Connected WM lesions are associated with reduced cortical thickness in long-standing multiple sclerosis

Martijn D. Steenwijk[1], Marita Daams[1,2], Lisanne J. Balk[3], Prejaas K. Tewarie[3], Jeroen J.G. Geurts[2], Frederik Barkhof[1], Hugo Vrenken[1,4], and Petra Pouwels[4]
[1]Department of Radiology and Nuclear Medicine, VU University medical center, Amsterdam, Noord-Holland, Netherlands, [2]Department of Anatomy and Neurosciences, VU University medical center, Amsterdam, Noord-Holland, Netherlands, [3]Department of Neurology, VU University medical center, Amsterdam, Noord-Holland, Netherlands, [4]Department of Physics and Medical Technology, VU University medical center, Amsterdam, Noord-Holland, Netherlands

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. Hypotheses of the mechanism underlying GM atrophy include primary damage, such as demyelination and neuronal loss; but also secondary damage due to axonal disconnection by WM lesions. Some MRI studies explored the spatial relationship between GM atrophy and WM pathology using voxel-wise statistics, and found that GM atrophy can be better explained by WM abnormalities tissue in co-localized areas.[1,2,3] Only a few studies, focusing on specific GM regions or WM tracts in early MS patients, used a direct analysis of structural connectivity (using diffusion tensor imaging; DTI) to assess the association between WM pathology and GM atrophy in connected areas.[4,5] A whole brain analysis of these mechanisms in established MS patients is necessary to obtain more insight into the relation between GM atrophy and WM pathology. Therefore we aimed to directly assess the association between focal white matter abnormalities and GM atrophy in the connected cortical regions using a new, state-of-the-art, whole brain tractography approach in a large cohort of long-standing MS patients.

Methods: MRI was performed at a 3T whole body scanner (GE Signa HDxt, Milwaukee, WI, USA) in 208 long-standing MS patients and 60 healthy controls. In the patients, clinical subtype was confirmed on the day of scanning and disease severity was measured using the Expanded Disability Status Scale (EDSS). Cortical thickness was quantified in all subjects on 3D 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) using FreeSurfer 5.1 and WM lesions were segmented in the patients on 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) using the kNN-TTP algorithm[6]. Whole brain probabilistic tractography was performed on DTI images (2D EPI; TR 13000 ms, TE 86 ms, 2.4 mm slices, 2.0 x 2.0 mm^2 in-plane resolution, 30 gradients, 5 non-weighted, b=900 mm/s^2) from the rim surrounding the WM lesions using probtrackx2 (part of FSL 5.0.4) and mapped onto the cortical surface in order to obtain vertex-wise measures of lesion connectivity. The tractography procedure included two termination masks: first, the lesion mask itself, to force tracking to only include streamlines 'departing' from lesions; and secondly, the FreeSurfer cortex segmentation, to prevent streamlines passing through the cortex. To minimize effects of registration inaccuracies between the T1-weighted and DTI-image, the voxel-wise lesion connectivity map was sampled onto the cortical surface by finding the highest connectivity value within 2 mm below the WM surface. The surface maps were subsequently smoothed using a Gaussian kernel with a FWHM of 10 mm and vertex-wise statistics were used to investigate group-wise differences and correlations with cortical thickness. If applicable, the vertex-wise lesion connectivity map was appended to the general linear model using a so-called *per-voxel regressor*. Cluster-wise correction for multiple comparisons was applied using Monte Carlo Z simulation while thresholding the statistical maps at $p<0.001$, using 5000 iterations and setting the cluster-level threshold at $p<0.05$.

Results: Table 1 summarizes the demographic characteristics of the groups. Age differed between progressive MS patients and controls, but not between RRMS patients and controls. MS patients showed extensive cortical atrophy, particular in the bilateral temporal lobe, frontal areas, insula, precentral cortex and medial occipital lobes. More pronounced cortical atrophy was found in SPMS patients, but not in PPMS patients. Lesion connectivity maps revealed a wide-spread effect of WM lesions on the cortex, which was even larger in SPMS patients. Vertex-wise correlations displayed large areas with negative associations between cortical thickness and lesion connectivity (see Fig. 1).

Discussion: The combination of tractography with the use of advanced post-processing allowed us for the first time to directly investigate the relationship between focal white matter pathology and local damage to the connected cortex on a whole brain level in a large patient cohort. This opened a new, unexplored, window of research opportunities, and possibly a better explanation for GM atrophy in MS. Some limitations apply to this work. First, our tractography methodology might be subject to improvement: it cannot be ruled out that the tractography algorithm was influenced by normal appearing tissue damage (i.e. reductions of fractional anisotropy) resulting in apparently less focal projections of lesions on the cortex. Second, the GM atrophic effects of remote WM lesions may be obscured by WM lesions closer to the cortex; our analysis do not allow streamlines to pass through those lesions even if the tissue structure within the lesions is sufficiently intact.

Conclusions: We developed a new method to directly investigate the relation between cortical atrophy and connected WM lesions. We applied the method on a large cohort of patients with long-standing MS. Vertex-wise statistics revealed large areas with significant associations between cortical thickness and lesion connectivity, indicating that cortical atrophy in MS –at least partly– can be explained by axonal damage or disconnection by connected WM lesions.

References: 1. Bodini B, Khaleeli Z, Cercignani M, et al. Exploring the relationship between white matter and gray matter damage in early progressive multiple sclerosis: an in vivo study with TBSS and VBM. Hum Brain Mapp. 2009;30(9); 2852-2861; 2. Mühlau M, Buck D, Förschler A, et al. White-matter lesions drive deep gray-matter atrophy in early multiple sclerosis: support from structural MRI. Mult Scler. 2013; 3. Sepulcre J, Goñi J, Masdeu J, et al. Contribution of white matter lesions to gray matter atrophy in multiple sclerosis: evidence from voxel-based analysis of T1 lesions in the visual pathway. Arch Neurol. 2009; 66(2);173-179; 4. Henry R, Shieh M, Amirbekian B, et al. Connecting white matter injury and thalamic atrophy in clinically isolated syndromes. J Neurol Sci. 2009;282(1-2): 61-66; 5. Jehna M, Langkammer C, Khalil M, et al. An exploratory study on the spatial relationship between regional cortical volume changes and white matter integrity in multiple sclerosis. Brain Connect. 2013; 6. 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.

Table 1. Demographic characteristics

	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

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

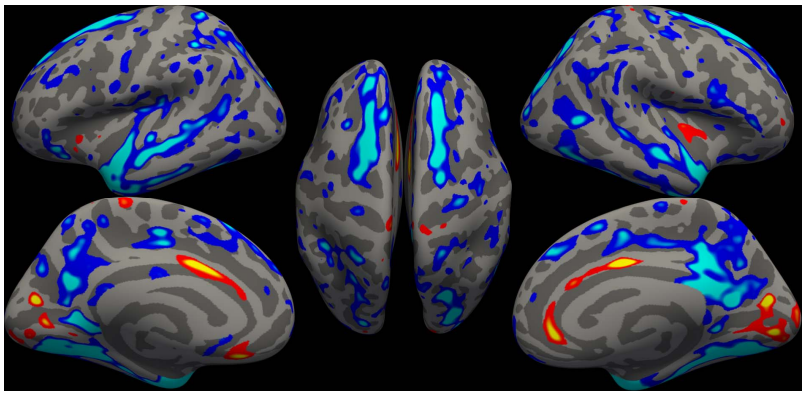

Fig. 1 Vertex-wise group-level correlations across 208 MS patients; higher lesion connectivity is associated with thinner cortex in many regions, indicated in blue to light-blue.