Cureus
Part of SPRINGER NATURE

Open Access Review Article

Harnessing Neuroplasticity for Rehabilitation: The Combined Effects of Experiential Music, Intermittent Fasting, and Daily Cognitive-Mindfulness Practices

Review began 10/07/2026
Review ended 10/12/2026
Published 10/20/2026

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DOI: 10.7759/cureus.118230

Agapios Nistor [1], George Fotakopoulos [2], Mary A. Vasilopoulou [3], Vasileios K. Kavouridis [2], Nikolaos Foroglou [2]

1. Independent Research, Holy Metropolis Veria, Veria, GRC 2. Department of Neurosurgery, AHEPA (American Hellenic Educational Progressive Association) University Hospital, Aristotle University of Thessaloniki, Thessaloniki, GRC 3. Institute of Chemical Biology, National Hellenic Research Foundation, Athens, GRC

Corresponding author: Mary A. Vasilopoulou, mary.vasilopoulou@hotmail.com

Abstract

Neuroplasticity, the capacity of the central nervous system to reorganize its structure and function in response to experience, is the biological basis of recovery in neurorehabilitation. It has been hypothesized that combining several experience-dependent interventions may produce additive or synergistic benefits, but this hypothesis has rarely been tested directly. This narrative review, based on a structured search of PubMed/MEDLINE (Medical Literature Analysis and Retrieval System Online), Scopus, and the Cochrane Library, examines the individual and potential combined contributions of three non-pharmacological adjunctive interventions to rehabilitation in adults with acquired brain injury, principally stroke and traumatic brain injury (TBI): experiential music-based practice, intermittent fasting (IF), and daily cognitive-mindfulness training, defined here as mindfulness-based practice combined with structured cognitive training. Music-based interventions recruit distributed sensorimotor, limbic, reward, and executive networks, and randomized trials and meta-analyses in stroke and TBI report benefits for gait, upper-limb function, communication, cognition, and mood, with mostly low-to-moderate certainty of evidence. IF upregulates brain-derived neurotrophic factor (BDNF) signaling and synaptic plasticity in animal models, but human data are inconsistent, no trials exist in rehabilitation populations, and malnutrition and frailty raise safety concerns. Mindfulness-based practice has been associated with improved attentional and emotional regulation and with a moderate reduction of fatigue after stroke, TBI, and multiple sclerosis, whereas cognitive training has low-certainty evidence for short-term attentional benefits. Multidomain lifestyle trials support structured multidomain programs, but because they lack single-domain arms, they do not show that combined interventions outperform single interventions; factorial trials provide more direct, though limited, evidence of additive effects. We propose a tentative, hypothesis-generating model in which these interventions may converge on shared neurotrophic and network-level mechanisms, and we discuss timing, safety, treatment burden, and the factorial trial designs needed to test it. The available evidence is insufficient to support clinical recommendations for the combined use of these three interventions.

Categories: Neurology, Physical Medicine & Rehabilitation, Integrative/Complementary Medicine
Keywords: brain-derived neurotrophic factor, cognitive training, default mode network, intermittent fasting, mindfulness, music-based intervention, neuroplasticity, neurorehabilitation, stroke rehabilitation, traumatic brain injury

Introduction And Background

Neurorehabilitation is based on the principle that the adult human brain retains a substantial capacity throughout life to reorganize its structure and function in response to experience [1,2]. This property, known as neuroplasticity, underlies the recovery of motor, cognitive, and emotional functions following stroke, traumatic brain injury (TBI), and other neurological conditions. It is shaped by mechanisms such as synaptic remodeling, long-term potentiation, and, in specific contexts, adult neurogenesis [3,4], although the extent of hippocampal neurogenesis in the adult human brain remains debated [5,6].

Historically, rehabilitative strategies have tended to target a single functional domain in isolation, such as motor training following stroke or cognitive training following TBI. However, an emerging body of evidence indicates that the brain's large-scale functional networks, including the Default Mode Network (DMN), the Salience Network (SN), and the Central Executive Network (CEN), operate as an integrated system [7,8]. In brief, the DMN, centered on the medial prefrontal and posterior cingulate cortices, is most active during internally directed thought and self-referential processing; the SN, anchored in the anterior insula and dorsal anterior cingulate cortex, detects behaviorally relevant events and switches activity between the other two networks; and the CEN, comprising the dorsolateral prefrontal and posterior parietal cortices, supports working memory, attention, and goal-directed control [7,8].

Neurological injury frequently disrupts the interactions among these networks [8,9], which has led to the hypothesis that interventions engaging several of these networks simultaneously might produce broader and more durable neuroplastic changes than single-domain approaches [10]. This remains a hypothesis: few trials have directly compared combined interventions with single-domain interventions, and the available evidence is critically examined here. Two types of combined benefit should be distinguished. An additive effect means that the benefit of a combined intervention equals the sum of the benefits of its components, whereas a synergistic effect means that the combined benefit exceeds that sum; the latter can only be demonstrated by a statistically significant positive interaction in a factorial design [11]. Showing that a combined intervention is superior to usual care, or to one of its components, establishes neither.

This narrative review examines three non-pharmacological interventions with distinct yet potentially convergent mechanisms of action on rehabilitative neuroplasticity: experiential music-based practice, intermittent fasting (IF), and daily cognitive-mindfulness training. Each intervention has an independent evidence base linking it to neuroplastic change; considered collectively, they may support an integrated, multimodal approach to neurorehabilitation. This review synthesizes the available literature on each intervention, incorporating recent (2022-2026) clinical and mechanistic studies alongside foundational literature. It also discusses the timing of interventions relative to the post-injury window of heightened plasticity, safety considerations, potential interactions among the three components, and the trial designs required to test their combined use. Finally, it proposes a tentative integrative framework while explicitly noting the current absence of trials testing the specific combination of all three interventions.

For clarity, the three interventions are defined as follows. Experiential music-based practice refers to structured, regular engagement with music that the patient experiences attentively or actively, including the receptive listening of self-selected music, singing, and instrument- or rhythm-based exercises, delivered either alone or embedded in conventional therapy; therapist-delivered techniques, such as rhythmic auditory stimulation and melodic intonation therapy, are discussed separately because they differ in mechanisms and therapeutic goals. IF refers to eating patterns that alternate periods of voluntary abstinence from caloric intake with periods of unrestricted eating, such as time-restricted eating, alternate-day fasting, or the 5:2 regimen. Daily cognitive-mindfulness training refers to two related but distinct components that may be delivered within the same daily session: mindfulness-based practice (e.g., focused-attention and open-monitoring meditation or mindfulness-based stress reduction (MBSR)), which trains attentional and emotional self-regulation, and cognitive training, defined as the structured, repeated practice of tasks targeting specific cognitive domains, such as attention, working memory, and executive function. Because these two components have been evaluated largely separately, their evidence is presented separately in this review.

These three interventions were selected for three reasons. First, each is non-pharmacological, low in cost, and potentially self-administered, so that it can be added to, rather than replace, conventional rehabilitation. Second, each targets a different level of experience-dependent plasticity: sensorimotor and reward-driven engagement (music), systemic metabolic and neurotrophic signaling (IF), and top-down attentional and emotional regulation (mindfulness and cognitive training). Third, each addresses factors that limit the effectiveness of task-specific training, such as low motivation, fatigue, mood disturbance, and limited therapy intensity. They are not proposed as alternatives to established approaches, such as therapeutic exercise, task-specific motor retraining, or technology-assisted rehabilitation, whose evidence base is considerably stronger [12-14], but as candidate adjuncts whose contribution would need to be demonstrated on top of such treatments. Importantly, the three interventions differ substantially in their mechanisms of action, level of clinical evidence, and applicability to neurological populations: music-based interventions have been evaluated in randomized trials and meta-analyses in stroke and TBI; mindfulness-based interventions and cognitive training have more limited trial data in neurological populations; and IF is supported mainly by preclinical studies and by human studies in healthy, metabolic, or cognitively impaired populations, with no trials in neurorehabilitation.

The target population of this review is adults undergoing rehabilitation after acquired brain injury, principally stroke and TBI. Evidence from other populations, such as healthy volunteers, older adults at risk of dementia, and patients with mild cognitive impairment or multiple sclerosis, is considered only as indirect evidence and is identified as such; neurodegenerative disorders are not a target population of the proposed model. Throughout the review, we distinguish between three levels of evidence: biological markers (e.g., circulating brain-derived neurotrophic factor (BDNF)), neuroimaging findings (e.g., structural or functional connectivity changes), and clinically meaningful rehabilitation outcomes, such as motor function, gait and balance, language, cognition, mood, fatigue, and functional independence. Changes at the first two levels do not necessarily translate into functional recovery.

Review

Literature search strategy and study selection

This narrative review was informed by a structured literature search of PubMed/MEDLINE (Medical Literature Analysis and Retrieval System Online), Scopus, and the Cochrane Library for articles published in English between January 2000 and September 2026. Search terms combined keywords and, where applicable,

Medical Subject Headings (MsSH) for the population (e.g., "stroke", "traumatic brain injury", "acquired brain injury", and "neurorehabilitation") with terms for each intervention ("music therapy", "music-based intervention", "rhythmic auditory stimulation", and "melodic intonation therapy"; "intermittent fasting", "time-restricted eating", and "caloric restriction"; "mindfulness", "meditation", "mindfulness-based stress reduction", and "cognitive training") and for mechanistic outcomes ("neuroplasticity", "brain-derived neurotrophic factor", "functional connectivity", and "default mode network"). The reference lists of relevant reviews were also hand-searched, and foundational books and articles were included when they provided essential conceptual or mechanistic background.

Priority was given to systematic reviews and meta-analyses, randomized controlled trials, and large controlled studies in adults with acquired brain injury. Smaller clinical studies, studies in non-neurological populations, and preclinical studies were included when they provided mechanistic insight or when clinical data in rehabilitation populations were lacking, and they are explicitly identified as such in the text. Multidomain lifestyle trials were included because they are frequently cited in support of combined interventions. Non-peer-reviewed sources and studies without outcomes relevant to neuroplasticity or rehabilitation were excluded. Study selection was performed by consensus among the authors. Consistent with the narrative design, no formal risk-of-bias assessment or quantitative synthesis was performed; the certainty of the evidence is therefore described qualitatively, drawing on the certainty ratings reported in the cited systematic reviews where available.

The remainder of the review is organized into three parts: a synthesis of the literature on the neurobiological mechanisms and on each intervention (Literature Synthesis); a critical discussion of the evidence for combined interventions and of the limitations of this review (Critical Discussion); and a hypothetical integrative model with its clinical implementation and the trials required to test it (Proposed Integrative Neurorehabilitation Model).

Literature synthesis

Neurobiological Foundations of Experience-Dependent Neuroplasticity

At the cellular level, experience-dependent plasticity is mediated by activity-dependent changes in synaptic strength, including long-term potentiation, as well as by neurotrophin signaling, particularly through BDNF and its high-affinity receptor, tropomyosin receptor kinase B (TrkB) [3,15]. BDNF/TrkB signaling promotes neuronal survival, synaptic remodeling, and adult neurogenesis in the hippocampus [4,15], and is considered a key molecular pathway through which diverse experience-dependent interventions, including physical exercise and dietary energy restriction, may exert their effects [16,17]. Genetic variation also modulates this pathway: the common BDNF Val66Met polymorphism reduces activity-dependent BDNF secretion and has been associated with differences in hippocampal function and episodic memory [18]; whether this polymorphism influences the response to rehabilitation has not been directly established, and it is mentioned here only as a potential source of inter-individual variability.

At the network level, psychological and neurological insults are frequently associated with disrupted interactions among the DMN, SN, and CEN, a phenomenon sometimes described as a triple-network imbalance. Such dysregulation may manifest as impaired self-referential processing, altered salience detection, and diminished executive control [7,8]. After TBI, for example, altered DMN connectivity and impaired SN-mediated regulation of the DMN have been linked to attentional and executive deficits [9]. Accordingly, effective rehabilitation may involve not only restoring function within an individual damaged brain region but also re-regulating the dynamic interactions among these large-scale networks [8,10].

Across rehabilitative modalities, several principles appear to influence the extent of neuroplastic adaptation, including the intensity and repetition of the stimulus, its behavioral salience and reward value, and the degree of active, task-specific engagement required from the individual [12,19]. These principles provide a common conceptual framework against which music-based practice, IF, and cognitive-mindfulness training can be compared and, potentially, combined.

The relationship between these neurobiological mechanisms and clinical recovery is best established for motor function after stroke. In animal models, the recovery of skilled forelimb use is accompanied by dendritic and synaptic remodeling and by the reorganization of motor maps in the peri-infarct cortex, and these changes depend on task-specific training [12,20]. In humans, motor recovery after stroke reflects an interaction between spontaneous biological repair and training-induced, experience-dependent plasticity [13], and after TBI, altered DMN connectivity and SN-DMN interactions have been associated with attentional and executive performance [9]. However, for most of the molecular and network-level changes discussed in this review, including changes in BDNF signaling and in resting-state connectivity, a direct link with clinically meaningful outcomes, such as motor function, balance, cognitive recovery, or functional independence, has not been demonstrated. Such changes should therefore be regarded as potential mechanisms rather than as surrogate markers of recovery.

Timing: Windows of Heightened Plasticity After Brain Injury

The brain's responsiveness to training does not remain constant after injury. In animal models of stroke, the first weeks after ischemia are characterized by the upregulation of growth-promoting genes, increased dendritic spine turnover, and axonal sprouting in the peri-infarct cortex. Rehabilitative training initiated during this period produces greater benefits than training begun later [13,20]. In humans, most spontaneous motor recovery occurs within the first months after stroke, and training during this period appears to interact with endogenous repair processes [13]. These observations have two implications for the interventions discussed here. First, adjunctive strategies intended to enhance plasticity are most likely to be effective when delivered during this early window, provided that they are safe and feasible in the subacute setting. Second, interventions with different safety profiles may need to be introduced in a staggered manner: music listening and brief mindfulness exercises have been delivered early after stroke [21,22], whereas dietary energy restriction is unlikely to be appropriate during the acute and early subacute phases, when malnutrition is common and independently associated with poor outcome [23].

Experiential Music-Based Practice and Neuroplastic Reorganization

Music engages a uniquely distributed network of neural systems, including auditory, motor, limbic, and executive regions, within a single emotionally salient activity, distinguishing it from most unimodal rehabilitative techniques [10,19]. Music also engages the mesolimbic reward system: positron emission tomography has shown striatal dopamine release during the anticipation and experience of peak emotional responses to music [24], a mechanism through which musical activities may enhance motivation and adherence during repetitive training. A systematic review of randomized controlled trials using neuroimaging outcomes found that music- and dance-based interventions were associated with structural and functional changes in regions relevant to perception and memory among individuals at risk of dementia, as well as in regions supporting language, emotional regulation, and motor control among patients with acute and chronic stroke [25]. A 2024 scoping review of 49 studies (1,663 participants), including randomized and non-randomized studies as well as case reports, found that 73% of the included studies reported positive results for executive functioning or emotional well-being after stroke; active interventions were the most frequently used, and the authors emphasized the need for standardized protocols and outcome measures [26].

Music-based interventions are heterogeneous, and four main approaches should be distinguished because they differ in mechanisms of action and therapeutic objectives. Receptive music listening, in which the patient attentively listens to (often self-selected) music, mainly targets arousal, mood, attention, and memory. Active music making, such as singing or playing instruments, additionally requires motor execution and auditory-motor coupling and is used to train motor, cognitive, and communicative functions. Rhythmic auditory stimulation (RAS) is a therapist-delivered technique in which an external rhythmic beat is used to entrain the timing of movement, primarily gait, whereas melodic intonation therapy uses intoned, rhythmically tapped phrases to facilitate speech production in nonfluent aphasia. The findings summarized below are therefore reported by type of intervention and should not be generalized as evidence supporting a single therapeutic approach. Active musical engagement has also been associated with improvements in speech production, mood, and treatment adherence [19]. A Cochrane review of 29 trials involving 775 participants concluded that music interventions may be beneficial for gait, the timing of upper-limb movements, communication, and quality of life after stroke; the quality of evidence was moderate for improvements in gait velocity and stride length with RAS, and low or very low for most other outcomes [27]. A recent systematic review and meta-analysis of music-based interventions after brain damage included 90 studies, 41 of which were meta-analyzed, and found significant pooled benefits for gait, upper-extremity function, communication, cognition, and emotional, behavioral, and social outcomes, but not for quality of life; heterogeneity was substantial for several outcomes (I^2 up to 94% for gait), interventions and durations varied widely, and no formal certainty-of-evidence rating was reported [28].

Receptive music listening has also been studied in the early post-stroke period. In a single-blind randomized controlled trial of 60 patients with middle cerebral artery stroke, daily listening to self-selected music during the first months after stroke improved recovery of verbal memory and focused attention more than listening to audiobooks or receiving no listening material. The music group also experienced less depressed and confused mood than the control group [21]. A subsequent voxel-based morphometry analysis of the same cohort found greater increases in gray matter volume in frontal and limbic regions among participants in the music group; these increases correlated with improvements in cognition and mood [29]. Furthermore, a pooled analysis of two randomized trials suggested that vocal music may particularly support verbal memory and language recovery [30].

In a randomized controlled study involving 116 patients with stroke, daily listening to experiential/traditional music combined with acupuncture during standard post-stroke rehabilitation was associated with greater improvement in upper-limb function than either music listening alone or standard care alone [31]. Because the trial did not include an acupuncture-only arm, it cannot isolate the contribution of each component or demonstrate a synergistic interaction; it does, however, support the feasibility of combining music with other adjunctive modalities. Similarly, among patients with stroke, a rehabilitation exercise program accompanied by daily experiential music listening was associated with greater cognitive and motor recovery gains, and a more favorable mood profile than standard care without music [32]. In a randomized trial of 79 patients with post-stroke aphasia, the addition of daily experiential music listening to

standard care was associated with a higher rate of aphasia recovery than standard care alone [33].

In patients with moderate-to-severe TBI, a music-based neurological rehabilitation protocol improved executive function and set-shifting. These improvements were accompanied by changes in gray matter volume in the right inferior frontal gyrus and altered connectivity within large-scale resting-state networks; both changes correlated with clinical improvement [34].

Taken together, this evidence suggests that music-based practice may simultaneously engage sensorimotor, cognitive, and affective systems, thereby offering an efficient means of activating the multiple networks implicated in post-injury network dysregulation [19,21,25-27,31-34]. These clinical findings, however, derive mainly from receptive listening and from RAS and should not be extrapolated to all forms of music-based intervention. However, the certainty of the clinical evidence is generally low to moderate; most trials are small and single-center, and blinding of participants is rarely possible [26,27]. Mechanistic studies in humans remain limited, and standardized protocols and dosage recommendations are lacking. Further research is needed to determine the dose, timing, and specific musical parameters that promote neuroplasticity.

Intermittent Fasting, Metabolic Switching and BDNF-Mediated Plasticity

IF comprises a range of protocols, including alternate-day fasting, time-restricted eating, and religiously observed fasting, such as the Ramadan model [35,36]. These protocols induce a metabolic shift from glucose-based to ketone-based energy metabolism during the fasting period [16]. In animal models, this metabolic switching is associated with the upregulation of BDNF/TrkB signaling, which promotes hippocampal neurogenesis and enhances long-term potentiation at hippocampal synapses [16,37]. In rodent models of focal cerebral ischemia, prior dietary energy restriction or IF reduced brain damage and improved functional outcome, although these effects were attenuated with advancing age [38]. Importantly, these preclinical studies examined neuroprotection when energy restriction preceded the injury, rather than its use as a post-injury rehabilitation adjunct.

A systematic review of human studies examining calorie restriction or IF and BDNF identified a heterogeneous pattern of findings: among the 16 eligible studies, conducted in healthy individuals and in patients with metabolic disorders, five reported a significant increase in BDNF, five reported a significant decrease, and six reported no significant change [35]. Among the five studies of Ramadan fasting in the review, three reported a reduction and two an increase in BDNF. Outcomes varied according to the protocol, population, and metabolic status, and none of the included studies involved patients undergoing neurological rehabilitation. This heterogeneity indicates that, unlike the more consistent preclinical findings, the translation of IF-induced neurotrophic effects into measurable cognitive benefits in humans cannot yet be assumed and should be interpreted cautiously [35]. Interpretation is further complicated by the fact that circulating BDNF is largely stored in and released from platelets, so that serum concentrations may not reflect brain BDNF [39]. A more recent narrative review reached a similar conclusion, noting that, although preclinical evidence robustly demonstrates IF-induced hippocampal neurogenesis and synaptic plasticity through BDNF- and cAMP response element-binding protein (CREB)-dependent pathways, human evidence involving individuals with mild cognitive impairment and other neurocognitive disorders remains limited [40]. In a small randomized trial in older adults with obesity and insulin resistance, both an eight-week 5:2 IF regimen and a healthy-living diet improved cognition, with IF producing greater improvement in executive function [41]. Similarly, in a 12-week assessor-blinded pilot randomized trial in 46 older adults with mild cognitive impairment, 15:9 time-restricted eating improved Montreal Cognitive Assessment scores compared with ad libitum eating ($\beta = 1.70$ points; 95% CI 0.46 to 2.94; $P = 0.007$), although the small sample and short follow-up limit the strength of this evidence [42]. Whether such effects extend to patients recovering from brain injury is unknown.

By comparison, the effect of physical exercise on circulating BDNF is more consistent: a meta-analysis found that a single bout of exercise produced a moderate increase in BDNF and that regular exercise intensified this acute response [17]. Because exercise is already a core component of rehabilitation, any additional neurotrophic contribution of IF would need to be demonstrated against an exercise-based background.

Several considerations limit the applicability of IF in neurorehabilitation. Malnutrition is present in a substantial proportion of patients at the time of stroke admission and is independently associated with poorer survival and functional outcome [23]. Dysphagia, sarcopenia, frailty, diabetes treated with insulin or sulfonylureas, and the need to take medications with food may make prolonged fasting unsafe, and fasting-related fatigue or hypoglycemia could reduce engagement in therapy [36]. Accordingly, if IF is investigated in rehabilitation settings, it should be restricted to medically stable patients in the chronic phase and to mild protocols, such as time-restricted eating, with nutritional monitoring and scheduling of therapy sessions during the fed state.

Nonetheless, the proposed mechanistic pathway, through which a bioenergetic challenge upregulates neurotrophic signaling associated with synaptic plasticity and neuronal resilience, offers a plausible physiological rationale for evaluating IF as an adjunctive, metabolism-based component of a broader

neuroplasticity-oriented rehabilitation strategy, provided that its use is individualized and medically supervised [16,37,40]. At present, this rationale is a hypothesis that requires testing in clinical trials rather than a basis for clinical recommendation. The effectiveness and safety of IF as an adjunct to neurorehabilitation have not been established, and IF should therefore not be used in rehabilitation populations outside controlled clinical trials.

Daily Cognitive-Mindfulness Practice and Prefrontal-Limbic Re-regulation

As defined above, daily cognitive-mindfulness training comprises two distinct components, mindfulness-based practice and cognitive training, which have largely been studied separately. The mechanistic and clinical evidence for mindfulness-based practice is reviewed first, followed by the evidence for cognitive training in neurological populations.

Structural brain changes after mindfulness training have been reported in some studies but not confirmed in others. In a small controlled study, an eight-week MBSR program was associated with increased gray matter concentration in the left hippocampus, posterior cingulate cortex, temporo-parietal junction, and cerebellum [43]. However, a pooled analysis of two randomized controlled trials including 218 meditation-naive participants found no evidence of structural change after MBSR compared with either an active or a waitlist control [44], whereas a meta-analysis of 11 randomized trials (581 participants) identified a single cluster of structural change associated with attention and pain processing [45]. Structural effects of short mindfulness programs should therefore be regarded as uncertain. Neuroimaging studies of experienced meditators indicate that sustained contemplative practice is associated with altered patterns of attentional monitoring and strengthened connectivity between prefrontal regulatory regions and limbic structures involved in emotional reactivity [46,47].

Mechanistically, mindfulness-based practices have been proposed to influence the same large-scale networks disrupted by neurological or psychological injury. They may enhance the regulatory role of the CEN while reducing hyperreactivity within the SN, thereby facilitating more adaptive engagement of the DMN in self-referential processing [46,48]. A 2024 systematic review concluded that MBSR in particular was associated with changes in brain regions involved in emotional processing and sensory perception, together with improvements in anxiety, depression, and pain [49]. Whether these changes reflect improved integration among the DMN, SN, and CEN remains to be established.

Evidence from neurological populations is more limited but clinically relevant. A systematic review of mindfulness-based interventions after transient ischemic attack and stroke identified four studies and reported a positive trend for anxiety, depression, mental fatigue, blood pressure, perceived health, and quality of life, without evidence of harm [22]. A meta-analysis of four randomized trials involving 257 patients with stroke, TBI, or multiple sclerosis found a moderate effect of mindfulness-based interventions on fatigue (standardized effect size -0.37; 95% CI -0.58 to -0.17) [50]. Because post-stroke and post-traumatic fatigue frequently limit participation in therapy, fatigue may be one of the most practically relevant targets of mindfulness in rehabilitation. The cognitive training component has a separate evidence base. A Cochrane review of six randomized trials (223 participants) of cognitive rehabilitation for attention deficits after stroke found an improvement in divided attention immediately after treatment (low-certainty evidence), but no convincing evidence of persisting effects or of benefits for global attention, daily function, mood, or quality of life [51]. In older adults with mild cognitive impairment, computerized cognitive training added to physical exercise improved global cognition compared with exercise alone in the SYNERGIC (SYNchronizing Exercises, Remedies in GaIt and Cognition) trial [52]. Whether combining cognitive training and mindfulness practice within the same daily session yields benefits beyond either component alone has not been tested.

In neurorehabilitation, improved top-down regulation may yield practical benefits, including reduced anxiety, greater emotional resilience, and increased patient engagement in therapy, all of which may influence functional outcomes independently of any direct effect on the primary injury [22,48,50]. As with the other interventions considered in this review, the evidence base for mindfulness-based practice in structural neurorehabilitation, as distinct from general cognitive and emotional well-being, remains at a relatively early stage. Larger controlled trials involving clinical rehabilitation populations are therefore needed [22,50]. Key clinical evidence discussed in this review is summarized in Table *1*.

Intervention	Study (Author)	Design and population	Main findings	Key limitations
Music	Magee et al. [27]	Cochrane review; 29 trials, 775 patients with acquired brain injury	Possible benefit for gait (RAS), timing of upper-limb movements, communication, and quality of life after stroke	Mostly low or very low certainty; small trials
Music	Särkämö et al. [21]	Single-blind RCT; 60 patients with MCA stroke	Daily music listening improved verbal memory, focused attention, and mood vs. audiobooks or no material	Single center; modest sample
Music	Pfeiffer et al. [26]	Scoping review; 49 studies, 1,663 stroke survivors	73% of studies reported positive effects on executive function or emotional well-being	Mixed designs, including case reports
Music	Syros et al. [31]	RCT; 116 stroke patients, three arms (music, music + acupuncture, standard care)	Music + acupuncture associated with greater upper-limb improvement than music alone or standard care	No acupuncture-only arm; synergy cannot be inferred
IF	Alkurd et al. [35]	Systematic review; 16 human studies (healthy and metabolic populations)	BDNF increased in 5, decreased in 5, unchanged in 6 studies	Calorie restriction and IF pooled; no rehabilitation populations
IF	Arumugam et al. [38]	Rodent focal ischemia models	Prior energy restriction reduced brain damage and improved outcome; effect attenuated with age	Preclinical; restriction preceded injury
Mindfulness	Kral et al. [44]	Two pooled RCTs; 218 healthy adults	No structural brain change after MBSR vs. active or waitlist control	Healthy volunteers; 8-week program
Mindfulness	Ulrichsen et al. [50]	Meta-analysis; 4 RCTs, 257 patients with stroke, TBI, or MS	Moderate reduction in fatigue (ES -0.37)	Few, heterogeneous trials
Multidomain	Ngandu et al. [53]	RCT; 1,260 at-risk older adults	Multidomain intervention superior to general health advice on cognition	No single-domain arm
Multidomain	Baker et al. [54]	RCT; 2,111 at-risk older adults	Structured multidomain program superior to self-guided multidomain program (0.243 vs. 0.213 SD/year)	Both arms multidomain; no single-domain arm
Multidomain	Montero-Odasso et al. [52]	Fractional factorial RCT; 175 adults with MCI	Exercise + cognitive training superior to exercise alone (ADAS-Cog-13, d = 0.39); vitamin D added no benefit	Secondary outcome not significant; not a rehabilitation population

TABLE 1: Summary of key clinical evidence discussed in this review.

RCT: randomized controlled trial; RAS: rhythmic auditory stimulation; MCA: middle cerebral artery; IF: intermittent fasting; BDNF: brain-derived neurotrophic factor; MBSR: mindfulness-based stress reduction; TBI: traumatic brain injury; MS: multiple sclerosis; ES: effect size; MCI: mild cognitive impairment; SD: standard deviation; ADAS-Cog-13: Alzheimer's Disease Assessment Scale-Cognitive Subscale, 13 items

Certainty of the Evidence for Each Intervention

The certainty of the evidence differs substantially across the three interventions (Table *1*). For music-based interventions, randomized trials and meta-analyses in stroke and TBI are available, but the certainty is low to moderate for most outcomes, with moderate-certainty evidence limited to gait parameters with RAS [27,28]. For mindfulness-based interventions, evidence in neurological populations comes from a few small trials and is of low certainty, with the most consistent signal for fatigue [22,50], and the evidence for cognitive training after stroke is of low to very low certainty [51]. For IF, the evidence relevant to neurorehabilitation is indirect, consisting of preclinical studies and small trials in non-neurological or cognitively impaired populations, and should be regarded as very low certainty for rehabilitation outcomes [35,38,40]. These differences should be taken into account when the three interventions are considered as candidate adjuncts.

Critical discussion

Interpretation of Multidomain and Factorial Trials: Additive Versus Synergistic Effects

This reasoning is often supported by references to multidomain lifestyle trials; however, these studies

should be interpreted with caution. The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial randomized 1,260 at-risk older adults to either a two-year multidomain intervention comprising diet, exercise, cognitive training, and vascular risk monitoring or to general health advice [53]. The trial found a statistically significant benefit of the multidomain intervention on a comprehensive neuropsychological test battery (between-group difference in the change of the total score per year: 0.022; 95% CI 0.002 to 0.042; P = 0.030). The US POINTER (U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk) trial randomized 2,111 at-risk older adults to two multidomain interventions that differed in structure, intensity, and accountability; the structured program, which combined physical activity, the Mediterranean-DASH (Dietary Approaches to Stop Hypertension) Intervention for Neurodegenerative Delay (MIND) diet, cognitive and social engagement, and cardiometabolic risk monitoring, produced a modestly greater improvement in global cognition than the self-guided program (0.243 vs. 0.213 standard deviations (SDs) per year; difference: 0.029 SDs per year; 95% CI 0.008 to 0.050; P = 0.008), with consistent effects across age, sex, ethnicity, heart-health status, and APOE ε4 genotype [54]. Neither trial included single-domain comparison arms. The FINGER trial therefore demonstrates that a multidomain program is superior to general health advice [53], while the US POINTER trial demonstrates that a more structured and intensive multidomain program is superior to a less structured one [54]. However, neither trial demonstrates that combining domains is more effective than any single domain, and neither was conducted in a rehabilitation population. Moreover, although both differences were statistically significant, they were small, and their clinical meaningfulness for individual patients remains uncertain.

More direct evidence comes from factorial designs, which allow the contribution of each component to be estimated. In the SYNERGIC trial, 175 older adults with mild cognitive impairment were randomized to five arms combining aerobic-resistance exercise, computerized cognitive training, and vitamin D, or their respective sham or placebo counterparts, for 20 weeks. Compared with exercise alone, the combination of exercise and cognitive training improved the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13) score (mean difference: -1.45 points; 95% CI -2.70 to -0.21; P = 0.02; d = 0.39), whereas the addition of vitamin D provided no benefit, and changes in the ADAS-Cog-Plus were not significant [52]. These findings indicate that some combinations may yield additive benefit, although superiority of the combination over a single component does not, by itself, establish a synergistic interaction, while also illustrating that adding a component does not necessarily improve outcomes. Comparable factorial data are unavailable for music, IF, or mindfulness.

Similarly, a recent narrative review summarized evidence that physical and emotional interventions, including mindfulness and cognitive training, modulate neuroplasticity-related outcomes across a range of neurological conditions, albeit with considerable heterogeneity across studies [10].

These distinctions are methodologically important. A combined intervention that outperforms usual care, or a more intensive multidomain program that outperforms a less intensive one, demonstrates neither an additive nor a synergistic effect of its components. An additive contribution can be inferred only when the effect of each component is estimated separately, as in factorial designs, and a synergistic effect additionally requires a statistically significant positive interaction indicating that the combined effect exceeds the sum of the individual effects [11]. In addition, statistically significant differences should be distinguished from clinically meaningful effects, particularly when, as in the multidomain trials discussed above, the between-group differences are small.

From Neurobiological Markers to Clinically Meaningful Outcomes

Across the literature reviewed, three levels of evidence should be distinguished. Biological markers, such as circulating BDNF, are indirect and, in the case of serum BDNF, may not reflect brain concentrations [39]; changes in these markers have not been shown to predict functional recovery after IF or mindfulness-based interventions in neurological populations. Neuroimaging findings, such as changes in gray matter volume or resting-state connectivity, have been correlated with clinical improvement in some music-based studies after stroke and TBI [29,34], but such correlations do not establish that the imaging changes mediate recovery. Clinically meaningful outcomes, such as motor function, gait, language, cognition, mood, fatigue, and functional independence, are the relevant endpoints for rehabilitation. At present, evidence at this level exists mainly for music-based interventions (gait, upper-limb function, communication, and cognition) [27,28], for mindfulness-based interventions (fatigue and emotional outcomes) [22,50], and, to a limited extent, for cognitive training (short-term divided attention) [51], whereas no such evidence exists for IF in rehabilitation populations.

Limitations of This Review

This review has several limitations that warrant explicit acknowledgment. First, no published study to date has directly examined the combination of experiential music, IF, and daily cognitive-mindfulness practice within a single rehabilitation protocol. Accordingly, the integrative model proposed here should be regarded as a conceptual synthesis rather than an evidence-based clinical recommendation. Second, the evidence supporting each individual intervention is heterogeneous in quality, with varied study designs, small sample

sizes, and inconsistent outcome measures, particularly regarding IF-related BDNF changes in humans [35]. Third, most mechanistic data linking these interventions to neuroplasticity are derived from neuroimaging correlates or animal models, and direct causal evidence in clinical rehabilitation populations remains limited [16,19,25]. Fourth, as a narrative rather than systematic review, the selection of studies may be subject to bias; although the literature search is described above, no formal risk-of-bias assessment or quantitative synthesis was performed, and the effect sizes reported here are those of the original studies; in addition, several of the clinical music studies cited were conducted by members of the authors' group [31-33], which readers should take into account.

Proposed integrative neurorehabilitation model (hypothesis)

Toward an Integrative Multimodal Model of Rehabilitation

Considered individually, experiential music, IF, and daily cognitive-mindfulness practice may each engage, through distinct proximal mechanisms, a partially overlapping set of distal targets: BDNF/TrkB-dependent synaptic plasticity, hippocampal integrity, and the re-regulation of the DMN-SN-CEN network triad [8,15,16,29,48]. It is important to emphasize that this convergence is a theoretical hypothesis that has not been directly demonstrated in neurorehabilitation populations: direct evidence showing that music or mindfulness increases BDNF in humans remains limited, no study has examined the effects of IF on DMN-SN-CEN connectivity after brain injury, and the convergence proposed here is inferred from separate bodies of literature. If confirmed, this convergence would suggest that the three interventions may act complementarily rather than redundantly: music provides a highly salient, multimodal sensorimotor and emotional stimulus; IF provides a metabolic priming signal for neurotrophic signaling; and daily mindfulness practice provides sustained, low-intensity training of the top-down attentional and emotional regulatory systems needed to consolidate gains from the other two modalities [16,19,46].

On this basis, we propose a tentative integrative model that combines experiential music, IF, and daily cognitive-mindfulness practice within a structured rehabilitation program, with the explicit aim of engaging complementary neuroplastic mechanisms simultaneously. The model is intended as an adjunct to, and not as a replacement for, established neurorehabilitation practices such as task-specific motor training and therapeutic exercise, and any claim that a combined protocol is more effective than individual interventions would require direct comparison with these established practices [12,14]. The model is intended for adults recovering from stroke or TBI, in whom disrupted interactions among the DMN, SN, and CEN have been described [9]. If additional benefits exist, they would be expected primarily in motor function (e.g., gait and upper-limb function), cognitive recovery (attention, memory, and executive function), mood and fatigue, and, ultimately, functional independence and quality of life. Beyond its hypothesized neurobiological effects, such a program might also support psychological adaptation after injury, including the processes described as post-traumatic growth [55], as well as the social and emotional factors known to influence neuroplasticity and well-being [56]; these outcomes have not yet been examined in this context.

Potential Interactions and Conflicts Among the Three Interventions

Combining interventions does not guarantee additive effects, and components may interfere with one another. Fasting-related fatigue, irritability, or reduced concentration, which are common during adaptation to a fasting regimen [36], could diminish engagement in demanding musical or cognitive tasks. Conversely, music may increase motivation during repetitive training [19,24], and mindfulness practice might help patients tolerate hunger-related discomfort and adhere to a dietary regimen, but these potential positive interactions have not been tested. The total time burden of three daily interventions added to conventional therapy may also reduce adherence, particularly among patients experiencing post-stroke or post-traumatic fatigue [50]. Practical integration might therefore involve embedding music within existing physical, occupational, or speech therapy sessions, delivering brief mindfulness exercises before or after therapy, and, where appropriate, applying time-restricted eating so that therapy sessions take place in the fed state. These suggestions are offered as hypotheses for testing rather than as clinical recommendations.

Clinical Implementation: Timing, Safety, Treatment Burden, and Individualization

The implementation of the proposed model in clinical practice would face several practical challenges. Patients in neurorehabilitation vary widely in motor, cognitive, communicative, and sensory capacities, and each component would need to be adapted to the individual's functional abilities: for example, receptive music listening or RAS rather than active instrument playing in patients with severe upper-limb paresis; brief, guided, and frequently repeated mindfulness exercises with simplified instructions in patients with attentional or language deficits; and cognitive training tasks graded to baseline performance. Treatment burden is a major concern, because rehabilitation programs are already time-intensive and post-stroke and post-traumatic fatigue are common [50]; the components should therefore be embedded within existing therapy sessions wherever possible rather than added as separate sessions, adherence should be monitored, and caregivers may need to be involved in patients with cognitive impairment.

With regard to timing and safety, music listening and brief mindfulness exercises appear to be feasible from

the early subacute phase [21,22], whereas IF should be considered only in medically stable patients in the chronic phase, after the assessment of nutritional status, swallowing function, comorbidities (particularly diabetes treated with insulin or sulfonylureas, sarcopenia, and frailty), medications, and overall functional capacity, and only under medical and dietetic supervision [23,36]. Within these constraints, the staged introduction of the components, beginning with music and cognitive-mindfulness training and adding IF only when appropriate, would allow tolerance to be assessed and would reduce the risk of overburdening patients.

Future Directions: Testing the Proposed Model

Future research should prioritize adequately powered, controlled trials that directly compare single-domain and combined multimodal protocols. Full or fractional factorial designs (for example, a 2 × 2 × 2 design for music, IF, and mindfulness) allow the main effect of each component and their interactions to be estimated within a single trial and are more resource-efficient than separate two-arm trials [11,52]. Such trials should incorporate standardized neuroimaging and neurotrophic biomarkers, and account for individual variability in fasting tolerance, musical background, baseline mindfulness experience, and BDNF genotype [18]. The primary outcome of such a trial should be a clinically meaningful functional measure selected according to the target population, for example, the upper-extremity Fugl-Meyer Assessment or gait speed after stroke, or a measure of functional independence, with neuroimaging and neurotrophic markers as secondary, mechanistic outcomes. Because, in a 2 × 2 factorial design, an interaction of the same magnitude as a main effect requires approximately four times the sample size to detect with the same power, trials should be powered primarily for the main effects, with interactions treated as exploratory unless a specific interaction is the primary hypothesis [11]. Feasibility in heterogeneous rehabilitation populations could be improved by stratifying randomization according to injury type, time since injury, and baseline impairment, and by first conducting a pilot feasibility study. Intervention timing must also be considered: because IF is proposed only for medically stable patients in the chronic phase, a full 2 × 2 × 2 design including IF would be applicable only to chronic-phase populations, whereas the music and cognitive-mindfulness components could be tested in a separate 2 × 2 factorial trial during the subacute phase.

Particular caution is warranted before recommending IF for clinically vulnerable rehabilitation populations, given the heterogeneity of its metabolic effects and the need for individualized medical supervision [23,35]. Key design elements are summarized in Table *2*.

Design element	Suggested approach	Rationale
Trial design	Full or fractional factorial (e.g., 2 × 2 × 2 for music, IF, mindfulness)	Estimates the effect of each component and their interactions [11, 52]
Population	Medically stable stroke or TBI survivors; IF arms restricted to the chronic phase, excluding malnutrition, dysphagia, frailty, and insulin- or sulfonylurea-treated diabetes	Safety and the high prevalence of malnutrition after stroke [23, 36]
Timing	Music and mindfulness from the subacute phase; IF only after medical stabilization	Early window of heightened plasticity [13, 20]
Control conditions	Active controls matched for time and attention (e.g., audiobooks, health education)	Separates specific from non-specific effects [21, 44]
Clinical outcomes	Motor (e.g., Fugl-Meyer Assessment, gait speed), cognitive, language, mood, fatigue, and quality-of-life measures	Domains with preliminary evidence for each intervention [27, 50]
Mechanistic outcomes	Resting-state connectivity of DMN, SN, and CEN; structural MRI; BDNF with BDNF genotyping	Tests the proposed convergence while accounting for platelet-derived serum BDNF and genetic variability [9, 18, 39]
Safety and adherence	Weight, nutritional status, glucose, falls, adverse events; session attendance and dietary logs	IF-related risks and time burden of combined protocols [23, 36]

TABLE 2: Suggested design elements for future trials of combined music, intermittent fasting, and mindfulness interventions.

IF: intermittent fasting; TBI: traumatic brain injury; DMN: default mode network; SN: salience network; CEN: central executive network; MRI: magnetic resonance imaging; BDNF: brain-derived neurotrophic factor

Conclusions

Experiential music-based practice, IF, and daily cognitive-mindfulness training may each engage overlapping neurotrophic and network-level substrates of experience-dependent neuroplasticity through distinct mechanisms. The evidence supporting each intervention is uneven: music-based interventions have the most clinical data in stroke and TBI; mindfulness has modest evidence for improving fatigue and emotional outcomes; cognitive training has low-certainty evidence for short-term attentional benefits; and IF remains supported mainly by preclinical findings and inconsistent human biomarker data, with no trials in rehabilitation populations. Multidomain lifestyle trials support the value of structured multidomain programs but do not demonstrate that combining domains is superior to single-domain interventions, and direct evidence for the combined use of these three interventions in rehabilitation is lacking.

The proposed convergence of these interventions on BDNF-mediated synaptic plasticity and on the re-regulation of the DMN-SN-CEN network triad remains a theoretical hypothesis that has not been demonstrated in neurorehabilitation populations; it provides a rationale for future research, not for clinical recommendations. Any additional benefit of a combined protocol would need to be demonstrated in adequately powered factorial trials conducted on top of, and compared against, established neurorehabilitation practices, using clinically meaningful outcomes such as motor function, cognitive recovery, and functional independence. Finally, IF should not be applied in neurological rehabilitation outside controlled studies; any future use would require careful assessment of nutritional status, comorbidities, medications, and overall functional capacity and should be limited to medically stable patients under medical supervision.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mary A. Vasilopoulou, Agapios Nistor, George Fotakopoulos, Vasileios K. Kavouridis, Nikolaos Foroglou

Critical review of the manuscript for important intellectual content: Mary A. Vasilopoulou, George Fotakopoulos, Vasileios K. Kavouridis, Nikolaos Foroglou

Acquisition, analysis, or interpretation of data: Agapios Nistor

Drafting of the manuscript: Agapios Nistor

Supervision: George Fotakopoulos, Nikolaos Foroglou

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors used Grammarly (Superhuman Platform Inc. (formerly Grammarly Inc.), San Francisco, California, United States) solely for spelling and grammar checks. The tool was not used to generate scientific content, to search, select, or interpret the literature, or to draw conclusions. All suggestions were reviewed by the authors, who take full responsibility for the content of this article.

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