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An Examination of the Combined Effects of Multi-Modality Therapy on Cognitive Rehabilitation in Traumatic Brain Injury Patients

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Abstract

This study investigates the combined effects of multi-modality therapy, including mild hyperbaric therapy (mHBT), photobiomodulation (PBM), and molecular hydrogen therapy (MH), on cognitive rehabilitation in individuals with mild-to-moderate traumatic brain injury (TBI). A total of 15 participants (7 males, 8 females, ages ranging from 20 to 78 years) diagnosed with mild-to-moderate TBI underwent 10 sessions of combined therapy. Cognitive performance was assessed using standardized neuropsychological tests before and after treatment, measuring cognitive processing speed, neural responsiveness, and executive function. The results demonstrated significant improvements across all metrics, including a 28.3 ms reduction in P300 latency, a 1.2 mV increase in P300 voltage, and reductions in completion times for the Trail-Making Tests A (14 seconds) and B (19 seconds). These findings suggest that multi-modality therapy may enhance cognitive recovery in TBI patients, with notable benefits across age and gender groups. Further research with larger sample sizes and extended follow-up is required to validate these results and explore their broader clinical applications.

Keywords

Traumatic Brain Injury, Treatment, Cognitive Rehabilitation, Hyperbaric Therapy, Photobiomodulation, Molecular Hydrogen

1. Introduction

Traumatic brain injury (TBI) is a leading cause of long-term disability, with

individuals often experiencing persistent cognitive impairments that affect their quality of life and ability to perform daily activities [1]. Cognitive deficits, including attention, memory, executive function, and processing speed, are commonly observed following TBI [2]. While traditional rehabilitation strategies such as cognitive therapy and neuropsychological interventions have shown promise in addressing some symptoms, these methods often fail to target the underlying neurological disruptions, leading to limited recovery of cognitive function [3]. Consequently, there is an urgent need for novel therapeutic approaches that promote neural repair, neuroplasticity, and long-term cognitive improvement.

Recent advances in neurorehabilitation have highlighted the potential of multimodality therapies, which integrate different treatment modalities to target distinct recovery mechanisms. Specifically, mild hyperbaric therapy (MHBT), photobiomodulation (PBM), and molecular hydrogen therapy (MH) have demonstrated individual efficacy in the rehabilitation of TBI patients. MHBT has been shown to improve oxygen delivery to brain tissues, supporting neuronal repair and reducing inflammation [4], while PBM uses near-infrared light to stimulate mitochondrial function, promoting cellular energy production and supporting neuroplasticity [5]. MH, a powerful antioxidant, reduces oxidative stress, protecting neurons from damage caused by reactive oxygen species [6].

The P300 waveform is a prominent component of the event-related potential (ERP), which is a measure of brain activity in response to specific stimuli. It is typically measured using electroencephalography (EEG) and is often associated with cognitive processes such as attention, decision-making, and memory [7]. The P300 is characterized by a positive deflection in the EEG signal occurring approximately 300 milliseconds after the presentation of an unexpected stimulus [7]. This wave reflects the brain's allocation of cognitive resources toward processing significant, novel, or task-relevant information. The latency (the time delay) and amplitude (the size) of the P300 wave provide insights into the efficiency and capacity of cognitive processing [7]. In the context of traumatic brain injury (TBI), alterations in the P300 waveform—such as longer latencies or reduced amplitudes—can indicate cognitive impairments, particularly in attention and processing speed. Thus, examining P300 latency and amplitude can offer valuable metrics for assessing neural responsiveness and cognitive function in TBI patients.

While each therapy has demonstrated positive effects on various aspects of TBI recovery, the combined impact of MHBT, PBM, and MH on cognitive function has not been adequately explored. This study aims to investigate the synergistic effects of these therapies on cognitive performance in individuals with mild-to-moderate TBI, focusing on cognitive processing speed, cognitive flexibility, and executive function. This study also seeks to understand how demographic factors such as age and gender might influence treatment outcomes, which could inform the tailoring of therapies for different patient groups.

2. Methods

This study included 15 participants diagnosed with mild-to-moderate TBI, all of whom met the inclusion criteria of documented cognitive impairments consistent with post-concussion syndrome. Exclusion criteria included individuals with severe TBI, psychiatric conditions, or substance abuse. The participants' age range was from 20 to 78 years, with a mean age of 49.8 years (SD = 19.6). The sample consisted of seven males and eight females. Participants were not divided into two distinct age groups as previously stated; instead, both younger (<50) and older (>50) individuals were considered within the overall sample to explore age-related differences in cognitive recovery following multi-modality therapy.

Participants underwent a treatment protocol consisting of 10 sessions combining MHBT, PBM, and MH. The therapies were administered in randomized order on the same day, with each session consisting of 40 minutes of MHBT, 20 minutes of PBM, and 20 minutes of MH. MHBT was delivered at a pressure of 1.5 ATA, PBM utilized near-infrared light at wavelengths of 530 - 940 nm, and MH therapy was delivered at a flow rate of 2100 cc/min.

Cognitive function was assessed before and after treatment using WAVi EEG to measure P300 latency and P300 voltage, which reflect brain activity associated with cognitive processes such as attention and decision-making. The P300 waveform, characterized by a positive peak occurring approximately 300 milliseconds after an unexpected stimulus, serves as an indicator of cognitive processing speed (latency) and neural responsiveness (amplitude). Longer latencies or smaller amplitudes are often associated with cognitive impairments. In addition to EEG measurements, participants completed the Trail-Making Test A (TMT A) and Trail-Making Test B (TMT B) to evaluate cognitive flexibility and executive function. Paired t-tests were used to compare pre- and post-treatment scores, while independent t-tests explored age- and gender-based differences in cognitive outcomes.

3. Results

Fifteen participants completed the study, with no dropouts. The average age of participants was 49.8 years (SD = 19.6), with seven males and eight females. Instead of categorizing the participants into specific age groups, both younger (<50 years) and older (>50 years) participants were included for analysis to examine age-related differences in cognitive outcomes.

3.1. Cognitive Processing Speed

After completing the multi-modality therapy, participants showed a significant reduction in P300 latency (28.3 ms, $p < 0.01$), indicating a marked improvement in cognitive processing speed. This reduction suggests enhanced efficiency in cognitive tasks, particularly those requiring attention and decision-making. The observed improvements are consistent with previous studies examining cognitive processing enhancements using hyperbaric oxygen therapy [4] and photobiomodulation [5]. As

Figure 1 shows, the reduction in P300 latency was consistent for all participants.

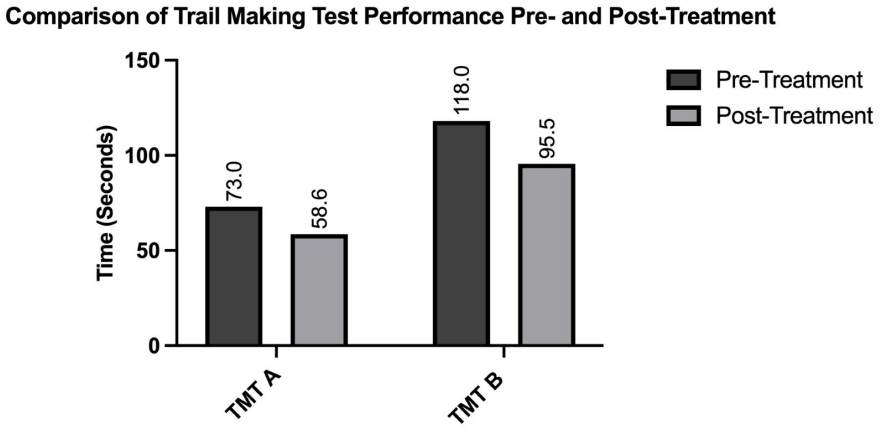

Figure 1. Comparison of trail-making test performance pre- and post-treatment. This graph shows the time (in seconds) required to complete TMT A and TMT B before and after multimodality therapy, demonstrating significant reductions in task completion time following treatment.

Gender differences were observed in the reduction of P300 latency, with males showing a larger reduction (31 ms) compared to females (27 ms), though the difference was not statistically significant. This suggests that while both genders benefitted from the therapy, males may have experienced a more pronounced improvement in cognitive processing speed. These findings align with previous research highlighting gender differences in cognitive recovery following brain injury [7]. Figure 2 illustrates these gender-based differences, clearly depicting the disparity in reductions between males and females.

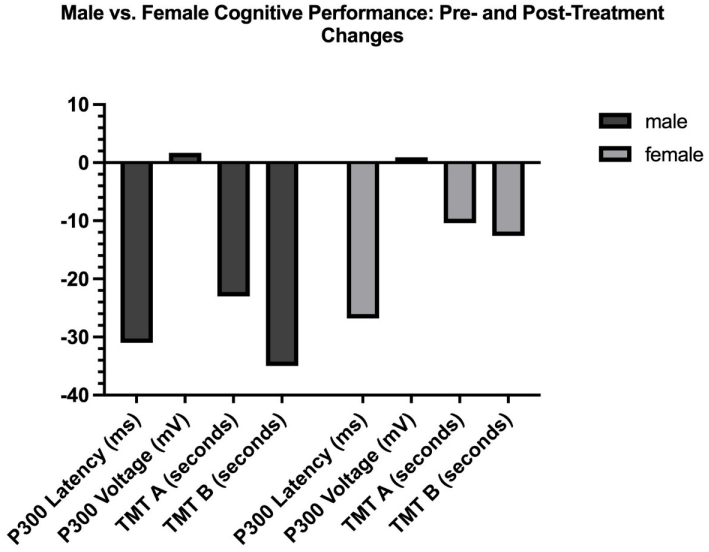

Figure 2. Male vs. female cognitive performance: Pre- and post-treatment changes. This graph presents the changes in cognitive performance, including P300 latency and TMT A and TMT B completion times, comparing males and females before and after therapy.

In examining the influence of age, both younger and older participants exhibited similar reductions in P300 latency (28 ms and 29 ms, respectively). The minimal age-related difference in cognitive processing speed suggests that the combined therapies were equally effective for improving processing speed across age groups. **Figure 3** visually represents these changes in P300 latency for both age groups, highlighting the therapy's broad applicability across different age groups.

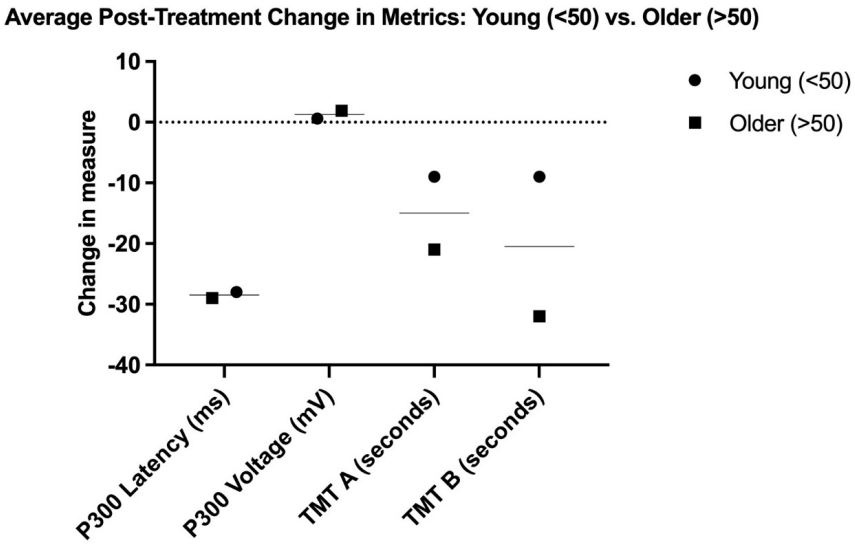

Figure 3. Average post-treatment change in metrics: Young (<50) vs. Older (>50). This graph compares the changes in cognitive performance, including P300 latency, P300 voltage, TMT A, and TMT B, between younger and older participants after multi-modality therapy.

3.2. Neural Responsiveness

Regarding P300 voltage, which measures neural responsiveness, participants experienced a mean increase of 1.2 mV ($p < 0.05$), indicating enhanced cortical activation and neural efficiency. This increase suggests that the therapy facilitated neural responsiveness, which is essential for supporting cognitive functions like attention, memory, and learning [1]. This improvement in P300 voltage aligns with findings from studies on multi-modality treatments and their effects on neural activation in TBI patients [5] [6]. **Figure 1** also visually represents this increase in P300 voltage after treatment.

Gender-based analysis revealed that males exhibited a greater increase in P300 voltage (1.7 mV) compared to females (0.9 mV). This suggests that males may have experienced a stronger cortical activation response, although both groups showed improvements in neural responsiveness. Age-based differences were also significant, with the older group demonstrating a larger increase in P300 voltage (1.9 mV) compared to the younger group (0.6 mV). This finding suggests that older participants may have experienced more substantial improvements in neural efficiency, possibly due to the targeted enhancement of age-related neuroplasticity [7]. These gender and age differences are further illustrated in **Figure 2**.

3.3. Cognitive Flexibility and Executive Function

Improvements were also observed in cognitive flexibility and executive function. Participants demonstrated a mean reduction of 14 seconds in TMT A and 19 seconds in TMT B, both statistically significant ($p < 0.01$), indicating significant improvements in cognitive flexibility and executive functioning following the multi-modality therapy. These results are visually represented in **Figure 1**, which shows the significant reductions in task completion times.

The male group showed greater improvements in cognitive flexibility, with a 23-second reduction in TMT A and a 35-second reduction in TMT B, compared to the 10-second and 13-second reductions observed in the female group, respectively. These results suggest that males experienced more pronounced improvements in cognitive flexibility, which may be attributed to baseline differences in cognitive function or differing responses to the therapy.

When analyzing the data by age group, the younger participants (<50 years) showed smaller improvements in cognitive flexibility, with reductions of 9 seconds in both TMT A and TMT B. In contrast, the older participants (>50 years) demonstrated more substantial improvements, with reductions of 21 seconds in TMT A and 32 seconds in TMT B. These findings suggest that older individuals may have experienced more substantial benefits from the multi-modality therapy in terms of cognitive flexibility and executive function. The greater improvements in the older group may reflect the therapy's effectiveness in enhancing neuroplasticity in aging brains, which is critical for the restoration of higher-order cognitive functions such as task-switching and problem-solving. **Figure 3** illustrates these post-treatment changes, highlighting the differences in cognitive flexibility between younger and older participants.

3.4. Summary of Results

Revised Version: In summary, the multi-modality therapy led to significant improvements in cognitive processing speed, neural responsiveness, and cognitive flexibility. Gender-based differences were observed, with males showing more pronounced improvements in cognitive processing speed and cognitive flexibility. Age-related differences were particularly notable in cognitive flexibility, with older participants demonstrating greater improvements in both TMT A and TMT B completion times. These findings suggest that the multi-modality therapy is effective in improving cognitive function and that treatment outcomes may vary based on gender and age, indicating the potential need for personalized treatment approaches to maximize therapeutic benefits.

4. Discussion

This study provides compelling evidence that multi-modality therapy, incorporating MHBT, PBM, and MH, significantly improves cognitive performance in individuals with mild-to-moderate TBI. The observed reductions in P300 latency and increases in P300 voltage are consistent with improvements in cognitive processing

speed and neural efficiency, both of which are critical for everyday functioning [1] [6]. These findings align with previous studies showing individual benefits of MHBT, PBM, and MH therapies, and our results suggest that their combined use yields enhanced cognitive outcomes [3].

In terms of cognitive flexibility, the reductions in TMT A and TMT B completion times indicate that multi-modality therapy not only improves basic cognitive functions but also supports higher-order executive functions such as task-switching, problem-solving, and planning [8]. These improvements are essential for the rehabilitation of individuals with TBI, who often experience deficits in these areas.

Gender-based differences in cognitive processing and flexibility were observed, with males showing more pronounced improvements. This suggests that gender may play a role in the efficacy of multi-modality therapy, and future research should explore these differences further to understand the mechanisms behind them [1].

Age-related differences were also observed, with younger participants showing faster improvements in cognitive processing speed and older participants demonstrating more substantial improvements in cognitive flexibility and neural responsiveness. These findings suggest that multi-modality therapy may have different effects depending on age, possibly due to variations in neuroplasticity and age-related cognitive decline [5].

5. Conclusions

This study demonstrates that multi-modality therapy, including MHBT, PBM, and MH, significantly improves cognitive function in individuals with mild-to-moderate TBI, enhancing cognitive processing speed, neural responsiveness, cognitive flexibility, and executive function. The study's findings suggest that multi-modality therapy may be an effective approach to addressing both fundamental cognitive functions and higher-order executive functions, such as task-switching and problem-solving.

Notable differences in treatment responses were observed across gender and age groups, suggesting that therapies could be tailored to optimize treatment outcomes based on these demographic factors. Future studies with larger sample sizes, randomized controlled designs, and long-term follow-up are needed to validate these findings and further explore the sustainability of cognitive improvements. Additionally, research into the underlying mechanisms of gender and age differences in treatment response will be crucial for refining treatment protocols and optimizing therapeutic strategies for TBI rehabilitation.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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