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Magnetic Resonance Therapy Improves Clinical Phenotype and EEG Alpha Power in Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is a disabling and prevalent psychiatric disorder with limited effective treatment options. In addition to the clinical features of the disease, pathologic changes in the electroencephalogram (EEG), including decreased alpha power, have been reported.
Objectives: To determine if magnetic brain stimulation can induce normalization of EEG abnormalities and improve clinical symptoms in PTSD in a preliminary, open-label evaluation.
Materials and Methods: We reviewed prospectively-collected data on 21 veterans that were consecutively-treated for PTSD. Magnetic resonance therapy (MRT) was administered for two weeks at treatment frequencies based on frequency-domain analysis of each patient's dominant alpha-band EEG frequencies and resting heart rate. Patients were evaluated on the PTSD checklist (PCL-M) and pre- and post-treatment EEGs before and after MRT.
Results: Of the 21 patients who initiated therapy, 16 completed treatment. Clinical improvements on the PCL-M were seen in these 16 patients, with an average pre-treatment score of 54.9 and post-treatment score of 31.8 ($P < 0.001$). In addition, relative global EEG alpha-band (8 - 13 Hz) power increased from 32.0 to 38.5 percent ($P = 0.013$), and EEG delta-band (1 - 4 Hz) power decreased from 32.3 percent to 26.8 percent ($P = 0.028$).
Conclusions: These open-label data show trends toward normalization of EEG and concomitant clinical improvement using magnetic stimulation for PTSD.

Keywords: Magnetic Resonance Therapy, Posttraumatic Stress Disorder, Electroencephalogram, Neuromodulation, Transcranial Magnetic Stimulation, Prefrontal Cortex

1. Background

Posttraumatic stress disorder (PTSD) is a disabling, prevalent, and difficult to treat psychiatric disorder characterized by response to a traumatic event that involves "intense fear, helplessness, or horror" (1). Cardinal diagnostic features of PTSD in patients who have experienced a definite traumatic event are 1) recurrent, intrusive recollections of the event, 2) avoidance of stimuli associated with trauma or generalized emotional numbing, 3) symptoms of hyperarousal including insomnia, and 4) functional distress or impairment in social, occupational, or other important areas (1). In addition, patients often have deficits in cognitive function, including deficits in attention, memory, and learning (2, 3). Lifetime prevalence of PTSD is estimated at 5 to 8 percent of men and 10 to 14 percent of women, making it the fourth most common psychiatric disorder (4-6). Despite pharmacologic and psychological therapies, 74 percent of patients have symptoms lasting over 6 months, and up to 30 percent of patients with PTSD will not recover from this illness at 10 years following diagnosis, and few spontaneous recoveries occur after 12 months (7, 8).

Neuroimaging studies consistently implicate the ventromedial prefrontal cortex (vmPFC) and amygdala as affected limbic circuit nodes in the pathogenesis of PTSD (9-15). In addition, electroencephalogram (EEG) analyses of PTSD-afflicted patients suggest abnormalities including globally decreased alpha power (16). Neuromodulation, including transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), has been suggested as a potential treatment option for the disorder (17). In animal studies of neuromodulation, high frequency stimulation of the amygdala in a rat model of PTSD ameliorates PTSD-associ-

ated behaviors (18). A recent human clinical study suggests some improvement in PTSD patients with a short course of repetitive TMS (19). In addition, magnetic stimulation of the brain has been shown to induce frequency changes on EEG. (For a review, please see Thut and Pascual-Leone (20)).

Magnetic resonance therapy (MRT) is a variation of transcranial magnetic stimulation where treatment frequencies are derived from patient's dominant alpha-band frequency and resting heart rate.

2. Objectives

In this study, MRT was utilized in the treatment of PTSD. Clinical results were followed with PTSD checklist (PCL-M), a validated, 17-item, self-report metric for PTSD symptomatology (21). Clinical improvements in PTSD checklist (PCL-M), as well as relative increases in post-treatment EEG alpha (8 - 13 Hz) power and relative decreases in delta power (1 - 4 Hz) were observed. This work suggests clinical improvements as well as trends of EEG toward normalization with magnetic stimulation of the brain in PTSD.

3. Materials and Methods

A retrospective review of prospectively collected data was performed at the Newport brain research laboratories (NBRL) and brain treatment center (BTC) Clinic. From June 2013 to March 2014, 21 veterans (ages 26 - 42 years, mean 32 years, all male) with prior diagnosis of PTSD underwent treatment with magnetic resonance therapy (MRT). Inclusion criteria included a prior diagnosis of PTSD by a psychiatrist, history of traumatic event, and symptoms from each of the three diagnostic categories (recurrence, avoidance, and arousal). Patients were identified by clinician referral to the clinic and underwent clinical and psychometric evaluation at the center prior to treatment. PCL-M score of greater than 44 was used as a guide (22, 23), however, two patients with borderline PCL-M scores were treated based on clinical assessment. Exclusion criteria included history of seizure disorder, history of intracranial lesion, history of intracranial implant, prior transcranial magnetic therapy, and inability to adhere to the treatment schedule. Informed consent was obtained for all patients and IRB approval obtained. Pre-treatment EEG as well as post-treatment EEG were obtained. In addition, patients were asked to complete the PCL-M prior to and following 2 weeks of treatment. PCL-MM is a 17-item, self-report metric for PTSD symptomatology, which maps to DSM criteria and correlates strongly with the Clinician Administered PTSD Scale (CAPS) (21, 24-26). Each item can be scored from 1 (most severe) to 5 (least severe). Therefore, 17 is the lowest (least symptomatic) and 85 is the highest possible score (most symptomatic). Cutoff scores suggested for PTSD diagnosis based on PCL-M range from 30 - 50 (21, 27-30). An initial five-day trial of stimulation was performed to assess efficacy and tolerability, at which point, patients could elect to continue with a full-course of treatment (2 weeks).

An awake, eyes-closed baseline EEG was recorded using standard 19-lead electrode setup. EEG and ECG time-series data were converted to frequency-domain using Fast Fourier Transform (FFT) (Mathematica, Wolfram, Champaign, Illinois). Dominant alpha-frequency is selected based on the frequency with highest power in the 8 - 13 Hz range as described previously in the treatment of other psychiatric disorders (31-33). Higher harmonic frequencies (5th to 10th) of the electrocardiogram resting heart rate were then calculated. The ECG harmonic frequency nearest the dominant alpha frequency was chosen as treatment frequency for MRT. For example, in a patient with a dominant alpha frequency of 9.7 Hz and resting heart rate of 72 bpm (1.2 Hz), the 8th harmonic of the heart rate (8×1.2 Hz = 9.6 Hz) was chosen as the treatment frequency. Stimulation intensity was at 80% of motor threshold, and stimulation was delivered to the region of highest EEG irregularity when compared to a normative database with regard to bandwidth powers at a specific location. In this study, treatment location was prefrontal cortices.

MRT was administered via MCF-B65 Butterfly coil (Magventure Inc, Denmark) to the prefrontal cortices at the above-assigned frequency. Magnetic pulses were delivered in 6 second trains with a 30 second intertrain interval, and 30 trains per session. Treatment was performed five times per week for two weeks.

Pre- and post-treatment EEG analyses were performed by assessing relative bandwidth power in the delta (1 - 4 Hz), theta (4 - 8 Hz), alpha (8 - 13 Hz), and beta (13 - 30 Hz). Pre- and post-treatment relative powers as well as pre- and post-treatment PCL-M were analyzed using paired, two-tailed, Student's T-test.

4. Results

Of the 21 patients who initiated treatment, 16 completed therapy (76 percent). Of the five patients that did not continue therapy, they cited inability to commit to daily treatment (3 patients) or that they did not feel improvement after initial treatment (2 patients). Of the 16 patients who completed therapy, average initial PCL-M was 54.9, range 41 - 75, and average post-treatment PCL-M was 31.8, range 17 - 47 (pre- to post-treatment, $P < 0.001$, Figure 1). This yields an average decrease of 23.2 points (average change 42 percent), and 16 of 16 patients had some decrease in PCL-M (range 9 - 39 points).

Relative EEG alpha power from pre- to post-treatment increased in 11 of 16 patients (68.8 percent) from an average of 32.0 percent to 38.5 percent (20.2 percent increase, $P = 0.013$, Figure 2). Relative EEG delta decreased in 10 of 16 patients (62.3 percent), and changed from 32.3 percent to 26.8 percent (16 percent decrease, $P = 0.028$). Relative theta-band and beta-band EEG changes appeared minor and were statistically insignificant (theta, 23.4 percent to 22.4 percent, $P = 0.545$; beta, 12.2 percent to 12.3 percent, $P = 0.961$). An example EEG pre- and post-treatment is shown in Figure 3. No adverse events (seizures, neurologic deficit, worsening of pretreatment condition) were reported.

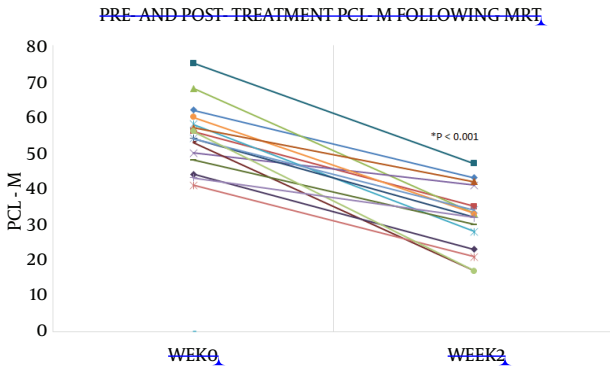

Figure 1. Pre- and Post-MRT PCL-M Scores, Average Initial PCL-M Was 54.9, Range 41 - 75, and Average Post-Treatment PCL-M Was 31.8, Range 17 - 47 (Pre- to Post-Treatment, P < 0.01)

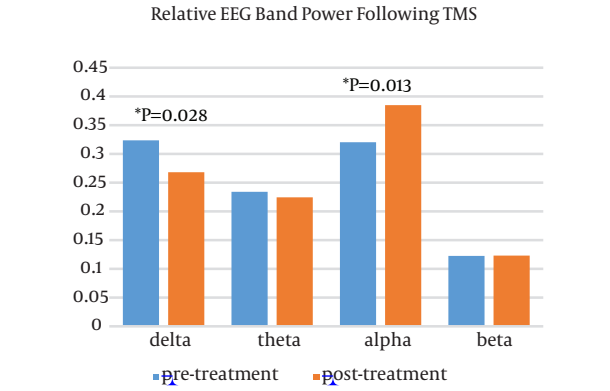

Figure 2. Pre- and Post-MRT EEG Band Power, Relative EEG Alpha Power From Pre- to Post-Treatment Increased From 32.0 Percent to 38.5 Percent (P = 0.013), Relative EEG Delta Decreased From 32.3 Percent to 26.8 Percent (P = 0.028). Relative Theta-Band and Beta-Band EEG Changes Were Minor and Statistically Insignificant (Theta, 23.4 Percent to 22.4 Percent, P = 0.545; Beta, 12.2 Percent To 12.3 Percent, P = 0.961).

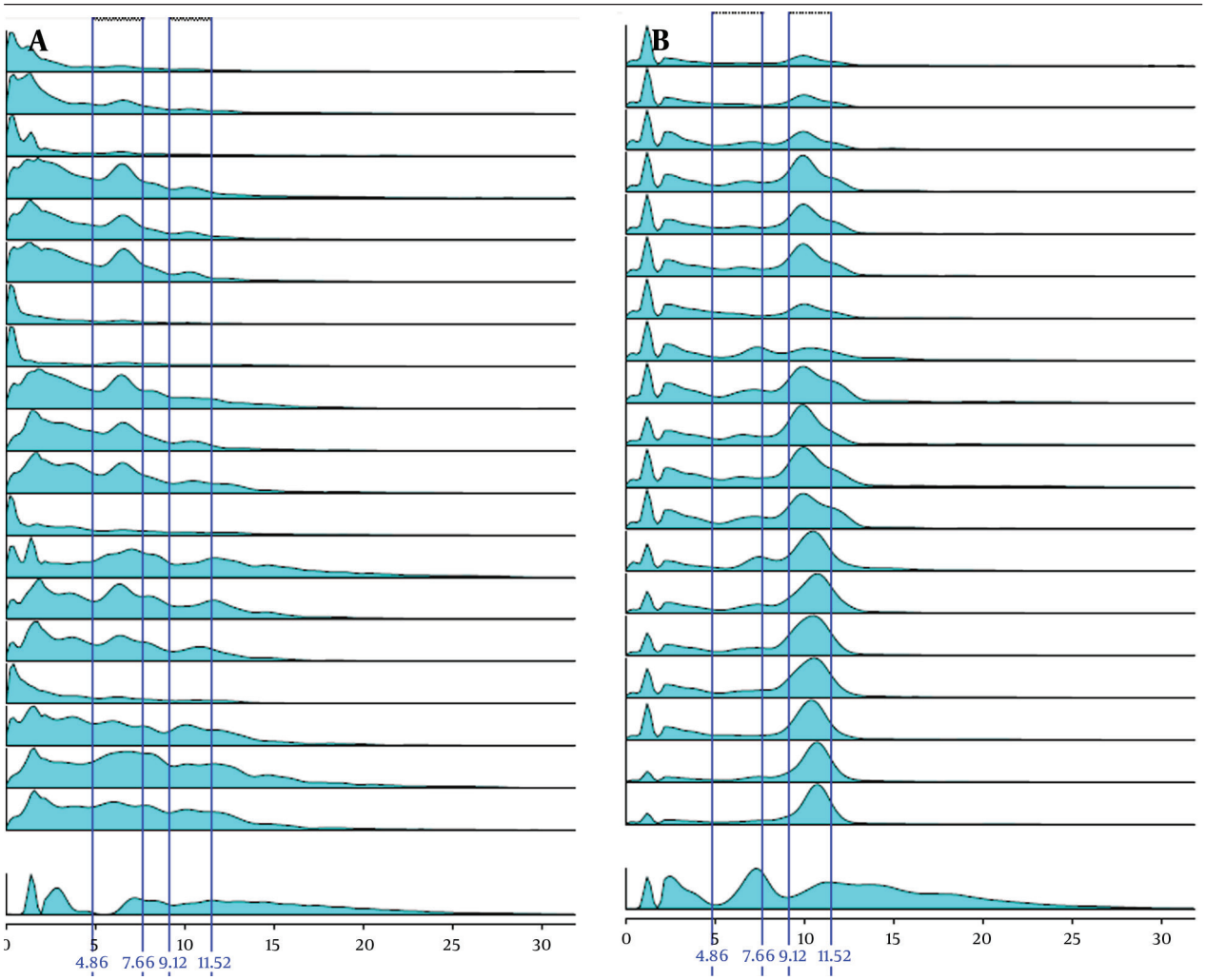

Figure 3. Sample Pre- and Post-MRT EEG Spectral Analysis. Rows Indicate Channels From Standard 19-Lead EEG With Average Power in Bottom Row. (A) Pre-Treatment EEG With Increased Relative Slow-Wave (Delta, Theta) Power Relative to Alpha Power. (B) Post-Treatment EEG With Decreased Slow-Wave Power and Increased Relative Alpha Power.

5. Discussion

PTSD is a prevalent, disabling illness with limited efficacy of available treatment options (7). Neuromodulatory therapies, including magnetic stimulation, have shown some initial promise in the treatment of this disorder (19, 34, 35). Prior works on repetitive transcranial magnetic stimulation suggest improvement with PTSD, though these have focused on low-frequency magnetic stimulation (1 Hz) (19, 34). Cohen in 2004 showed greater clinical benefit with high-frequency stimulation (10 Hz) than with low-frequency stimulation (1 Hz) (35). This clinical difference may be due to "high-frequency" stimulation being nearer to alpha frequencies (8 - 13 Hz). In the treatment paradigm of this paper, a patient's dominant alpha frequency is used to determine stimulation frequency. Neuroimaging studies indicate that the primary neurocircuitry dysfunction in PTSD lies in the ventromedial prefrontal cortices (9-14). There is precedent for treatment of frontal circuit disorders with magnetic stimulation, including the treatment of major depressive disorder (MDD), with positive clinical results (36, 37). Frontocortical circuitry defects are also thought to belie the clinical dysfunction in MDD (38). Furthermore, magnetic stimulation of the brain has been shown to create EEG changes that persist beyond the duration of treatment (20), but to our knowledge, no study has shown trends toward normalization in EEG power spectra concomitant with clinical improvement using these modalities.

In this study, MRT of the brain is used as a form of "non-invasive neuromodulation." 21 veterans with prior diagnosis of PTSD were treated with MRT. Treatment frequency was selected based on dominant alpha frequency on pretreatment EEG. Of the 21 patients, 16 completed the study and had improvement in clinical metrics (PCL-M). Therefore, based on an intention-to-treat analysis, 16 of 21 patients (76 percent) had at least modest improvements in their PTSD symptoms. On average, these improvements amounted to approximately 1.4 points per item on the PCL-M questionnaire. In addition, global alpha power increased on EEG with relative decreases in delta-band power. Electrophysiology studies suggest alpha power is decreased in the PTSD population (16), so this may indicate amelioration of this defect.

With that in mind, it is notable that while 16 patients had improvement of clinical symptoms, only 11 had increases in global EEG alpha. Therefore, more sophisticated analyses including localized versus global EEG band power, EEG coherence, or information theoretic analyses such as EEG entropy may be required to correlate with this treatment effect. Aberrations in neural oscillatory activity are present in many neuropsychiatric disorders including movement disorders, schizophrenia, and Alzheimer's disease (39). Subjective review of post-treatment EEGs in our population suggest synchronization of brain regions with regard to dominant alpha frequency post-MRT, and we believe this effect requires further study and characterization.

Obvious study limitations here include lack of control arm, open-label design, lack of female participants, and lack of long-term treatment persistence data. Given these shortcomings, randomized, controlled, double-blinded studies are underway. Despite these shortcomings, these results show EEG trends toward normal as well as concomitant clinical improvements with MRT and suggest a role for non-invasive neuromodulation in the treatment of PTSD.

PTSD is a serious, prevalent, and disabling psychiatric illness that is often refractory to currently available treatments. Given the significant burden of this disease, there needs to be continued exploration for new treatment approaches, especially interventions that may be effective for those individuals refractory to existing treatments. The success of neuromodulation with other conditions marked by frontal lobe dysfunction makes it a potential treatment option for PTSD, especially given the well-described alterations in neurocircuitry evident in this condition. This study suggests that non-invasive neuromodulation magnetic resonance therapy may lead clinical improvements as well as a trend toward normalization of EEG pathophysiology in PTSD.

Authors' Contributions

Alexander Taghva, Robert Silvetz, and Yi Jin co-developed the idea of applying magnetic resonance therapy to PTSD and developed protocols regarding this. Alexander Taghva wrote the manuscript. Alex Ring, Alexander Taghva, Robert Silvetz performed data analysis, collection, and interpretation of results. Keun-young A. Kim, Kevin T. Murphy, and Charles Y. Liu provided editorial support. Yi Jin developed the basic principles regarding magnetic resonance therapy.

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Robert Silvetz, Yi Jin, and Alex Ring are employees and have equity interest in Newport Brain Research Laboratories, which administers magnetic resonance therapy.

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