White matter hyperintensities as a confounder in diffusion tensor imaging analysis of elderly cohorts

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Target audience: Researchers using diffusion tensor imaging analysis, especially in the elderly population.

Purpose: White matter hyperintensities (WMH), assumed to result from inadequate perfusion, are characterized histopathologically by enlarged perivascular spaces, demyelination, and gliosis.[1] WMH appear as hyperintensities on T2-weighted and FLAIR images and are frequently encountered in normal aging as well as in neurodegenerative disease.[2] In spite of their abundance, studies on the effect of WMH on diffusion tensor imaging (DTI) parameters are scarce but indicate that areas with WMH are associated with increased mean diffusivity (MD) and reduced fractional anisotropy (FA).[3,4] We therefore hypothesized that the presence of WMH could be a confounding factor in DTI studies and here determine the effect size of WMH on MD and FA in a large healthy elderly cohort.

Methods: DTI data (60 slices, voxel size of 2×2×2 mm^3) were acquired from 208 healthy elderly (mean age 71.2±4.5 years, 44.4% males) using a Siemens Trio 3T with 2D SE pulse sequence (TE/TR = 86/8200 ms) and diffusion weighting along 64 encoding directions with *b* values of 0 and 1000 s/mm^2. Motion and eddy current correction was performed using Elastix.[5] Parameter maps were calculated using software developed in-house in Matlab. Four regions of interest (ROI) were defined according to the four areas described by Fazekas WMH scoring system[6]: right periventricular (PV-R), left periventricular (PV-L), right deep white matter (DWM-R), and left deep white matter (DWM-L) (Fig. 1). A semi-automated method based on software developed in-house using Matlab and FSL code was employed to achieve this.[7] Because of the proximity of PV-R and PV-L to the ventricle system this method was designed to exclude voxels that could be affected by partial volume effect. Three different groups were created for each ROI based on Fazekas score (0–3 for each ROI; higher score denote more pronounced WMH; highest possible score = 12)[6]: (1) ≤ 1 in total within all ROIs i.e. nearly no WMH ('No WMH'), (2) ≥ 2 within the ROI i.e. pronounced WMH within the specific ROI ('Pronounced WMH'), and (3) ≤ 1 within the ROI and > 3 in total within the adjacent three ROIs i.e. nearly no WMH within the specific ROI but WMH in some of the adjacent ROIs ('Adjacent WMH') (Fig. 2). After matching for age and sex, 95 subjects (mean age 70.2±2.8 years, 46.3% males) fulfilled these criteria. Finally, MD and FA were calculated for each ROI and an independent *t*-test was performed to compare the 'No WMH' group to 'Pronounced WMH' and the 'No WMH' group to 'Adjacent WMH' for each ROI. Hedge's *g* was calculated to describe the effect size.

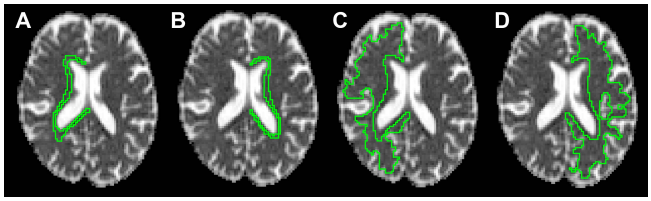

Fig. 1. Generated ROIs according Fazekas shown on MD maps: (A) right periventricular (PV-R), (B) left periventricular (PV-L), (C) right deep white matter (DWM-R), and (D) left deep white matter (DWM-L).

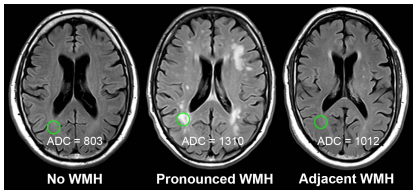

Fig. 2. FLAIR images of subjects illustrating the 'No WMH', 'Pronounced WMH', and 'Adjacent WMH' group in the area defined as DWM-R. ADC measured in selected area.

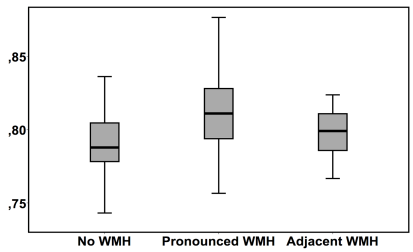

Fig. 3. Boxplot of diffusion parameter MD to visualize the effect size between the 'No WMH', 'Pronounced WMH', and 'Adjacent WMH' group in the area defined as DWM-R.

Table 1. Diffusion parameters MD and FA (mean±SD), *p*-value and Hedge's *g* when comparing the 'No WMH' group to 'Pronounced WMH' and the 'No WMH' group to 'Adjacent WMH' for each ROI (PV-R, PV-L, DWM-R, and DWM-L).

* Statistically significant vs. 'No WMH' ($p < 0.05$)

		No WMH	Pronounced WMH			Adjacent WMH		
	ROI	**Mean±SD**	**Mean±SD**	***p* (*t*-test)**	**Hedge's *g***	**Mean±SD**	***p* (*t*-test)**	**Hedge's *g***
MD	**PV-R**	0.77±0.03	0.82±0.05	< 0.001	1.16*	0.79±0.03	0.008	0.65*
	PV-L	0.77±0.03	0.82±0.04	< 0.001	1.36*	0.80±0.03	0.006	0.98*
	DWM-R	0.79±0.02	0.82±0.03	< 0.001	1.13*	0.80±0.02	0.202	0.49
	DWM-L	0.79±0.02	0.81±0.03	0.001	0.75*	0.80±0.02	0.059	0.49
FA	**PV-R**	0.44±0.03	0.42±0.03	0.008	-0.66*	0.42±0.02	0.175	-0.72
	PV-L	0.44±0.03	0.42±0.03	0.018	-0.66*	0.43±0.02	0.355	-0.40
	DWM-R	0.31±0.01	0.30±0.01	< 0.001	-0.99*	0.31±0.01	0.899	< -0.01
	DWM-L	0.31±0.01	0.30±0.02	0.004	-0.60*	0.30±0.01	0.109	-0.98

Results: Results are presented in Table 1 and Fig. 3. When comparing the 'No WMH' group to 'Pronounced WMH' MD and FA was increased and reduced, respectively, in all four ROIs (PV-R, PV-L, DWM-R, and DWM-L). When comparing the 'No WMH' group to 'Adjacent WMH' MD was increased in PV-R and PV-L, whereas FA did not differ significantly in any ROI.

Discussion: Our results indicate that WMH increase MD and reduce FA, which is consistent with previous work.[3,4] When comparing the 'No WMH' group to 'Pronounced WMH' Hedge's *g* ranged from 0.75 to 1.16 for MD and from -0.60 to -0.99 for FA. This should be compared to neurodegenerative disease such as mild cognitive impairment (Hedge's *g* ranges from 0.32 to 1.08 for MD and from -0.42 to -0.97 for FA) and Alzheimer's disease (Hedge's *g* ranges from 0.47 to 0.73 for MD and -0.05 to -1.14 for FA) with the specific effect size depending on cohort selection and MRI protocol.[8] Furthermore, the increase in MD in the 'Adjacent WMH' group compared to 'No WMH' may suggest that diffusion parameters could be affected by WMH even in areas where they are not visually present.

Conclusion: WMH may be an important confounding factor to be considered in any DTI study comparing groups with potential different WMH load. The most straightforward method to handle this issue may be to match the different groups according to WMH load.

References: 1. Scheltens *et al*., Neurol, 1995; **2.** Barber *et al*., J Neurol Neurosurg Psychiatry, 1999; **3.** Jones *et al*., Stroke, 1999; **4.** Lange *et al*., J Neurotraum, 2013; **5.** Klein *et al*., IEEE Trans Med Img, 2010; **6.** Fazekas *et al*., Am J Roentgenol, 1987; **7.** Jenkinson *et al*., Neuroimg, 2012. **8.** Sexton *et al.*, Neurobiol. Aging, 2011.