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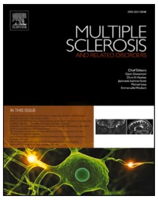

Original article

Association of brain structure and motor function in older persons with multiple sclerosis and healthy controls: A cross-sectional study

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ABSTRACT

Introduction: Brain structure deteriorates with aging as well as with neurodegenerative diseases such as multiple sclerosis (MS). While these brain changes are accompanied by deterioration of motor function, the association between brain structures and motor function in older people with MS (pwMS) has been scarcely investigated, especially across a broad range of outcomes.
Objective: To investigate the association between a broad range of brain structures and motor function outcomes in older pwMS as well as in older, healthy controls (HC).
Methods: The present cross-sectional study included $n = 41$ older pwMS ($\geq$60 years) and $n = 27$ age- and sex-matched HC. Assessments included volume and diffusivity of brain structures (evaluated via magnetic resonance imaging) and lower extremity motor function including neuromuscular function (muscle strength evaluated via leg press dynamometry; muscle power via chair rise test) and physical function (walking capacity evaluated via tests of walking speed, endurance, and balance/coordination).
Results: Associations between brain volumes and motor function were observed (generally weak, although moderate for lesion load), with more frequent and pronounced associations for walking capacity compared to neuromuscular function. Regarding brain diffusivity, associations were observed (generally weak-to-moderate), again with more frequent and pronounced associations for walking capacity compared to neuromuscular function.
Conclusion: Neurodegeneration – specifically the changes in brain volumes and diffusivity - remains a primary driver of motor decline in older pwMS (as well as in age- and sex-matched HC). This appears particularly evident for lesion load and brain diffusivity, being critically linked to various motor outcomes, most notably walking capacity.

1. Introduction

Multiple sclerosis (MS) is a debilitating autoimmune disease affecting the central nervous system (Jakimovski et al., 2023). It is often diagnosed in the mid-thirties but is becoming increasingly prevalent in those aged 60 years or older (Amankwah et al., 2017), currently comprising more than one-third of all MS cases (Magyari and Sorensen, 2019). MS neurodegeneration is hallmarked by demyelinated lesions (Lassmann, 2013; Thompson et al., 2018) as well as both regional and global brain atrophy (Schippling et al., 2017; Fjell et al., 2009; Peters, 2006; Eshaghi et al., 2018). Furthermore, brain microstructural integrity as measured by MRI-based diffusivity decreases in white and grey matter (De Kouchkovsky et al., 2016; Raz et al., 2013; Fuchs et al., 2019; Bester et al., 2015; Calabrese et al., 2011) as well as regionally (Fuchs et al., 2019; Hannoun et al., 2012; Cavallari et al., 2014; Reich et al., 2007). This MS-induced neurodegeneration is closely linked to disability

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progression (Matthews et al., 2023; Rocca et al., 2017).

The symptomatic presentation of MS varies substantially as neurodegeneration occurs across the CNS (Jakimovski et al., 2023). However, symptoms almost always include motor symptoms (Jakimovski et al., 2023; Compston and Coles, 2008) as evidenced by reduced neuromuscular function (e.g., maximal voluntary muscle contraction (MVC), rate of force development (RFD), and maximal muscle power) (Gaemelke et al., 2023; Geßner et al., 2024; Taul-Madsen et al., 2022; Sieljacks et al., 2020; Stagsted et al., 2021) and physical function (e.g., walking capacity such as speed, endurance, and balance/coordination) (Sieljacks et al., 2020; Stagsted et al., 2021; Hvid et al., 2020; Skjerbaek et al., 2023).

Even though increased neurodegeneration (Azevedo et al., 2019; Tokarska et al., 2023) and impaired motor function (i.e., neuromuscular function and walking capacity) (Gaemelke et al., 2023; Sieljacks et al., 2020; Stagsted et al., 2021) have frequently been observed in older people with MS (pwMS), associations between these characteristics have received little attention. In young and middle-aged pwMS, associations have been reported between walking capacity, walking speed and endurance, the volumes of white matter, grey matter thalamus, caudate, pallidum, putamen, and lesion load or volume (Motl et al., 2015; Hubbard et al., 2016; Motl et al., 2016; Jakimovski et al., 2018; Nygaard et al., 2021). In addition, walking speed and endurance have been shown to be associated with brain microstructural integrity. (Jakimovski et al., 2018; Nygaard et al., 2021) As for neuromuscular function, assessed as muscle strength of the knee extensors, knee flexors, and ankle dorsi flexors, associations with microstructural integrity of the corticospinal tract have also been reported (Baird et al., 2018; Reich et al., 2008), but not with brain volumes (Reich et al., 2008). Surprisingly, only two previous studies have involved older pwMS. The first study did observe an association between a composite motor function measure and brain lesion load, but not with brain diffusivity (measured as white matter integrity of the fronto-striatal circuits) (Wagshul et al., 2023). In contrast, the other study did observe associations between functional connectivity of certain brain networks and gait speed (Nayak et al., 2025). In comparison, associations between brain structures and motor function have been studied extensively in healthy aging, with systematic reviews revealing associations between both brain volumes and diffusivity and a broad range of walking capacity measures (Holtzer et al., 2014; Kilgour et al., 2014) alongside neuromuscular function (Kilgour et al., 2014). This supports the notion that both brain volumes and diffusivity are closely linked to motor function.

Altogether, the current knowledge involving older individuals (pwMS in particular) - a highly relevant population due to increased neurodegeneration and impaired motor function – is limited, and there is a need for studies that include a broad range of motor function outcomes (including neuromuscular function) along with brain volumes and diffusivity. Therefore, the objective of the present study was to investigate the association patterns of brain volumes and diffusivity with neuromuscular function and walking capacity in older pwMS and older age- and sex-matched HC.

It was hypothesized that associations of brain volumes and diffusivity with neuromuscular and walking capacity would exist in older pwMS and age- and sex-matched HC.

2. Methods

The present cross-sectional study includes n = 41 older pwMS and n = 27 older age- and sex-matched HC and adhered to the STROBE reporting guideline (von Elm et al., 2007). Data originates from baseline data collected in the Power Training in Older Multiple Sclerosis (PoTOMS) trial, a study investigating the effects of power training in older pwMS (Gaemelke et al., 2024). A published study protocol provides details on methodologies for outcome measures as well as recruitment and eligibility criteria for pwMS and HC; these criteria were identical for both groups, excluding MS-specific requirements and the exercise intervention (Gaemelke et al., 2024). Relevant information is therefore only briefly summarized here, with further details on neuroimaging provided in Supplementary materials 1.

The PoTOMS is preregistered at clinicaltrial.gov (NCT04762342), approved by the Central Denmark Region Committees on Health Research Ethic with reference number 1-10-72-222-20, and approved by the Danish Data Protection Agency with reference number 2016-051-000,001.

2.1. *Study design and participants*

Recruitment was conducted with four Danish regional MS clinics and The Danish MS Society. The inclusion criteria for pwMS were as follows: 1) $\geq$ 60 years of age, 2) diagnosis of MS, 3) EDSS 6.5 or lower, 4) capable of self-transportation to testing and exercise sessions, and 5) willing to participate in an exercise study. Exclusion criteria were: 1) comorbidity affecting testing or training participation, (2) participation in $\geq$ 2 resistance exercise sessions a week, and (3) cognitive impairments hindering understanding of test instructions. HC, who was age- (±5 years) and sex-matched, was recruited in a 3:2 ratio through the social network of participating pwMS and the network of the authors. Inclusion and exclusion criteria HC were comparable to those of older pwMS, except for the MS-related criteria. Participants provided informed written ethical consent and data processing consent before inclusion.

2.2. *Neuroimaging*

Brain MRI scans were performed on a 3T MRI scanner (MAGNETOM Skyra, Siemens Medical Systems, Erlangen, Germany). MRI sequences included a T1-weighted 3D Magnetization Prepared 2 Rapid Acquisition Gradient Echo sequence (MP2RAGE) (Marques et al., 2010), a T2 fluid-attenuated inversion recovery (T2FLAIR) sequence, and a diffusion kurtosis imaging (DKI) sequence. The study protocol (Gaemelke et al., 2024) as well as Supplementary materials 1 outlines details of neuroimaging scan processing methods.

Brain volumes were measured as whole-brain, white matter, grey matter, and T2 lesions, along with volumes for the corpus callosum, thalamus, hippocampus, putamen, cervical spine, caudate, and globus pallidus. These brain regions were a priori defined in the PoTOMS trial protocol due to their involvement in motor function (Gaemelke et al., 2024). All brain volumes were normalized to estimated intracranial volume (white matter + grey matter + cerebrospinal fluid).

Brain microstructural integrity was measured as mean diffusivity (with a higher value indicating less integrity) was assessed for the brain regions: corpus callosum, thalamus, hippocampus, putamen, caudate, globus pallidus, motor cortex, cingulate cortex, and corticospinal tract. As a supplementary outcome, fractional anisotropy (lower values indicating less integrity) was measured in the same brain regions; data is presented in Supplementary materials 2.

2.3. *Motor function*

Neuromuscular function was assessed via leg press muscle strength of the weakest leg (MVC and RFD) and concentric chair rise muscle power, with specific testing procedures provided in the PoTOMS protocol paper (Gaemelke et al., 2024). Leg press was assessed using a custom-built digital dynamometer, which consisted of piezoelectric force transducers Kistler 9367/8 B (Kistler Group, Winterthur, Schweiz) embedded in the footplate, sampling at 1 kHz. During each leg press trial, participants were instructed to contract as hard and fast as possible and to maintain maximal force exertion for approximately 4 s. A minimum of three trials were carried out; if MVC values differed by $\geq$ 5%, additional trials were performed until consistency was achieved. From the trial with the highest MVC, RFD was also calculated, specifically from contraction onset to 50 ms (RFD_{50}, early phase RFD) and 200 ms ($RFD_{200,}$ late phase RFD). All leg press outcome measures were normalized to body weight. A maximal chair rise test assessed lower limb muscle power during the concentric phase, using a linear encoder (Cronojump, Bosco system, v1.8.1, Spain; sampling rate 1000 Hz) (Stagsted et al., 2021). Participants were instructed to cross their arms across the chest and rise from the chair as fast and powerfully as possible, fully extending the knees and hip joints (i.e., the ascending/-concentric phase). The linear encoder measured movement speed, which was used to determine maximal concentric chair rise power normalized to body weight.

Walking capacity was assessed using the Timed 25-foot Walk Test (T25FWT) to measure walking speed expressed in m/s (Goldman et al., 2008; Hochsprung et al., 2014), the Six Spot Step Test (SSST) to measure walking balance/coordination expressed in 1/s (Callesen et al., 2019), and the 6-Minute Walk Test (6 MWT) to measure walking endurance expressed in m (Bennett et al., 2017).

2.4. Statistics

The present study was conducted as part of the PoTOMS trial (Gaemelke et al., 2024). Consequently, the sample size was determined according to the primary outcome of the PoTOMS trial (Gaemelke et al., 2024).

Prior to statistical analysis, assumptions regarding independence, comparable distributions, and normal distributions of variance were checked using Q-Q plots. The lesion load was logarithmically transformed to better approximate a normal distribution. Group differences (pwMS vs. HC) were analyzed using linear mixed-effects models (participant ID set as a random effect; group set as a fixed effect), reported as mean difference with 95% confidence intervals (CI). Associations between separate motor function outcomes and brain metrics (volume or diffusivity) were evaluated using (numerical) standardized β coefficients from linear regression models. These models pooled data from both pwMS and HC to capture a broader spectrum of variance across both motor function outcomes and brain metrics (volume or diffusivity), mitigating potential ceiling effects in HC and floor effects in pwMS. Additionally, all models were adjusted for age and sex, as these factors are known to influence both motor function and brain volumes/diffusivity.

All statistical analyses were performed in STATA v. 17.0 (StataCorp, College Station, TX, USA), while figures were created using GraphPad Prism v. 7.0 (GraphPad Software, Boston, MA, USA). A p-value <0.05 was considered statistically significant. Standardized β coefficients (numerical) were interpreted as negligible (0.00–0.09), weak (0.10–0.39), moderate (0.40–0.69), strong (0.70–0.89), and very strong (0.90–1.00) (Schober et al., 2018). Of note, we emphasized standardized β coefficients and mean differences [95%CI] alongside p-values when interpreting study findings.

3. Results

Participant characteristics were comparable between pwMS and age- and sex-matched HC (Table 1). The age- and sex-matching of HC to pwMS was deemed successful as there were no group differences in age and sex or other baseline characteristics. The older pwMS had an age of 65.7 ± 3.6 years and 56% were women, while HC had an age of 66.7 ± 4.0 and 56% were women. The dataset was complete for all measures, with the exception of maximal chair rise power, which was missing for n = 2 older pwMS who were unable to perform the test. The brain structure and motor function outcome measures are presented in Table 2.

3.1. Brain volumes and motor function

Brain volumes showed weak associations with motor function outcomes, except for lesion load showing weak-to-moderate association (Fig. 1). The T25FWT and SSST were the walking capacity outcomes most frequently associated with brain volumes, with the whole brain, lesion load, corpus callosum, and thalamus showing consistent associations. Additionally, the T25FWT is associated with caudate, while SSST is associated with putamen and cervical spine. As for the 6MWT associations, they were observed with the lesion load, corpus callosum, cervical spine, and thalamus. Maximal chair rise power was associated with lesion load and caudate, while leg press MVC and RFD (at 50 ms and 200 ms) were associated with lesion load only. The age and sex-adjusted analysis found comparable but more consistent patterns across motor functions.

Table 1
Participant characteristics.

	Older pwMS n = 41	HC n = 27	Mean diff. [95%CI]
Females (n (%))	23 (56)	15 (56)	-
Age (years)	65.7 ± 3.6	66.7 ± 4.0	−1.0 [−2.8;0.8]
Height (cm)	171.6 ± 9.0	172.5 ± 11.0	−1.0 [−5.3;3.3]
Weight (kg)	75.0 ± 11.7	72.2 ± 2.1	2.8 [−2.7;8.3]
BMI (kg × m^{-2})	25.6 ± 4.4	24.3 ± 3.4	1.3 [−0.6;3.2]
TSD (yrs)	16.1 ± 10.5	-	-
EDSS (score)	3.5 (3.0–4.5)	-	-
MS phenotype (n (%))			
Relapse-remitting	14 (34)	-	-
Secondary progressive	21 (51)	-	-
Primary progressive	6 (15)	-	-
DMT (n (%))	14 (34)	-	-
Walking aids (n (%))	8 (20)	0 (0)	-

Data on older people with multiple sclerosis and healthy controls are presented as mean and standard deviation, median and interquartile range, percentages, or numbers. Differences are presented as mean differences with a 95% confidence interval. Abbreviations: pwMS: People with multiple sclerosis; HC: age- and sex-matched healthy controls; mean diff: Mean differences; 95%CI: 95% confidence interval; BMI: Body mass index; TSD: Time since diagnosis; EDSS: Expanded disability status scale; DMT: Disease-modifying treatment.

3.2. Brain microstructure and motor function

Regional mean diffusivity showed weak to moderate associations with motor outcomes (Fig. 2). The walking outcomes 6MWT, T25FWT, and SSST were the most consistently associated with brain diffusivity outcomes, with 6MWT showing association across all outcomes. Leg press MVC and RFD 200 ms showed a weak association with the diffusivity of the putamen and caudate, and additionally, MVC showed an association with the corticospinal tract. Maximal chair rise power and leg press RFD 50 ms showed negligible to weak associations, which did not reach statistical significance for any brain region MD. The age and sex-adjusted analysis found comparable patterns across motor functions. Regional fractional anisotropy across all nine investigated regions showed an association with walking capacity outcomes, and the age and sex-adjusted analysis found comparable patterns across walking capacity outcomes (Supplementary materials 2). Putamen fractional anisotropy was most frequently associated with walking capacity outcomes, and to some extent also with neuromuscular function outcomes.

4. Discussion

In the present study, brain volumes and diffusivity (global, regional, and tract) were associated with motor function outcomes in older pwMS and age- and sex-matched HC. Our overall hypothesis was thus confirmed. Interestingly, across a broad range of motor function outcomes comprising muscle strength and power as well as walking capacity, association patterns were more pronounced for brain regional diffusivity (weak to moderate associations) than for volumes (generally weak associations, except for lesion load often showing moderate associations). Across brain volume measures, lesion load was the most frequently associated with the motor function outcomes (associated with all motor function outcomes), whereas thalamus and corpus

Table 2

Brain structure and motor function of older pwMS and age- and sex-matched HC.

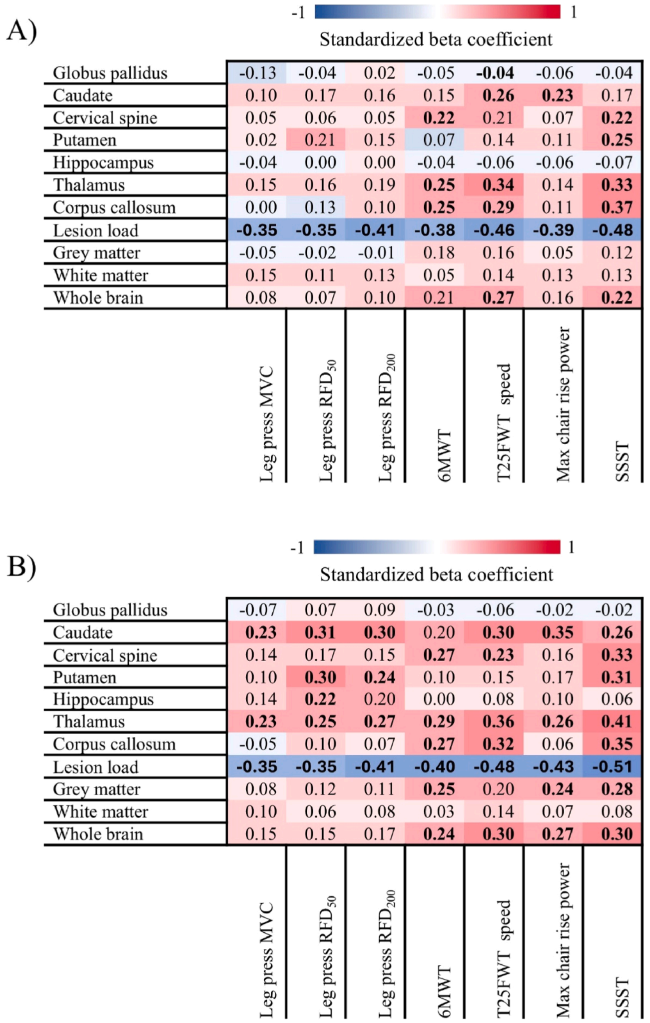
	Older pwMS n = 41	HC n = 27	Mean diff. [95%CI]
Physical function			
MVC [N/kg]	12.7 ± 4.7	19.3 ± 4.9	−6.6 [−8.9;−4.3]
RFD50ms [N/s/kg]	15.7 ± 11.8	37.1 ± 15.5	−21.4 [−27.8;−15.0]
RFD200ms [N/s/kg]	20.2 ± 12.1	39.5 ± 14.2	−19.4 [−25.5; −13.2]
6MWT [m]	442±146	632±61	−191 [−247;−133]
T25FWT [m/s]	1.16±0.32	1.85±0.22	−0.7 [−0.8;−0.6]
Chair maximal power [W/kg]	12.0 ± 3.9	18.4 ± 4.5	−6.4 [−8.4;−4.4]
SSST [1/s]	0.113±0.040	0.173±0.032	−0.06 [−0.08;−0.04]
Brain volumes [cm^3]			
Whole brain	805±32	824±25	−20 [−34;−5]
White matter	324±28	334±20	−10 [−22;2]
Grey matter	481±27	490±34	−9 [−24;5]
Lesion load (ln)	2.02±0.74	0.85±0.84	1.18 [0.80;1.55]
Lesion load	*6.5 (5.2–13.7)*	*2.3 (1.4–4.7)*	*not applicable*
Corpus callosum	0.391±0.088	0.419±0.071	−0.029 [−0.068;0.011]
Thalamus	7.272±1.236	8.196±0.701	−0.913 [−1.421;−0.406]
Hippocampus	4.205±0.576	4.285±0.502	−0.080 [−0.344;0.183]
Cervical spine	1.601±0.213	1.674±0.164	−0.073 [−0.167;0.021]
Putamen	6.093±0.657	6.371±0.572	−0.278 [−0.578;0.023]
Caudate	5.281±0.644	5.563±0.601	−0.282 [−0.583;0.020]
Globus pallidus	1.603±0.197	1.583±0.190	0.020 [−0.074;0.113]
Brain diffusivity [mm^2/s]			
Corpus callosum	1.202±0.119	1.161±0.085	0.042 [−0.011;0.094]
Thalamus	0.979±0.063	0.957±0.029	0.022 [−0.004;0.048]
Hippocampus	1.061±0.046	1.040±0.029	0.022 [0.002;0.042]
Putamen	0.897±0.102	0.869±0.035	0.028 [−0.013;0.069]
Caudate	0.959±0.086	0.928±0.031	0.031 [−0.003; 0.066]
Globus pallidus	0.927±0.092	0.900±0.064	0.027 [−0.013;0.068]
Corticospinal tract	0.904±0.041	0.887±0.032	0.017 [−0.001;0.037]
Motor cortex	1.273±0.103	1.232±0.091	0.041 [−0.008;0.090]
Cingulate cortex	1.128±0.077	1.101±0.072	0.028[−0.010;0.065]

Values are presented as mean (SD) (lesion load is logarithmically transformed; raw values are also shown as median and interquartile range in italics) as well as group mean difference [95%CI]. Brain volumes are presented normalized to inter-cranial volume, except for the cervical spine, which is normalized to inter-cervical spine volume. Brain diffusivity is presented as mean diffusivity within the designated region. Abbreviations: pwMS: People with MS; HC: Healthy controls; MVC: Maximal voluntary contraction; RFD: Rate of force development; 6MWT: 6-minute walk test, T25FWT: Timed 25-foot walk test, and SSST: Six-spot step test; ln: logarithm, and MD: Mean diffusivity.

callosum were the second most frequently associated measures (associated with all walking capacity outcomes). Across brain diffusivity measures, putamen and caudate were the ones most frequently associated with the motor function outcomes (associated with almost all motor function outcomes), followed by the corticospinal tract. Walking capacity was the motor function with the most robust association pattern across brain outcomes, yet with no apparent differences between T25FWT, SSST, and 6MWT. Altogether, these results expand our current knowledge of the association between brain volumes / diffusivity and motor function outcomes in older pwMS, a population at high risk of neurodegeneration, and age- and sex-matched HC.

The present study shows more frequent associations between motor function and the brain’s regional and tract diffusivity (β value range 0.00–0.45, Fig. 2A) than volumes (β value range 0.00–0.48, Fig. 1A; highest values consistently observed for lesion load). This corroborates findings previously observed in young and middle-aged pwMS (Motl et al., 2015; Hubbard et al., 2016; Motl et al., 2016; Jakimovski et al., 2018; Nygaard et al., 2021). Moreover, one previous study involving older pwMS reported an association between walking speed and brain network connectivity (i.e., resting state functional connectivity of fronto-parietal, cerebellar, and language networks) (Nayak et al., 2025). However, another study by the same research group failed to observe any associations between white matter integrity and mobility impairments (Wagshul et al., 2023). A study involving young pwMS reported volumetric measures of the grey and white matter alongside MD of normal-appearing grey and white matter, with only the former being associated (Spearman's ρ of −0.48) with walking capacity but no other outcomes (Jakimovski et al., 2018). A longitudinal study involving older HC reported an association between the long-term (years) change in volume and MD of brain outcomes and the change in daily walking time (r-values range of 0.18–0.21), also after adjusting for influential factors such as the carrier status of the APOE ε4 polymorphism (Best et al., 2017). This supports a causal association of brain structure and motor-related outcomes. Synthesizing the findings from the present study and previous studies, motor-related brain regions and tract diffusivity appear to be stronger and more consistently associated with motor function than more global measures of brain volumes or diffusivity (with the exception of lesion load). This suggests that changes in walking capacity and microstructural integrity – whether elicited from neurodegeneration or through pharmacological or non-pharmacological interventions – influence each other.

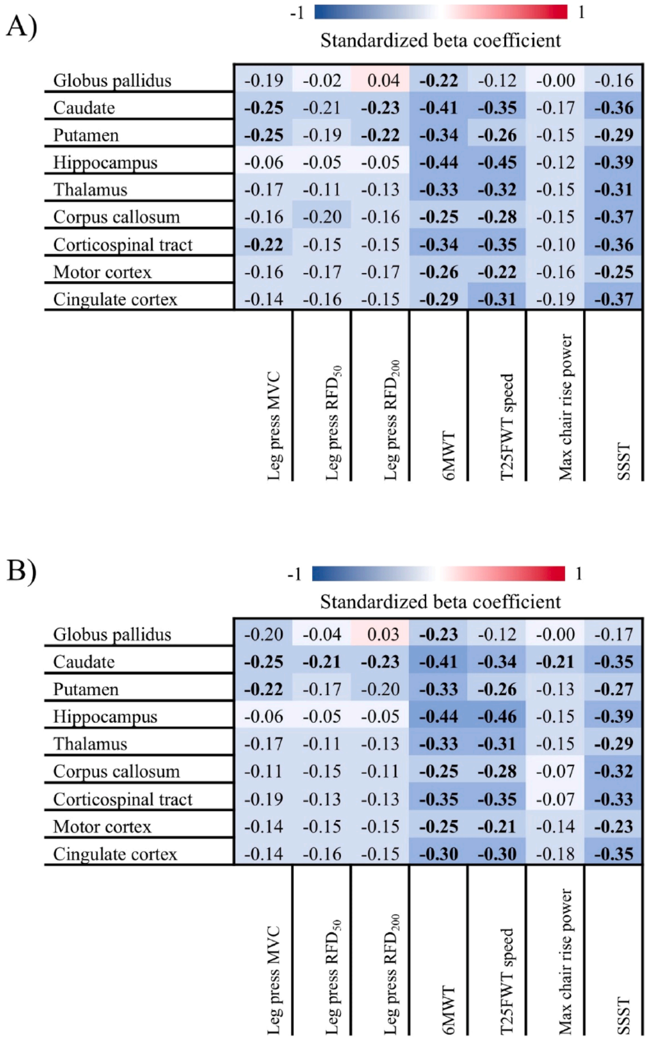
Brain volumes and diffusivity were consistently found to be more pronounced associated with walking capacity than with neuromuscular function in the present study, also after adjusting for age and sex. This is a novel observation, as previous studies have rarely carried out comprehensive evaluation of both walking and neuromuscular function, i.e., across a broad range of outcomes. To our knowledge, the only previous study with such data involved middle-aged pwMS, although with one measure of neuromuscular function only. Their results suggested comparable association patterns of neuromuscular function and walking capacity for the corticospinal tract (Fritz et al., 2017). Further comparison to previous studies relies on inter-study comparisons, introducing the caveat that differences in analytic approach and study population characteristics such as age and disability status. Considering this, a systematic review involving healthy individuals reported weak associations between brain volumes and neuromuscular function (Kilgour et al., 2014), thus corroborating the present study observations involving older pwMS and HC. Furthermore, the sparse data suggested that regional volumes were associated numerically stronger with neuromuscular function than global volume. The association of brain



	Leg press MVC	Leg press RFD_{50}	Leg press RFD_{200}	6MWT	T25FWT speed	Max chair rise power	SSST
Globus pallidus	-0.13	-0.04	0.02	-0.05	**-0.04**	-0.06	-0.04
Caudate	0.10	0.17	0.16	0.15	**0.26**	**0.23**	0.17
Cervical spine	0.05	0.06	0.05	**0.22**	0.21	0.07	**0.22**
Putamen	0.02	0.21	0.15	0.07	0.14	0.11	**0.25**
Hippocampus	-0.04	0.00	0.00	-0.04	-0.06	-0.06	-0.07
Thalamus	0.15	0.16	0.19	**0.25**	**0.34**	0.14	**0.33**
Corpus callosum	0.00	0.13	0.10	**0.25**	**0.29**	0.11	**0.37**
Lesion load	**-0.35**	**-0.35**	**-0.41**	**-0.38**	**-0.46**	**-0.39**	**-0.48**
Grey matter	-0.05	-0.02	-0.01	0.18	0.16	0.05	0.12
White matter	0.15	0.11	0.13	0.05	0.14	0.13	0.13
Whole brain	0.08	0.07	0.10	0.21	**0.27**	0.16	**0.22**

	Leg press MVC	Leg press RFD_{50}	Leg press RFD_{200}	6MWT	T25FWT speed	Max chair rise power	SSST
Globus pallidus	-0.07	0.07	0.09	-0.03	-0.06	-0.02	-0.02
Caudate	**0.23**	**0.31**	**0.30**	0.20	**0.30**	**0.35**	**0.26**
Cervical spine	0.14	0.17	0.15	**0.27**	**0.23**	0.16	**0.33**
Putamen	0.10	**0.30**	**0.24**	0.10	0.15	0.17	**0.31**
Hippocampus	0.14	**0.22**	0.20	0.00	0.08	0.10	0.06
Thalamus	**0.23**	**0.25**	**0.27**	**0.29**	**0.36**	**0.26**	**0.41**
Corpus callosum	-0.05	0.10	0.07	**0.27**	**0.32**	0.06	**0.35**
Lesion load	**-0.35**	**-0.35**	**-0.41**	**-0.40**	**-0.48**	**-0.43**	**-0.51**
Grey matter	0.08	0.12	0.11	**0.25**	0.20	**0.24**	**0.28**
White matter	0.10	0.06	0.08	0.03	0.14	0.07	0.08
Whole brain	0.15	0.15	0.17	**0.24**	**0.30**	**0.27**	**0.30**

Fig. 1. Association of brain volumes and motor function outcomes in older pwMS and age- and sex-matched healthy controls. A shows standardized β coefficients for simple regression, and B shows standardized β coefficients adjusted for age and sex. The standardized β coefficients are colored according to strength (red marking positive and blue marking negative association), and statistical significance ($p < 0.05$) is marked by bold text. Abbreviations: MVC: Maximal voluntary contraction, 6MWT: 6-minute walk test, T25FWT: Timed 25-foot walk test, and SSST: Six-spot step test, RFD: Rate of force development, MVC: Maximal voluntary contraction.



	Leg press MVC	Leg press RFD_{50}	Leg press RFD_{200}	6MWT	T25FWT speed	Max chair rise power	SSST
Globus pallidus	-0.19	-0.02	0.04	**-0.22**	-0.12	-0.00	-0.16
Caudate	**-0.25**	-0.21	**-0.23**	**-0.41**	**-0.35**	-0.17	**-0.36**
Putamen	**-0.25**	-0.19	**-0.22**	**-0.34**	**-0.26**	-0.15	**-0.29**
Hippocampus	-0.06	-0.05	-0.05	**-0.44**	**-0.45**	-0.12	**-0.39**
Thalamus	-0.17	-0.11	-0.13	**-0.33**	**-0.32**	-0.15	**-0.31**
Corpus callosum	-0.16	-0.20	-0.16	**-0.25**	**-0.28**	-0.15	**-0.37**
Corticospinal tract	**-0.22**	-0.15	-0.15	**-0.34**	**-0.35**	-0.10	**-0.36**
Motor cortex	-0.16	-0.17	-0.17	**-0.26**	**-0.22**	-0.16	**-0.25**
Cingulate cortex	-0.14	-0.16	-0.15	**-0.29**	**-0.31**	-0.19	**-0.37**

	Leg press MVC	Leg press RFD_{50}	Leg press RFD_{200}	6MWT	T25FWT speed	Max chair rise power	SSST
Globus pallidus	-0.20	-0.04	0.03	**-0.23**	-0.12	-0.00	-0.17
Caudate	**-0.25**	**-0.21**	**-0.23**	**-0.41**	**-0.34**	**-0.21**	**-0.35**
Putamen	**-0.22**	-0.17	-0.20	**-0.33**	**-0.26**	-0.13	**-0.27**
Hippocampus	-0.06	-0.05	-0.05	**-0.44**	**-0.46**	-0.15	**-0.39**
Thalamus	-0.17	-0.11	-0.13	**-0.33**	**-0.31**	-0.15	**-0.29**
Corpus callosum	-0.11	-0.15	-0.11	**-0.25**	**-0.28**	-0.07	**-0.32**
Corticospinal tract	-0.19	-0.13	-0.13	**-0.35**	**-0.35**	-0.07	**-0.33**
Motor cortex	-0.14	-0.15	-0.15	**-0.25**	**-0.21**	-0.14	**-0.23**
Cingulate cortex	-0.14	-0.16	-0.15	**-0.30**	**-0.30**	-0.18	**-0.35**

Fig. 2. Association of brain regional mean diffusivity and motor function outcomes in older pwMS and age- and sex-matched healthy controls. A shows standardized β coefficients for simple regression, and B shows standardized β coefficients adjusted for age and sex. The standardized β coefficients are colored according to strength (red marking positive and blue marking negative association), and statistical significance ($p < 0.05$) is marked by bold text. Abbreviations: MVC: Maximal voluntary contraction, 6MWT: 6-minute walk test, T25FWT: Timed 25-foot walk test, and SSST: Six-spot step test, RFD: Rate of force development, MVC: Maximal voluntary contraction.

volume and walking capacity outcomes is generally reported to be more pronounced for regional volumes than associations with global volumes (Motl et al., 2015; Motl et al., 2016; Jakimovski et al., 2018; Dumurgier et al., 2012; Aribisala et al., 2013; Shiee et al., 2012), with whole-brain, white matter, and grey matter showing only weak associations as previously reported (Motl et al., 2015; Jakimovski et al., 2018; Dumurgier et al., 2012; Aribisala et al., 2013; Shiee et al., 2012). Moreover, the observed associations between brain metrics (volume or diffusivity) and motor function remained largely stable after adjusting for age and sex. This indicates that neurodegenerative changes – rather than age and sex – are the main drivers of motor dysfunction, at least in the present small populations of older pwMS and HC. Summarized, the present study and previous studies show that brain volumes and diffusivity are more pronounced associated with walking capacity outcomes than with neuromuscular function. Such a stronger association of walking to brain volumes and diffusivity could infer that a walking task may be more dependent on the integrity of the brain than is the case for neuromuscular function. The neuromuscular function test applied mainly relies on a maximal neural drive to the agonist muscle and inhibition of the antagonist muscle (Alkner et al., 2000). In contrast, walking predominantly requires the up- and downregulation of a submaximal neural drive between several muscles to coordinate the walking movement (Agostini et al., 2020; Winter and Yack, 1987). This dynamic neural regulation during walking may make walking more susceptible to neurodegeneration and be an explaining factor in the more pronounced associations between walking and the brain's volumes and diffusivity. Furthermore, the repetitive nature of walking may contribute to this effect, as neurodegeneration that impairs walking could repeatedly affect performance throughout a walking capacity test, forming a cumulative impact that may result in a stronger observed association. A noticeable observation was that different walking capacity tests (6MWT, T25FWT, and SSST) – which captures different aspects of walking (i.e., speed, endurance and balance/coordination) (Skjerbaek et al., 2023) - showed comparable associations with brain structure. As described above, brain volumes were associated with walking capacity outcomes resembling findings from earlier studies. However, diffusivity of brain regions exhibited more pronounced and consistent association patterns with walking capacity outcomes also extending to neuromuscular function. This could suggest that brain diffusivity are more closely associated to motor function than brain volume. One possible explanation is that microstructural changes may occur earlier than volumetric changes, as observed in the hippocampus of mice (Islam et al., 2020) and suggested in humans (Riemenschneider et al., 2022). Therefore, brain microstructure may better reflect the body's current motor function capacity than brain volume. A notable exception was lesion load, which demonstrated consistent weak-to-moderate associations with motor function outcomes. These findings suggest that lesion load remains a critical factor that should be accounted for alongside diffusivity and other volume metrics.

4.1. Methodological considerations

The present study employed a cross-sectional design using baseline data from the PoTOMS trial (Gaemelke et al., 2024), which introduces specific considerations when interpreting the findings. First, the associations between a broad range of motor function and brain MRI outcomes observed in the present study do not imply causal relationships, and the interpretation should be done accordingly. Second, selection bias may be present in the baseline data from the PoTOMS trial (Gaemelke et al., 2024), which specifically recruited for an exercise trial: such participants are typically more physically active than the general population (Harris et al., 2008). This potential bias is underlined by the present study population displaying superior walking capacity – and likely socio-economic status - compared to age-matched pwMS from previous studies (Hvid et al., 2020). This may also provide a plausible explanation for the unexpected absence of major differences in brain metrics (volumes and diffusivity) between HC and pwMS. Future studies would benefit from recruiting a more representative spectrum – potentially accounting for lifestyle factors and varying disability levels - to ensure findings are generalizable to the broader MS population. Third, the present investigation of associations between motor function and brain MRI outcomes includes different brain regions and tracts. These regions and tracts were a priori defined, as they are all involved in motor function. However, due to the complex structure and function of the brain, other brain regions and tracts as well as brain networks may also be associated with motor function outcomes. Fourth, we did not adjust for the potential inflation of the familywise error rate associated with multiple testing. This choice was driven by the exploratory nature of the study and the desire to maintain adequate statistical power. Consequently, this factor should be considered when interpreting the findings, placing emphasis on standardized β coefficients and mean differences with confidence intervals alongside p-values.

4.2. Clinical perspectives

Neurodegeneration in aging and young to middle-aged MS is linked to motor function, and the present findings suggest that this association persists in older pwMS. Therefore, managing motor functions in MS and aging might benefit from shared therapeutic strategies as disease-modifying treatment efficacy appear to decrease in older pwMS (Jakimovski et al., 2021). In relation to this, exercise present itself as a very potent strategy for pwMS as previously highlighted (Dalgas et al., 2019), especially in terms of having a beneficial impact on neuromuscular function and walking capacity. Moreover, understanding and managing motor symptoms in MS might be improved by examining microstructure to understand the relation between motor symptoms and neurodegeneration. However, establishing true associations requires further investigation, ideally through longitudinal/prospective studies.

5. Conclusion

The present study suggests that both brain volumes and diffusivity are associated with motor function (i.e., neuromuscular function and walking capacity) in older pwMS as well as in age- and sex-matched HC. Notably, brain diffusivity measures showed more pronounced association patterns with motor function than brain volumes, and walking capacity showed more pronounced association patterns than neuromuscular function.

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CRediT authorship contribution statement

Tobias Gaemelke: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Simon F Eskildsen:** Writing – review & editing, Validation, Resources, Methodology, Data curation, Conceptualization. **Theo Skjøt:** Writing – review & editing, Investigation. **Jens G Ottesen:** Writing – review & editing, Investigation. **Mikkel KE Nygaard:** Writing – review & editing, Validation, Resources, Data curation. **Steffen Ringgaard:** Writing – review & editing, Resources. **Peter Feys:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Christoffer Laustsen:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Ulrik Dalgas:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Lars G Hvid:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

In relation to the present work, the authors have nothing to declare.

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Supplementary materials

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