Normal-appearing white matter changes vary with distance to lesions in Multiple Sclerosis

H. Vrenken[1,2], J. J. Geurts[1], D. L. Knol[3], C. H. Polman[4], J. A. Castelijns[1], P. J. Pouwels[2], F. Barkhof[1]

[1]Department of Radiology, VU University Medical Center, Amsterdam, Netherlands, [2]Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, Netherlands, [3]Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands, [4]Department of Neurology, VU University Medical Center, Amsterdam, Netherlands

Not many studies have investigated the relation between Multiple Sclerosis (MS) normal-appearing white matter (NAWM) disease and the lesions visible on in vivo magnetic resonance images. Abnormalities in Magnetization Transfer Ratio (MTR) and T_1 relaxation time have been reported to be larger close to lesions, using region-of-interest analyses (1,2). To assess the global properties of NAWM at different distances to lesions, we performed histogram analyses of B1-corrected T_1 (3) and MTR. Both were measured with a 3D-FLASH sequence (1.5T;TE 4 ms; TR 15ms for T_1 measurement, 27 ms for MTR measurement; in case of the MTR measurement with a Gaussian MT prepulse of 7.68 ms duration, effective flip angle 500°), in 63 MS patients (11 primary progressive, 34 relapsing-remitting [RRMS], 18 secondary progressive [SPMS]). We investigated lesions, four consecutive 1x1 mm^2 in-plane pixel layers of NAWM around lesions, and "distant NAWM" located at least 4 mm from lesions in all directions. In 22 healthy controls we measured white matter (WM) MTR and T_1 histograms. Statistical analyses used a linear mixed model.

MTR and T_1 histograms were significantly abnormal in lesions. MTR histogram peak position was significantly lower in the first and second pixel layers around lesions than in distant NAWM. In contrast, T_1 histogram peak position was similar between all NAWM layers around lesions and distant NAWM. Furthermore, MTR histograms of distant NAWM were statistically indistinguishable from those of control WM, while T_1 histograms of distant NAWM had significantly decreased peak height for RRMS and SPMS, and significantly increased peak position for SPMS.

NAWM far from lesions thus has almost normal MTR, but significantly abnormal T_1 values. Histopathological studies show that axonal damage in NAWM, though significant, is limited, and strongly related to focal lesions (4-6). In accordance, large volumes of NAWM did not exhibit significant evidence for axonal damage in *in vivo* MR spectroscopy studies (7,8). We conclude that axonal damage and demyelination in NAWM mainly seem to arise as a secondary result of visible lesions, and therefore have the largest effect close to these lesions. NAWM further from lesions could then be mainly characterized by subtle blood brain barrier damage with leakage of fibrinogen into the parenchyma, and microplaque formation.

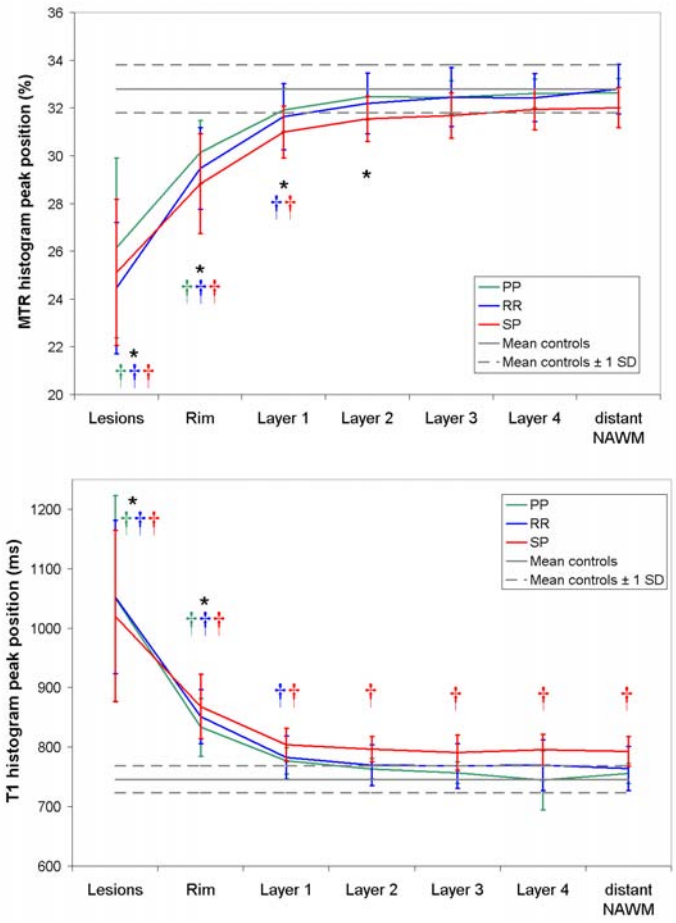

Figure: Mean (±SD) histogram peak positions of MTR (top) and T_1 (bottom) for the seven pixel classes in each of the three MS groups. The horizontal lines indicate the mean and standard deviation of the values for control WM. Statistically significant differences with "Distant NAWM", averaged over disease types, are indicated with black asterisks (*). Statistically significant differences with control WM are indicated for each of the three MS disease types by daggers (†) in the corresponding color.

References

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