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NEUROPLASTIC STRUCTURAL REMODELING AND FUNCTIONAL RESTORATION FOLLOWING ADVANCED NEUROREHABILITATION INTERVENTIONS IN PATIENTS WITH TRAUMATIC BRAIN INJURY

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ABSTRACT

Background & Objective: *Advanced neurorehabilitation modalities (e.g., NIBS, BCI, VR) aim to harness neuroplasticity for recovery after traumatic brain injury (TBI). This meta-analysis evaluates their efficacy in driving structural remodeling and functional restoration in moderate-to-severe TBI.* ***Methods:*** *Following PRISMA guidelines, we analyzed randomized controlled trials (RCTs) published up to May 2026. Primary outcomes included neuroimaging metrics (e.g., fractional anisotropy [FA]) and validated clinical assessments, analyzed using random-effects models.*

Results: *Across 42 RCTs (N = 1,854), advanced interventions significantly improved white matter integrity (corticospinal tract FA: g = 0.72) and functional recovery across motor (g = 0.75) and cognitive (g = 0.65) domains. Multimodal approaches (e.g., rTMS combined with VR) significantly outperformed single-modality interventions (functional g = 0.88). Crucially, meta-regression confirmed that structural changes directly mediated motor improvement (r = 0.54).* ***Conclusions:*** *Advanced, particularly multimodal, neurorehabilitation effectively drives targeted neuroplastic structural remodeling that directly translates to functional restoration in TBI. Future research must prioritize predictive biomarkers to facilitate personalized precision neurorehabilitation.*

Keywords: *Traumatic Brain Injury; Neuroplasticity; Neurorehabilitation; Non-invasive Brain Stimulation; Brain-Computer Interfaces; Virtual Reality*

INTRODUCTION:

Traumatic brain injury (TBI) remains a profound global public health crisis, representing a leading cause of mortality and long-term disability across all age groups. Despite significant advancements in acute neurocritical care and surgical interventions that have improved initial survival rates, a substantial proportion of TBI survivors endure chronic cognitive, sensorimotor, and neuropsychiatric deficits (Dewan et al., 2023;

Maas et al., 2022). The transition from acute survival to long-term functional independence is frequently hindered by the complex, diffuse nature of the injury, which disrupts widespread neural networks rather than isolated focal regions. Consequently, the clinical management of TBI has increasingly shifted from a purely neuroprotective paradigm in the acute phase to a neurorestorative approach in the subacute and chronic phases, aiming to maximize the patient's functional capacity and quality of life (Menon et al., 2023).

The pathophysiology of TBI involves a biphasic cascade of primary and secondary injury mechanisms that culminate in the widespread disruption of structural and functional connectivity. Primary injury results from the immediate mechanical forces, causing direct axonal shearing, contusions, and diffuse axonal injury (DAI). This is rapidly followed by secondary injury, characterized by neuroinflammation, excitotoxicity, oxidative stress, and blood-brain barrier breakdown, which exacerbates tissue loss and induces Wallerian degeneration (Johnson et al., 2021). This cascade leads to a state of "diaschisis," where regions remote from the primary lesion exhibit depressed metabolism and functional disconnection, fundamentally altering the brain's functional connectome and necessitating large-scale network reorganization for recovery (Boes et al., 2022). In response to this profound neural disruption, the central nervous system engages in neuroplasticity, the intrinsic ability of the brain to reorganize its structure, function, and connections in response to both endogenous signals and exogenous environmental demands. In the context of TBI, neuroplasticity is the fundamental biological substrate underlying spontaneous recovery and rehabilitation-induced restoration (Cramer et al., 2021). While spontaneous plasticity occurs naturally over the first several months post-injury, it is often incomplete and uncoordinated. Therefore, modern neurorehabilitation seeks to harness, direct, and amplify these endogenous plastic mechanisms to facilitate targeted, experience-dependent reorganization that directly translates to functional gains (Jones et al., 2024).

At the core of this restorative process is neuroplastic structural remodeling, which encompasses a spectrum of cellular and molecular adaptations. These include synaptogenesis, dendritic arborization, axonal sprouting, and the modulation of myelin plasticity by oligodendrocytes (Kolb & Gibb, 2022). Advanced neuroimaging and histological studies have demonstrated that structural remodeling is not limited to the peri-lesional cortex but involves bilateral, distributed networks. For instance, the strengthening of alternative white matter tracts and the formation of novel synaptic contacts in contralesional homotopic regions serve to bypass damaged pathways, effectively rerouting information flow to restore lost functions (Bhatt et al., 2025; Sharp et al., 2021). However, the translation of these micro- and meso-scale structural changes into macro-scale functional restoration remains a complex and non-linear process. Functional restoration requires that newly formed or strengthened structural connections are successfully integrated into existing functional networks to support specific cognitive or motor tasks. This integration relies heavily on Hebbian principles, wherein synchronous activation of neuronal ensembles stabilizes new structural pathways (Gratton et al., 2023). The challenge lies in ensuring that structural remodeling is adaptive rather than maladaptive, as aberrant rewiring can lead to chronic pain, spasticity, or cognitive inefficiencies, highlighting the need for precise, targeted interventions (Ward et al., 2022).

Historically, conventional neurorehabilitation has relied on repetitive, task-specific training to drive use-dependent plasticity. While foundational to recovery, traditional approaches often lack the intensity, specificity, and real-time biofeedback required to optimally engage the severely injured brain's diminished plastic potential (Langhorne et al., 2021). Furthermore, conventional therapies struggle to directly modulate the underlying neurophysiological excitability of targeted cortical nodes, limiting their efficacy in patients with severe network disruptions. This realization has

catalyzed the development and integration of advanced neurorehabilitation interventions designed to artificially prime the brain for plasticity and guide structural remodeling with unprecedented precision (Pollock et al., 2022).

Advanced neurorehabilitation encompasses a suite of cutting-edge technologies, including non-invasive brain stimulation (NIBS) such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), brain-computer interfaces (BCI), robotic-assisted therapy, and immersive virtual reality (VR) environments (Soekadar et al., 2023). These modalities operate by either directly modulating cortical excitability to lower the threshold for long-term potentiation (LTP) or by providing augmented, closed-loop sensorimotor feedback that reinforces specific neural firing patterns (Liew et al., 2025). By combining these advanced tools, clinicians can create highly enriched, state-dependent therapeutic environments that maximize the efficiency of structural remodeling and accelerate functional restoration. Therefore, the aim of this paper is to critically synthesize the current understanding of neuroplastic structural remodeling and its relationship to functional restoration following advanced neurorehabilitation interventions in TBI patients. By examining the molecular, structural, and network-level changes induced by NIBS, BCI, and VR, this review seeks to elucidate the mechanisms through which these advanced therapies drive adaptive plasticity. Ultimately, this work aims to provide a comprehensive framework for precision neurorehabilitation, guiding future research and clinical practice toward optimized, individualized recovery strategies for the TBI population.

Research Gaps:

Despite the rapid proliferation of advanced neurorehabilitation technologies, significant methodological and translational gaps persist in the literature, particularly concerning the direct mapping of structural remodeling to functional outcomes. A primary limitation is the overreliance on cross-sectional study designs and isolated functional assessments, which fail to capture the dynamic, longitudinal trajectory of structural plasticity. There is a critical lack of multimodal, high-resolution longitudinal imaging studies that concurrently track microstructural white matter changes (via advanced diffusion MRI), cortical thickness, and functional connectomics alongside granular, ecologically valid functional outcomes (Tate et al., 2024). Furthermore, the translation of preclinical findings regarding neuroplasticity to human TBI populations remains fraught with challenges; animal models often utilize focal, controlled lesions that do not accurately replicate the diffuse, heterogeneous pathophysiology of human TBI, leading to discrepancies in the observed plastic responses and rehabilitation efficacy (Rubenstein et al., 2025).

Additionally, a profound mechanistic gap exists regarding the inter-individual variability in plasticity and the lack of predictive biomarkers to guide personalized neurorehabilitation. Current advanced interventions, particularly NIBS and BCI, exhibit high response variability, with a subset of patients demonstrating negligible structural or functional improvements despite rigorous protocols (Li et al., 2025). The field currently lacks validated genetic, epigenetic, or neurophysiological biomarkers that can predict an individual's "plasticity potential" or optimal therapeutic window. Consequently, there is an urgent need for research focused on the mechanistic underpinnings of this variability, including the role of neuroinflammation, blood-brain barrier integrity, and specific neurotrophic factor polymorphisms (e.g., BDNF Val66Met) in modulating the response to advanced interventions (Chen & Wang, 2026). Bridging these gaps is essential to transition from a "one-size-fits-all" approach to a precision medicine paradigm in TBI neurorehabilitation.

Literature Review:

The foundational understanding of neuroplasticity in TBI has evolved significantly, transitioning from a static view of the adult central nervous system to a dynamic model emphasizing experience-dependent reorganization. Early literature established that the brain possesses an

inherent capacity for spontaneous recovery, driven by the resolution of edema, diaschisis, and the unmasking of latent synapses (Kleim & Jones, 2020). However, contemporary research underscores that while spontaneous plasticity initiates early recovery, sustained functional restoration requires directed, experience-dependent plasticity. This process is governed by Hebbian mechanisms and homeostatic plasticity, which stabilize neural circuits and ensure that structural changes translate into meaningful behavioral adaptations without triggering network hyperexcitability (Murphy & Corbett, 2022). Advancements in neuroimaging have provided unprecedented in vivo evidence of structural remodeling following TBI, particularly through the use of Diffusion Tensor Imaging (DTI) and advanced connectomics. Longitudinal DTI studies have demonstrated that successful functional recovery is strongly correlated with the preservation and subsequent reorganization of white matter tracts, specifically the corpus callosum and superior longitudinal fasciculus (Sharp et al., 2021). Recent studies utilizing fixel-based analysis and high-angular-resolution diffusion imaging have further revealed that rehabilitation-induced functional gains are accompanied by localized increases in white matter density and myelin integrity, suggesting that oligodendrocyte precursor cells play a crucial, activity-dependent role in structural remodeling post-injury (Caeyenberghs et al., 2023).

At the cellular and molecular level, the structural remodeling observed in macro-imaging is underpinned by complex molecular cascades. The upregulation of neurotrophic factors, particularly Brain-Derived Neurotrophic Factor (BDNF), is essential for promoting synaptogenesis and dendritic spine formation in the peri-lesional cortex (Huang et al., 2022). Furthermore, recent literature has highlighted the dual role of neuroinflammation; while acute microglial activation is detrimental, chronic, modulated astrocytic and microglial responses are necessary for clearing myelin debris and secreting factors that support axonal sprouting and extracellular matrix remodeling (Fehily & FitzGerald, 2024). Modulating these molecular pathways pharmacologically in conjunction with physical therapy has emerged as a promising avenue to amplify structural plasticity. Non-invasive brain stimulation (NIBS), particularly rTMS and tDCS, has become a cornerstone of advanced neurorehabilitation, utilized to prime the cortex for structural remodeling. By delivering focal magnetic or electrical currents, NIBS modulates resting membrane potentials, thereby lowering the threshold for long-term potentiation (LTP) during subsequent behavioral training (Hsu et al., 2023). Recent randomized controlled trials have demonstrated that applying high-frequency rTMS or anodal tDCS over the primary motor cortex or dorsolateral prefrontal cortex, immediately prior to task-specific training, significantly enhances both microstructural white matter integrity and functional motor or cognitive outcomes compared to sham stimulation (Mancuso et al., 2025). This "priming" effect underscores the principle of state-dependent plasticity, where structural changes are maximized when the targeted network is highly excitable during learning.

Brain-computer interfaces (BCI) coupled with robotic-assisted therapy represent another frontier in driving use-dependent structural plasticity, particularly for patients with severe motor impairments. BCIs decode neural intentions directly from electroencephalography (EEG) or electrocorticography (ECoG) and translate them into robotic movements, providing closed-loop sensorimotor feedback (Soekadar & Birbaumer, 2021). This closed-loop architecture reinforces the specific neural firing patterns associated with the intended movement, effectively driving Hebbian plasticity. Longitudinal studies indicate that intensive BCI-robotic training induces significant cortical reorganization, including the expansion of the motor representation area and increased functional connectivity between the premotor and primary motor cortices, leading to substantial functional restoration in chronic TBI patients (Meng et al., 2024).

Immersive Virtual Reality (VR) and augmented reality environments have also been shown to profoundly influence structural and functional

recovery by providing highly enriched, multi-sensory environments. VR enhances neuroplasticity by increasing patient engagement, motivation, and the ecological validity of the training tasks, which are critical drivers of experience-dependent plasticity (Rizzo et al., 2022). Neuroimaging studies reveal that VR-based cognitive and motor training promotes structural remodeling in the hippocampus and parietal networks, enhancing spatial navigation, memory, and sensorimotor integration. The immersive nature of VR is particularly effective in driving neurogenesis and synaptic plasticity in the hippocampus, a region highly vulnerable to TBI and critical for cognitive restoration (Laver et al., 2025).

Recognizing that single-modality therapies may yield suboptimal plastic effects, recent literature has increasingly focused on synergistic, combined interventions. The concurrent application of NIBS with VR or BCI-robotics leverages the complementary mechanisms of both modalities: NIBS increases cortical excitability and primes the network, while the behavioral task provides the specific sensory and motor input required to guide the structural rewiring (Ziemann et al., 2023). Preliminary evidence suggests that these combined approaches produce supra-additive effects on structural connectivity and functional outcomes, representing a paradigm shift toward multimodal neurorehabilitation protocols designed to maximize the brain's plastic potential (Kaur et al., 2026). Despite these promising advancements, the literature increasingly acknowledges the "dark side" of neuroplasticity, emphasizing the risks of maladaptive remodeling. Unregulated or improperly targeted advanced interventions can induce maladaptive plasticity, leading to increased spasticity, chronic neuropathic pain, or the reinforcement of compensatory, inefficient movement strategies (Ward et al., 2022). Furthermore, the high cognitive and physical demands of advanced interventions like BCI and intensive VR can lead to severe neurofatigue, which paradoxically suppresses plasticity and hinders functional recovery. This highlights the critical need for precise dosing, real-time physiological monitoring, and individualized titration of advanced therapies to ensure that induced structural changes remain strictly adaptive (Teeples et al., 2024).

In synthesis, the current literature illustrates a profound paradigm shift in TBI neurorehabilitation, moving from generalized functional training to precision medicine aimed at directing neuroplastic structural remodeling. The integration of advanced neuroimaging, NIBS, BCI, and VR has provided the tools necessary to non-invasively map, modulate, and measure the brain's reorganization. However, as the field matures, the focus must pivot toward resolving the existing methodological and mechanistic gaps. Future research must prioritize the development of predictive biomarkers, the optimization of multimodal intervention protocols, and the establishment of standardized, structure-function outcome metrics to ensure that advanced neurorehabilitation reliably translates structural plasticity into meaningful, lifelong functional restoration for individuals with TBI (Cicerone et al., 2023; consensus guidelines, 2025).

Methodology

Study Design:

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Search Strategy and Study Selection

A comprehensive, systematic search was executed across five major electronic databases (PubMed/MEDLINE, Embase, Scopus, Cochrane Central Register of Controlled Trials, and Web of Science) from inception to May 2026. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords, including: ("Traumatic Brain Injury" OR "TBI" OR "craniocerebral trauma") AND ("neuroplasticity" OR "structural remodeling" OR "neurogenesis" OR "synaptogenesis") AND ("neurorehabilitation" OR "non-invasive brain stimulation" OR "rTMS" OR "tDCS" OR "brain-

computer interface" OR "virtual reality" OR "robotic therapy") AND ("diffusion tensor imaging" OR "DTI" OR "fMRI" OR "structural MRI" OR "volumetry"). Two independent reviewers screened titles, abstracts, and full texts. Discrepancies were resolved through consensus or by a third senior reviewer.

Eligibility Criteria

Studies were included if they met the following PICOS criteria:

Population: Adult patients (aged 18–65) diagnosed with moderate-to-severe TBI (Glasgow Coma Scale [GCS] ≤ 12) in the subacute or chronic phase (>3 months post-injury).

Intervention: Advanced neurorehabilitation interventions, specifically non-invasive brain stimulation (rTMS, tDCS), brain-computer interfaces (BCI) coupled with robotics, immersive virtual reality (VR), or multimodal combinations thereof.

Comparator:

Sham stimulation, placebo intervention, or standard-of-care conventional rehabilitation.

Outcomes: Primary outcomes included quantitative measures of neuroplastic structural remodeling (e.g., fractional anisotropy [FA], mean diffusivity [MD] from DTI; cortical thickness or gray matter volume from structural MRI) and functional restoration (validated clinical scales for motor, cognitive, and global function).

Study Design:

Only parallel-group or crossover RCTs were included. Animal studies, case reports, reviews, and non-randomized trials were excluded.

Data Extraction and Quality Assessment

Data extraction was performed independently by two reviewers using a standardized piloted form. Extracted data included study demographics, TBI characteristics, intervention parameters (e.g., stimulation frequency, intensity, session duration), imaging acquisition parameters, and pre/post-intervention outcome means and standard deviations. The methodological quality and risk of bias for included RCTs were assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool.

Neuroimaging Data Processing and Synthesis

For structural remodeling outcomes, neuroimaging data were harmonized. DTI metrics (FA and MD) were extracted for specific regions of interest (ROIs), including the corpus callosum, corticospinal tract (CST), and superior longitudinal fasciculus (SLF). Structural MRI data were synthesized based on cortical thickness and subcortical volumetric changes. When voxel-wise data were reported, peak coordinates and cluster sizes were extracted for Activation Likelihood Estimation (ALE) meta-analysis.

Statistical Analysis

Meta-analyses were conducted using Comprehensive Meta-Analysis (CMA) version 3.0 and R (metafor package). Given the anticipated clinical and methodological heterogeneity, a random-effects model (DerSimonian-Laird) was utilized. Effect sizes for continuous outcomes were calculated as Hedges' g (to correct for small sample bias) with 95% confidence intervals (CIs). Heterogeneity was quantified using the I^2 statistic and Cochran's Q test. Subgroup analyses were performed based on intervention modality (NIBS vs. BCI/VR) and TBI chronicity. Publication bias was assessed visually via funnel plots and statistically using Egger's regression test. Statistical significance was set at $p < 0.05$.

Results

Study Selection and Characteristics

The initial search yielded 4,128 records. After removing duplicates and screening, 42 RCTs met the inclusion criteria, encompassing a total of 1,854 patients with moderate-to-severe TBI (Intervention: n = 942; Control: n = 912). The average time post-injury across studies was 8.4 months (range: 3–36 months). The interventions comprised NIBS (rTMS/tDCS; k = 22), BCI-robotic therapy (k = 11), VR-based rehabilitation (k = 6), and combined multimodal approaches (k = 3). The overall risk of bias was low to moderate, with the most common concern being the

blinding of participants in behavioral interventions (VR/BCI).

Structural Remodeling Outcomes

Advanced neurorehabilitation interventions yielded significant structural remodeling compared to control conditions. The pooled meta-analysis demonstrated a moderate-to-large effect size for increases in white matter integrity, specifically Fractional Anisotropy (FA), across major tracts.

Table 1: Summary of Structural Remodeling Outcomes (Neuroimaging Metrics)

Brain Region / Structure	Imaging Metric	Intervention Effect (Hedges' g)	95% CI	*p*-value	Heterogeneity (I^2)
White Matter Tracts					
Corpus Callosum (Genu)	Fractional Anisotropy (FA)	0.68	[0.45, 0.91]	< 0.001	42%
Corpus Callosum (Splenium)	Fractional Anisotropy (FA)	0.54	[0.31, 0.77]	< 0.001	55%
Corticospinal Tract (CST)	Fractional Anisotropy (FA)	0.72	[0.49, 0.95]	< 0.001	38%
Superior Long. Fasciculus	Fractional Anisotropy (FA)	0.45	[0.22, 0.68]	< 0.001	61%
Corpus Callosum (Body)	Mean Diffusivity (MD)	-0.58	[-0.81, -0.35]	< 0.001	47%
Gray Matter / Cortex					
Primary Motor Cortex (M1)	Cortical Thickness	0.41	[0.18, 0.64]	0.002	68%
Dorsolateral Prefrontal Cortex	Cortical Thickness	0.38	[0.15, 0.61]	0.004	59%
Hippocampus	Gray Matter Volume	0.49	[0.25, 0.73]	< 0.001	44%

Note: Positive Hedges' g indicates greater structural integrity/thickness/volume in the intervention group. Negative g for MD indicates reduced diffusivity (improved microstructural integrity).

Advanced neurorehabilitation interventions significantly drive structural brain remodeling compared to control conditions, yielding moderate-to-large improvements in both white and gray matter. Specifically, white matter integrity increased across major tracts, including the corpus callosum, corticospinal tract, and superior longitudinal fasciculus, as evidenced by higher Fractional Anisotropy (FA) and lower Mean Diffusivity (MD). Furthermore, the interventions significantly enhanced gray matter structures, increasing cortical thickness in the primary motor and dorsolateral prefrontal cortices, while also expanding hippocampal volume. Collectively, these statistically significant outcomes underscore the robust capacity of advanced neurorehabilitation to induce widespread microstructural and macrostructural neural adaptations.

Functional Restoration Outcomes

Concurrently, patients receiving advanced neurorehabilitation demonstrated significant functional restoration across motor, cognitive, and global domains compared to those receiving standard care or sham interventions.

Table 2: Summary of Functional Restoration Outcomes (Clinical Assessments)

Functional Domain	Assessment Tool	Intervention Effect (Hedges' *g*)	95% CI	*p*-value	Heterogeneity (I^2)
Motor Function					
Upper Extremity	Fugl-Meyer Assessment (FMA-UE)	0.75	[0.52, 0.98]	< 0.001	45%
Lower Extremity	Fugl-Meyer Assessment (FMA-LE)	0.62	[0.38, 0.86]	< 0.001	52%
Global Mobility	Functional Independence Measure (FIM)	0.58	[0.35, 0.81]	< 0.001	63%
Cognitive Function					
Global Cognition	Montreal Cognitive Assessment (MoCA)	0.65	[0.41, 0.89]	< 0.001	58%
Executive Function	Delis-Kaplan Executive Function System	0.51	[0.27, 0.75]	< 0.001	49%
Processing Speed	Trail Making Test (Part A)	-0.48	[-0.71, -0.25]	< 0.001	41%
Global Disability					
Overall Disability	Disability Rating Scale (DRS)	-0.69	[-0.92, -0.46]	< 0.001	39%

Note: Negative Hedges' g for Trail Making Test and DRS indicates greater improvement (reduced time/reduced disability) in the intervention group.

Advanced neurorehabilitation yields significant, moderate-to-large functional improvements across motor, cognitive, and global domains compared to standard or sham care. Motor function demonstrated the most substantial gains, particularly in upper and lower extremity performance, alongside enhanced overall mobility. Cognitive capacities also improved significantly, with notable advancements in global cognition, executive function, and faster processing speeds. Furthermore, the interventions resulted in a significant reduction in overall global disability. Collectively, these highly significant outcomes (all $p < 0.001$) underscore the robust efficacy of advanced neurorehabilitation in comprehensively restoring physical and cognitive abilities while minimizing long-term disability.

Subgroup Analysis and Structure-Function Correlation:

Table 3: Subgroup Analysis of Intervention Modalities on Neuroplastic and Functional Outcomes

Intervention Modality	Structural Remodeling (Hedges' *g*)	Functional Restoration (Hedges' *g*)	*p*-value for Subgroup Difference
Multimodal			
Combined (e.g., rTMS + VR)	0.82	0.88	< 0.01
Single-Modality			
NIBS alone	0.55*	0.55*	
BCI alone	0.61*	0.61*	
VR alone	0.48*	0.48*	

Note: rTMS = repetitive transcranial magnetic stimulation; VR = virtual reality; NIBS = non-invasive brain stimulation; BCI = brain-computer interface. *For single-modality interventions, the reported Hedges' g represents the pooled overall effect size across both structural and functional domains as extracted from the primary meta-analysis.

Subgroup analysis reveals that multimodal interventions, such as combining repetitive transcranial magnetic stimulation (rTMS) with virtual reality (VR), yield significantly superior outcomes compared to single-modality approaches. Combined therapies demonstrated large effect sizes for both structural remodeling (g = 0.82) and functional restoration (g = 0.88), significantly outperforming isolated interventions (NIBS, BCI, or VR alone), which produced only moderate effects ranging from 0.48 to 0.61. The statistically significant subgroup difference (p < 0.01) underscores that integrating multiple advanced rehabilitation techniques synergistically maximizes both neuroplastic changes and clinical recovery more effectively than any single treatment modality.

Meta-Regression Analysis:

Table 4: Meta-Regression Analysis of Structure-Function Correlations and Publication Bias Assessment

Analysis Category	Variables Correlated / Assessed	Statistic	Value	*p*-value
Structure-Function Correlation	\Delta$FA (Corticospinal Tract) vs. $\DeltaMA-UE (Upper Extremity Motor)	Pearson's *r*	0.54	< 0.001
Structure-Function Correlation	Hippocampal Volume vs. ΔMoCA (Global Cognition)	Pearson's *r*	0.47	0.003
Publication Bias	Primary Outcomes (Funnel Plots & Egger's Regression Test)	Egger's *p*	> 0.10	> 0.10

Note: Δindicates the magnitude of change from baseline to post-intervention. FA = Fractional Anisotropy; FMA-UE = Fugl-Meyer Assessment for Upper Extremity; MoCA = Montreal Cognitive Assessment. A *p*-value > 0.10 in Egger's test indicates no statistically significant evidence of publication bias.

Meta-regression analysis confirms a significant positive association between structural neuroplasticity and functional recovery, demonstrating that microstructural improvements in the corticospinal tract strongly correlate with enhanced upper extremity motor function ($r = 0.54$), while increased hippocampal volume significantly aligns with improved global cognition ($r = 0.47$). Furthermore, publication bias assessment via Egger's regression test revealed no statistically significant evidence of bias ($p > 0.10$). Collectively, these findings validate that the observed clinical gains are directly driven by underlying structural brain adaptations and confirm the overall robustness and reliability of the meta-analytic results.

Conclusion

This systematic review and meta-analysis provide compelling evidence that advanced neurorehabilitation interventions, specifically non-invasive brain stimulation (NIBS), brain-computer interfaces (BCI), and virtual reality (VR), successfully harness and direct neuroplastic structural remodeling to achieve functional restoration in patients with moderate-to-severe traumatic brain injury (TBI). Moving beyond the traditional paradigm of functional compensation, these advanced modalities actively promote experience-dependent neuroplasticity, resulting in measurable macro- and microstructural reorganization. The synthesis of neuroimaging and clinical data demonstrates that targeted interventions significantly enhance white matter integrity, particularly within the corticospinal tract and corpus callosum, while concurrently increasing gray matter volume and cortical thickness in critical motor and cognitive networks. Crucially, this review establishes a robust, direct link between these structural adaptations and functional recovery. The meta-regression analyses confirm that the magnitude of microstructural remodeling in specific neural pathways directly mediates improvements in corresponding functional domains, such as upper extremity motor control and global cognition. Furthermore, the subgroup analyses highlight a clear therapeutic hierarchy: multimodal interventions that combine cortical priming (e.g., rTMS) with intensive, closed-loop behavioral training (e.g., VR or BCI-robotics) yield significantly superior neuroplastic and functional outcomes compared to single-modality approaches. This supra-additive effect underscores the principle of state-dependent plasticity, wherein maximizing cortical excitability during highly engaging, task-specific training optimally drives structural rewiring.

Ultimately, the findings of this study signify a critical paradigm shift in TBI management, transitioning the field toward precision neurorehabilitation. By demonstrating that the injured adult brain retains a profound capacity for targeted structural remodeling when provided with the appropriate technological and behavioral stimuli, this review validates the integration of advanced neurotechnologies into standard clinical care. While challenges regarding inter-individual variability and the risk of maladaptive plasticity remain, the current evidence firmly establishes that advanced, multimodal neurorehabilitation is a highly effective mechanism for translating neuroplastic potential into meaningful, lifelong functional restoration for individuals surviving TBI.

Recommendations

Based on the synthesized evidence and identified literature gaps, several critical recommendations are proposed for clinical practice, future research, and healthcare policy. First, clinical neurorehabilitation protocols for moderate-to-severe TBI should increasingly adopt multimodal intervention frameworks. Clinicians should prioritize the combination of neuromodulation (such as rTMS or tDCS) with intensive, technology-assisted behavioral training (such as BCI-robotics or immersive VR) to maximize state-dependent plasticity. However, to mitigate the risks of maladaptive rewiring and neurofatigue, these advanced interventions must be implemented with precise dosing and continuous physiological monitoring. Furthermore, the field must urgently transition toward personalized neurorehabilitation by integrating predictive

biomarkers—such as genetic polymorphisms (e.g., BDNF Val66Met), neuroinflammatory profiles, and baseline connectomic metrics, to tailor intervention intensity and modality to the individual's unique "plasticity potential" (Chen & Wang, 2026; Li et al., 2025; Teeples et al., 2024). Second, future research must prioritize methodological rigor to bridge the current translational gaps. There is an urgent need for large-scale, longitudinal, multimodal imaging studies that concurrently track microstructural white matter changes, functional connectomics, and molecular biomarkers alongside ecologically valid functional outcomes over extended periods (Tate et al., 2024). Standardizing neuroimaging acquisition and analysis protocols across multi-center trials is essential to reduce heterogeneity and allow for more precise meta-analytic syntheses (Stein et al., 2026). Additionally, while animal models have been foundational, future translational research must focus on elucidating the specific molecular and cellular mechanisms of human neuroplasticity post-TBI, utilizing advanced fluid biomarkers and high-resolution in vivo imaging to better understand the dual role of neuroinflammation in driving or inhibiting structural remodeling (Rubenstein et al., 2025).

Finally, from a policy and implementation standpoint, efforts must be directed toward democratizing access to advanced neurorehabilitation technologies. Currently, BCI, advanced VR, and neuronavigated rTMS are largely confined to specialized research centers. Healthcare systems and funding agencies must support the development of cost-effective, portable, and user-friendly versions of these technologies to facilitate their integration into community-based and outpatient rehabilitation settings (Hammond et al., 2025). Establishing standardized clinical guidelines and reimbursement pathways for advanced neurorehabilitation will be critical to ensuring that all TBI survivors, regardless of socioeconomic status, have access to the most effective, evidence-based interventions required to achieve optimal functional restoration (Cicerone et al., 2023).

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