ORIGINAL COMMUNICATION

Cortical thickness and cognition in older people with multiple sclerosis

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Abstract

Background The structural changes associated with cognitive performance in older people with multiple sclerosis (PwMS; age ≥ 50 years old) remain unknown.

Objective To determine the relationship between whole-brain (WBV), thalamus as the largest deep gray matter nuclei, and cortex-specific volume measurements with both cognitive impairment and numerical performance in older PwMS. The main hypothesis is that cognitive impairment (CI) in older PwMS is explained by cortical thinning in addition to global and thalamic neurodegenerative changes.

Methods A total of 101 older PwMS underwent cognitive and neuroimaging assessment. Cognitive assessment included tests established as sensitive in MS samples (Minimal Assessment of Cognitive Function in MS; MACFIMS), as well as those tests often utilized in Alzheimer's dementia studies (Wechsler's Memory Scale, Boston Naming Test, Visual Motor Integration and language). Cognitive impairment (CI) was based on -1.5 standard deviations in at least 2 cognitive domains (executive function, learning and memory, spatial processing, processing speed and working memory and language) when compared to healthy controls. WBV and thalamic volume were calculated using SIENAX/FIRST and cortical thickness using FreeSurfer. Differences in cortical thickness between CI and cognitively preserved (CP) were determined using age, sex, education, depression and WBV-adjusted analysis of covariance (ANCOVA). The relationship between domain-specific cognitive performance and cortical thickness was analyzed by linear regression models adjusted for age, sex, education, depression, WBV and thalamic volume. Benjamini-Hochberg-adjusted p-values lower than 0.05 were considered significant.

Results The average age of the study population was 62.6 (5.9) years old. After adjustment, CI PwMS had significantly thinner left fusiform ($p = 0.0003$), left inferior ($p = 0.0032$), left transverse ($p = 0.0013$), and bilateral superior temporal gyri ($p = 0.002$ and $p = 0.0011$) when compared to CP PwMS. After adjusting for age, sex, education, depression WBV, and thalamic volume, CI status was additionally predicted by the thickness of the left fusiform ($p = 0.001$) and left cuneus gyri ($p = 0.004$). After the adjustment, SDMT scores were additionally associated with left fusiform gyrus ($p < 0.001$) whereas letter-based verbal fluency performance with left pars opercularis gyrus ($p < 0.001$).

Conclusion In addition to global and thalamic neurodegenerative changes, the presence of CI in older PwMS is additionally explained by the thickness of multiple cortical regions.

Introduction

Multiple sclerosis (MS) is a neuroinflammatory, demyelinating, and neurodegenerative disease characterized by chronic accrual of neurological disability commonly affecting people aged 18–50 years old [1]. In addition to physical limitations, many people with multiple sclerosis (PwMS) also exhibit insidious cognitive decline that can negatively

impact employment status and quality of life [2]. Cognitive impairment (CI) affects 30–60% of PwMS, with higher percentages reported in older PwMS with longer disease duration, progressive MS phenotype and more severe MS pathology [2].

Over the past 30 years, advances in pharmacological and rehabilitative treatment of PwMS have drastically improved overall MS life expectancy, slowed disability worsening, and prolonged quality of life maintenance well into the expected retirement years [3]. These improvements

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to care resulted in a substantial epidemiological shift from a young (18–50 years old) PwMS population to an older, comorbid, and more frail population of older people with MS (> 50 years old, PwMS) [3]. For example, the peak prevalence age of PwMS in the US was 30–39 years in 1976, whereas the latest epidemiological queries (performed in 2010) resulted in a peak age of 55–64 years old [4].

Because aging is intrinsically associated with questions regarding changes to cognitive functioning, it is challenging to determine whether cognitive declines in older PwMS result from normal aging, disease progression, or some combination of the two. While it is known that processing speed and memory typically represent the most common cognitive deficits in MS, several studies showed that other domains (such as language) may be more relevant in older PwMS [5, 6]. These changes were initially recognized by Müller et al., where aging secondary-progressive MS (SPMS) patients had verbal fluency deficits similar to those that can be seen in amnestic mild cognitive impairment (aMCI), a prodromal stage of Alzheimer's disease (AD) [7]. Similar comparisons also demonstrate significant deficits in cognitive processing speed and categorical verbal fluency of older PwMS when compared to aging healthy controls (HCs) [8]. Lastly, our group has utilized a comprehensive panel of MS and AD-specific tests to fully characterize the domain-specific cognitive performance in more than 100 older PwMS and showed deficits in processing speed and verbal fluency [9]. These findings have since been replicated in the literature in other MS samples [10–12].

Aging in MS is also associated with greater neurodegenerative processes resulting in increased brain atrophy when compared to healthy individuals and younger PwMS [13, 14]. Studies suggest that brain structures have a differential vulnerability to pathological atrophy, which can vary throughout the lifespan and MS disease, resulting in different ratios of age-associated brain loss versus MS-specific atrophy [14, 15]. For example, the thalamus is highly vulnerable to atrophy during early disease while the cerebral cortex is predominantly affected in long-standing and older PwMS [15–17]. It is well established in the literature that early changes in the thalamic structures are highly correlated with MS cognitive processing speed [18, 19]. Such relationships between cortical thickness and cognitive performance of older PwMS have not yet been established.

The main hypothesis of this study is that cognitive impairment in older PwMS may be additionally explained by cortical thinning in addition to global and thalamic atrophy. For this purpose, we examined 101 older PwMS (age > 50 years old) using a comprehensive neuropsychological battery and correlated their performance with cortical thickness and deep gray matter (DGM) MRI measures. Since such analyses were not previously reported in the literature, we considered all gyri equally and corrected for false discovery rate. We also directly compared the cortical thicknesses between CI and cognitively preserved (CP) PwMS and between PwMS with and without isolated cognitive domain impairments. Findings from such analyses could determine the age-specific vulnerable regions that could serve as future exploratory neurodegenerative outcomes in neuroprotective and cognitive rehabilitative studies for older PwMS.

Materials and methods

Study population

All study participants were enrolled at the Jacobs MS Center for Treatment and Research, University at Buffalo and participated as research participants in the cardiovascular, environmental and genetic risk factors in MS (CEG-MS) study [9]. The inclusion criteria for the older PwMS were: (1) MS diagnosis based on 2010 and 2017-revised McDonald criteria based on their time of recruitment [20, 21], (2) age of at least 50 years old, (3) availability of MRI examination and neuropsychological assessment within 6 months of each other and (4) availability of MS-specific and dementia-specific neuropsychological assessment. The exclusion criteria were: (1) diagnosis of additional major neurological disorder, (2) major depressive disorder, (3) use of psychoactive agents that could affect the cognitive performance, (4) vision acuity worse than 20/70 that could affect the performance on multiple vision-dependent cognitive tests and (5) clinically-determined relapse or received intravenous corticosteroid therapy within the previous 30 days of the MRI acquisition.

The inclusion criteria for the HCs were: (1) age of at least 50 years old and (2) availability of MS and AD-specific neuropsychological assessment for comparative purposes and calculation of normative values. The exclusion criteria for the HCs were: (1) presence of current or history of a major neurological disorder, (2) diagnosis of major depressive disorder, (3) use of psychoactive agents that could affect the cognitive performance, (4) vision acuity worse than 20/70 that could affect the performance on multiple vision-dependent cognitive tests. The study population has been previously published elsewhere [9]. The discrepancy in PwMS between the two publications is due to the lack of MRI examination in 3 PwMS [9].

Neurostatus-certifed examiners calculated the Expanded Disability Status Scale (EDSS) for all patients [22]. Additional clinical data regarding disease duration, years of formal education and the type of disease-modifying treatment (DMT) were collected using standardized questionnaires. Disease phenotype was classified according to the 2013 Lublin criteria using clinical presentation and medical history. PwMS diagnosed with primary-progressive MS (PPMS) and secondary-progressive MS (SPMS) were merged into one

progressive MS (PMS) group [23]. Motor performance was measured using the Timed 25-Foot Walk Test (T25FWT) and 9-Hole Peg Test (9HPT) for dysfunction of the lower and upper extremities, respectively [24, 25].

Neuropsychological assessment

Neuropsychological testing of the older PwMS was performed by trained technicians under the supervision of a board-certified neuropsychologist. The specific neuropsychological tests, their contribution to specific cognitive domains and their references are outlined in Supplement Table 1. Cognitive reserve was estimated with years of formal education. Patient-reported depressive and fatigue symptoms were quantified with the Beck Depression Inventory – Fast Screen (BDI-FS) and Fatigue Severity Scale (FSS) questionnaires, respectively. The majority of cognitive assessment was performed using the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery, which evaluates cognitive processing speed [Paced Auditory Serial Addition Test – 3 s (PASAT-3) and Symbol Digit Modalities Test (SDMT)], learning and memory [California Verbal Learning Test–second edition (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMT-R)], language [Controlled Oral Word Association Test (COWAT)] and executive function [Delis-Kaplan Executive Function System (D-KEFS)]. Additional AD-specific cognitive tests were included: Logical Memory from Wechsler Memory Scale-Revised (WMS-R), Boston Naming Test (BNT), Beery Visual-Motor Integration (VMI), and clock drawing test. In all tests, higher scores indicate better performance.

The older PwMS were considered CI when they scored -1.5 standard deviations (SD) in at least two out of five cognitive domains (executive control, learning and memory, spatial processing, processing speed and working memory, and language) when compared to age-matched healthy control data [9]. Based on common classification from the literature, PwMS with performance comparable to the HCs or with an isolated impairment in one domain were initially considered as CP. Moreover, comparisons between PwMS with and without isolated impairment within the specific domains of processing speed and language were performed. The definition of impairment in one specific cognitive domain was also based on performance in at least one domain-specific test of -1.5 SD when compared to the healthy control data.

MRI acquisition and analyses

All MS patients were scanned on the same 3 T Signa Excite HD 12.0 Twin Speed MRI scanner (GE, Milwaukee, WI, USA) using an 8-channel head and neck coil. The two main sequences utilized for this study were: (1) high-resolution 3D T1-weighted fast spoiled gradient-echo with magnetization-prepared inversion recovery (IR-FSPGR) with repetition time (TR)/echo time (TE)/ inversion time (TI) of 5.9/2.8/900 ms, field of view (FOV) of 25.6 X 19.2 cm^2 (256×256 matrix), flip angle of 10 degrees and 180 1 mm slices without gaps, (2) 2D T2-Fluid attenuated inversion recovery (FLAIR) scans with TR/TE/TI of 8500/120/2100 ms, FOV of 25.6 X 19.2 cm^2 (256×256 matrix), flip angle of 90 degrees, echo train length (ETL) of 24 and 48 3 mm slices without gaps.

Semi-automated quantification of white matter (WM) lesion volume (T2-FLAIR hyperintensities) were assessed using Java Image Manipulation software (JIM, Xinapse systems, Essex, UK) by an experienced operator. The image analyses were blinded from the clinical and neuropsychological status. Volumes of whole-brain (WBV), WM, and gray matter (GM) were derived using cross-sectional Structural Image Evaluation, using Normalisation, of Atrophy (SIENAX, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA), normalized for head-size. Lesion filling was performed prior to segmentation to minimize tissue misclassification. Normalized DGM volume and specific volumes of the thalamus, caudate, putamen, globus pallidus, and hippocampus were obtained with FMRIB's Integrated Registration and Segmentation Tool (FIRST, https://fsl.fmrib.ox.ac.uk/fsl, version 6.0). Lastly, FreeSurfer (version 6.0, http://surfer.nmr.mgh.harvard.edu) was used to parcellate the cortex into 68 different regions (34 per hemisphere) based on the Desikan-Killiany atlas and cortical thickness was obtained [26]. Full description of each gyrus is available elsewhere [27]. Outputs from all MRI analyses were visually inspected and corrections were made if necessary (e.g. editing brain masks, adding control points) during the FreeSurfer analysis.

Statistical analyses

All statistical analyses were performed in SPSS version 24.0 (IBM, Armonk, NY, USA). The data distribution was assessed using visual inspection of the histograms and Q-Q plots. Normally distributed data is shown as mean and SD whereas data without normal distribution are reported using median and interquartile range (IQR).

The demographic, clinical and neuropsychological measures between the older PwMS and HCs were compared using χ^2 test, Student's t-test and Mann–Whitney U test, as appropriate. Differences in MRI measures and cognitive measures between the CP and CI PwMS were determined using analysis of covariance (ANCOVA) adjusted for age, sex, years of education, patient-reported depression (BDI-FS), whole brain volume and thalamic volume. Cohen's d was used to determine the effect size for the comparisons.

All MRI comparisons between the CP vs. CI PwMS groups were initially corrected for age, years of education, patient-reported depression (BDI-FS), WBV, and thalamic volume. Based on the hypothesis, thalamic volume was included in the corrections to determine the relationship between cortical thickness and cognitive performance after excluding the effect of already established thalamic associations with cognitive performance in MS. The multiple comparisons of cortical thickness in all 34 cortical regions on both sides (total of 68 comparisons) between the groups and their per-domain classifications were further adjusted using Benjamini–Hochberg procedure. Only p-values that survived multiple comparison adjustment were considered as statistically significant. To ensure that no single subject was driving our comparison findings, bootstrapping using 1000 Monte Carlo simulations was performed [28]. The same comparisons were performed between pwRRMS and pwPMS. For comparisons of general demographic, clinical and neuropsychological data, a p-value lower than 0.05 was considered statistically significant.

The relationship between cognitive performance in domain-specific tests and cortical thickness was assessed using linear regression models that were adjusted for age, sex, education, BDI-FS scores, WBV and thalamic volume. Step-wise criteria to determine the best predictors of cognitive performance used entry and exit tolerance of 0.01 and 0.05, respectively. R^2 and standardized β from the regression models were reported. Additional logistic regression models and receiver operating characteristic (ROC) curves were used to determine the best measures to accurately predict the presence of CI in the older PwMS. In both the comparison and regression analyses, the FSS and disease duration were not included as covariates due to their collinearity (high variance inflation factor; VIF) with BDI-FS and age, respectively.

Results

Demographic and clinical characteristics of older PwMS

The demographic and clinical characteristics of the total PwMS population, HCs, the CI PwMS and CP PwMS are shown in Table 1. The PwMS were on average 62.6 (SD = 5.9) years old, 75.2% were female and had an average disease duration of 21.2 (SD = 12.6) years. The differences between PwRRMS and PwPMS groups are shown in Supplement Table 2. The overall fraction of cognitive impairment in PwMS was 36.6% with only a numerically greater fraction of CI in the PwPMS (40.5% vs. 34.4%, $p = 0.536$). There were no demographic differences between the CI and CP PwMS in age (62.5 vs. 62.7 years old, $p = 0.84$), disease

duration (23.9 vs. 19.7 years, p = 0.101), years of education (14.7 vs. 15.1 years, $p = 0.375$), patient-reported depression (BDI-FS median 1.0 vs. 1.0 $p = 0.824$) and fatigue (FSS median 5.2 vs. 4.7, $p = 0.15$). The CI PwMS were more disabled when compared to the CP PwMS in EDSS (median 5.5 vs. 3.25, $p = 0.003$), T25FWT (median 9.1 s vs. 6.1 s, $p = 0.011$) and 9HPT (27.2 s vs. 23.5 s, $p = 0.001$).

Neuropsychological performance of the older PwMS

The neuropsychological performance of the HCs vs. older PwMS and between the CI vs. CP PwMS are described in detail in Table 2. The biggest differences in cognitive performance between HCs and PwMS per effect size were in SDMT (55.4 vs 43.9, Cohen's d = 1.059, $p < 0.001$) and categorical verbal fluency (45.9 vs. 37.1, Cohen's d = 0.967, $p < 0.001$). As expected, CI PwMS had significantly worse performance in all cognitive tests when compared to CP PwMS ($p < 0.002$). The biggest effect sizes were seen in processing speed (SDMT, Cohen's d = 1.384; PASAT-3, Cohen's d = 1.218), verbal and visuospatial memory (CVLT-II, Cohen's d = 1.455 and BVMT-R, Cohen's d = 1.454) and language (COWAT, Cohen's d = 1.239 and 1.336 for letter and categorical verbal fluency). Of note, only 61.4% of the PwMS had data available for the executive function (D-KEFS test). The differences in cognitive performance between PwRRMS and PwPMS are shown in Supplement Table 3.

Cortical parcellation and neuroimaging characterization of the older PwMS

The global neuroinflammatory and neurodegenerative characteristics of the older PwMS population are shown in Table 3. After adjusting for multiple comparisons, CI PwMS had significantly lower WBV (1374.1 mL vs. 1427.6 mL, $p < 0.001$), GM volume (682.5 mL vs. 724.8 mL, $p < 0.001$) and putamen volume (9.2 mL vs. 10.2 mL, $p = 0.018$) when compared to CP PwMS.

Of note, FreeSurfer failed in 9 PwMS and the median time between the MRI and neuropsychological examination was 2 months. The sample size in each table hereafter accounts for these failures. The comparisons regarding the cortical thickness between CI and CP PwMS are shown in Table 4. After correction for age, sex education, BDI-FS scores, WBV and thalamic volume, the CI PwMS had significantly thinner left fusiform gyrus ($p = 0.0003$, partial η [2] = 0.149), left inferior ($p = 0.0032$, partial η2 = 0.101), superior ($p = 0.001$, partial η2 = 0.128) and transverse temporal gyri ($p = 0.0013$, partial η2 = 0.119) and the right superior frontal ($p = 0.002$, partial η2 = 0.11) and superior temporal gyri ($p = 0.0011$, partial η2 = 0.121), when compared to the CP PwMS group (all surviving after

Table 1 Demographic and clinical characteristics of the study population

Demographic and clinical characteristics	PwMS ($n=101$)	HCs ($n=56$)	PwMS vs. HCs p-value	CI PwMS ($n=37$)	CP PwMS ($n=64$)	CI vs. CP PwMS p-value
Female, n (%)	76 (75.2)	35 (62.5)	0.532[a]	28 (75.7)	48 (75.0)	0.569[a]
Age, mean (SD)	62.6 (5.9)	62.3 (8.1)	0.79[b]	62.5 (7.2)	62.7 (5.1)	0.84[b]
Years of education, mean (SD)	14.9 (2.3)	15.6 (2.3)	0.7[b]	14.7 (2.4)	15.1 (2.2)	0.375[b]
Disease duration, mean (SD)	21.2 (12.6)	–	–	23.9 (12.5)	19.7 (12.5)	0.101[b]
RRMS, n (%)	64 (63.4)	–	–	22 (59.5)	42 (65.6)	0.688[a]
FSS, median (IQR)	4.9 (3.7–5.9)	2.73 (2.0–3.6)	**< 0.001[c]**	5.2 (4.0–6.0)	4.7 (3.2–5.9)	0.15[c]
BDI-FS, median (IQR)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	**< 0.001[c]**	1.0 (0.0–2.8)	1.0 (1.0–2.0)	0.824[c]
EDSS, median (IQR)	3.75 (3.0–6.0)	–	–	5.5 (3.1 – 6.5)	3.3 (2.9- 6.0)	**0.003[c]**
T25FWT, median (IQR)	6.8 (5.1–10.5)	4.7 (4.1–5.1)	**< 0.001[c]**	9.1 (5.5–28.6)	6.1 (4.9–7.9)	**0.011[c]**
9HPT, median (IQR)	25.0 (22.5–29.6)	21.5 (20.4–23.5)	**< 0.001[c]**	27.2 (24.1–35.9)	23.5 (21.8–26.5)	**< 0.001[c]**
Cognitive impairment, n (%)	37 (36.6)	–	–	–	–	–
No DMT	25 (24.8)	–	–	10 (27.0)	15 (23.4)	0.792[a]
Interferon-β	35 (34.7)			14 (37.8)	21 (32.8)	
Glatiramer acetate	18 (17.8)			5 (13.5)	13 (20.3)	
Oral DMT	15 (14.9)			6 (16.2)	9 (14.1)	
Natalizumab	6 (5.9)			2 (5.5)	4 (6.3)	
Off-label DMT	2 (1.9)			–	2 (3.1)	

PwMS people with multiple sclerosis, *RRMS* relapsing–remitting multiple sclerosis, *CI* cognitively impaired, *CP* cognitively preserved, *FSS* Fatigue Severity Scale, *BDI-FS* Beck Depression Inventory – Fast Screen, *EDSS* Expanded Disability Status Scale, *25FWT* Timed 25-foot walk test, *9HPT* 9-hole peg test, *DMT* disease-modifying therapy, *SD* standard deviation, *IQR* interquartile range

Age and disease duration are shown in years. 25-FWT and 9HPT are shown in seconds. In both 25-FWT and 9HPT, longer times demonstrate greater lower and upper extremity limitation. Higher FSS and BDI-FS scores indicate greater patient-reported fatigue and depression, respectively. Oral DMT group consisted of PwMS treated with teriflunomide and dimethyl fumarate. Off-label DMT group consisted of PwMS treated with methotrexate and rituximab

[a] chi-square test, [b]Student's *t*-test, [c]Mann–Whitney *U* test. *P*-values lower than 0.05 were considered statistically significant and shown in bold

Benjamini–Hochberg multiple comparison correction). (Table 4) No changes were noted after bootstrapping.

In an age, sex, education, BDI-FS, WBV and thalamic volume-adjusted logistic regression model, CI status was predicted using the thickness of the left fusiform ($p=0.001$) and left cuneus gyri ($p=0.004$). It successfully predicted CI in PwMS with 77.8% accuracy. The ROC curve predicting CI PwMS is also shown in Fig. 1. The area under the curve (AUC) was 0.863 (95% confidence intervals from 0.786 to 0.94).

Detailed analyses of the global and cortical thickness between older PwRRMS and older PwPMS groups are shown in Supplement Tables 3 and 4.There were no differences in cortical thickness in any investigated gyrus between the older PwPMS and PwRRMS.

Relationship between domain-specific cognitive performance scores and neuroimaging characteristics

The differences in cortex-specific MRI measures between older PwMS with isolated impairment within the domains of cognitive processing speed/working memory and language when compared to older PwMS without the respective domain impairment are shown in Supplement Table 5 and Supplement Table 6, respectively. There were no demographic differences between the 29 PwMS with cognitive processing speed impairment and the remaining 72 PwMS with no impairment in age (63.1 vs. 63.6 years old, $p=0.697$), education (14.7 vs. 15.7 years, $p=0.076$), disease duration (22.8 vs. 20.3 years, $p=0.453$), BDI-FS (2.0 vs. 1.0, $p=0.272$) and FSS (4.7 vs. 4.9, $p=0.499$).

After adjusting for age, sex, years of education, BDI-FS, WBV and thalamic volume, PwMS with isolated impairment in the cognitive processing speed had multiple significantly thinner cortical gyri including bilateral fusiform ($p=0.0002$, partial η2 = 0.152 and $p=0.002$, partial η2 = 0.11 for left and right respectively), bilateral inferior temporal gyrus ($p=0.0005$, partial η2 = 0.138 and $p=0.014$, partial η2 = 0.07), bilateral superior frontal/temporal gyri ($p<0.0091$, smallest partial η2 = 0.08)

Table 2 Cognitive performance in the study populations and differences between cognitively impaired and preserved older PwMS

Neuropsychological characteristics	HCs (n = 56)	PwMS (n = 101)	Cohen's d	p-value	CI PwMS (n = 37)	CP PwMS (n = 64)	Cohen's d	p-value
CVLT-II total score	54.9 (10.4)	47.6 (12.3)	0.641	**< 0.001***	38.4 (9.4)	52.9 (10.5)	1.455	**< 0.001***
CVLT-II – short delay	11.2 (3.3)	9.1 (4.1)	0.564	**0.001***	6.0 (3.7)	10.8 (3.2)	1.388	**< 0.001***
CVLT-II—long delay	11.9 (3.3)	9.9 (3.8)	0.562	**0.001***	7.3 (3.3)	11.5 (3.1)	1.312	**< 0.001***
BVMT-R total score	22.5 (5.6)	18.5 (7.8)	0.589	**< 0.001***	12.6 (6.9)	22.0 (6)	1.454	**< 0.001***
BVMT-R delay	8.5 (2.7)	7.6 (3.0)	0.315	0.064	5.4 (3)	8.8 (2.3)	1.272	**< 0.001***
SDMT	55.4 (9.2)	43.9 (12.3)	1.059	**< 0.001***	34.6 (12.9)	49.4 (7.9)	1.384	**< 0.001***
PASAT-3	45.8 (12.3)	40.3 (13.9)	0.419	**0.015***	29.9 (15.8)	45.6 (9.1)	1.218	**< 0.001***
Letter verbal fluency	43.0 (10.2)	38.7 (13.9)	0.353	0.044	29.4 (11.5)	44.1 (12.2)	1.239	**< 0.001***
Categorical verbal fluency	45.9 (8.9)	37.1 (9.3)	0.967	**< 0.001***	30.4 (8.2)	40.9 (7.5)	1.336	**< 0.001***
D-KEFS—correct sorts*	9.3 (2.2)	8.6 (2.9)	0.272	0.118	6.8 (2.8)	9.6 (2.4)	1.074	**0.001***
D-KEFS—correct descriptions*	34.9 (8.9)	31.5 (11.2)	0.336	0.059	25.9 (11.3)	35.1 (9.6)	0.877	**< 0.001***
Boston Naming Test	56.9 (3.3)	55.5 (4.6)	0.349	0.046	52.9 (6)	56.9 (2.8)	0.854	**< 0.001***
Beery VMI	24.2 (2.6)	22.9 (3.4)	0.429	**0.014***	20.7 (3.3)	24.1 (2.9)	1.094	**< 0.001***
Clock drawing test	9.1 (1.2)	8.7 (1.7)	0.272	0.121	7.9 (2.2)	9.2 (1.1)	0.747	**0.002***
WMS-R Logical Memory—IR	26.4 (6.4)	23.1 (6.9)	0.496	**0.004***	19.1 (6.8)	25.3 (6.1)	0.959	**< 0.001***
WMS-R Logical Memory—DR	21.7 (8.1)	18.1 (7.3)	0.467	**0.005***	14 (6.5)	20.4 (6.7)	0.969	**< 0.001***
% of WMS-R Retention	79.3 (18.3)	76.8 (17.5)	0.139	0.4	0.7 (0.2)	0.8 (0.1)	0.632	0.12

HCs healthy controls, *PwMS* people with multiple sclerosis, *FSS* Fatigue Severity Scale, *BDI-FS* Beck's Depression Inventory Fast Screen, *CVLT-II* California Verbal Learning Test – Second Edition, *BVMT-R* – Brief Visuomotor Memory Test – Revised, *SDMT* Symbol Digit Modalities Test, *PASAT-3* Paced Auditory Serial Addition Test 3 Second version, *DKEFS* – Delis-Kaplan Executive Function System, *VMI* Beery-Buktenica Visual Motor Integration, *IR* immediate recall, *DR* delayed recall, *WMS-R* Wechsler Memory Scale—Revised

All measures are shown as mean and standard deviation. All comparisons are performed using Student's *t*-test. In all measures, higher score demonstrates better cognitive performance. *P*-values lower than 0.05 were considered statistically significant and shown in bold. *—Only 61.4% of the PwMS had data available for the D-KEFS test

P-values lower than 0.05 that only survive multiple comparison adjustment using Benjamini–Hochberg procedure were considered statistically significant and shown in bold and labeled with asterisks

and bilateral transverse temporal gyri ($p = 0.0007$ and $p = 0.0076$ for left and right, respectively, smallest partial $\eta2 = 0.083$).

A smaller number of cortical regions were significantly thinner in the PwMS with impairment in the language domain when compared to those without. After correction for age, sex, years of education, WBV and thalamic volume, the language-impaired PwMS had thinner left fusiform gyrus ($p = 0.0032$, partial $\eta2 = 0.101$), left pars opercularis ($p = 0.0024$, partial $\eta2 = 0.107$), left precentral ($p = 0.0025$, partial $\eta2 = 0.106$), left superior ($p = 0.0019$, partial $\eta2 = 0.111$) and transverse temporal gyri ($p = 0.0008$, partial $\eta2 = 0.127$) and the left insula ($p = 0.0005$, partial $\eta2 = 0.135$) as well as thinner right post-central gyrus ($p = 0.045$, partial $\eta2 = 0.094$) when compared to language-intact PwMS.

Additional linear regression analyses determined the best predictors of cognitive processing speed performance (as measured by SDMT scores) and verbal fluency performances

(as measured by letter-based and categorical-based COWAT scores) after adjusting for age, sex, education, BDI-FS, WBV and thalamic volume. In addition to the significant effects from the WBV (standardized $\beta = 0.31$, $p = 0.009$), SDMT performance was significantly associated with left fusiform gyrus thickness (standardized $\beta = 0.507$ $p < 0.001$) with R^2 increase from 0.214 to 0.294. Letter-based verbal fluency performance was significantly associated with WBV (standardized $\beta = 0.312$, $p = 0.009$), and left pars opercularis gyrus thickness (BA44) (standardized $\beta = 0.438$, $p < 0.001$) with R^2 increase from 0.121 to 0.279. Similarly, categorical fluency performance was significantly associated with WBV (standardized $\beta = 0.26$, $p = 0.036$), and left pars opercularis gyrus (BA44) thickness (standardized $\beta = 0.371$, $p = 0.001$) with R^2 increase from 0.094 to 0.204.

Table 3 Global neuroimaging characteristics of the study population

Neuroimaging characteristics	PwMS ($n = 101$)	CI PwMS ($n = 37$)	CP PwMS ($n = 64$)	CI vs. CP Age-adjusted p-value
T2 LV	18.8 (17.7)	13.2 (14.3)	28.3 (18.9)	0.372
WBV	1406.9 (80.1)	1374.1 (86.9)	1427.6 (68.6)	**< 0.001***
GMV	708.5 (56.9)	682.5 (64.7)	724.8 (44.9)	**< 0.001***
WMV	698.4 (50.5)	691.6 (61.2)	702.7 (42.5)	0.288
DGM	46.0 (8.8)	43.4 (9.1)	47.7 (8.2)	0.021
Thalamus	15.3 (3.2)	14.4 (3.3)	15.9 (3.0)	0.028
Caudate	6.9 (1.4)	6.5 (1.6)	7.2 (1.3)	0.039
Putamen	9.8 (2.0)	9.2 (2.1)	10.2 (1.9)	**0.018***
Globus pallidus	3.4 (0.9)	3.3 (0.8)	3.5 (0.9)	0.197
Hippocampus	7.3 (1.5)	6.9 (1.5)	7.5 (1.5)	0.069

PwMS people with multiple sclerosis, *CI* cognitively impaired, *CP* cognitively preserved, *LV* lesion volume, *WBV* whole brain volume, *GMV* gray matter volume, *WMV* white matter volume, *DGM* deep gray matter

All measures are shown as mean and standard deviation. All measures are represented in milliliters (mL). Age-adjusted analysis of covariance (ANCOVA) was used. *P*-values lower than 0.05 that only survive multiple comparison adjustment using Benjamini–Hochberg procedure were considered statistically significant and shown in bold and labeled with asterisks

Discussion

The findings of this study are multifold. As initially hypothesized, CI older PwMS had significantly thinner cortical gyri when compared to CP PwMS. In particular, the thickness of the fusiform gyrus and pars opercularis was associated with cognitive processing speed and verbal fluency performance. These findings were significant despite correcting for WBV and DGM-based measures.

Over a period of 5 years, a study by Eijlers et al. suggested that cognitive decline in older PMS is driven by significantly greater cortical atrophy [29]. In comparison, cognitive decline in the younger RRMS group was associated with lesion accrual rate whereas cognitive decline in the transitioning group (pwMS that transition from RRMS to PMS over follow-up) was associated with DGM atrophy [29]. Further, no differences were observed in DGM atrophy rates between the younger RRMS and older PMS groups [29]. As an extension to their work, we suggest that CI in older PwMS is driven by asymmetrically left-sided cortical pathology and localized to the fusiform gyrus, the inferior, transverse and superior temporal gyri. With the proposition that the cortical atrophy in long-standing MS may happen through a distinct and non-random pattern, a similar pattern of domain-specific cognitive impairments may follow suit [17].

A recent analysis based on progressive and older PwMS from the lipoic acid trial (NCT03161028) demonstrated that poorer verbal and visual memory were associated with lower mean cortical thickness [30]. This study has the most comparable demographic and clinical characteristics to our population, with patients having an average age of 59.2 years old

and 22.4 years of disease duration [30]. While this study did not publish gyri-specific correlations, the same directionality of findings is highly encouraging. Although the relationship between verbal fluency and specific cortical gyri thickness has not been investigated in an older MS sample, recent studies of younger MS populations do report an association with global and WM-based MRI outcomes [31]. Based on our literature search, Amato et al. were the first to find an association between total neocortical atrophy and verbal fluency performance (the study included 28 considerably younger RRMS PwMS when compared to our population) [32]. A more recent study with a much larger cohort of 1,212 PwMS (average age of 41 years old) demonstrated that mild verbal memory and verbal fluency impairments were the most common cognitive phenotype (29.9%) and were associated with decreased hippocampal volume [11]. Other studies do suggest associations between damage within the ventral and dorsal pathway streams with categorical and letter-based verbal fluency, respectively. [33] Resting-state functional connectivity analysis in PwMS suggested that deviations in the default mode network and language networks are associated with poorer verbal fluency and such analysis can provide greater explanatory power when compared to only structural measures [34, 35]. Our study expands on the literature, pinpointing cortical anatomical changes within Brodman's areas 37, 41/42 and 44.

The findings regarding the role of the fusiform gyrus, the pars opercularis and the superior/transversal temporal gyrus associations with the language/verbal fluency impairment

Table 4 FreeSurfer-based cortical differences between cognitively impaired and cognitively preserved older PwMS

| Left cortex	CI ($n=35$)	CP ($n=57$)	Partial η^2	Adjusted p-value	Right cortex	CI ($n=35$)	CP ($n=57$)	Partial η^2	Adjusted p-value
Banks of superior temporal sulcus	2.2 (0.3)	2.4 (0.2)	0.056	0.031	Banks of superior temporal sulcus	2.3 (0.3)	2.5 (0.2)	0.061	0.024
Caudal anterior cingulate	2.5 (0.4)	2.6 (0.3)	0.001	0.8	Caudal anterior cingulate	2.5 (0.3)	2.6 (0.3)	0.016	0.258
Caudal middle frontal	2.3 (0.2)	2.4 (0.2)	0.01	0.371	Caudal middle frontal	2.3 (0.2)	2.5 (0.2)	0.055	0.031
Cuneus	1.7 (0.2)	1.7 (0.1)	0.0	0.974	Cuneus	1.7 (0.2)	1.7 (0.1)	0.012	0.313
Entorhinal	2.9 (0.5)	3.2 (0.4)	0.022	0.176	Entorhinal	2.9 (0.5)	3.3 (0.4)	0.076	0.011
Fusiform	2.4 (0.3)	2.6 (0.2)	**0.149**	**0.0003***	Fusiform	2.4 (0.3)	2.7 (0.2)	0.082	0.008
Inferior parietal	2.2 (0.2)	2.4 (0.2)	0.036	0.083	Inferior parietal	2.2 (0.2)	2.4 (0.2)	0.039	0.072
Inferior temporal	2.7 (0.3)	2.9 (0.2)	**0.101**	**0.0032***	Inferior temporal	2.7 (0.3)	2.9 (0.2)	0.041	0.066
Isthmus cingulate	2.2 (0.3)	2.4 (0.2)	0.082	0.008	Isthmus cingulate	2.2 (0.3)	2.4 (0.3)	0.027	0.135
Lateral occipital	2 (0.2)	2.1 (0.1)	0.017	0.239	Lateral occipital	2.1 (0.2)	2.2 (0.2)	0.002	0.658
Lateral orbito-frontal	2.5 (0.2)	2.6 (0.2)	0.036	0.085	Lateral orbito-frontal	2.5 (0.2)	2.6 (0.2)	0.054	0.034
Lingual	1.8 (0.2)	1.8 (0.1)	0.018	0.222	Lingual	1.8 (0.2)	1.9 (0.1)	0.002	0.671
Medial orbito-frontal	2.3 (0.2)	2.4 (0.2)	0.018	0.227	Medial orbito-frontal	2.4 (0.2)	2.4 (0.2)	0.003	0.594
Middle temporal	2.7 (0.3)	2.8 (0.2)	0.06	0.025	Middle temporal	2.7 (0.3)	2.9 (0.2)	0.074	0.012
Parahippocampal	2.4 (0.4)	2.6 (0.4)	0.008	0.411	Parahippocampal	2.4 (0.3)	2.5 (0.3)	0.025	0.153
Paracentral	2 (0.3)	2.2 (0.2)	0.037	0.079	Paracentral	2 (0.3)	2.2 (0.2)	0.044	0.056
Pars opercularis	2.3 (0.2)	2.5 (0.2)	0.075	0.011	Pars opercularis	2.3 (0.2)	2.4 (0.2)	0.059	0.027
Pars orbitalis	2.6 (0.3)	2.7 (0.2)	0.017	0.241	Pars orbitalis	2.6 (0.3)	2.7 (0.3)	0.0	0.871
Pars triangularis	2.2 (0.2)	2.4 (0.2)	0.016	0.246	Pars triangularis	2.3 (0.2)	2.4 (0.2)	0.007	0.456
Pericalcarine	1.4 (0.1)	1.4 (0.1)	0.004	0.568	Pericalcarine	1.5 (0.2)	1.4 (0.1)	0.044	0.055
Postcentral	1.9 (0.2)	2 (0.1)	0.031	0.106	Postcentral	1.9 (0.2)	2 (0.2)	0.069	0.016
Posterior cingulate	2.2 (0.3)	2.4 (0.2)	0.046	0.051	Posterior cingulate	2.3 (0.3)	2.5 (0.2)	0.054	0.034
Precentral	2.1 (0.3)	2.4 (0.2)	0.07	0.015	Precentral	2.2 (0.3)	2.3 (0.2)	0.041	0.063
Precuneus	2.1 (0.2)	2.3 (0.2)	0.011	0.077	Precuneus	2.1 (0.2)	2.3 (0.2)	0.073	0.013
Rostral anterior cingulate	2.7 (0.2)	2.8 (0.2)	0.005	0.534	Rostral anterior cingulate	2.8 (0.3)	2.9 (0.2)	0.01	0.368
Rostral middle frontal	2.3 (0.2)	2.4 (0.2)	0.026	0.141	Rostral middle frontal	2.2 (0.2)	2.4 (0.2)	0.037	0.08
Superior frontal	2.4 (0.3)	2.6 (0.2)	0.083	0.008	Superior frontal	2.4 (0.2)	2.6 (0.2)	**0.11**	**0.002***
Superior parietal	2 (0.2)	2.1 (0.2)	0.021	0.188	Superior parietal	2 (0.2)	2.1 (0.2)	0.01	0.373
Superior temporal	2.4 (0.3)	2.6 (0.2)	**0.128**	**0.001***	Superior temporal	2.5 (0.3)	2.7 (0.2)	**0.121**	**0.0011***
Supramarginal	2.3 (0.3)	2.4 (0.1)	0.04	0.067	Supramarginal	2.3 (0.2)	2.5 (0.1)	0.067	0.017
Frontal pole	2.7 (0.4)	2.8 (0.4)	0.03	0.114	Frontal pole	2.8 (0.3)	2.8 (0.3)	0.0	0.895
Temporal pole	3.3 (0.5)	3.5 (0.5)	0.007	0.45	Temporal pole	3.2 (0.7)	3.5 (0.5)	0.026	0.146
Transverse temporal	2 (0.3)	2.3 (0.3)	**0.119**	**0.0013***	Transverse temporal	2.1 (0.4)	2.3 (0.3)	0.081	0.009
Insula	2.7 (0.3)	2.9 (0.2)	0.091	0.0052	Insula	2.7 (0.3)	2.9 (0.2)	0.055	0.031

CI PwMS cognitively impaired people with multiple sclerosis, *CP PwMS* cognitively preserved people with multiple sclerosis

The comparisons were performed using analysis of covariance (ANCOVA) corrected for age, sex, years of education, patient-reported depression (BDI-FS), whole brain volume and thalamic volume. Additional correction for multiple comparisons using Benjamini–Hochberg procedure was performed. Multiple comparison-adjusted p-values lower than 0.05 were considered statistically significant

can be substantiated by other studies linking these regions language-related tasks. First, data from functional MRI and event-related potentials performed during cerebral processing of unseen masked words (thinking but not vocalizing the target word) has significantly implicated the fusiform gyrus in the unconscious process of word priming [36]. In comparison to visible words which activate left-lateralized parietal cortex, anterior cingulate, fusiform, inferior prefrontal,
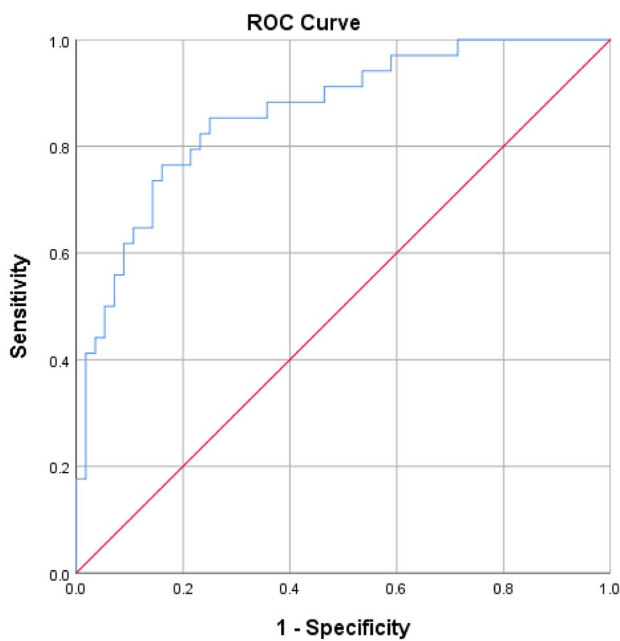
Fig. 1 ROC curve predicting cognitive impairment using demographic, clinical and neuroimaging measures. *ROC* receiver operating characteristic curve. The predictive measure utilized data from patient age, education, patient-reported depression (BDI-FS), whole brain volume, thalamic volume and thickness of the left fusiform and left cuneus gyr

precentral cortex and supplementary motor areas (previously established as word reading network), masked words were sizably localized mainly in the left fusiform gyrus and precentral sulcus [36]. The older PwMS with verbal fluency deficits had significant thinning in exactly these two left-sided areas. The left fusiform gyrus has been significantly associated with auditory word recognition and potentially implicated in the initiation of a semantic category decision [37]. Even in highly specific pathological states such as semantic dementia (a variant of frontotemporal lobar degeneration), the level of semantic impairment is mainly associated with hypometabolism of the fusiform cortex [38]. In particular, the left anterior fusiform cortex has been associated with expressive verbal tasks whereas the right fusiform cortex with non-verbal tests of semantic knowledge [38].

Together with pars orbitalis and pars triangularis, the pars opercularis is commonly considered a building block of Broca's area and main site of speech production [39]. In normal aging, worse verbal fluency performance is associated with thinner pars opercularis [40]. Moreover, findings from a recent case-controlled study of people with primary progressive aphasia isolated the damage within the frontal aslant tract (pathway connecting the pars opercularis from

Broca's region with the anterior cingulate and supplementary motor area) and suggested it as the main underlying factor of verbal fluency and semantic processing [41]. Lastly, the superior and transversal temporal gyri, areas primarily associated with the auditory cortex, are shown to activate during covert (inner) speech and influence the generation of verbal speech [42].

The findings of this study should also be interpreted in comparison to the findings in younger pwMS that are published in the literature. A study by Nygaard et al. investigated the cortical features in 61 PwMS (average age 34.2 years old) and demonstrated that depression, fatigue and verbal memory were correlated regionally with smaller cortical surface and volume [43]. Interestingly, the cortices indicated in their study did coincide with our analysis, having the fusiform, orbital frontal, and temporal gyri as the most implicated [43]. The laterality of greater cortical thinning favoring the left hemisphere has also been shown in a large phase 3 trial (CombiRx trial with 250 PwMS and average age of 38.2 years old) [44]. In this analysis, the EDSS scores and disease duration were significantly associated with the thickness coinciding with the same left-sided gyri such as the middle and superior and middle temporal, pars opercularis, fusiform and paracentral [44]. Similar findings were also seen in a recent study that suggested multiple cognitive tasks from the 5 domains are associated with cortical regions of the left hemisphere, predominantly correlating with the temporal, gyrus frontalis and insular gyri [45].

Another future analysis should investigate the difference in cortical thinning versus central atrophy (including the DGM/thalamus) between aging adult-onset MS and late-onset MS (disease onset > 50 years old). Such an analysis could provide insights regarding the brain vulnerability to early MS pathophysiological processes in different age circumstances. In a previous study, late-onset MS demonstrated significantly faster lateral ventricular expansion when compared to age-matched adult-onset MS, suggesting that the central brain structures may be most vulnerable to pathology during the early onset stage regardless of the age of the PwMS [46]. Lastly, our analysis demonstrated a lack of cortical thickness differences between older PwRRMSand older PwPMS. Based on these findings, cortical thinning and the emergence of specific cognitive impairments may be related to an interaction between age and disease duration-related pathology when compared to the phenotype classification.

The current study has several limitations. First, it is cross-sectional in nature and cannot assess directionality between cognitive performance and cortical thickness. Future longitudinal studies should determine the temporal

and spatial course of cortical thickness and its relationship with cognitive phenotypical changes. The cognitive and neurodegenerative changes in these age groups typically follow an exponential trajectory and could be misrepresented by conventional linear-based statistics. Given that our analysis includes up to 68 different cortical regions (34 regions on each hemisphere), spurious relationships may be only true in our specific sample and not representative of the disease changes in general. However, we used strict correction for multiple comparisons which was necessary in this exploratory study without a single hypothesis of what cortical regions would be involved.

Another limitation is the lack of amyloid PET or another biomarker that may have screened for AD in this older age MS cohort. Distinguishing between cognitive impairment in older pwMS and early AD or its prodromal stage called aMCI is an important clinical problem that we are trying to address. We and others have proposed that rapid forgetting and semantic processing deficits are akin to AD and may signal this comorbidity. The ultimate test of course, will be to verify this hypothesis using valid biomarker that has not been done in this study. We have recently reported on an older PwMS that was deemed as potentially having a dual diagnosis of MS and AD where amyloid-based PET scan demonstrated minimal focal uptake within the occipital lobe [6]. While the inclusion criteria for the study was 50 years old or greater, the median age of the entire population was 63 years and less than 25% of the PwMS were younger than 58 years old. As the MS population continues to age, the age limit for such analyses should increase. Another limitation is the fact that only a portion of PwMS were assessed for executive function performance and the proportion of CI PwMS may have been slightly underrepresented. Lastly, while we did not perform the MRI analysis in the HCs, the literature does demonstrate significant differences in all inflammatory and neurodegenerative MRI measures between older PwMS and age-matched HCs [47].

In conclusion, after correcting for global neurodegenerative changes, CI older PwMS have significantly thinner cortical regions when compared to CP older PwMS. The associations between cognitive performance and anatomical changes in older PwMS may shift from DGM-based pathology to cortical-centric neurodegenerative processes.

Declarations

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