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ORIGINAL ARTICLE

Subcortical volume alterations indicate structural atrophy patterns over time in relapsing–remitting multiple sclerosis: a volBrain-based analysis

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Abstract

Background Multiple Sclerosis (MS), a neurodegenerative disorder affecting central nervous system, predominantly manifests as Relapsing–Remitting MS (RRMS), with subcortical volume loss serving as a prognostic indicator.

Aims This study aimed to assess time-dependent volumetric changes in thalamus and basal nuclei using a validated automated tool, volBrain software, on MR images (MRI) across three years and relationship between structural changes and disease progression.

Methods The study included 50 RRMS patients (33.5 ± 6.3 years; 68% female, 32% male) and 50 healthy controls (38.0 ± 5.8 years; 64% female, 36% male). T1-weighted brain MRI scans (from 2017, 2019, 2022) were analyzed via volBrain. Statistical analyses included Shapiro–Wilk, Mann–Whitney U, Friedman, and Dunn tests.

Results Thalamus, nucleus caudatus (nuc. caudatus), and nucleus lentiformis (nuc. lentiformis) volumes were significantly lower in RRMS ($p < 0.05$). Significant volume loss was observed between 1st-3rd MRI and 2nd-3rd MRI ($p < 0.05$), but difference between 1st-2nd MRI was not statistically significant ($p > 0.05$). The most pronounced volume loss occurred between 1st-3rd MRI, with the greatest reduction observed in left nuc. caudatus (7.92%). This loss was followed by right thalamus (5.68%) and nuc. lentiformis (4.35%). Although atrophy was observed across disease duration groups, this difference was not statistically significant ($p > 0.05$). Volume loss in thalamus and basal nuclei indicated significant atrophy in RRMS patients.

Conclusions Findings highlighted MS-induced subcortical atrophy that significantly impacts brain structure. This study was distinguished through volBrain, highlighting its effectiveness in providing data with clinical relevance. Subcortical volume changes show potential as biomarkers for disease progression and guiding targeted therapies.

Keywords Atrophy · Automated volumetry · Basal nuclei · Relapsing remitting multiple sclerosis · Thalamus

Introduction

Multiple sclerosis (MS) is a complex neurological disorder that affects the central nervous system (CNS) and is characterized by inflammatory processes, myelin degradation, and neuronal degeneration. Similar to other neurodegenerative diseases, MS is linked to psychological stress and is typically diagnosed between the ages of 20 and 40 years [1, 2]. MS leads to demyelinating lesions in both white and gray matter regions of the brain and spinal cord. These lesions cause a wide range of clinical symptoms including optic neuritis, diplopia, sensory disturbances, motor deficits, gait instability, sphincter dysfunction, and cognitive impairment [3]. The observed symptoms are closely linked to structural alterations caused by the neurodegenerative mechanisms of

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the disease. A hallmark feature of MS progression is gradual volumetric reduction or atrophy of subcortical structures, most notably the thalamus and basal nuclei. This atrophic process becomes more pronounced as the disease progresses [4]. Recent investigations have focused on volumetric changes in subcortical structures to elucidate the role of MS in neurodegenerative processes [4–6]. Particularly in patients with RRMS, atrophy in deep gray matter structures, such as the thalamus and basal nuclei, has been linked to cognitive and motor impairments, even in the early stages of the disease [7].

Magnetic Resonance Imaging (MRI) is a pivotal tool for diagnosing and managing MS, and offers detailed insights into lesion characteristics, locations, and structural alterations in the brain. Beyond the initial diagnosis, MRI is instrumental for tracking disease progression and evaluating treatment efficacy over time. Standardized MRI protocols for MS include T2-weighted imaging, Fluid-Attenuated Inversion Recovery (FLAIR), and contrast-enhanced T1-weighted imaging. These sequences are critical for the accurate identification and characterization of MS lesions across disease stages. To ensure imaging quality, both axial and sagittal slices should be obtained with a minimum field strength of 1.5 Tesla. When available, a 3 Tesla scanner is preferred because of its enhanced spatial resolution and sensitivity [8, 9]. Automated brain volume measurement techniques have recently gained prominence in MS research and in clinical practice. Among these, volBrain is a widely used, free, web-based software platform designed for automatic brain volume analysis using T1-weighted MRI scans. Automated tools, such as volBrain, provide an objective and efficient method for evaluating subcortical structural changes in MS, making them valuable for both research and clinical applications [10]. This platform facilitates the assessment of subcortical structures, advances our understanding of MS pathology, and supports the development of improved strategies for diagnosis and management.

In our research, volBrain was utilized to perform detailed volumetric analyses of key brain regions, including the thalamus and basal nuclei, in patients with relapsing–remitting multiple sclerosis (RRMS). The study relied on longitudinal data derived from T1-weighted MRI scans collected over a five-year period, from 2017 to 2022. This approach enabled quantification of percentage changes in brain atrophy and facilitated monitoring of its progression over time. Furthermore, these volumetric measurements were correlated with disease duration, allowing for in-depth exploration of the temporal relationship between structural brain changes and RRMS progression. We hypothesized that reductions in the volume of the thalamus and basal nuclei are strongly associated with disease duration and progression. These regions are increasingly recognized as structural markers of motor and cognitive impairment in patients with RRMS, reinforcing their clinical significance. These findings emphasize the utility of innovative automated tools, such as volBrain, which offer precise and reliable assessments of subcortical atrophy, as valuable assets in MS management and research. A distinguishing feature of this study was its longitudinal design, which facilitated evaluation of subcortical structural changes over time. By employing volBrain, a relatively underutilized tool in existing MS research, our study provided novel insights into the patterns of subcortical atrophy in RRMS. In addition, the relationship between volumetric changes and clinical parameters, such as disease duration, was analyzed in detail to provide a nuanced understanding of the progressive nature of RRMS. This methodology highlighted the potential of automated volumetric tools to deepen our understanding of MS pathology and enhance their applicability in both research and clinical settings. By bridging the gap between advanced imaging technologies and clinical outcomes, this study underscored the value of integrating such tools into routine clinical practice to better monitor disease progression and inform therapeutic strategies.

The primary objective of this investigation was to conduct a comprehensive analysis of volumetric changes in the thalamus and basal nuclei of patients with RRMS, the most prevalent subtype of MS. Using the advanced capabilities of volBrain software, the study focused on evaluating percentage changes in the volumes of critical subcortical structures, including the thalamus, nucleus caudatus (nuc. caudatus), and nucleus lentiformis (nuc. lentiformis). These analyses were based on longitudinal MRI data collected at three time points, 2017, 2019, and 2022. By assessing how disease progression influences these structures over time, we generated a robust dataset that provides valuable insights into MS-related neurodegeneration. This dataset not only contributes to a deeper understanding of the pathological mechanisms underlying RRMS but also establishes a solid foundation for future research. In our study, the thalamus, nuc. caudatus, and nuc. lentiformis were selected because their clinical relevance in MS had been widely documented [11]. The thalamus was identified as an early and vulnerable structure associated with disability progression, while the nuc. caudatus and nuc. lentiformis, as key components of the basal ganglia, had been linked to motor and cognitive impairments [12]. Their inclusion allowed clinically meaningful structural changes to be captured, reinforcing the translational value of this research. The longitudinal design of this study emphasized the dynamic nature of structural changes in the brain, offering a more nuanced perspective on how subcortical atrophy correlates with disease progression. Furthermore, this investigation highlighted the clinical potential of integrating detailed volumetric analyses into routine RRMS follow-up. By leveraging the precision and automation of advanced neuroimaging tools, such as

volBrain, this study underscored their value in enhancing MS management. The novelty of our research was reflected in the use of volBrain, a validated automated volumetric tool that was applied to provide objective and reproducible measurements of subcortical structures. Through its integration into the analysis, the potential translational role of automated volumetry in clinical decision-making was highlighted, offering reliable biomarkers for disease monitoring and management in RRMS. These tools provide clinicians and researchers with a means to monitor disease progression more effectively and to develop targeted therapeutic and diagnostic strategies aimed at improving patient outcomes. We hypothesized that progressive volumetric reductions in the thalamus, nuc. caudatus, and nuc. lentiformis would serve as early and clinically meaningful markers of neurodegeneration in RRMS, and that these structural changes would be closely associated with disease duration and disability progression. This research demonstrated the importance of combining innovative imaging technologies with longitudinal studies to foster advancements in MS care and support the design of personalized treatment approaches. This study was aimed at addressing the existing gap in longitudinal volumetric research by incorporating three repeated MRI assessments in patients with RRMS, thereby providing a more comprehensive understanding of progressive subcortical atrophy over time.

Materials and methods

Participants

All procedures carried out in this study adhered to the guidelines set forth in the Declaration of Helsinki, and ethical approval was granted by the Non-Interventional Clinical Research Ethics Committee of the Kocaeli University (project number: GOKAEK-2022/19.13 2022/321), Kocaeli, Turkey. Our study followed the guidelines outlined by the Non-Interventional Clinical Research Ethics Committee of the Kocaeli University. Subsequently, a retrospective analytical approach was used to analyze the analysis of collected data. The study cohort consisted of individuals aged 20–40 years who had been diagnosed with RRMS at the Department of Neurology, Training and Research Hospital of Kocaeli University, Kocaeli, Turkey. All participants had T1-weighted brain MRI scans obtained at three distinct time points between 2017 and 2022 and were followed up at the same institution. For both the patient and control groups, T1-weighted brain MRI scans were acquired using the same MRI device. The control group comprised healthy controls who presented to the Department of Neurology, Training and Research Hospital of Kocaeli University, Kocaeli, Turkey with complaints of headache, but were confirmed to have no cranial pathology. Exclusion criteria included the presence of neoplastic, degenerative, or vascular pathologies that could be mistaken for multiple sclerosis, the detection of cranial pathologies in control subjects, and the absence of MRI data from at three distinct time points between 2017 and 2022. The 'MS Base' program provided access to information regarding MS subtypes, diagnosis dates, disease duration, patient demographics, Expanded Disability Status Scale (EDSS) scores, and medications administered during the follow-up period. Volumetric measurements of the right and left thalamus, nuc. caudatus, and nuc. lentiformis were performed on T1-weighted brain MRI scans obtained at the Department of Neurology, Training and Research Hospital of Kocaeli University, Kocaeli, Turkey. A retrospective analysis of T1-weighted brain MRI scans from 1317 individuals diagnosed with MS or admitted for headache complaints was conducted using the Kocaeli University PACS system in the Department of Radiology between 2017 and 2022. Following the application of exclusion criteria, 1217 individuals were excluded from the study. The final cohort included 50 patients with RRMS and 50 healthy controls.

Data collection

Volumetric measurements of the right and left thalamus, nuc. caudatus, and nuc. lentiformis, obtained from T1-weighted brain MRI scans of 50 patients with RRMS and 50 healthy controls were performed. For the RRMS patient group, volumetric measurements were conducted on three separate T1-weighted MR images acquired at different time points (2017, 2019, and 2022) over the study period from 2017 to 2022. By contrast, the healthy control group underwent volume measurements on a single T1-weighted brain MRI scan for each participant. The volBrain software was utilized to perform automated and standardized measurements of these subcortical brain structures. To evaluate alterations over time in the patient group, differences in volume and thickness across the three time points were calculated, and the results were expressed as percentages to provide a clear representation of the progression of structural changes.

Structural MRI protocol

The MRI protocol encompassed cranial MRI for all participants. Imaging was conducted using a 3-Tesla (3 T) scanner equipped with an eight-channel head coil. The protocol included two sequences: an axial three-dimensional T1 turbo field echo and a fluid-attenuated inversion recovery (FLAIR). For the T1-weighted sequence, the acquisition parameters were as follows: repetition time (TR) of 11 ms, echo time (TE) of 5 ms, slice thickness of 1 mm, and no interslice gap. For the FLAIR sequence, the parameters included a TR of 11,000 ms, a TE of 140 ms, a slice

thickness of 5 mm, an interslice gap of 0.5 mm, and a matrix size of 512 × 512.

Quantitative image analysis with volBrain

The 3D T1-weighted brain MRI scan data of 100 participants were transferred from a picture archiving and communication system to a personal computer for analysis. The T1-weighted brain MRI scans, saved in the Digital Imaging and Communications in Medicine (DICOM) format, were organized into a designated folder for processing. DICOM files were converted to compressed Neuroimaging Informatics Technology Initiative (NIfTI,.nii) files using the MRIcron's dcm2nii application. These files were then uploaded to the volBrain platform. Alongside the uploaded files, participants' age and gender details were entered into the system. The data workflow was visually depicted in Fig. 1.

Once processed, the platform provided volumetric measurement results via e-mail in a portable document format (PDF). The processing methodology was visually depicted in Fig. 2. The automated processing ensured consistency and

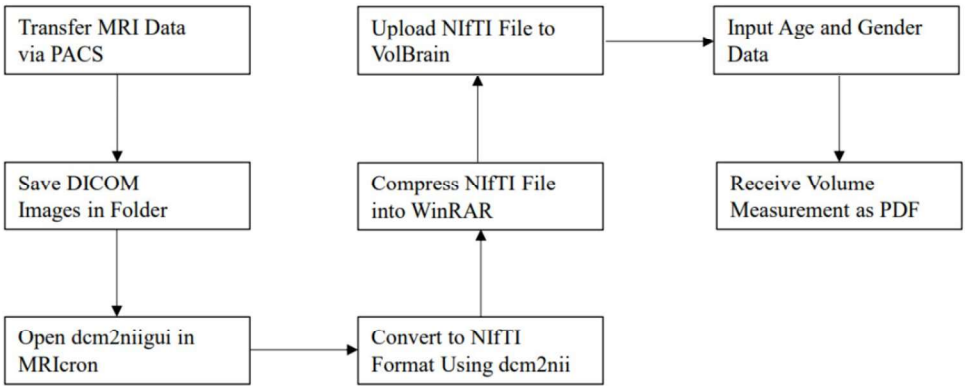


Fig. 1 Flowchart of volBrain analysis process

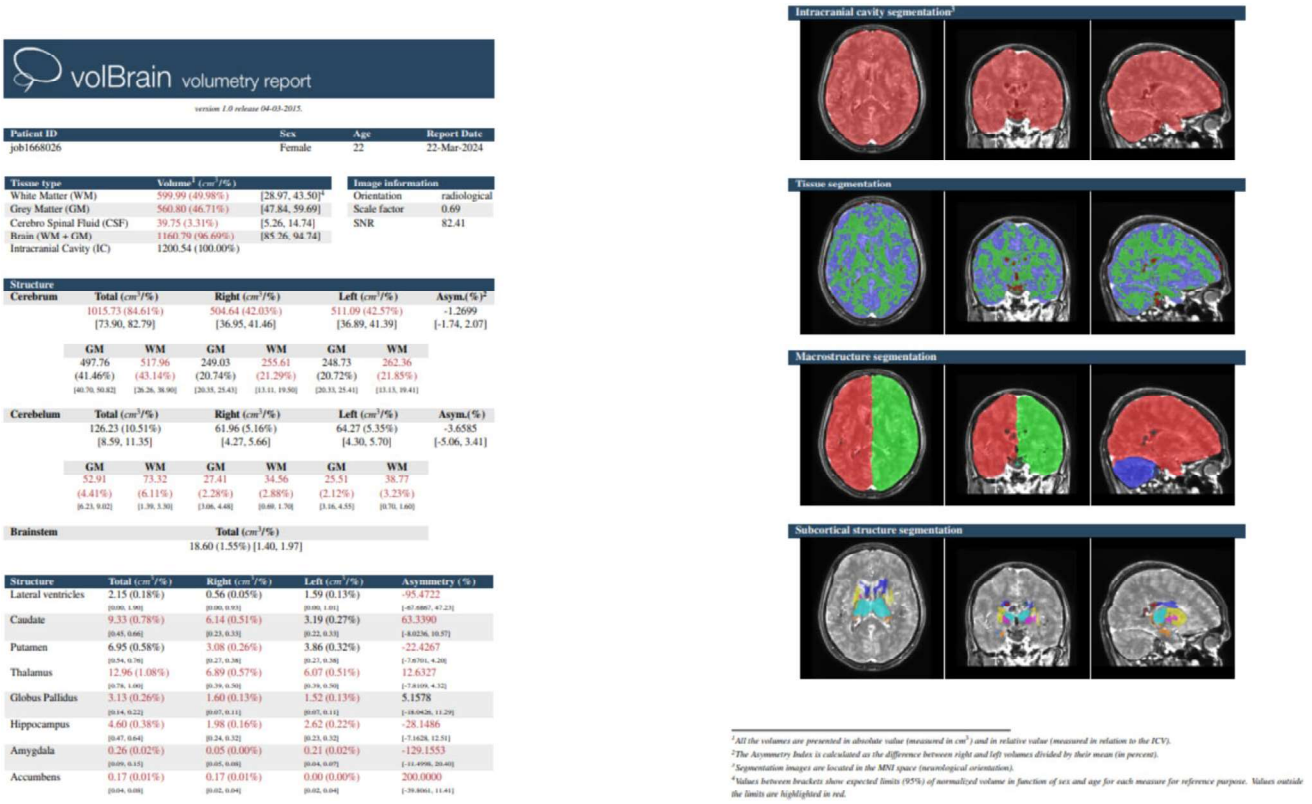


Fig. 2 volBrain volumetry report results and images of an individual in the study

minimized human error, thereby providing a standardized framework for volumetric analysis [10].

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) [13]. The normality of data distribution was assessed using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. As the data were not normally distributed, numerical variables were described using medians and interquartile ranges (25th–75th percentiles), whereas categorical variables were expressed as frequencies and percentages [14]. The Mann–Whitney U test was used to compare differences between independent groups. For repeated measures within dependent groups, the Friedman two-way analysis of variance was applied, followed by Dunn's test for pairwise comparisons. The relationships between categorical variables were evaluated using the chi-square analysis. Statistical significance was defined as a p-value less than 0.05.

Results

The study included 50 patients with RRMS and 50 healthy controls. The patient group consisted of 16 males (32%) and 34 females (68%), whereas the control group included 18 males (36%) and 32 females (64%). The median age of the patient group was 33.50 years (IQR: 25.75–38.00), whereas the control group had a median age of 38.00 years (IQR: 29.75–40.00). Among the patients with RRMS, 26 individuals (52%) had a disease duration of 0–5 years, and 24 individuals (48%) had a disease duration of 5–10 years (Fig. 3).

Upon comparing the volume values of the thalamus, nuc. caudatus, and nuc. lentiformis between the patient and control groups and the control group exhibited significantly higher volume values across most regions. The volume measurements of the right thalamus, right nuc. caudatus, right nuc. lentiformis, left thalamus, and left nuc. lentiformis were significantly lower in the RRMS group than in the control group ($p < 0.05$). However, no significant difference was observed in the left nuc. caudatus (Fig. 4A-B).

When subcortical volume measurements in the RRMS group were compared over three time points (2017, 2019, and 2022), the following trends were observed: The volume values of the right and left thalamus, nuc. caudatus, and nuc. lentiformis decreased progressively over time. The 1 st MRI values were higher than the 2nd MRI values, the 2nd MRI values were higher than the 3rd MRI values, and the most significant differences were observed between the 1 st and 3rd MRI measurements ($p < 0.05$) (Fig. 5A-B).

Time-dependent percentage changes in the volumes of subcortical structures were calculated for the RRMS group. The volume reduction percentages for the thalamus, nuc. caudatus, and nuc. lentiformis were highest between the 1 st MRI (2017) and the 3rd MRI (2022). Notably, the percentage decrease was smaller between the 1 st and 2nd MRIs (2017–2019) and between the 2nd and 3rd MRIs (2019–2022), indicating an accelerated reduction over longer durations (Fig. 6).

When the MRIs of the individuals in the patient group belonging to 3 different times in which the volume values of the subcortical areas were measured were compared, a significant difference was obtained in the volume values of the right and left thalamus, nuc. caudatus and nuc. lentiformis in the 2nd-3rd MRI and 1st-3rd MRIs. MRIs, a significant difference was found in the volume values of right and left thalamus, nuc. caudatus and nuc. lentiformis ($p < 0.05$) (Fig. 7).

When the volume measurements were compared between patients with RRMS by disease durations of 0–5 years and 5–10 years, no statistically significant difference was observed in the volume measurements of the right and left thalamus, nuc. caudatus, or nuc. lentiformis across the three MRI time points ($p > 0.05$). This indicates that while all patients with RRMS experienced subcortical atrophy over time, the rate of atrophy was independent

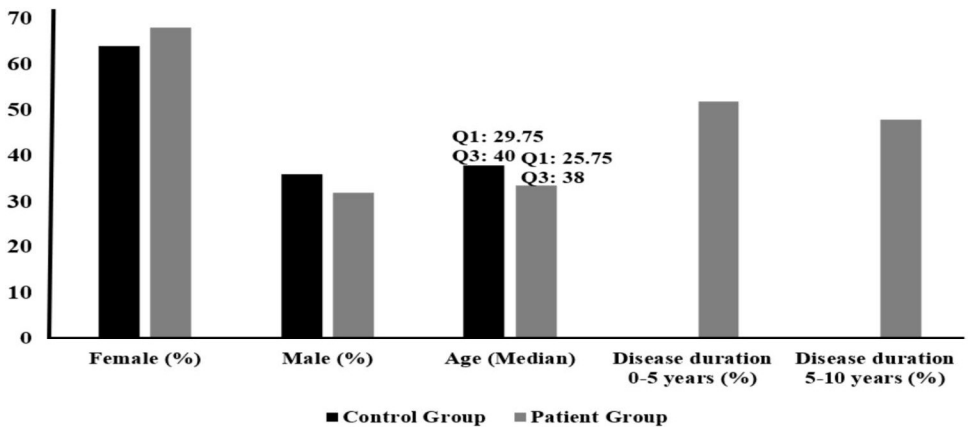


Fig. 3 Descriptive data of the groups included in the study. The demographic characteristics of the study showed a younger median age in the RRMS patients compared to healthy controls and a predominance of female participants in both groups

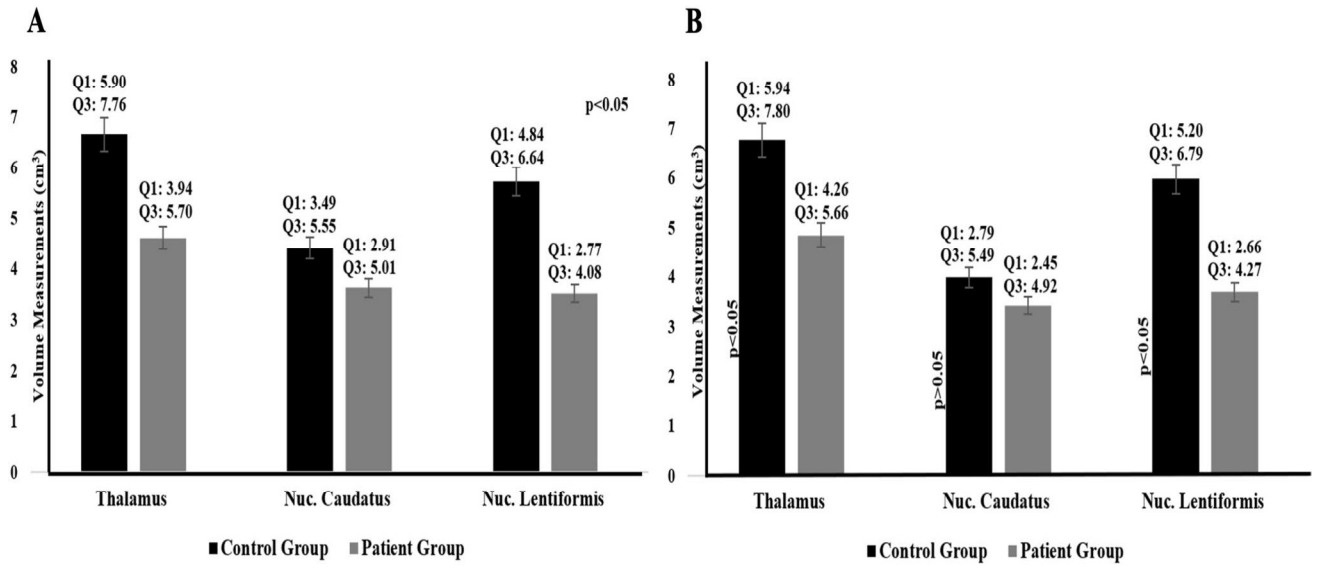


Fig. 4 Comparison of volume measurements of subcortical areas. **A** Representative comparison of volumes of subcortical areas' graphic for right thalamus, nuc. caudatus, and nuc. lentiformis structures. **B** Representative comparison of volumes of subcortical areas' graphic for left thalamus, nuc. caudatus, and nuc. lentiformis structures. Volumetric comparison of subcortical structures between RRMS patients and healthy controls, showing significantly lower volumes in the thalamus, nuc. caudatus, and nuc. lentiformis, except for the nuc. caudatus which did not differ significantly. *P values indicated statistical significance ($p < 0.05$). * The volume measurement unit of the subcortical structures in the graphs was cm^3

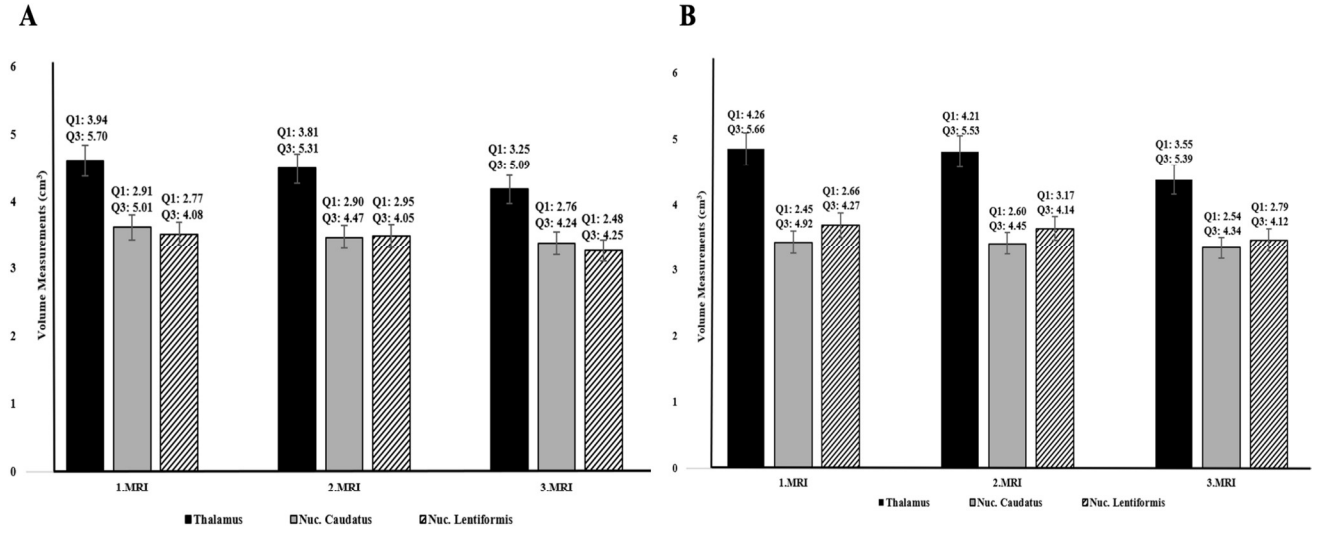


Fig. 5 Volume values of subcortical areas in the patient group. **A** Representative 1 st MRI, 2nd MRI, and 3rd MRI values comparison of volumes of subcortical areas' graphic for right thalamus, nuc. caudatus, and nuc. lentiformis structures **B** Representative 1 st MRI, 2nd MRI, and 3rd MRI values comparison of volumes of subcortical areas' graphic for left thalamus, nuc. caudatus, and nuc. lentiformis structures. Longitudinal volumetric analysis of subcortical structures in RRMS patients showed progressive reductions in the thalamus, nuc. caudatus, and nuc. lentiformis across three MRI time points (2017, 2019, and 2022), with the most pronounced decline observed between the 1 st and 3rd MRI. *1st MRI referred to the MRI image taken in 2017, 2nd MRI in 2019, and 3rd MRI in 2022

of the disease duration (Fig. 8). Overall, the results demonstrated a consistent pattern of progressive subcortical volume loss in the thalamus, nuc. caudatus and nuc. lentiformis of RRMS patients. This longitudinal decline highlighted the vulnerability of these clinically relevant structures and underscored their potential role as biomarkers for monitoring disease progression.

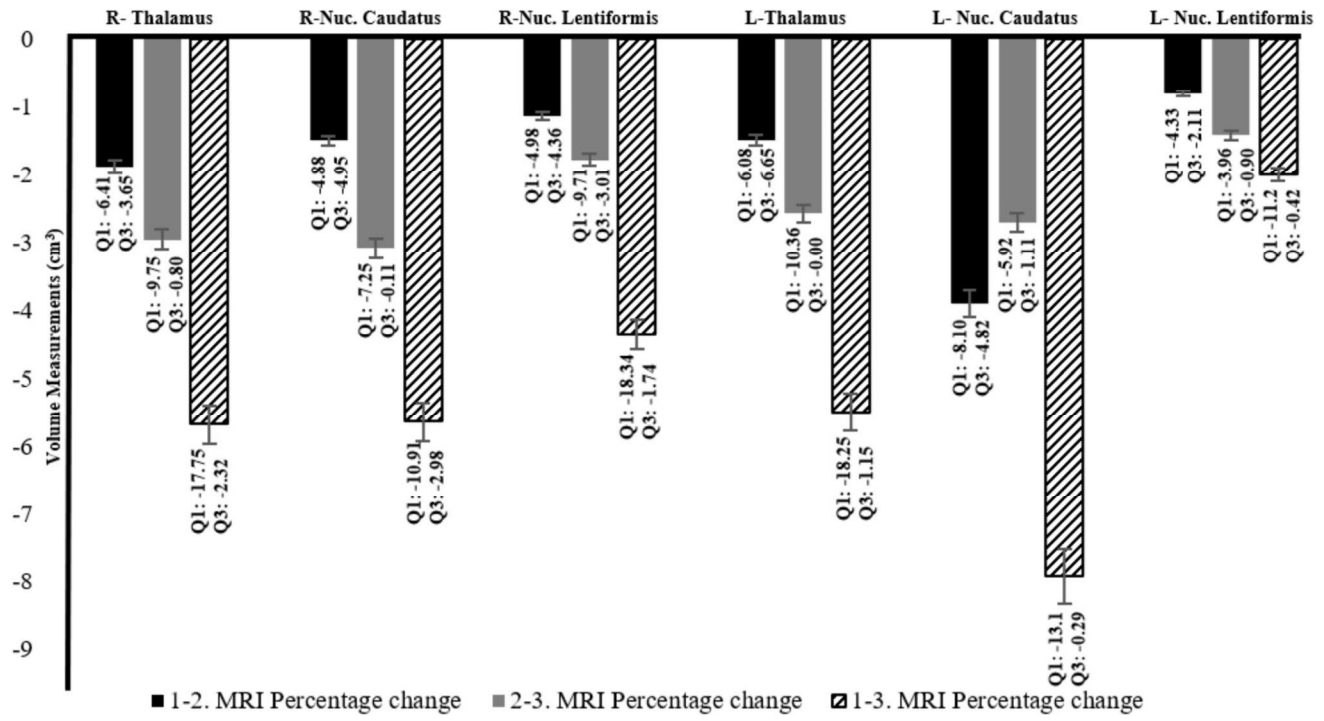


Fig. 6 Percentage change of subcortical area volumes in patient group. *R:right, L:left *In the graph, negative values indicated a decrease. Time-dependent percentage changes in subcortical volumes in RRMS patients demonstrated the greatest reductions between the 1st and 3rd MRI scans, while smaller decreases were observed between the consecutive intervals (1st-2nd and 2nd-3rd)

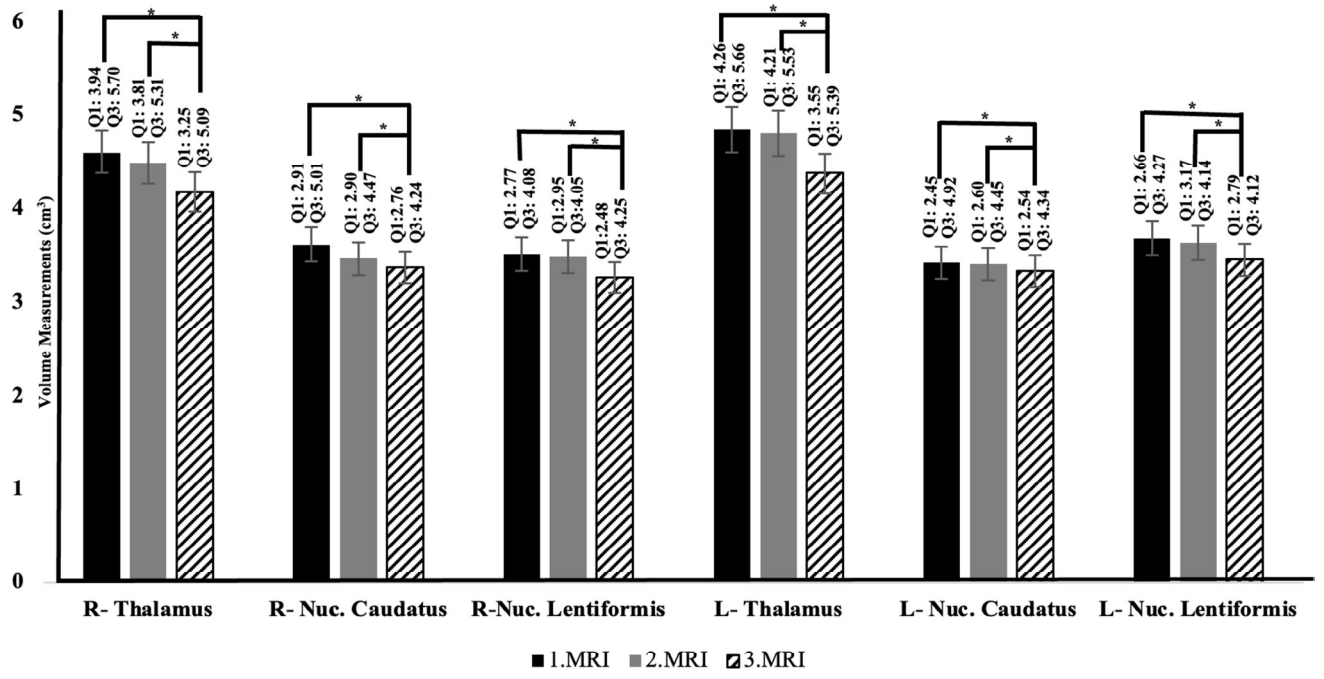


Fig. 7 Multiple comparison of measurement parameters of the patient group. Multiple comparisons of volumetric measurements in RRMS patients showed significant reductions in the thalamus, nuc. caudatus and nuc. lentiformis between 1st and 3rd MRI and 2nd and 3rd MRI measurements. The ''*'' sign indicated statistically significance ($p < 0.05$)

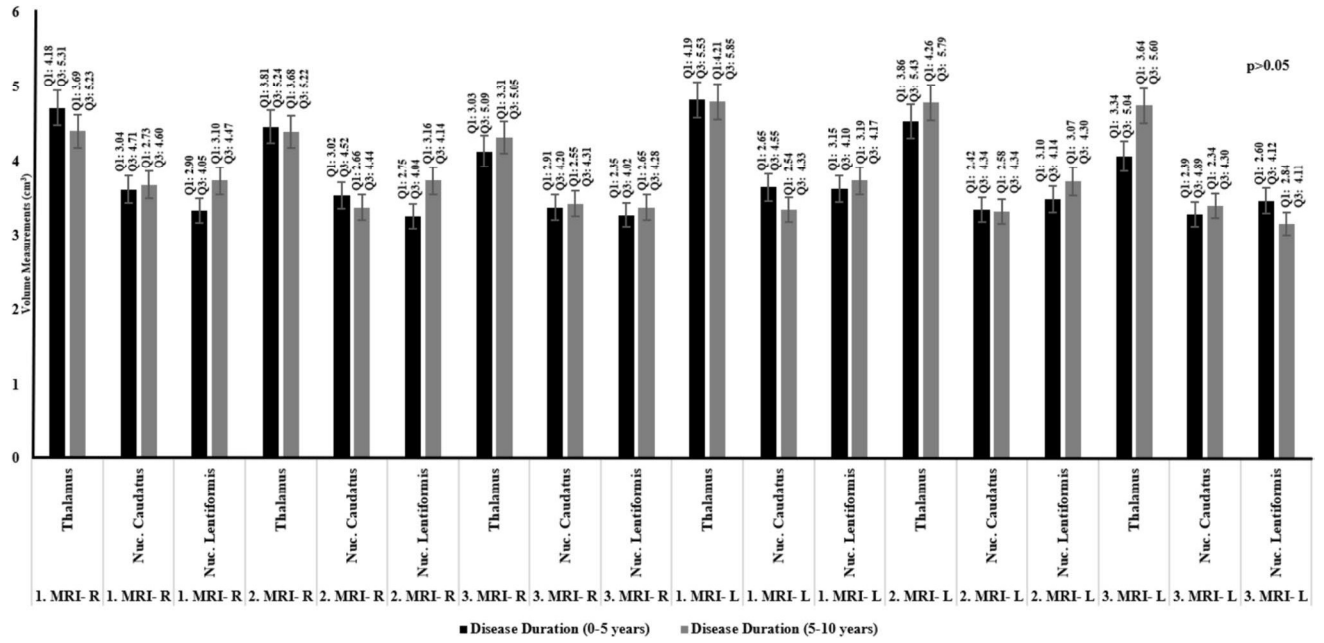


Fig. 8 Comparison of subcortical area volumes with disease duration. Subcortical volumes in RRMS patients with disease durations of 0–5 years and 5–10 years revealed no statistically significant differences, indicating that atrophy occurred regardless of disease duration

Discussion

RRMS, the most prevalent subtype of MS, is characterized by alternating phases of neurological relapse, during which symptoms worsen or new symptoms emerge, followed by periods of remission, during which symptom progression stabilizes or partially improves. Despite these remission phases, the disease often culminates in a progressive decline in neurological function over time, indicating its chronic and debilitating nature [15]. Understanding the structural brain changes underlying RRMS progression is crucial for identifying biomarkers that can enhance disease monitoring and therapeutic strategies. In this study, we investigated subcortical atrophy in the thalamus and basal nuclei using advanced neuroimaging tools. A cohort of 50 patients diagnosed with RRMS and 50 age- and gender-matched healthy controls was included in the analysis. Longitudinal data were obtained from T1-weighted MRI scans acquired at three distinct time points (2017, 2019, and 2022). These images were processed and analyzed using volBrain software to evaluate volumetric changes in subcortical structures over time. Our findings revealed a significant atrophy in the thalamus, nuc. caudatus, and nuc. lentiformis in patients with RRMS compared with healthy controls. The most pronounced reductions in volume were observed between the 1 st and 3rd imaging intervals, highlighting the progressive nature of subcortical atrophy in patients with MS. These results support the utility of volumetric measurements of subcortical brain structures as reliable biomarkers for tracking disease progression and correlating these changes with clinical symptoms. Such observations align with prior research, which has consistently demonstrated that reductions in regional and total brain volumes, largely driven by underlying mechanisms, such as demyelination and axonal injury, are hallmark features of MS pathology and are strongly associated with clinical decline [16, 17].

Examination of structural changes in the brains of patients with MS provides invaluable insights into disease progression and offers potential avenues for improved therapeutic interventions. A growing body of research has been dedicated to understanding these alterations in order to enhance disease management and patient outcomes [18–20]. Among the pathological hallmarks of MS, brain atrophy is one of the most detrimental, reflecting widespread and progressive damage to the central nervous system. This phenomenon is closely associated with degradation of the myelin sheath, axonal degeneration, and subsequent functional impairments in neural connectivity [21, 22]. Unlike the gradual and comparatively slower brain atrophy observed in normal aging, the rate of atrophy in MS is significantly accelerated and estimated to be approximately five times faster [23]. Moreover, gray matter demyelination and neuronal loss often begin in the early stages of MS and predate the onset of overt clinical symptoms. These changes contribute to the development of irreversible disabilities and cognitive impairments as the disease progresses [24, 25]. These findings highlight the urgent need for early diagnosis and targeted therapeutic strategies to slow down or prevent neurodegeneration and mitigate its

long-term effects. Importantly, gray matter atrophy in MS is not uniform across the brain. Certain regions, particularly those with high functional and structural demands, are more vulnerable to neurodegeneration [26, 27]. In RRMS, early atrophic changes have been identified in the limbic system, temporal cortex, and deep gray matter structures, which are critical for both cognitive and motor functions [28]. Building on this foundation, the present study focused on the longitudinal assessment of atrophic changes within key deep gray matter structures, including the thalamus, nuc. caudatus, and nuc. lentiformis in patients with RRMS. By tracking these regions over time, we aimed to elucidate the progression of subcortical atrophy and its potential role as a biomarker for monitoring disease progression and informing targeted interventions.

The median age of the patient group was 33.50 years (25.75–38.00), while that of the control group had a median age of 38.00 years (29.75–40.00) (Fig. 3). Prior studies have reported similar findings, with mean ages of 38.32 ± 8.74 for patients and 32.88 ± 6.87 for controls in grey matter studies [7] and 34.22 ± 7.23 for patients versus 41.44 ± 8.06 for controls in thalamus volume research [29]. Such age ranges align closely with the epidemiological profile of MS, wherein the majority of diagnoses occur between 20 and 40 years of age [30, 31]. The gender distribution in the present study revealed a predominance of females in both groups, with 68% of the patient cohort and 64% of the control cohort being female, while males accounted for 32% and 36%, respectively. This gender disparity is well-documented in the literature, which consistently reports a higher prevalence of MS among women, reflecting a global female-to-male ratio of approximately 2–3:1 [30, 32]. The role of the thalamus in MS pathology is particularly significant because of its central involvement in sensory processing, motor coordination, and cognitive functions. The thalamus has been shown to undergo significant volumetric reduction due to MS-related atrophy, which is strongly correlated with disease progression and the manifestation of clinical symptoms [29, 32]. In this study, volumetric analysis confirmed that thalamic volumes in patients with RRMS were markedly lower than those in healthy controls (Fig. 4), further substantiating the substantial atrophic changes observed in the MS pathology. This atrophy has been strongly linked to microstructural degeneration, which contributes to a cascade of neurological and functional impairments. Notably, thalamic degeneration has been associated with rapid cognitive decline, particularly in domains such as attention, memory, and executive functions [29, 33]. Furthermore, a reduction in thalamic volume has been implicated in structural and functional abnormalities underlying common MS symptoms, including fatigue, motor deficits, and sensory impairments [34]. Collectively, these findings underscore the pivotal role of the thalamus as a biomarker for understanding the pathological mechanisms of MS and as a potential target for therapeutic interventions aimed at mitigating cognitive and motor deterioration.

In our investigation, longitudinal volumetric changes in the thalamus were assessed across three distinct time points, as illustrated in Fig. 5. The results revealed a clear pattern of progressive atrophy in both the right and left thalamus over time, underscoring the degenerative nature of RRMS. This progressive volume reduction reflects the ongoing neurodegenerative processes characteristic of the disease, such as demyelination and axonal loss, which contribute to the structural and functional decline observed in the affected patients. Detailed statistical analyses of thalamic volumes within the patient group revealed significant differences between the 2nd and 3rd MRIs, as well as between the 1 st and 3rd MRIs, for both the right and left thalamus (Fig. 7). These findings highlighted the accelerated rate of atrophy during the later stages of the study period, suggesting that neurodegenerative changes intensify over time. Such temporal dynamics in thalamic atrophy not only emphasize the importance of longitudinal monitoring in MS but also reinforce the utility of volumetric MRI as a sensitive tool for detecting and quantifying these changes. This evidence further supported the role of the thalamus as a critical region for tracking disease progression and evaluating the efficacy of therapeutic interventions aimed at preserving brain structure and function in patients with RRMS. Specifically, the percentage median change in the right thalamus volume between the 2nd and 3rd MRIs was −2.96 (−9.75 to −0.80), and between the 1 st and 3rd MRIs, it was −5.68 (−17.15 to −2.32). For the left thalamus, the percentage median change was −2.58 (−10.36 to 0.00) between the 2nd and 3rd MRIs, and −5.49 (−18.25 to −1.15) between the 1 st and 3rd MRIs (Fig. 6). These findings underscored the progression of thalamic atrophy over time and revealed significant differences in the volumetric decline between specific time points. Although individuals with a disease duration of 0–5 years exhibited slightly higher thalamic volume values than those with a disease duration of 5–10 years, this difference was not statistically significant (Fig. 8). This lack of significance could be attributed to the relatively similar range of volume values within the patient group, as well as the possibility that thalamic atrophy progresses at variable rates among individuals. Variability in atrophy rates is consistent with previous research, which demonstrated that thalamic atrophy progressed differently over a five-year period in patients with RRMS compared to healthy controls [35]. Moreover, the existing literature supports a weak association between brain atrophy and both disease duration, and MS subtypes [32]. These findings suggest that the mechanisms underlying thalamic atrophy may not be entirely dependent on the disease duration or its clinical classification. Instead, the progression of atrophy may reflect a complex interplay of factors, including neuroinflammatory

processes, demyelination, and neurodegeneration, which are not fully captured by conventional clinical or radiological measures. This highlights the need for more nuanced approaches to study MS-related neurodegeneration, with an emphasis on exploring the diverse mechanisms contributing to atrophy patterns. Such insights are essential for developing targeted interventions aimed at mitigating disease progression and preserving neural integrity.

Atrophy in MS is known to affect the nuc. caudatus and nuc. lentiformis, which include the putamen and globus pallidus, both of which are critical components of basal nuclei [26, 36]. These structures play essential roles in motor control, cognitive function, and the regulation of various neurological processes. In this study, volumetric comparisons were performed between patient and control groups to assess the degree of atrophy in these regions. The results demonstrated that the patient group exhibited significantly lower volumes in the right nuc. caudatus, right nuc. lentiformis and left nuc. lentiformis compared to that in the control group (Fig. 4). The atrophy observed in the basal nuclei has been strongly linked to both motor and cognitive decline in patients with MS as well as the overall rate of disease progression [37, 38]. Prior research has highlighted that the putamen in particular undergoes rapid volumetric reduction during the early stages of MS, which then slows as the disease advances. This finding underscores the importance of monitoring atrophy in this structure to gain insights into disease onset and progression [39]. Abdominal atrophy was also nuc. caudatus and globus pallidus have been shown to correlate with impairments in walking function, independent of the MS subtype, as well as with total brain white and gray matter volumes [40, 41]. In the present study, further analysis revealed time-dependent atrophy in both the nuc. caudatus and nuc. lentiformis on the right and left sides, respectively, as observed in the MR images obtained at three distinct time points (Fig. 5). Multiple comparisons of the volumetric measurements in the patient group revealed significant differences between the 2nd and 3rd MRIs, as well as between the 1 st and 3rd MRIs, for both the right and left nuc. caudatus and nuc. lentiformis (Fig. 7). These findings provided additional evidence of the progressive nature of basal nuclei atrophy in MS and highlighted the importance of longitudinal volumetric assessments for tracking disease progression and its impact on motor and cognitive functions. In the comparison of the time-dependent percentage decrease as % median, 2nd-3rd MRIs right nuc. caudatus −3.09 (−7.25–0.11), right nuc. lentiformis −1.78 (−9.71–3.01); 2nd-3rd MRIs left nuc. caudatus −2,71 (−5,92–1,11) and left nuc. lentiformis −1,42 (−3,96–0,90) (Fig. 6). 1st-3rd MRIs showed −5.64 (−10.91–2.98) in right nuc. caudatus, −4.35 (−18.34–1.74) in right nuc. lentiformis, −7.92 (−13.1–0.29) in left nuc. caudatus and −2.01 (−11.2–0.42) in left nuc. lentiformis (Fig. 6). These findings underscored the significant relationship between basal nuclei atrophy and the severity of MS, particularly highlighting the clinical implications of atrophy in the nuc. caudatus in RRMS. Notably, the observed reduction in the volume of the nuc. caudatus have been shown to directly influence the manifestation and progression of clinical symptoms in patients with RRMS [41]. This association suggests that the nuc. caudatus plays a pivotal role in the pathophysiology of MS, serving as a critical region in which neurodegenerative changes translate into functional impairments. The importance of monitoring nuc. caudatus atrophy lies in its potential to provide valuable insights into the clinical trajectory of the disease, as its progressive degeneration has been linked to key symptoms, such as motor dysfunction, cognitive decline, and fatigue. These findings further emphasize the need to integrate advanced neuroimaging techniques into clinical practice to quantify atrophic changes in basal nuclei. Such assessments may improve the understanding of MS-related neurodegeneration, enhance the ability to predict disease progression, and tailor therapeutic interventions accordingly.

Volumetric comparisons of the nuc. caudatus and nuc. lentiformis were performed between patient subgroups categorized according to disease duration (0–5 years and 5–10 years). The analysis revealed no statistically significant differences in the volumes of these structures between the two subgroups (Fig. 8). This lack of significant variation could be attributed to the relatively similar volume values observed across individuals within the patient cohorts. Furthermore, MS progression is highly heterogeneous with substantial inter-individual variability in the timing, rate, and extent of morphological changes in the brain [42]. Such variability likely diminishes the direct relationship between disease duration and the degree of structural atrophy in specific regions, regardless of the time elapsed since the diagnosis. These findings align with the general trends reported in the literature, which emphasize the unpredictable and individualized nature of MS progression [43]. Our study extended the existing body of knowledge by providing focused insights into the longitudinal progression of atrophy within the thalamus and basal nuclei, which are critical components of deep gray matter structures. By quantifying the degree of atrophy in these regions, our research contributed to a deeper understanding of the relationship between structural changes and disease progression in MS. These findings have potential clinical significance, offering valuable implications for the assessment of disease prognosis and development of therapeutic interventions aimed at slowing or mitigating neurodegeneration. Such targeted approaches may ultimately enhance disease management and improve the quality of life of patients with MS.

This study had several limitations. The relatively small sample size, shaped by stringent exclusion criteria, was

one such limitation. Participants with cranial pathologies; demyelinating symptoms; or conditions potentially mimicking MS, such as neoplastic, degenerative, or vascular disorders, were excluded to ensure diagnostic precision. While this approach enhanced the specificity of the study, it also reduced the pool of eligible participants, potentially narrowing the scope of comparative analyses. Additionally, the retrospective design of the study, which relied on data extracted from the hospital registration system, limited the ability of participants to incorporate cognitive assessments. This aspect might have restricted the comprehensive evaluation of the interplay between structural atrophy and functional impairments. Despite these constraints, the findings of this research underscored the significant atrophy observed in the thalamus and basal nuclei of patients with RRMS, emphasizing their pivotal role in the progression of neurological and cognitive impairments. By employing advanced volumetric tools such as volBrain, this study demonstrated the utility of these structures as potential biomarkers for monitoring disease progression and predicting clinical outcomes. The observed reduction in the volume of these regions correlated with functional deficits in motor coordination, memory, learning, and sensory processing, all of which substantially impact the quality of life of patients with RRMS. This study contributed valuable insights into the neuropathology of MS, enriching the current understanding of disease mechanisms and progression. Furthermore, this study provided a foundation for the development of individualized therapeutic strategies and highlights the potential of integrating advanced imaging technologies into future investigations. By fostering a deeper comprehension of MS-related neurodegeneration, these findings will pave the way for improving both clinical management and research methodologies in this domain.

Our research demonstrated significant atrophy in the thalamus and basal nuclei in patients with RRMS, underscoring their pivotal role in the progression of both neurological and cognitive impairments. The thalamus, as a central relay station, and the basal nuclei, as key regulators of motor and executive functions, are critical for maintaining neural integration; therefore, their structural decline directly translates into functional deterioration. By highlighting these alterations, the present study emphasized the critical importance of utilizing automated volumetric tools, such as volBrain, to objectively quantify and monitor such changes over time. Unlike conventional imaging methods that focus primarily on lesion burden, automated volumetric analysis captures subtle but clinically meaningful atrophic changes, thereby providing a more comprehensive picture of disease activity. These tools serve as reliable and precise biomarkers for assessing disease progression and evaluating the effectiveness of therapeutic interventions in both research and clinical settings. The findings further revealed that progressive shrinkage of the thalamus and basal nuclei was strongly associated with deficits in motor coordination, memory, learning capacity, and sensory processing. Such impairments profoundly affect the quality of life of patients with RRMS, illustrating the wide-ranging consequences of subcortical atrophy in the physical, cognitive, and psychosocial domains. Therefore, the ability to accurately measure these changes through longitudinal volumetric analyses offers valuable insights into the dynamic and multifactorial nature of MS-related neurodegeneration, providing clinicians with tools to better predict outcomes and adapt treatment strategies accordingly.

In addition, this study not only advanced the current understanding of MS pathology but also laid a foundation for the development of more personalized therapeutic approaches. By identifying distinct patterns of atrophy in key subcortical regions, the research provided a framework for designing interventions that specifically target neurodegenerative mechanisms while addressing the functional deficits most relevant to patient well-being. Such region-specific insights could guide the prioritization of therapeutic strategies, from neuroprotective agents to rehabilitation programs, aimed at preserving the structural integrity and functional capacity. Furthermore, the integration of advanced imaging technologies into MS research and clinical practice holds considerable promise for transforming the management of this disease. volBrain offers clinicians and researchers powerful, reproducible, and time-efficient methods for monitoring disease progression, complementing traditional radiological assessments. Their use may enhance the early detection of atrophy, facilitate treatment response monitoring, and ultimately contribute to the development of predictive models of disease trajectory. In future studies, expanding longitudinal cohorts and integrating volumetric analyses with clinical, neuropsychological, and molecular data will be essential to deepen our understanding of MS-related neurodegeneration. Such multidisciplinary approaches have the potential to refine prognostic markers, optimize therapeutic interventions, and advance personalized medicine strategies, thereby improving the long-term outcomes and quality of life of RRMS patients. Future research should also prioritize multi-center investigations and the integration of volumetric findings with clinical outcome measures, ensuring that imaging-based biomarkers are directly translatable to patient care and real-world therapeutic decision-making.

Author contributions **Buket Kılıç:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing–original draft, Writing–review and editing. Ayla Tekin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing–original draft, Writing–review and editing. Sena Destan Bünül: Data curation, Investigation, Methodology. Hüsnü Efendi: Data curation, Investigation, Methodology. Özgür Çakır: Data curation, Investigation, Methodology. Kamil Can Kılıç: Data curation, Investigation,

Methodology, Writing–original draft, Writing–review and editing. Tuncay Çolak: Data curation, Investigation, Methodology. This collaborative effort ensured a comprehensive approach to the research from its inception through to the final written version of manuscript.

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Data availability The data will be made available upon request. The necessary information can be obtained from the corresponding author.

Declarations

Ethics approval Our study was received ethical approval from the Non-Interventional Clinical Research Ethics Committee of the Kocaeli University (project number: GOKAEK-2022/19.13 2022/321), Kocaeli, Turkey.

Author statements All authors have reviewed, approved, and provided their consent for the publication of this manuscript. The data associated with this study constitutes part of the data of my PhD thesis, as a corresponding author. On behalf of my co-authors, I hereby declare that the data pertaining to the other part of my PhD thesis were previously included in the article titled "Morphological Evaluation of Corpus Callosum Atrophy Over Time in Relapsing Remitting Multiple Sclerosis," published in Acta Medica Nicomedia (Vol. 7, pp. 332–338; https://doi.org/10.53446/actamednicomedia.1514240). Within the scope of this doctoral study, data pertaining to the Thalamus and Nuclei Basales (Putamen and Globus Pallidus) regions, obtained with the approval of the same ethics committee, were analyzed to address a distinct scientific inquiry. The objective was to assess the volumetric changes of these structures over time in patients with RRMS. Consequently, Therefore, these data have been re-evaluated within the context of an original scientific hypothesis, and the current manuscript was structured on the basis of these analyses. Our present study utilized automated volumetric analysis via volBrain software to assess longitudinal volume changes in key subcortical structures, including the thalamus, nucleus caudatus, and nucleus lentiformis. By shifting the anatomical focus from commissural white matter to deep gray matter nuclei and incorporating a fully automated, quantitative imaging approach, this study offered novel insights into subcortical atrophy progression in RRMS. Employing the volBrain platform, the study quantitatively assessed volume changes in these structures over a five-year period and evaluates their relationship with disease duration. By analyzing three serial MRI scans from RRMS patients and comparing them to a control group, the research aimed to establish temporal volume loss patterns and identify potential imaging biomarkers for MS-related neurodegeneration. Furthermore, it correlated structural degeneration with disease duration, thereby expanding upon and differentiating itself from our previously published study. This longitudinal volumetric analysis offered valuable insights into disease progression, enhanced our understanding of MS-related neurodegeneration by evaluating separate yet functionally relevant brain regions using advanced neuroimaging techniques and contribute to improved monitoring strategies in clinical settings.

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

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