Noninvasive EEG-EKG guided trans-magnetic stimulation at natural resonance frequency in veterans with PTSD: a randomized double-blinded sham-control study

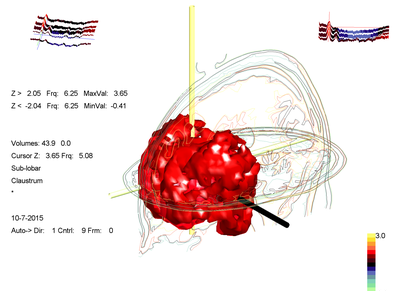
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Introduction

Neuromodulation has been investigated as a therapeutic modality for neuropsychiatric disorders, such as PTSD. Recent human clinical studies of transcranial magnetic stimulation (TMS) suggest some improvement in clinical symptomatology and EEG phenotype in PTSD patients with a short course of treatment. We hypothesize clinical improvement in patients with PTSD coinciding with changes in EEG measures.

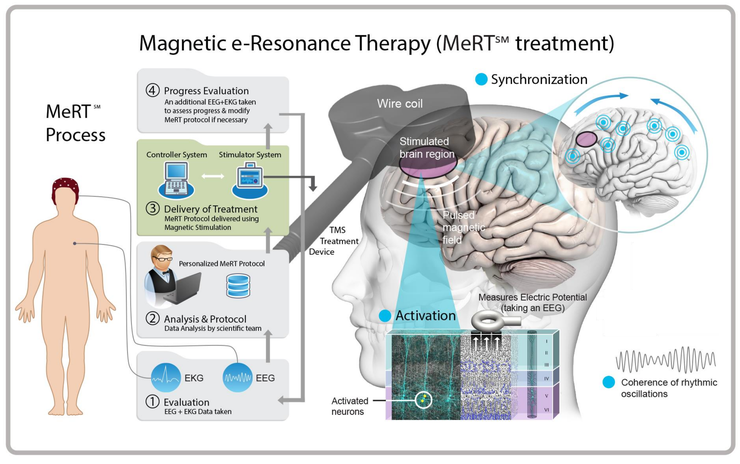
Low resolution brain electromagnetic tomography (LORETA) of dominant EEG frequencies compared with normative database



LORETA of 24-year old patient with post-traumatic stress disorder demonstrating abnormally high theta distribution in bilateral frontal, and fronto-temporal regions. Excess is marked in red; Z score >=1.95).

Methods

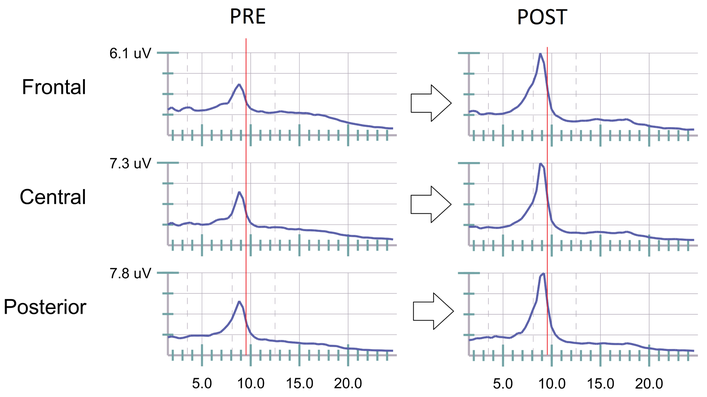
80 veterans with PTSD were included in a randomized, double-blinded, placebo-controlled trial. In phase 1, veterans were divided randomly into treatment versus sham group and treated daily for 2 weeks. In Phase 2, all veterans were treated openly for an additional 2 weeks. Subjects' EEG, QEEG, FFT and symptoms were scored at baseline and every week and compared with existing normative data[1] for same age group. EEG and EKG were used to determine the treatment frequency for TMS, typically the computed dominant natural resonant frequency, $\mathbf{f_{NR}}$, for each patient (defined as Magnetic e-Resonant Therapy, MeRT)[2]. EEG measures were calculated (scalp electrode grid 19x19 matrix) for each EEG obtained. P-values were obtained for EEG data comparing EEG changes over time with treatment versus sham. EEG band power and coherence measures were compared for trending towards or away from normative EEGs[3].



Results

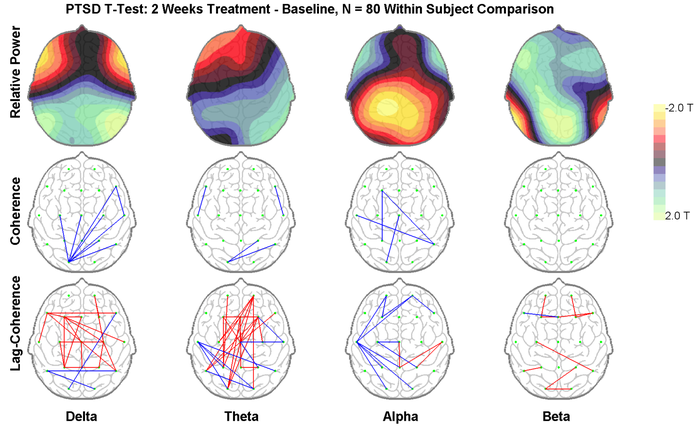
Patients who received 2 weeks of MeRT showed significant reductions on clinical symptom scores compared to sham p<0.05, with 46% reduction in PCL-M severity. After open label, the sham group showed average reduction of 44% in PCL-M severity. After open label, 56 of 80 patients showed PCL-M reduction of 10 points or greater, with 79 of 80 patients showing reduction of 10 or more points from baseline. Overall PCL-M symptom reduction of 64.7% was achieved from baseline. Of the 37 patients who had suicidal ideation by HAM-D at baseline, 29 patients denied ideation by 4 weeks. Reduction in symptom scores were also noted in the PSQI-A sleep severity measures (p<0.05). EEG measures, including coherence and phase-lag coherences were altered across bands following treatment (p<=0.05).

Changes in resting EEG



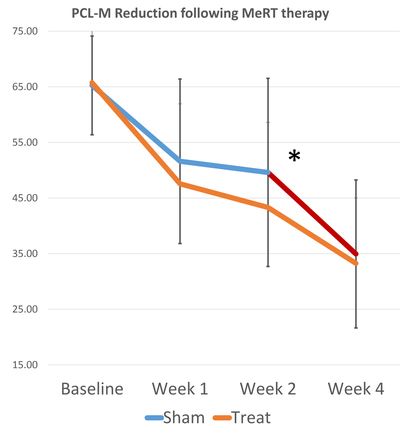
Fast fourier transform (FFT) of clean eyes-closed EEG data at baseline (Pre) and following (Post) 2 weeks, 10 sessions, of EEG/EKG-guided transmagnetic stimulation in a patient with PTSD. Frontal, central and posterior EEG leads were averaged to generate regional FFTs. The red line indicates $\mathbf{f_{NR}}$, the frequency calculated for therapy. Note the increase in the voltage of the dominant activity in frontal, central and posterior regions.

PTSD T-Test: 2 Weeks Treatment - Baseline, N = 80 Within Subject Comparison

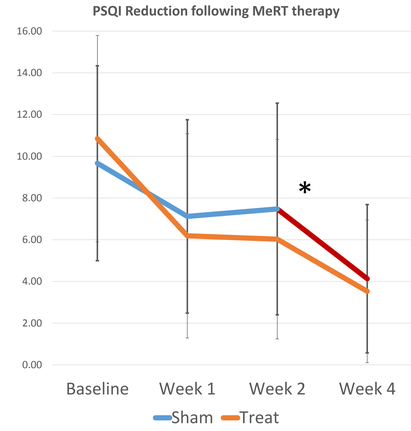


Wire-mesh head maps describing all inter-electrode coherence and phase-lag coherence wide-band frequency components. Blue lines indicate a significant reduction, whereas red lines indicate an increase (p<0.05). Group TREAT-TREAT and SHAM-TREAT EEGs were combined for the data points prior to, and following 2 weeks of MeRT therapy (n=80). Note posterior relative power and shifts in lag-coherence measures.

Clinical Changes over 4 Weeks



PCL-M Reduction following Phase I (Baseline to Week 2) and Phase II (Week 2 to Week 4) of trial. Sham group response was not equally distributed at baseline to week 2 (p<0.01). Group treat showed significant* reduction in PCL-M severity compared to sham (Mann-Whitney U p < 0.02) at week 2 compared to baseline. Sham group received treatment at weeks 2-4.



PSQI-A Reduction following Phase I (Baseline to Week 2) and Phase II (Week 2 to Week 4) of trial. Group treat showed significant* reduction in PSQI-A symptom severity compared to sham (p< 0.05) at week 2 compared to baseline. Sham group received treatment at weeks 2-4.

Discussion

Following 2 weeks of EEG-EKG guided transmagnetic stimulation, significant changes in symptom severity and EEG measures are reported for 80 retired military veterans with post-traumatic stress disorder. Patients had greatest comparative reductions in PCL-M subscales VII "avoid situation indicator" XII "short future indicator" and XIII "trouble falling or staying asleep indicator". The improvement in sleep was confirmed for treated vs sham group in PSQI-A, and, may suggest correlation between sleep disorder and PTSD symptoms. Of the 37 patients who had suicidal ideation by HAM-D, 29 patients denied ideation by 4 weeks. No patient worsened in clinical PTSD symptoms after receiving therapy. Noted changes in EEG measures, including coherence and phase-lag coherence may be associated with clinical improvement. Given probable placebo response, further study with a longer sham versus treat arm, and greater number of subjects is necessary. Further analysis of narrow-band EEG measures is to be conducted.

References

1. John E. Neurometrics: clinical applications of quantitative electrophysiology. New York, NY: L. Erlbaum Associates; 1977.
2. Taghva A, Silvetz R, Ring A, Kim KY, Murphy KT, Liu CY, Jin Y. Magnetic Resonance Therapy Improves Clinical Phenotype and EEG Alpha Power in Posttraumatic Stress Disorder. Trauma Mon. 2015;20:e27360.
3. Stam C, Nolte G, Daffertshofer A. Phase lag index: Assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Human Brain Mapping 2007;28(11):1178-93.