurophysiological measures after ibogaine reflect normalizing or compensatory changes in brain function.

Evidence from concurrent fMRI-EEG suggests that the observed shift in the oscillatory profile post-ibogaine may also reflect changes in the activity of functional brain networks<sup>113</sup>. For example, both increased resting-state theta power and reduced resting-state beta power have been correlated with less activity in regions of the default mode network<sup>114,115</sup>. Source analysis revealed that enhanced theta power and reduced beta power after ibogaine were localized to several regions of the default mode network. Further investigation into the relationships between changes in spectral power and functional network activity and connectivity will help to clarify the full picture of cortical reorganization after ibogaine treatment.

## Limitations

The findings reported here should be considered in the context of study limitations. First, this was a single-arm, open-label observational study, and future work including randomization to a control condition is needed to validate these initial findings and clarify the specificity of any effects of ibogaine administration. Expectation effects and other elements of the study intervention, such as coaching and the social context in which treatment was delivered, could have contributed to the current findings. However, the EEG effects were associated with the large psychiatric and cognitive benefits observed after treatment that are unlikely to have been driven exclusively by these other elements of the intervention. Additionally, prior studies on the effects of placebo interventions on EEG spectral power have not consistently shown the changes in spectral measures reported here; for example, studies have reported no changes in power after placebo<sup>116–119</sup>, increases in alpha power during placebo analgesia<sup>120,121</sup>, and broadband (delta to beta) decreases in power after placebo in a psychedelics study<sup>31</sup>. Expanding on these prior studies, we also analyzed changes in power after placebo intervention in the EMBARC trial, and did not identify significant changes in theta, beta, or gamma power, however left parietal alpha power was significantly increased after placebo (Supplement, Extended Data Fig.2). The observed increases in alpha power in particular after ibogaine may therefore be related to placebo effects. Second, the sample size was modest, with high homogeneity. As such, while our sample is largely representative of SOVs, future work in larger, more diverse populations, including other clinical populations, is needed to generalize these findings to other groups. Third, although the primary findings largely persisted when accounting for aperiodic activity, non-oscillatory components of the signal may have influenced post-acute beta and gamma power findings in particular. Lastly, correlations with clinical improvement were limited by the low variability in clinical responses; although associations with one-month clinical outcomes were assessed instead of post-ibogaine clinical outcomes in order to mitigate this problem, the majority of participants still showed >80% improvement in MADRS, CAPS and HAM-A scores at one month. Future work with more variability in treatment outcomes will help to clarify associations between cortical oscillations and clinical change.

## Conclusions

In sum, as part of the first prospective investigation of ibogaine treatment for veterans suffering from the sequelae of TBI, we identified both post-acute and persisting changes in neural complexity and the nature of cortical oscillations after ibogaine, which were related to psychiatric and cognitive treatment outcomes. By advancing our understanding of the neural mechanisms underlying this promising rapid treatment, our work identified several potential biomarkers of early drug effects and treatment response. With further investigation into the validity and replicability of these results, these biomarkers could enable (a) brain-based ibogaine dosing, (b) the optimization of treatment to engage specific therapeutic mechanisms, and (c) the selection of optimal candidates for ibogaine treatment based on pre-treatment neurophysiological profiles.

**Data Availability:** Owing to the sensitivity of psychiatric patient data, our IRB requires individualized review before data sharing. We have produced anonymized data related to the present findings for sharing with all scientists with research and data safeguarding plans that comport with Stanford University guidelines. Please contact N. Williams at nolanw@stanford.edu with data-sharing requests.

**Code Availability:** The Matlab EEGLAB toolbox used for pre-processing and sensor-space spectral measures can be downloaded from <https://scn.ucsd.edu/eeglab/download.php>. ROI-based statistical analyses were performed using R version 4.3.1 publicly available packages readxl, lmerTest, emmeans, rstatix, and stats. Cluster-based permutation tests were performed using the freely available python MNE toolbox (mne.stats.permutation\_cluster\_1samp\_test). Source estimation was performed using MATLAB Brainstorm, which is freely available (<https://neuroimage.usc.edu/bst/download.php>). Lempel-Ziv complexity measures were computed using publicly available code from Shartner et al. 2015 (<https://doi.org/10.1371/journal.pone.0133532.s002>) and the SIFT EEGLAB plugin ([https://github.com/scn/SIFT/blob/master/stat/stat\\_surrogateGen.m](https://github.com/scn/SIFT/blob/master/stat/stat_surrogateGen.m)). Other scripts used to analyze the data of this study are available at [https://github.com/achaiken/Ibogaine\\_rsEEG\\_project](https://github.com/achaiken/Ibogaine_rsEEG_project).

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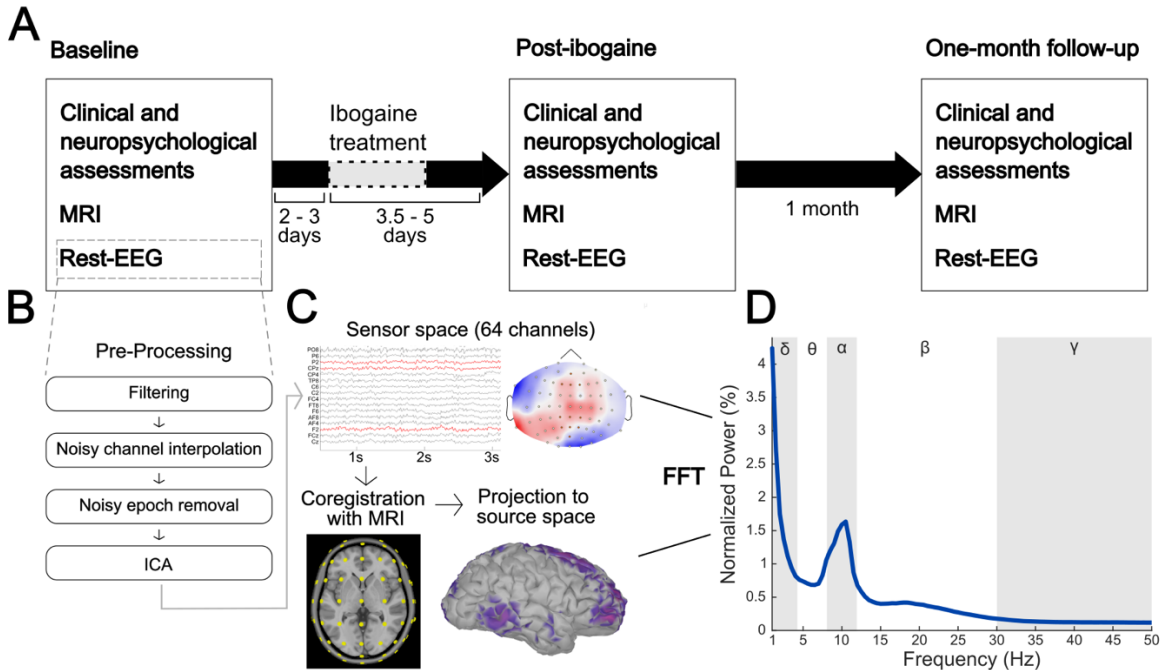
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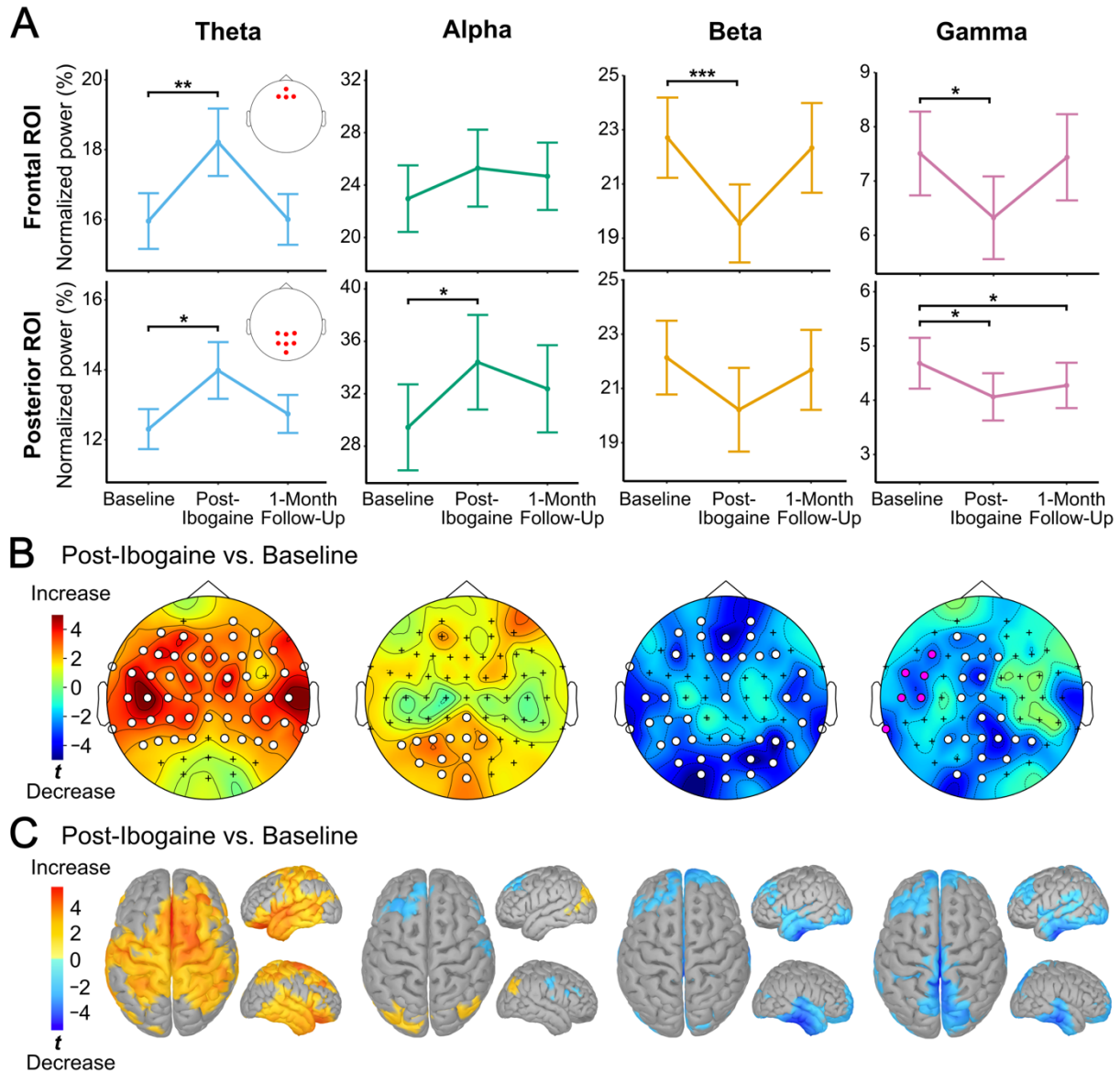
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Figures

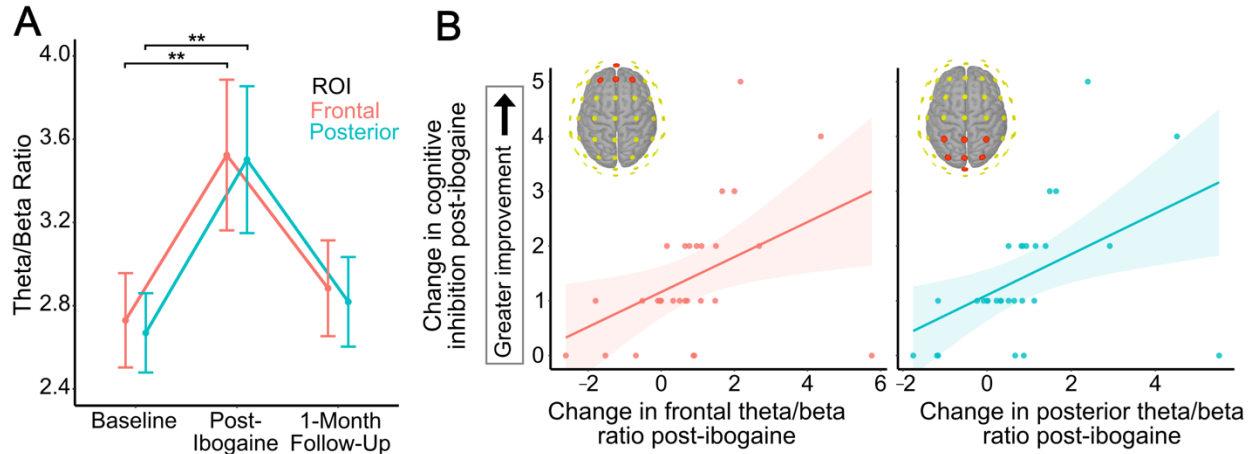


**Figure 1. Study workflow.** **A.** Timeline of data collection. Clinical and EEG data were collected at Stanford University 2-3 days before, 3.5 days after (4-5 days after for clinical assessments), and 1 month after ibogaine treatment. **B.** Resting-state EEG data from each timepoint were pre-processed by an experienced rater blinded to recording identifiers. **C.** Pre-processed data in sensor space were coregistered with individual anatomical scans and projected into brain space for source localization. **D.** A fast Fourier transform (FFT) was applied to the EEG data in sensor and source space to decompose cortical oscillations into their component frequencies. Power in predefined frequency bands was normalized to broadband power. Abbreviations: magnetic resonance imaging (MRI), electroencephalography (EEG), independent component analysis (ICA).

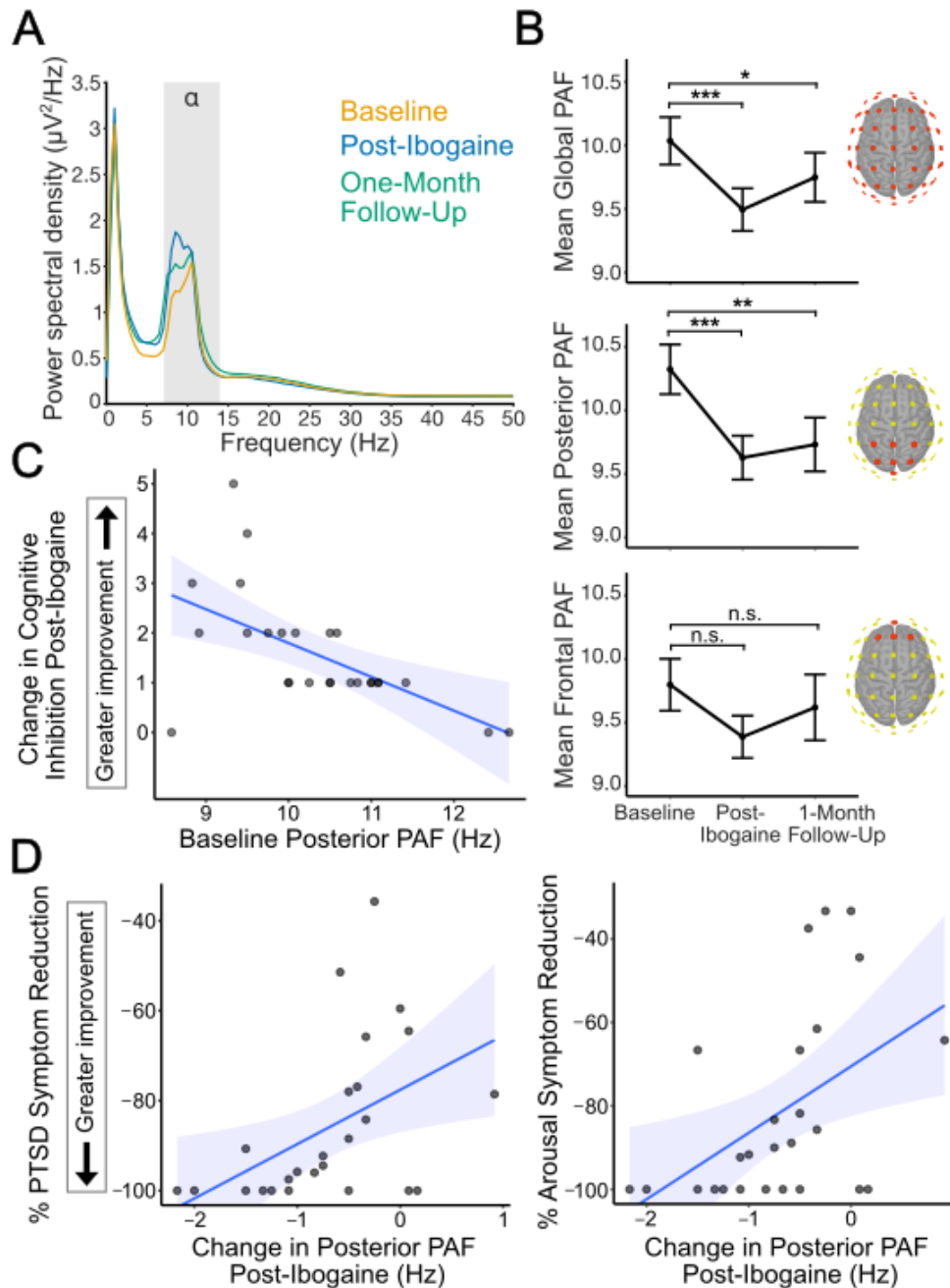


**Figure 2. Enhancement of slower frequency activity and reduction of faster frequency activity after ibogaine treatment.** **A.** In predefined frontal and posterior regions of interest (ROIs), theta (n=29) and alpha (frontal n=30, posterior n=29) power increased post-ibogaine, and beta and gamma power (n=30) decreased post-ibogaine, as compared to baseline. Reductions in posterior gamma power persisted at one-month follow-up. Error bars represent the standard error of the mean. \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$ . **B.** Channel-wide cluster-based permutation tests comparing normalized power post-ibogaine vs. baseline at the sensor level similarly revealed widespread increases in theta power, posterior increases in alpha power, and reductions in beta and gamma power. Significant clusters are displayed as white circles. A second

significant cluster is displayed with pink circles for gamma power. **C.** Source estimation localized post-ibogaine increases in theta power to fronto-central and temporal regions, alpha power to parietal and occipital regions, and reductions in beta and gamma power to frontal and temporal regions.

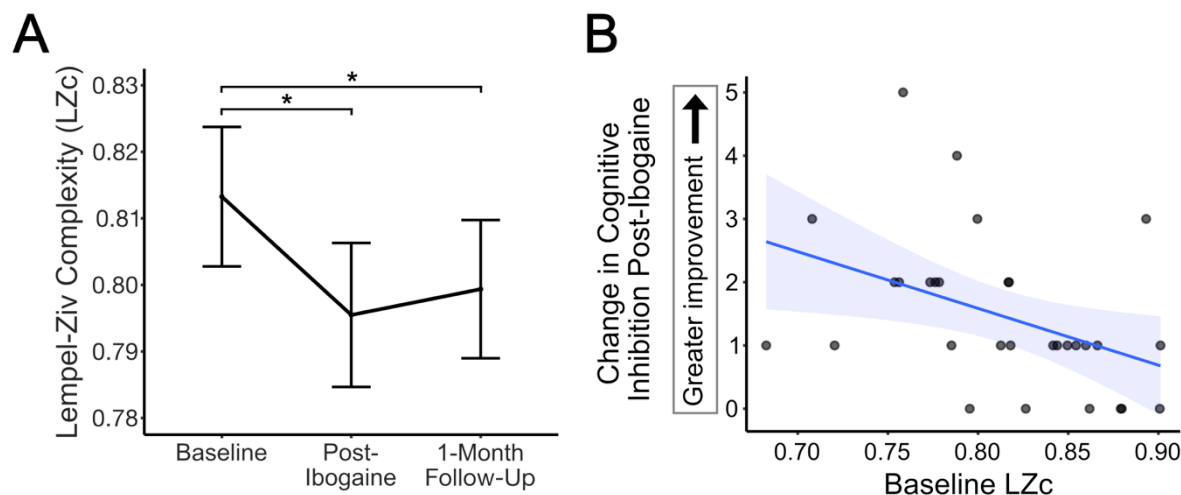


**Figure 3. An increased ratio of slower to faster oscillations after ibogaine treatment, as indexed by theta/beta ratio, correlated with executive function improvements. A.** In the frontal and posterior ROIs, theta/beta ratio increased significantly after ibogaine treatment ( $n = 29$ ) compared to baseline, and these effects were not observed at one-month follow-up ( $n = 25$ ). Error bars represent the standard error of the mean.  $** p \leq 0.01$ . **B.** Scatterplots of the relationship between increased theta/beta ratio post-ibogaine in each ROI and improved cognitive inhibition post-ibogaine ( $n = 29$ ). Cognitive inhibition was indexed using the Color-Word Inhibition scaled score. Red electrodes overlaid on the brain template represent the region of interest for the respective theta/beta ratio.

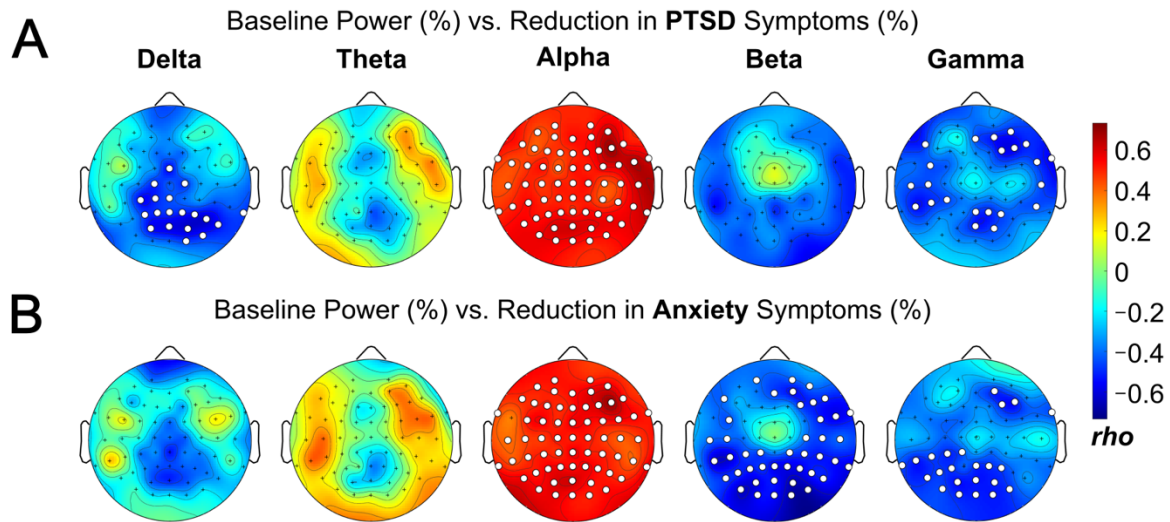


**Figure 4. Ibogaine treatment lowers peak alpha frequency (PAF), which was associated with psychiatric and cognitive outcomes.** **A.** PAF was extracted from the power spectrum for each channel at each timepoint as the local maximum within the 7-14 Hz range. **B.** Global PAF was significantly lower post-ibogaine ( $n = 26$ ), reflecting primarily a shift to a lower PAF in the posterior cortex, and this effect persisted one month after treatment ( $n = 23$ ). Red electrodes overlaid on the brain template represent the region of interest for the respective PAF calculation. \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$ , n.s. non-significant. **C.** Lower PAF prior to

treatment showed a significant correlation with greater improvement in cognitive inhibition post-  
 ibogaine (n = 26). **D.** Greater reductions in PAF post-ibogaine were significantly correlated with  
 greater improvement in PTSD symptoms, and arousal in particular, at one-month follow-up (n =  
 25).



**Figure 5. Ibogaine treatment reduces Lempel-Ziv complexity (LZc).** **A.** LZc was significantly lower post-ibogaine (n = 30), and this effect persisted at one-month follow-up (n = 27). \*  $p \leq 0.05$ . After accounting for changes in spectral power, reductions in Lempel-Ziv complexity were specific to spatiotemporal complexity, rather than temporal complexity within electrodes (see Supplement), suggesting that ibogaine may primarily influence the diversity of neural activity patterns across electrodes. **B.** Lower LZc before treatment was significantly correlated with greater improvement in cognitive inhibition post-ibogaine (n = 30).



**Figure 6. Pretreatment EEG measures of spectral power correlated with reduced PTSD and anxiety symptoms after ibogaine treatment. A.** Topoplots showing channel-wide correlations between normalized baseline power and percentage reduction in CAPS scores at one-month follow-up. **B.** Topoplots showing channel-wide correlations between normalized baseline power and percentage improvement in HAM-A scores at one-month follow-up. White electrodes signify statistical significance after FDR correction ( $p_{\text{FDR}} < 0.05$ ).