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THE IMPACT OF PHYSICAL ACTIVITY AND NON-PHARMACOLOGICAL INTERVENTIONS ON NEUROPLASTICITY IN EPILEPSY: MECHANISMS, EVIDENCE, AND CLINICAL IMPLICATIONS

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ABSTRACT

Epilepsy is a chronic brain disorder characterized by recurrent epileptic seizures and long-lasting alterations in neuronal excitability and connectivity. Although pharmacological and surgical interventions currently play a primary role in epilepsy treatment, growing evidence indicates that non-pharmacological approaches-such as brain stimulation, cognitive training, and physical exercise-can induce neuroplastic mechanisms underlying this group of disorders, which may have important clinical implications.

The aim of this review is to summarize experimental and clinical evidence regarding the effects of non-pharmacological techniques on brain plasticity in epilepsy. Numerous animal studies suggest that physical activity-both aerobic and resistance training-may reduce seizure frequency, improve cognitive functions, and stimulate hippocampal neurogenesis. Physical exercise has also been shown to promote synaptic reorganization, modulate GABAergic and glutamatergic systems, improve mitochondrial function and cerebral perfusion, and increase the expression of neurotrophic factors such as BDNF and IGF-1. However, further research is needed to identify biomarkers of neuronal plasticity and optimize the effectiveness of these interventions. This review aims to highlight the importance of a multidirectional- including non-pharmacological-therapeutic strategy in epilepsy management.

KEYWORDS

Epilepsy, Neuroplasticity, Physical Activity, Non-Pharmacological Interventions, BDNF, Neurostimulation, Cognitive Training, Mindfulness, Rehabilitation

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Methodology

This review was prepared as a narrative synthesis with elements of a semi-systematic literature review, aiming to integrate mechanistic, experimental, and clinical data on the effects of physical activity and non-pharmacological interventions on neuroplasticity in epilepsy. A comprehensive search was conducted in PubMed, Scopus, Web of Science, and ScienceDirect, covering the years 2000–2025. Included were original experimental and clinical studies on the effects of physical activity or non-pharmacological interventions on neuroplasticity in epilepsy, as well as review articles and meta-analyses published in peer-reviewed journals.

The extracted information was grouped into four thematic categories:

1. neuroplasticity mechanisms in epilepsy,
2. effects of physical activity,
3. effects of cognitive and behavioral interventions,
4. multimodal approaches.

Introduction

In recent years, interest in the role of neuroplasticity in the development and course of neurological disorders-including epilepsy-has been increasing. Neuroplasticity comprises the ability of the central nervous system to undergo structural and functional remodeling in response to environmental stimuli. These processes determine not only the development of epileptogenic foci (so-called maladaptive plasticity) but also the potential for regeneration and restoration of proper neuronal connections after injury (1).

Epilepsy affects approximately 65 million people worldwide. Although antiepileptic drugs effectively control the disease in many patients, about 30% remain drug-resistant, which significantly worsens prognosis and encourages the search for new therapeutic strategies targeting neuroplastic mechanisms (2).

Increasing attention is given to the potential of brain stimulation, mindfulness techniques, cognitive training, and physical activity, which may influence hippocampal neurogenesis and modulate the expression of neurotrophic factors (3).

The aim of this paper is to review and synthesize current data on neuroplasticity mechanisms in epilepsy and evaluate the impact of physical activity and non-pharmacological interventions on their modulation.

Neuroplasticity in Epilepsy: Mechanisms and Dysfunctions

Neuroplasticity refers to the nervous system's ability to reorganize synaptic connections in response to external stimuli, injury, or learning (4). In epilepsy, these processes may support the compensation of lost neuronal networks after seizures, but they may also contribute to the formation of new epileptogenic foci by reinforcing excessive excitability (1). Thus, neuroplasticity exerts a complex and heterogeneous influence on the course of the disease.

Epileptogenesis involves neuronal network remodeling, modulation of neurotrophic factor expression, and changes in dendritic spine density (5).

Epilepsy is associated with complex neurophysiological processes such as oxidative stress, neuroinflammation, neuronal network reorganization, neurotransmitter imbalance, and alterations in neurotrophic factor expression. A better understanding of these mechanisms may support the development of new treatments targeting the foundations of epileptogenesis.

The main neurotransmitters involved in epilepsy are glutamate and GABA. In epilepsy, the balance between them is disrupted, with decreased GABA receptor expression and increased activity of NMDA and AMPA receptors (6), which lowers the seizure threshold.

Inflammation and oxidative stress also play key roles, damaging neuronal membranes. Microglial and astroglial activation and the release of pro-inflammatory cytokines (IL-1β, TNF-α) modulate neuronal excitability and disrupt neuroplasticity (7). Increased expression of BDNF in the neocortex and hippocampus enhances excitability through TrkB-mediated MAPK/ERK pathway activation (8). NGF and IGF-1 also contribute to epileptogenesis.

Two types of neuroplasticity are particularly relevant in epilepsy: functional (which may be compensatory or pathological) and maladaptive, which increases seizure susceptibility and complicates treatment. Functional neuroplasticity enables other brain regions to assume lost functions but can also destabilize neuronal networks (9).

In temporal lobe epilepsy (TLE), reorganization of connections in the hippocampus, prefrontal cortex, and cingulate gyrus, as well as shifts in lateralization of language and memory functions, have been observed (10).

Maladaptive neuroplasticity results from chronic synaptic hyperactivity, excessive glutamate release, and loss of inhibitory neurons, contributing to the formation of persistent “epileptogenic loops” (11).

Understanding these processes opens pathways toward new therapeutic interventions. Regular physical activity, cognitive stimulation, and transcranial direct current stimulation (tDCS) may help restore the balance between neuronal excitation and inhibition and promote beneficial reorganization of brain networks (12).

Non-pharmacological Interventions in Epilepsy

Growing evidence indicates that non-pharmacological interventions such as physical activity, cognitive training, brain stimulation, relaxation techniques, and dietary interventions influence neuroplasticity and neurotrophic factor expression, potentially improving the clinical course of epilepsy by reducing seizure frequency and enhancing cognitive functions (3).

Cognitive rehabilitation supports long-term synaptic potentiation in patients with epilepsy by increasing BDNF levels (13). Clemens' studies using fMRI have demonstrated correlations between attention, memory,

and executive-function training in TLE patients and increased activation in the cingulate gyrus and prefrontal cortex, translating into improved neuropsychological outcomes (14). This suggests that neuropsychological interventions may stimulate functional neuroplasticity and activate alternative neuronal pathways (15).

Neurostimulation techniques with potential therapeutic applications in epilepsy include transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and neurofeedback. Neurofeedback enables patients to consciously modulate their own brain activity. Studies show seizure reductions of 50–70% in some patients, along with improved concentration and memory (16). tDCS is a non-invasive method of modulating cortical excitability using weak direct currents (1–2 mA). Repeated tDCS sessions induce lasting plastic changes (17), and anodal or cathodal stimulation over epileptogenic foci has reduced seizure frequency by 40–50% (18).

rTMS induces postsynaptic potentials through alternating magnetic fields. Low-frequency stimulation (≤1 Hz) can reduce cortical excitability and epileptogenic activity while promoting neuronal network reorganization (19). Cognitive-behavioral therapy (CBT) and relaxation techniques positively influence hypothalamic–pituitary–adrenal axis regulation and reduce oxidative stress (20). Emotional disorders such as anxiety and depression frequently co-occur in epilepsy and further impair neuroplasticity. Mindfulness-based stress reduction (MBSR) programs have been shown to reduce seizure frequency and improve sleep quality and cognitive functioning in epilepsy patients (21). The ketogenic diet has documented antiepileptic and neuroplastic effects. Increased ketone body production stimulates BDNF and CREB expression, reduces oxidative stress, and improves mitochondrial energy efficiency (22). In animal models, the ketogenic diet increased dendritic spine density in the hippocampus and improved spatial memory (23).

Physical Activity in Epilepsy

There is now strong scientific evidence that physical activity exerts neuroprotective, pro-plastic, and anti-seizure effects in patients with epilepsy (3).

Both resistance and aerobic training exert multidirectional molecular effects supporting neuronal plasticity. Aerobic exercise increases BDNF concentrations in both serum and hippocampus, promoting dendritic spine growth and synaptogenesis (24).

Physical activity also lowers cortisol levels, reducing chronic HPA axis activation (25), improves the GABA/glutamate balance (26), and enhances hippocampal neurogenesis, which may protect against cognitive deficits (27). It improves cerebral perfusion, glucose metabolism, circadian rhythm regulation, and sleep quality. These changes translate into clinical benefits: better cognitive functioning, reduced seizure frequency, improved well-being, and higher quality of life (3).

Importantly, studies have not shown an increased risk of seizures during exercise; rather, a higher seizure threshold has been observed (28).

Types of activity with the strongest documented pro-plastic effects:

- aerobic training (walking, running, swimming)
- resistance training
- moderate-intensity interval training

Biomarkers of Neuroplasticity in Epilepsy

A key aspect of implementing non-pharmacological therapies is the reliable assessment of their effectiveness using neuroplasticity biomarkers (29). These include biochemical, electrophysiological, and neuroimaging markers.For example, studies involving aerobic exercise show that increased BDNF levels coincide with improved hippocampal volume and enhanced P300 amplitude, indicating coherent adaptive changes (13, 24).Biochemical markers include NGF, IGF-1, BDNF, synaptophysin, PSD-95, and pro-inflammatory cytokines. BDNF is the most widely studied marker due to its central role in neurogenesis. Clinical studies have shown that regular physical activity increases plasma BDNF levels, correlating with improved cognitive performance in epilepsy patients (12, 13). IGF-1 also supports cognitive functions, and increases in IGF-1 after exercise may further enhance neuronal plasticity (24).Structural markers such as synaptophysin and PSD-95 are reduced in epilepsy models, while brain-activating interventions partially normalize their expression (30). Cytokines (IL-1β, TNF-α, HMGB1) negatively affect neuroplasticity (31), whereas moderate physical activity or the ketogenic diet reduce their levels (22).EEG enables non-invasive evaluation of functional plasticity-related changes. Shifts toward alpha and beta power may indicate improved neuronal synchronization (32). Changes in evoked potentials—such as increased P300 amplitude after

cognitive training or tDCS-reflect enhanced cognitive processing (17).Neuroimaging biomarkers include MRI, DTI, and fMRI. Van Praag's work showed that physical activity improves white-matter integrity and protects against hippocampal volume loss (27). DTI studies revealed increased fractional anisotropy (FA) after aerobic training, suggesting enhanced neuronal connectivity (24).fMRI allows assessment of functional connectivity patterns.

After interventions such as meditation or neurostimulation, normalization of default-mode and frontotemporal network connectivity has been reported (20).

Magnetic resonance spectroscopy (MRS) studies have shown improved GABA/Glu ratios following physical therapy or ketogenic diet (23).

Clinical Implications

Non-pharmacological interventions have therapeutic potential as adjunctive treatments in epilepsy (33). Regular physical activity may reduce seizure frequency and improve cognitive functions (28). Interventions such as aerobic training, meditation, or tDCS are important components that should be considered alongside pharmacological and surgical treatment (17, 20).

Rehabilitation programs combining exercise, diet, and cognitive training produce better outcomes in quality of life and stress reduction (15).

Treatment must be individualized and tailored to comorbidities, age, epilepsy type, and cognitive and physical abilities (5). For example, patients with temporal lobe epilepsy may particularly benefit from combined memory training and moderate aerobic exercise (14). Multidisciplinary collaboration—among neurologists, physiotherapists, psychologists, dietitians, and occupational therapists—is essential for safe and effective therapy (3).

Conclusions

Evidence indicates that physical activity, cognitive training, diet, and relaxation techniques promote neuroplasticity in epilepsy. Integrating these approaches with pharmacological treatment may positively influence disease course (34).

However, the lack of standardized methods for neuroplasticity assessment limits cross-study comparisons. Small clinical sample sizes and the scarcity of randomized controlled trials restrict firm conclusions (1). Large-scale studies are needed to enable the implementation of effective interventions into clinical practice.

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