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Review
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ANATOMICAL BASIS AND CLINICAL IMPLICATIONS OF NEURODEGENERATIVE VOLUMETRIC CHANGES IN MULTIPLE SCLEROSIS

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Abstract: Multiple sclerosis is a complex disease that affects the central nervous system and has chronic, inflammatory, demyelinating, and neurodegenerative characteristics. Recent morphometric and functional imaging studies have shown that in MS, not only white matter but also grey matter is significantly affected from the early stages of the disease. This has brought to the fore the need to redefine MS beyond its classical inflammatory window, incorporating neurodegenerative processes. In this review, volumetric brain changes observed in MS patients are systematically addressed. Volumetric changes observed in various brain regions, including the thalamus, hippocampus, prefrontal and temporal cortex, cerebellum, and brainstem, were evaluated in terms of their correlations with multidimensional clinical parameters such as cognitive function, motor performance, mood regulation, and fatigue. In addition, the review provides a detailed explanation of the process of examining these structures using current imaging methods (voxel-based morphometry, surface-based morphometry, automatic segmentation software, and artificial intelligence-based algorithms) in volumetric analyses. The review highlights the need to evaluate structural brain changes in MS not only from an anatomical perspective but also from a clinical perspective. The usability of volumetric biomarkers in monitoring disease progression, subtype differentiation, and determining individualised treatment approaches is emphasised with support from the current literature. In this context, the study contributes to the literature by comprehensively addressing the clinical implications of MS-specific neurodegenerative volume losses with an interdisciplinary approach.

Keywords: Thalamus, Hippocampus, Brain atrophy, Imaging, Clinical correlation, Artificial intelligence

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1. Introduction

Multiple sclerosis (MS) is a chronic neuroimmune disease that affects the central nervous system, begins in young adulthood, and has a heterogeneous course. As of 2023, MS affects more than 2.8 million people worldwide and is one of the most common causes of irreversible neurological disability. While MS was previously characterised by its inflammatory and demyelinating features, it is now widely accepted in scientific circles that the disease has a significant neurodegenerative component. In this regard, not only plaque-based lesion burden but also volumetric changes in grey matter and deep nuclei have become key factors shaping the clinical course of the disease (Wallin et al., 2019; Solana et al., 2021; Ziccardi et al., 2024).

The traditional understanding was that MS was characterised by focal plaques developing in the white matter. However, advancements in 3D high-resolution magnetic resonance imaging (3T and 7T MRI), diffusion tensor imaging (DTI), and ultra-sensitive PET imaging techniques over the past decade have demonstrated that grey matter involvement in MS occurs much earlier and is more widespread than previously believed (Geurts et al., 2011; Madsen et al., 2021). Importantly, these technological improvements have revealed that neurodegenerative processes may begin independently of inflammatory activity, demonstrating that MS pathology involves more diffuse and silent mechanisms. In particular, cortical and subcortical structures such as the thalamus, hippocampus, cerebellum, and frontal cortex undergo volumetric shrinkage independent of inflammation, and these changes have become direct predictors of clinical symptoms (Eshaghi et al., 2018).

Neurodegenerative volumetric changes are not merely anatomical observations; they also reflect the structural foundations underlying disease progression, cognitive decline, motor dysfunction, and mood disorders. Atrophy in grey matter has become a better predictor of disease course, independent of lesion burden (Sormani and De Stefano, 2013). Nonetheless, integrating grey matter volumetry into clinical follow-up has only recently gained momentum, emphasising the need for more systematic approaches.

In this review, neurodegenerative volumetric brain changes observed in MS patients are discussed in detail

in the context of anatomical regions such as the thalamus, hippocampus, cortical areas, cerebellum, and brainstem. Additionally, the relationship between volumetric data obtained using modern imaging techniques and clinical symptoms and findings, neuropsychological implications, and integration with biomarkers are also evaluated. The aim of this review is to present the correlations between volumetric changes and neurological symptoms, to outline the functional implications of region-specific atrophy, and to contribute to the development of individualized treatment strategies by identifying clinically meaningful structural biomarkers. This review integrates evidence from recent (2021–2025) volumetric imaging studies, emphasizing the topical relevance and contemporary scientific value of its synthesis.

2. Basic Mechanisms of Neurodegeneration in Multiple Sclerosis

Neurodegeneration in MS results from a complex interaction of axonal injury, synaptic dysfunction, chronic inflammation, and metabolic impairment. While demyelination has historically been considered the primary pathological hallmark of MS, recent evidence highlights that axonal and neuronal loss represent core components of disease progression, occurring even in regions without overt lesions.

2.1. Axonal Damage and Energy Metabolism Disorders

At the centre of the neurodegenerative processes observed in MS is not only demyelination but also axonal loss. Axonal degeneration, observed not only in white matter plaques but also in lesion-free grey matter regions, is a primary cause of progressive functional loss (Trapp et al., 1998). Importantly, chronic mitochondrial dysfunction leads to impaired ATP production and disrupted axonal transport, ultimately triggering metabolic collapse (Mahad et al., 2009).

This vulnerability is further intensified by oxidative stress. In iron-rich regions such as the basal ganglia and thalamus, iron-mediated free radical formation directly damages axonal cytoskeleton and DNA, accelerating neuronal death (Hametner et al., 2013).

2.2. Microglial Activation and Chronic Inflammation

Microglial cells, as the resident immune elements of the CNS, form the first line of defence against pathogens. However, in MS, the chronic activation of these cells leads to the formation of a neurotoxic microenvironment through pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines (Correale and Farez, 2015). This sustained inflammatory state is not restricted to demyelinated plaques but affects the entire grey matter landscape, thereby contributing to diffuse degeneration.

PET imaging studies further demonstrate that microglial activation is elevated in cortical grey matter and deep nuclei, even in areas lacking MRI-visible lesions, revealing the widespread and silent nature of MS-related inflammation (Rissanen et al., 2018).

2.3. The Role of Synaptic Loss

In addition to axonal loss, synaptic loss also highlights the neurodegenerative aspect of MS. Postmortem brain tissue studies have revealed a significant reduction in synaptic density, particularly in cognitive centres such as the hippocampus and prefrontal cortex (Dutta et al., 2011). Glutamate-mediated excitotoxicity, driven by NMDA receptor overactivation, accelerates synaptic injury, leading to impairments in learning, memory, and executive functions.

Taken together, these findings underscore that neurodegeneration in MS is not merely a downstream consequence of demyelination but a parallel pathological process with distinct mechanisms.

3. Volumetric Changes in Anatomical Structures

Brain volume loss in multiple sclerosis (MS) is not only a consequence of inflammation and lesion accumulation but also a hallmark of a widespread, progressive, and partially independent neurodegenerative process. These changes occur at variable rates across anatomical regions and often emerge earlier than clinical disability, underscoring their importance for early detection. MRI-based morphometric methods now enable submillimetre resolution of structural changes, highlighting the increasing clinical value of volumetric biomarkers (Sormani and De Stefano, 2013).

3.1. Thalamus: The Key to Silent and Early Neurodegeneration

The thalamus is the central hub connecting the cortex with subcortical structures. It plays a critical role in both sensory-motor information transmission and higher-order cognitive functions such as attention, information processing speed, and working memory. Volume reduction in the thalamus is one of the earliest signs of atrophy in MS and can occur independently of lesion burden (Eshaghi et al., 2018).

Importantly, in a longitudinal study by Azevedo et al., it was reported that thalamic atrophy can be detected from the onset of the disease even in RRMS (Relapsing-Remitting Multiple Sclerosis) patients and that this atrophy may be a predictive biomarker for the development of progressive disability. Additionally, thalamic atrophy indicates a significant correlation with decreases in SDMT scores and increases in fatigue levels. The presence of thalamic atrophy in the early stages may be more sensitive than brain lesion burden in predicting disease progression (Azevedo et al., 2018).

3.2. Hippocampus: The Anatomical Basis of Cognitive Reserve

The hippocampus, as the centre of the limbic system, plays a role in memory formation, spatial learning, and emotional regulation. In MS, hippocampal atrophy is concentrated in the CA1, subiculum, and dentate gyrus regions and is an important structural indicator of early cognitive impairment (Planche et al., 2017). A study by

Sicotte et al. showed that hippocampal volume was significantly lower in RRMS patients compared to controls (Sicotte et al., 2008).

Additionally, it has been demonstrated that hippocampal volume loss is positively correlated with depression severity, indicating that emotional impairment also has an anatomical basis. Recent 7T MRI studies have shown that these atrophies are not only caused by cortical plaques but also by synaptic dysfunction and glucocorticoid exposure (Stadelmann et al., 2008).

Table 1. Summary of thalamic atrophy and cognitive function in multiple sclerosis

Category	Description
Key Findings	Thalamic atrophy—particularly pronounced in the left thalamus—is commonly observed in multiple sclerosis and leads to significant impairments in information processing speed and attention.
Associations With Cognitive Tests	Numerous studies have reported strong correlations between thalamic volume and cognitive test performance, including SDMT, BVMT-TR, CVLT-TR, and DKEFS.
Clinical Significance	The thalamus is considered both an early biomarker of cognitive dysfunction and a structural indicator of disease progression.
Relevance for Therapeutic Research	Thalamic volume may serve as an ideal biomarker for studies evaluating neuroprotective or restorative treatments targeting cognitive outcomes.
Key References	Azevedo et al. (2018); Amin and Ontaneda (2021); Mirmosayyeb et al. (2024)

Table 2. Summary of hippocampal subregion atrophy and cognitive function in multiple sclerosis

Category	Description
Key Findings	Volume reduction in hippocampal subregions such as CA1, CA3, and the dentate gyrus is strongly associated with impairments in verbal and visual memory.
Broader Clinical Effects	These structural alterations may influence not only memory performance but also depressive symptoms.
Biomarker Significance	MRI-based hippocampal volume is considered a sensitive biomarker for monitoring cognitive function.
Future Clinical Use	Hippocampal volumetry has the potential to be integrated into personalised treatment monitoring strategies in future MS management.
Key References	Rocca et al. (2018); Cortese et al. (2024)

3.3. Cortical Grey Matter: The Scene of Invisible Destruction

Although MS is defined as a white matter disease, atrophy in grey matter is now accepted as a parameter that better reflects the burden and course of the disease. Cortical atrophy is concentrated particularly in the temporal, parahippocampal, and prefrontal regions, directly affecting patients' cognitive and behavioural profiles. Ziccardi et al. showed that patients who experienced volume loss in these structures within the first two years had a high risk of developing permanent memory and attention impairments 20 years later (Ziccardi et al., 2024).

A 2021 meta-analysis revealed that cortical volume loss occurs at a rate of 2–4% within the first 5 years in patients with RRMS and that this loss is generally 'faster than normal ageing' (Zivadinov et al., 2016). Additionally, a significant association has been reported between the rate of cortical atrophy and increases in Expanded Disability Status Scale (EDSS) scores, with cortical involvement being more common in progressive MS subtypes (Filippi et al., 2018). When evaluated alongside 'grey matter lesions,' cortical atrophy may be a stronger predictor of progression than MRI lesion burden.

3.4. Cerebellum: Key Centre for Motor and Cognitive Coordination

Atrophy detected particularly in lobulus VI, Crus I–II and vermis IX regions of the cerebellum indicates a strong correlation with clinical functions such as walking speed, balance, upper extremity coordination and information processing speed. Takla et al. identified significant volume reductions in these regions in MS patients with a history of falls and demonstrated that these findings are directly related to motor/cognitive performance (Takla et al., 2025). Similarly, Wenger et al. reported that diffuse demyelination begins in both the anterior (motor) and posterior (cognitive) regions of the cerebellum even in the early stages, and that these changes often appear before EDSS progression (Wenger et al., 2024). Importantly, the degree of cerebellar atrophy, as measured by fMRI data, shows a significant correlation with both Timed 25 Foot Walk Test (T25-FWT) scores and BICAMS subtest scores (Parmar et al., 2022).

3.5. Brain Stem: Neuroanatomical Junction of Autonomic Functions and Trajectory Passages

The brain stem is a critical neuroanatomical junction that includes the mesencephalon, pons, and medulla oblongata, through which motor and sensory pathways pass and which also houses the autonomic centres. The

volumetric shrinkage observed in this region in multiple sclerosis (MS) patients is considered not only a result of local demyelinating lesions but also part of a global neurodegenerative process (Wenger et al., 2024).

Table 3. Summary of cortical lesion burden and cortical atrophy in multiple sclerosis

Category	Description
Key Findings	Studies indicate that cortical lesion burden is more sensitive than white matter lesions in determining disease progression and is helpful in predicting EDSS worsening.
Disease Dynamics	Cortical grey matter atrophy progresses insidiously; by the time it becomes clinically apparent or MRI-detectable, significant damage has often already occurred.
Clinical Implications	Early detection is essential — MRI-based cortical volume measurements should be prioritised as evaluation tools for cognitive protection and disability management.
Key References	Van Munster et al. (2015); Solana et al. (2021)

Table 4. Summary of cerebellar atrophy and functional outcomes in multiple sclerosis

Category	Description
Key Findings	Volumetric reduction in the cerebellum is associated not only with imbalance and ataxia, but also with cognitive decline, increased fall risk, and loss of functional independence.
Clinical Implications	These findings highlight the cerebellum's critical role in both motor and cognitive functioning.
Importance for Patient Management	Cerebellar volume measurements should be considered essential for early risk classification, personalised rehabilitation planning, and the development of fall-prevention programmes.
Key References	Parmar et al. (2022); Wenger et al. (2024); Takla et al. (2025)

Table 5. Summary of brainstem atrophy and clinical outcomes in multiple sclerosis

Category	Description
Key Findings	Brainstem volume loss is associated not only with symptoms such as dysarthria, diplopia, and imbalance, but also with an increased risk of disability progression and falls.
Clinical Implications	These associations underline the brainstem's central role in both motor coordination and autonomic/cranial nerve functions.
Importance for Patient Management	High-resolution brainstem volumetric analyses provide substantial clinical value for early risk classification and prediction of disease progression.
Key References	Lee et al. (2018); Elzayady et al. (2021); Nguyen et al. (2021); Wenger et al. (2024)

In a morphometric analysis study conducted by Lee and colleagues in 2018, significant structural atrophy was detected in the mesencephalon and pons in MS patients. These volumetric losses showed a statistically significant correlation with objective clinical measures such as EDSS scores and the 9-Hole Peg Test (Lee et al., 2018). Elzayady et al. (2021) reported significant reductions in medulla oblongata, pons, and total brainstem volumes, with these decreases indicating a negative correlation with both EDSS scores and attack frequency. Nguyen et al. demonstrated that imaging using the FGATIR sequence revealed MS-specific damage patterns in nuclei and tracts such as the vestibular nuclei, facial nerve, MLF, and corticospinal tract (Nguyen et al., 2021). The findings suggest that brainstem atrophy may not only explain existing neurological deficits but also serve as a potential structural biomarker for predicting disease progression.

Anatomically, the brainstem serves as a 'neurological crossroads' through which corticospinal and corticobulbar pathways, as well as sensory tracts such as the medial lemniscus, pass. In this context, brainstem atrophy is directly associated with multiple clinical findings such as gait disorders, bulbar dysfunction, loss of balance, ophthalmoplegia, and dysphasia. Systematic evaluation of volumetric reduction offers a neuroimaging-based sensitive approach to monitoring functional loss, particularly in advanced forms of MS (Lee et al., 2018).

4. Volumetric Evaluation with Modern Imaging Methods

The quantitative evaluation of structural brain changes observed in multiple sclerosis has become more accessible, accurate, and reproducible thanks to advances in neuroimaging techniques in recent years. In particular, grey matter-focused volumetric analyses have emerged as an important biomarker for monitoring disease progression. This section discusses four fundamental volumetric imaging approaches commonly used in MS.

4.1. Voxel-Based Morphometry (VBM)

VBM is a method that divides brain images into very small three-dimensional cubes (voxels) and compares the volume of these regions between groups of individuals. It particularly highlights differences in grey

matter density and volume.

Studies in MS patients have shown early volume losses in regions such as the thalamus, hippocampus, and cortex using VBM (Eshaghi et al., 2018; Filippi et al., 2018).

VBM can be used both for inter-individual group comparisons and longitudinal analyses, contributing to the objective, measurable, and reproducible monitoring of disease progression.

4.2. Surface-Based Morphometry (SBM)

SBM is another volumetric analysis method that evaluates the geometric properties of the brain surface. This technique allows for the measurement of cortical thickness, surface area, and gyral convolutions. FreeSurfer, a commonly used SBM software in MS patients, enables the sensitive detection of cortical atrophy even in the early stages.

SBM outputs show a high level of correlation with cognitive test performance (e.g., SDMT, CVLT-II). In this respect, SBM not only supports research purposes but also contributes to emerging clinical decision systems.

4.3. Automatic Segmentation Software

Automatic segmentation software developed in recent years divides brain structures into regions based on a predefined atlas and enables volumetric analysis of these structures. Software such as FreeSurfer, SPM12, FSL-FIRST, and MRICloud enable volumetric assessment of specific anatomical structures such as thalamic nuclei, hippocampal subregions, cortical regions, and cerebellar lobules (Iglesias et al., 2015; Riederer et al., 2021; Soysal et al., 2022).

These systems are preferred for standardised data production, especially in multi-centre studies. However, the accuracy of segmentation depends on the atlas used, the quality of magnetic resonance imaging, and the algorithm's parameter settings.

4.4. Artificial Intelligence-Supported Systems

Artificial intelligence (AI) and, in particular, deep learning-based algorithms offer revolutionary approaches to the analysis of neuroimaging data. Convolutional neural networks (CNNs) can automatically classify, segment, and produce volumetric measurements of brain structures by processing high-volume MRI data. These systems offer advantages over classical methods in terms of higher accuracy, speed, and generalizability (Eshaghi et al., 2018).

Models trained on datasets from different centres form the basis of AI-supported decision frameworks that may assist in the detection and staging of MS.

Table 6. Comparative features of modern volumetric brain imaging methods

Method	Basic Principle	Targeted Anatomical Feature	Advantages	Disadvantages	When to Prefer	Clinical and Research Applications
Voxel-Based Morphometry (VBM)	Voxel-based gray matter comparison using MRI data	Gray matter density and volume (regional differences)	Automated analysis, strong in group comparisons, sensitive in deep nuclei	Low surface sensitivity, sensitive to deformations	When early gray matter atrophy and group-level comparison are needed	Tracking atrophy in regions such as thalamus, hippocampus, cerebellum in MS
Surface-Based Morphometry (SBM)	Analysis of the surface geometry of the cerebral cortex	Cortical thickness, gyrification, surface area	Precisely detects cortical thinning, applicable at the individual level	Cannot analyze deep structures, long computation time	Early cortical atrophy, diagnosis and follow-up at individual level	Relationship between cortical degeneration and cognitive impairment (correlation with SDMT, CVLT-II)
Automated Segmentation Software (FreeSurfer, FSL, SPM12, MRICloud)	Atlas-based parcellation of MRI images	Whole brain + substructures (thalamic nuclei, cerebellar lobules, hippocampal subfields)	Provides regional measurement, reproducible, widely accessible	Algorithmic inconsistency may occur, accuracy varies by structure	When volumetric comparison of specific anatomical structures is needed	Clinical correlation studies, longitudinal follow-up, pre/post-treatment volume monitoring
Artificial Intelligence-Assisted Methods	Automated volume extraction from large MRI datasets	Whole brain structures (multiple features), dynamic changes	Very fast and highly accurate, independent of human error, suitable for multicenter analyses	Dependent on training data, transition to clinical application still ongoing	Large-sample data analysis, personalized risk prediction models	MS staging, AI-based clinical decision support systems, predictive modeling

5. Clinical Correlations of Volumetric Changes

It has been demonstrated that brain volume loss in MS is highly correlated with clinical symptoms. These correlations increase the value of volume measurements in the diagnosis and course evaluation of the disease and provide guidance for early intervention and individualized treatment planning.

5.1. Cognitive Impairment

Cognitive impairments in MS patients are most commonly observed in areas such as information processing speed, verbal and visual memory, executive functions, and attention. Morphometric studies have shown that volume reductions in the thalamus, hippocampus, dorsolateral prefrontal cortex, and orbitofrontal areas are associated with significant declines in neuropsychological test scores such as the SDMT, CVLT-II, and BVMT-R (Amin and Ontaneda, 2021; Cortese et al., 2024; Meira et al., 2024; Mirmosayyeb et al., 2024). In a one-year follow-up study conducted by Meira and colleagues, volume losses detected in the left amygdala and right lateral orbitofrontal cortex were reported to be independent predictors of declines in verbal memory (P=0.009) on the CVLT-II test and visual-spatial memory (P=0.001) on the BVMT-R test (Meira et al., 2024).

Additionally, Lageman et al. (2025) reported that when analysing grey and white matter cognitive effect models together, the explained variance in executive function and visual memory correlations reached 30–35%. This finding underscores the importance of evaluating not only individual structures but also broader cortical networks for a more realistic modelling of MS-related cognitive impairments. It has also been shown that band damage in white matter structures affects cognitive speed (Lageman et al., 2025).

Grothe et al. reported a positive correlation between superior longitudinal fasciculus (SLF) integrity and SDMT scores using diffusion tensor imaging (DTI). This finding emphasises that, in addition to grey matter-focused assessments, the structural integrity of white matter is also a structural determinant of cognitive speed; thus, tractographic analyses should not be overlooked in clinical interpretation (Grothe et al., 2022). These data reveal that cognitive impairments in MS arise not only from volume loss in core structures but also from widespread degeneration in both grey matter and white matter connection systems.

5.2. Motor Performance

In MS, volume losses in regions associated with the motor system, such as the cerebellum, brainstem, and motor cortex, show significant correlations with test scores such as fine motor skills (9HPT), walking speed (T25-FWT), and overall motor function (EDSS). In a study by Parmar et al., it was reported that the level of atrophy in cerebellar lobules IV–VI and VIII was associated with 9HPT scores and could predict progressive losses in motor function (Parmar et al., 2022). Takla et al. (2025) demonstrated that volume reduction in the cerebellum, particularly in the Crus I and lobulus VI regions, is associated with fall risk and coordination disorders. Additionally, Matthews et al. reported a negative correlation between total brain volume and both 9HPT and T25-FWT performance, meaning that as volume decreases, motor performance worsens (Matthews et al., 2023). A decrease in brainstem volume was similarly found to be associated with EDSS scores and motor function decline (Elzayady et al., 2021).

Importantly, these findings collectively indicate that volumetric reductions in both cerebellar and brainstem regions may serve as meaningful biomarkers for monitoring motor impairment in MS.

5.3. Mood and Fatigue

Neuropsychiatric symptoms such as depression, anxiety, and fatigue, which are common in MS, are associated with degenerative processes in limbic system structures. Decreases in the volumes of the hippocampus and anterior cingulate cortex (ACC) show an inverse correlation with Beck Depression Inventory (BDI) and Fatigue Severity Scale (FSS) scores (Margoni et al., 2023; Meira et al., 2024). Nguyen et al. (2021) demonstrated that volumetric reductions in structures such as the vestibular nuclei and medial longitudinal fasciculus (MLF) in the brainstem may be associated with mental fatigue. Additionally, deep structures involved in affective circuits, such as the medial nuclei of the thalamus, are also linked to these clinical symptoms (Nguyen et al., 2021). Large-scale analyses have reported that widespread volume losses in both grey and white matter show a weak to moderate correlation with fatigue levels (Ziccardi et al., 2024).

These findings highlight that neuropsychiatric symptoms can be explained by neuroanatomical foundations and that volumetric data can support clinical decision-making processes in this field. Therefore, MRI volumetric analyses may also serve as an important structural source for monitoring and managing neuropsychiatric symptoms.

6. Conclusion and Future Perspectives

Multiple sclerosis is not merely an inflammatory process, but a complex and progressive disease that also includes significant neurodegenerative components. Volumetric changes detected in grey and white matter serve as a decisive biomarker across a wide range of applications, from diagnosis to treatment and monitoring of disability progression. Advancements in neuroimaging techniques and artificial intelligence-supported segmentation systems in recent years have enabled the early and precise detection of these neurodegenerative changes, thereby introducing a new dimension to clinical neurological practice. This review highlights that volumetric analyses are not only a diagnostic tool but also offer strategic value in terms of monitoring prognosis, personalised treatment planning, and risk

classification. In particular, evaluating changes in structural volumes in MS alongside multidisciplinary measures such as cognitive scores, motor performance tests, and quality of life will enable the development of multimodal biomarker models that will strengthen clinical decision-making processes.

Table 7. Volumetric correlations of anatomical structures in MS with clinical tests

Anatomical Structure	Related Clinical Domain	Clinical Assessment/Test	Volume-Clinical Correlation
Thalamus	Cognitive functions (processing speed, attention)	Symbol Digit Modalities Test (SDMT)	Decreased thalamic volume is significantly associated with lower SDMT scores.
Hippocampus	Verbal and visual memory	California Verbal Learning Test-II (CVLT-II), Brief Visuospatial Memory Test-R (BVMT-R)	Atrophy in hippocampal CA1–CA3 subfields reduces CVLT-II/BVMT-R performance.
Dorsolateral Prefrontal Cortex (DLPFC)	Executive functions, processing speed	SDMT, Stroop Test	Positive correlation observed between DLPFC volume and cognitive processing speed.
Prefrontal Cortex	Planning, decision-making, attention	Wisconsin Card Sorting Test, Tower of London	Prefrontal atrophy is associated with impairments in executive functions.
Temporal Cortex	Attention, memory integration	Rey Auditory Verbal Learning Test	Reduced temporal cortex volume impairs memory performance.
Parahippocampal Gyrus	Spatial learning and navigation	Spatial Recall Test	Parahippocampal atrophy is associated with impaired navigation test performance.
Cerebellum (Lobule VI, Crus I–II)	Motor coordination, fine motor skills, gait	9-Hole Peg Test (9HPT), Timed 25-Foot Walk (T25FW), SDMT	Cerebellar lobule atrophy is associated with poorer motor test performance.
Vermis IX	Balance control, postural stability	Berg Balance Scale, Posturography	Vermis volume is directly correlated with balance test scores.
Brainstem (Pons, Medulla)	Motor output pathways, balance, speech	Expanded Disability Status Scale (EDSS), 9HPT, T25FW	Reduced brainstem volume correlates with higher EDSS and motor deficits.
Anterior Cingulate Cortex	Mood regulation, depression, fatigue	Beck Depression Inventory (BDI), Fatigue Severity Scale (FSS)	Reduced anterior cingulate volume is associated with higher depression and FSS scores.
Thalamus (Medial Nucleus)	Motivational fatigue and affective responses	FSS, Hospital Anxiety and Depression Scale (HADS)	Medial thalamic atrophy is associated with subjective fatigue levels.

Future research should focus on the following:

- Integrating volumetric data with longitudinal clinical data will contribute to more accurate monitoring of disease progression.
- Identifying volume-based degeneration patterns specific to MS subtypes (RRMS, SPMS, PPMS) will both increase diagnostic accuracy and guide personalized treatment planning.
- The use of artificial neural networks and other machine learning methods, combined with the integration of volumetric, biomarker, and clinical data, will enable the development of new algorithms for the staging and differential diagnosis of MS.
- Multimodal biological modelling approaches will pave the way for a new classification of MS that is enriched not only with anatomical but also functional and digital data.
- Objective monitoring of treatment responses based on volume changes will enable more precise evaluation of pharmacological and rehabilitation-based interventions.

In conclusion, the clinical significance of volumetric changes will become a central paradigm in future MS management, not only through the development of neuroimaging techniques but also through the integration of these techniques with biomarkers and advanced analytical models. In this context, this review addresses a critical gap in the literature by bringing together the clinical correlates of volumetric neuroimaging findings in MS in a structure-based, function-based, and test-based manner, and provides an integrative framework for the clinical applicability of volumetric biomarkers.

Author Contributions

The percentages of the authors' contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	F.B.	E.B.
C	60	40
D	60	40
S	40	60
DCP	70	30
DAI	70	30
L	60	40
W	65	35
CR	60	40
SR	50	50

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The authors declared that there is no conflict of interest.

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