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Abstract

A traumatic brain injury (TBI) triggers a complex cascade of biological changes following a forceful impact to the head. Long-term effects are often life-altering and include cognitive impairment, reduced synaptic plasticity, mood instability, and motor dysfunction. Current pharmacological treatments are limited in their ability to address the evolving and multifaceted nature of TBI pathology and may carry adverse side effects or risk of dependence. This literature review synthesizes emerging evidence supporting non-pharmacological interventions (NPIs) that are currently in their clinical trial phase as complementary or alternative approaches. Virtual reality (VR), hyperbaric oxygen therapy (HBOT), nutritional therapy, and exercise-based interventions demonstrate promising early results. VR therapy has been shown to improve cognitive function and mood, particularly when combined with physical rehabilitation to enhance balance and mobility. HBOT may mitigate secondary injury processes, including hematoma progression, and improve pain outcomes. Nutritional interventions are associated with improved cognitive function and earlier hospital discharge, while exercise-based therapy supports executive function and allows for individualized rehabilitation strategies. Together, these findings suggest that NPIs may enhance post-TBI care when integrated with pharmacological treatment within personalized rehabilitation models. However, larger controlled studies are needed to confirm long-term efficacy and clinical feasibility.

Keywords: traumatic brain injury, cognitive recovery, non-pharmacological interventions, aerobic exercise, virtual reality, hyperbaric oxygen therapy

1. Introduction

Traumatic brain injury (TBI) is the primary source of mortality and impairment in non-elderly groups in industrialized countries.[1] It is defined as neurological injury resulting from external mechanical force. Patients with TBI experience debilitating cognitive symptoms that hinder their quality of life, including decreased language abilities, reasoning skills, and executive function limitations. In the United States, TBIs were responsible for approximately 214,110 hospitalizations in 2020 and 69,473 related deaths in 2021.[2] Beyond the initial injury, TBI can cause long-term symptoms including post-traumatic epilepsy (PTE), post-traumatic stress disorder (PTSD), and post-traumatic cognitive impairment (PTCI). Among

these, cognitive dysfunction is one of the most common and weakening outcomes. Patients may experience difficulties with memory, attention, emotional regulation, language, reasoning, and executive function, all of which can affect quality of life. Memory impairments have been reported in up to 90% of cases, attentional difficulties in 82%, and executive dysfunction in 75% of TBI populations.[3] Additionally, persistent cognitive impairment occurs in approximately 65% of patients with moderate to severe TBI and 15% of patients with mild TBI.[3] These deficits persist long after the initial injury, making cognitive recovery an important focus of TBI treatment.

The standard of care for pharmacological management of cognitive dysfunction following TBI is ever-evolving as more drugs are developed and tested for their efficacy in treating the various cognitive deficits following TBI. Some common drugs used to support cognitive recovery include methylphenidate, donepezil, and amantadine. Although pharmacological interventions are standardly used to support cognitive recovery following TBI, many of these interventions demonstrate inconsistent efficacy, limited long-term benefit, or adverse side effects, highlighting the need to investigate alternative treatments.[3,4] Methylphenidate has little evidence to support a strong dose-response relationship.[5] Donepezil has been shown to have a partially safe and tolerable profile with chances of harmful quality of life side effects such as diarrhea, nausea, and dehydration.[6] Amantadine has been shown to have unreliable effects, improving functional recovery in some patients but not others, with risks of adverse side effects such as seizures and gastrointestinal problems.[7]

The purpose of this review is to assess non-pharmacological interventions (NPIs), or treatment approaches that do not involve medications for TBIs. Despite growing interest in NPIs for TBI, existing literature reviews largely examine these interventions in isolation, limiting cross-modal comparison and mechanistic integration. This review addresses that gap by comparatively synthesizing virtual reality (VR), hyperbaric oxygen therapy (HBOT), nutritional therapy, and exercise-based rehabilitation through a comparative, mechanism-informed approach. By evaluating how these distinct modalities may influence common recovery processes, including neuroplasticity, cerebral oxygenation, metabolic stabilization, and functional recovery, this review highlights the potential of these NPIs to be combined with pharmacological treatments.

1.1 Limitations of Pharmacological Interventions

While the current TBI-related pharmacological interventions have been shown to improve some aspects of cognitive dysfunction following TBI, much of the existing data is preliminary, inconsistent, and not sufficiently conclusive in the overall efficacy and safety of the interventions. To date, many pharmacological clinical trials for TBI recovery have not produced consistently effective treatments capable of improving long-term cognitive outcomes, highlighting the complexity of TBI pathophysiology and the difficulty of developing targeted therapies.[3] This lack of confidence warrants the investigation into the potential efficacy and safety of NPIs.

While pharmacological interventions are effective at treating acute disruptions resulting from TBIs, the injury is dynamic with long-term consequences that often require continual management.[3] A TBI requires constant re-prescription of drugs, subsequently increasing the risk of adverse reactions and side effects with each new drug.[6] NPIs may offer certain advantages in TBI rehabilitation when compared to pharmacological interventions, including a lower risk of adverse effects and greater flexibility to adapt interventions to the evolving nature of recovery. They also present a considerably lower long-term economic burden on

healthcare systems compared to pharmacological therapies, which require constant research and development funding.

Methylphenidate, a pharmacological intervention that targets dopamine and norepinephrine pathways commonly impaired following TBI, has been shown to produce modest improvements in cognitive functioning in TBI patients (effect size d = 0.34, 95% CI: 0.12–0.56), particularly in processing speed and executive tasks.[4] However, as with many pharmacological interventions, these benefits should be considered alongside the potential for adverse effects. Although the following safety estimates were derived from a study of 71 children receiving methylphenidate for ADHD rather than patients with TBI, they are included to illustrate the broader tolerability profile of the medication across clinical populations. In that study, anorexia was reported in 74.3% of participants, irritability in 57.1%, and insomnia in 47.2%.[8] While these frequencies may not directly generalize to TBI populations, they highlight the importance of considering adverse effects when evaluating pharmacological approaches for cognitive recovery. Donepezil has demonstrated larger effect sizes for certain cognitive outcomes (d = 1.68), although this finding is based on a limited number of studies and requires further validation.[4] The following adverse effect estimates are likewise drawn from broader safety reporting rather than TBI-specific populations and are included to contextualize the medication's general tolerability profile. More than 10% of users experience nausea, headache, and diarrhea, while 1–10% experience insomnia, tremor, epigastric pain, hypertension, atrial fibrillation, eczema, nocturia, anorexia, hallucination, cataracts, and arthritis.[9]

It is important to note that many of the methodological limitations used to critique pharmacological studies are also found in non-pharmacological research and should be considered with equal weight. Across the field of TBI research, there remains a limited number of rigorous double-blind clinical trials, and the absence of validated biomarkers makes it difficult to objectively determine whether interventions are truly effective in human populations. In addition, the substantial heterogeneity of TBI injuries and patient characteristics complicates the interpretation of treatment outcomes and requires very large sample sizes to detect meaningful effects. The clinical TBI field is currently undergoing a reassessment of traditional mild, moderate, and severe classifications in an effort to better classify patient populations and improve the design and feasibility of clinical trials. These challenges increase the cost and complexity of conducting high-quality studies and apply to both therapies. While limitations in pharmacological trials are often scrutinized more heavily due to regulatory requirements and potential side effects, the methodological burdens are shared across all intervention types and reflect broader challenges within TBI research rather than weaknesses specific to any single treatment approach.

2. Virtual Reality as an Effective Tool for Cognitive Training, Spatial Orientation, and Balance

Virtual Reality (VR) has emerged as a promising NPI for TBI due to its capacity for task specificity, adaptability, and immersive cognitive engagement. VR is a technology that uses computer-generated simulations to create immersive, interactive environments. There are various iterations of VR targeting specific TBI-related cognitive dysfunctions, including executive dysfunction and balance. The customizability of VR opens a completely new field that requires rigorous investigation to determine the possible benefits and side effects of its iterations.

2.1 Task-Based VR Rehabilitation

A pilot controlled clinical study by De Luca et al. (2023) suggests that task-based VR has the potential to improve visuo-executive abilities, coping

strategies, and mood in TBI patients.[10] Participants were seated in front of a virtual device and performed various tasks aided by a therapist. Patients completed a VR rehabilitation system program of interactive visual exercises that targeted executive skills, attention, and problem-solving. The authors found that task-based VR rehabilitation may be a more efficient and cost-effective approach to improve coping strategies and mood in TBI patients than the current non-pharmacological treatment standard of rehabilitation. The current standard of care for a non-pharmacological task-based model is based on a face-to-face approach between a therapist and the patient using traditional materials such as paper and pencil tools. The task-based VR model is an expansion of this, offering greater adaptability and enjoyment that may be more effective at improving cognitive deficits following TBI.

2.2 Virtual Reality Orientation Therapy (VRot)

Similarly, an exploratory clinical study by De Luca et al. (2024) suggests that virtual reality orientation therapy (VRot) may optimize cognitive and behavioral functioning post-severe acquired brain injury.[11] The authors found that VRot may be a more efficient way of using simulated situations to reduce depressive symptoms and improve the reality orientation deficit caused by TBIs than standard reality orientation therapy (ROT). The current non-pharmacological model of ROT involves a classroom teaching approach or a guided household chore approach. The VRot used in this study used virtual scenarios that simulate real-world situations to repeat time, place, and person orientation with meaningful stimuli to help the patient develop a better understanding of their environment and gain a sense of control. The patients were presented with scenarios, such as driving, shopping at the supermarket, and household chores to perform on their own with virtual guidance. The authors found statistically significant improvements in cognitive function and depression in the subjects, larger improvements than those in the standard ROT group.

VRot therapy, like the task-based VR, offers greater adaptability and comfort for patients since a wide variety of simulations can be generated without having to travel anywhere and avoids the fear of possible consequences for choosing certain responses to social interactions. The data also suggests that this virtual extension may be more effective at improving spatial orientation than standard conventions. These two studies highlight the possible benefits of transforming current NPIs into virtual iterations.

2.3 VR Combined with Exercise

Another development in the VR field involves combining VR interventions with other NPIs. A randomized control pilot trial by Tefertiller et al. (2022) suggests that coupling VR rehabilitation with treadmill training may be a safer and more effective way to treat balance and endurance deficits post-TBI than treadmill training or stationary training on their own.[12] The patients in the VR-coupled treadmill training group interacted with virtual feedback games while walking at various paces on a treadmill. The authors found that no patients experienced serious adverse events and that the VR coupled with the treadmill group showed significantly greater improvements in balance and mobility than the solely VR and solely treadmill groups. While the sample size was small, the preliminary data highlights the possible benefits of combining a virtual reality model with other TBI-related non-pharmacological models.

2.4 Synthesis of the Literature

These three studies highlight the potential advantages of VR-based interventions over existing non-pharmacological rehabilitation approaches by increasing adaptability and patient engagement. Both the task-based VR and the VRot studies suggest that virtual extensions of the current standard of care outperform their traditional

counterparts in treating specific cognitive dysfunctions. Rather than requiring the invention of a new type of treatment framework, VR seems to enhance the current methods of treating cognitive dysfunctions and can potentially be used to build upon the framework already established to treat TBIs. This new enhancement allows researchers to further individualize treatments, repeat intervention exposure, and receive real-time feedback. The preliminary data from the coupled study proposes investigation into combining VR-focused rehabilitations with other low-risk NPIs, such as exercise, diet changes, and hyperbaric oxygen therapy, to evolve the standard of care for TBIs to minimize risks and increase adaptability and efficacy.

Some limitations to consider across these studies include small sample sizes and pilot or exploratory designs, which limit statistical power, generalizability to different TBI populations, and ability to draw definitive conclusions about efficacy. In the VRot study, the inclusion of severe acquired brain injury patients rather than exclusively TBI participants restricts the application of the conclusions to TBI-related deficits. For the VR combined with exercise study, it is important to consider its design as a pilot randomized controlled trial to determine whether the intervention was practical and safe to implement, rather than to determine its effectiveness. Additionally, its focus on balance and mobility outcomes restricts making broader conclusions about neurocognitive recovery. Short follow-up periods across studies also make it unclear whether observed improvements in executive function, mood, balance, and spatial orientation were sustained over time. These limitations suggest that while VR-based interventions demonstrate potential, the current evidence is preliminary and should be interpreted cautiously until further validated by larger, standardized trials.

Directly comparing the studies is challenging due to the differing outcome measures, iterations of VR, and cognitive dysfunctions targeted. Further research within each of these iterations should investigate the true efficacy of each intervention. Nonetheless, there is a promising pattern that suggests VR can improve and evolve the current standard of care for TBIs.

3. Hyperbaric Oxygen Therapy as a Neurorehabilitation Tool for Cognitive Function

Hyperbaric Oxygen Therapy (HBOT) is a treatment in which a patient is placed within a pressurized chamber, allowing the blood to carry more oxygen throughout the body, improving and accelerating recovery.

3.1 Clinical Evidence for Functional and Quality-of-Life Outcomes

A prospective clinical intervention study by Ablin et al. (2023) evaluated the effects of standard HBOT procedures as TBI treatments by having participants breathe 100% oxygen through a mask.[13] The study suggested that HBOT enhances activation in the frontal and temporal lobes, corresponding with improvements in pain control, emotional regulation, and cognitive function. Patients in the HBOT group reported greater satisfaction and improvements in quality-of-life measures compared with participants receiving pharmacological treatment (Pregabalin or Duloxetine). This was supported by significant increases in SF-36 Health Survey scores, a validated measure of health-related quality of life, where higher scores indicate better functioning, particularly in the vitality (energy), social functioning, and pain domains. While HBOT demonstrates promising clinical outcomes, comparisons with other NPIs remain limited as variability in protocols and outcome make it difficult. The evidence suggests that HBOT represents one of many potentially effective NPIs, and future research should explore its combined use with other NPIs to evaluate potential synergistic effects.

3.2 Mechanistic Evidence from Preclinical Models

A study conducted by Sakas et al. (2023) further supports HBOT's neurological recovery abilities.[14] They found that HBOT administered early in disease progression lessens the effects of the secondary injury cascade of metabolic dysfunction following TBI using a rodent-model. At a cellular level, increasing oxygen delivery may help injured neurons restore energy production. Post-TBI, mitochondrial dysfunction limits the amount of ATP made, leaving neurons without an energy source and more vulnerable to apoptosis. By improving oxygen availability, HBOT may support ATP-formation which stabilizes cellular energy balance thereby reducing secondary cell death. This neuroprotection also preserves mitochondrial function through increased oxygenation of the bloodstream.[14]

Sakas et al. (2023) also suggest that HBOT can decrease oxidative stress, reduce inflammatory signaling, and promote angiogenesis, potentially improving blood flow to damaged brain tissue. However, most of this mechanistic evidence comes from animal models, where oxygen dosing and timing are tightly controlled. While human studies have demonstrated improvements in cerebral blood flow, direct confirmation of the exact cellular mechanisms in the preclinical models in humans is limited.[13] Therefore, although these pathways work in theory, further translational research is needed.

Additionally, the protective mechanisms of reducing glial proliferation and apoptosis improve cognitive and motor recovery while also addressing the metabolic dysfunction issue, for which pharmacological interventions have shown inconsistent results.[4] These findings build upon those of Ablin et al. (2023) by confirming HBOT's potential benefits of improving cognitive function and cognition-linked metabolic processes.[13]

3.3 Clinical Evidence for Functional and Quality-of-Life Outcomes

These studies collectively demonstrate HBOT's potential as a treatment for TBI. Clinical findings suggest improvements in quality of life, including social and emotional functioning, while preclinical rodent studies provide mechanistic evidence that HBOT may reduce secondary brain damage and neuronal apoptosis following injury.[13,14] Additional clinical evidence further supports these findings.

One study conducted by Chen et al. (2022) examined whether HBOT could reduce hematoma volume in patients with TBI.[15] Differences in recovery were measured using Glasgow Coma Scale (GCS) scores and the Coma Recovery Scale–Revised (CRS-R). Consistent with the previous studies mentioned, the findings suggest that HBOT is an effective treatment to improve consciousness, cognitive function, and prognosis. As HBOT reduced hematoma volume, patients showed improved patterns of electrical brain activity on an electroencephalogram (EEG).[15] Hematomas can increase pressure in the cranium, compressing brain tissue and disrupting the neural signaling necessary for cognition and consciousness. By reducing the volume of hematomas, HBOT relieves this pressure buildup in the brain, facilitating blood flow and oxygen delivery to the brain, which is associated with neural recovery and improved EEG activity, as shown by the patients in the study.[12] Compared to Ablin et al. (2023), whose results depend on symptoms, this study demonstrates physiological benefits.[13] The above studies collectively demonstrate HBOT's versatility and treatment range as a NPI. These findings suggest that HBOT may influence aspects of TBI recovery, such as oxygenation and metabolic function.

Some limitations should be considered when interpreting these findings. In Ablin et al.'s (2023) study, many of the improvements were measured

using patient-reported outcomes and quality-of-life scales, which may be influenced by patients' expectations about the treatment rather than reflecting objective neurological improvement.[13] The sample size was also limited, which makes it difficult to generalize the results to the broader TBI population. In the preclinical study by Sakas et al. (2023), the use of a rat model limits translation of the results to humans, as recovery, brain function, and metabolic rates differ across species.[14] Additionally, laboratory conditions cannot fully replicate the complexity and variability of TBI cases in real life. In Chen et al.'s (2022) study, HBOT was administered alongside standard medical treatment rather than as a standalone intervention.[13-15] Therefore, although reductions in hematoma volume and improvements in GCS and CRS-R scores suggest additional physiological benefit, the multifactorial nature of TBI recovery makes it difficult to attribute these outcomes only to HBOT. Across studies, differences in oxygen dosage, treatment duration, and timing of intervention also make direct comparison challenging. Ultimately, while HBOT shows promising potential, the current evidence remains preliminary and should be regarded with caution until supported by larger clinical trials.

4. Nutritional Therapies as a Metabolic Enhancement Tool

A randomized controlled study by Yang et al. (2023) examined the effects of intermittent fasting (IF) in mice on the activation of the ferroptosis pathway, a type of programmed cell death that contributes to neuronal loss following TBI, and related outcomes.[16] IF is a dietary pattern that alternates between food consumption and absence from consumption. The major finding was that a 1-month period of IF in mice led to the alleviation of TBI-induced ferroptosis. This potentially aids cognitive repair by increasing metabolically active cells. The researchers reported that IF reduced markers of ferroptosis. By limiting ferroptotic signaling, more neurons survived and metabolism stabilized. The study also included behavioral cognitive testing, such as spatial learning and memory assessments, which demonstrated improved performance in mice undergoing intermittent fasting compared to controls. An important finding to note is that IF must be practiced for a long time to be effective. In this study, shorter periods of IF (<1 mo.) resulted in no significant changes in metabolic activity.

4.1 Intermittent Fasting and Neuroprotection

A review article by Finnegan and colleagues (2022) assessed the effects of nutrition on TBI recovery.[17] TBI exists along a spectrum of severity, including mild, moderate, and severe classifications based on neurological findings. Mild TBI encompasses the majority of cases and is characterized by subtle yet persistent cognitive and emotional deficits, despite limited structural abnormalities in the brain on imaging. While moderate and severe TBIs frequently require immediate, life-saving intervention right after the injury and intensive pharmacological management, mTBI recovery often relies more heavily on rehabilitation-based approaches that target neuroplasticity, metabolic repair, and functional reintegration. Therefore, mTBI provides a relevant framework to evaluate rehabilitative NPIs, which may have the greatest long-term impact on cognitive restoration. Post-mTBI (mild TBI), metabolic demand increases as the body prioritizes repair, resulting in greater nutritional requirements. An observational study analyzed in this review gave post-mTBI patients dietary journals to track how much food they were consuming in regards to calorie and protein intake. With the dietary journals, the researchers found that those who consumed the average dietary intake of 2,232 calories and 121.3 g/day, which served as a benchmark for evaluating patients' nutritional status. Patients whose intake

was near or met this benchmark were discharged earlier than those whose intake fell below these levels. This suggests that ensuring nutrition levels are met may improve recovery time from acute mTBI, as adequate calorie and protein intake are crucial in supplying the body with sufficient nutrients to facilitate recovery.

4.2 Synthesis of the Literature

The above findings suggest that nutrition is an important factor in TBI recovery. In fact, it may even be a more accessible intervention than some of the other discussed NPIs. For example, HBOT often requires repeated treatment sessions in specialized facilities, contributing to a treatment burden of travelling and time.[18] A recent Medicare cost analysis estimated that a standard course of 40 HBOT sessions cost approximately USD $23,834 per patient in 2022, with each session averaging $595.86.[18] In contrast, nutritional interventions can generally be incorporated into existing routines without requiring specialized infrastructure. However, other treatments may be more promising in terms of timeliness, as dietary modifications do not always result in drastic enough improvements necessary for recovery. It's important to note that direct cost-effectiveness comparisons between nutritional interventions and other TBI treatments have not yet been found.

Despite these promising findings, limitations should be acknowledged. Yang et al.'s intermittent fasting study was conducted on mice, which limits translation to human TBI populations, as metabolic processes, recovery timelines, and dietary needs differ between species. Additionally, the optimal duration, timing, and implementation of fasting protocols in clinical TBI populations remain unclear.[19] The observational study assessing calorie and protein intake in post-mTBI patients also relied on self-reported dietary journals, so it is difficult to determine whether earlier discharge was directly caused by nutritional intake or other factors. It is possible that patients with milder injuries felt better and were therefore able to eat more, that healthier individuals had stronger appetites, or that patients recovering more quickly consumed greater amounts of food. Furthermore, the absence of standardized dietary protocols limits the ability to form concrete clinical recommendations. Ultimately, while nutritional strategies show theoretical promise, the current evidence requires more human trials with clearer guidelines.

5. Exercise Interventions as a Tool for the Optimization of Surviving Cognitive Neuronal Networks

A preclinical study by Gomez-Porcuna and colleagues (2024) found that aerobic exercise (AE) using a motorized running wheel could improve cognitive recovery following TBI in rats.[20] AE is physical activity that uses large muscle groups in a consistent manner and relies on oxygen to make energy over an extended period of time. The target speeds were chosen as 8 m/min for TBI-8 (low intensity), 12 m/min for TBI-12 (moderate intensity), and 16 m/min for TBI-16 (high intensity). The researchers measured hippocampal volume, surviving neuron amounts, and neurogenesis after rat euthanization.

Short and long-term memory improvements in the object recognition test were observed across all exercise groups compared to TBI sedentary rats (TBI-sed); however, they did not reach baseline levels. This suggests that while exercise may support cognitive recovery following TBI, exercise alone may not be enough to restore function. One possible explanation is that adequate nutrition supplies the energy necessary to support the physical demands of exercise and promote recovery in surviving neural networks. This points to the potential value of combining interventions that target different aspects of recovery. Supporting this broader idea, Finnegan et al. (2022) found that patients who met nutritional

benchmarks during acute mTBI recovery were discharged earlier, suggesting that recovery may benefit from addressing factors like energy availability rather than relying on a single intervention.[17] However, because Finnegan et al. studied humans while these exercise findings were observed in rats, this comparison should be interpreted with caution.

One potential explanation for the combined effects of AE and IF on cognitive recovery is that IF has been shown to produce metabolic improvements by preventing neuronal cell death after four weeks.[17] By limiting neuronal loss, IF could preserve a greater number of surviving neural networks post-TBI. In contrast, AE improves the function of existing neural networks, as demonstrated in this preclinical study by memory improvements observed after four weeks of exercise. Therefore, if IF helps preserve neurons while AE enhances the function of surviving networks, the combined effects of these interventions may lead to greater improvements in cognitive recovery. Although hippocampal volume loss and neuronal death were not fully affected by exercise, both sexes in the exercise groups, independent of intensity, showed recovery in memory retention that came with enhanced neurogenesis and reduced microglial activation.

Nonetheless, several limitations affect how these findings are interpreted. This study was conducted in a rodent model, which limits direct translation to human TBI populations. The researchers also ensured exercise intensity and duration were strictly followed by the rodents, whereas human patients may vary widely in motivation, fatigue tolerance, and physical capacity.

5.1 Synaptic Plasticity and Neurotransmitter Regulation

Another preclinical study by Bonsale et al. (2023) found that long-term treadmill exercise could reverse cognitive and emotional injury in male mice post-TBI.[21] The TBI exercise (TBI-ex) mice ran on the treadmill for 8 weeks for 20 minutes every day at 5 min at 8 m/min, 10 min at 12 m/min, then 5 min at 5 m/min (cool-down). The study tested behavior (as a measure of cognitive recovery) through an open field, depression, and aggression test, as well as neurotransmitters and synaptic plasticity. Synaptic plasticity was evaluated through long-term potentiation (LTP). Beyond mechanistic findings supporting AE as a non-pharmacological intervention, this study demonstrated that AE directly improves emotional regulation. Cognitive recovery post-TBI is often limited by emotional barriers beyond memory and attention, including anxiety or depression that often interferes with learning and motivation to continue an intervention.

Behaviorally, researchers found the TBI-ex had a much higher exploration time, suggesting lower anxiety, lower fighting time, and a lower immobility time than TBI-sed. This suggests that AE could be a viable non-pharmacological intervention for promoting emotional regulation and social cohesion by reducing anxiety, aggression, and depression. In the hippocampus and nucleus accumbens, there were elevated levels of glutamate and gamma-aminobutyric acid (GABA) post-TBI, disrupting the balance between excitatory and inhibitory signaling and contributing to neuronal imbalance. The hippocampus contributes to learning and memory processes, while the nucleus accumbens is involved in reward processing, motivation, and emotional behavior.[22] Disruptions in neurotransmitter signaling within these regions post-TBI contribute to cognitive impairment and emotional dysregulation. TBI-ex had much lower levels of both compared to TBI-sed. Many pharmacological interventions have shown inconsistent results on neurotransmitter balance.[23] Conversely, these findings suggest that AE improves cognition post-TBI by restoring different types of neurotransmitters at the same time, fixing the damage itself in areas of the brain that control

memory, emotion, and motivation. Compared to TBI-sed, TBI-ex also had stronger synaptic plasticity. Because LTP is the mechanism behind memory and learning, the TBI-ex findings suggest that exercise may support cognitive recovery by enhancing synaptic plasticity and strengthening communication within surviving neural networks.[24] However, LTP is likely only one of several mechanisms contributing to these improvements.

These findings also suggest that maximizing the benefits of AE may require adjusting exercise intensity based on sex, supporting the idea that personalized intervention plans may be more effective than standardized treatment approaches.[20] The finding that AE repairs communication in neural networks also complements Yang et al.'s (2023) finding that IF suppresses ferroptosis, by suggesting that cognitive recovery needs to both protect surviving neural circuits and prevent further neuronal death.[16] Gómez-Porcuna et al. (2024) demonstrated what outcomes improved after AE, while Bonsale et al. (2023) offer mechanisms behind these improvements.[20,21] These studies support the idea that an effective intervention does not need to replace the damaged neural tissue, but rather improve upon the efficiency and plasticity of surviving neural networks to restore cognition.

An important limitation to consider here, as with the other preclinical models, is that the use of male mice limits generalizability across sexes and to human populations.

5.2 Clinical Evidence

Clinically, López et al. (2024) investigated the effect of exercise on memory-like executive function.[25,20] Participants completed supervised AE three times per week and were evaluated for executive function using a test for cognitive flexibility, attention, and memory. The exercises were personalized based on their physical capability and included treadmill walking, stationary cycling, and use of a motorized leg trainer. They found that 20-week AE programs could help improve executive function in six participants with severe chronic TBI. Although Gómez-Porcuna et al.'s (2024) findings came from a rat model during the acute phase of TBI recovery, López et al.'s clinical study observed benefits of AE in patients during the chronic phase.[20,25] While these studies cannot be directly compared, they suggest that exercise may have a wide intervention period. This also connects to Bonsale et al.'s (2023) finding that the TBI-ex group had less anxiety, aggression, and depression than the TBI-ex group because executive function depends on emotional regulation.[21] By first improving emotional regulation, AE removes barriers to cognitive improvement, which could facilitate recovery of executive functions.[21,25] The personalized design with the motorized leg trainer also highlights one of NPIs' greatest strengths compared to pharmacological interventions, which are typically applied to every patient equally. There are few pharmacological interventions available for treating cognitive recovery post-TBI, and while doctors can change dosages and medication timing, the medications themselves are standardized. The drugs are made to target broad areas rather than certain patterns or recovery trajectories specific to the patient. As a result, pharmacological interventions follow a trial-and-error approach that fail to address the root neurological issues.[26]

These gains in the chronic phase not only support AE as an effective non-pharmacological intervention, but also challenge the assumption that cognitive recovery plateaus at the chronic level and demonstrate that targeting behavior using exercise as an intervention can create measurable cognitive improvement. Researchers also found that the AE "spilled over" into participants' daily behavior, which is especially valuable in TBI recovery, as consistency is a necessity for meaningful improvement. This is in contrast with pharmacological interventions, which focus on symptom management rather than

behavioral changes, and have limited use in the chronic phase.[27]

These findings should be interpreted with caution due to limitations. The clinical study included only six participants, limiting generalizability. The absence of a large randomized control group makes it difficult to isolate aerobic exercise as the sole contributor to improvements in executive function, as gains may have been influenced by therapist interaction or healthier habits.

6. Conclusion

Overall, NPIs demonstrate potential for improving cognitive function impaired by TBIs. Due to the long-term, often worsening, effects of TBI, a non-pharmacological treatment plan can mitigate the side effects and risks of current pharmacological treatments. The preliminary trials of NPIs have shown significant improvement in recovery post mild-TBI, and clinical studies aim to increase applicability for more severe TBI cases. VR-based interventions demonstrated improvements across several domains relevant to TBI recovery, including cognitive functioning, emotional regulation, and physical rehabilitation outcomes. Beyond this, VR's immersive and adaptable design may enhance patient engagement as it is often enjoyable and allows therapies to be tailored to individual recovery needs. Similarly, HBOT showed promise as a NPI by targeting physiological mechanisms associated with secondary injury following TBI. Rather than focusing solely on symptom management, HBOT may influence underlying biological processes such as cerebral oxygenation, metabolic dysfunction, and neuronal survival. However, HBOT is expensive and requires extensive training and special equipment, limiting accessibility depending on a patient's location and financial circumstances. A focus on nutrition improved the speed of recovery as well as pain from the body trying to recover post-TBI. However, dietary recommendations are subjective, making this a difficult intervention to prescribe compared to other NPIs. Exercise helped improve memory, learning, and emotional regulation; however, it is important to acknowledge the differences between mice and human models and how the efficacy of these treatments can change between the two. Exercise is one of the most accessible NPIs, as it can often be done in the home and be personalized to the patient.

However, current research on NPIs remains limited due to studies with small sample sizes and misunderstood mechanisms of recovery. Future research should focus on expanding sample sizes and standardizing outcome measures to make results more applicable to mild, moderate, and severe TBIs. It is also critical for researchers to work on coupling these approaches with existing pharmacological approaches to see how they may improve the standard of care and cognitive recovery post-TBI.

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