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The influence of physical activity on changes in brain structure in patients with multiple sclerosis

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Abstract

Introduction: Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system that lads to brain atrophy, demyelination, and functional reorganization. Physical activity has been proposed as a non-pharmacological intervention with potential neuroprotective effects. Magnetic resonance imaging (MRI) enables objective assessment of exercise-related brain changes in patients with MS.

Purpose of the work: This study aimed to summarize the effects of physical activity on brain structure and microstructure in patients with multiple sclerosis, based on MRI findings.

Materials and methods: A narrative review of cross-sectional and longitudinal studies was conducted using PubMed, Scopus and Google Scholar. Original research and review articles published between 2006 and 2025 were identified using the following keywords: multiple sclerosis, neurological rehabilitation, brain atrophy and magnetic resonance imaging. The reviewed studies examined various forms of physical activity, such as aerobic exercise, endurance exercise, balance exercise, and multimodal rehabilitation programs, and their effectiveness based on imaging studies.

Results: Most studies reported no significant effect of physical activity on global brain volume or overall brain atrophy. However, physical activity was associated with preservation or increased hippocampal volume, increased cortical thickness in motor regions, improved white matter integrity, and more efficient functional organization of motor networks. Spectroscopy findings suggested enhanced neuronal integrity without increased inflammatory activity.

Conclusions: Physical activity in multiple sclerosis is associated with favorable regional and microstructural brain changes despite minimal effects on global brain atrophy, supporting its potential neuroprotective role and positive impact on cognitive function.

Keywords

Multiple sclerosis, neurological rehabilitation, brain atrophy, magnetic resonance imaging

1. Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system that affects the brain and spinal cord. It is of the leading causes of non-traumatic neurological disability in young adults. The disease is characterized by a complex interplay of inflammatory process, focal and diffuse demyelination, axonal loss and progressive neurodegeneration. Multiple sclerosis can progress in various ways, but these pathological processes evolve over time and contribute not only to relapse and acute neurological deficits but also to long term disability accumulation. Some patients may experience a single episode of attack or a radiologically isolated syndrome, depending on whether they present clinical symptoms or typical MRI findings. Consequently, multiple sclerosis leads to structural and functional brain changes, including global and regional brain atrophy, white matter disruption, and reorganization of functional networks[1]. Progressive disease is not only visible on imaging studies but also causes symptoms such as cognitive, motor and sensory impairments[5]. Magnetic resonance imaging (MRI) plays a central role in the assessment of disease activity and progression, providing sensitive markers of neurodegeneration beyond conventional clinical measures[1].

Despite advances in disease-modifying therapies, neurodegeneration and brain atrophy often progress independently of inflammatory activity, highlighting the need for complementary non-pharmacological interventions[5]. Physical activity has emerged as a promising therapeutic strategy due to its well-documented benefits on cardiovascular fitness, mobility, fatigue, and quality of life in patients with MS. Aerobic exercise stimulates the growth of new capillaries and influences neurons by increasing the number and length of dendritic connections. Cardiovascular exercise improves cognitive function, including memory and multitasking. In the general population, regular physical activity is associated with increased brain volume,

improved white matter integrity, and enhanced synaptic plasticity, suggesting potential neuroprotective effects[2].

In recent years, an increasing number of studies have investigated the impact of physical activity on brain structure and function in MS using advanced MRI techniques, including structural MRI, functional MRI, diffusion tensor imaging, magnetic resonance spectroscopy, and magnetic resonance elastography. However, the results remain heterogeneous, with inconsistent findings regarding global brain atrophy and more consistent evidence for regional and microstructural changes.

Therefore, a comprehensive synthesis of MRI-based evidence is warranted to clarify the extent, consistency, and clinical significance of exercise-induced brain changes in individuals with multiple sclerosis. Such an integrative approach may help identify specific brain regions and imaging markers that are most responsive to physical activity and inform the development of targeted, evidence-based rehabilitation and lifestyle interventions aimed at mitigating neurodegeneration and improving long-term outcomes in multiple sclerosis.

2. MRI indicators of the progression of multiple sclerosis

Magnetic resonance imaging (MRI) is a fundamental tool for monitoring disease progression in multiple sclerosis (MS). In studies investigating the effects of physical activity, MRI is primarily used to assess markers of neurodegeneration and structural integrity rather than acute inflammatory activity. This methodological focus reflects both the biological mechanisms targeted by exercise and the practical limitations of intervention-based research.

Global and regional brain atrophy represent the most robust and reproducible MRI indicators of long-term disease progression in MS. Measures such as normalized brain volume, brain parenchymal fraction, and regional gray matter volumes are sensitive to cumulative neuroaxonal loss and correlate strongly with physical disability and cognitive impairment[3]. As physical activity is hypothesized to exert neuroprotective rather than anti-inflammatory effects, these markers are particularly relevant outcome measures in exercise intervention studies.

In contrast, gadolinium-enhancing lesions reflect transient blood–brain barrier disruption and acute inflammatory activity. Their occurrence is sporadic, highly variable over time, and strongly influenced by disease-modifying therapies[4]. Consequently, gadolinium-enhancing lesions are less suitable as primary outcome measures in physical activity studies, which

typically involve relatively small sample sizes and intervention periods lasting weeks to months. The low incidence of new enhancing lesions in clinically stable or treated patients further limits the statistical power to detect exercise-related effects.

White matter lesion burden assessed on T2-weighted or FLAIR imaging is often included as a secondary outcome; however, changes in lesion load evolve slowly and show limited sensitivity to short-term behavioral interventions. For this reason, many studies incorporate advanced MRI techniques, such as diffusion tensor imaging, magnetic resonance spectroscopy, functional MRI, and magnetic resonance elastography, to capture subtle microstructural, metabolic, and functional changes that may precede or occur independently of macroscopic lesion formation[4].

Overall, the emphasis on brain atrophy and advanced MRI metrics in physical activity research reflects a shift toward evaluating neurodegenerative processes and neural plasticity, which are more plausibly modifiable by exercise than acute inflammatory lesion activity.

3. The influence of physical activity on general brain atrophy in people with multiple sclerosis

Long-term interventional studies consistently indicate that physical activity has no statistically significant effect on global brain atrophy in people with multiple sclerosis. In a 24-week randomized controlled trial, Langeskov-Christensen et al. recruited 84 participants, aged 18-65 years. Participants were divided into two groups: an exercise group and a group without lifestyle modification. The study group performed high-intensity progressive aerobic exercise (PAE) twice a week for 24 weeks. Training sessions consisted of interval and continuous training sessions. There was no significant difference between the exercise and control groups in percent brain volume change (PBVC), nor were there differences in cortical volume or deep gray matter volume. A positive trend was observed for a 0.22 percentage point increase in the brain parenchyma fraction (BPF) in the PAE group over 24 weeks. The authors speculated that extending training to 48 weeks could induce significant changes in BPF. Improvements in cardiorespiratory fitness were also demonstrated and were associated with increased total gray matter (GMPF) on MRI[5].

Orban et al. reached similar conclusions regarding the effects of aerobic exercise. Their study assessed the effect of 30-minute training sessions performed four times per week for eight weeks. This study showed no changes in total brain volume or brain atrophy using phosphate-

enhanced magnetic resonance spectroscopy. Despite the lack of imaging changes, aerobic exercise positive affect on markers of energy production. The changes were accompanied by improvements in cognitive function and physical performance in these inviduals[6].

Similar results were reported by Leavitt et al. in an analysis of a 12-week program of progressive aerobic training program. The study did not demonstrate a significant effect on global brain volume or cerebral cortex volume, although regional changes were observed[7].

These findings are further supported by a longer, 48-week intervention study by Riemenschneider et al. In this case, the participants were individuals with early multiple sclerosis, defined as less than two years of disease duration. They performed twice-weekly supervised exercise sessions throughout the study. No differences were found between the control and treatment groups in overall brain atrophy rates. The study also found no effect of exercise on lesion burden, including lesion number and volume[8]. This suggests that even early initiation and prolonged duration of physical activity may be insufficient to modify diffuse neurodegenerative processes measurable at the whole-brain level.

Block et al., in a cross-sectional study assessing habitual physical activity levels over a month, found no common association with global brain volume, despite reporting beneficial effects on specific brain regions[9].

Taken together, current MRI evidence indicates that physical activity does not exert a robust or reproducible effect on general brain atrophy in people with multiple sclerosis. The lack of observable global volumetric change likely reflects the slow progression of whole-brain atrophy, limited sensitivity of global measures, and the primarily neuroprotective rather than regenerative mechanisms associated with physical activity.

4. The influence of physical activity on hippocampal volume in people with multiple sclerosis

In contrast to global brain volume measurements, hippocampal volume appears to be more sensitive to the effects of physical activity in people with multiple sclerosis. Several cross-sectional and longitudinal MRI studies indicate that both regular physical activity and structured exercise interventions are associated with maintaining or increasing hippocampal volume. Evidence from cross-sectional studies suggests a positive association between physical activity levels and hippocampal volume. A cross-sectional study comparing physically active and inactive individuals with MS during leisure time found that participants

who engaged in regular physical activity maintained larger hippocampal volume, independent of disability level and cognitive status[10]. These findings support the idea that regular physical activity can mitigate atrophy of the hippocampus, a structure particularly susceptible to neurodegenerative processes in MS.

Similar associations were observed in the study by Negaresh et al., which used a lifetime assessment of physical activity. Participants first reported their physical activity levels and then wore an accelerometer during walking hours for seven days. Based on the self-assessment, participants were classified into inactive/moderately active or high-intensity physical activity groups. Individuals with high levels of physical activity had significantly larger hippocampal and overall brain volume. These effects were observed despite the lack of significant changes in other deep gray matter structures. This findings suggests that the hippocampus may be particularly responsive to physical activity, possibly because exercise increases perfusion and attenuates atrophy. This may contribute to better cognitive performance, particularly memory and learning, over time[11].

Interventional studies further support these observations. In the previously mentioned study, Leavitt et al. demonstrated that a 12-week aerobic training program consisting of 30 minutes of training three times a week resulted in a significant 16.5% increase in hippocampal volume. This change was associated with significant improvements in memory function [7] . Similar conclusions were drawn from a randomized controlled trial in which the group undergoing 12 weeks of low-intensity resistance training showed maintenance of hippocampal volume, whereas the control group, which underwent treadmill walking training, showed progressive atrophy [12] . Advanced MRI techniques, such as magnetic resonance elastography, also allow hippocampal viscoelasticity to be examined. This technique was used in a study assessing the effects of 12 weeks of aerobic treadmill walking performed three times per week. Sandroff et al. demonstrated increased hippocampal stiffness and decreased hippocampal viscosity. These changes indicate improved tissue integrity and reduced neurodegenerative processes, which may contribute to improved memory and learning despite the lack of an increase in hippocampal volume [13] . Overall, the available MRI evidence consistently indicates that physical activity is associated with preservation or improvement of hippocampal volume in people with multiple sclerosis. The previously cited MRI data indicate that physical activity is related to the maintenance or improvement of ng hippocampal volume in individuals with MS. Physical activity may also influence hippocampal microstructure. Hippocampal volume appears to be a more sensitive marker for assessing the neuroprotective effects of physical activity than global brain atrophy. These effect may be related to neuroplasticity, synaptic

remodelling, and metabolic remodelling. Such changes may contribute to improved cognitive functions, including learning and memory, in individuals with MS.

5. The influence of physical activity on the cerebral cortex in patients with multiple sclerosis

MRI studies consistently indicate that the cerebral cortex, particularly motor and associative regions, exhibits greater sensitivity to physical activity than global brain measures in patients with multiple sclerosis. Both cross-sectional and interventional studies report exercise-related changes in cortical volume, thickness, and functional organization.

Cross-sectional analyses suggest a positive correlation between habitual physical activity and cortical gray matter metrics. In a group of 50 participants, objectively measured daily physical activity over one month, assessed by step count, was significantly correlated with larger cortical gray matter volume, despite no correlation with total brain volume[9].

Intervention studies provide converging evidence for region-specific cortical plasticity. Kjølhede et al. recruited 35 participants with relapsing-remitting MS. The study group performed supervised long-term resistance training twice weekly for 24 weeks. MRI revealed an absolute increase in cortical thickness in 19 of 74 cortical regions. The largest increases in cortical thickness were found in the orbital H-shaped sulcus, followed by the anterior cingulate cortex, temporal pole, and inferior temporal sulcus. The study did not show an increase in the number of demyelinating lesions, which may suggest a neuroprotective, or even neuroregenerative, effect on neurodegenerative processes. It is worth noting that these changes in the cerebral cortex occurred without a concomitant increase in total gray or white matter. This demonstrates the regional specificity of exercise-related cortical adaptations[14].

Functional magnetic resonance imaging studies provide important insights into exercise-related cortical reorganization in patients with multiple sclerosis, revealing changes that cannot be captured by structural volumetric measures. Several interventional studies demonstrate that physical activity is associated with changes in task-related activation patterns and resting-state functional connectivity, primarily within movement-related cortical networks.

Short-term aerobic training interventions have been shown to reduce diffuse and excessive activation of the primary motor cortex (M1) during motor tasks. Wachowski et al. conducted a study of two groups of 14 participants each, examining the effects of aerobic training using a

recumbent cycle ergometer on cortical motor areas in patients with MS over a four-week period. The study group demonstrated a significant reduction in cluster and peak activation in the contralateral motor cortex, which was interpreted as improved neural efficiency and normalization of the motor network [15] . These findings suggest that physical activity may attenuate compensatory hyperactivation commonly observed in MS.

Resting-state fMRI studies further support this interpretation. After a structured rehabilitation program combining aerobic and resistance training, consisting of two 30-45-minute sessions per day, five days per week for four weeks, patients demonstrated reduced functional connectivity within motor networks immediately after the intervention, consistent with decreased reliance on widespread compensatory cortical recruitment [16] . Importantly, this effect was transient; follow-up imaging performed three months after the intervention showed a return toward baseline connectivity patterns, indicating that continued physical activity may be necessary to maintain functional network adaptations.

Overall, fMRI findings consistently indicate that physical activity in MS primarily induces functional reorganization rather than persistent structural remodeling at the cortical level. Exercise-related reductions in maladaptive hyperactivation and normalization of motor network connectivity support the concept of improved cortical efficiency, although these effects appear to be time-dependent and require sustained training to persist.

However, not all studies have reported positive cortical effects. Several aerobic training interventions lasting 12–24 weeks failed to demonstrate significant changes in global cortical volume or thickness, despite favourable trends or regional findings[5,17] . Overall, the available evidence indicates that physical activity is associated with region-specific structural and functional changes in the cerebral cortex of patients with MS, particularly within motor-related areas. While global cortical volume measures often remain unchanged, localized increases in cortical thickness and improved functional efficiency suggest that the cortex represents a key target of exercise-related neuroplasticity in multiple sclerosis.

6. The effect of physical activity on the basal ganglia and cerebellum of patients with multiple sclerosis

MRI studies investigating the effects of physical activity on deep gray matter structures and the cerebellum in patients with multiple sclerosis (MS) report heterogeneous and predominantly region-specific findings. Overall, neither the basal ganglia nor the cerebellum

demonstrate consistent global volumetric changes in response to physical activity; however, selected nuclei and cerebellar pathways appear responsive to targeted motor interventions.

With respect to the basal ganglia, most aerobic training studies failed to demonstrate significant volumetric changes. A 24-week progressive aerobic exercise intervention did not result in significant alterations in the volume of the putamen, caudate nucleus, globus pallidus, or thalamus, despite favorable trends in other MRI markers. However, the study showed improved cardiorespiratory fitness and annualized relapse rate[5]. Similarly, a 12-week aerobic training consisting of 30 minutes of training 3 times per week for 3 months showed no significant changes in basal ganglia volume, even though hippocampal volume, hyppocampal resting state conectivity as well as memory increased in the same cohort. [7] .

In contrast, isolated nucleus-specific effects have been reported. A 12-week walking and running–based aerobic training program resulted in a significant increase in left globus pallidus volume, while no changes were observed in total brain volume or other basal ganglia structures. 42 people with multiple sclerosis were randomised to either experimental or waiting control group. After 12 weeks of training 3 times per week not only did volume of globus palidus increased, but also aerobic capacity, functional mobility, visuospatial memory, fatigue, and quality of life [18] . Given the role of the globus pallidus in automatic motor control, the authors suggested that repetitive gait-related motor activity may selectively induce plastic changes within this structure.

Evidence regarding the cerebellum points primarily toward microstructural and regional effects rather than global volumetric changes. In patients with progressive MS, a combined aerobic and cognitive rehabilitation program did not prevent generalized brain atrophy but was associated with reduced atrophy in the bilateral middle cerebellar peduncles and inferior temporal gyrus. Seventy-three patients were randomized into four groups receiving a combination of cognitive rehabilitation and excercise rehabilitation or their sham versions: CR + EX, CR + EX-sham, EX + CR-sham, and CR-sham + EX-sham. Participants attended a 12-week intervention twice/week. In few cognitively relevant areas, the combined CR interventions might have affected patterns of volume changes, while EX modified cerebellar motor regions. [19] . These findings suggest that cerebellar pathways involved in motor coordination and sensorimotor integration may be partially preserved through targeted rehabilitation.

Diffusion-based studies provide further support for cerebellar responsiveness. An intensive balance training program led to significant increases in fractional anisotropy and reductions in

radial diffusivity within the superior cerebellar peduncles, without detectable changes in other major white matter tracts [20] . These results indicate exercise-related microstructural reorganization potentially reflecting remyelination or improved axonal coherence.

Collectively, current evidence suggests that physical activity does not exert a uniform effect on basal ganglia or cerebellar volume in MS. Instead, selective nuclei and cerebellar pathways—particularly those directly engaged by motor tasks—may exhibit localized volumetric or microstructural adaptations. These findings underscore the importance of task-specific training paradigms when targeting subcortical and cerebellar structures in rehabilitation strategies for multiple sclerosis.

7. The effect of physical activity on the volume and structure of white matter

Across MRI studies investigating physical activity in multiple sclerosis, white matter outcomes have been assessed both at the macrostructural level (total white matter volume, lesion load) and the microstructural level using diffusion-based metrics. Overall, physical activity does not appear to significantly influence global white matter volume; however, consistent effects have been observed in white matter microstructure, particularly within motor- and cerebellar-related pathways.

Intervention studies assessing aerobic exercise over periods ranging from 12 to 48 weeks generally reported no significant changes in total white matter volume or overall lesion burden. A 24-week progressive aerobic training program did not demonstrate differences between exercise and control groups in normalized white matter volume or T2 lesion load[5] . Similarly, a 48-week supervised aerobic exercise intervention in patients with early multiple sclerosis found no effect on total white matter volume or lesion accumulation, despite advanced diffusion-based analyses[8] . These findings suggest that global white matter volume and lesion metrics are relatively insensitive to exercise-related effects over typical intervention durations.

In contrast, diffusion tensor imaging (DTI) studies provide converging evidence of exercise-related microstructural adaptations. Balance training conducted over 12 weeks resulted in significant increases in fractional anisotropy (FA) and reductions in radial diffusivity (RD) within the superior cerebellar peduncles, with no corresponding changes in mean or axial diffusivity [20] . These changes were interpreted as improved myelin integrity or axonal coherence, potentially reflecting activity-dependent remyelination processes.

Additional support for microstructural responsiveness comes from studies employing combined rehabilitation protocols. Intensive sensorimotor and task-oriented upper limb training was associated with increased FA and reduced mean diffusivity within the corpus callosum, suggesting enhanced interhemispheric connectivity following targeted motor activity [21] . Importantly, these effects were observed without concurrent changes in global white matter volume, underscoring the dissociation between macrostructural and microstructural MRI markers.

Cross-sectional studies further reinforce these findings. Higher levels of habitual physical activity have been associated with improved diffusion metrics in selected white matter tracts, including corticospinal pathways and thalamic radiations, even in the absence of differences in total white matter volume[9] . This suggests that physically active individuals may preserve white matter integrity at the tract level despite ongoing disease-related atrophy.

Collectively, available evidence indicates that physical activity does not exert a measurable effect on overall white matter volume or lesion burden in multiple sclerosis. However, consistent microstructural changes detected using diffusion-based MRI suggest that physical activity may support white matter integrity in selected pathways, particularly those engaged by motor and balance-related tasks. These findings highlight the importance of microstructural MRI markers as sensitive indicators of exercise-related neuroplasticity in MS.

8. Discussion

There are many evindence suggesting positive impact of physical activity on brain function of people with multiple sclerosis. The study of Elkhooly M et all. reviewed the effects of aerobic exercise and non-invasive brain stimulation on cognitive performance in people with Multiple Sclerosis. The authors analyzed 26 studies evaluating functions such as memory, attention, processing speed, and executive functioning.

The results showed that aerobic exercise improved at least one cognitive domain in most studies, particularly processing speed, attention, and memory. The authors concluded that aerobic exercise is an effective non-pharmacological intervention to support cognitive function in MS[22].

The study by Bae and VanNostrand, *"Cognition and Measures of Physical Activity, Mobility, and Gait in Individuals With Multiple Sclerosis: A Systematic Review,"* examined the relationship between cognitive function, physical activity, mobility, and gait performance in

people with Multiple Sclerosis. The review included 26 studies involving over 3,000 participants with MS.

The results showed that higher levels of physical activity and better gait performance were associated with improved cognitive functioning, especially processing speed, executive function, and memory. The authors concluded that mobility and physical activity are closely linked with cognitive health in people with MS[23].

The study by Adammek and colleagues, *"Functional exercise training in persons with multiple sclerosis: a systematic review,"* analyzed the effects of functional exercise training in people with Multiple Sclerosis. The review evaluated interventions focused on balance, coordination, strength, gait, and daily functional activities.

The results showed that functional exercise training improved mobility, balance, walking ability, coordination, and quality of life in people with MS. The authors concluded that combined functional training programs may be an effective rehabilitation approach to enhance motor performance and daily functioning in MS patients[23].

The study by Bae and Kasser, *"High intensity exercise training on functional outcomes in persons with multiple sclerosis: A systematic review,"* examined the effects of high-intensity exercise training on functional outcomes in people with Multiple Sclerosis. The review analyzed studies assessing mobility, balance, walking performance, muscle strength, and physical fitness.

The results showed that high-intensity exercise training improved functional capacity, walking speed, balance, muscle strength, and overall physical performance without increasing the risk of disease relapse. The authors concluded that high-intensity exercise appears to be a safe and effective rehabilitation strategy for people with MS[24].

The present review synthesizes MRI-based evidence on the influence of physical activity on brain structure in patients with multiple sclerosis, with a particular focus on global and regional markers of neurodegeneration. Across the analyzed studies, a consistent pattern emerges: physical activity does not exert a robust effect on global brain atrophy but is associated with region-specific structural and functional adaptations, suggesting a primarily neuroprotective and plasticity-driven mechanism rather than a global disease-modifying effect.

The lack of significant changes in global brain volume observed across most intervention studies is not unexpected. Whole-brain atrophy in MS progresses slowly and reflects diffuse neuroaxonal loss accumulated over years, making it relatively insensitive to short- and

medium-term behavioral interventions, most training interventions last weeks to months. Additionally, global volumetric measures may lack the spatial specificity required to detect subtle, localized exercise-related effects. Brain volume measures can be influenced by hydration, scanner differences, segmentation pipelines, and treatment-related fluid shifts. These findings are consistent with the hypothesis that physical activity modulates downstream neurodegenerative processes rather than directly influencing the inflammatory mechanisms that drive early lesion formation and widespread tissue loss.

In contrast, several brain regions appear more responsive to physical activity. The hippocampus consistently demonstrates preservation or volume increase in both cross-sectional and longitudinal studies, supporting its role as a key substrate of exercise-induced neuroplasticity. This aligns with evidence from non-MS populations, where physical activity promotes hippocampal neurogenesis, synaptic remodeling, and metabolic resilience. Importantly, the relative vulnerability of the hippocampus to neurodegeneration in MS may render it particularly sensitive to neuroprotective interventions.

Cortical findings further reinforce the region-specific nature of exercise effects. While global cortical volume often remains unchanged, increases in cortical thickness and normalization of functional activation patterns within motor-related regions suggest improved network efficiency. Functional MRI studies consistently demonstrate reduced maladaptive hyperactivation and transient reorganization of motor networks following exercise, highlighting functional plasticity that may precede or occur independently of structural remodeling.

Evidence concerning deep gray matter structures and the cerebellum is more heterogeneous. Basal ganglia volumes generally appear resistant to short-term exercise interventions, although isolated nucleus-specific effects and cross-sectional associations with habitual activity suggest potential long-term sensitivity. Cerebellar findings are primarily limited to microstructural changes within cerebellar pathways rather than volumetric adaptations, indicating that task-specific motor training may influence connectivity and coordination circuits without altering gross anatomy.

Methodological factors likely contribute to the observed heterogeneity. Differences in study design, duration and intensity of exercise interventions, MS phenotype, disability level, and MRI analysis techniques complicate direct comparisons. Moreover, many studies rely on relatively small sample sizes, limiting statistical power to detect subtle volumetric changes.

The predominance of cross-sectional designs also restricts causal inference, particularly in regions where physical activity may reflect preserved neural integrity rather than induce it.

Overall, the available evidence supports a model in which physical activity acts as a modulatory factor that promotes regional neuroplasticity and preserves vulnerable brain structures rather than reversing global neurodegeneration. Global measures such as percentage brain volume change are clinically meaningful but may be underpowered in short trials, whereas hippocampal volumetry, cortical thickness, DTI metrics, and spinal cord gray matter measures may better capture exercise-related signals. These findings underscore the importance of selecting sensitive, region-specific MRI outcomes and designing longer, adequately powered longitudinal studies to clarify the long-term impact of physical activity on brain health in multiple sclerosis.

9. Disclosure

Author's Contributions:

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While preparing this manuscript, the authors used the ChatGPT 4 tool to enhance language quality and readability. After using this tool, the authors thoroughly reviewed and edited the text as necessary and accept full responsibility for the scientific content of the publication.

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