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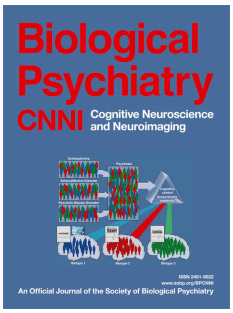

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Neural correlates of ibogaine: Evidence from functional neuroimaging of military veterans

Neuroimaging driven exploration of ibogaine in humans

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Abstract

Background: Ibogaine was recently found to result in significant functional improvements in treating the sequelae of traumatic brain injury (TBI) among Special Operations Forces veterans (SOVs). In the present article, we use multimodal neuroimaging to elucidate the neural correlates of ibogaine in 30 male SOVs who received ibogaine treatment.

Methods: Arterial spin labeling and blood oxygen level-dependent functional magnetic resonance imaging data were collected before, immediately after ibogaine treatment, and at 1-month follow-up. A whole-brain exploratory analysis was conducted to examine the effects of ibogaine on resting-state regional cerebral blood flow (rCBF) and functional connectivity.

Results: The results revealed gradual increases in rCBF in the cortical, limbic, and striatal subregions, and changes in functional connectivity across a wide range of functional networks. The magnitude of treatment-induced rCBF changes in the left insula and left anterior cingulate cortex correlated significantly with improvements in TBI-related disability symptoms.

Conclusion: Our results suggest that ibogaine may involve widespread reorganization of functional connections in the brain, and that persisting regional changes in metabolic activity after ibogaine treatment, particularly within paralimbic brain regions, might be related to the observed therapeutic effects of ibogaine. Our findings serve to generate future hypotheses for larger, controlled neuroimaging studies of ibogaine in humans, necessary to validate these initial findings.

Introduction

Traumatic brain injury (TBI) is a major public health concern, with chronic effects ranging from a reduced ability to perform daily tasks to various emotional and cognitive impairments (1), such as post-traumatic stress disorder (PTSD), major depressive disorder, and generalized anxiety disorder (2–5). Special Operations Forces veterans (SOVs) have one of the highest rates of TBI and PTSD, both of which greatly increase the risk of suicide (6). Compared to civilians, combat veterans from the Iraq and Afghanistan conflicts exhibit a much higher prevalence of TBI (9-28%) and PTSD (lifetime prevalence 29%) (7). TBI can occur from a sudden blow to the head, blasts, or blunt force falls (4). Currently, the standard of care for TBI includes rehabilitation therapy, talk therapy, and medication, which focus on symptom management rather than remission, and have limited efficacy for many veterans (8). Improved treatment strategies for the sequelae of TBI are urgently needed.

Ibogaine is a naturally occurring psychoactive compound derived from the root bark of the *Tabernanthe iboga* plant found in Gabon, Central Africa. Ibogaine has traditionally been used by the Bwiti tribe in spiritual ceremonies (9). In the Western world, it has been explored as a potential treatment for addiction (10), as well as various other neurological and psychiatric disorders (11). Ibogaine research in humans has been limited due to legal restrictions, abuse potential, and safety concerns associated with increased cardiovascular risk (12). Coadministration of ibogaine with a cardioprotective agent like magnesium (13), however, may mitigate this risk. We conducted the first-of-its-kind proof-of-principle observational study of the Magnesium-Ibogaine: Stanford Traumatic Injury to the Central Nervous System (MISTIC) protocol in special operations veterans (SOVs) with chronic disability and psychiatric symptoms following TBI. Participants experienced remarkable and sustained clinical improvements (14,15) after treatment with MISTIC. The neural mechanisms of action of MISTIC, however, are not yet clear.

Ibogaine is rapidly converted into an active metabolite (16), noribogaine, which is eliminated more slowly than ibogaine, allowing the prolonged release of small proteins called neurotrophic or growth factors (17–19) that can promote neuroplasticity (20). Neuroplasticity is often paralleled by brain-wide metabolic changes that can be captured via functional magnetic resonance imaging (fMRI) methods. Previous fMRI studies have shown that TBI is associated with long-term changes in blood perfusion, such as reduced blood flow (21,22). These changes often precede observable structural abnormalities in neurodegenerative diseases, making blood perfusion a sensitive marker of cerebrovascular dysfunction seen in TBI (23,24). Normal neuronal cell activity and brain function require an increased flow of oxygenated blood (via neurovascular coupling) in response to increased metabolic demand at activated regions (25). Two predominant methods to capture neurovascular coupling are arterial spin labeling (ASL) and blood-oxygen-level-dependent (BOLD) neuroimaging techniques. Both BOLD and ASL fMRI methods have been used to examine changes in brain activity in response to psychedelic and psychotropic compounds (26,27), as well as in psychiatric populations (28,29). A summary of the first neuroimaging studies of common serotonergic psychoactive compounds can be found in the Supplementary Table S1. To the best of our knowledge, however, no previous fMRI studies have investigated the neuroplastic effects of ibogaine on brain metabolic activity and functional connectivity in humans.

Here, we implement a multimodal approach using ASL and BOLD fMRI to elucidate the neural mechanisms of action of MISTIC treatment and its associated therapeutic benefits in SOVs. In

particular, this pilot study used ASL to examine regional cerebral blood flow (rCBF) changes and BOLD fMRI to examine resting-state functional connectivity (rsFC) changes immediately and one month after MISTIC treatment.

Methods

Inclusion and ethics

The research procedures of this study were approved by the Stanford University Institutional Review Board (IRB). Informed written consent was obtained from all participants, and the process was compliant with all relevant ethical regulations (15). Roles and responsibilities were agreed upon among authors and collaborators. The trial was preregistered at ClinicalTrials.gov (NCT04313712) and osf.io (https://osf.io/24trc/).

Participants

Thirty SOVs who had voluntarily enrolled in an ibogaine treatment at a clinic in Mexico were enrolled in the original observational pilot clinical study (15). Of our final sample of 27 that completed neuroimaging, 26 SOV males were included in imaging analyses based on data quality (image distortion), all with mild to moderate TBI and most meeting diagnostic criteria for PTSD (Figure 1). Two of the 27 participants were unable to report the exact number of TBIs due to a large number of blast exposures. Hence, this value was imputed from the original cohort's (N = 30) mean and standard deviation (SD) as Mean + 5 x SD. Further participant demographics can be found in Supplementary Table S2 and previously published work from this study (15).

Figure 1. Study Design and data collection at three time points

Study Design: Following enrollment, participants undertook initial baseline evaluations over a secure video platform with a clinical neuropsychologist (two months to one week before in-person assessments), including a review of medical and psychiatric history, history of combat exposures, history of TBI and blast exposure, and a psychodiagnostics interview. Imaging data were acquired and analyzed at baseline, immediately post-treatment, and one month after treatment (Figure 1). All participants presented with a history of TBI, according to the Ohio State University Screening for TBI exposure (30) and the Department of Defense TBI classification (31). In addition, the Boston Assessment of TBI-Lifetime was administered to quantify blast exposure (32). For further details of these methods, refer to Cherian et al. (15).

Treatment: The MISTIC treatment involved the administration of oral ibogaine (mean ± s.d. total dose = 12.1 ± 1.2 mg kg^{-1}) with intravenous magnesium sulfate (15). Participants were evaluated medically and received coaching from a licensed therapist about the ibogaine experience prior to treatment. No psychotherapy was delivered during treatment. The effects of ibogaine may last 24–72 hours or longer (33), and participants underwent continued monitoring for 72 hours after dosing.

MRI Acquisition: All participants were screened for MRI safety before scanning procedures. Scans were acquired using a 3 Tesla GE Discovery MR750 scanner with a 32-channel head-neck imaging coil at the Center for Cognitive and Neurobiological Imaging at Stanford University. Whole-brain structural images were collected using GE's BRAVO sequence (3D, T1-weighted, FOV = 256x256mm; matrix = 256 x 256 voxel; TR = 6.39ms, TE = 2.62ms, slice thickness =

0.9mm, flip angle = 12°). One whole-brain dual BOLD-ASL scan was acquired during all three time points. The ASL component was a 6-minute HyperMEPI Pseudo-continuous ASL (pcASL) image (2D, FOV = 80x80mm, matrix = 80x80 voxel, TE = 11.3ms, TR = 3.1s, slice thickness = 3mm, flip angle = 60°, Imaging frequency = 127.8, Multiband Acceleration Factor = 4). Two whole-brain 8-minute resting state scans were acquired consecutively (TR = 1300ms, TE = 30ms, flip angle=60°, slice multiband acceleration factor = 6, FOV = 230x230mm, matrix = 128 × 128 voxel). All participants were instructed to keep their heads still and eyes open during the scan. During the resting state task, they were asked *to let their minds wander freely and avoid repetitive thoughts* while attending to a white fixation cross on a black screen. Memory foam and inflatable padding were used to restrict head motion. Additionally, participants' alertness was monitored using in-scanner video cameras.

Preprocessing:
ASL: The pcASL data were preprocessed on ASLtbx (34) and implemented in MATLAB (R2021b 9.11.0). PCASL images were reoriented, aligned, and coregistered to the anatomical T1w image. Next, six motion parameters (x, y, z translations, and 3 rotations), spin labeling, and control labeling time paradigm (the zigzag pattern) were all regressed from the motion time courses. This was followed by temporal Butterworth high-pass filtering (0.04-1 Hz), spatial smoothing, and normalization to standard MNI space. The outputs were then Z-scored and skull-stripped using a whole-brain mask from the FMRIB software library (FSLv5.0).

BOLD: All data were preprocessed using fMRIPrep 20.2.6 (35,36), based on Nipype 1.7.0 (37,38). Anatomical data, T1-weighted (T1w) images, were corrected for intensity non-uniformity, skull-stripped, and brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM), and gray matter (GM) was performed on the brain-extracted T1w volume-based spatial normalization to standard spaces (MNI152NLin2009cAsym) was performed through nonlinear registration. The preprocessing steps were performed on both BOLD resting-state runs for each subject. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. This was followed by an in-house pipeline applied, where all data were spatially smoothed (6-mm-full-width, half-maximal Gaussian kernel), nuisance variables from non-brain tissue signals (CSF, WM), global signal, and 24 motion parameters were regressed from the data, and a temporal bandpass filter (0.01-0.1 Hz) was applied.

Analyses: All analyses mentioned regressed effects of age, combat exposure scale (CES), and number of TBIs. Due to the novelty of this study, the results serve to generate hypotheses for similar future studies.

ASL: To investigate changes in rCBF, a one-way repeated-measures ANOVA, using a *flexible factorial* model across all three time points, was designed on SPM12 for 26 participants. The results were corrected for multiple comparisons using the FWER method. While best practices for fMRI analysis (39) due to low perfusion signal-to-noise-ratio and our modest sample size (N<30), a cluster-level threshold of $p<0.001$, $P_{cFWER}<0.05$, and extent thresholding $k>100$, and voxel-level primary threshold of $p<0.005$ ($T>2.65$, $Z > 2.57$) was chosen. To enhance transparency, we also display the primary threshold of $p<0.001$ thresholded maps in Supplementary Figure S1. The significant clusters were then identified using the Harvard-Oxford atlas (40) on FSL to derive cortical and subcortical brain regions.

BOLD Region of Interest (ROI) Selection: To understand network-level alterations from ibogaine, the brain was parcellated into 12 networks and 120 ROIs spanning whole-brain cortical and subcortical regions. The cortical parcellation was extracted from Schaefer's 100 brain parcellation (41), including 7 cortical networks: central executive network, default mode network, ventral attention or salience network, dorsal attention network, limbic network, somatomotor network, and visual network. The bilateral dorsolateral prefrontal cortex (DLPFC) was also included and extracted from the Multi-Subject Dictionary Learning atlas (42). To cover subcortical regions, we included 20 regions classified into 6 networks: amygdala, ventral striatum, thalamus, hippocampus, and sgACC. The bilateral executive, sensorimotor, and striatum limbic sub-regions were predefined using the Oxford-GSK-Imanova Striatal Connectivity Atlas (43). We extracted 6 sub-regions of the amygdala using the Juelich histological atlas (44): the bilateral centromedian amygdala (CMA), bilateral laterobasal amygdala (LBA), and bilateral superficial amygdala (SA). Lastly, bilateral thalamus and hippocampus were extracted from the Harvard-Oxford cortical and subcortical structural atlases (FSL v5.0.9) (45), and bilateral sgACC were extracted from the Yale Brodmann atlas (46). The full list of 120 ROIs is available in Supplementary Table S3.

BOLD rsFC: Functional scans were merged into a single time series for analysis. All FCs were calculated from Pearson correlation coefficients using the Python nilearn toolbox, which was then transformed into Fisher's Z scores for further study. All statistical analyses were conducted in MATLAB. A one-way ANOVA was used to evaluate FC pairs statistically different across time points (baseline/immediate post/1-month post). Due to the novel and hypothesis-generating nature of this study, and the small sample size (power calculation = 0.3), we used liberal statistical thresholds for BOLD rsFC analysis, i.e., *uncorrected* $p<0.005$. A post hoc t-test following ANOVA was used to determine the directionality of effects, and a Cohen's d effect size between each group pair was also calculated (Supplementary Table S4).

Correlations to clinical scores: For subregions that showed significant changes in rCBF after treatment, we used a 2-way repeated measures ANOVA, conducted in MATLAB, to see if changes in imaging modalities predict clinical outcomes seen in the cohort (15); WHODAS (47), and CAPS-5 (48) from baseline to immediate and 1-month post-treatment. Results were corrected for sphericity using the Greenhouse-Geisser $p<0.05$ threshold. To understand clinical associations, the rCBF changes within significant subregions of the ASL results were modeled in linear regression to visualize the relationships.

Results

ASL: A one-way repeated measures analysis of variance (ANOVA) showed increased rCBF in specific clusters. Overall, we observed a gradual increase in the mean rCBF after ibogaine treatment in cortical, limbic, and striatal regions.

Figure 2. Pairwise contrasts of regional cerebral blood flow (rCBF) after ibogaine treatment (n = 26). [A] Regions in yellow show an increase in rCBF from baseline to immediately post-treatment, anterior cingulate cluster: p = 0.0063**; insular and surrounding cluster: p = 0.014* (*uncorrected results shown for visualization only*). **[B]** Regions in yellow show a significant increase in rCBF from baseline to one-month follow-up, anterior & middle cingulate cluster: p = 0.000073***, p_{cFWER} = 0.0090**; insular and surrounding cluster: p = 0.00037***, p_{cFWER} = 0.024* (cluster-level FWER corrected). **[C]** Mean cluster values were extracted per participant at all three time points and visualized using boxplots (exclusive median quartile calculation) with whiskers representing the 1.5 interquartile range (IQR). The black cross ('x') represents mean rCBF values. **[D]** Atlas of significant clusters (in yellow) with rCBF changes from baseline to one-month follow-up.

At the 1-month follow-up, a significant increase in rCBF was observed from baseline in 2 clusters, parceled into 6 subregions (cluster $p_c<0.001$, voxel $p_v<0.005$, and family-wise error correction rate $p_{FWER}<0.05$). These increases were observed bilaterally in the anterior and middle cingulate cortex, and in the left insula, planum polare, orbitofrontal cortex, and putamen (Figure 2B). Increases in rCBF (*uncorrected* p = 0.0063 and p = 0.014) were also observed at the immediate-post follow-up but did not pass FWER (Figure 2A). Detailed values are shown in Supplementary Figure S2.

BOLD: Exploratory analyses of the resting-state BOLD fMRI data revealed the reorganization of widespread functional brain networks post-treatment. A repeated measures one-way network-level ANOVA was conducted across the 12 networks: central executive network, default mode network (including the dorsolateral prefrontal cortex), ventral attention or salience network, dorsal attention network, limbic network, somatomotor network, visual network, amygdala, ventral striatum, thalamus, hippocampus, and subgenual anterior cingulate cortex (sgACC) networks.

We found 16 rsFC pairs that met our statistical threshold (*uncorrected* p<0.005), providing preliminary evidence of a whole-brain network reorganization following ibogaine treatment. These results suggest that visual, somatosensory, limbic (temporal pole, hippocampus, and amygdala), default mode, dorsal attention, and salience networks are subject to the most changes in functional connectivity after ibogaine treatment. Detailed information and effect sizes for all 16 rsFC pairs are provided in Supplementary Table S4. Six rsFC pairs with the most notable changes are shown in Figure 3A. Since none of these pairs passed the correction for multiple comparisons, further investigation of clinical correlations is not reported.

Figure 3. Whole-brain functional network reorganization after ibogaine treatment. [A] Boxplots of group-level trends in rsFC of the 6 most significant pairs. Note: These are group averages of changes in relative connectivity. The whiskers are drawn within the 1.5 IQR value. **[B]** 16 rsFC pairs (*uncorrected* p<0.005) are plotted on a glass brain to visualize the widespread nature of the effects on functional connectivity. Each colored dot represents the node for each ROI.

Clinical correlations: We conducted a repeated measures ANOVA with the 6 significant subregions ($p_{cFWER}<0.05$) from the ASL results and explored if rCBF changes were associated with clinical disability and PTSD outcomes, yielding 12 tests. Although no associations survived FDR correction, specific findings (*uncorrected* p<0.05) show moderate effect sizes (r≈0.5), which we

report as exploratory findings. Our model showed a relationship between rCBF increases in the left insula and left cingulate cortex and reductions in functional disability from baseline to one-month follow-up, as measured by World Health Organization Disability Assessment Schedule 2.0 (WHODAS)(47) total scores (the primary clinical outcome of this study). See Figure 4 for scatterplots of changes in rCBF and changes in WHODAS scores. The six subscales of the WHODAS (cognition, mobility, self-care, getting along, life activities, and participation) were further explored, and rCBF increases in the left insula showed strong ($r>0.6$) associations with improvement in *mobility* and *life activity*. No associations were found with the clinician-administered PTSD scale for the DSM-5 CAPS-5 (48).

Figure 4. Increases in left insular and anterior cingulate cerebral blood flow one month after ibogaine treatment were associated with improvements in functional disability. Scatterplots show individual data points with linear regression lines, 95% confidence intervals, uncorrected p-values, and Pearson's correlation coefficients for visualization. **[A]** Change in rCBF in the left insula vs. changes in WHODAS overall score, *life activity* subscales, and *mobility* subscales from baseline to one-month follow-up. **[B]** Change in rCBF in the left cingulate cluster vs. change in WHODAS overall score from baseline to one-month follow-up.

Discussion

Our multimodal imaging findings indicate broad changes in functional connectivity and increase in regional metabolic activity following a single session of MISTIC in combat veterans. ASL imaging showed increases in rCBF in the left insula, orbitofrontal cortex, putamen, and planum polare, and bilaterally in the anterior and middle cingulate cortex immediately post-treatment, and further increases one month after ibogaine treatment, compared to baseline. Importantly, increases in rCBF in the insula and anterior cingulate that persisted one month after treatment were associated with sustained improvements in overall disability. Exploratory BOLD functional connectivity analyses revealed pre- to post-treatment functional connectivity changes between 16 network pairs, notably between limbic, default mode, dorsal attention, and salience networks.

The limbic system, including the amygdala, hippocampus, and cingulate gyrus, is involved in cognition, emotional and social processing, learning, and memory (49). Several studies of adults with TBI and/or PTSD have found altered rCBF and dysfunction in limbic and paralimbic regions (50–52). Using ASL, we found a significant increase in rCBF in similar limbic regions such as the anterior and middle cingulate cortex, suggesting a potential shift in rCBF patterns after ibogaine treatment. While the anterior cingulate connects to the "emotional" limbic system and the "cognitive" prefrontal cortex, the middle cingulate plays a role in social behavior and monitoring the outcomes of decisions during social interactions (53,54). Using BOLD fMRI, global widespread changes in rsFC were found after treatment with MISTIC, which included limbic regions. A similar global effect has been reported in the study of other psychedelic substances (55). Among these widespread effects, changes in functional connections to the prefrontal hub of the default mode network were observed; specifically, amygdala-medial prefrontal cortex (mPFC) connectivity was significantly reduced after ibogaine treatment compared to baseline. The amygdala regulates emotion processing and fear conditioning (56,57). Functional imaging studies of patients with PTSD have shown heightened resting amygdala-frontal connectivity that underlies emotional dysregulation (58). The hyperactivity of the mPFC can lead to excessive self-referential thinking and rumination (subclinical features of depression) and anxiety, which are comorbid in this cohort. Therefore, the treatment-induced reduction of the amygdala-default mode network functional connectivity may reflect a MISTIC-related dampening of emotionally reactive circuitry.

Following ibogaine treatment, increased functional connectivity between the left dorsal attention network (implicated in goal-directed attention maintenance) and the hippocampus (implicated in memory consolidation and learning) could suggest treatment-induced improvements in memory integration with the attention network (59). This is particularly important as memory impairment and difficulty maintaining attention on a task are common, disabling effects of TBI (60,61). The dorsal attention and hippocampal networks have been implicated in PTSD and TBI, so it is promising that their reconfiguration persists ~3-4 days and 1-month post-treatment. We postulate that ibogaine may involve a gradual reshaping of this neural network away from the disordered state.

Across our analyses, changes in regions associated with sensory processing were also found. Using ASL, significant increases were seen in the putamen, which affects motor control, learning, language processing, and addiction (62,63); the *planum polare*, a portion of the superior temporal gyrus involved in auditory and receptive language processing (64); the *orbitofrontal cortex*, responsible for sensory integration, emotion, and reward-related behavior (65); and the *insula*, a convergent point of interoceptive processing (or a sense of inner self) (66,67) with a role in affective-perceptual and cognitive-evaluative forms of empathy. Another interesting network arising from our BOLD analysis is the salience network, which detects and filters important sensory and emotional stimuli. Daniels et al. (2010) found that compared to controls, PTSD groups have difficulties in working memory tasks and task-induced switching, engaging, and disengaging the default mode and central executive networks, a function of the salience network (68). The salience network may become hyperactive, leading to an overemphasis on traumatic stimuli and a heightened sensitivity to environmental cues (69). These changes in the somatosensory network warrant further investigation into their contribution to post-treatment reconfiguration. Overall, our exploratory analyses revealed overlap in the limbic and sensorimotor regions implicated by both modalities.

Lastly, we explored the associations of the observed rCBF alterations in MISTIC-induced clinically significant therapeutic outcomes. Several studies have shown that decreases in rCBF resulting from TBI are related to worse histopathologic and behavioral outcomes (52,70). In particular, evidence suggests that cognitive impairment in patients with mild TBI could be due to regional CBF abnormalities (71). Lowered CBF is also associated with poorer memory and executive function/processing speed (72) and is linked to neurodegeneration (73). We found moderate associations ($r>0.5$) between rCBF increases in the left insula and ACC and greater improvements in functional disability one month after ibogaine treatment (Figure 4). With a role in explicit motivation (74,75), greater insular activity is thought to induce a conscious desire to get around and complete domestic roles. Evidence also suggests that the insula plays a role in self-determined behavior, such as engaging in intrinsically motivated leisure activities (76). This is perhaps reflected in the strong associations of the insular rCBF change ($r>0.6$) with improvements in WHODAS subscales of *mobility* and *life activity* (77). The left ACC has also been shown to have a role in external motivation and social cognition (78,79). It is worth noting that the disability scores showed gradual improvement until the 1-month time point, at which stage the change in disability symptoms compared to the baseline was found to be most significant. This gradation is similar to the gradual rCBF increases observed in the left insula and ACC from baseline to one month post-treatment.

Based on existing psychedelic literature on substances such as LSD, psilocybin, N, N-Dimethyltryptamine, and methylenedioxy-methamphetamine, Carhart et al. proposed a unified model for the therapeutic action of psychedelics, formulated as "relaxed beliefs under psychedelics" (REBUS) that integrates the free-energy principle and the entropic brain hypothesis (80). The model suggests that psychedelics relax high-level brain patterns, liberating the flow of information from intrinsic sources like the limbic system, although additional research into how ibogaine may align with the REBUS framework is still needed.

Limitations: While this exploratory work represents the first multimodal functional neuroimaging investigation of ibogaine's neural correlates, there are limitations to consider. Our sample size was modest and homogenous; limited to adult, middle-aged, male combat veterans with TBI. The low statistical power prevented some results from meeting the standard statistical rigor of multiple comparisons, and thus, larger, adequately powered studies are needed to verify these findings. Due to the novel, proof-of-principle nature of this work, this was a single-arm, open-label observational study and did not include a blind or control group. Since most of the SOVs had several TBIs across their lifetime, we did not have the necessary information to include the radiological characteristics of the site of brain injury. Next, when correlating neuroimaging changes with clinical improvements in PTSD symptoms, results were limited by the lack of variance in CAPS, since the majority of participants showed near-complete to complete improvement. In the future, data collected in larger, more diverse groups with a placebo control would be required to account for other influential factors and to confirm the findings from our study (15).

Conclusion

Modern imaging techniques and years of indigenous medicine bring us to an enigmatic intersection, to systematically unveil the therapeutic potential of psychedelic medicines. Special forces veterans have particularly high rates of TBI and PTSD and often have limited and less efficacious treatments available for their complex symptomology (8). Therefore, there is a strong impetus to understand the neural basis of emerging alternative treatments. Our multimodal imaging findings provide initial insights into the neural processes of magnesium-ibogaine treatment for combat-related TBI. Importantly, specific alterations in regional metabolic activity were associated with the large improvements in functional disability ($p_{corrected} < 0.001$; Cohen's $d = 2.20$) observed after treatment (15). This was the driving force of this imaging analysis: to explore the neural underpinnings of the striking clinical improvements. Additional research replicating and expanding the current findings in larger, controlled studies is needed to further elucidate the neural mechanisms underlying the promising clinical effects of ibogaine.

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Disclosures

Competing Interests: Nolan R. Williams is an inventor in a related provisional patent application number 63448116. The application is related to the safety of the MISTIC administration described in the manuscript. Nolan R. Williams, Manish Saggar, Azeezat Azeez, and Malvika Sridhar are inventors in a related provisional patent application number 63/586,991. The application is related to therapeutically changing human brain patterns using MISTIC administration. All other authors report no biomedical financial interests or potential conflicts of interest.

Supplement Description:

Figures S1-S2 and Tables S1-S4

Data availability

Due to the privacy concerns surrounding psychiatric patient data, our Institutional Review Board (IRB) mandates individualized review before data sharing. We have generated anonymized data relating to our research findings and are prepared to share it with scientists who have established research and data protection protocols consistent with Stanford University guidelines. Please contact M. Saggar at saggar@stanford.edu with data-sharing requests.

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Contributions: M.Sr. and A.A. performed acquisition, preprocessing, statistical analysis, and interpretation of imaging data and participated in the literature review and writing of the paper. A.D.G. performed imaging data acquisition, assisted in statistical analysis, and participated in writing the paper. J.I.L. participated in figure generation, writing, reviewing, and editing the paper. A.F. assisted in statistical analysis, psychological assessments and provided feedback on the paper. K.N.C. performed screening and psychological assessments, led study execution at Stanford for all participants, provided feedback, and reviewed the paper. S.H. performed imaging data acquisition, participated in the literature review, and assisted in writing. J.N.K. guided the primary analyses and figure generation. I.H.K. assisted with study design, supported study execution at Stanford, assumed the role of protocol director while N.R.W. was on leave, and provided feedback and reviewed the paper. C.E.R. provided guidance on analyses and interpretation of data, reviewed, and critiqued the paper. M.Sa. contributed to the design of statistical analysis, provided guidance, reviewed, and critiqued the paper. N.R.W. conceived the study; supervised study design, budgeting, and execution at Stanford; was protocol director of the study until his leave; and reviewed and critiqued the paper. All authors approved the final manuscript. M.Sr. and A.A. were co-first authors; M.Sa. and N.R.W. were co-senior authors.

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Supplementary Information

Supplementary Information
Supplementary Tables 1–4 and Figs. 1-2.

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