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BRIEF COMMUNICATION

Percentage brain volume change in multiple sclerosis mainly reflects white matter and cortical volume

Markus Lauerer[1,2], Matthias Bussas[1,2], Viola Pongratz[1,2], Achim Berthele[1], Jan S Kirschke[3], Benedikt Wiestler[3], Claus Zimmer[3], Bernhard Hemmer[1,4] & Mark Mühlau[1,2]

[1]Department of Neurology, School of Medicine, Technical University of Munich, Munich, Germany
[2]TUM-Neuroimaging Center, School of Medicine, Technical University of Munich, Munich, Germany
[3]Department of Neuroradiology, School of Medicine, Technical University of Munich, Munich, Germany
[4]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Correspondence
Mark Mühlau, Department of Neurology, School of Medicine, Technical University of Munich, Ismaninger Str. 22, D-81675 Munich, Germany. Tel: +49 89 4140 4661; Fax: +49 89 4140 4867; E-mail: mark.muehlau@tum.de

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Abstract

Brain atrophy in multiple sclerosis (MS), as measured by percentage brain volume change (PBVC) from brain magnetic resonance imaging (MRI), has been established as an outcome parameter in clinical trials. It is unknown to what extent volume changes within different brain tissue compartments contribute to PBVC. We analyzed pairs of MRI scans (at least 6 months apart) in 600 patients with relapsing–remitting MS. Multiple regression revealed that PBVC mainly reflects volume loss of white and cortical gray matter, while deep gray matter and white matter lesions were less represented. Our findings aid the interpretation of PBVC changes in MS.

Introduction

The pathophysiology of multiple sclerosis (MS) comprises inflammation and neurodegeneration.[1] The latter can be assessed through the surrogate of global brain atrophy, for which the percentage of brain volume change (PBVC) has become the most established measure,[2] even in clinical trials.[3–5] In determining PBVC, however, all

longitudinal volume effects are reduced to a single value; consequently, compartmental correlates of atrophy, along with any potential confounders, remain implicit. We analyzed magnetic resonance imaging (MRI) scans from relapsing–remitting MS (RRMS) patients across two different time points to estimate the contributions of volume changes within different brain compartments to PBVC. In this study, we make two main assumptions. First, volume changes in a particular brain compartment translate into PBVC largely independent of their pathomechanism (if it is not strictly local such as in a tumor). Second, volume changes in a particular brain compartment translate into PBVC independent from changes in other brain compartments, so that contributions of volume changes of different brain compartments to PBVC can be disentangled by regression models. We focused on supratentorial volumes, as PBVC is determined through estimates of brain surface motion by mainly tracking supratentorial surface points.[2,6] We divided the supratentorial part of the brain into deep gray matter (GM), cortical GM (via cortical thickness), white matter (WM), and WM lesions and determined their change over time using voxel-based and surface-based methods to assess their contributions to PBVC. The inclusion of WM lesion volume was made under the assumption that – besides constituting a tissue compartment in its own right – any lesion changes may be paralleled by an increase or decrease in inflammation and shifts in brain water content (edema), potentially contributing to PBVC.

Methods

Participants

This retrospective study was part of the single-center cohort study on MS at the Technical University of Munich (TUM-MS), which was approved by the internal review board and performed in accordance with the Declaration of Helsinki. Patient data for this study were derived from a cohort of 600 patients with a diagnosis of RRMS and an interscan interval of at least 6 months as previously described.[7]

MRI acquisition and processing

All MRI scans were acquired on the same 3 Tesla scanner (Achieva; Philips Healthcare, Best, Netherlands) with the same protocol. Three-dimensional spoiled gradient echo T1-weighted sequences were acquired applying the following parameters: voxel size = 1 mm isotropic; time to repetition (TR) = 9 ms; time to echo (TE) = 4 ms. Turbo-spin echo T2-weighted fluid-attenuated inversion recovery images were acquired using the following parameters: voxel size = 1.0 mm × 1.0 mm × 1.5 mm; TR = 10,000 ms; TE = 140 ms; inversion time = 2750 ms.

PBVC was calculated using the structural image evaluation of normalized atrophy (SIENA) software (version 6.04).[2] Lesion volume and, after lesion filling, compartmental changes were obtained through statistical parametric mapping 12 with the computational analysis toolbox 12 and the lesion segmentation toolbox. Deep GM was defined as thalamus + putamen + caudate. WM lesion change was calculated by subtracting WM lesion volume of the first scan from that of the second scan. All images were visually inspected to rule out MRI artifacts and errors along the processing pipeline.

Statistical analysis

Absolute changes in WM lesion volume were annualized. All other measures of volume change were transformed to annualized percentage volume changes. Statistical testing and graphical plotting were done with the software R (4.1.2) and its packages effsize, ppcor, corrr, lmPerm, olsrr, ggplot2, and patchwork. Significant differences in volume changes from zero were evaluated by one-sample *t*-tests. Measures of volume changes were compared via paired *t*-tests. Cohen's *d* was used as a measure of effect size relative to zero. Logarithmic values of lesion change were taken to approach a normal distribution, and Pearson's correlation coefficient (*r*) was used for simple correlation analyses of volume change parameters. Multiple regression analysis was performed according to the model $PBVC = \beta_0 + \beta_1 \Delta WM + \beta_2 \Delta corticalGM + \beta_3 \Delta deepGM + \beta_4 \Delta WMlesions$ using permutation tests (10,000 iterations) to minimize bias by outliers and non-normal distributions. To allow for the interpretation of regression coefficients in terms of relative effect sizes on PBVC, semi-partial correlations were calculated, now yielding semi-partial Pearson's coefficients (*sr*). To establish a frame of reference, effect sizes from three clinical trials, having reported significant group differences in PBVC,[3–5] were calculated by obtaining Cohen's *d* through $(\mu_2 - \mu_1)/\sqrt{\left(SD_1^2 + SD_2^2\right)/2}$, which was converted to *r* through $\sqrt{(d/d^2 + 4)}$.[8] Finally, we performed another regression analysis using a stepwise procedure to determine the drivers of (i.e. independent contributions to) PBVC. Thresholds for variable entry and exclusion were defined as $P < 0.05$ and $P > 0.10$, respectively.

Results

Characteristics of study participants and relation to percentage brain volume change

These data are given in Table 1. At first scan, expanded disability status scale, volumes of WM lesions, cortical

Table 1. Baseline characteristics of study participants.

	Total (n = 600)	Association with PBVC, P-value
Age at first scan (years)		
Mean (SD)	35 (9.5)	
Median [Min, Max]	33 [18, 67]	0.116
Sex		
Female	405 (67.5%)	
Male	195 (32.5%)	0.209
EDSS at first scan		
Mean (SD)	1.3 (1.1)	
Median [Min, Max]	1.0 [0, 6.5]	**0.010**
Disease duration at first scan (years)		
Mean (SD)	1.5 (2.6)	
Median [Min, Max]	0.33 [0, 14.2]	0.168
Time between scans (years)		
Mean (SD)	4.0 (2.2)	
Median [Min, Max]	4.0 [0.50, 8.8]	0.718
Relapses between scans		
0	461 (76.8%)	
≥1	139 (23.2%)	0.368
Time to first relapse between scans (years, n = 139)	(years)	
Mean (SD)	1.2 (1.4)	0.638
Median [Min, Max]	0.74 [0, 7.7]	
Disease-modifying therapy at first scan		
Interferon β	120 (20.0%)	
Glatiramer acetate	41 (6.8%)	
Natalizumab	30 (5.0%)	
Dimethyl fumarate	13 (2.2%)	
Fingolimod	6 (1.0%)	
Teriflunomide	1 (0.2%)	
Azathioprine	1 (0.2%)	
None	388 (64.7%)	0.689 (yes or no)
Disease-modifying therapy at last scan		
Interferon β	134 (22.3%)	
Glatiramer acetate	93 (15.5%)	
Fingolimod	83 (13.8%)	
Dimethyl fumarate	79 (13.2%)	
Natalizumab	40 (6.7%)	
Teriflunomide	14 (2.3%)	
Rituximab	5 (0.8%)	
Azathioprine	1 (0.2%)	
Alemtuzumab	1 (0.2%)	
Daclizumab	1 (0.2%)	
None	149 (24.8%)	0.166 (yes or no)
Therapy between scans		
No therapy all through	117 (19.5%)	
Initiation of new therapy	271 (45.2%)	
Same therapy all through	91 (15.2%)	
Switch to different therapy	89 (14.8%)	
Termination of therapy	32 (5.3%)	
Lesion volume at first scan (mL)		
Mean (SD)	4.8 (7.9)	
Median [Min, Max]	2.1 [0, 72.0]	**<0.001**
Cortical thickness at first scan (mm)		
Mean (SD)	2.7 (0.10)	
Median [Min, Max]	2.7 [2.3, 3.0]	**<0.001**
Deep gray matter at first scan (mL)		
Mean (SD)	26.3 (3.1)	
Median [Min, Max]	26.5 [13.2, 36.5]	**<0.001**
White matter (mL)		
Mean (SD)	481 (58.1)	
Median [Min, Max]	475 [306, 672]	0.565

P-values, in bold if significant (<0.05), derived from Spearman correlations for interval and continuous variables, from independent sample *t*-tests for dichotomous variables.
EDSS, expanded disability status scale; Max, maximum; Min, minimum; PBVC, percentage brain volume change; SD, standard deviation.

GM, and deep GM showed a significant association with later PBVC.

Brain volume measures and their contribution to percentage brain volume change

All measures of volume change (Fig. 1A) differed significantly from zero ($P < 0.001$) and showed overall volume loss, except for an increase in WM lesion volume. PBVC was the most sensitive measure of volume change. In descending order, effect sizes given as Cohen's d (means ± SD) were 0.78 (−0.44 ± 0.56%) for PBVC, 0.62 (−1.13 ± 1.83%) for deep GM, 0.47 (−0.38 ± 0.81%) for WM, 0.33 (−0.22 ± 0.67%) for cortical GM (cortical thickness), and 0.22 (0.19 ± 0.86) for WM lesion change. Compared to PBVC, changes in deep GM were significantly greater ($P < 0.001$), while changes in cortical GM and WM were both lower ($P < 0.001$ and $P = 0.013$, respectively).

Simple correlation analyses (Fig. 1B) with PBVC yielded significant results for all compartmental volume changes. In descending order, r values were 0.66 for WM, 0.56 for cortical GM, 0.51 for deep GM, and 0.07 for WM lesion change. Of note, this order was preserved in the multiple regression model, indicating independent contributions of all four measures to PBVC, although the distances between measures changed; in descending order,

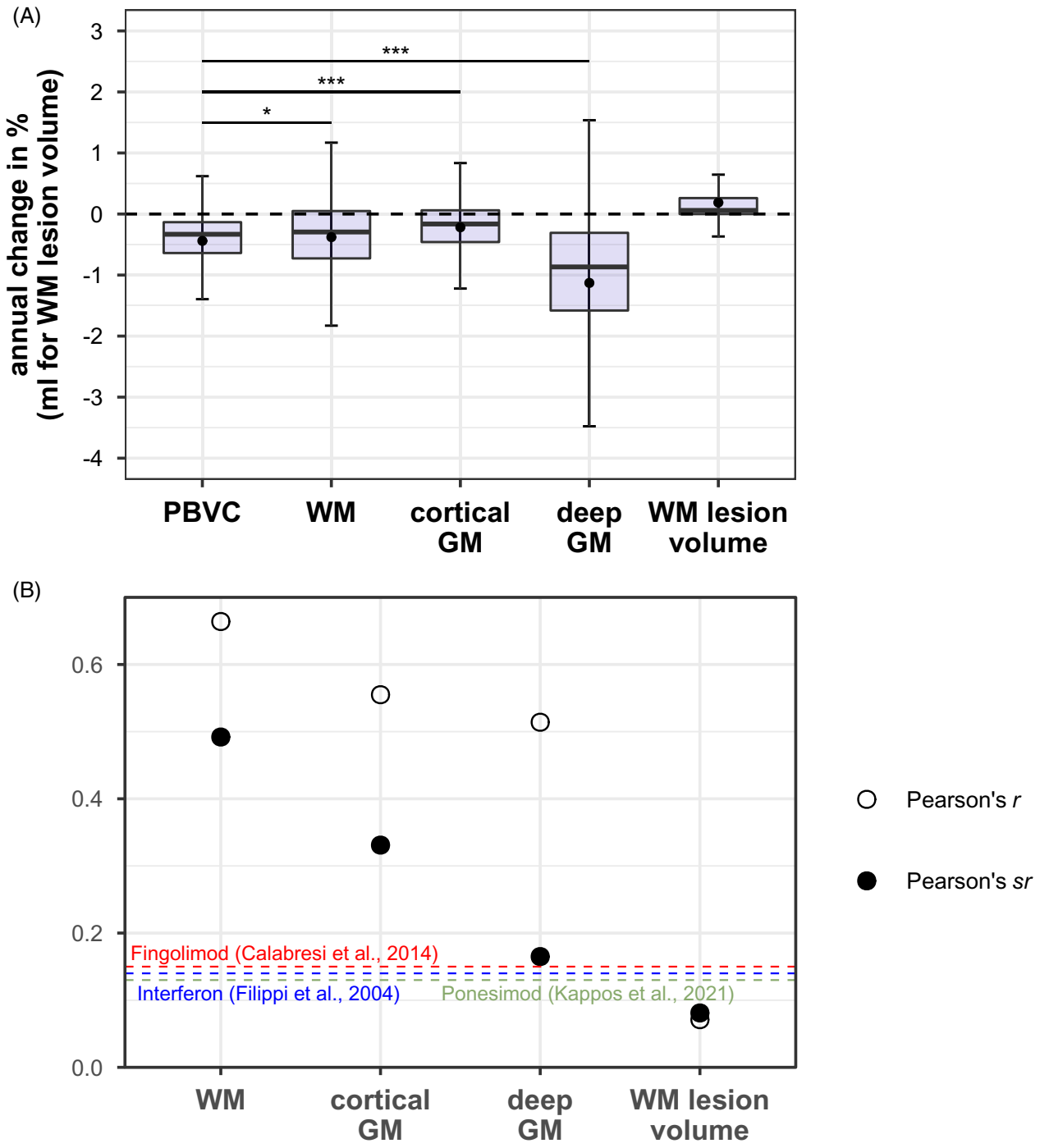

Figure 1. Brain volume change measures and their effect sizes in a cohort of relapsing–remitting multiple sclerosis patients. (A) Scatter–/boxplots showing annual percentage volume change for whole brain (PBVC), WM, cortical GM, and deep GM, and annual changes in WM lesion volumes. Paired *t*-tests were performed between PBVC and compartmental volume changes (*$P < 0.05$, ***$P < 0.001$). (B) Effect size for all compartmental volume change measures. Pearson's *r* and semi-partial Pearson's *r* (*sr*) were determined by simple and multiple regression models with PBVC as response variable. As a frame of reference, effect sizes (Pearson's *r* for comparability) from three clinical trials were estimated and added as dashed horizontal lines. GM, gray matter; WM, white matter.

sr values were 0.49 for WM, 0.33 for cortical GM, 0.17 for deep GM, and 0.08 for WM lesion change.

To rule out potential biases, we performed control analyses. Addressing the comparatively small volume of deep GM regions, we repeated our regression analysis with annualized percentage changes of corpus callosum instead of WM, the absolute volume of which was even smaller than that of deep GM (17.91 ± 2.81 vs. 25.81 ± 3.24 mL). This, however, yielded virtually the same results. Addressing the possibility that the overall change in WM lesion volume might not be the optimal surrogate of inflammatory activity or changes thereof,[9] we further modified our model by entering either the increase (i.e. new or enlarged lesions) or decrease in WM lesion volume (instead of WM lesion change) into our model. Again, these modifications did not change our results in a meaningful way.

Finally, we re-ran our model, this time using a stepwise approach to identify the main drivers of PBVC, which were the changes in WM volume and cortical GM, together accounting for 62.6% (R^2) of the total variance in PBVC. The addition of changes in deep GM and WM lesion volumes improved the model fit only to 65.4% (R^2).

Discussion

In this analysis of a large RRMS cohort, we have found volume changes in all supratentorial brain compartments (WM, cortical and deep GM, WM lesions) to be reflected by PBVC. However, contributions of compartmental volumes to PBVC varied largely. While changes in WM and cortical GM strongly predicted PBVC with independent effect sizes clearly above those reported in clinical trials,[3–5] changes in deep GM hardly exceeded these effect sizes and changes in WM lesion volume remained below them.

Our numbers for PBVC were in line with observations from the literature using similar cohorts of mildly affected RRMS patients.[10,11] Thus, when interpreting results based on PBVC, it should be kept in mind that deep GM is likely to be underrepresented. This is remarkable, as evidence exists that brain atrophy in early MS is predominantly located in this compartment.[12,13] These changes were seen without a decrease in overall brain GM volume[14] or total brain volume.[15] Along the same lines, we found that deep GM volume change was more than twice as high as PBVC and more than five times higher than the change in cortical thickness. Tissue loss in deep GM has shown the most rapid progression among all brain compartments and has been identified as the only GM correlate of disability accumulation in a large study with over 1000 MS patients.[16] It may therefore be advisable to combine PBVC with measures of deep GM atrophy.

Changes in WM lesion volume were a significant but rather weak predictor of PBVC. Our study cohort mainly consisted of early RRMS patients and was comparable with cohorts of pivotal trials.[17,18] Substituting (overall) WM lesion change with other measures of lesion dynamics in our regression model had no meaningful effect on the outcome. Therefore, it seems unlikely that changes in WM lesions considerably influence PBVC.

We acknowledge limitations. We cannot directly prove our two main assumptions (generalizability and independence of observed associations). A control cohort to study these associations in age-related changes would have been an option. Moreover, our cohort may not fully represent the different patterns of brain atrophy occurring in MS. The measures used to better understand PBVC were obtained from estimates of volumes. Therefore, we cannot rule out contributions to PBVC different from atrophy in the sense of neurodegeneration, such as pseudoatrophy after initiation of disease-modifying therapy that has been related to changes in brain WM[19] and GM.[20] Finally, only two scans per patient were analyzed with heterogeneous intervals between scans, so that temporal evolutions could not be taken into account; this may have hampered the detection of volume changes not following a constant progression over time.

In summary, our findings suggest that PBVC is an overall robust parameter of global brain volume loss, well representative of WM and cortical GM but less so of deep GM. WM lesions are unlikely to considerably interfere with PBVC.

Author contributions

M.L., M.B., and M.M. contributed to the conception, and design of the study as well as data analyses. V.P., B.W., A.B., J.S.K., C.Z., and M.M. participated in the acquisition of data. M.L. and M.M. drafted the text and figures.

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Conflict of Interest

None declared.

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