MEG Source Imaging Reveals Neuronal Changes in Combat-related Mild Traumatic Brain Injury after Transcranial Electrical Stimulation using Nexalin

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Introduction: Mild traumatic brain injury (mTBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in OEF/OIF/OND Veterans and the general public. However, the underlying pathophysiology is not completely understood, and there are few effective treatments for post-concussive symptoms (PCS). In addition, PCS and post-traumatic stress disorder (PTSD) symptoms overlap considerably. Many studies also report higher rates (nearly double) of comorbid PTSD in individuals with mTBI in both military and civilian settings, compared to those with PTSD without mTBI. Neuromodulation treatment techniques such as transcranial electrical stimulation (tES) have shown promise in treating PCS in mTBI, but the neural mechanisms underlying the effects of tES treatment are unknown, owing to the dearth of neuroimaging investigations of this therapeutic intervention. Conventional neuroimaging techniques such as MRI and CT have limited sensitivity in detecting physiological abnormalities caused by mTBI, or in assessing the efficacy of mTBI treatments. In contrast, evidence is mounting in support of resting-state magnetoencephalography (rs-MEG) hyperactivity in delta- (1-4 Hz) and gamma- (30-80 Hz) bands as noninvasive imaging markers for neuronal abnormalities in mTBI. Delta-wave hyperactivity directly results from axonal injury and/or a neurochemical blockage/limitation in mTBI. Gamma-band hyperactivity in mTBI is a proxy of dysfunction or injury to GABA-ergic inhibitory interneurons causing disinhibition in the neural network, directly up-regulating spontaneous gamma activity, owing to a lack of inhibition of pyramidal and other excitatory neurons. The present study used rs-MEG to assess the neuronal changes in Veterans with combat-related mTBI after tES treatment delivered by the Nexalin™ device.

Materials and Methods: The total treatment contains 12 sessions at ~3 sessions/week. In each session, the Nexalin tES pulses were at 15mA current, delivered through three electrodes placed at the forehead and left-right mastoids, with three repetition frequencies at 4 Hz, 40 Hz, and 77.5 Hz, and ~20mins for each frequency. Rs-MEG was conducted at both pre-treatment baseline and post-treatment follow-up exams. MEG is a non-invasive functional imaging technique that directly measures the magnetic signal due to neuronal activation in grey matter with high temporal resolution (< 1 ms) and spatial localization accuracy (2-3 mm at the cortical level). Twenty-four Veterans with combat-related mTBI completed the active tES (N=15) or sham (N=9) treatments, with both pre- and post-treatment rs-MEG exams. Ten participants finished the 12-session active (N=7) or sham (N=3) treatments but without both pre- and post-treatment rs-MEG, whereas 9 did not finish the active (N=5) or sham (N=4) treatment. We focused on delta (1-4Hz) and gamma (30-80Hz) frequency bands. A repeated measure ANOVA tested for the treatment effect in rs-MEG data. PCS were assessed using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Neurobehavioral Symptom Inventory (NSI), and McGill Pain Questionnaire (MPQ).

Results: None of the Veterans reported adverse effects, although one participant noted some discomfort only during impedance checking due to poor electrode-skin contact. This was quickly corrected. Compared with the sham group, Veterans in the active treatment group showed significant (corrected $p<0.01$) reductions in 1) delta-band activity mainly from the frontal pole and inferior frontal gyri, suggesting improvement in deafferentation; and 2) abnormal gamma-band activity mainly from the frontal pole, orbital frontal cortex, and

posterior parietal regions, suggesting improvement in GABA-ergic inhibitory interneuron functions. Although the active treatment group showed reduced RPQ and NSI symptoms (total score) relative to the sham group, this did not reach statistical significance, potentially due to the limited sample sizes and the failure of 10 subjects to fully complete treatments. In contrast, the MPQ score in the Nexalin not only did the treatment group show significant reduction in pain (pre-Nexalin vs post-Nexalin, $p = 0.00031$), the amount of MPQ reduction in Nexalin treatment group was significantly more pronounced than the sham group ($p = 0.0027$).

Conclusions: These findings demonstrate that MEG is a sensitive and objective functional imaging technique for assessing neuronal changes due to tES treatment in combat-related mTBI. The reduction of hyperactivity of delta- and gamma-band activities in mTBI suggest Nexalin tES treatment can reduce deafferentation and GABA-ergic inhibitory interneuron dysfunctions in chronic mTBI. Furthermore, the Nexalin treatment group not only showed a significant reduction in pain, as measured by MPQ, the reduction in pain was more significant than that in the sham group. A follow up study with larger sample size may be required to further validate these initial results and to study the associations of the MEG measures with changes in clinical outcomes.

Disclaimer:

The authors have no conflicts of interest or other issues to disclaim.

Learning Objectives: Three (3) are required. These should answer the question - What do you expect the attendee to be able to do at the end of the session? Each learning objective should start with an action verb (e.g., Describe, Analyze, Discuss, etc). Each learning objective has a limit of 255 characters (includes spacing).

- To understand the neural mechanisms of MEG-based biomarkers for combat-related mild traumatic brain injury, especially those associated with MEG hyperactivity in delta (1-4 Hz) and gamma (30-80 Hz) bands.
- To analyze the resting-state MEG data using high resolution MEG source imaging technique.
- To examine the efficacy of novel mTBI treatment using transcranial electrical stimulation with a Nexalin device, especially its pulse strength and repetition frequencies.
- To understand the significant effect of Nexalin treatment for reducing post-traumatic pain.

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Introduction

Mild traumatic brain injury (mTBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in OEF/OIF/OND Veterans and the general public. However, the underlying pathophysiology is not completely understood, and there are few effective treatments for post-concussive symptoms (PCS). In addition, PCS and post-traumatic stress disorder (PTSD) symptoms overlap considerably. Many studies also report higher rates (nearly double) of comorbid PTSD in individuals with mTBI in both military and civilian settings, compared to those with PTSD without mTBI. Neuromodulation treatment techniques such as transcranial electrical stimulation (tES) have shown promise in treating PCS in mTBI, but the neural mechanisms underlying the effects of tES treatment are unknown, owing to the dearth of neuroimaging investigations of this therapeutic intervention. Conventional neuroimaging techniques such as MRI and CT have limited sensitivity in detecting physiological abnormalities caused by mTBI, or in assessing the efficacy of mTBI treatments. In contrast, evidence is mounting in support of resting-state magnetoencephalography (rs-MEG) hyperactivity in delta- (1-4 Hz) [1] and gamma- (30-80 Hz) [2] bands as noninvasive imaging markers for neuronal abnormalities in mTBI. Delta-wave hyperactivity directly results from axonal injury and/or a neurochemical blockage/limitation in mTBI. Gamma-band hyperactivity in mTBI is a proxy of dysfunction or injury to GABA-ergic inhibitory interneurons causing disinhibition in the neural network, directly up-regulating spontaneous gamma activity, owing to a lack of inhibition of pyramidal and other excitatory neurons. The present study used rs-MEG to assess the neuronal changes in Veterans with combat-related mTBI after tES treatment delivered by the Nexalin™ device.

Research Subjects and Method

The total treatment contains 12 sessions at ~3 sessions/week. In each session, the Nexalin tES pulses were at 15mA current, delivered through three electrodes placed at the forehead and left-right mastoids, with three repetition frequencies at 4 Hz, 40 Hz, and 77.5 Hz, and ~20mins for each frequency. Rs-MEG was conducted at both pre-treatment baseline and post-treatment follow-up exams. MEG is a non-invasive functional imaging technique that directly measures the magnetic signal due to neuronal activation in grey matter with high temporal resolution (< 1 ms) and spatial localization accuracy (2-3 mm at the cortical level). Twenty-four Veterans with combat-related mTBI completed the active tES (N=15) or sham (N=9) treatments, with both pre- and post-treatment rs-MEG exams. Ten participants finished the 12-session active (N=7) or sham (N=3) treatments but without both pre- and post-treatment rs-MEG, whereas 9 did not finish the active (N=5) or sham (N=4) treatment. We focused on delta (1-4Hz) and gamma (30-80Hz) frequency bands. A repeated measure ANOVA tested for the treatment effect in rs-MEG data. PCS were assessed using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and Neurobehavioral Symptom Inventory (NSI).

Results

None of the Veterans reported adverse effects, Compared with the sham group, Veterans in the active treatment group showed significant reductions (voxel-wise paired t-test, corrected $p<0.01$) in 1) delta-band activity mainly from the frontal pole and inferior frontal gyri, suggesting improvement in deafferentation; and 2) abnormal gamma-band activity mainly from the frontal pole, inferior frontal gyri, orbital frontal cortex, and posterior parietal regions, suggesting improvement in GABA-ergic inhibitory interneuron functions (Fig. 1). Although the active treatment group showed reduced RPQ and NSI symptoms (total score) relative to the sham group, this did not reach statistical significance, potentially due to the limited sample sizes and the failure of 10 subjects to fully complete treatments.

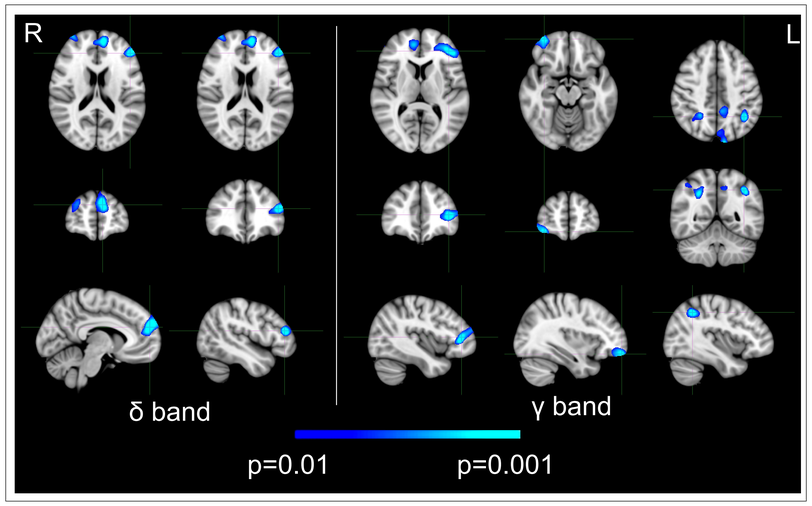

Fig. 1: Veterans in the active treatment group showed significant reductions in 1) delta-band activity mainly from the frontal pole and inferior frontal gyri; and 2) abnormal gamma-band activity mainly from the frontal pole, inferior frontal gyri, orbital frontal cortex, and posterior parietal regions.

Discussion and Conclusion

These findings demonstrate that MEG is a sensitive and objective functional imaging technique for assessing neuronal changes due to tES treatment in combat-related mTBI. The reduction of hyperactivity of delta- and gamma-band activities in mTBI suggest Nexalin tES treatment can reduce deafferentation and GABA-ergic inhibitory interneuron dysfunctions in chronic mTBI. A follow up study with larger sample size may be required to further validate these initial results and study the associations of the MEG measures with changes in clinical outcomes.

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[2] Huang et al., (2020). Marked Increases in Resting-State MEG Gamma-Band Activity in Combat-Related Mild Traumatic Brain Injury. Cereb Cortex 30, 283-295.

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