The Road to Recovery by Interventions Focused on Neuroplasticity, Cognition, and Behavior after Acquired Brain Injury: A Systematic Review

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Abstract

Objective: This systematic review explores the potential of neuroplasticity-focused rehabilitation for individuals with acquired brain injury by examining various interventions. *Method*: A systematic search was performed in PubMed. Studies were included if they involved adults with stroke or traumatic brain injury (TBI), evaluated a clearly described intervention, and focused on improving cognitive or behavioral functioning. Nine studies met the inclusion criteria and were categorized into six intervention types. Methodological quality was assessed with the Jadad Scale. *Results*: Several interventions showed promising results by improving neuroplasticity, functional connectivity, and cognitive or behavioral functioning in individuals with stroke or TBI. Neurological music therapy (NMT) enhanced executive functioning and resting-state functional connectivity within key cognitive networks. A social peer-mentoring program reduced loneliness and enhanced perceived social support. Cognitive training reorganized brain networks and improved cognitive performance. Blue light therapy improved sleep, cognition and thalamocortical connectivity. Low-level light therapy (LLLT) and low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) enhanced resting-state functional connectivity. Targeted rTMS reduced depressive symptoms. The combination of transcranial direct current stimulation (tDCS) with cognitive training improved cognitive flexibility and information updating processes. Deep brain stimulation increased the arousal in a minimally conscious patient with severe TBI. *Conclusion*: This review highlights the potential of various neuroplasticity-focused interventions to enhance cognitive and behavioral recovery in individuals with ABI. Most consistent effects were found for NMT, cognitive training and blue light therapy. Future research with larger samples and standardized methods is needed to gain more insight into the potential of neuroplasticity-focused interventions.

Samenvatting

Doelstelling: Deze systematische review onderzoekt de effectiviteit van interventies gericht op neuroplasticiteit, cognitie en gedrag bij mensen met niet-aangeboren hersenletsel (NAH). *Methode*: Er werd een systematische zoekactie uitgevoerd in PubMed met de volgende inclusiecriteria: volwassenen met een CVA of traumatisch hersenletsel (THL) en een expliciet beschreven interventie met een focus op het verbeteren van cognitief of gedragsmatig functioneren. Negen studies werden ingedeeld in zes interventietypes. De methodologische kwaliteit werd beoordeeld met de Jadad Schaal. *Resultaten*: Verschillende interventies laten positieve effecten zien op het gebied van neuroplasticiteit, functionele connectiviteit, cognitie en gedrag bij mensen met NAH. Neurologische muziektherapie verbeterde het executief functioneren en de functionele connectiviteit. Een sociaal *peer-mentoring* programma verbeterde de waargenomen sociale steun en verminderde eenzaamheid. Cognitieve training reorganiseerde hersennetwerken en verbeterde cognitieve prestaties. Therapie met blauw licht verbeterde slaap, cognitie en functionele connectiviteit. Lichttherapie op laag niveau en laagfrequente repetitieve transcraniële magnetische stimulatie (rTMS) verhoogde de functionele connectiviteit in rusttoestand. Gerichte rTMS verminderde depressieve symptomen. De combinatie van transcraniële gelijkstroomstimulatie en cognitieve computertraining verbeterde het executief functioneren. Diepe hersenstimulatie verhoogde de responsiviteit van een patiënt in een toestand van minimaal bewustzijn. *Conclusie*: Deze review geeft een overzicht van de effectiviteit van verschillende interventies die zich richten op neuroplasticiteit, cognitief herstel en gedrag bij mensen met NAH. De meest consistente effecten werden gevonden voor muziektherapie, cognitieve training en blauwlichttherapie. Toekomstig onderzoek met grotere, homogene steekproeven en gestandaardiseerde methoden wordt aanbevolen om meer inzicht te krijgen in de effectiviteit en werkingsmechanismen van interventies gericht op neuroplasticiteit.

The Road to Recovery by Different Interventions Focused on Neuroplasticity, Cognition, and Behavior after Acquired Brain Injury: A Systematic Review

Acquired brain injury (ABI) is a serious public health concern leading to substantial mortality and disability worldwide. ABI refers to an injury to the brain after birth caused by traumatic or non-traumatic causes (Cullen et al., 2008). It is associated with significant cognitive, emotional, physical, social, and behavioral changes (Dua et al., 2024). This review focuses on the two most common forms of ABI: traumatic brain injury (TBI) and stroke.

Traumatic brain injury (TBI) is defined as “a change in brain function, or other evidence of brain pathology caused by an external force” (Menon et al., 2010). Depending on the mechanism of injury, TBI can result in diffuse axonal injury, bleeding, and contusions. This may disrupt neural networks and reduce functional connectivity, which refers to the extent to which different brain regions are simultaneously active and communicating with each other (Martinéz-Molina et al., 2021). In most TBI patients, the prefrontal cortex is most affected. This leads to cognitive impairments, particularly in executive functions such as cognitive flexibility and information updating (Barman et al., 2016). These impairments severely impact a person’s ability to live independently and adjust to life difficulties. Severe TBI can also affect critical areas, including the thalamus and midbrain, potentially impairing alertness. In addition to the neurobiological and cognitive consequences, TBI frequently leads to behavioral and social changes, such as social isolation and feelings of loneliness (Struchen et al., 2011).

Another common form of ABI is stroke. This is defined as an acute condition that disrupts blood flow to the brain due to either a clot blocking an artery (ischemic stroke) or a ruptured blood vessel (hemorrhagic stroke) (American Stroke Association., z.d.). Stroke survivors often experience lasting cognitive, emotional, and physical impairments. The course of recovery varies widely, with some individuals achieving partial recovery, while others remain disable for the long-term.

One of the most disabling symptoms of ABI is fatigue, which is strongly linked to cognitive impairments. Sleep and circadian rhythms play a key role in neurobiology, human health, cognitive function, and recovery after brain injury (Gao et al., 2010). Around 50% of individuals with mild TBI experience chronic sleep disturbances and cognitive deficits, which is often due to disrupted melatonin production (Orff et al., 2009). Nearly 70% of ABI survivors show impairments on neuropsychological tests (Lagogianni et al., 2018). A recent review found a strong association between fatigue and reduced sustained attentional performance after ABI (Dillon et al., 2022). In addition, cognitive fatigue and cognitive dysfunctions are related to lower quality of life and reduced participation (van Markus-Doornbosch et al., 2020). These findings highlight fatigue and cognitive deficits as key targets for intervention following ABI.

Given the long-lasting impact of ABI, continuous care and support for both patients and their families are essential (British Society of Rehabilitation Medicine & Turner-Stokes, 2003). However, due to the heterogeneity of ABI, a one-size-fits-all approach might be ineffective. Clinical treatment guidelines emphasize personalized, goal-oriented care that considers patient's views, cultural backgrounds, and pre-morbid lifestyles (British Society of Rehabilitation Medicine & Turner-Stokes, 2003). After the onset of ABI, rehabilitation usually starts as soon as possible. In stroke recovery, the acute phase is especially critical, as immediate admission to a specialized stroke unit improves survival and reduces disability risk (NICE, 2023). Rehabilitation typically begins with stabilization in the acute phase and progresses to focus on daily activities, social integration, and return to work or education. Rehabilitation of ABI consists of multidisciplinary care, including neurology, psychology, physiotherapy, and social support (NICE, 2022).

Despite established clinical guidelines, many individuals with ABI show limited recovery, highlighting the need for more effective interventions (Davies et al., 2023). One promising approach focuses on targeting neuroplasticity, which is the brain's ability to change and adapt in response to injury or experience. Neuroplasticity plays a crucial role in recovery after ABI because it helps the brain to reorganize its networks by strengthening existing connections or forming new ones (Jasey & Ward, 2019). This reorganization may improve the brain's functional connectivity, facilitating the recovery of cognitive and motor functions.

Various interventions, including cognitive training, music therapy, and transcranial magnetic stimulation (TMS) show promising results in promoting neuroplasticity and improving cognitive functioning. Cognitive training is associated with enhanced efficiency of brain networks, boosting cognitive performance (Han et al., 2020). Music therapy activates widespread brain regions and is linked to cognitive and social improvements (Zatorre et al., 2007; Vik et al., 2019). TMS can reduce the extent of neural injury and stimulate plastic changes that support learning and functional recovery in damaged neural tissue (Villamar et al., 2012). Repetitive transcranial magnetic stimulation (rTMS) is proven effective for stroke, neuropathic pain, and depression and it is widely used in neurological and psychiatric rehabilitation (Lefaucheur et al., 2020). In addition, rTMS targeting the left dorsolateral prefrontal cortex (DLPC) has shown antidepressant effects in individuals with TBI (Liston et al., 2014).

Building on the concept of neuroplasticity, Neuro Rejuvenation Center (NeuroRC) has developed an innovative brain training specifically targeting the brain's plasticity. The training aims to activate the brain more effectively by increasing energy at the cellular level and enhancing the processing of stimuli (NeuroRC, 2024). The program combines cognitive and physical exercises to stimulate brain activity. Although promising, this intervention is not yet evidence-based.

This systematic review aims to explore the potential of neuroplasticity-focused rehabilitation by examining various interventions and their underlying mechanisms. The primary research question is: “Which interventions are effective in improving cognition and behavior in individuals with acquired brain injury?” The secondary question is: “What underlying mechanisms regarding neuroplasticity are presented in these studies?” By providing a comprehensive overview, this review seeks to highlight effective strategies to improve cognitive and behavioral recovery for ABI patients.

Method

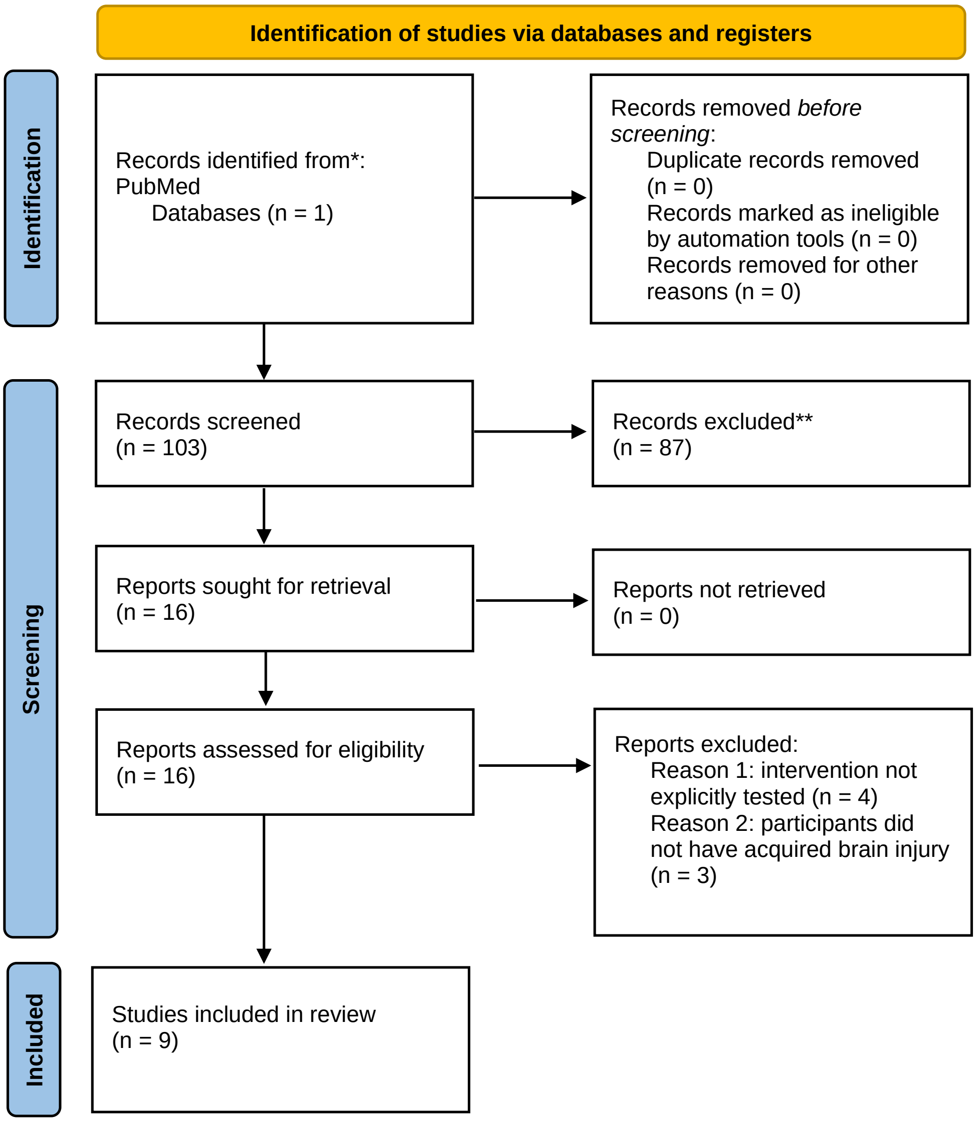
PubMed was searched for relevant studies published in English. The title, keywords, abstract and conclusion of were reviewed independently by two students to determine eligibility based on predefined inclusion criteria: 1). Participants have acquired brain injury; 2). Participants are 18 years or older; 3). Examination of a specific intervention or treatment that is described explicitly; 4). Neuropsychological or psychological intervention focused on improving cognitive or behavioral functioning. Exclusion criteria were: 1). Meta-analyses, systematic reviews, and observational studies; 2). Description of a study protocol without assessment of the intervention; 3). Pharmacological treatment consists solely of medication or surgery. Disagreements between the two students were addressed by discussion until the agreement was made. The following search string was used in PubMed on the 5th of December 2024:

(neuroplasticity) AND (treatment) OR (intervention) OR (training) AND (acquired brain injury) AND (functional connectivity) OR (neurovascular coupling)

The search string identified 103 results in PubMed (figure 1). The methodological quality of the included studies was assessed with the use of the Jadad Scale. See table 1 (Appendix A) for an overview of the scores on the Jadad Scale.

Figure 1

Search Strategy PRISMA Flow Diagram



Results

Sixteen studies initially met the inclusion criteria. After full-text screening, seven articles were excluded due to several reasons (figure 1). The nine included studies were grouped into six intervention types (N=341). The groups are neurological music therapy (n=1), social-peer mentoring program (n=1), cognitive training (n=1), light therapy (n=2), bilateral deep brain stimulation (n=1), and transcranial stimulation (n=3). Table 1 summarizes the key details of all studies. For an overview of the results, see Appendix B.

Table 1

Overview of Studies

Study	Intervention	Intervention Duration	Sessions	Study Design	Participants	Control Group	Primary Outcomes	Key Findings
Martínez-Molina et al. (2021)	Neurological Music Therapy (NMT)	3 months	20 sessions of 60 mins	Pre-post-follow-up	40 moderate-to-severe TBI patients	TBI patients waiting list	Resting-state functional connectivity (rsFC), executive function (EF)	Increased rsFC in key cognitive networks, reduced hyperconnectivity, improvements in EF
Struchen et al. (2011)	Social Peer-Mentoring Program	3 months	Variable	Pre-post only	30 adults with TBI	TBI patients waiting list	Social integration, social network, social activity levels	Improved perceived social support, reduced loneliness, no significant change in social activity or network size
Killgore et al. (2019)	Blue Wavelength Light Exposure	6 weeks	42 sessions of 30 mins	Pre-post-follow-up	32 mTBI patients	mTBI patients	Sleep onset, daytime sleepiness, cognitive performance	Earlier sleep onset, reduced daytime sleepiness, improved cognitive performance, increased gray matter volume in thalamus, improved connectivity
Chan et al. (2024)	Low-level Light Therapy (LLLT)	3 months	3 sessions of 20 mins	Pre-post-follow-up	17 LLLT, 21 sham	Healthy controls, moderate TBI patients	Resting-state functional connectivity (rsFC)	Increased rsFC in LLLT group from acute to subacute phase, no significant difference in clinical outcomes
Han et al. (2020)	Cognitive Training (SMART vs. BHW)	8 weeks	12 sessions of 90 mins	Pre-post-follow-up	64 civilians and veterans with TBI	TBI patients	Cognitive performance, modularity, efficiency of brain networks	Reduced modularity, increased global and local efficiency, improved trail-making scores, reorganized modular networks
Schiff et al. (2008)	Bilateral Deep Brain Electrical Stimulation (DBS)	69 weeks	Not specified	Single-subject multiple baseline design	1 patient in minimally conscious state	Patient served as own control	Arousal, motor, and communication subscales of Coma Recovery Scale-Revised	Increased responsiveness, improved functional limb control, oral feeding
Xie et al. (2023)	Low-frequency (LF) and high-frequency (HF)-rTMS	Not specified	1 session	Pre-post only	68 subacute stroke patients	Stroke patients	Cerebral hemodynamic responses, cortical activation, functional connectivity	LF-rTMS induced activation in motor areas and regulated functional networks. HF-rTMS showed limited effects
Afsharian et al. (2024)	Transcranial Direct Current Stimulation (tDCS) combined with Computer-based Cognitive Training	2 weeks	10 sessions of 20 mins	Pre-post only	30 TBI patients with executive dysfunction	TBI patients	Prefrontal cortical activity, cognitive flexibility, information updating	Improved performance on n-back task and WCST, increased prefrontal cortical activity, enhanced working memory
Siddiqi et al. (2019)	Repetitive Transcranial Magnetic Stimulation (rTMS)	Not specified	20 daily sessions	Pre-post-follow-up	15 TBI patients with treatment resistant depression	TBI patients	Depression severity (MADRS)	Improvement in depression scores and self-reported emotional measures

Abbreviations: SMART = Strategic Memory Advanced Training, BHW = Brain Health Workshop, MADRS = Montgomery-Asberg Depression Rating Scale, WCST = Wisconsin Card Sorting Test

Neurological Music Therapy (NMT)

Intervention

Martínez-Molina et al. (2021) examined the effects of neurological music therapy (NMT) on brain function. The therapy was provided by a trained music therapist and focused on improving executive functioning (EF), attention, and working memory. The intervention involved active musical production with different instruments, such as drums and piano. Each session included rhythmical training, structured cognitive-motor training and assisted music playing. Cognitive outcomes included general EF, reasoning, verbal memory, and specific EF components.

Mechanism

NMT was associated with functional connectivity changes across key cognitive networks. It enhanced connectivity between the frontoparietal (FPN), dorsal attention (DAN), and sensory networks. It reduced maladaptive connectivity within the FPN and salience (SAL) networks, which are typically hyperconnected after TBI. Executive improvements were linked to changes in FPN and default mode network (DMN) connectivity. In addition, increased connectivity was found between the right inferior frontal gyrus (IFG) and parietal regions. These findings show that NMT supports cognitive recovery after TBI by promoting more efficient and integrated network communication. The Jadad score for this study is 3.

Social Peer-Mentoring Program

Intervention

Struchen et al. (2011) conducted a pilot study to assess the feasibility of a social peer-mentoring program designed to improve social integration among TBI adults. Individuals with TBI who had successfully maintained social networks after their injuries served as Social Peer Mentors (SPMs). The rationale for using TBI peers rather than non-injured mentors was to provide relatable role models who better understand the challenges of TBI. Outcomes included social integration, network size, social activity levels, emotional well-being, and program feasibility. The meetings had the goal of increasing social networking opportunities for the participants (PPs) through introductions to people and activities in the mentor's own community.

Mechanism

Both the participants serving as SPMs and the PPs reported overall satisfaction with the social peer-mentoring program. The mentored group showed significant improvements in perceived social support and reduced feelings of loneliness compared to the control group. The authors suggest that higher levels of perceived social support may lead to overall positive adjustment and can serve as a buffer against stress. However, no significant changes were found in objective measures of social activity level or social network size. The Jadad Score is 2.

Blue Wavelength Light Exposure

Intervention

Killgore et al. (2019) examined whether morning blue-light exposure of 30 minutes could improve sleep and cognitive recovery in mild TBI patients. Participants were randomly assigned to a blue light (active) or amber light (placebo) condition. Assessments included sleep monitoring, neuropsychological tests, sleep latency tests, and MRI scans. Blue light was expected to enhance circadian regulation, alertness, and attention-related brain connectivity. Participants received sleep monitor wristwatches and completed daily online sleep diaries.

Mechanism

Blue light was associated with earlier sleep onset in 80% of participants, compared to 58.3% in the amber group. Blue light exposure affected the timing of sleep-wake cycles by stimulating the retinohypothalamic system. It significantly improved sleep-wake regulation, cognitive functioning, and brain structure. In addition, it was associated with improved structural and functional thalamocortical connectivity and increased gray matter volume in the posterior thalamus. Blue light enhanced functional connectivity between the left thalamus and frontal and parietal regions, which was associated with reduced sleepiness and improved language and executive function. Notably, total sleep time did not increase, but participants needed less sleep to feel rested. The Jadad score is 4.

Low-level Light Therapy (LLLT)

Intervention

Low-level light therapy (LLLT) is an innovative therapy consisting of the transcranial or intranasal delivery of near-infrared light to the brain. Chan et al. (2024) used fMRI to examine the effect of LLLT on whole-brain resting-state functional connectivity (rsFC) in patients with moderate TBI at acute (within 1 week), subacute (2-3 week), and late subacute (3 months) recovery phases. Treatment was provided within 72 hours post-injury.

Mechanism

LLLT was associated with increased rsFC in seven brain regions from the acute to subacute phase, particularly between the left temporal pole and contralateral temporal, parietal, and occipital regions. In contrast, the sham group showed decreased connectivity in the frontal, insular, limbic, subcortical, and temporal regions. The change in rsFC from the acute to subacute phases of recovery was greater in LLLT-treated than sham-treated participants. This suggests that acute-phase LLLT may affect the resting-state neuronal circuits during the early recovery phase of moderate TBI. The Jadad score is 4.

Cognitive Training

Intervention

Han et al. (2020) examined the effect of cognitive training in individuals with TBI. Participants were randomly assigned to either a Strategic Memory Advanced Reasoning Training (SMART) or a Brain Health Workshop (BHW). The SMART group focused on selective attention targeting strategic memory, abstract reasoning, and other cognitive strategies to enhance cognitive control. The BHW group was taught about brain structure and function, with a focus on the impact of sleep and exercise on brain health, particularly in relation to learning and memory.

Mechanism

Cognitive training reorganized modular networks by increasing connectivity between several modules. This reorganization shifted the balance between network integration and segregation, leading to more efficient and effective communication between brain regions. The neural plasticity shown in this study may be related to compensation of altered neural circuitry rather than full restoration of the original neural pathways. The SMART group showed significant improvements in trail-making scores compared to the BHW group. These improvements were linked to reduced modularity and increased global efficiency and local efficiency across brain regions over time. The Jadad score is 2.

Bilateral Deep Brain Electrical Stimulation (DBS) of the Central Thalamus

Intervention

Schiff et al. (2008) examined whether deep brain stimulation (DBS) of the central thalamus could improve a patient's responsiveness while in a chronic minimally conscious state (MCS) following severe TBI. The patient showed no improvement despite years of treatment. An fMRI revealed a preserved bi-hemispheric language network, suggesting potential for recovery.

Mechanism

To boost arousal regulation, which is normally controlled by the frontal lobe, researchers implanted bilateral DBS electrodes in the central thalamus. It was hypothesized that DBS could enhance behavioral responsiveness by stimulating nuclei connected to the frontal cortex and brainstem, potentially activating brain networks that were functionally connected but inconsistently active. The patient showed an increase in cognitively mediated behaviors during DBS-on periods compared to when DBS was off. The authors suggested that these improvements might be due to direct activation of frontal cortical and basal ganglia systems innervated by thalamic nuclei. The DBS was thought to compensate for the loss of arousal regulation that is normally controlled by the frontal lobe. The Jadad score is 0.

Low-Frequency (LF-) and High-Frequency (HF-) Repetitive Transcranial Magnetic Stimulation (rTMS)

Intervention

Xie et al. (2023) aimed to elucidate the underlying neurological mechanisms of TMS by examining the effects of low-frequency (LF)- and high frequency (HF-)rTMS on cortical functional networks using functional near-infrared spectroscopy (fNIRS). The researchers hypothesized that LF- and HF-rTMS induce different neurovascular coupling responses and do not have consistent or stable cumulative regulatory effects during the intervention period. Participants were randomly assigned to one of three groups: LF-rTMS, HF-rTMS or a sham group.

Mechanism

LF-rTMS induced significantly more activation in the contralesional superior frontal cortex, and premotor cortex compared to the sham group. This activation of motor areas may contribute to motor recovery. LF-rTMS continuously regulated functional networks in the ipsilesional hemisphere. The authors suggest that LF-rTMS can regulate interhemispheric competition and adjust cortical excitability. There were significant changes in connectivity within and between hemispheres in different time-windows. HF-rTMS had no significant effect on cortical activation and showed limited modulation of brain networks. In addition, the HF-rTMS group showed changing network connections over time. The Jadad score is 5.

Combining transcranial direct current stimulation (tDCS) with computer-based cognitive training

Intervention

Afsharian et al. (2024) examined the effects of combining transcranial direct current stimulation (tDCS) with computer-based cognitive training on two executive functions: cognitive flexibility and information processing. This neuromodulation technique applies low-intensity electrical current to specific brain areas, such as the prefrontal cortex (PFC), to enhance cognitive functioning. Anodal tDCS increases PFC excitability and may reduce the amount of training needed to improve executive functions. Participants received anodal tDCS while performing game-like cognitive tasks.

Mechanism

The combination of tDCS and cognitive training enhanced neuroplasticity and connectivity in prefrontal regions involved in cognitive flexibility and information updating. The experimental group showed significant improvement in working memory on the n-back task and on the Wisconsin Card Sorting Test (WCST). The Jadad score is 2.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Intervention

Siddiqi et al. (2018) examined the effect of rTMS targeted with individualized resting-state network mapping (RSNM) of dorsal attention network (DAN) and default mode network (DMN) in individuals with treatment-resistant depression associated with concussive or moderate TBI. The authors hypothesized that rTMS would be feasible and enhance mood in patients with treatment-resistant depression following TBI.

Mechanism

RSNM-targeted rTMS was feasible in TBI patients with depression. Treatment was linked to improvements in clinician-rated depression scales. It modulated interhemispheric connectivity and restored cortical excitability, which are often compromised after TBI. The antidepressant effects were linked to changes in attention-shifting and self-referential interoceptive awareness related to the DAN and DMN. In addition, improvements were found in self-reported emotional measures and crystallized cognition. The Jadad score is 4.

Discussion and Conclusion

This systematic review highlights the potential of several interventions that focus on enhancing neuroplasticity, as well as cognitive and behavioral recovery, following ABI. The interventions vary in their effectiveness at strengthening brain networks and improving cognitive and behavioral functioning.

Interventions Targeting Neuroplasticity and Cognitive Functioning

Most of the interventions focused on targeting neuroplasticity to enhance cognitive recovery. Neurological music therapy (NMT) was associated with improved executive functioning by increasing the rsFC within key cognitive networks and reducing maladaptive hyperconnectivity (Martínez-Molina., 2021). Similarly, cognitive training was found to reorganize brain networks in TBI, supporting neuroplasticity across the entire brain (Han et al., 2020). The authors suggest that these improvements in overall network organization and efficiency after training come from rerouting existing brain connections instead of restoring individual ones. These findings show the potential of cognitive and musical interventions in improving cognition by strengthening neural pathways and improving neural communication.

Light therapy showed promising results as well. Blue light therapy enhanced functional connectivity between the left thalamus and frontal and parietal regions, which was associated with reduced sleepiness and improved language and executive functioning (Killgore et al., 2019). Daily exposure to morning blue light seemed to be an effective intervention to reset the circadian rhythm and support both cognitive and structural brain recovery in individuals with recent TBI. These findings highlight the key role of sleep in brain processes and recovery after injury.

Chan et al. (2024) showed that low-level light therapy (LLLT) supported recovery in individuals with TBI by increasing the rsFC. These findings are in line with previous studies showing increased rsFC following LLLT in patients with chronic stroke (Naeser et al., 2020) and dementia (Chao et al., 2019). No significant differences in clinical outcomes were found between LLLT-treated and sham-treated participants; both groups showed greater interhemispheric connectivity between the bilateral superior frontal regions across all three recovery phases compared to healthy controls. This may be explained by the mechanism of injury-related hyperconnectivity. Future research with larger samples is needed to elucidate the clinical potential of LLLT in TBI recovery.

Deep brain stimulation (DBS) of the central thalamus improved arousal and motor responsiveness in a patient in a minimally conscious state following severe TBI (Schiff et al., 2008). This improvement is thought to result from the activation of frontal cortical and basal ganglia systems connected to the targeted thalamic nuclei. However, the single-case design limits the generalizability of these findings. Future research with larger samples is needed to clarify the potential of DBS in TBI recovery.

Non-invasive stimulation techniques have shown promising results as well. Low-frequency rTMS (LF-rTMS) appears to be more effective than high-frequency rTMS (HF-rTMS) in regulating brain activity and functional networks (Xie et al., 2023). LF-rTMS can effectively stimulate motor-related areas and regulate functional networks in the ipsilesional hemisphere in patients with subacute subcortical stroke. In contrast, HF-rTMS appeared less effective in inducing cortical activation and regulating brain networks in this patient group, This may be due to the limited and temporary regulation of brain networks. These findings emphasize the importance of selecting the appropriate rTMS modality in stoke rehabilitation.

The combination of transcranial direct current stimulation (tDCS) and cognitive training enhanced plasticity and connectivity in prefrontal regions, thereby improving cognitive flexibility and information updating processes in TBI patients (Afsharian et al., 2024). In addition, targeted rTMS improved depressive symptoms and improved self-reported emotional measures and crystallized cognition in TBI patients (Siddiqi et al., 2019).

Intervention Targeting Social and Behavioral Outcomes

The social peer-mentoring program was associated with improved social and behavioral outcomes (Struchen et al., 2011). The program showed promising effects in enhancing perceived social support and reducing loneliness in individuals with TBI. However, no significant improvements were observed in objective measures of social activity level or social network size, possibly due to the limited number of mentor meetings. In addition, there was an unexpected increase in depressive symptoms in the peer-mentored group. The authors suggest this may result from increased awareness of TBI-related difficulties through mentor discussions. Further research is needed to explore this explanation.

Comparison with NICE Guidelines

The NICE guidelines (2022) emphasize the importance of a multidisciplinary and individualized approach to ABI rehabilitation, with a focus on early intervention, patient-centered care, and evidence-based treatments. The studies included in this review do not mention these principles explicitly, but some do focus on intervention during the acute stage of brain injury. Further research is needed to develop more detailed and practical guidelines that can be directly implemented in clinical practice.

Methodological Quality

The methodological quality of the studies varied, with some relying on pilot data or single-subject designs. Most studies demonstrate adequate methodological quality (Appendix A). All studies, except the study of Schiff et al. (2008), used a randomization procedure. The

Jadad score for the study of Schiff et al. (2008) is 0 because they used a single-subject design without a blinding procedure. The study of Xie et al. (2023) scored 5 on the Jadad scale, reflecting a well designed randomized, double-blind design. The remaining studies scored between 2 and 4 on the Jadad scale.

Limitations and Scientific Recommendations

Several limitations of the studies should be considered when interpreting the results. First, the small sample sizes in most studies limit the generalizability of results. Second, the heterogeneity of ABI patients complicates direct comparison between interventions and patient groups. There is a wide variety in injury severity, type of injury, time since onset and comorbidities, which makes it likely that the patients experienced different cognitive and non-cognitive impairments. As a result, these patients may require different intervention approaches. Although TBI and stroke are both types of ABI, their nature and course vary widely. Future research should focus on these types of ABI separately to assess whether these groups require different intervention approaches. In addition, the interventions used different outcome measures, which complicates direct comparison between the studies. Future research should compare studies with similar outcome measures and homogenous samples. In addition, future studies should include a follow-up period to assess the long-term effects of interventions and the long-term consequences for daily life.

This systematic review provides valuable insights into the working mechanism of various interventions for individuals with ABI. However, several limitations of this review should be acknowledged. First, relying on one database and search string may have resulted in the exclusion of relevant studies in this field. Although the current search string led to 103 results, much more literature exists on this topic, especially regarding cognitive rehabilitation (Spikman et al., 2010) and physical rehabilitation (Devine & Zafonte, 2009). Future research should use expanded search strategies and multiple databases to identify these studies to provide a more comprehensive overview of effective treatments for ABI. Furthermore, it would be recommended to analyze the relevant in-text cited articles. Due to limited amount of time, these steps were not performed in this review. Another limitation of the current review is the use of the Jadad scale to assess the methodological quality of the included studies. It is a simple tool that provides limited information about the methodology as it assesses only five broad aspects of the study design. Furthermore, it may be influenced by the subjectivity of the researcher. For future research, the Cochrane Risk of Bias Tool 2 (RoB 2) is recommended. This tool is more detailed and provides extensive information regarding the methodological quality of randomized controlled trials.

Recommendations for Clinical Practice and NeuroRC

NMT and cognitive training demonstrated the most consistent improvements in executive functioning and brain connectivity, making them suitable for rehabilitation programs. Therefore, it would be recommended for NeuroRC to integrate music-based interventions with cognitive training to enhance neuroplasticity and cognitive outcomes in individuals with ABI. Additionally, incorporating blue light therapy could support sleep regulation and cognitive performance, which are both crucial for recovery. Future research should explore the effectiveness of combining multiple interventions. It has already been shown that pairing TMS with cognitive training strengthened neuroplasticity more effectively than either intervention alone (Afsharian et al., 2024).

Conclusion

This review highlights the potential of several interventions that enhance neuroplasticity, functional connectivity, and cognitive recovery in individuals with ABI. Neurological music therapy, cognitive training, and blue light therapy showed the most consistent improvements in cognitive functioning and brain connectivity. While social peer-mentoring, LLLT, DBS and rTMS showed promising results, further research is needed to clarify their underlying mechanisms. Future research should aim to refine existing interventions, explore effective combinations, and develop standardized treatment protocols. This review aimed to contribute to the development of evidence-based treatments for ABI patients by showing the working mechanisms of different interventions that focus on neuroplasticity, cognition, and behavior.

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References

Afsharian, F., Abadi, R. K., Taheri, R., & Sarajehlou, S. A. (2024). Transcranial direct current stimulation combined with cognitive training improves two executive functions: Cognitive flexibility and information updating after traumatic brain injury. *Acta Psychologica*, *250*, 104553. https://doi.org/10.1016/j.actpsy.2024.104553

American Stroke Association. (z.d.). *About stroke*. American Heart Association. https://www.stroke.org/en/about-stroke

Barman A, Chatterjee A, Bhide R. Cognitive Impairment and Rehabilitation Strategies After Traumatic Brain Injury. *Indian Journal of Psychological Medicine*. 2016;38(3):172 181. doi:10.4103/0253-7176.183086

British Society of Rehabilitation Medicine, & Turner-Stokes, L. (2003). *Rehabilitation following acquired brain injury*. Royal College of Physicians. https://www.headway.org.uk/media/3320/bsrm-rehabilitation-following-acquired brain injury.pdf

Chan, S., Mercaldo, N., Longo, M. G. F., Welt, J., Avesta, A., Lee, J., Lev, M. H., Ratai, E., Wenke, M. R., Parry, B. A., Drake, L., Anderson, R. R., Rauch, T., Diaz-Arrastia, R., Kwong, K. K., Hamblin, M., Vakoc, B. J., & Gupta, R. (2024). Effects of Low-Level Light Therapy on Resting-State Connectivity Following Moderate Traumatic Brain Injury: Secondary Analyses of a Double-blinded Placebo-controlled Study. *Radiology*, *311*(2). https://doi.org/10.1148/radiol.230999

Chao LL. Effects of Home Photobiomodulation Treatments on Cognitive and Behavioral Function, Cerebral Perfusion, and Resting-State Functional Connectivity in Patients with Dementia: A Pilot Trial. Photobiomodul Pho tomed Laser Surg 2019;37(3):133 141.

Cullen, N., Bayley, M., Teasell, R., Marshall, S., Hildritch, M., Lippert, C., Welch-West, P., McCabe, P., Weiser, M., Ferrie, C., Rees, L., McCormick, A., Tu, L., & Aubut, J. (2008). Poster 5: An Update of the Systematic Review of the Rehabilitation of Moderate-to-Severe Acquired Brain Injuries. *Archives Of Physical Medicine And Rehabilitation*, *89*(10), e10. https://doi.org/10.1016/j.apmr.2008.08.032

Davies, A., Rogers, J. M., Baker, K., Li, L., Llerena, J., Nair, R. D., & Wong, D. (2023). Combined Cognitive and Psychological Interventions Improve Meaningful Outcomes after Acquired Brain Injury: A Systematic Review and Meta-Analysis. *Neuropsychology Review*, *34*(4), 1095–1114. https://doi.org/10.1007/s11065-023 09625-z

Devine, J. M., & Zafonte, R. D. (2009). Physical Exercise and Cognitive Recovery in Acquired Brain Injury: A Review of the Literature. *PM&R*, *1*(6), 560 575. https://doi.org/10.1016/j.pmrj.2009.03.015

Dillon, A., Casey, J., Gaskell, H., Drummond, A., Demeyere, N., & Dawes, H. (2022). Is there evidence for a relationship between cognitive impairment and fatigue after acquired brain injury: a systematic review and meta-analysis. *Disability and Rehabilitation*, *45*(26), 4359–4372. https://doi-org.proxy ub.rug.nl/10.1080/09638288.2022.2152503

Dua S, Kumar R, Prasannanshu, Narang KS. Impact of Acquired Brain Injury on Quality of Life. *Annals of Neurosciences*. 2024;0(0). doi:10.1177/09727531241263670

Gao, B., et al., 2010. Sleep disruption aggravates focal cerebral ischemia in the rat. Sleep. 33, 879-887.

Han K, Chapman SB, Krawczyk DC. Cognitive Training Reorganizes Network Modularity in Traumatic Brain Injury. *Neurorehabilitation and Neural Repair*. 2019;34(1):26-38. doi:10.1177/1545968319868710

Jasey, N., Ward, I. Neuroplasticity in Brain Injury: Maximizing Recovery. *Curr Phys Med Rehabil Rep* 7, 333–340 (2019). https://doi.org/10.1007/s40141-019-00242-7

Killgore, W. D., Vanuk, J. R., Shane, B. R., Weber, M., & Bajaj, S. (2019). A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. Neurobiology Of Disease, 134, 104679. https://doi.org/10.1016/j.nbd.2019.104679

Lagogianni, C., Thomas, S., & Lincoln, N. (2018). Examining the relationship between fatigue and cognition after stroke: A systematic review. *Neuropsychological rehabilitation*, *28*(1), 57–116. https://doi.org/10.1080/09602011.2015.1127820

Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipović, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jääskeläinen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J. P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., Padberg, F., … Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, *131*(2), 474–528. https://doi.org/10.1016/j.clinph.2019.11.002

Liston, C., Chen, A.C., Zebley, B.D., Drysdale, A.T., Gordon, R., Leuchter, B., Voss, H.U., Casey, B.J., Etkin, A., and Dubin, M.J. (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol. Psychiatry 76, 517–526.

Martínez-Molina, N., Siponkoski, S., Kuusela, L., Laitinen, S., Holma, M., Ahlfors, M., Jordan-Kilkki, P., Ala-Kauhaluoma, K., Melkas, S., Pekkola, J., Rodríguez-Fornells, A., Laine, M., Ylinen, A., Rantanen, P., Koskinen, S., Cowley, B. U., & Särkämö, T.

(2021). Resting-State Network Plasticity Induced by Music Therapy after Traumatic Brain Injury. *Neural Plasticity*, *2021*, 1–18. https://doi.org/10.1155/2021/6682471

Menon, D. K., Schwab, K., Wright, D. W., & Maas, A. I. (2010). Position Statement: Definition of Traumatic Brain Injury. *Archives Of Physical Medicine And Rehabilitation*, *91*(11), 1637–1640. https://doi.org/10.1016/j.apmr.2010.05.017

Naeser MA, Ho MD, Martin PI, Hamblin MR, Koo BB. Increased Functional Connectivity Within Intrinsic Neural Networks in Chronic Stroke Following Treatment with Red/Near-Infrared Transcranial Photobiomodulation: Case Series with Improved Naming in Aphasia. Photobiomodul Photomed Laser Surg 2020;38(2):115–131.

NICE. (2022, 18 januari). *Recommendations | Rehabilitation after traumatic injury | Guidance | NICE*. https://www.nice.org.uk/guidance/ng211/chapter/Recommendations

NICE. (2023, 18 oktober). *Overview | Stroke rehabilitation in adults | Guidance | NICE*. https://www.nice.org.uk/guidance/ng236

NeuroRC. (2024, 6 november). *Home*. https://www.neurorc.nl/

Orff, H.J., et al., 2009. Traumatic brain injury and sleep disturbance: a review of current research. J. Head Trauma Rehabil. 24, 155–165.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., Fritz, B., Eisenberg, B., O'Connor, J., Kobylarz, E. J., Farris, S., Machado, A., McCagg, C., Plum, F., Fins, J. J., & Rezai, A. R. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, *448*(7153), 600–603. https://doi.org/10.1038/nature06041

Siddiqi, S. H., Trapp, N. T., Hacker, C. D., Laumann, T. O., Kandala, S., Hong, X., Trillo, L., Shahim, P., Leuthardt, E. C., Carter, A. R., & Brody, D. L. (2018). Repetitive Transcranial Magnetic Stimulation with Resting-State Network Targeting for Treatment-Resistant Depression in Traumatic Brain Injury: A Randomized, Controlled, Double-Blinded Pilot Study. *Journal Of Neurotrauma*, *36*(8), 1361 1374. https://doi.org/10.1089/neu.2018.5889

Spikman, J. M., Boelen, D. H. E., Lamberts, K. F., Brouwer, W. H., & Fasotti, L. (2010). Effects of a multifaceted treatment program for executive dysfunction after acquired brain injury on indications of executive functioning in daily life. *Journal of the International Neuropsychological Society*, *16*(1), 118–129. https://doi.org/10.1017/S1355617709991020

Struchen, M. A., Davis, L. C., Bogaards, J. A., Hudler-Hull, T., Clark, A. N., Mazzei, D. M., Sander, A. M., & Caroselli, J. S. (2011). Making connections after brain injury. *Journal Of Head Trauma Rehabilitation*, *26*(1), 4–19. https://doi.org/10.1097/htr.0b013e3182048e98

van Markus-Doornbosch F, van der Holst M, de Kloet AJ, et al. Fatigue, participation and quality of life in adolescents and young adults with acquired brain injury in an outpatient rehabil itation cohort. Dev Neurorehabil 23. Epub ahead of print 2020. DOI: 10.1080/17518423.2019.1692948

Vik, B. M. D., Skeie, G. O., & Specht, K. (2019). Neuroplastic effects in patients with traumatic brain injury after music-supported therapy. *Frontiers in Human Neuroscience*, *13*. https://doi.org/10.3389/fnhum.2019.00177

Villamar, M. F., Santos Portilla, A., Fregni, F., & Zafonte, R. (2012). Noninvasive brain stimulation to modulate neuroplasticity in traumatic brain injury. *Neuromodulation : journal of the International Neuromodulation Society*, *15*(4), 326–338. https://doi.org/10.1111/j.1525-1403.2012.00474.x

Xie, H., Li, X., Xu, G., Huo, C., Fan, Y., Li, Z., & Dou, Z. (2023). Effects of transcranial magnetic stimulation on dynamic functional networks in stroke patients as assessed by functional near-infrared spectroscopy: a randomized controlled clinical trial. *Cerebral Cortex*, *33*(24), 11668–11678. https://doi.org/10.1093/cercor/bhad404

Zatorre, R., Chen, J. & Penhune, V. When the brain plays music: auditory–motor interactions in music perception and production. *Nat Rev Neurosci* 8, 547–558 (2007). https://doi.org/10.1038/nrn2152

Appendix A

Table 1

Overview of Jadad Scale Score

Studies	Randomization	Method Randomization	Double-blind	Method Double-blinding	Withdrawals and Dropouts	Total Score
Martínez-Molina et al. (2021)	1	1	0	0	1	3
Struchen et al. (2011)	1	0	0	0	1	2
Killgore et al. (2019)	1	1	1	1	0	4
Chan et al. (2024)	1	0	1	0	1	3
Han et al. (2020)	1	0	1	0	0	2
Schiff et al. (2008)	0	0	0	0	0	0
Xie et al. (2023)	1	1	1	1	1	5
Afsharian et al. (2024)	1	1	0	0	0	2
Siddiqi et al. (2019)	1	0	1	1	1	4

Appendix B

Table 2

Overview of Significance of Results Studies

Authors	Intervention	Key Results
Martínez-Molina et al. (2021)	Neurological Music Therapy (NMT)	• Executive function improvement: p=0.003
Struchen et al. (2011)	Social Peer-Mentoring Program	• The majority (67%) of participants felt their social peer mentor was helpful in increasing social activity participation and in decreasing feelings of loneliness.
Killgore et al. (2019)	Blue Wavelength Light Exposure	• Neurocognitive speed: p=0.01 • Neurocognitive speed and accuracy: p=0.049 • Visual construction: p=0.014 • Delayed memory: p=0.007 • Total neuropsychological performance: p=0.048 • Falling asleep earlier: p=0.022 • Awakening earlier: p=0.037 • Daytime sleepiness: p=0.027
Chan et al. (2024)	Low-level Light Therapy (LLLT)	• Brain connectivity: p=0.01
Han et al. (2020)	Cognitive Training (SMART vs. BHW)	• Global and local brain efficiency: P<0.5 • Regional network densities: P<0.5 • Trailmaking test scores (executive function): p=0.2
Schiff et al. (2008)	Bilateral Deep Brain Electrical Stimulation (DBS)	• Arousal improvement: p<0.001 • Chew and swallow ability improvement: p<0.001 • Reflex improvement: p<0.001
Xie et al. (2023)	Low-frequency (LF) and High-frequency (HF)-rTMS	• Cortical activation (LF) compared to (HF): p=0.003-0.04 • Cortical activation (LF) compared to (C): p=0.01-0.05 • Functional connectivity (LF) compared to (C): p=0.002-0.05
Afsharian et al. (2024)	Transcranial Direct Current Stimulation combined with Cognitive Training	• Activation in cortical regions: p<0.05 • Executive function N-back improvement: p<0.05 • WCST improvement: p<0.05
Siddiqi et al. (2019)	Repetitive Transcranial Magnetic Stimulation (rTMS)	• MADRS improvement was greater in the active treatment group than in the sham group (Cohen's d=1.43)

Abbreviations: LF = low-frequency, HF = high-frequency, C = control group, WCST = Wisconsin Cart Sorting Test, MADRS = Montgomery-Asberg Depression Rating Scale