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Case Report

Personalized Repetitive Transcranial Magnetic Stimulation (PrTMS®) Coupled with Transcranial Photobiomodulation (tPBM) For Co-Occurring Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD)

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Abstract

This study provides further evidence demonstrating the beneficial effects of PrTMS® treatment in co-occurring disorders. Furthermore, this study illustrates the benefit of augmenting PrTMS® with tPBM for superior outcomes. The positive results of this novel case study can be attributed to brain wave neuromodulation and increased neuronal ATP production, resulting in synergistic enhanced neuroplasticity and brain optimization. Further, large-scale, randomized and blinded studies are recommended to validate our promising preliminary observations utilizing multifaceted interventions for co-occurring disorders.

Keywords: Personalized Repetitive Transcranial Magnetic Stimulation (PrTMS®); Spectral Electroencephalography (EEG); Neurocognitive Psychometric Diagnostics; Transcranial Photobiomodulation (tPBM); Traumatic Brain Injury (TBI); Post-Traumatic Stress Disorder (PTSD) ; Co-Occurring Disorders

Introduction

This study focuses on using Personalized Repetitive Transcranial Magnetic Stimulation (PrTMS®) and Transcranial Photobiomodulation (tPBM) as a therapeutic alternative to conventional psychiatric interventions for treating conditions such as Post-Traumatic Stress Disorder (PTSD), Traumatic Brain Injury (TBI), Affective Disorders, and Obsessive-Compulsive Disorder (OCD). To our knowledge this is the first study that explores the benefits of such novel interventions for the treatment of multiple co-occurring diagnoses.

Thus, symptom reduction with PrTMS® treatment coupled with tPBM was evaluated with systematic clinical assessments to measure changes in symptomatology. Standardized neurocognitive diagnostic assessments, and weekly spectral electroencephalographic (EEG) measurements were also obtained.

The PrTMS® approach utilizes an assessment of a patient's spectral brain electrical activity (Spectral EEG) and administration of structured psychometric diagnostic assessments to generate a repetitive transcranial magnetic stimulation (rTMS) treatment protocol tailored specifically to the individual [1]. A treatment plan is developed with the use of a proprietary EEG spectral frequency algorithm. PrTMS® protocols involve continual rTMS stimulus frequency adjustments and progressive activation of multiple cortical sites [2]. Normal brainwave frequencies range from 8 to 12 hertz, with the exact frequency varying from individual to individual [3]. In the context of a relaxed state of wakefulness, the dominance of alpha rhythm is the defining feature in a neurotypical adult [4]. The duration of individual treatments progressively changes over 6 weeks, contingent to responsiveness but generally lasts around 30 minutes per patient. PrTMS® has been scientifically proven to modulate the symptoms of PTSD [5] and concussions [6].

Transcranial photobiomodulation (tPBM) is a novel form of neuromodulation, based on non-retinal exposure to light at specific wavelengths [7]. The core mechanism behind this process from a clinical perspective involves the penetration of near-infrared photons into the brain's cortical layers [8]. This photonic energy activates the *cytochrome c oxidase enzyme*, and subsequently increases cellular energy through adenosine triphosphate (ATP) production [9]. ATP Production is facilitated with tPBM due to the nature of the molecular aspect of the treatment. tPBM influences neuronal activity by enhancing action potentials through mechanisms such as modulation of sodium-potassium pumps, which affect the balance of ions involved in hyperpolarization and depolarization of specific neurons. These biochemical changes stimulate neurogenesis and improve neural connectivity [10]. For the purposes of our study, we employed dual therapeutic treatment windows spanning from 650 to 1200 nm. Specifically, in accordance with traditional metrics, the ATP therapeutic window encompassed frequencies of 800 to 900 nm, while the Ion-Channel frequencies ranged from 900 to 1100 nm [11].

Case History

The male patient aged 28 presented with significant traumatic brain injury (TBI), general anxiety disorder (GAD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). The patient reported being physically assaulted and sustaining a head injury at a Navy boot camp in 2020. Following serious agitation and dysregulated mood symptoms, the patient was involuntarily admitted to a psychiatric hospital for treatment. He was discharged from the Navy following this incident, after which he was diagnosed with symptoms consistent with PTSD, MDD, GAD, and OCD. The patient's symptoms included confusion, poor attention and concentration, lack of motivation, decrease in fluency of speech, aimless wandering, prolonged staring episodes, rigid adherence to rituals, insomnia, and avoidance of social gatherings. The patient displayed paucity and latency of speech, ambiguity in responses, and problems with registration and recall during examination. A collateral history from parents revealed significant impairment from his aforementioned symptoms since 2020; thus, resulting in an inability to maintain employment and a productive social life.

Methods

Neurocognitive psychometric diagnostic assessments administered to track the study patient's subjective, self-reported symptoms included the Generalized Anxiety Disorder -7 (GAD-7), Patient Health Questionnaire -9 (PHQ-9), Neurobehavioral Symptom Inventory (NSI), Post-Traumatic Stress Disorder Checklist (PCL-5), Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Sleep Condition Indicator (SCI), and the Yale-Brown OCD Scale (Y-BOCS). The vast majority of these tests were administered on a 5-point Likert Scale, on a scale of 0 to 4, where patients selecting a low score indicated a lack of negative symptoms, and a high score indicated an increase in negative symptoms. A lower

score (excluding SCI) would imply a reduction in symptom severity, thus indicating an improvement in neuro-cognitive functions following PrTMS® and tPBM treatment.

Additional cognitive assessments were utilized to measure the benefits of tPBM. The Deary-Liewald Test (DLTA) measures reaction times, cognitive processing speed, and the ability to make an accurate choice when presented with multiple stimuli [12]. The Eriksen's Flanker Test (EFT) evaluates selective attention and inhibitory control by requiring participants to focus on a central target stimulus while ignoring distracting stimuli [13]. The Inhibition of Return Test (IRT) studies attentional mechanisms by measuring slower responses to previously attended locations. Participants respond to stimuli at previously cued or new locations, investigating how attention disengages from previously attended spots [14]. The Trail Making Test (TMT) assesses visual attention and task switching. It has two parts: Part A, where participants connect numbered circles in a sequence, and Part B, where they need to alternate between letters and numbers in a sequence.[15] The Sustained Attention to Response Test (SATA) requires participants to respond to frequent non-target stimuli and withhold responses to infrequent target stimuli, testing their ability to stay focused and control their responses [16]. Together, these tests provide a comprehensive assessment of various cognitive functions.

The spectral EEG is an electrophysiological technique used to measure electrical brain wave activity. Given its exquisite temporal sensitivity, the main utility of spectral EEG is in the evaluation of disrupted brain wave activity, otherwise known as Brain Arrhythmia [17]. In this study, electrodes were arranged in compliance with the 10-20 system for EEG placement [18]. This system is organized by denoting letters and numbers to specific electrodes based on the brain region [19]. EEGs were administered weekly using a CGX high-impedance, dry electrode headset, and lasted 4 minutes to ensure accuracy and validity.

Treatment plan

PrTMS® was delivered by certified neurotechnologists using PeakLogic® software installed in the Apollo TMS Therapy System under the supervision of a board-certified psychiatrist. The following locations were collectively targeted for an approximate duration of 30 minutes a day, 5 days per week, for 10 weeks: Central Zero (Cz), Frontal Zero (Fz), Left Dorsolateral Prefrontal Cortex (F3), and the Right Dorsolateral Prefrontal Cortex (F4). Treatment parameters were administered at the aforementioned locations based on the 10-20 EEG system. Customized stimulus frequency and amplitude protocols were generated weekly based on the PeakLogic® computerized PrTMS® algorithm using the weekly spectral EEG readings and neurocognitive psychometric diagnostic scores. Reference Tables 1-5 for a more detailed review of the treatment protocol. PrTMS® was administered at approximately 10 Hz across cortical sites as indicated in the initial protocol (Cz, Fz, F3, and F4).

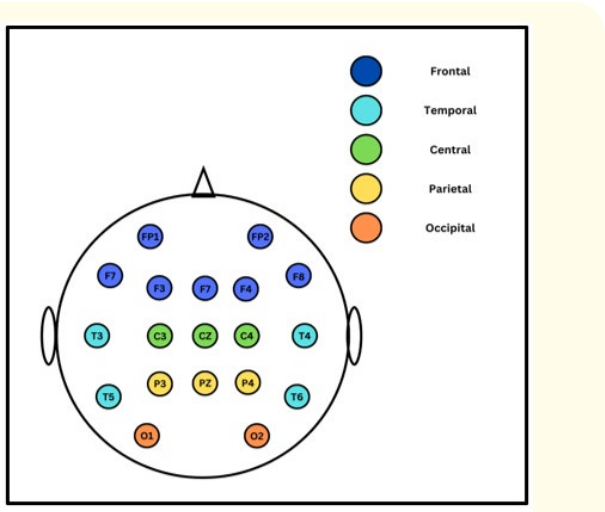

Figure 1: EEG Placement According to The "10 - 20" System.

In week 4, the patient's clinical course was characterized by experienced increased impulsivity (violent reactivity to pet dog), obsessive thoughts (negative ruminations regarding his failures), and compulsive rituals (showering 3-4 times a day). This was consistent with an increase in Y-BOCS scores from 17 in week 4 to 26 in week 5. Further confirmation was obtained by observing incoherence in Fp2 cortical spectral EEG activity in both alpha and theta brain waves, the area associated with impulse control [20]. Following week 5, Prefrontal Zero (Fpz) treatments and tPBM were incorporated into the protocol to target enhanced neuromodulation and create coherent alpha brain wave activity [21]. Energy levels were enhanced through administration of tPBM for 15 minutes a day at a continuous output (Table 1-5).

Cz				
Date	**Trains**	**Frequency**	**Pulses**	**Amplitude**
5/13/2024	20	10.2	102	20
6/12/2024	10	9.9	150	28
7/17/2024	10	10.3	156	32

Table 1: Cz Treatment Plan.

Fz				
Date	**Trains**	**Frequency**	**Pulses**	**Amplitude**
5/13/2024	10	10.1	102	20
6/12/2024	15	9.8	149	26
7/17/2024	10	10.2	155	32

Table 2: Fz Treatment Plan.

F3				
Date	**Trains**	**Frequency**	**Pulses**	**Amplitude**
5/13/2024	5	10.1	102	20
6/12/2024	15	9.8	149	26
7/17/2024	10	10.2	155	28

Table 3: F3 Treatment Plan.

F4				
Date	**Trains**	**Frequency**	**Pulses**	**Amplitude**
5/13/2024	1	1	600	34
6/12/2024	1	1	600	34
7/17/2024	1	1	600	34

Table 4: F4 Treatment Plan.

Fz				
Date	**Trains**	**Frequency**	**Pulses**	**Amplitude**
6/12/2024	5	9.7	147	18
7/17/2024	15	10.1	153	20

Table 5: Fpz Treatment Plan.

Expected outcome of treatment plan

The patient was expected to demonstrate increased fluency in speech, decreased latency in response time when speaking to others, linear and goal-directed thought processes, improved cognitive speed, regulated mood, and improved insight into his condition. The patient's baseline EEG capture depicted a combined pattern of pronounced brainwave activity in delta, theta, and alpha frequencies, suggesting a slower than typical average neuronal firing rate. Some research suggests that PrTMS® administration over a defined period of time results in a reduction of delta and theta activity and an emergence of coherent alpha activity, suggestive of positive neuromodulation [2,5,6].

Furthermore, a progressive reduction in GAD-7, PHQ-9, NSI, PCL-5, RPQ, and Y-BOCS scores corroborates coherent modulation of alpha wave activity. Conversely, an increase in scores is expected for the Sleep Condition Indicator (SCI). As a result of heightened ATP production and accelerated neuronal firing, the additional cognitive assessments related to tPBM (DLTA, EFT, IRT, TMT, and SATA) should optimally demonstrate improvements indicative of improved cognitive processing speed and sustained task focus and attention.

Results

Spectral EEG treatment results

Baseline spectral EEG analysis demonstrated prominent delta and theta waves and subdued alpha waves. This was consistent with the patient's clinical symptoms including drowsiness, inattention, and mood dysregulation, suggesting that the brain was operating at a reduced firing rate [22]. The goal of treatment was to restore and enhance the presence of coherent alpha wave states across cortical sites. By the fifth week of treatment, a notable shift to alpha wave coherence in the frontal cortical sites was observed. This was correlated clinically with improved cognitive functions such as attention and executive control[23]. By week ten of the treatment protocol, a significant shift of alpha wave coherence across all cortical sites was accomplished, corresponding with improved clinical presentation. Reference figure 2-4 for detailed Spectral EEG measurements.

Neurocognitive psychometric diagnostic results

There were observed reductions in GAD-7, PHQ-9, NSI, PCL-5, RPQ, and Y-BOCS, while an increase was observed in SCI scores by the fifth week of treatment. Progressive improvements in scores

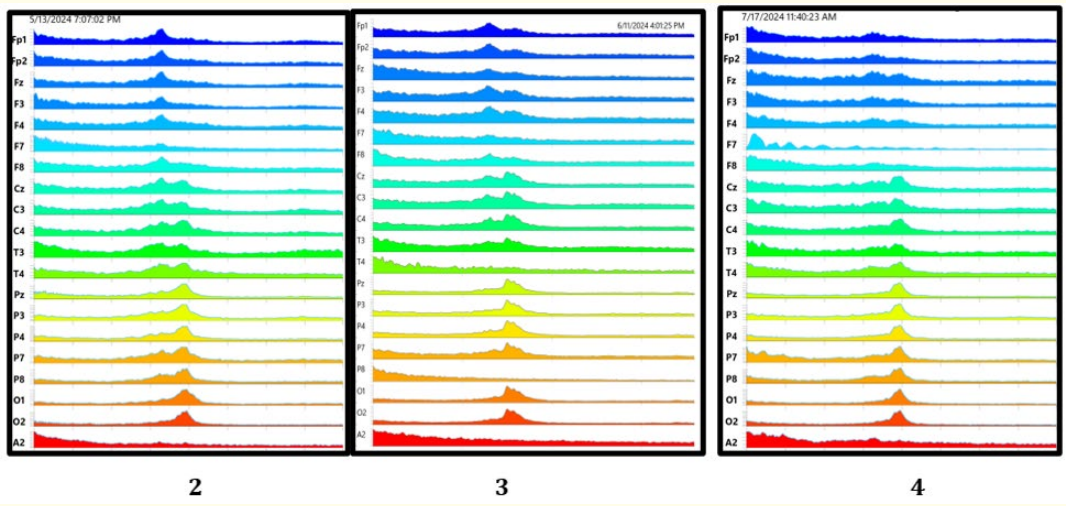

Figure 2-4: 2: Preliminary EEG, 3: MidPoint EEG, 4: Final EEG.

were observed by the 10th week of treatment. The reduction in scores corresponded with improved clinical signs and symptoms. The changes from baseline scores were as follows: a 64.29% reduction in GAD-7 scores, a 50% decrease in PHQ-9 scores, a 74.07% reduction in NSI scores, a 68.63% decrease in PCL-5 scores, an 86.05% reduction in RPQ scores, a 40.09% increase in SCI scores, and a 77.78% reduction in OCD scores. Reference Figure 5 and Table 6 for neurocognitive psychometric diagnostic results in graphical and numerical forms. These results demonstrate that by the end of the treatment, substantial improvements were achieved in reducing symptoms and enhancing overall neurocognitive function.

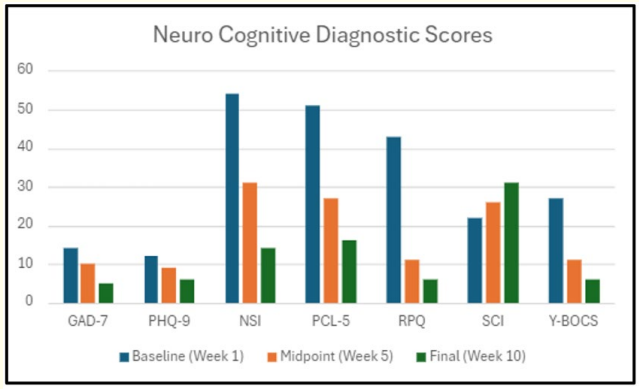

Figure 5: Bar graph of Neuro-Cognitive Diagnostics Across Treatment Duration.

DATE	GAD-7	PHQ-9	NSI	PCL-5	RPQ	SCI	Y-BOCS
5/13/2024	14	12	54	51	43	22	27
6/11/2024	10	9	31	27	11	26	11
7/17/2024	5	6	14	16	6	31	6

Table 6: Raw Neuro-Cognitive Diagnostics Scores Across Treatment Duration.

tPBM associated cognitive assessments results

Following the implementation of tPBM in week 5, additional cognitive assessments were administered to evaluate its impact in combination with PrTMS®. By the 10th week of treatment, compared to baseline, the patient demonstrated improvement in all testing domains. The changes from baseline scores were as follows:

a 14.5% reduction in reaction time for the EFT, 5.0% decrease for the IRT, 21.6% reduction for the TMT, and a 10.5% decrease for the DLT. In the SAT, there was a slight increase in reaction time by 2.4%; however, this was accompanied by an improvement in accuracy, increasing from 98% to 100%. Reference Figures 6-7 and Table 7 for the results of tPBM associated cognitive assessments in graphical and numerical forms. These results highlight significantly advanced treatment outcomes following the introduction of tPBM.

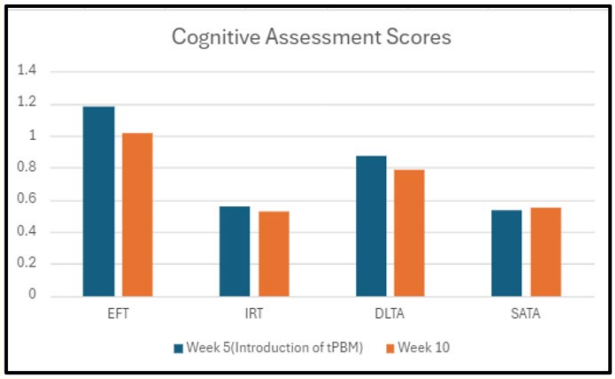

Figure 6: Bar graph of Cognitive Assessment Reaction Times Across Treatment Duration.

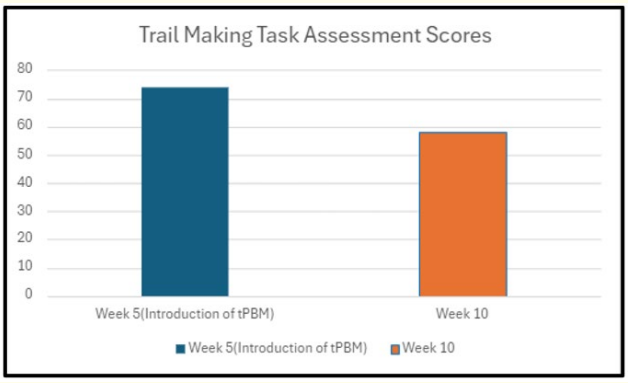

Figure 7: Bar graph of Trail Making Task Assessment Reaction Time Across Treatment Duration.

DATE	EFT	IRT	DLTA	SATA	TMTA
6/11/2024	1.186	0.556	0.877	0.534	74
7/17/2024	1.014	0.528	0.785	0.547	58

Table 7: Raw cognitive assessment reaction times across treatment duration.

Discussion

Affective and cognitive deficit symptoms are commonly associated with TBI and PTSD induced psychiatric disorders. In turn, these deficits affect satisfactory interpersonal and social performance, leading to executive dysfunction and occupational impairment [23]. Conventional treatment interventions may do little to mitigate disabling symptoms of co-occurring disorders. Disability and impairment from cognitive and affective dysregulation are consistently noted in patients receiving conventional pharmacological interventions due to partial responsiveness and severe adverse effects [24,25].Throughout this study, the combination of PrTMS® and tPBM treatments serves as a novel approach that should be further studied in clinical trials to prove their effectiveness in mitigating disabling symptoms and improving brain health.

Importantly, to the best of our knowledge, this is the first study to combine tPBM with PrTMS® in co-occurring TBI and PTSD patients. A PUBMED search Using "Personalized TMS coupled with Transcranial photobiomodulation" resulted in 3 studies, none of which actually combined PrTMS® with tPBM treatments. All 3 studies, including Mosilhy., *et al.* [26], Khoodoruth., *et al.* [27], and Hao., *et al.* [28], mention both PrTMS® and tPBM as discrete independent interventions without combining them. Specifically, Hao., *et al.* [28], compared the results of PrTMS® intervention in one set of patients independently with the results of tPBM neuromodulation in a second set of patients. While this method does compare the two neuromodulation interventions, it does not demonstrate their effectiveness when used in combination. Thus, our combination of treatment interventions serves as a novel proof of concept study in successfully treating co-occurring psychiatric disorders.

The positive results of this novel study can be attributed to an increase in ATP production, as evidenced by increased motivation, attention and concentration levels, decreased fatigue, and improved affect in the patient's daily routine. For instance, the patient described participating in exercise routines following tPBM that involved daily running, weight training, and walking activities that had been discontinued for several years. Furthermore, improved spectral EEG alpha wave coherence across cortical sites was correlated with progressive clinical improvement as evidenced by decreased impulsivity and improved mood regulation.

Limitations

This novel combination of treatments for psychiatric co-occurring disorders was limited to a single case study. The benefits of concurrently using PrTMS® and tPBM need to be studied with larger sample sizes to confirm the effectiveness of augmenting these treatments versus independently utilizing them in co-occurring disorders.

Another limitation was the utilization of self-reported neurocognitive psychometric diagnostic scores that may have led to a self-selection bias. However, this was mitigated to a significant extent by utilizing objective spectral EEG analyses to corroborate the results of cognitive assessments. Computer based cognitive assessments further mitigated self-selection bias following tPBM treatments.

Conclusion

PrTMS® and tPBM are increasingly being researched, promising noninvasive neuromodulation interventions for seriously disabling neuropsychiatric disorders. Our pilot study shows promising results for using PrTMS® treatment in combination with tPBM when treating co-occurring disorders. It is indeed noteworthy; the male patient improvement was monitored for 10 weeks through the use of systematic clinical observation and quantitative diagnostic assessments. Neurocognitive diagnostic assessment revealed patient improvements at midpoint (Week 5) of the PrTMS® treatment course. However, tPBM was introduced following Week 5 to address self-reported energy deficits and cognitive impairment. At conclusion, the patient exhibited increased coherence in alpha brain wave activity and significant improvement (> 40%) in neurocognitive psychometric diagnostics.

Further systematic studies need to be conducted with a larger cohort of patients subject to randomization in order to generalize the results across populations. Quantitative neuroimaging methods in combination with psychometrics and spectral EEG data analysis are recommended for future studies to validate our preliminary observations.

Author Contributions

KS conceptualized this work. The initial first draft was developed by SM, AB, AK, EA, AM, CV, and KS. The second draft was developed by KB and DB. The final draft was approved by all authors.

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The authors want to thank Margaret A. Madigan for expert edits. SM is currently a student at Palm Desert High School, Palm Desert, CA., USA. AK is currently a student at Chaparral High School, Temecula, CA., USA.

Conflict of Interest Statement

The authors report no conflicts of interest.

Consent

Participation in the research study, patient privacy, and HIPAA guidelines were strictly met following a thorough informed consent process. This ensured that the subject understood the potential risks and benefits of diagnostic testing and treatment interventions. PrTMS® and tPBM treatments were administered under the supervision of a board-certified psychiatrist by certified neurotechnologists.

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