What explains gray matter atrophy in long-standing multiple sclerosis?

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Target audience: Radiologists, Neurologists, MS researchers

Purpose: Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. Although white matter (WM) lesions are still the most important MRI characteristic used in today's MS diagnostics and clinical trials, it has been recognized that gray matter (GM) atrophy is an unmistakable component of the disease.[1] Several studies investigated the presumed relationship between GM atrophy and WM pathology with MRI and found an association between GM loss and WM lesion load.[2,3] However, most of these studies were performed in patients with a relatively short disease duration, at low field strength, did not investigate normal appearing white matter (NAWM) damage or had methodological limitations, such as the lack of lesion filling. In order to investigate the relationship between GM atrophy and WM pathology in MS patients with long disease duration, we set up a large cohort using state-of-the-art imaging techniques. The aim of this study was to identify the WM measures that are related to whole brain GM, cortical and subcortical atrophy.

Methods: MRI was performed at a 3T whole body scanner (GE Signa HDxt, Milwaukee, WI, USA) in 208 MS patients and 60 healthy controls. Normalized GM volumes (NGMV), normalized deep GM volumes (NDGMV), cortical thickness (CT), normalized WM volumes (NWMV) and normalized lesion volumes (NLV) were quantified on T1-weighted images (repetition time (TR) 7.8 ms, echo time (TE) 3 ms, inversion time (TI) 450 ms, flip angle 12º, sagittal 1.0 mm slices, 0.94 x 0.94 mm^2 in-plane resolution) and 3D FLAIR images (TR 8000 ms, TE 125 ms, TI 2350 ms, sagittal 1.2 mm slices, 0.98 x 0.98 mm^2 in-plane resolution) after lesion filling using respectively FSL 5.0.2, FreeSurfer 5.1 and the kNN-TTP WM lesion segmentation algorithm.[4] Tissue integrity was measured by quantifying fractional anisotropy (FA) and mean diffusivity in the normal appearing WM (NAWM) and lesions using diffusion tensor imaging. In the patients, clinical subtype (i.e. relapsing-remitting (RR), secondary-progressive (SP) or primary-progressive (PP)) was confirmed on the day of scanning and disease severity was measured using the Expanded Disability Status Scale (EDSS). Stepwise linear regression was used in the patients to identify the independent predictors of GM atrophy. The analyses were repeated for each clinical subtype to investigate potential differences.

Table 1. Demographic and main MRI characteristics[a]

	Healthy controls (n=60)	MS patients (n=208)
Age, y	50.33±7.08	53.70±9.62**
F/M	37/23	141/67
Disease duration, y	-	20.20±7.08
EDSS[b]	-	4.0 (3.0-6.0)
Clinical subtype (RR/SP/PP)	-	130/53/25
NGMV, L	0.80±0.05	0.75±0.06***
NWMV, L	0.70±0.03	0.66±0.05***
NDGMV, mL	63.45±4.71	57.27± 6.62***
CT, mm	2.56±0.09	2.47±0.10***
NLV, mL[b]	-	18.09 (9.93-29.67)
FA_{NAWM}	0.39±0.02	0.37±0.03***

[a] mean±SD; [b] median (IQR); * p< 0.05; ** p< 0.01; *** p< 0.001

Results: Table 1 summarizes the demographic and main MRI characteristics of the groups (data for clinical subtypes not shown). Age differed between progressive MS patients and controls, but not between RRMS patients and controls. Sex distribution was equal in all groups. GM atrophy measures were reduced in patients. The MS patients had a median lesion volume of 11.24 mL, consistent with moderate to advanced disease. In whole brain gray matter volume, 58% of the variance was explained by WM atrophy, lesion volume, age and sex (see Fig. 1). Deep gray matter volume was predicted by WM atrophy, lesion volume and sex; this model accounted for 75% of the variance. The model for cortical thickness consisted of FA_{NAWM}, lesion volume, age and sex, and accounted for 32% of the variance. Models for different disease types showed a less pronounced relationship between GM atrophy and WM pathology in progressive patients.

Discussion: The data for this study were acquired at high, near isotropic spatial resolution allowing us to perform state-of-the art lesion measurements and sub-voxel accurate cortical thickness measurements. Furthermore, the inclusion of DTI allowed us for the first time to investigate the influence of NAWM on GM atrophy at such a large scale in MS. Some limitations apply to this work. The MS patients were on average older than controls. To prevent an unwanted influence of age on the main study outcome, we added age (and sex) as covariates in the analyses. Furthermore, the size of the SPMS and PPMS groups were relatively small for the large number of explanatory variables. Univariate analyses were first performed to reduce the number of explanatory variables as much as possible.

Conclusions: White matter atrophy and lesion volume were the most important measures predicting whole brain GM and subcortical atrophy, while cortical atrophy was associated with diffuse WM integrity loss. Analyzing the clinical subgroups revealed a weaker relationship between GM atrophy and WM pathology in progressive patients, which might indicate a more independent neurodegenerative disease process in these patients.

References: 1. Hulst H, Geurts J. Gray matter imaging in multiple sclerosis: what have we learned? BMC Neurol. 2011;11(1):153. 2. Roosendaal S, Bendfeldt K, Vrenken H et al. Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. Mult Scler. 2011;17(9):1098-1106; 3. Bergsland N, Horakova D, Dwyer MG, et al. Subcortical and cortical gray matter atrophy in a large sample of patients with clinically isolated syndrome and early relapsing-remitting multiple sclerosis. AJNR Am J Neuroradiol. 2012;33(8):1573-1578; 4. Steenwijk M, Pouwels P, Daams M, et al. Accurate white matter lesion segmentation by k nearest neighbor classification with tissue type priors (kNN-TTPs). NeuroImage Clin. 2013;9:462–469.

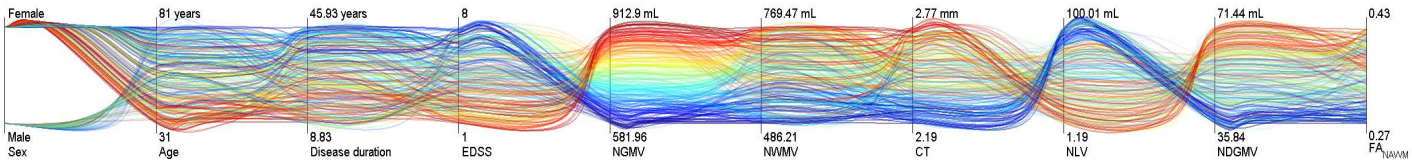

Fig. 1 Parallel coordinate plot illustrating the multivariate behavior of the MS patients with respect to normalized whole brain GM volume (NGMV). Each curve corresponds to a single patient and shows the values observed for that patient on each of the outcome measures.