J Neurol
DOI 10.1007/s00415-016-8374-y

ORIGINAL COMMUNICATION

Global and regional annual brain volume loss rates in physiological aging

Sven Schippling[1] · Ann-Christin Ostwaldt[2] · Per Suppa[2] · Lothar Spies[2] · Praveena Manogaran[1] · Carola Gocke[3] · Hans-Jürgen Huppertz[4] · Roland Opfer[1,2]

Received: 24 October 2016 / Revised: 16 December 2016 / Accepted: 19 December 2016

Abstract The objective is to estimate average global and regional percentage brain volume loss per year (BVL/year) of the physiologically ageing brain. Two independent, cross-sectional single scanner cohorts of healthy subjects were included. The first cohort ($n = 248$) was acquired at the Medical Prevention Center (MPCH) in Hamburg, Germany. The second cohort ($n = 316$) was taken from the Open Access Series of Imaging Studies (OASIS). Brain parenchyma (BP), grey matter (GM), white matter (WM), corpus callosum (CC), and thalamus volumes were calculated. A non-parametric technique was applied to fit the resulting age–volume data. For each age, the BVL/year was derived from the age–volume curves. The resulting BVL/year curves were compared between the two cohorts. For the MPCH cohort, the BVL/year curve of the BP was an increasing function starting from 0.20% at the age of 35 years increasing to 0.52% at 70 years (corresponding values for GM ranged from 0.32 to 0.55%, WM from 0.02 to 0.47%, CC from 0.07 to 0.48%, and thalamus from 0.25 to 0.54%). Mean absolute difference between BVL/year trajectories across the age range of 35–70 years was 0.02% for BP, 0.04% for GM, 0.04% for WM, 0.11% for CC, and 0.02% for the thalamus. Physiological BVL/year rates were remarkably consistent between the two cohorts and independent from the scanner applied. Average BVL/year was clearly age and compartment dependent. These results need to be taken into account when defining cut-off values for pathological annual brain volume loss in disease models, such as multiple sclerosis.

Keywords Magnetic resonance imaging · Brain volumetry · Thalamus · White matter · Grey matter · Multiple sclerosis · Physiological aging · Brain atrophy

Introduction

Brain volume loss (or brain atrophy) determined by structural magnetic resonance imaging (MRI) is an increasingly recognized quantitative in vivo measure of degenerative pathology in neuro-immunological diseases, such as multiple sclerosis (MS). Whole brain volume as well as white matter volume changes lack specificity for the underlying pathology and can be confounded by tissue fluid dynamics [1]. Grey matter atrophy may be less susceptible to these confounding factors, more sensitive throughout different disease stages, and correlate better with clinical findings [2, 3]. In recent studies, thalamic atrophy has been identified as a promising MRI metric for MS, since it likely reflects multiple downstream mechanisms in MS pathology [4–6]. Thalamic atrophy is a predictor for conversion from clinically isolated syndrome (CIS) to MS [7] and correlates well with cognitive and physical disability [7–9]. Corpus

Electronic supplementary material The online version of this article (doi:10.1007/s00415-016-8374-y) contains supplementary material, which is available to authorized users.

✉ Sven Schippling
sven.schippling@usz.ch

[1] Neuroimmunology and Multiple Sclerosis Research, Department of Neurology, University Hospital Zurich and University of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland

[2] jung diagnostics GmbH, Martinistrasse 52, 20251 Hamburg, Germany

[3] Medical Prevention Center Hamburg (MPCH), Falkenried 88, 20251 Hamburg, Germany

[4] Swiss Epilepsy Centre, Bleulerstrasse 60, 8008 Zurich, Switzerland

Published online: 04 January 2017

callosum (CC) atrophy rates have been studied to a lesser extent. It has been shown, however, that all segments of the CC are significantly reduced when comparing early onset MS patients to healthy subjects [10]. Next to lesion load, CC and thalamic atrophy have been shown to predict the long-term disability in MS [11]. In sum, both thalamus and the CC seem to be sensitive MRI metrics of MS-related brain atrophy at the earliest clinical stages of the disease. It is against this background that we decided for these two sites. For the interpretation of disease-related atrophy, it is important to better understand the magnitude of change related to aging, in addition to other biological or methodological confounders. In diseases, such as MS, discerning pathological brain atrophy from physiological aging is crucial in the interpretation of brain volume loss rates. In a recent study by De Stefano et al. [12], pathological cutoffs for whole brain atrophy were suggested to differentiate MS patients from healthy controls. However, cross-sectional [13–17] as well as longitudinal studies [18–20] found that the rate of brain volume loss critically depends on age, brain region, and tissue compartment. In this study, we aimed to extend work presented previously by others in several aspects. Two independent, cross-sectional single scanner cohorts of healthy subjects were included into our study. Global and regional brain volumes were computed using a recently described atlas-based volumetry approach [21, 22]. A non-parametric approach was applied to estimate age–volume relationships for each cohort at each age epoch and for each brain region separately. As a result of our study, we present detailed listings of average global and regional percentage brain volume loss rates per year in physiological aging. The resulting annual brain volume loss curves were compared between the two cohorts.

Materials and methods

Patient cohort and image acquisition

Two independent, single scanner cohorts of healthy individuals with a broad age range were included in our cross-sectional study.

The first cohort was selected from a group of asymptomatic subjects undergoing a brain MRI scan as part of an extensive medical prevention program between 2008 and 2012 at the Medical Prevention Center (MPCH) in Hamburg, Germany. All subjects gave written informed consent. The study was approved by the Ethics Board of the Ärztekammer, Hamburg, Germany. Subjects participating in the prevention program were included into the final cohort if they turned out to be healthy, meaning that they had no history of or currently ongoing neurological or psychiatric disease and if there were no structural abnormalities on brain MRIs according to visual inspection by an experienced radiologist (CG). All images were obtained with the same 1.5 T Magnetom Avanto Scanner (Siemens Medical Solutions, Erlangen, Germany). A 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was acquired with repetition time (TR) of 980 ms, echo time (TE) of 2.95 ms, time interval (TI) of 600 ms, a flip angle of 15°, and isotropic voxel grid of 1 mm. The sequence was obtained before contrast agent administration. Scanner, protocol settings, head coil, and software version remained unchanged for all subjects enrolled into our study.

The second cohort was taken from the Open Access Series of Imaging Studies (OASIS) [14, 18]. OASIS is a series of MRI data sets that are publicly available for study and analysis. The whole OASIS data set consists of a cross-sectional collection of 316 healthy and 100 demented subjects aged 18–96 years. We included only the 316 healthy individuals from that study. Young and middle-aged adults were asked by a trained technician about their medical histories and use of psychoactive drugs before inclusion. Older adults, aged 60 and older, underwent the full clinical assessment to exclude active neurological or psychiatric illness (e.g., major depression), serious head injury, history of clinically meaningful stroke, and use of psychoactive drugs (see [14] for detailed description of the cohort). For each subject, 3–4 repeated back-to-back T1-weighted MPRAGE images were acquired on a 1.5 Tesla Vision scanner (Siemens Medical Solutions, Erlangen, Germany) (TR 9.7 ms, TE 4.0 ms, TI 20 ms, flip angle of 10°, slice thickness of 1.25 mm, no gap, and isotropic voxel grid of 1 mm and 128 sagittal slices were used throughout). The sequence was acquired before any contrast agent administration. From the series of repeated scans for each patient, the first MRI scan was used for the analysis.

Tissue segmentation

T1 MPRAGE images were segmented into probabilistic tissue class images of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using a combined segmentation and registration approach (unified segmentation) [23] as implemented in the Statistical Parametric Mapping 12 (SPM12, 2013) software package. GM and WM volumes were determined by an integration of all voxels of the corresponding probabilistic tissue class images. Brain parenchymal volume was defined as the sum of GM and WM volume.

Atlas-based corpus callosum and thalamus volumetry

Global and regional brain volumes were computed by a previously described atlas-based volumetry approach

[21, 22]. To determine regional brain volumes, the resulting tissue class images of the GM and WM were warped into an atlas space using a high-dimensional elastic image registration technique [24]. Volumetric measures of brain structures were calculated by an integration of warped tissue class images (GM and WM) restricted to pre-defined binary masks in the atlas space. The thalamus mask was taken from the WFU Pick Atlas (http://fmri.wfubmc.edu/software/pickatlas). The CC mask, taken from the ICBM DTI-81 white matter labels atlas (http://www.loni.usc.edu/ICBM/Downloads/Downloads_DTI-81.shtml) was composed of binary masks from the sub-regions genu, body, and splenium [25]. Thalamic volumes were estimated using the sum of GM and WM components, while for the CC volumes, only the WM component was taken into account.

To estimate total intracranial volume (TIV), a recently introduced and validated algorithm was used [26]. The algorithm uses a TIV mask defined in a template space which is inversely transformed from the template space into the individual patient space resulting in a patient-specific TIV mask [27]. The algorithm integrates the probabilistic tissue class images of the GM, WM, and CSF. The summation is restricted to the patient-specific TIV mask.

Annual brain volume loss

Regional and global brain volumes correlate with TIV and age [28]. Therefore, the brain volumes were adjusted for TIV by computing the residuals with a linear regression function (we regressed out the confounder TIV). We used a student's t test to assess whether there was still an association between sex and brain volume after adjustment for TIV.

A kernel smoothing technique was employed to estimate a smooth function describing the age–volume associations. A kernel smoother is a statistical technique for estimating a real-valued function using its noisy observations when a parametric model for this function is unknown [29]. We deployed a local linear regression with a Gaussian kernel. Local linear regression solves for each point x(age in our case) a local linear least square problem:

$$\min_{\alpha,\beta} \sum_{i=1}^{n} K_{\lambda}(x, x_i)(y_i - \alpha - \beta x_i)^2,$$

where x_i, y_i are the age–volume measurements, and $K_{\lambda}(x, y)$ is a Gaussian kernel with bandwidth λ. The solution $\bar{\alpha}, \bar{\beta}$ of the local least square problem then estimates the value of the non-parametric function $f(x) = \bar{\alpha} + \bar{\beta}x$ at the point x. The optimal and fixed kernel width λ was computed as suggested by Bowman et al. [30]. The kernel width was first estimated for each data set separately. Then, the average from the two estimations was used as the final kernel width for both data sets. The value $f(x)$ at point x is influenced by measurements which are adjacent to the point x. It might lead to biases if there are no measurements at one side of the point x. To avoid these boundary effects, we compute the function $f(x)$ only at points which are sufficiently far away from the boundary of the measurements x, e.g., $\min(x_i) + \lambda < x < \max(x_i) - \lambda$.From the non-parametric fit functions, we derived annual percentage brain volume loss (BVL) by taking the local differences $\mathrm{BVL}(x) = 100 \cdot \frac{f(x) - f(x+1)}{f(x)}$ (positive sign indicates brain volume loss). The resulting BVL/year curves were compared between the two cohorts.

Results

248 individuals from the MPCH cohort and 316 non-demented individuals from the OASIS study were included in the analysis. A comparison between the two cohorts is detailed in Table 1, and the distribution of age and sex is shown in Fig. 1.

The mean global and regional brain volumes (in ml) of the two cohorts before and after adjustment for TIV are shown in Table 2. After adjustment for TIV, the initial analysis found no statistically significant gender effect (smallest p value was 0.24); therefore, an additional adjustment for this factor was not performed.

The optimal kernel bandwidth for fitting the age–volume data according to the described methods was 10.36 years for the MPCH cohort and 16.63 years for the OASIS cohort. The average of both (13.5 years) was used as a bandwidth for both cohorts in all reported results.

In Fig. 2, age is plotted against the adjusted brain volumes together with the non-parametric fit function for both cohorts in the left and in the middle column. In the right column of Fig. 2, the associations between age and BVL/year for the MPCH and the OASIS cohort are shown. Table 3 summarizes the BVL/year rates for GM, WM, CC, and thalamus as shown in the right column of Fig. 2. For an easier comparison between the cohorts, the values of the BVL function were averaged over 5 year intervals. Mean absolute difference between both BVL/year curves derived from the two cohorts across an age range of 35–75 years was 0.02% for BP, 0.06% for GM, 0.04% for WM, 0.11% for CC, and 0.02% for the thalamus. For the MPCH cohort, the BVL/year curves of the BP were an increasing function starting from 0.2% at the age of 35 years accumulating to 0.52% at the age of 70 years (corresponding values for GM ranged from 0.32 to 0.55%, WM from 0.02 to 0.47%, CC from 0.07 to 0.48%, and thalamus from 0.25 to 0.54%).

Discussion

Our study revealed remarkable consistency for estimates of mean physiological BVL/year between the two independent data sets. In addition, our findings appear to be largely independent of the scanners used for acquisition and from the cohorts (see Fig. 2). In accordance with previously

Fig. 2 Association between age and adjusted brain volume for the MPCH (*left column*) and the OASIS cohort (*middle column*). The non-parametric fit functions are shown as a dotted (MPCH) and as a solid (OASIS) black line. The curves are shifted by ±1.96 standard deviations to illustrate the 95% range. Association between age and the annual percentage brain volume loss for the MPCH (*dotted line*) and the OASIS (*solid line*) cohort is shown in the right column. *BP* brain parenchyma, *GM* grey matter, *WM* white matter, *CC* corpus callosum ▶

Table 1 Distribution of sex and age of the MPCH and the OASIS cohort

	Sex		Age			
	Number of males (%)	Number of females (%)	Mean	Standard deviation	Minimum	Maximum
MPCH	170 (68.5)	78 (31.5)	58.6	13.2	18.3	89
OASIS	119 (37.7)	197 (62.3)	45.1	23.9	18	94

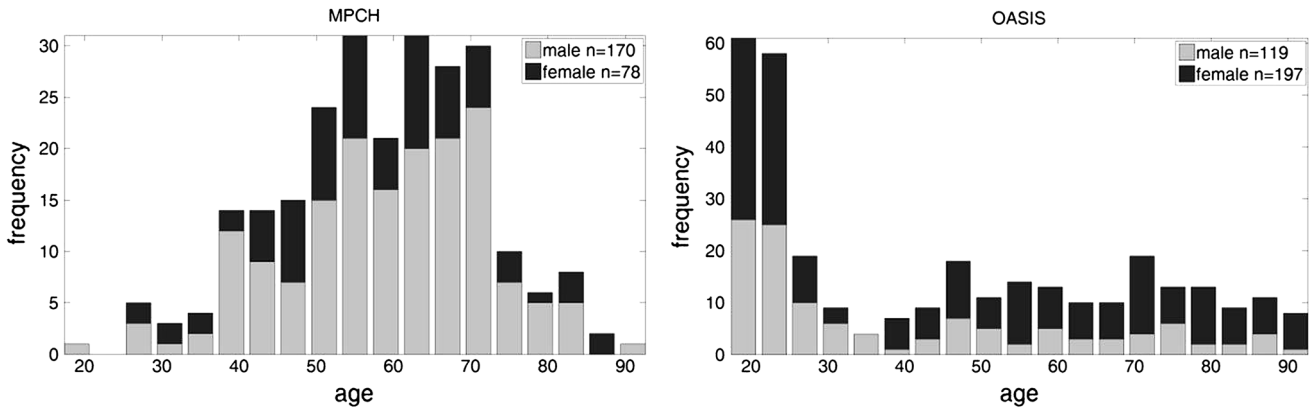

Fig. 1 Histogram of sex and age of the MPCH and the OASIS cohort

Table 2 Mean (standard deviation) global and regional brain volumes (in ml) before and after adjustment for total intracranial volume (TIV)

	MPCH cohort			OASIS cohort		
	M (n = 170)	F (n = 78)	p	M (n = 119)	F (n = 197)	p
BP	1187.94 (103.43)	1076.21 (86.69)	<0.001	1254.95 (124.52)	1109.40 (124.45)	<0.001
adj BP	1149.38 (70.55)	1160.25 (58.00)	0.24	1170.03 (97.10)	1160.69 (94.98)	0.40
GM	689.62 (61.86)	636.75 (53.78)	<0.001	754.10 (93.22)	669.94 (90.04)	<0.001
adj GM	671.13 (50.37)	677.03 (42.77)	0.37	706.10 (84.02)	698.93 (77.23)	0.44
WM	498.33 (52.26)	439.46 (41.77)	<0.001	500.85 (49.03)	439.46 (46.21)	<0.001
adj WM	478.25 (33.97)	483.21 (27.18)	0.26	463.93 (31.89)	461.76 (31.18)	0.55
CC	22.42 (2.81)	19.74 (2.58)	<0.001	22.70 (2.46)	20.22 (2.57)	<0.001
adj CC	21.51 (2.14)	21.74 (2.13)	0.43	21.04 (1.93)	21.22 (1.84)	0.40
Thal	12.51 (1.01)	11.60 (0.98)	<0.001	12.85 (1.27)	11.78 (1.24)	<0.001
adjThal	12.22 (0.87)	12.23 (0.82)	0.92	12.22 (1.11)	12.16 (1.09)	0.67

Standard deviations are shown in brackets

BP brain parenchyma, *GM* grey matter, *WM* white matter, *CC* corpus callosum, *Thal* thalamus, *adj* adjusted, *m* male, *f* female

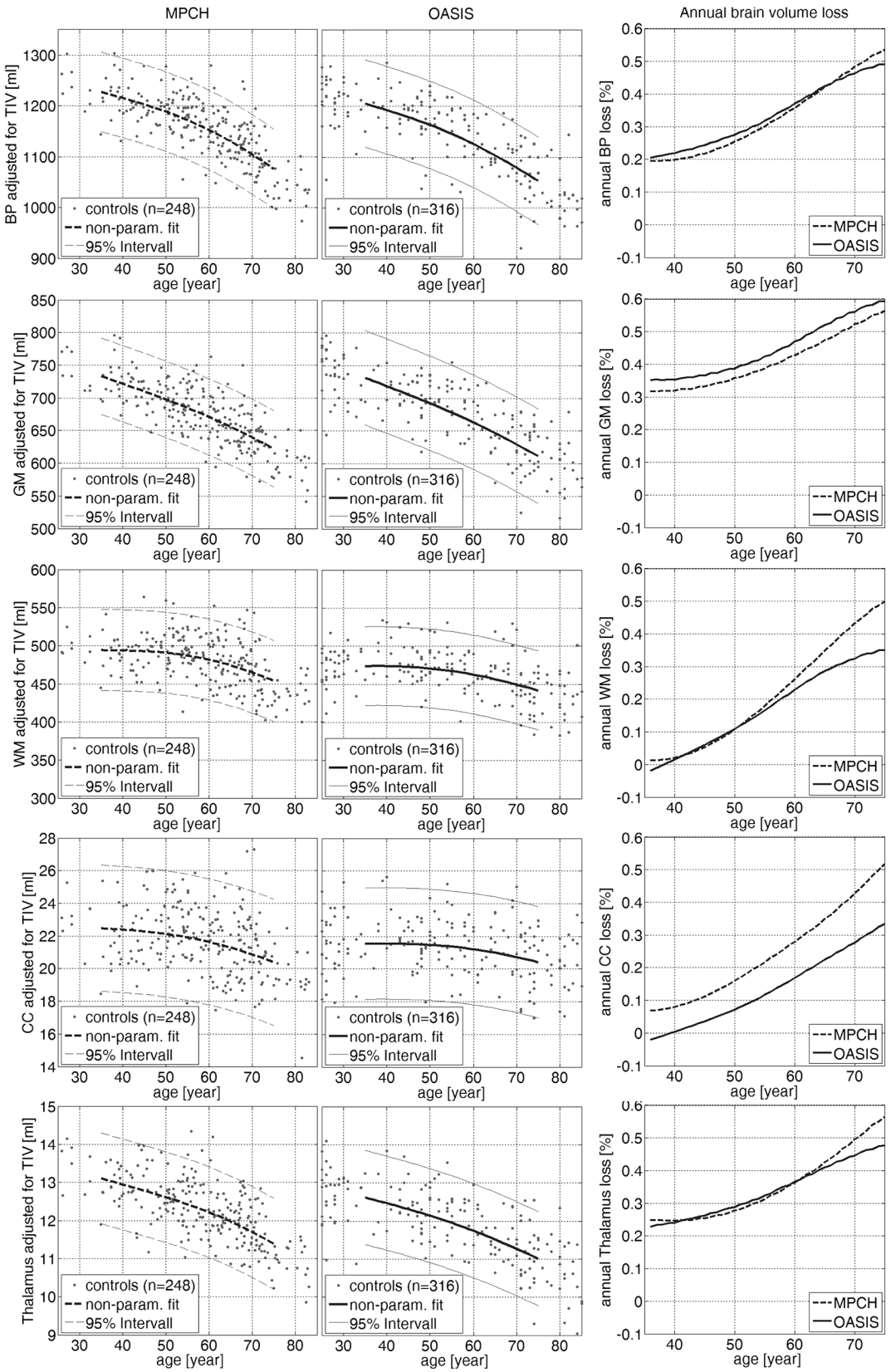
Schippling 1
MPCH
OASIS
Annual brain volume loss
BP adjusted for TIV [ml]
GM adjusted for TIV [ml]
WM adjusted for TIV [ml]
CC adjusted for TIV [ml]
Thalamus adjusted for TIV [ml]
annual BP loss [%]
annual GM loss [%]
annual WM loss [%]
annual CC loss [%]
annual Thalamus loss [%]
controls (n=248)
controls (n=316)
non-param. fit
95% Intervall
MPCH
OASIS
age [year]

Table 3 Annual brain volume loss (BVL) in % for the MPCH and the OASIS cohort for brain parenchyma (BP), grey matter (GM), white mater (WM), corpus callosum (CC), and thalamus

Age, range (years)	BP			GM			WM			CC			Thalamus		
	MPCH	OASIS	Abs diff	MPCH	OASIS	Abs diff	MPCH	OASIS	Abs diff	MPCH	OASIS	Abs diff	MPCH	OASIS	Abs diff
(35, 40)	0.20	0.21	0.01	0.32	0.35	0.03	0.02	0.00	0.02	0.07	−0.01	0.08	0.25	0.24	0.01
(40, 45)	0.21	0.23	0.02	0.33	0.36	0.03	0.04	0.04	0.00	0.10	0.02	0.08	0.25	0.25	0.00
(45, 50)	0.24	0.26	0.02	0.35	0.38	0.03	0.08	0.09	0.00	0.14	0.06	0.08	0.27	0.28	0.01
(50, 55)	0.28	0.30	0.02	0.37	0.41	0.04	0.15	0.14	0.01	0.19	0.10	0.09	0.30	0.31	0.01
(55, 60)	0.33	0.35	0.02	0.41	0.45	0.04	0.23	0.20	0.03	0.25	0.15	0.10	0.34	0.35	0.01
(60, 65)	0.40	0.40	0.00	0.45	0.50	0.05	0.31	0.26	0.05	0.32	0.20	0.12	0.40	0.39	0.01
(65, 70)	0.46	0.45	0.01	0.50	0.55	0.05	0.40	0.31	0.09	0.39	0.26	0.13	0.47	0.43	0.04
(70, 75)	0.52	0.48	0.04	0.55	0.58	0.03	0.47	0.34	0.13	0.48	0.31	0.17	0.54	0.47	0.07
Mean	0.33	0.34	0.02	0.41	0.45	0.04	0.21	0.17	0.04	0.24	0.14	0.11	0.35	0.34	0.02

The BVL is averaged for 5 year intervals. For each interval, the absolute differences (abs diff) between the two cohorts were determined. The last row shows average BVL and the average difference in BVL between the cohorts over the complete age range

published data, we also found that BVL/year rates increased with greater age. BVL/year for whole brain volumes is only 0.2% at the age of 35, while it increases to 0.52% at the age of 75. These results are in good agreement with the magnitude of change reported in longitudinal studies. In the longitudinal study by Fjell et al. [31], a mean BVL/year of 0.44% was reported in a cohort of 132 individuals with an age range between 55 and 91 years. In another recent longitudinal study by De Stefano [12] and co-workers, healthy controls aged ≤35 years ($n = 16$) had a BVL/year of 0.2%, whereas subjects with an age of 35 years or higher ($n = 19$) had a mean BVL/year of 0.32%. In that same study, pathological brain atrophy cut-off values of 0.40% and 0.52% were thought to distinguish between MS and healthy individuals with satisfying sensitivity and specificity. Taken together these results suggest that cut-off values need to be interpreted specifically in light of the age range of the MS population investigated.

In another study by De Stefano et al. [32], it was shown that more advanced MS patients feature higher BVL/year rates than patients in early stages of the disease. However, it was also shown that when correcting BVL/year rates for the baseline normalized brain volume, the differences in BVL/year rates between different MS phenotypes disappeared. An alternative approach and an interesting application of our results would be to correct the measured BVL/year rates by the rate of normal BVL/year as presented in our study. Since normalized brain volumes are confounded by age as well as by the disease this approach might better disentangle age-related effects from disease-related effects.

Volume loss in healthy individuals is remarkably heterogeneous between different tissue compartments (e.g., grey matter and white matter). While there is hardly any observable loss of WM at the age of 35, GM is reduced by 0.32% per year at this age. This difference, however, is no longer observed at the age of 70; BVL/year in the WM is 0.47 and 0.55% in the GM compartment among healthy individuals. The tissue loss rates observed in the older individuals in our study are in good agreement with results of the longitudinal study by Fjell et al. [31]. In this study, 132 healthy individuals between 55 and 91 years showed a mean BVL/year of 0.49% for both GM and WM. These findings are in contrast with results observed in patients with relapsing forms of MS. Here, WM loss is present in the earliest disease stages, whereas GM loss starts later but increases rapidly over time and overtakes WM loss [3].

Relevant to clinical trials in MS, as much as for MS research and imaging evaluation, is the volume loss observed in deep grey matter, especially in the thalamus. We demonstrated that thalamic atrophy closely resembles the whole BP volume loss/year, with an average of 0.25% at the age of 35, increasing to 0.54% at the age of 70. A thalamic BVL/year of 0.62% was reported in the longitudinal study [31]. In a placebo-controlled MS phase-3 trial, a yearly thalamic volume loss of 0.9% in the placebo group and 0.65% in the treatment arm has been reported [33]. In the study by Zivadinov et al. [7], thalamic atrophy was assessed longitudinally in a group of 90 MS patients with sustained diseases progression (mean thalamic volume loss 6.2% within 5 years) and in 90 RRMS patients with stable disease (mean thalamic volume loss 4.5% within 5 years). The rate of thalamic atrophy in these MS patients was four times higher than thalamic atrophy rates reported in our study.

The BVL/year in the CC closely mirrored annual volume loss that was found in the WM, with 0.02% (WM) and 0.07% (CC) at age 35 increasing to 0.47% (WM) and

0.48% (CC) at age 70. These results are in contrast to the results reported in a study on longitudinal trajectories [34], where the author did not observe any volumetric changes of the CC with increasing age. Since we observed a similar pattern in both cohorts, this discrepancy might be explained by different methodical approaches.

As detailed in Fig. 2, there appears to be a wider distribution of volumes for white matter and corpus callosum in comparison with grey matter and thalamus. As it can be calculated from Table 2, the coefficient of variation (std/mean) for the GM (MPCH, adjusted, male) is 50.37/671.13 ml = 0.07, whereas for the WM and CC, it is 52.26/498.33 ml = 0.10 and 2.14/21.51 ml = 0.09, respectively. Thus, GM loss has approximately 25% less variability than WM or CC volume change. This phenomenon has also been observed in other studies [15, 3]. A possible explanation would be that GM may have less biological variability than the WM due to confounding factors, such as hydration status.

A general limitation of our study is its cross-sectional nature. We infer age-related changes in brain volume of healthy individuals. The extent to which atrophy rates extrapolated based on cross-sectional data can be compared to data generated in true prospective longitudinal studies remains controversially discussed [34–36]. Cross-sectional studies, in general, can be compromised by cohort effects or by selection bias. In our study, we analysed brain volumes of different individuals over a wide age range. Young individuals in our cohorts might have been exposed to different environmental and socio-economic factors than older individuals. For instance nutrition, lifestyle and healthcare changed considerably over the past 50 years. This can potentially influence brain volumes. Another drawback of cross-sectional studies is the possibility of hidden selection biases within the cohorts (e.g., young versus older controls) or between the two cohorts. The observed differences in annual brain volume loss rates can potentially be explained by difference in educational or fitness level between the two cohorts. In the study by Gordon et al. [37], a positive effect of education was found for the anterior white matter, specifically, in the rostrum of the corpus callosum. Although the educational level of the MPCH cohort is unknown, the higher educational level among individuals over 60 years in the OASIS cohort might partially explain the lower annual brain volume loss in the white matter (including the corpus callosum) in comparison with the MPCH cohort.

Given these potential limitations, we tried to address them as precisely as possible.

It is known that scanners hardware and protocols can lead to a bias in volumetric measurements (see [5, 6]). Some authors combined cohorts from different scanners to obtain larger cohort sizes [7, 8]. The two presented cohorts are single scanner cohorts. For each cohort, the identical scanner hardware and protocol was used for all subjects. We, therefore, can exclude scanner-related selection bias in our study.

We included and compared two independent cohorts in our study. The results between the cohorts are very consistent. This renders a larger selection bias within the cohort less likely.

Young and older individuals in our cohorts might have been exposed to different environmental and socio-economic factors. However, if these effects were present in the two cohorts, this should not only impact the size of brain volumes but also the size of the total intracranial volume (TIV) as a surrogate for the head size. However, there was no association between age and TIV in our cohorts (Spearman correlation coefficient for OASIS and MPCH combined female: $r = -0.02$, $p = 0.64$, male $r = 0.06$, $p = 0.27$). This suggests that environmental and socio-economic factors did not significantly impact on head size in our two cohorts.

It is important to emphasize that the curves in Fig. 2 do not represent age trajectories of an individual subject. The curves show how the mean of a healthy population evolves over time (with the limitations of cross-sectional studies as discussed). The derived BVL/year rates (right column in Fig. 2) can, therefore, be interpreted as the mean BVL/year rates of a healthy population for a specific age range. To understand and describe this in a bit more detail, we make the following side note. We assume that the age–volume trajectories of n individuals are known and they are described by the set of functions $g_i(x), 1 \leq i \leq n$. The variable x describes the age and each function $g_i(x)$ describes how brain volumes evolve over time. The BVL/year rates at age x of these individuals are given by the first derivative of the functions g_i, i.e., $\mathrm{bvl}_i(x) = g_i'(x)$. The mean curve of the trajectories is given by $G(x) = \frac{\sum_{i=1}^{n} g_i(x)}{n}$. Since taking the derivative of a function is a linear operation, we obtain

$$G'(x) = \frac{\sum_{i=1}^{n} g_i'(x)}{n}.$$

The equation above tells us that it is the same computing the BVL/year from the mean trajectories (as proposed in the right column of Fig. 2) or computing the mean of the individual BVL/year rates. However, in a cross-sectional study, usually, $g_i'(x)$ is unknown and only one point on each curves $g_i(x)$ is available (a computer simulation is shown in Fig. 3 provided in the supplementary material). In our manuscript, we use these cross-sectional points to estimate the function $G(x)$. An individual subject can deviate from this mean and it is not possible to derive the standard

deviations for presented BVL/year rates (Table 3) from the cross-sectional data.

In most cross-sectional studies so far, non-linearity of age–volume relationships is modelled using quadratic or higher polynomial approaches. In the work by Fjell et al. [40], the disadvantages of quadratic fit models are critically discussed and a non-parametric fitting approach was suggested instead. A similar non-parametric fitting approach was used in this study. In a recent study by the same group [17], age–brain structure relationships were investigated using a non-parametric fitting model on cross-sectional data. The fitting models were used to identify critical age ranges in which regional brain volume loss appears to accelerate. The focus of this paper was to present a detailed listing of average global and regional percentage brain volume loss rates per year for a broad age range.

Conclusion

Physiological BVL rates can be assessed cross sectionally using a non-parametric fitting approach and results appear in line with those reported in longitudinal studies. Our results were remarkably consistent between the two cohorts and largely independent of the scanner used. Average BVL/year was clearly age dependent and heterogeneous between different tissue compartments. Overall rates of loss increased with greater age, independently of the MRI technology and the tissue compartment.

Our results are relevant to clinical trials executed in the field of MS using thalamic atrophy as a pre-defined endpoint. They also need to be taken into account when defining cut-off values to dissect pathological from physiological annual brain volume loss rates at different age ranges.

Acknowledgements The OASIS database is made available by the Washington University Alzheimer's Disease Research Center, Dr. Randy Buckner at the Howard Hughes Medical Institute (HHMI) at Harvard University, the Neuroinformatics Research Group (NRG) at Washington University School of Medicine, and the Biomedical Informatics Research Network (BIRN), and supported by NIH grants P50 AG05681, P01 AG03991, R01 AG021910, P50 MH071616, U24 RR021382, R01 MH56584.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard The study (MPCH cohort) was approved by the Ethics Board of the Ärztekammer, Hamburg, Germany.

Informed consent All patients gave written informed consent.

References

1. Barkhof F et al (2009) Imaging outcomes for neuroprotection and repair in multiple sclerosis trials. Nat Rev Neurol 5(5):256–266
2. Steenwijk MD et al (2016) Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant. Brain 139(Pt 1):115–126
3. Fisher E et al (2008) Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol 64(3):255–265
4. Sepulcre J et al (2006) Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. Arch Neurol 63(8):1175–1180
5. Audoin B et al (2006) Localization of grey matter atrophy in early RRMS: a longitudinal study. J Neurol 253(11):1495–1501
6. Datta S et al (2015) Regional gray matter atrophy in relapsing remitting multiple sclerosis: baseline analysis of multi-center data. Mult Scler Relat Disord 4(2):124–136
7. Zivadinov R et al (2013) Evolution of cortical and thalamus atrophy and disability progression in early relapsing-remitting MS during 5 years. AJNR Am J Neuroradiol 34(10):1931–1939
8. Rocca MA et al (2010) Thalamic damage and long-term progression of disability in multiple sclerosis. Radiology 257(2):463–469
9. Schoonheim MM et al (2012) Subcortical atrophy and cognition: sex effects in multiple sclerosis. Neurology 79(17):1754–1761
10. Pelletier J et al (2001) A longitudinal study of callosal atrophy and interhemispheric dysfunction in relapsing-remitting multiple sclerosis. Arch Neurol 58:105–111
11. Uher T et al (2016) Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year disability in multiple sclerosis. Mult Scler. doi:10.1177/1352458516642314
12. De Stefano N et al (2016) Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. J Neurol Neurosurg Psychiatry 87(1):93–99
13. Ziegler G et al (2012) Brain structural trajectories over the adult lifespan. Hum Brain Mapp 33(10):2377–2389
14. Marcus DS et al (2007) Open access series of imaging studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. J Cogn Neurosci 19(9):1498–1507
15. Ge Y et al (2002) Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am J Neuroradiol 23(8):1327–1333
16. Fotenos AF et al (2005) Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. Neurology 64(6):1032–1039
17. Fjell AM et al (2013) Critical ages in the life course of the adult brain: nonlinear subcortical aging. Neurobiol Aging 34(10):2239–2247
18. Marcus DS et al (2010) Open access series of imaging studies: longitudinal MRI data in nondemented and demented older adults. J Cogn Neurosci 22(12):2677–2684
19. Hedman AM et al (2012) Human brain changes across the life span: a review of 56 longitudinal magnetic resonance imaging studies. Hum Brain Mapp 33(8):1987–2002
20. Enzinger C et al (2005) Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. Neurology 64(10):1704–1711
21. Opfer R et al (2016) Atlas based brain volumetry: how to distinguish regional volume changes due to biological or physiological effects from inherent noise of the methodology. Magn Reson Imaging 34(4):455–461
22. Huppertz HJ et al (2010) Intra- and interscanner variability of automated voxel-based volumetry based on a 3D probabilistic atlas of human cerebral structures. Neuroimage 49(3):2216–2224

23. Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26(3):839–851
24. Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38(1):95–113
25. Mori S et al (2008) Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage 40(2):570–582
26. Malone IB et al (2015) Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. Neuroimage 104:366–372
27. Keihaninejad S et al (2010) A robust method to estimate the intracranial volume across MRI field strengths (1.5T and 3T). Neuroimage 50(4):1427–1437
28. Pell GS et al (2008) Selection of the control group for VBM analysis: influence of covariates, matching and sample size. Neuroimage 41(4):1324–1335
29. Friedman J, Hastie T, Tibshirani R (2001) The elements of statistical learning (chapter 6), vol 1. Springer Series in Statistics, Springer, Berlin
30. Bowman AW, Azzalini A (1997) Applied smoothing techniques for data analysis: the kernel approach with S-Plus illustrations: the kernel approach with S-Plus illustrations. OUP, Oxford
31. Fjell AM et al (2013) Brain changes in older adults at very low risk for Alzheimer's disease. J Neurosci 33(19):8237–8242
32. De Stefano N et al (2010) Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. Neurology 74(23):1868–1876
33. Filippi M et al (2014) Placebo-controlled trial of oral laquinimod in multiple sclerosis: MRI evidence of an effect on brain tissue damage. J Neurol Neurosurg Psychiatry 85(8):851–858
34. Pfefferbaum A et al (2013) Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. Neuroimage 65:176–193
35. Pfefferbaum A, Sullivan EV (2015) Cross-sectional versus longitudinal estimates of age-related changes in the adult brain: overlaps and discrepancies. Neurobiol Aging 36(9):2563–2567
36. Lindenberger U et al (2011) Cross-sectional age variance extraction: what's change got to do with it? Psychol Aging 26(1):34–47
37. Gordon BA et al (2008) Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. Psychophysiology 45(5):825–838
38. Noble KG et al (2012) Hippocampal volume varies with educational attainment across the life-span. Front Hum Neurosci 6:307
39. Foubert-Samier A et al (2012) Education, occupation, leisure activities, and brain reserve: a population-based study. Neurobiol Aging 33(2):423.e15–25
40. Fjell AM et al (2010) When does brain aging accelerate? Dangers of quadratic fits in cross-sectional studies. Neuroimage 50(4):1376–1383