









Structural brain changes and functional recovery following neurorehabilitation interventions in traumatic brain injury: A systematic review

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Abstract

Background: Traumatic brain injury (TBI) remains a leading cause of long-term cognitive and functional impairment worldwide. Neurorehabilitation strategies have shown promise in promoting recovery, but the underlying structural brain changes remain poorly understood.

Objective: To systematically evaluate the evidence for structural brain changes associated with neurorehabilitation interventions in patients with TBI, and their relationship with cognitive and functional recovery.

Materials and methods: A systematic review was conducted according to PRISMA 2020 guidelines and registered in PROSPERO (CRD420251072783). A comprehensive search of PubMed, Scopus, Web of Science, MEDLINE and SciELO identified studies reporting neurorehabilitation interventions in TBI populations with structural neuroimaging outcomes. Study quality was assessed using the Newcastle–Ottawa Scale (NOS).

Results: Eleven studies met the inclusion criteria. Interventions included cognitive training, neurologic music therapy, and multimodal programs. Most studies used MRI, DTI, or fMRI to assess neuroanatomical changes. Improvements were consistently observed in attention, memory, and executive function, often correlated with increased gray matter volume or enhanced functional connectivity in prefrontal and frontoparietal regions. NOS scores ranged from 2 to 9, with a median of 7. While methodological heterogeneity was present, most studies reported positive structural and clinical outcomes.

Conclusion: Neurorehabilitation interventions may be associated with measurable changes in brain structure and connectivity, even in chronic TBI, supporting the concept of preserved neuroplasticity. These findings highlight the value of integrating neuroimaging into rehabilitation protocols to monitor and guide recovery. However, standardized methodologies and larger trials are needed to validate these effects and inform precision rehabilitation approaches.

Keywords: Traumatic Brain Injury, Neurological Rehabilitation, Neuronal Plasticity, Cognitive Training, Brain, Systematic review.

Cambios estructurales cerebrales y recuperación funcional tras intervenciones de neurorrehabilitación en el traumatismo craneoencefálico: una revisión sistemática


Resumen

Antecedentes: el traumatismo craneoencefálico (TCE) sigue siendo una de las principales causas de discapacidad cognitiva y funcional a largo plazo a nivel mundial. Las estrategias de neurorrehabilitación han demostrado ser prometedoras para favorecer la recuperación, pero los cambios estructurales cerebrales subyacentes aún no se comprenden completamente.

Objetivo: evaluar sistemáticamente la evidencia disponible sobre los cambios estructurales cerebrales asociados a intervenciones de neurorrehabilitación en pacientes con TCE, y su relación con la recuperación cognitiva y funcional.

Materiales y métodos: se realizó una revisión sistemática siguiendo las directrices PRISMA 2020, con registro en PROSPERO (CRD420251072783). Se buscaron estudios en PubMed, Scopus, Web of Science y SciELO. La calidad metodológica se evaluó mediante la escala de Newcastle–Ottawa (NOS).

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Resultados: se incluyeron once estudios. Las intervenciones evaluadas incluyeron entrenamiento cognitivo, musicoterapia neurológica y programas multimodales. La mayoría utilizó MRI, DTI o fMRI para analizar cambios neuroanatómicos. Se observaron mejoras consistentes en atención, memoria y funciones ejecutivas, correlacionadas con aumentos en el volumen de sustancia gris o una conectividad funcional mejorada en regiones prefrontales y frontoparietales. La mayoría de los estudios reportaron resultados estructurales y clínicos positivos.

Conclusión: las intervenciones de neurorrehabilitación pueden estar asociados a cambios cerebrales medibles, incluso en fases crónicas del TCE, lo que respalda la existencia de neuroplasticidad preservada. Estos hallazgos refuerzan el valor de integrar la neuroimagen en los protocolos de rehabilitación para guiar la recuperación. Se necesitan estudios más amplios y estandarizados para confirmar estos efectos y avanzar hacia una rehabilitación de precisión.

Palabras clave: lesiones cerebrales traumáticas, rehabilitación neurológica, plasticidad neuronal, entrenamiento cognitivo, encéfalo, revisión sistemática.

Introduction

Traumatic brain injury (TBI) remains a leading cause of long-term disability worldwide. In 2019, an estimated 27.16 million new TBI cases, 48.99 million prevalent cases, and 7.08 million years lived with disability (YLDs) were reported globally (1). TBI involves structural brain damage that often leads to disrupted function, manifesting as cortical volume loss and alterations in white matter connectivity, changes detectable through neuroimaging modalities such as diffusion tensor imaging (DTI) and functional MRI (fMRI) (2). Clinical outcomes vary widely depending on injury severity and location, ranging from mild cognitive or behavioral disturbances to profound neurological deficits. The Glasgow Coma Scale remains the standard tool for classifying TBI severity into mild, moderate, or severe (3,4).

The brain's intrinsic capacity to reorganize its structure and function, a phenomenon known as neuroplasticity, forms the basis of neurorehabilitation (5). These interventions aim to utilize this plasticity to restore lost functions and enhance quality of life (6). Approaches include motor-based therapies such as neurophysiotherapy, as well as cognitive and language therapies, sensory stimulation techniques and structured programs targeting memory and executive functioning.

Although neuropsychological rehabilitation has been shown to improve cognition, independence and emotional well-being (7-9), the neurobiological mechanisms supporting these improvements are not fully understood. In Particular, the structural correlates of cognitive recovery, such as changes in brain volume or connectivity, remain under-explored.

The current literature reveals fragmented and heterogeneous evidence, with studies varying widely in terms of design, intervention type, outcome metrics, and populations. While some studies have attempted to characterize the impact of cognitive rehabilitation on structural brain variables using volumetric MRI or connectivity analyses (10), but their findings are not readily comparable or generalizable.

It is essential to bridge the gap between clinical outcomes and neuroanatomical changes to develop effective and personalized neurorehabilitation strategies. While functional gains can be measured using neuropsychological assessments, these tools alone do not elucidate the neural mechanisms underlying recovery (11). Identifying links between brain plasticity, as evidenced by volumetric or connectivity changes, and cognitive improvements could help to tailor therapy to individual profiles, facilitate the development of neurobiological biomarkers, and enhance clinical decision-making. However, relatively few studies have concurrently assessed both structural brain changes and functional outcomes concurrently, which limits our understanding of how cognitive stimulation translates into anatomical remodeling and real-life improvement.

This systematic review aims to address this gap by synthesizing the available evidence on the impact of neuropsychological interventions in TBI, with a particular focus on the relationship between structural brain changes and functional recovery. Specifically, the review will explore: 1. The effect of interventions on brain structure (e.g., volume, connectivity); 2. Functional recovery measured via standardized cognitive and independence scales; and 3. Quality of

life outcomes. Additionally, we situate these findings within the public health context of TBI in Colombia, where the burden of disability remains substantial.

Materials and methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (12). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251072783.

Literature search strategy

A comprehensive literature search was conducted across five electronic databases: PubMed, Scopus, Web of Science, the Cochrane Library (Medline), and SciELO, without date restrictions, for articles published up to July 2024. The search aimed to identify original studies evaluating the impact of neurorehabilitation or neuropsychological interventions on structural brain changes and functional recovery in patients with traumatic brain injury.

The search strategy combined controlled vocabulary (e.g., MeSH terms) and free-text keywords grouped into four core concepts: TBI (traumatic brain injury, TBI); interventions (neurorehabilitation, cognitive rehabilitation, neuropsychological intervention); structural change terms (neuroanatomy, cerebral volume, functional connectivity, neuroplasticity); and functional outcomes (functional recovery, functional independence, quality of life, neuropsychological assessment). Boolean operators (AND/OR) were used to combine the terms.

Eligibility criteria

Inclusion criteria

Studies were included if they met the following criteria:

- Published in English or Spanish between 2014 and 2024.
- Included human subjects diagnosed with TBI, confirmed by neuroimaging or clinical criteria.
- Implemented neurorehabilitation interventions (cognitive, behavioral, psychotherapeutic, or sensory based).

- Reported at least one of the following outcomes: a) structural brain changes (e.g., gray matter volume, connectivity); b) functional outcomes (e.g., standardized neuropsychological scales); c) Quality of life measures.

Eligible study designs included randomized controlled trials (RCTs), pilot studies, quasi-experimental studies, longitudinal studies, descriptive studies, and case reports.

Exclusion criteria

The following were excluded:

- Review articles, editorials, opinion pieces, book chapters, and conference abstracts.
- Studies without original empirical data.
- Studies lacking a clear description of the intervention.
- Animal studies or studies focusing exclusively on pharmacological interventions.
- Articles not peer-reviewed.

Additionally, reference lists of included studies and relevant systematic reviews were manually screened to identify additional eligible articles.

Study selection process

All records retrieved from the databases were imported into a reference management software and duplicates were removed. Four reviewers (SIL, DFE, MA and DE) screened the titles and abstracts independently. Articles deemed potentially eligible were reviewed in full. Any disagreements were resolved through discussion, with a fifth reviewer (JSR) acting as arbitrator in cases of uncertainty. The study selection process is illustrated by a PRISMA flow diagram (Figure 1), which includes the reasons for exclusion.

Data extraction

Data extraction was performed independently by five reviewers using a standardized extraction template in Microsoft Excel. Extracted data were cross-verified to minimize bias. Discrepancies were resolved by consensus or by consulting senior reviewers.

The following information was extracted from each study:

- General study information: authors, year, country, study design, sample size.
- Patient characteristics: age, sex, TBI severity.
- Intervention details: type of intervention, duration, number of sessions, frequency.

Outcomes reported:

- Neuroanatomical changes (e.g., brain volume, functional connectivity).
- Functional recovery (e.g., cognitive performance, independence).
- Quality of life.
- Adverse effects (if reported).
- Neuroimaging methods used.

Risk of bias and quality assessment

The quality and risk of bias of included studies were independently assessed by two reviewers using the Newcastle–Ottawa Scale (NOS) (13), which evaluates three domains: selection, comparability, and outcome assessment (Table 1). Most studies demonstrated adequate representativeness of the exposed cohort and clear ascertainment of exposure, but comparability between cohorts and handling of non-response or follow-up completeness were more variable across studies.

These findings suggest that while the overall methodological quality was acceptable, variability in study design and reporting may have influenced the strength and reliability of the evidence.

Data synthesis and analysis

Given the heterogeneity of interventions and outcomes, a narrative synthesis was conducted to qualitatively summarize findings across studies. The synthesis was structured into the following thematic areas:

- Neuroanatomical changes (e.g., gray matter volume, connectivity) assessed via neuroimaging.
- Functional recovery outcomes, including attention, memory, executive functions.

- Quality of life and adverse effects, where available.

Due to variation in study designs, populations and outcome measures, a meta-analysis was not performed.

Results

A total of 50 records were identified through systematic database searches. After the removal of duplicates, 48 unique studies were screened by title and abstract. Of these, 19 were selected for full-text assessment. Following detailed evaluation, 11 studies that met all the inclusion criteria and were incorporated into the final qualitative synthesis. Figure 1 illustrates the selection process according to the PRISMA 2020 guidelines.

The final sample comprised 361 participants diagnosed with TBI, including subjects from both the experimental and control groups. Of these, 227 were male (62.8%) and 133 were female (36.8%), with the sex of one participant not reported. Participants' ages ranged from 9 to 69 years, with a median age of 39.4 years and an interquartile range (IQR) of 26 to 52 years. In terms of TBI severity, vast majority of studies (72.7%) focused predominantly on mild TBI, including chronic cases, while the remainder included patients with a spectrum ranging from mild to severe TBI. Two case reports described individuals with moderate-to-severe lesions, including subdural hematomas and subarachnoid hemorrhages (Table 2).

The study designs varied; four were randomized controlled trials (RCTs), three were pilot or quasi-experimental studies, two were case reports, one was longitudinal, and one was descriptive. Excluding case reports, the average sample size was 42.5 participants (range: 10–83; SD: ± 21.7). Despite the variability in design, all studies implemented structured neurorehabilitation interventions with defined durations, protocols, and outcome measures.

The interventions were varied in both content and duration. The most commonly used approaches were brain plasticity-based cognitive training (BPCT), music-mediated therapies, and strategy-based cognitive rehabilitation. The median intervention was 10.5 weeks (IQR: 8 to 13 weeks), with sessions typically lasting ranging between 30 to 90 minutes, and occurring 3 to 5 times per week. One study involved an

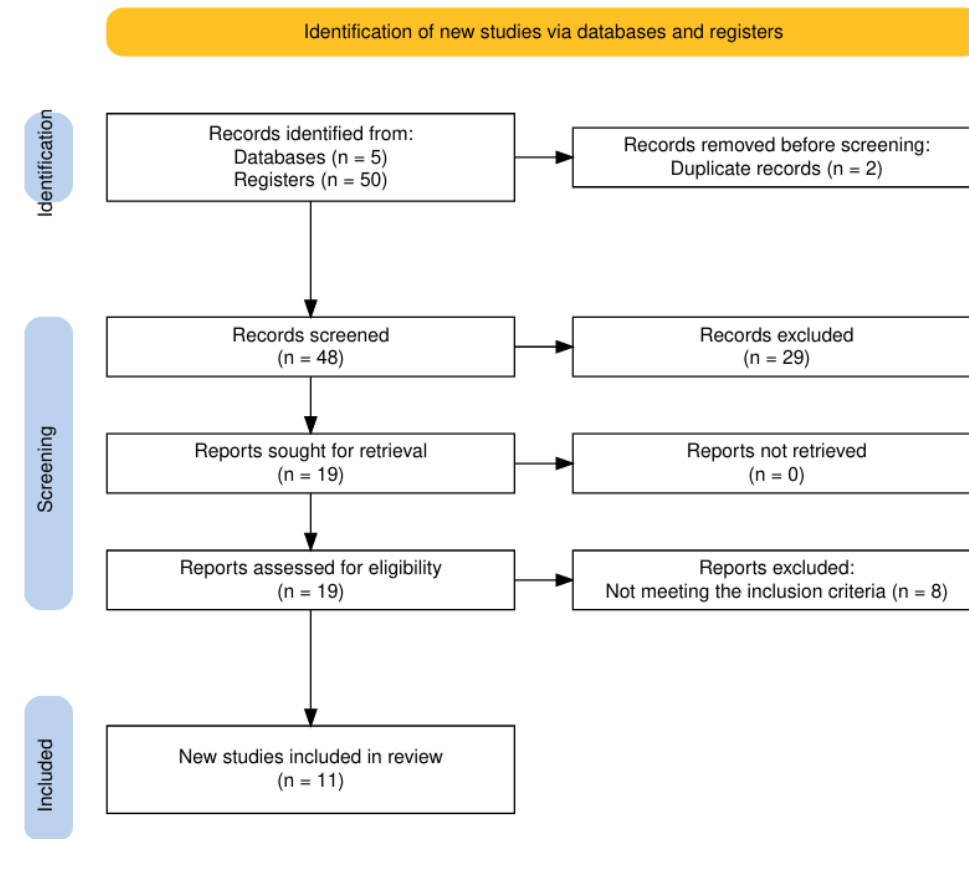


Figure 1. PRISMA flow chart

Source: Prepared by the authors.

intensive 3-day intervention, while another reported a 10-year longitudinal follow-up. Most protocols involved 40–50 sessions in total, with patients receiving over 30 hours of rehabilitation.

All 11 studies reported some degree of functional improvement, although the magnitude of the effects varied. Objective improvements on standardized neuropsychological tests were observed in 8 studies (72.7%). The domains with the most consistent improvements were attention, verbal memory, executive functioning, and language processing. Specifically, three studies (27.3%) reported statistically significant gains in processing speed and sustained attention ($p < 0.05$), while two additional studies described enhanced verbal fluency and lexical retrieval abilities. Improvements in global cognitive composite scores were also reported in studies using computerized training platforms. Three studies do-

cumented meaningful subjective improvements in everyday functioning and perceived independence based on patient self-report or long-term clinical observation. No study reported deterioration in function, and none documented an absence of effect.

Neuroanatomical changes were assessed in 9 of the 11 studies (81.8%), all of which used MRI, with one also incorporating DTI. Of these, 8 studies reported some form of change following the intervention, including increased functional connectivity in networks associated with executive function and motor planning, as well as increased grey matter volume in regions such as the prefrontal cortex and supplementary motor areas (Figure 2). One study reported decreased functional activity in the dorsolateral prefrontal cortex, which was interpreted as an increase in neural processing efficiency. In contrast, one study did not detect any structural changes in the

Table 1. New-castle ottawa scale

Study	Year	Selection				Comparability		Results			Total
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts (a)	Comparability of cohorts (b)	Outcome assessment / Exposure ascertainment	Sufficient follow-up duration? / Same ascertainment method for cases and controls	Complete follow-up? / Non-response rate and adequate handling	
Voelbel et al.	2021	1	0	1	1	1	0	1	1	0	6
Yuan et al.	2016	1	1	1	1	1	1	1	1	0	8
Lebowitz et al.	2012	1	0	1	1	0	0	1	1	1	6
Lindsey et al.	2022	1	1	1	1	1	0	1	1	1	8
Bitan et al.	2018	1	0	1	1	1	0	1	1	0	6
Krasovsky et al.	2017	1	0	0	0	0	0	1	0	0	2
Han et al.	2018	1	1	1	1	1	1	1	1	0	8
Siponkoski et al.	2019	1	1	1	1	1	1	1	1	1	9
Strangman et al.	2009	1	1	0	0	1	1	1	0	0	5
Mahncke et al.	2021	1	1	1	1	1	1	1	1	1	9
Vik et al.	2018	1	0	1	1	1	0	1	1	0	6

Source: Prepared by the authors.

Table 2. Characteristics of the studies reviewed

Author	Year	Study design	Neuropsychological intervention	Duration of therapy	Number of sessions	Duration of each session (minutes)	Sample size	Age (Mean & range)	Sex	TBI Severity	Functional Recovery Results	Neuroanatomical changes	Neuroanatomical assessment method	Adverse effects of therapy	Main Findings
Bitan et al. (14)	2018	CR	Melody-based therapy	16 weeks	48	30	n = 2 (1 treated, 1 control)	Treated: 48 y; Control: 54 y	F: 2	Moderate - severe (subdural and subarachnoid hemorrhage)	Improved speech production and trained responses; gains maintained at 8-week follow-up	Increased connectivity in supplementary motor areas, insula and right IFG (pars triangularis/opercularis); Decreased connectivity in bilateral linguistic areas.	fMRI	Not reported	Melody-based therapy increased functional connectivity between language areas of the right hemisphere and speech motor control areas, suggesting compensation for left hemisphere damage for language production.
Han et al. (15)	2018	RCT	Cognitive Strategy SMART and BHW	8 weeks	12	90	n = 56 (SMART: 26, BHW: 30)	SMART: 40.5 ± 14.0 y; BHW: 42.8 ± 12.4 y	SMART - M: 16, F: 10; BHW - M: 19, F: 11	Chronic mild	Improved cognitive control and performance; significant Trail Making gains in SMART group (p = 0.04)	Increased functional connectivity in cognitive control networks (cingulo-opercular and fronto-parietal); changes were observed in DLPFC, insula, IPS, medial cingulate, and precuneus.	fMRI	Not reported	Cognitive training improved cognitive performance and induced neuroplastic changes in control-related networks.
Krasovsky et al. (16)	2017	CR	Pediatric rehabilitation for 6 months as inpatient, and continuous functional evaluation and support until age 22	10 years	NA	NA	n = 1	22 y	F: 1	Severe (multifocal damage, edema, agnosia, apraxia)	Independent ADLs at 10 years. Persisting difficulties in novel motor tasks, uses verbal compensatory strategies	No structural changes observed at 10-year follow-up	MRI	Not reported	Despite deficits in praxis and body representation, patients maintained functional capacity and effective integration of compensatory strategies in daily life, highlighting functional plasticity in the absence of structural changes.

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Lebowitz et al. (17)	2012	Descriptive study	Computerized BPCT (Cortex with InSight)	6 weeks	30	40	n = 10	46.3 y (34–62 y)	M: 1, F: 9	Mild to severe (5 mild, 2 moderate, 2 severe, 1 unclassified)	Subjective improvements in attention, memory, planning, and processing speed (7/10 reported functional gains). Objective gains on CFQ (d = 1.45), ANAM4 (d = 0.58), FrSBe (d = 0.29); other effects: d = 0.03–0.47	Not reported	NA	Fatigue (n = 8), headache (n = 2), eye strain (n = 1); all mild to moderate and transient	BPCT was feasible and well tolerated, even years post-injury. Perceived improvements were supported by small to moderate objective gains. The intervention can be implemented at home, with remote support. Controlled clinical trials are recommended to confirm its efficacy.
Lindsey et al. (18)	2022	Pilot study	Computerized BPCT (BrainHQ)	12 weeks	60	60	n = 18 (TBI: 11, controls: 7)	39.4 y (26–52 y)	TBI - M: 7; F: 4; Control - M: 3, F: 4	Chronic mild–moderate (≥6 months post-injury)	Improvements observed in computerized tasks (battery not specified); Perceived improvements in attention, memory, and processing speed	Increase in resting-state connectivity in bilateral prefrontal cortex, right IPL, DLPFC, precuneus; Changes correlated with task performance (r > 0.5, p < 0.05).	rsfMRI	Not reported	After an effective intervention in neurorehabilitation, cognitive function and brain connectivity improved, favoring functional recovery in adults with chronic TBI.
Mahncke et al. (19)	2021	RCT	Computerized BPCT (BrainHQ)	13 weeks	65	60	n = 83 (experimental: 41, active control: 42)	Experimental: 35.4 ± 8.8 y; Control: 32.3 ± 8.5 y	M: 67, F: 16	Mild (52 closed-head, 29 blast injury, 2 impact)	Significant cognitive improvement Post-training (+6.9 pts, p = 0.025) and 3-month follow-up (+7.4 pts, p = 0.039)	Not reported	NA	Anxiety, headache, and mental fatigue (n = 2)	Cognitive rehabilitation based on plasticity improved cognitive function and reorganized brain connectivity. Brain changes correlated with cognitive performance.

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Siponkoski et al. (20)	2019	RCT	NMT	3 months	20	60	n = 40 (AB group: 20, BA group: 20)	36.3 y (18–57 y)	M: 29, F: 11	Moderate - severe	Improved executive functions in AB group (p = 0.045), gains maintained at follow-up (p = 0.003)	Increased GMV in IFG (correlated with cognitive flexibility), middle/superior frontal gyri, insula, cingulate, cerebellum, and temporal lobes	MRI	Transient fatigue (n not specified)	NMT improved executive function and cognitive flexibility, associated with structural changes in right IFG. No significant gains in memory, attention, inhibition, or motor skills.
Strangman et al. (21)	2009	Experimental study	Semantic clustering	<3 days	1	30–45	n = 45 (TBI: 25, controls: 20)	TBI: 46.8 y (25–60 y); Control: 45.9 y (25–60 y)	TBI - M: 19, F: 6; Control - M: 15, F: 5	Mild to severe (6 mild, 3 moderate, 14 severe)	Both groups improved in recall and semantic clustering; TBI group remained below controls	Reduced activation in left DLPFC and anterior AG; Disrupted connectivity between DLPFC and AG, mid-cingulate, frontal pole, insula, and medial frontal gyrus	fmMRI	Not reported	TBI patients improve memory with strategy but have impaired connectivity affecting working memory and executive control.
Vik et al. (22)	2018	RCT	Active musical training through structured piano lessons	8 weeks	16	30 (and daily practice of >15 min)	n = 30 (mTBI: 7, trained controls: 11, untrained controls: 12)	mTBI: 38 y; Trained controls: 33 y; Untrained controls: 33y	mTBI - M: 4, F: 3; Trained controls - M: 5, F: 6; Untrained controls - M: 4, F: 7	Mild	Significant CVLT-2 gains: 90% resumed work or study; improved focus, less fatigue, better social reintegration	Increased activation in right medial orbitofrontal cortex (correlated with musical learning)	rsfMRI	Not reported	Musical training led to neural network reorganization, improving executive function, attention, and verbal memory, with specific cognitive gains linked to orbitofrontal cortex changes and no effects on processing speed.

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Author	Year	Study design	Neuropsychological intervention	Duration of therapy	Number of sessions	Duration of each session (minutes)	Sample size	Age (Mean & range)	Sex	TBI Severity	Functional Recovery Results	Neuroanatomical changes	Neuroanatomical assessment method	Adverse effects of therapy	Main Findings
Voelbel et al. (23)	2021	Pilot QRCT	Neuroplasticity-based auditory therapy (BrainHQ Auditory Training software)	13 weeks	40	60	n = 48	44.5 ± 12.7 y (24–69 y)	M: 25, F: 23	Chronic Mild to Severe (15 mild, 5 moderate, 27 severe)	Improvement in verbal attention, working memory (WJ-III), processing speed (TMT-A); positive self-assessment (CSRQ-Cognitive); minor improvements in cognitive flexibility and auditory processing (PASAT)	Increase in GMV in left superior temporal gyrus and left IFG	rsfMRI	Not reported	The auditory training improved auditory processing speed and verbal attention, positive self-perceived cognitive gains, and significant changes in DMN functional connectivity; effective and accessible intervention for chronic TBI
Yuan et al. (24)	2016	Longitudinal study	AIM Program	10 weeks	10 (and 11-32 home based sessions)	60–90 min (and home-based sessions of 20–40 min)	n = 28 (TBI: 17, controls: 11)	TBI: 13.7 ± 2.8 y (9–18 y); Control: 13.4 ± 2.1 y (9–15 y)	TBI - M: 10, F: 7; Control - M: 3, F: 8	Complicated mild to severe	Improved sustained attention (TEA-Ch) and executive functions as reported by parents (BRIEF)	Decreased small-worldness (p < 0.001) and normalized clustering coefficient (p < 0.001); Increased path length (λ), correlated with improved attention (r = 0.70). Regional network connectivity involvement of: superior frontal gyrus, Inferior parietal gyrus, fusiform gyrus, paracentral lobule, supramarginal gyrus, AG, STG, and thalamus.	MRI and DTI tractography	Not reported	AIM improved sustained attention and intervention, verbal inhibition and daily executive function: based on parent (BRIEF p<0.001) and self-reports (BRIEF MI correlated with neural efficiency changes)

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Author	Year	Study design	Neuropsychological intervention	Duration of therapy	Number of sessions	Duration of each session (minutes)	Sample size	Age (Mean & range)	Sex	TBI Severity	Functional Recovery Results	Neuroanatomical changes	Neuroanatomical assessment method	Adverse effects of therapy	Main Findings
				Median: 12.5 weeks (IQR: 8.5–13)*	Median: 30.8 (IQR: 17–46) Range: (1–65)	Median: 60 (IQR: 38–60)	Total: n = 361	Median: 39.4 y (Range: 9–69)	M: 227, F: 133	Mild: 72.7% (8/11); Moderate: 64% (7/11); Severe: 63.6% (7/11)			MRI: 82%; fMRI: 27%; rsfMRI: 27%; DTI: 9%		

(*). Excludes 1 long-term follow-up (10 yrs) and 1 brief protocol (<3 days).

Note. TBI: Traumatic brain injury; CR: Case report; RCT: Randomized Controlled Trial; QRCT: quasi Randomized Controlled Trial; SMART: Strategic Memory Advanced Reasoning Training; BHW: Brain Health Workshop; BPCT: Brain Plasticity-Based Cognitive Training; NMT: Neurologic Music Therapy; AIM: Attention Improvement and Management; ADL: Activities of Daily Living; CFQ: Cognitive Failures Questionnaire; ANAM4: Automated Neuropsychological Assessment Metrics, Version 4; FrSBe: Frontal Systems Behavior Scale; CVLT-2: California Verbal Learning Test, 2nd Edition; WJ-III: Woodcock-Johnson Tests of Cognitive Abilities, 3rd Edition; TMT-A: Trail Making Test, Part A; CSRQ: Cognitive Symptom Rating Questionnaire; PASAT: Paced Auditory Serial Addition Test; TEA-Ch: Test of Everyday Attention for Children; BRIEF: Behavior Rating Inventory of Executive Function; IFG: Inferior Frontal Gyrus; DLPFC: Dorsolateral Prefrontal Cortex; dlPFC: Dorsolateral Prefrontal Cortex; IPS: Intraparietal Sulcus; IPL: Inferior Parietal Lobule; GMV: Gray Matter Volume; AG: Angular Gyrus; STG: Superior Temporal Gyrus; rsfMRI: Resting-State Functional Magnetic Resonance Imaging; DTI: Diffusion Tensor Imaging; DMN: Default Mode Network.

Source: Prepared by the authors.

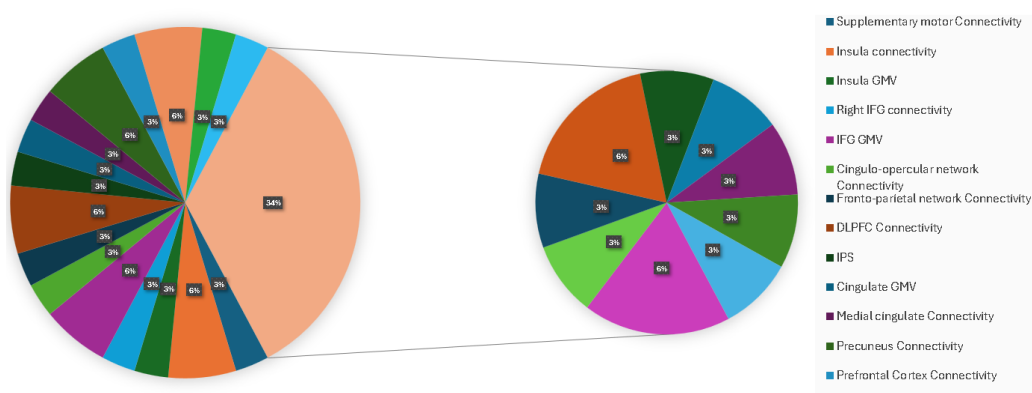


Figure 2. Qualitative summary of brain regions with post-intervention changes in gray matter volume (GMV) or functional connectivity among patients with traumatic brain injury (TBI)

Note. GMV: Gray Matter Volume; Connectivity: functional connectivity; IFG: Inferior Frontal Gyrus; DLPFC: Dorsolateral Prefrontal Cortex; IPS: Intraparietal Sulcus; IPL: Inferior Parietal Lobule; STG: Superior Temporal Gyrus; AG: Angular Gyrus.

Changes were mainly observed in frontal, parietal, and temporal regions, as well as in functional networks such as the fronto-parietal and cingulo-opercular systems.

Source: Prepared by the authors.

post-intervention scans, while another described a reduction in network organization that was interpreted as a sign of maladaptive plasticity rather than recovery.

Notably, integrating of neuroimaging and behavioral outcomes enable several studies to establish correlations between structural brain changes and improvements in cognitive performance. For example, increased connectivity within frontoparietal networks has been associated with improved attention and executive function in two RCTs ($p < 0.01$). However, due to methodological heterogeneity and limited sample sizes, these associations were not consistently reported across all studies.

Only three studies (27%) explicitly reported adverse effects of the interventions. All adverse events were non-serious and self-limiting. The most common symptoms were transient fatigue ($n = 8$), mild headache ($n = 2$), and occasional anxiety ($n = 2$). One study reported post-intervention decreases in language-related connectivity, although this finding lacked clinical correlation. The remaining studies either reported no adverse effects or did not include safety monitoring in their methodology.

Discussion

This systematic review synthesized evidence from 11 studies evaluating the effects of neurorehabilitation interventions on structural brain changes and functional recovery in patients with traumatic brain injury (TBI). The available data suggest that neurorehabilitation interventions, including cognitive training, music-based therapy, and attention rehabilitation, can lead to measurable improvements in attention, memory, and executive functions, as well as changes detectable through structural and functional neuroimaging.

Functional gains were reported in all included studies, with 72.7% demonstrating statistically significant improvements in at least one cognitive domain using standardized assessments. The most frequently targeted domains—sustained attention, processing speed, memory, and executive functioning—are capacities that are often impaired in TBI and are closely linked to prefrontal and frontoparietal cortical networks. These improvements were observed across a broad range of injury severities and durations, suggesting that neurorehabilitation may have potential beyond the acute phase. How-

ver, the strength of these inferences is restricted by small sample sizes, a lack of blinded assessments, and limited use of control groups in several studies.

Converging neuroimaging data are consistent with the idea that experience-dependent neuroplasticity is a possible mechanism of recovery. Of the nine studies that incorporated structural or functional imaging, 88.9% reported some form of change following the intervention change, such as increased functional connectivity in executive control networks and increased grey matter volume. These findings are in line with recent literature showing that targeted cognitive interventions alter neural architecture, particularly in the default mode network, the frontoparietal control network and the supplementary motor areas, regions critical for cognitive control and adaptive behavior (25,26). However, the pattern of changes was not uniform across studies. In some cases, reduced activation or connectivity was interpreted as increased neural efficiency than functional loss.

A central aspect of this review is the degree of convergence between neuroanatomical and behavioral outcomes. Studies such as those by Han et al. (15) and Lindsey et al. (18) found that changes in frontoparietal connectivity correlated with improvements in attention and executive function. This is consistent with the idea that structural and network reorganization contributes to recovery (27,28). This is consistent with the findings of Gallen and D'Esposito (29), who suggested that metrics such as modularity and network efficiency could be candidate biomarkers of cognitive training response. Furthermore, interventions involving multimodal or emotionally salient stimuli, such as music therapy, also tended to demonstrate parallel behavioral and imaging changes, potentially due to the activation of wider sensorimotor, limbic and associative cortices.

These results also support the idea that neural recovery following TBI is not limited to the acute phases. Several of the included studies demonstrated structural or connectivity changes in patients with chronic TBI, some of whom had experienced the injury years earlier. This reinforces the concept that the adult brain retains the capacity for structural reorganization long after the presumed 'therapeutic window', particularly when interventions are sustained, intensive and task-specific (30-33).

However, several methodological limitations warrant cautious interpretation. Sample sizes were modest

in most studies, with five involving fewer than 25 participants. Small cohorts limit statistical power and increase the risk of both type I and type II errors. Additionally, considerable heterogeneity in intervention protocols, ranging from 3-day interventions to decade-long follow-ups, complicates direct comparison and meta-analytic synthesis. The variability in outcome measures, imaging modalities, and definitions of recovery also limits the generalizability of the findings.

Additionally, while neuroimaging provides compelling evidence of anatomical and functional changes, most studies used structural MRI alone. Only one study incorporated diffusion tensor imaging (DTI), very few used resting-state functional magnetic resonance imaging (fMRI), and none employed positron emission tomography (PET) or MR spectroscopy, limiting insight into microstructural and metabolic correlates of recovery (34-36). Future research should incorporate multimodal neuroimaging to better characterize the biological mechanisms of intervention effects and to determine whether specific patterns of network reorganization reliably predict functional improvement.

From a clinical perspective, these preliminary findings support the feasibility of structured neurorehabilitation programs as part of TBI management, particularly for individuals with persistent cognitive sequelae. From a systems perspective, the potential to reduce long-term disability through low-risk, non-invasive interventions is highly relevant from a public health perspective, particularly in settings with limited resources, although further cost-effectiveness data are required (37).

Moreover, the observed variability in individual responses to similar interventions underscores the importance of personalization. The emergence of imaging-based biomarkers, such as network efficiency or white matter integrity, could support the development of precision rehabilitation protocols tailored to individual structural profiles. Such approaches would allow clinicians to predict which patients are most likely to benefit from specific interventions, maximizing therapeutic efficacy and resource allocation (38,39-41).

Furthermore, recent epidemiological data reinforce the urgency of implementing effective rehabilitation strategies. According to GBD 2021 (42), Colombia has an estimated 293,306 prevalent TBI cases and 43,367 YLDs, highlighting a significant public health

burden of TBI comparable to global GBD 2019 estimates, despite being slightly lower (prevalence at 599/100,000; YLDs at 87/100,000). Notably, falls are the lead cause of TBI in 74% of countries (1), a pattern that is particularly relevant given Colombia's ageing population. Underreporting, especially of mild cases and in underserved areas, likely contributes to apparent disparities in burden.

The available evidence suggests that neurorehabilitation interventions, including cognitive training and executive function therapies, can lead to significant improvements in memory, attention, processing speed, and reintegration. Using GBD 2021 data for Colombia, and GBD 2019 disability weights (0.094 for mild TBI, 0.231 for moderate TBI, and 0.637 for severe TBI), it is estimated suggests that if 50% of patients with moderate to severe TBI received effective rehabilitation leading to a 20% reduction in disability weights, around 4,337 years lived with disability (YLDs) could be averted annually, accounting for approximately 10% of the national TBI disability burden. While this estimate is necessarily approximate, it underscores the potential public health impact of scalable, evidence-based neurorehabilitation programs.

Limitations

This systematic review has several limitations. Firstly, substantial heterogeneity was observed across studies in terms of design, intervention protocols, outcome measures and TBI severity. This precluded quantitative synthesis and reduces the generalizability of the findings. Secondly, sample sizes were generally small, with several cohorts involving fewer than 25 participants and two case reports involving a single patient, which increases the risk of type I and II errors and limits the precision of effect estimates. Thirdly, women were underrepresented in the aggregated sample (consistent with epidemiological trends in TBI), and the wide age ranges were constrained the ability to explore sex- or age-related differences in treatment response. Fourth, outcome measures, especially those relating to functional recovery and quality of life, were not standardized, and only a few studies used comparable validated scales, which reduced interpretability.

Fifthly, neuroimaging protocols mainly relied on conventional structural MRI; only one study incorporated DTI; few employed rsfMRI; and none used

PET or MR spectroscopy. This limited insights into the microstructural and metabolic mechanisms of recovery, and thus, the depth of neurobiological interpretation. Sixthly, the duration and intensity of interventions varied widely, ranging from brief 3-day protocols to multi-year follow-ups, which made it difficult to identify of optimal therapeutic windows or dose-response relationships. Finally, while most studies reported no serious adverse effects, safety monitoring and reporting were addressed inconsistently, making it difficult to draw definitive conclusions regarding the tolerability of neurorehabilitation protocols.

Conclusions

This systematic review highlights the therapeutic potential of neurorehabilitation interventions in promoting cognitive recovery and structural brain changes in patients with traumatic brain injury. Most studies reported improvements in areas such as attention, memory, and executive function, which were often accompanied by increased connectivity or grey matter volume in key brain regions. These results support the notion that the adult brain retains neuroplastic capacity well beyond the acute phase of injury, and that structured, task-specific interventions can modulate recovery trajectories. However, the evidence is limited by methodological heterogeneity, small sample sizes, and lack of standardized outcome measures.

Future studies should adopt larger, well-controlled designs, integrate multimodal neuroimaging, and move towards personalized rehabilitation protocols. Overall, neurorehabilitation appears to be a safe and promising approach for improving function and quality of life in TBI patients.

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