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Patients with relapsing-remitting multiple sclerosis show accelerated whole brain volume and thalamic volume loss early in disease

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Abstract

Background The aim of this study was to investigate the dynamics of annual whole brain volume loss (BVL/year) and annual thalamic volume loss (ThalaVL/year) in patients with relapsing-remitting multiple sclerosis (PwRRMS) during the course of the disease.

Methods A longitudinal database of magnetic resonance imaging (MRI) scans of 195 healthy individuals (age range, 22.8–63.7 years) and longitudinal MRI data of 256 PwRRMS (age range, 20.1–60.8 years) were analyzed and compared. BVL/year and ThalaVL/year were computed for healthy individuals as well as for all patients with MS using a Jacobian integration approach. A linear regression was used to compute the relationship between age and BVL/year and ThalaVL/year for healthy individuals. The linear regression was then used to decompose the BVL/year and ThalaVL/year into a multiple sclerosis (MS)-related and an age-related component for each PwRRMS. PwRRMS were dichotomized into early-phase RRMS (disease duration ≤ 6 years) and later-phase RRMS (disease duration > 6 years), and a *t*-test was performed to test for differences between these groups.

Results The 135 early-phase patients (disease duration, ≤ 6 years) had statistically significantly higher MS-related BVL/year than the later-phase patients ($n = 121$) (−0.21% vs. −0.06%, $p = 0.007$). For MS-related ThalaVL/year, the difference between the groups was even more pronounced (−0.39% vs. −0.00%, $p < 0.0001$).

Conclusions Our results indicate that in PwRRMS, the MS-related components of BVL/year and ThalaVL/year are accelerated in early phases and slowdown in later phases of the disease. This might explain why early intervention often leads to improved outcomes in patients with MS.

Keywords Magnetic resonance imaging · Multiple sclerosis · Whole brain volume loss · Thalamic volume loss · Normal aging

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Introduction

It has been shown in many studies that the annual percentage whole brain volume loss (BVL/year) increases with increasing age in normal (physiological) aging. This effect has been observed in cross-sectional studies [1, 2], as well as in longitudinal studies [3–5]. These study results are remarkably consistent and reveal that BVL/year increases in normal aging from approximately −0.2% at an age of 35 years to approximately −0.5% at an age of 70 years. Although mathematically these numbers represent decreases, the more negative numbers imply higher atrophy; therefore, we will use the term "increase" throughout this paper. It is also widely known that patients with multiple sclerosis (PwMS) exhibit higher BVL/year compared with

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healthy individuals [6, 7]. In a study of pooled data from the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) and the FREEDOMS-II studies, a cutoff of − 0.4% BVL/year (independent of age) was proposed to distinguish physiological BVL/year from pathological BVL/year for PwMS [8]. In an extension of that study, age-dependent cutoffs were provided to account for the increasing BVL/year in normal aging [5]. Eventually, age-dependent cutoffs were also introduced for physiological annual thalamic volume loss (ThalaVL/year) [4].

Measurement of BVL/year in individual PwMS is clinically relevant since high BVL/year is associated with an increased risk of neurologic and cognitive impairment [9, 10]. Besides BVL, there is growing interest in MRI-based volumetry of the thalamus for the management of PwMS [11]. The thalamus is among the brain structures that show the earliest signs of atrophy in MS detectable on MRI [12]. In addition, MRI-based thalamus volume is a promising marker to predict the transition from clinically isolated syndrome to clinically definite MS [13], and thalamus atrophy is the strongest predictor of cognitive impairment in MS [14].

The dynamics of BVL/year or ThalaVL/year in MS during disease progression are the subject of some controversy. In a recent study by Uher et al. [15], that sheds light on this topic, BVL/year in 1903 patients with relapsing-remitting MS (PwRRMS) remained stable throughout the course of RRMS. Other studies have found that BVL/year is independent of disease subtype [16, 17], while some have reported the opposite [18]. Additionally, some research suggests that BVL/year is higher in the early phase of MS compared to the later phase [19, 20].

The goal of the current study was to investigate the dynamics of BVL/year as well as of ThalaVL/year in PwRRMS during the course of disease. To our knowledge, previous studies examining the dynamics of BVL/year in PwMS have not fully accounted for the effects of normal aging [15–17]. To address this limitation, we used longitudinal MRI data from healthy individuals to estimate the relationship between age and BVL/year and ThalaVL/year in normal aging. By computing the residuals to the linear regression function describing the relationship between age and BVL/year and ThalaVL/year, the MS-related component of BVL can be computed and then interpreted.

Methods

Longitudinal database of T1-weighted MRI scans in healthy individuals

The reference cohort comprised 195 healthy individuals who had at least two 3D gradient-echo T1-weighted (T1w) MR images in a longitudinal database that were obtained using the same scanner and same acquisition protocol at different time points. All included individuals had no history of or no current neurologic or psychiatric conditions and no structural abnormalities on brain MRIs according to visual inspection by an experienced radiologist. Data were extracted from brain MRI scans from consecutive asymptomatic healthy individuals taking part in an extensive medical prevention program at Conradia Hamburg MVZ GmbH. The database is an extension of one used to collect data from 117 healthy participants in a longitudinal brain volumetry study [5].

Longitudinal T1w MRI data from 256 PwRRMS

Data from a cohort of 256 PwRRMS with a mean age of 37.8 (range, 20.1–60.8) years were retrospectively pooled from 4 sites (3 university hospitals and 1 tertiary hospital). We included PwRRMS who had at least two 3D gradient-echo T1w MR scans obtained using the same scanner and same acquisition protocol with an observation interval of at least 2 years. All patients received a disease-modifying therapy (DMT) during the observation period (between first and last MRI scan). DMTs included dimethyl fumarate ($n = 64$), fingolimod ($n = 45$), natalizumab ($n = 37$), interferon beta-1a ($n = 35$), glatiramer acetate ($n = 22$), teriflunomide ($n = 16$), peginterferon beta-1a ($n = 9$), alemtuzumab ($n = 9$), ozanimod ($n = 8$), cladribine ($n = 4$), ponesimod ($n = 2$), ocrelizumab ($n = 2$), azathioprine ($n = 1$), daclizumab ($n = 1$), and ofatumumab ($n = 1$). Therapies were categorized as lower efficacy (dimethyl fumarate, interferon beta-1a, glatiramer acetate, teriflunomide, peginterferon beta-1a, and azathioprine) and high efficacy (fingolimod, natalizumab, alemtuzumab, ozanimod, cladribine, ponesimod, ocrelizumab, daclizumab, and ofatumumab) according to the Multiple Sclerosis Therapy Consensus Group classification [21]. The mean (SD) Expanded Disability Status Scale score was 1.9 (1.4) at baseline (BL) MRI examination. The PwRRMS cohort had a mean (SD) disease duration (defined as time since first diagnosis) of 7.2 (6.2) years at BL. The overall cohort was pooled from 4 MRI scanner-specific cohorts. Details are provided in Table 1.

Table 1 Patient characteristics and MRI protocol details

	Healthy Individuals			PwRRMS				
	Cohort 1	Cohort 2	Pooled	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Pooled
Patients, n	166	29	195	122	30	56	48	256
Mean age at BL, years (range)	49.2 (26.0-63.7)	51.2 (22.8–63.2)	50.8 (22.8–63.7)	38.8 (21.9–59.4)	38.1 (22.5–60.8)	38.6 (23.0–56.9)	34 (20.1–54.0)	37.8 (20.1–60.8)
Female, n (%)	56 (33)	6 (20)	62 (31)	81 (66)	19 (63)	40 (71)	30 (62)	170 (66)
Mean scans per patient, n	2.6	1.2	2.4	2	4	3.2	2.9	2.7
Mean scan interval between first and last scan, years	3.6	2.9	3.5	2	3	2.3	2.4	2.3
Mean, median (interquartile range) EDSS at BL	NA	NA	NA	2.2, 2.0 (1.5,2.5)	2.5, 2.0 (1.5,3.4)	1.2, 1.0 (0.0,1.0)	1.4, 1.2 (0.7,2.0)	1.9, 1.5 (1.0,2.5)
Mean, median (interquartile range) disease duration, years	NA	NA	NA	9.5, 8.0 (4.2,13.8)	5 ,2.8 (0.5,8.2)	8 ,6.5 (3.2,11.5)	2.2, 0.8 (0.5,2.4)	7.2, 6.0(2.0,11.0)
Patients on lower-efficacy, high-efficacy DMT, n	NA	NA	NA	68, 54	13, 17	31, 25	35, 13	147, 109
MRI scanner	**1.5 T Siemens Avanto**	**3 T Siemens MAGNETOM Vida**		**3 T Siemens TrioTim Syngo**	**3 T Siemens Verio**	**1.5 T Siemens Avanto**	**3T Philips Ingenia**	
Voxel size, mm	1	1		1	1.25	0.9	0.7	
Slice thickness, mm	1	1		1	1.5	0.9	0.9	
Flip angle, ◦	15	15		9	9	8	8	
TR, ms	980	1540		2300	2000	1900	8.9	
TE, ms	2.95	2.26		3.03	2.8	2.82	4.07	

The overall PwRRMS cohort was pooled from 4 MRI scanner-specific cohorts. BL, baseline; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NA, not applicable; PwRRMS, patients with relapsing-remitting multiple sclerosis; TE, echo time; TR, repetition time

Standard protocol approvals, registrations, and patient consent

The datasets comprised anonymized data from retrospective studies that had been approved by local ethics committees. Patients had given written informed consent, or the need for written informed consent was waived by the local ethics committee (ethics committee of the board of physicians in Hamburg, Germany; ethics committee of the Canton Zurich, Switzerland; ethics committee of the University Hospital Carl Gustav Carus, Dresden, Germany; and ethics committee of the University Hospital in Jena, Germany).

Whole BVL and ThalaVL using Jacobian integration

BVL and ThalaVL were computed using a Jacobian determinant integration approach described previously [4]. The longitudinal pairwise registration toolbox as provided by SPM12 (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) was used [22]. The longitudinal registration technique is based on a pairwise inverse-consistent highly elastic diffeomorphic alignment [23] of a BL and a follow-up (FU) scan. The approach incorporates rigid registration into a halfway space (artificial image between BL and FU [MRI] image) and correction for intensity heterogeneities [22]. Using the deformation field provided by the registration, the Jacobian determinant image (the Jacobian) was computed, indicating for each voxel the percentage volume loss or gain. For each person, the halfway MRI image was segmented automatically into the brain parenchyma (gray matter and white matter) and the thalamus using a dedicated trained convolutional neural network [24]. To calculate the percentage BVL and ThalaVL, we computed the sum over the Jacobian restricted to the corresponding segmentation masks (indicating voxels belonging to the brain parenchyma or the thalamus) for each pair of 2 consecutive MRI images. If more than 2 MRI scans were available, we calculated the BVL and ThalaVL for each pair of 2 consecutive MRI scans. For each person, the total BVL and ThalaVL between the first and last MRI scan were each subsequently calculated as a sum over the consecutive MRI scans. Finally, the total BVL and ThalaVL were each annualized by dividing the total BVL and ThalaVL by the time interval between the first and the last MRI scan (in years). BVL/year and ThalaVL/year were obtained for each patient.

BVL/year and ThalaVL/year in healthy aging

For healthy individuals, a linear regression function was computed between age and the corresponding BVL/year or ThalaVL/year measurements. Since BVL is a process that occurs between 2 time points, age was defined as the mean of the age at BL and the age at last FU scan. As regression can be affected by outliers, an iterative 2-step approach was used for regression modeling. After the first regression, scans with residuals lower than the lower quartile (− 1.5 * interquartile-range) or residuals greater than the upper quartile (+ 1.5 * interquartile-range) were considered outliers. Outliers were identified separately for BVL/year and ThalaVL/year. The final linear regression function described the relationship between age and BVL/year for healthy individuals, denoted by *regressionHC_BVL* and *regressionHC_ThalaVL* for BVL/year and ThalaVL/year, respectively. The PwRRMS and healthy individuals featured different age distributions, because only 41 healthy individuals were younger than age 45 years. Consequently, the linear regression estimating the relation between age and BVL/year in normal aging might be biased towards older individuals. To detect bias, we further increased the weights in the linear regression for healthy individuals younger than age 45 years by a factor of 3.

BVL/year and ThalaVL/year in PwRRMS Adjusted for Age

BVL/year and ThalaVL/year increases in normal aging. For the correct interpretation of BVL/year and ThalaVL/year in PwRRMS, it is important to distinguish between MS-related and age-related components of the overall volume loss. We therefore adjusted all BVL/year measurements for age by computing the residuals to the linear regression function. BVL/year adjusted for age (MS-related component) was defined as *MS-related BVL/year = BVL/year– regressionHC_BVL(age)*. The *MS-related ThalaVL/year* was computed analogously.

Statistical analysis

The median disease duration in the PwRRMS cohort was 6 years. PwRRMS were dichotomized into early-phase RRMS (disease duration ≤ 6 years) and later-phase RRMS (disease duration > 6 years). A standard *t*-test was performed between these 2 groups for the variables BVL/year, ThalaVL/year, MS-related BVL/year, and MS-related ThalaVL/year. To test the influence of treatment, a second dichotomization was performed for PwRRMS on lower-efficacy and high-efficacy MS therapies and the same *t*-tests for these groups were performed. Cohen's effect size d was computed in cases with statistically significant differences.

Results

Detailed protocol settings, number of scans per patient, time interval between scans, as well as a clinical characterization of all cohorts are provided in Table 1. In the computation of the linear regression between age and volume loss in normal aging, 10 of the 195 healthy individuals were removed from the regression analysis as outliers for BVL/year and 8 were removed for ThalaVL/year. In normal aging, there was a statistically significant correlation between BVL/year and age ($r = -0.23$, $p = 0.001$) and between ThalaVL/year and age ($r = -0.30$, $p < 0.0001$) (see Fig. 1A and B). The final linear regression revealed an acceleration in BVL/year in normal aging from − 0.09% at age 35 years to − 0.26% at age 55 years and a ThalaVL/year increase from − 0.14% to − 0.30% at the same ages. The increased weights in the regression model for healthy individuals younger than age 45 years had nearly no effect on the resulting regression model. The slope and intercept agreed up to 2 decimal places when comparing the regression with and without the weighting of younger individuals. In the regression analysis of the 256 PwRRMS, 11 patients were removed as outliers for BVL/year and 14 were removed for ThalaVL/year. In contrast to the regression in normal aging, no significant correlations between BVL/year and age ($r = -0.07$, $p = 0.22$) or between ThalaVL/year and age ($r = -0.05$, $p = 0.37$) were observed for PwRRMS (see Fig. 1C and D).

Table 2 shows the mean BVL/year and ThalaVL/year with and without adjustment for age. The adjustment for age removes the age-related component from the measurement; the results after adjustment for age therefore represent the MS-related component. The 256 PwRRMS had a mean (SD) BVL/year of − 0.29% (0.46%) and a mean (SD) ThalaVL/year of − 0.34% (0.70%). The mean (SD) MS-related components (after adjustment for age) were − 0.14% (0.45%) for BVL/year and − 0.20% (0.70%) for ThalaVL/year. The 135 patients in the early-phase RRMS cohort (disease duration ≤ 6 years) had a statistically significantly higher BVL/year and a statistically significantly higher ThalaVL/year than the patients in the later-phase RRMS cohort (− 0.35% vs. − 0.23%, $p = 0.04$; −0.49% vs. − 0.17%, $p = 0.0001$, respectively). The difference between the 2 groups was even more pronounced for the MS-related component of BVL/year and ThalaVL/year (− 0.21% vs. − 0.06%, $p = 0.007$; −0.39% vs. − 0.00%, $p < 0.0001$, respectively; Fig. 2). Cohen's effect size d increased after age adjustment from 0.25 to 0.34 for BVL/year and from 0.48 to 0.57 for ThalaVL/year. From the 135 early-phase PwRRMS 88 (65.1%)

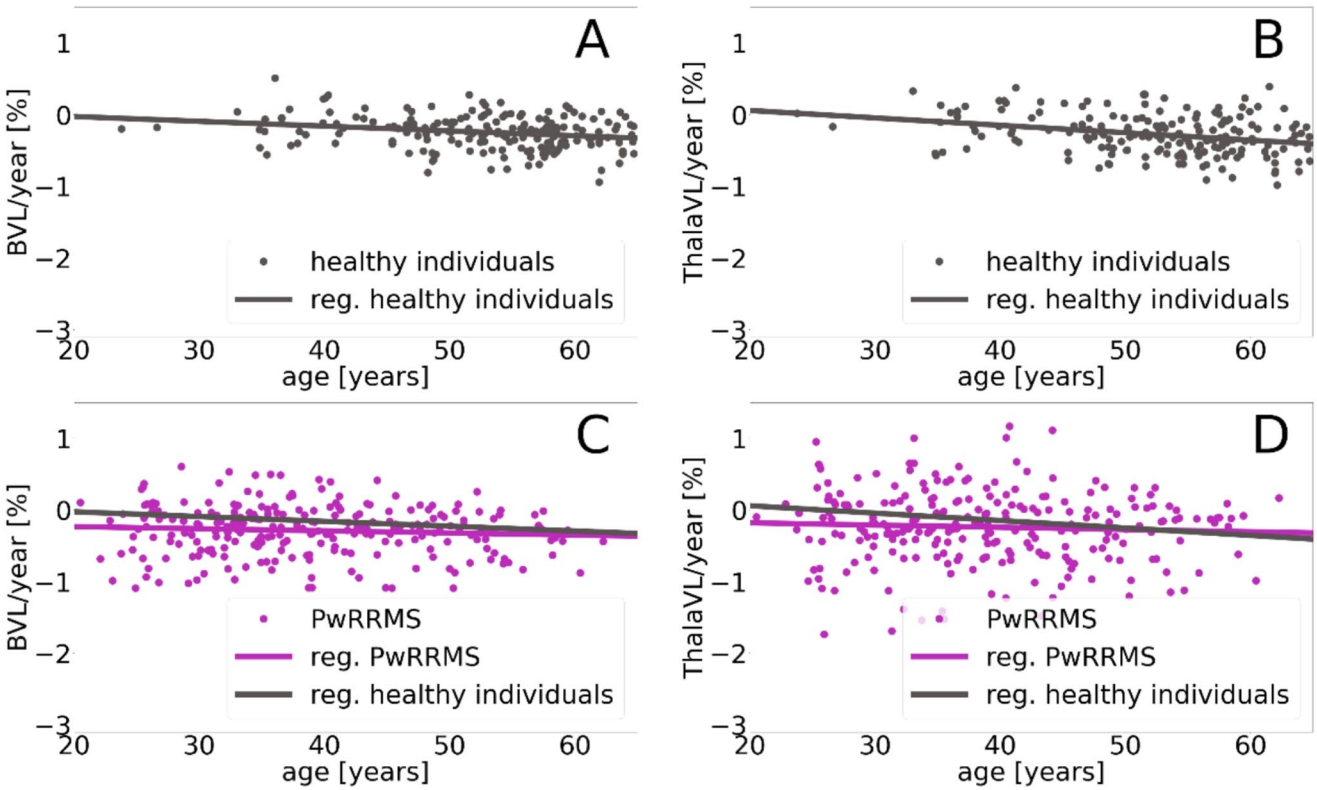

Fig. 1 Age versus BVL/year (**A**) and age versus ThalaVL/year (**B**) for healthy individuals and the PwRRMS cohort (**C** and **D**)
Green lines represent the linear regression line for the database of healthy individuals, and the gray line represents the regression for the PwRRMS. BVL, brain volume loss; MS, multiple sclerosis; PwRRMS, patients with relapsing-remitting multiple sclerosis; reg., regression; ThalaVL, thalamic volume loss

Table 2 MRI results of healthy individual and PwRRMS

	healthy individuals	PwRRMS	disease duration ≤ 6 years	disease duration > 6 years	Cohen's d	*p*	lower-efficacy DMT	high-efficacy DMT	*p*
n	195	256	135	121			147	109	
BVL/year	-0.24 (0.3)	-0.29 (0.46)	-0.35 (0.46)	-0.23 (0.44)	0.25	0.0457	-0.3 (0.49)	-0.28 (0.42)	0.7234
MS-specific BVL/year	0.03 (0.28)	-0.14 (0.45)	-0.21 (0.46)	-0.06 (0.43)	0.34	0.007	-0.15 (0.48)	-0.13 (0.41)	0.8097
ThalVL/year	-0.26 (0.35)	-0.34 (0.7)	-0.49 (0.75)	-0.17 (0.58)	0.48	0.0001	-0.35 (0.67)	-0.32 (0.73)	0.7607
MS-specific ThalVL/year	0.03 (0.33)	-0.2 (0.7)	-0.39 (0.76)	0.00 (0.57)	0.57	< 0.0001	-0.21 (0.69)	-0.19 (0.72)	0.8523

Patients were dichotomized into a group with short disease duration (≤ 6 years) and longer disease duration (> 6 years), as well as in groups treated with lower-efficacy and with high-efficacy DMTs. Values shown are mean (SD). BVL/year, annual whole brain volume loss (in percentage), DMT, disease-modifying therapy; PwRRMS, patients with relapsing-remitting multiple sclerosis; ThalaVL/year, annual thalamic volume loss (in percentage)

were treated with lower efficacy therapy, and from the 121 later-phase PwRRMS 59 (48.1%) were treated with lower-efficacy therapy. However, there were no statistically significant differences between the groups treated with high-efficacy DMT ($n = 109$) or lower-efficacy DMT ($n = 147$) for any of the volume-loss parameters (Table 2).

Discussion

This study demonstrated in normal aging, BVL/year as well as ThalaVL/year accelerate with increasing age. For the correct interpretation of volume losses in PwMS, it is important to distinguish between MS-related volume loss and age-related volume loss. This adjustment is particularly important if BVL/year is related to disease duration in PwMS, because longer disease duration is usually associated with

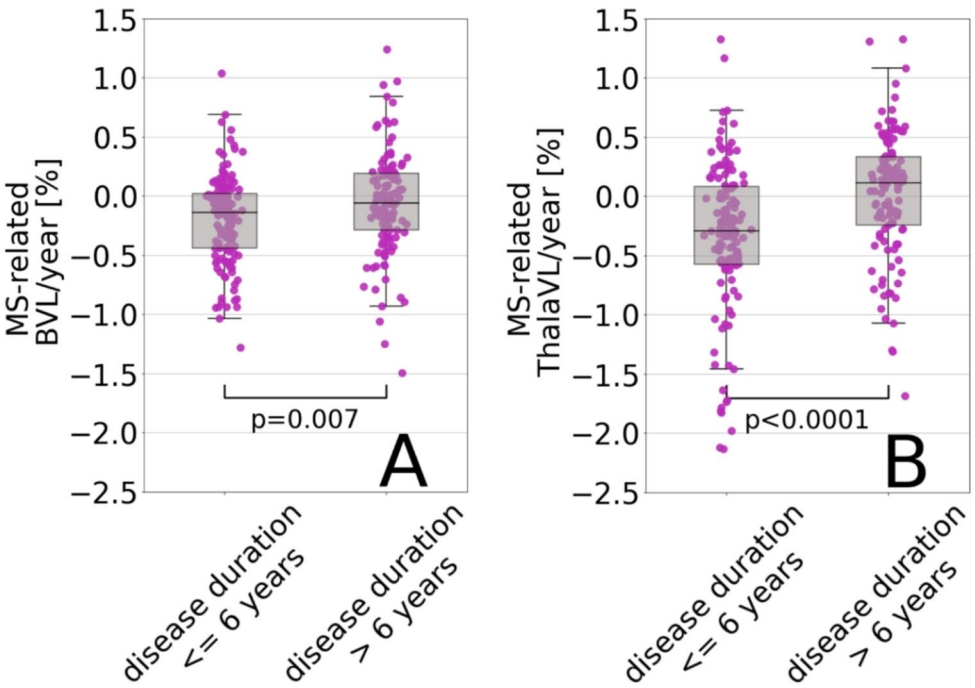

Fig. 2 Box plots between early-phase and later-phase RRMS groups for MS-related BVL/year (**A**) and MS-related ThalaVL/year (**B**). The cohort of 256 PwRRMS was dichotomized into early-phase RRMS (disease duration ≤ 6 years) and later-phase RRMS (disease duration > 6 years). BVL, brain volume loss; MS, multiple sclerosis; PwRRMS, patients with relapsing remitting MS; RRMS, relapsing remitting MS; ThalaVL, thalamic volume loss

older age. Therefore, the direct correlation between disease duration and BVL/year may be confounded by the aging effect. In this study, we showed that MS-related BVL/year and ThalaVL/year seem to be accelerated in an early phase of the disease. There was a clear and statistically significant difference between the early-phase RRMS cohort and the later-phase RRMS cohort in both MS-related BVL/year and MS-related ThalaVL/year. The median disease duration of the PwMS cohort was 6 years. This threshold was chosen to balance the sample size in both groups. The results for other threshold such as 5 or 7 years were very similar. The higher volume loss in an early phase of the disease appears not to be related to potentially lower-efficacy DMT, because there was no difference between patients treated with lower-efficacy DMT or high-efficacy DMT; however, the sample might have been too small or the FU too short for the detection of such treatment effects.

The MS-related component of BVL/year and ThalaVL/year in the PwRRMS cohort was also considered by Azevedo et al. [20, 25]. However, in their study, volume loss was not related to disease duration, as proposed in this study, but to the age of the population of PwRRMS. In that study, the authors found that in PwRRMS, BVL/year and ThalaVL/year remained relatively constant (as we observed in our study, see Fig. 1C and D) between ages of 30 and 60 years. However, the MS-related component of the volume loss decreased in that study from age 30 to 60 years, whereas in the same age period the component related to normal aging increased. Since age and disease duration are usually associated, this seems to be consistent with the findings of our study, which showed an accelerated volume loss in an early phase of the disease.

In our study, the mean ThalaVL/year of the pooled PwRRMS was −0.34%, whereas a mean ThalaVL/year of −0.71% at an age of 40 years was reported by Azevedo et al. [25] An explanation for the discrepancy might be that in the study by Azevedo et al., ThalaVL/year was measured by FreeSurfer software [26], whereas in our study a Jacobian integration approach was used. Further studies are needed to better understand the difference between the FreeSurfer algorithm and the Jacobian integration approach.

In this study, the mean BVL/year of the pooled cohort with RRMS was −0.29%. Slightly higher loss rates were also reported by Uher et al. [15]. In that study, 1903 PwMS had a mean BVL/year of −0.48%, and in the study by Azevedo et al. [20], a mean BVL/year −0.39% at age 40 years was reported.

We found a correlation between age and BVL/year or ThalaVL/year in normal aging; however, for the cohort of PwRRMS, no correlations were observed between age and BVL/year or ThalaVL/year. This is also consistent with results shown by Uher et al. [15]. Since BVL accelerated with older age in normal aging but appeared to be constant with increasing age in PwRRMS, it can be concluded that the MS-related component of volume loss is greater in younger PwRRMS. In the study by Uher et al. [15], the authors found no association between disease duration and BVL/year and concluded that "the rate of BVL is relatively stable throughout the course of RRMS". This statement is contrasted by our results. Even if absolute BVL/year is

stable over the course of the disease, our results showed that the MS-related component of BVL/year and ThalaVL/year is not stable throughout the course of RRMS, but is greater for patients in an early phase of the disease.

Our results on volume loss in normal aging are in line with many previous studies. In this study, a mean BVL/year of −0.09% at age 35 years was observed, compared with −0.07% in Opfer et al. [4]; likewise, mean ThalaVL/year at age 35 years has been reported to be −0.16% [4], compared with −0.14% in this study. By contrast, Battaglini et al. [3] found mean BVL/year at age 35 to be −0.23%, while Schippling et al. calculated mean ThalaVL/year to be −0.25% [2]. These discrepancies may be due to differences in the composition of the cohorts of healthy individuals or, alternatively, to differences in the applied methods used to compute volume loss (Jacobian integration as used in this study vs. Siena [27] or FreeSurfer [26]). Differences could also be caused by the applied fitting model. In this study, we used a simple linear regression model with an iterative 2-step approach to account for outliers. Quadratic modeling as performed in Opfer et al. [4] is an alternative approach. However, the disadvantage of quadratic modeling is a potential artificial "overshooting" at the boundary of the data [1]. We also tested a nonparametric fitting model [1, 2]; however, the data available for younger patients in our study were too scarce, and the model might have been less reliable for younger ages. We therefore concluded that a simple linear modeling was adequate.

A potential limitation in our study is that the scans for the cohorts of healthy individuals and PwRRMS were acquired on different scanners. Most of the scans from healthy individuals were acquired on a 1.5 T scanner, whereas most of the scans from PwRRMS were acquired on 3 T scanners. However, all scans were performed using a 3D gradient echo sequence to ensure consistency of the data. Correcting for potential scanner bias is challenging, as the extent of any such bias is unknown. BVL rates appear to be consistent across different studies, even when different scanners and cohorts are used. For instance, in our study, the mean BVL per year at age 55 was −0.26%, which aligns closely with the −0.36% and −0.23% reported in [3] and the −0.26% reported in [28]. Importantly, all these studies examining BVL in normal aging have observed an acceleration of BVL with increasing age. Considering this, it seems reasonable to adjust the MS patients' data using the BVL rates of the HC, despite the cohorts being scanned on different machines. However, we acknowledge that it cannot be excluded that scanner bias may have influenced our results. Therefore, further studies are needed to confirm our findings.

Battaglini et al. [3] found that the BVL/year in normal aging was slightly higher on 1.5 T scanners compared with 3 T scanners. The difference in BVL/year between healthy individuals and PwRRMS might therefore have been more pronounced if all PwRRMS had been scanned with a 1.5 T MRI. Another potential limitation is that the PwRRMS and healthy individuals featured different age distributions, with only 41 healthy individuals younger than age 45 years. As a consequence, the linear regression estimating the relation between age and BVL/year in normal aging might have been biased towards older individuals. However, increasing the weights in the linear regression for healthy individuals younger than age 45 years by a factor of 3 did not change the result. We therefore assume that the shown regression line correctly estimates volume loss in normal aging also for younger individuals. The cohort of healthy individuals includes 23% females whereas the PwRRMS includes 66% females. However, this should not lead to bias since there seems to be no difference in BVL/year between males and females [2, 5]. A potential hidden confounding factor might be the variety of DMTs applied in our cohort. While there was no significant difference between high-efficacy DMTs or lower-efficacy DMTs in this study, we cannot exclude that certain choices of DMT might have influenced our results. An analysis of subgroups of patients on the same DMT was not feasible due to the resulting small sample sizes. Future research should consider repeating the analysis presented in this study with a cohort of either untreated PwRRMS patients or with a cohort of PwRRMS who all received the same DMT. Further studies might also examine how increased BVL/year and ThalaVL/year in early phases of RRMS relate to recent investigations of progression independent of relapse activity (PIRA); Lublin et al., for example, found evidence of BVL, independent of relapse-associated worsening occurring from the onset of disease [29].

Our results indicate that in PwRRMS, the MS-related components of BVL/year and ThalaVL/year are accelerated in an early phase and slow down in a later phase of the disease. This is an important finding because it suggests not only that studies investigating the association between BVL/year or ThalaVL/year and other parameters (such as therapeutic interventions or disability worsening) should focus on PwRRMS who are in an early phase of the disease, but that the failure to distinguish cohorts by disease duration may result in confounded conclusions. Moreover, our results might explain why early intervention can lead to improved outcomes in patients with MS.

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Data availability Data that support the findings of this study is

available from the corresponding author upon reasonable request.

Declarations

Ethics approval/informed consent The datasets comprised anonymized data from retrospective studies that had been approved by local ethics committees (ethics committee of the board of physicians in Hamburg, Germany; ethics committee of the Canton Zurich, Switzerland ethics committee of the University Hospital Carl Gustav Carus, Dresden, Germany; and ethics committee of the Carl Jena University Hospital, Jena, Germany). All patients had given written informed consent.

Competing interests RO, JK, and LS: Employees of jung diagnostics GmbH, a company that received funding from Bristol Myers Squibb to conduct this research. MS: Has served on advisory boards for and received funding for travel or speaker honoraria from Actelion-Janssen, Almirall, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; received research support from Bayer and Novartis. DS, SB, and MB: Employees and/or shareholders of Bristol Myers Squibb. CGo: Employee of Conradia Hamburg MVZ GmbH and has nothing to disclose. CGa: Received research support from Novartis. SS: Reports compensation for consulting, serving on scientific advisory boards, speaking, or other activities from Biogen, Celgene, Merck, Sanofi, and Teva; currently an employee of Roche, Basel. HHK: Has received travel grants, speaker honoraria, financial research support, and consultancy fees from Bayer, Biogen Idec, Novartis, Siemens, and Teva; served on advisory boards for Biogen, Ixico, and Novartis; received research grants from Novartis. TZ: Has received advisory board fees from Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi, and Teva; received speaker fees from Alexion, Almirall, Biogen, and Bristol Myers Squibb.

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