ONLINE APPENDIX: HEALTHY CONTROL WM VALUES

Healthy Control White Matter Masks

WM masks of HCs were created using SIENAX (Version 2.6)[1] and by subtracting subcortical GM and infratentorial structures from FreeSurfer (Version 5.3) segmentations. Given that anisotropy-related NODDI and DTI metrics (ie, ODI and FA) are location-dependent within the WM, we registered each subject to the age- and sex-matched HC scan and extracted median values of HCWM NDI, ODI, and DTI metrics from only those regions included in the masks of subjects with MS (NAWM, DAWM).

Creation of an ODI Atlas and Extraction of ODI Lesional Values in Healthy Controls

ODI represents the incoherence of neurite directions. In the normal human brain, WM fiber coherence is higher in the major bundles than in the subcortical regions. To address this regional variability, we created an Atlas of ODI values with reference values for each lesion. We used antsMultivariateTemplateConstruction.sh (https://github.com/ANTsX/ANTs/issues/553)[2] to register HC ODI maps in a common space; then, we concatenated the images warped to the template in the z-direction using fslmerge (https://www.rdocumentation.org/packages/fslr/versions/2.24.1/topics/fsl_merge) and got HC mean and SD maps from it using fslmaths (https://johnmuschelli.com/fslr/reference/fslmaths.html). To get rid of noise due to the registrations, after visual assessment of SD maps, we excluded voxels with ODI SD above 0.1325 across HCs from further analyses. We registered the final atlas to the T1WI space of each subject and extracted median values of ODI within GELs, GEL-FU, NGELs, and NGEL-FU masks. An additional upper ODI threshold of 0.5 was used to minimize Partial volume effect (PVE), within CSF and GM in the HCWM template. Thus, each lesion had a HCWM ODI value of reference.

REFERENCES

1. Smith SM, Zhang Y, Jenkinson M, et al. **Accurate, robust and automated longitudinal and cross-sectional brain change analysis.** *Neuroimage* 2002;17:479–89 CrossRef Medline
2. Avants BB, Tustison NJ, Song G, et al. **A reproducible evaluation of ANTs similarity metric performance in brain image registration.** *Neuroimage* 2011;54:2033–44 CrossRef Medline
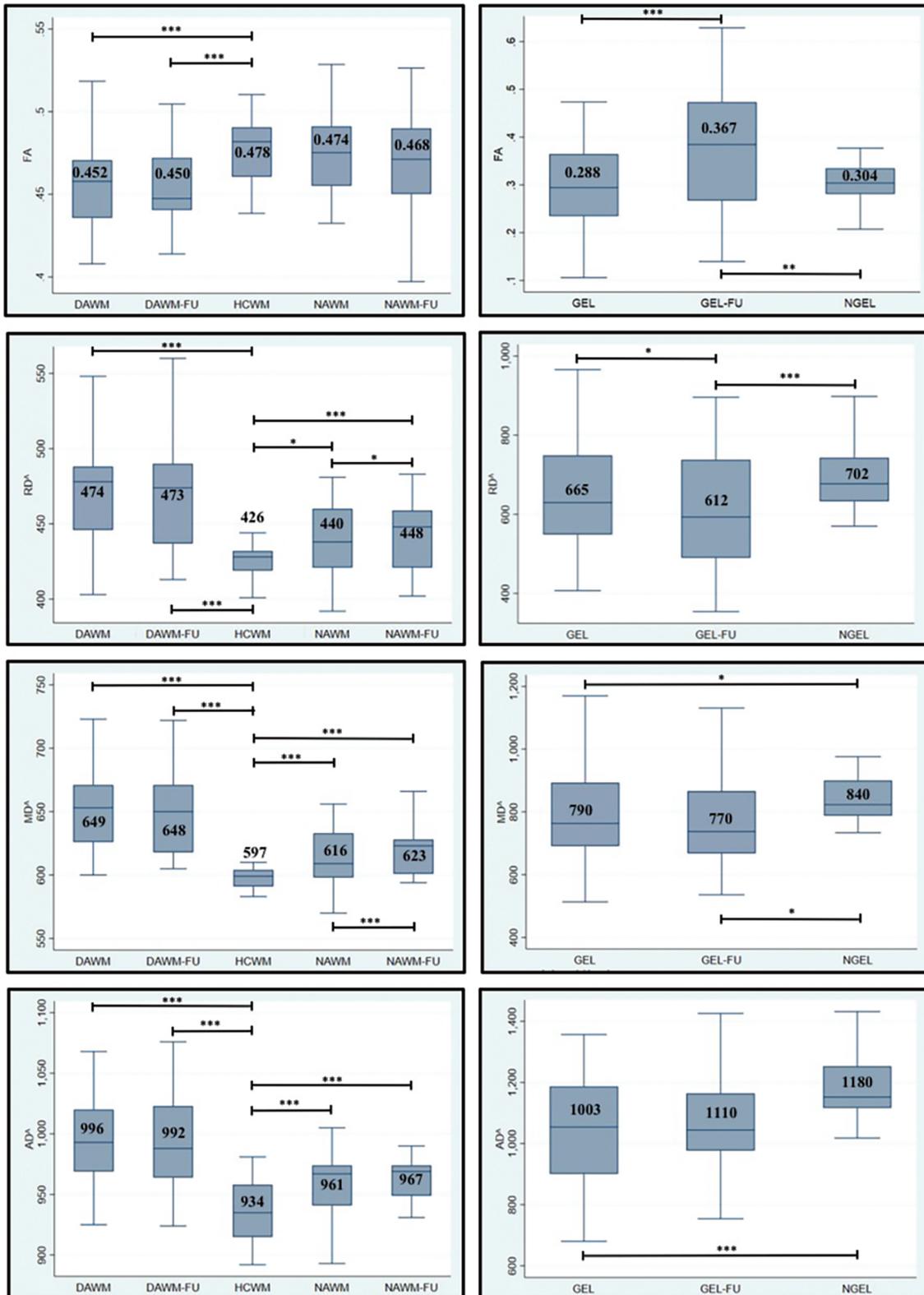
ONLINE FIGURE. Average FA, RD, MD, and AD values within HCWM, DAWM, NAWM, and GEL masks at baseline and follow-up as well as average values within the NGEL mask at baseline. Parametric *t* tests among DAWM, HCWM, NAWM, GEL, and NGEL. Pair-wise *t* tests between DAWM and DAWM-FU as well as NAWM and NAWM-FU. Statistically significant difference *P* values are reported (*asterisk = P < .05; 2 asterisks = P < .01; 3 asterisks = P < .005*). The caret indicates that MD, RD, and AD values are multiplied by 10^{-6}.

Online Table: Radiologic features of lesion subtypes[a]

Parameters	Lesion Type 1 (*n* = 30)				Lesion Type 2 (*n* = 28)			
	Baseline (Mean) (SD)	Follow-Up (Mean) (SD)	P^b	% Change with Time	Baseline (Mean) (SD)	Follow-Up (Mean) (SD)	P^b	% Change with Time
No. of voxels	217 (180)	106 (80)	.006	−50%	133 ± 85	80 ± 55	.002	−38%
NDI	0.37 (0.09)	0.48 (0.11)	<.001	+30%	0.473 (0.1)	0.39 (0.11)	<.001	−17%
nODI	1.30 (0.29)	1.07 (0.21)	<.001	−21%	1.46 (0.46)	0.97 (0.25)	<.001	−33%
MD[c]	864 (134)	729 (122)	<.001	−15%	711 (118)	814 (156)	<.001	+15%
RD[c]	741 (155)	578 (128)	<.001	−21%	582 (117)	648 (144)	.001	+11%
FA	0.256 (0.09)	0.365 (0.12)	<.001	+46%	0.323 (0.09)	0.370 (0.13)	.001	+16%
AD[c]	1119 (13)	1037 (16)	.001	−7%	980 (15)	1187 (28)	<.001	+21%

[a] Changes in size with time as well as NODDI and DTI metrics within the 2 subtypes of lesions. All differences in percentage changes among the 2 subtypes of lesions are statistically significant (2-sided *t* test; *P* = .04 for the number of voxels; *P* < .001 for the other parameters).

[b] *P* value for 2-sided paired *t* test assessing changes with time within lesions.

[c] $\times 10^{-6}$.