The linear-model formalism introduced here to explain the performance of conventional beamformers for correlated (brain or artifact) sources can be easily expanded to more than two sources, which will be done in our future study.

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PROCEEDINGS #18. TRANSCRANIAL INFRARED BRAIN STIMULATION MODULATES EEG ALPHA POWER

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1. Abstract

Transcranial Infrared Brain Stimulation (TIBS) with a 1064-nm laser applied to the right forehead has been shown to improve human cognitive function. To explore the neurophysiological effect of this photobiomodulation, we measured the 64-channel electroencephalogram (EEG) before, during and after the laser stimulation. After data collection from 20 human subjects, we applied time-frequency analysis to the time series taken from an electrode (Fp2) near the TIBS site and found significant dose-dependent TIBS-induced increases of Alpha (8-13 Hz) band power. After performing 3D source reconstruction based on 64-channel Alpha power densities, we were able to clearly demonstrate, for the first time, that TIBS neuromodulated an ipsilateral, fronto-parieto-occipital network and also a contralateral, parieto-occipital network at the Alpha frequency throughout the 11-min stimulation period.

2. Introduction

Transcranial Infrared Brain Stimulation (TIBS) uses coherent infrared light to stimulate neurological functions for cognitive or emotional benefits. According to previous placebo-controlled behavioral studies, enhanced attention, working memory and executive functions were observed after performing TIBS on the human forehead [1-3]. The mechanism of TIBS is that infrared laser at 1064 nm is able to up-regulate the respiratory enzyme cytochrome c oxidase (CCO) in the mitochondrial electron transport chain, which further results in a hemodynamic increase of cerebral oxygenation [4].

Electroencephalography (EEG) is a non-invasive brain imaging tool that can detect mass field potentials originating from the cerebral cortex in real time with a high temporal resolution. According to previous studies, desynchronization of Alpha (8-13 Hz) and Beta (13-30 Hz) frequencies has been associated with enhanced cognitive operations and memory performance [5]. Previous clinical research-based TIBS studies also reported that TIBS was able to enhance cognitive operations and memory functions [1-3]. However, to the best of our knowledge, no study has mapped cerebral EEG changes in response to TIBS. The purpose of this study was to explore EEG signal changes throughout the cerebral cortex at different frequency bands before, during, and after TIBS. In this study, we utilized a placebo-controlled protocol and recorded 64-channel EEG time series before, during, and after 11-min TIBS so as to investigate the electrophysiological effects of TIBS.

3. Methods

We employed a 1064-nm laser that was provided by Cell Gen Therapeutics LLC, Dallas, TX (Model CG-5000) to administer TIBS. The stimulation target was on the right pre-frontal cortex above the right eye. The laser beam was well collimated with a power of 2.2 W. The laser aperture had a beam area of 13.6 cm^2. Thus, the power density of the laser was 0.16 W/cm^2. The energy density dose per minute was 9.7 J/cm^2. The stimulation period in each experiment was 11 minutes (660 seconds), which resulted in a total energy of 1452 J (=2.2 W × 660 s) for each individual. We employed a 64-channel 10-10 EEG system (BioSemi instrumentation) to record electrophysiological data from 20 human healthy participants. During the placebo procedure, the laser's power was at near-zero level.

Both placebo and TIBS experiments lasted 16 minutes, including a 2-minute baseline, 11-minute TIBS/placebo period, and 3-minute recovery period. EEG data acquisition was continuous throughout the 16-min experiment. Subjects were instructed to keep their eyes open and to stay awake. All subjects were blinded between placebo and TIBS conditions.

All EEG data processing were performed using MATLAB. Specifically, (1) the recorded 64-channel time series were band-pass filtered between 1-40 Hz to exclude the power-line signals at 60 Hz and other high frequencies. (2) Independent Component Analysis (ICA) was performed to remove artifacts from eye blinks, improper electrode contact, electromyography and electrocardiography [6]. (3) The noise/artifact free EEG data were analyzed by a time-frequency method in order to determine/select a major frequency band for image source reconstruction. This time-frequency analysis focused on an electrode at Fp2 since it was located the nearest to the TIBS site. For each subject, the time series from electrode at Fp2 was extracted. It was sectioned into 15 temporal pieces, including a 2-minute baseline piece, 11 1-minute TIBS/placebo pieces and 3 1-minute recovery pieces. Next, the power spectrum of each temporal piece was calculated. After that, the power spectra during TIBS/placebo and recovery pieces were normalized with respect to the baseline. The 14 normalized power spectra representing TIBS-induced power alteration during 11 minutes of stimulation and 3 minutes of recovery were then combined to form a time-frequency map. We repeated the above process for each of the 20 subjects and averaged the time-frequency map across all the subjects for TIBS and placebo, respectively. Finally, we subtracted the averaged placebo time-frequency map from the TIBS time-frequency map.

The pre-processed 64-channel data were also analyzed to observe the cortical regions modulated by TIBS based on EEG power densities at the Alpha band. Specifically, (1) the EEG data was band-pass filtered at four different frequency bands: 1-4 Hz (Delta band), 4-8 Hz (Theta band), 8-13 Hz (Alpha band) and 13-30 Hz (Beta band). (2) Each frequency band was then temporally sectioned as described above. (3) The power density of each electrode was then calculated for each temporal piece, yielding 15 64-element vectors representing power topographies across the entire 16-min experiment. (4) Next, eLORETA [7] was employed to perform 3D EEG source reconstruction and thereby convert the 64-element scalp topographies into a 3D (6239-element) cortical voxel map. For each voxel, the values under TIBS and recovery sections were normalized to the baseline of the same voxel. The normalized values at each voxel represented the percentage of increase/decrease of regional cortical activity during treatment/placebo and recovery sections. By performing two sample t-tests of these normalized voxel values between TIBS and placebo experiments, the t values across all voxels among 20 subjects were computed and imaged. A threshold of t=2.5 was applied to extract TIBS-modulated regions with a p-value < 0.01.

4. Results

Fig. 1 shows the time-frequency representation of the electrode (at Fp2) closest to the stimulation site. Among 20 subjects, a gradual and strong increase of power density in the Alpha band (8-13 Hz) and a small portion of Beta band (13-30 Hz) was observed across time during TIBS. TIBS started at t=0 and ended at t=11 min. The

strongest activation was between 8-10 min (77-97 J/cm^2) after TIBS started, and the Alpha power density diminished rather quickly during the recovery period, 2-3 min after TIBS stopped.

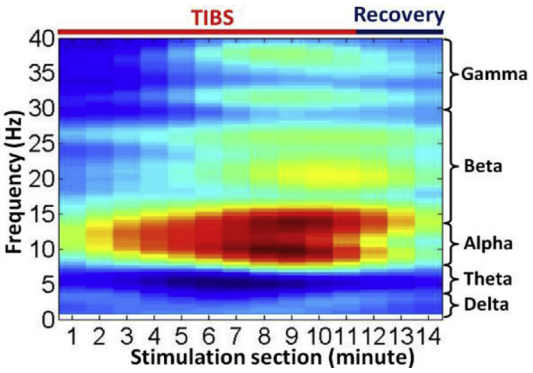

Fig. 1. The subtraction of averaged time-frequency map between TIBS and Placebo at electrode Fp2. (N=20).

Fig. 2 shows several rendered cortical maps and 3D tomographic images at 6, 8, 9, 10, and 11 min after TIBS onset. These t-maps showed TIBS-induced significant changes in Alpha-band power relative to baseline. Moreover, (i) this change manifested after approximately 2 minutes, (ii) the neuromodulation propagated from anterior to posterior cortical regions, (iii) TIBS modulated ipsilateral activity at the anterior cortex, while also modulating bilateral activity at the posterior cortex. (iv) TIBS modulated an ipsilateral, fronto-parieto-occipital network and also a contralateral, parieto-occipital network at the Alpha frequency throughout the 11-min stimulation period.

5. Discussion and Conclusion

We performed a placebo-controlled experiment to record EEG data from 20 human subjects before, during, and after prefrontal TIBS. A gradual and strong dose-dependent increase of EEG power in the Alpha band was observed, suggesting that electrophysiological signals in cortical networks are modulated by the transcranial application of coherent infrared light.

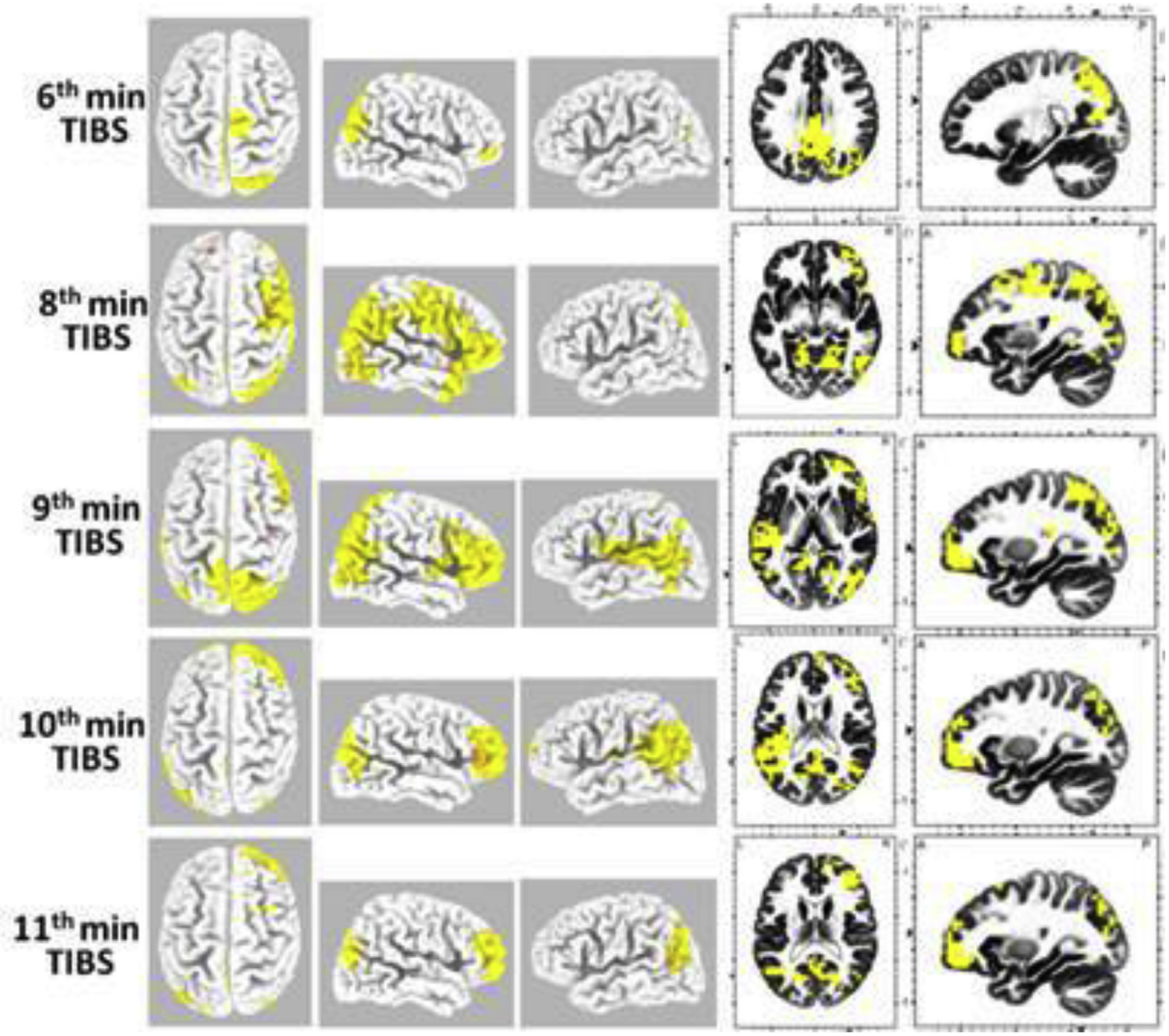

Fig. 2. 3D views of t-maps ($p<0.01$) between TIBS and placebo conditions based on Alpha-band (8-13 Hz) power density at 6, 8, 9, 10, and 11 min after right-side prefrontal TIBS was initiated. EEG data were averaged over 20 subjects.

Our findings provide a mechanistic understanding of the effects of TIBS on human cognition.

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PROCEEDINGS #19. MAINTENANCE TDCS: A CASE OF FULL AND DURABLE RECOVERY FROM MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME (ME/CFS)

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1. Abstract

A middle-aged man with progressive myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) was referred for neuromodulation. His condition, likely virally induced decades ago, was characterized by recurring periods of extreme fatigue, lasting months at a time. Medication trials provided partial benefit. Transcranial direct current stimulation (tDCS) was chosen as a neuromodulation treatment, allowing cumulative, ongoing treatment to target ongoing inflammation [1]. Patient was trained with tDCS in the office and then treatment was self-administered at home daily. The protocol was: anode (left dorsolateral prefrontal cortex), cathode (right dorsolateral prefrontal cortex), 2 mA/min, 20 minutes, 40 mA total dose, using 1.5" diameter electrode pads. Patient reported significant benefit early in the day during the first month of daily tDCS. After four weeks, maintenance tDCS sessions were increased to twice daily. Over the next few months the patient experienced full clinical recovery. Follow-up quantitative EEG (qEEG) and neurophysiological testing was done 14 months after initial presentation; pre- and post- comparison studies provide insight into possible treatment biomarkers that may help to explain this patient's full and unexpected recovery.

2. Introduction

Chronic neuro-psychiatric diseases are the third leading cause of disability world-wide [2]. Individuals who experienced adverse childhood events, including medical illness or developmental trauma, have higher risk for altered immunity and stress response increasing the risk of medical illnesses later in life. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), like other early immune activation syndromes, is poorly understood and subsequently lacks reliable and effective treatment options. Finding efficacious, durable, and efficient interventions that might increase chance of full and lasting recovery are a clinical priority.

Case Summary: A 61-year-old man with treatment-resistant progressive ME/CFS was referred for consultation. His condition, likely virally induced decades before, was characterized by recurring periods of extreme fatigue, which had become unrelenting over the prior two years, impairing many dimensions of his life. Expert immunological and neurological work-ups were negative. Fibromyalgia had been ruled out. The patient failed many medically advised approaches, including empirical antidepressant trials of Fluoxetine and Bupropion, an extensive course of acupuncture and a gluten-free diet.
Presenting complaints: For the prior two years his life was severely circumscribed due to severe, persistent fatigue, with inability to exercise. He social life was curtailed as he focused his limited energy on teaching and his family. His sleep was intact, without difficulty initiating or maintaining asleep. He was not depressed. On the Montgomery-Asberg Depression Rating Scale (MADRS) his score was 5 with notable lassitude. On the Patient Health Questionnaire (PHQ-9) his score was 3 with notable low energy nearly every day.
Childhood Medical History: At age of 2 the patient had serious neurological problems including weakness of lower extremities with abnormal gait. He was suspected of having polio and endured a very stressful quarantine in the hospital for several weeks. No diagnosis was confirmed and his condition resolved with normal development.
Adult Medical History: In his early 20's while travelling abroad in a third world country he had acute illness with high fevers and delirium. No diagnosis was confirmed, though viral illness was suspected. His problems with intermittent severe fatigue problems began within the following year.

3. Methods

We considered his ME/CFS as a treatment-resistant, chronic, neuro-inflammatory syndrome, likely related to his earlier infections. Limited genetic analysis through Genomind, Inc. revealed $COMT_{158}$[1] Val/Val variant implying that the patient might have better response to dopaminergic agents and/or neuromodulation [3]. The patient failed trials of Vyvanse (long-acting amphetamines) and Concerta (long-acting methylphenidate), but Provigil (modafinil) 200 mg provided partial relief of fatigue. Further analysis revealed brain-derived neurotrophic factor (BDNF V66M) variants of Met/Val.
In light of the failure of all previous treatment modalities, we decided that neuromodulation was a valid treatment approach. Turning to tDCS, we used initial neurophysiological studies to help guide protocol selection. We performed EEG and qEEG analysis, HRV, ERP, and several behavioral measures. TDCS was chosen as a safe off-label neuromodulation treatment option, allowing cumulative, ongoing treatment to target persistent chronic neuro-inflammation. Patient was trained with tDCS in the office with anode on left dorsolateral prefrontal cortex (LDLPFC), cathode on right (RDLPFC), 2 mA/min, 20 minutes, 40 mA total dose per tDCS session, using 1.5" diameter electrode pads. Treatment was self-administered at home daily.

4. Results

Patient reported significant benefit early in the day during the first month of daily tDCS. We increased tDCS sessions to twice daily (6 AM and 12 Noon). This provided consistent benefit, though we needed to lower modafinil to 100 mg due to insomnia. Over the next few months, he experienced full recovery with improved exercise tolerance and a return to physical exercise several times each week. During this period, we stopped modafinil, but he felt less well, so it was resumed at 100 mg daily.
Follow-up: We repeated neurophysiological studies 14 months after initial presentation. The patient had been in full remission for almost a year. Before treatment, patient demonstrated normal motor speed, normal reactive variance with no commission errors, but high omission errors (14.29%, selective attention) as compared to the normative database. After treatment, all behavioral measures were within the normal rage.
Evoked Reaction Potentials: Pre-treatment visual ERP findings (156 ms, -12.6 mV) improved substantially at post-treatment (180 ms, -13.2 mV).
Heart Metrics: Heart-rate variability (25 ms) and total power (287 ms^2) were both low at pre-treatment. Post-treatment heart-rate variability improved significantly (35 ms); total power improved substantially (511 ms^2).
We performed qEEG analysis to assess brain wave states that might explain his full and unexpected recovery (see Fig. 1 showing Pre vs. Post qEEG after one year of maintenance tDCS). Before treatment, qEEG showed higher than normal incidence of alpha in the right frontal lobe (7-9 Hz), higher than normal incidence of alpha in both temporal lobes (7-9 Hz, left greater than right) and lower than normal incidence of frontal Beta (22-30 Hz). At follow-up, in full recovery, the qEEG showed

[1] Catechol-O-methyltransferase V158M or rs4680.