Cognitive Enhancement in PSCI: a Retrospective Study on rTMS and HBO therapy

Wenye Hu[1], Yufeng Xi[2], Chengrui Xu[3], Rong Luo[1*]

[1] School of Psychology, Jiangxi Normal University, Nanchang, Jiangxi, China

[2] Shenzhen Hyzen Hospital, Shenzhen, Guangdong, China

[3] Department of Psychology, Soochow University, Suzhou, Jiangsu, China

[*] Corresponding author

Abstract: Post-stroke cognitive impairment (PSCI) severely impacts quality of life. Though repetitive transcranial magnetic stimulation (rTMS) and hyperbaric oxygen (HBO) have been researched for PSCI, their combined efficacy remains understudied. This study enrolled ninety-five stroke patients, and categorized them into control group, rTMS group, HBO group, and combined rTMS-HBO group, assessing cognitive function with the Mini-Mental State Examination (MMSE). The combined group demonstrated improvements in total score and domains (namely orientation, memory, attention-calculation, and language). Notably, hemorrhagic stroke patients in this group had better attention-calculation enhancement. Thus, combined rTMS-HBO effectively alleviates PSCI cognitive deficits, offering a new approach for clinical management.

***Keywords*:** post-stroke cognitive impairment; repetitive transcranial magnetic stimulation; hyperbaric oxygen therapy; Mini-Mental State Examination

1. Introduction

Post-stroke cognitive impairment (PSCI) refers to cognitive deficits arising after acute cerebrovascular events, usually in the acute stroke phase and over half of stroke patients have long-term PSCI [1]. Stroke, which linked to cognitive dysfunction, is classified into ischemic and hemorrhagic subtypes. PSCI severely impairs quality of life and daily activities, presenting with deficits in memory, aphasia, apraxia, agnosia, visuospatial processing, often accompanied by anxiety and depression[2]. Its established risk factors include advanced age, unhealthy lifestyle, low education, depression, and increased stroke severity[3]. Contemporary research rarely distinguishes ischemic and hemorrhagic stroke in cognitive impairment studies, often grouping them or using one as control[4] . Yet clinical evidence shows stroke lesion anatomy impacts cognitive domains differently . Lesion features (location, size, depth) determine cognitive deficit severity.

Current therapeutic approaches for PSCI encompass pharmacological treatments, including donepezil and memantine, as well as cognitive rehabilitation programs. Nevertheless, these interventions are frequently constrained by adverse drug reactions and the demanding nature of rehabilitation protocols. As a result, alternative treatment modalities have been investigated, such as acupuncture , Ba Duan Jin exercise [5], music therapy [6], and VR based interventions [7]. Empirical findings indicate that these interventions exhibit partial efficacy in mitigating specific cognitive deficits. For instance, Ba Duan Jin exercise has been associated with improvements in memory, executive function, and attention, whereas music therapy primarily enhances executive function. Despite these advances, challenges persist, such as optimizing user engagement to facilitate a flow state and effectively managing cognitive load during interventions [8]. Furthermore, non-invasive neuromodulation techniques, including rTMS and HBO therapy, have recently emerged as promising therapeutic alternatives for PSCI.

Repetitive transcranial magnetic stimulation (rTMS) modulates cortical excitability by applying magnetic stimulation at varying frequencies. Empirical evidence has demonstrated that rTMS effectively enhances global cognitive function and mitigates aphasia in PSCI [9]. A considerable corpus of literature has documented the beneficial impact of rTMS on cognitive outcomes, language impairments, and diverse physical deficits following stroke [10]. Moreover, a meta-analytic review indicated that combining rTMS with cognitive training yields significant improvements in global cognition, executive functions, and working memory, although no significant effects were observed on memory performance specifically [11]. Hyperbaric oxygen therapy (HBO) delivers 100% oxygen in >1 absolute atmosphere (via hyperbaric chamber) to boost tissue dissolved oxygen. Studies show HBO normalizes cerebral water content to promote neuroplasticity in chronically damaged neural tissue, effective for stroke recovery and chronic phases[12]. It improves memory, attention and executive function in cardiac arrest-related chronic cognitive deficits. After 2-month HBO, PSCI plus motor dysfunction had better neurological function and quality of life [13]. Despite strong neurorestorative potential, HBO is underused in stroke care due to lingering doubts about its efficacy .

Both rTMS and HBO improve cognitive deficits in stroke survivors, yet studies on their combined use to elucidate PSCI mechanisms and prognosis are lacking . Prior research suggests rTMS barely affects memory, while HBO enhances it in PSCI patients, raising the question of their synergistic potential[14] . Whether combination treatment should be adjusted by stroke etiology remains unclear. Can a uniform rTMS frequency supplement HBO to improve multiple cognitive domains across stroke subtypes?

This study aims to assess whether combined rTMS-HBO intervention yields better overall and domain-specific cognitive gains for PSCI patients than monotherapy, with a special focus on differentiating outcomes between ischemic and hemorrhagic stroke subgroups. Cognitive function will be evaluated using the eleven dimensions of the Mini-Mental State Examination (MMSE), including time/place orientation, immediate memory, attention-calculation, recall, naming, retelling, three-step command execution, reading comprehension, writing, and description.

2. Methods

2.1 Participants

Ninety-five stroke patients (56 ischemic, 39 hemorrhagic) admitted to Shenzhen Hyzen Hospital from September 2023 and April 2025 were enrolled. Inclusion criteria: (1) stroke diagnosed via CT, MRI, or angiography; (2) recovery/sequelae phase; (3) PSCI with pre-stroke normal cognition; (4) aged 17–93 years; (5) stable vital signs. Exclusion criteria: metal implants, epilepsy history, or non-stroke-related cognitive impairment. The study was approved by the hospital's ethics committee, and informed consent was waived due to retrospective design. Patients were stratified into four groups by treatment: control ($n=35$, age: 74.40±12.81), rTMS ($n=19$, age: 73.84±10.78), HBO ($n=22$, age: 60.14±16.28), and combined ($n=19$, age: 51.32±15.61).

All groups received standard treatment (neurotrophic agents, antihypertensives, antidiabetics, antiplatelets) plus 30-min daily cognitive training (5 days/week, targeting visuospatial ability, attention, memory, executive function). rTMS was delivered via YRD CCY-II stimulator: 5 Hz high-frequency stimulation on left dorsolateral prefrontal cortex (80% motor threshold), 20 min/day, 5 days/week (circular coil). HBO was conducted in multi-chamber facility (1.8–2.0 ATA): 20-min pressurization/decompression + 70-min 100% oxygen inhalation, 100 min/session, once daily, 5 days/ week. Groups differed in additional treatment: control (only standard), rTMS (standard + rTMS), HBO (standard + HBO), combined (all three). Due to retrospective design, individual treatment duration was undocumented. Data collection and treatment ceased when MMSE scores met clinician-defined discharge criteria.

2.2 Materials

Cognitive function was assessed via the Mini-Mental State Examination (MMSE), which evaluats 11 domains: time/ place orientation (0–10 points), immediate memory (0–3), attention-calculation (0–5), delayed recall (0–3), language abilities (naming, repetition, comprehension, writing; 0–8), and visuospatial skills (0–2). The MMSE has a total of 30 points. The score <24 indicates cognitive impairment, with lower scores reflecting more severe impairment. SPSS 27.0 was used to analyze the data. The mean ± standard deviation was used to express continuous variables. Paired t-tests were used to compare groups before and after therapy, and independent t-tests were used to evaluate group differences. Chi-square tests were used to assess categorical variables.

3. Results

Baseline MMSE scores did not differ among groups ($p>0.05$). Post-treatment, the control group had no significant total MMSE change ($p=0.079$) but improved language ($p=0.043$), indicating pharmacotherapy + cognitive training benefits language deficits. The rTMS group showed significant improvements in total MMSE ($p=0.000$) and orientation ($p=0.011$), memory ($p=0.015$), attention-calculation ($p=0.047$), recall ($p=0.000$), with no significant changes in language ($p=0.098$) or visuospatial ($p=0.480$). The HBO group improved total MMSE ($p=0.000$), orientation ($p=0.000$) and language ($p=0.001$), but not memory ($p=0.310$), attention-calculation ($p=0.788$), recall ($p=0.736$), or visuospatial ($p=0.051$). Unexpectedly, the combined group had no additive effects, with no significant recall ($p=0.072$) or visuospatial ($p=1.000$) improvement.

Group comparisons showed the combined therapy group had significantly higher total MMSE scores and better performance in most cognitive domains than the control and rTMS groups (Table 1). Compared to the combined group, the rTMS group differed significantly in orientation ($p=0.003$), attention-calculation ($p=0.018$) and the total MMSE ($p=0.023$) while the HBO only differed in attention-calculation ($p=0.049$). Overall, the combined group had broader cognitive improvements, with significant enhancements in total MMSE ($p=0.000$), orientation ($p=0.000$), memory ($p=0.002$), and attention-calculation (p=0.000) compared to the control group. However, improvements in recall (p=0.056), language (p=0.130), and visuospatial (p=0.054) were not significant.

Participants were grouped by stroke etiology (ischemic/hemorrhagic). Post-intervention differences in overall and domain-specific MMSE scores between control and combined groups are in Table Pre-treatment, no significant differences in total or domain MMSE scores existed between ischemic and hemorrhagic participants within each group. Post-treatment analysis showed hemorrhagic participants in the combined group had significantly higher attention-calculation scores than ischemic counterparts (p = 0.024, MD = 1.93).

Table 1. Post-treatment of total MMSE and dimensional scores between groups compared with combined group

Domain	Combined vs. Control (95%CI)	Combined vs. rTMS (95%CI)	Combined vs. HBO (95%CI)
orientation	2.774 [1.371, 4.178] ***	2.474 [0.876, 4.072] **	1.359 [-0.184, 2.902]
memory	1.030 [0.400, 1.660] **	0.474 [-0.244, 1.191]	0.361 [-0.331, 1.054]
attention-calculation	1.821 [0.904, 2.738] ***	1.263 [0.219, 2.307] *	1.012 [0.004, 2.020] *
recall	0.543 [-0.015, 1.010]	0.053 [-0.583, 0.688]	0.318 [-0.295, 0.931]
language	0.962 [-0.290, 2.215]	0.684 [-0.742, 2.110]	-0.213 [-1.589, 1.164]
visuospatial	0.206 [-0.003, 0415]	0.158 [-0.080, 0.396]	-0.100 [-0.331, 0.130]
total Score	7.308 [3.456, 11.160] ***	5.105 [0.719, 9.491] *	2.737 [-1.497, 6.971]

Note: * means p < 0.05, ** means p<0.01, *** means p<0.001

Table 2. Post-treatment effects of stroke types differed between the control and combined groups

Domains	Control (n=35)	Combined (n=19)
	Ischemic (n=24) vs. Hemorrhagic (n=11) [95%CI]	Ischemic (n=5) vs. Hemorrhagic (n=19) [95%CI]
orientation	0.341 [-1.515, 2.196]	-1.043 [-3.698, 1.612]
memory	0.246 [-0.535, 1.027]	0.700 [-0.417, 1.817]
attention-calculation	0.053 [-1.114, 1.220]	1.929 [0.259, 3.598] *
recall	0.261 [-0.410, 0.933]	1.027 [-0.961, 0.961]
language	0.189 [-1.410, 1.789]	-0.400 [-2.689, 1.889]
visuospatial	0.049 [-0.194, 0.292]	0.086 [-0.262, 0.434]
total Score	1.231 [-3.444, 5.906]	1.271 [-5.417, 7.960]

Note: * means p < 0.05.

4. Discussion

This retrospective study shows combined rTMS-HBO therapy improves overall cognitive function and specific domains (orientation, memory, attention-calculation, language) in PSCI patients, superior to single-modality treatments. The lack of effects on recall and visuospatial skills highlights the need for targeted interventions. Though total efficacy was similar for ischemic and hemorrhagic stroke subtypes, hemorrhagic patients had more noticeable attention-calculation improvements, possibly due to lesion localization differences (e.g., subcortical regions linked to arithmetic) or variable neurovascular responses to combined treatment.

HBO enhances oxygen-dependent neuroregeneration and rTMS promotes cortical plasticity, suggesting potential synergies on neural substrates critical for language and attention. The HBO monotherapy group had limited cognitive gains, possibly due to lower treatment frequency (5 sessions/week vs. daily protocols in prior studies) , highlighting the need to optimize HBO dosing. Additionally, the rTMS group's modest memory improvements contradict prior meta-analyses, which may stem from varied stimulation parameters or concurrent cognitive training's confounding effect.

This study has limitations, including retrospective design, heterogeneous stroke subtypes, and small sample size. Future randomized controlled trials with larger cohorts, consistent intervention regimens, and longer follow-up are needed to confirm initial results and clarify mechanisms (e.g., microvascular remodeling, neurotrophic factor upregulation). In conclusion, combined rTMS-HBO is a viable PSCI treatment, especially beneficial for hemorrhagic stroke patients (with notable attention-calculation improvements). These findings support further clinical research to verify the combination's efficacy as a therapeutic adjunct.

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