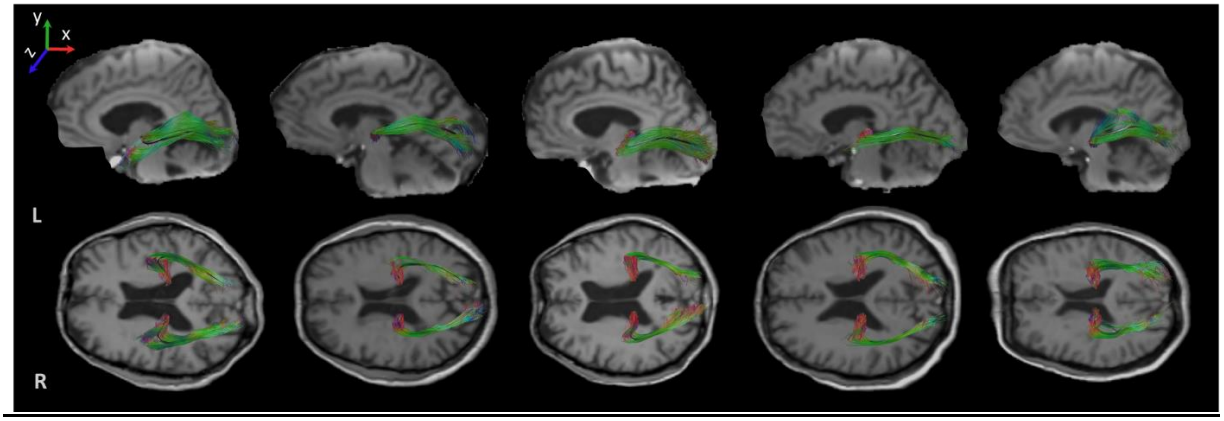
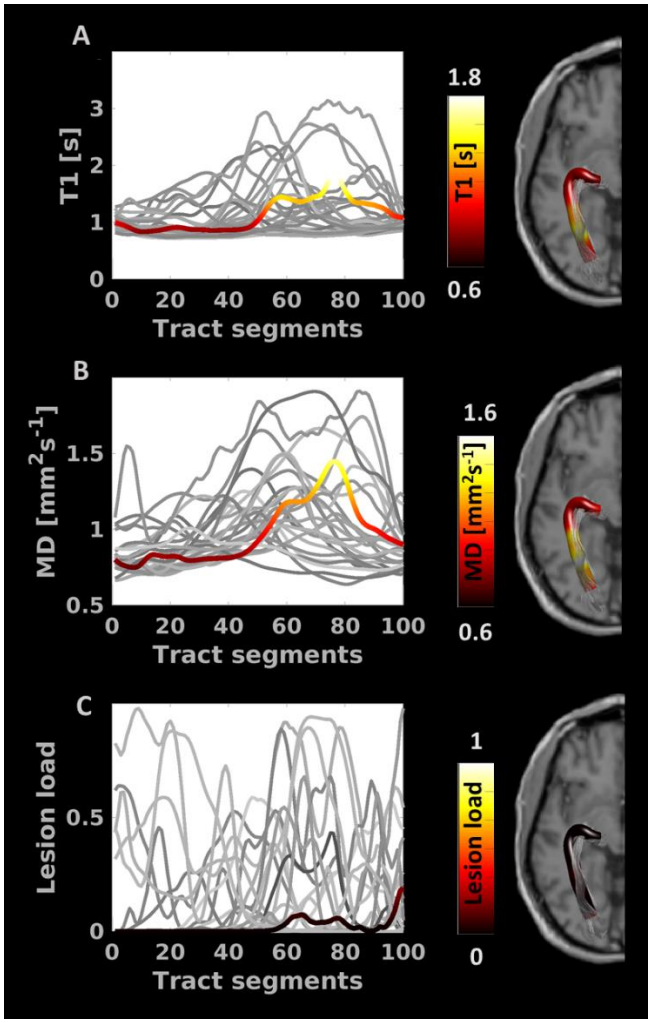
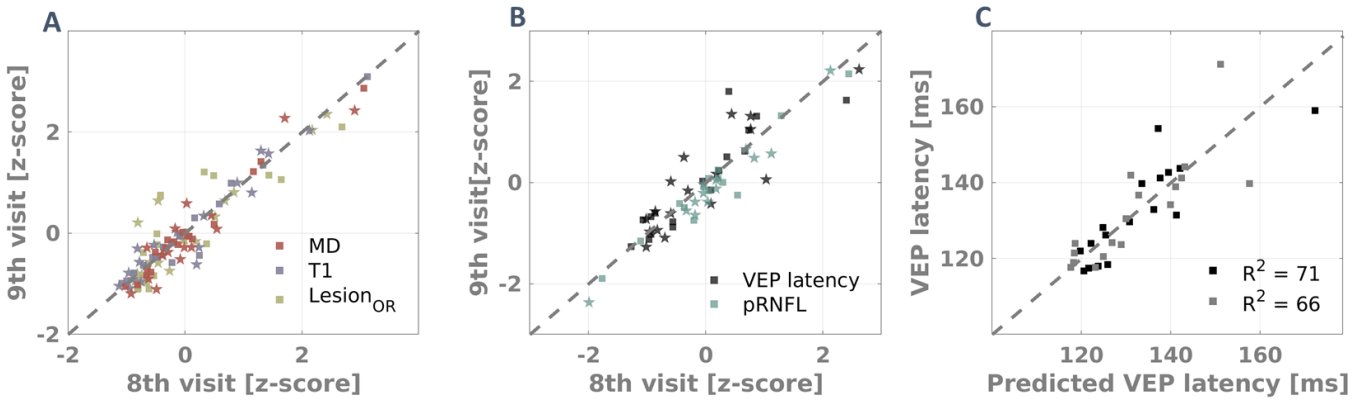
Supplementary Material



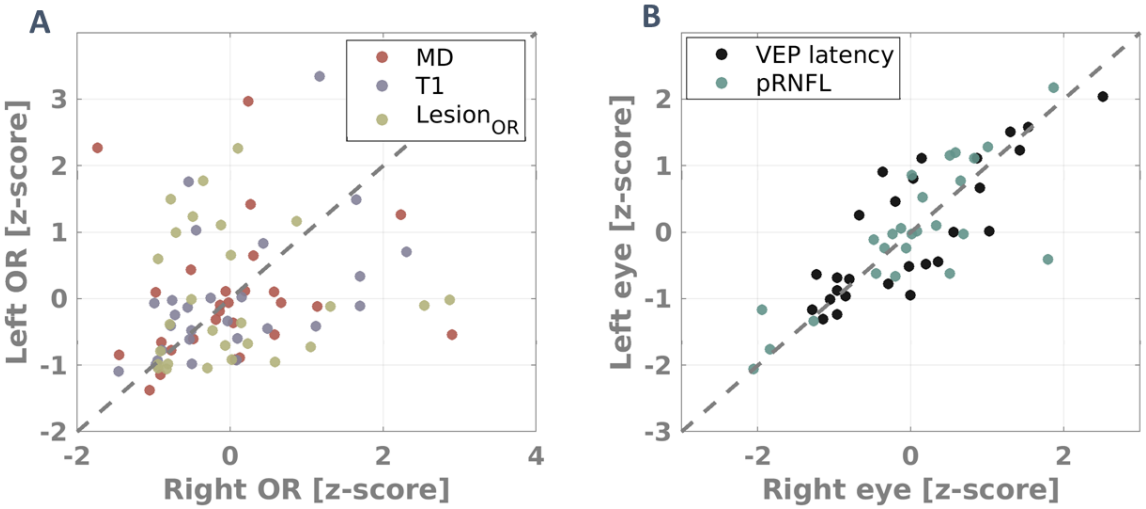
Supp. Figure 1: OR tract profiles. For 5 randomly chosen subjects, we display the left OR tract in a sagittal view (top), and the bilateral OR from an upward facing axial view (bottom). The figure plots 1000 of the streamlines for each tract, colored according to the preferred orientation in each voxel, on top of a T1-weighted axial slice. Additionally, the tract core is plotted as a black tube, though it is concealed from view in some cases.



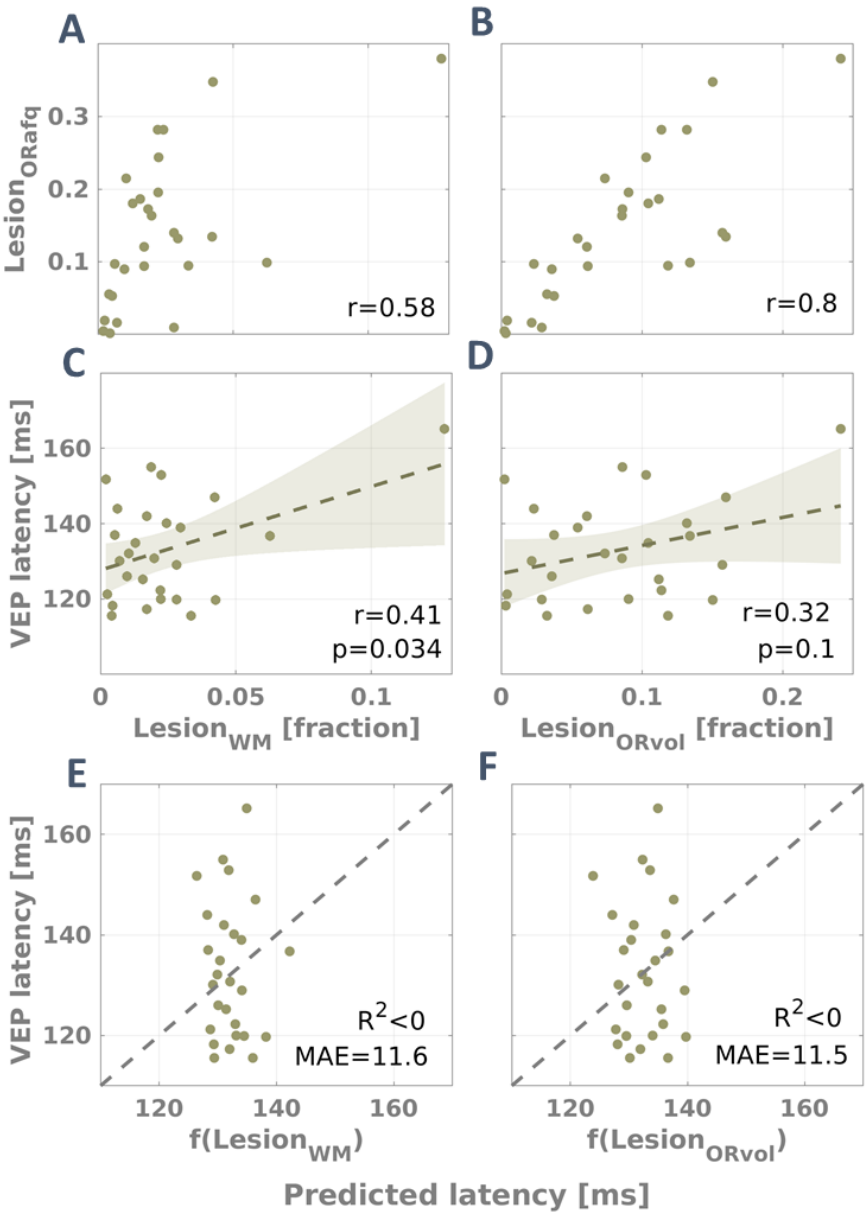
Supp. Figure 2: OR tract profiles. The tract profiles of T1 (A) MD (B) and lesion load (C) values along the left OR for all non-ON subjects. For one randomly chosen subject, the tract profile is plotted in color according to the tract profile. For this subject, the tract profile is shown along the tract core, overlaid on a T1w image (right column).



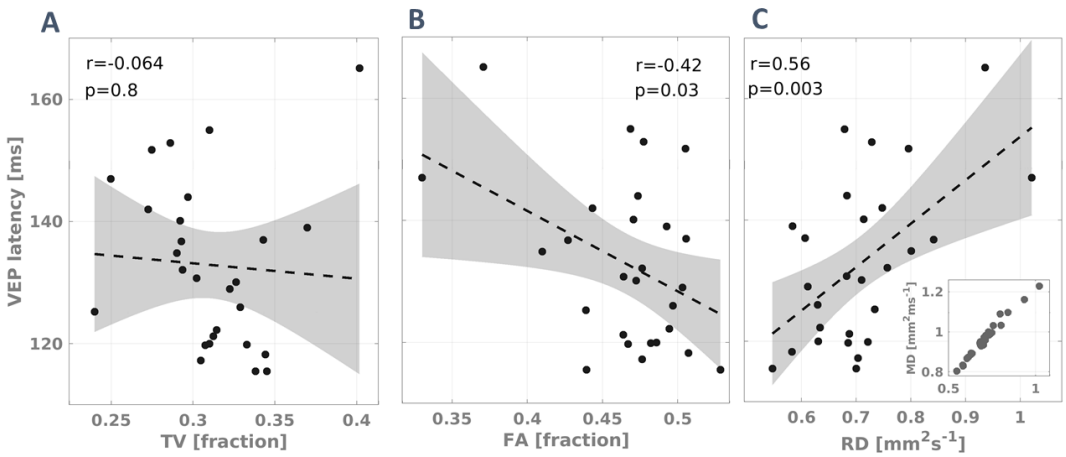
Supp. Figure 3: measures' stability with time. The data used in this study was acquired at two consecutive visits, held 3 months apart. A. MD (red), T1 (blue) and the lesion mask (yellow) were sampled along the right (star) and left (square) ORs, and show a large congruence between the two visits. B. The VEP latency (black) and pRNFL thickness (blue), measured in the left and right eyes, also show an agreement between the two visits. The data was z-scored to easily plot all measures on the same axes. C. We used leave-one-out cross-validation to estimate the explained variance of repeated measures: predicting VEP latency of the 8th visit from the 9th visit (black) and vice versa (gray). The variance explained is around 66% and 71% for the left and right eyes, respectively.



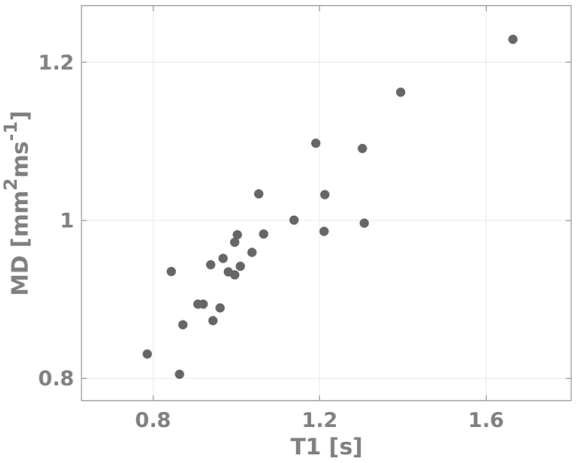
Supp. Figure 4: right and left correspondence. After averaging the datasets of the two visits, we compare the data coming from the two hemispheres (A), and eyes (B). The measures along the OR are not as bilaterally symmetric as the pRNFL and VEP latency, but no clear bias is evident.



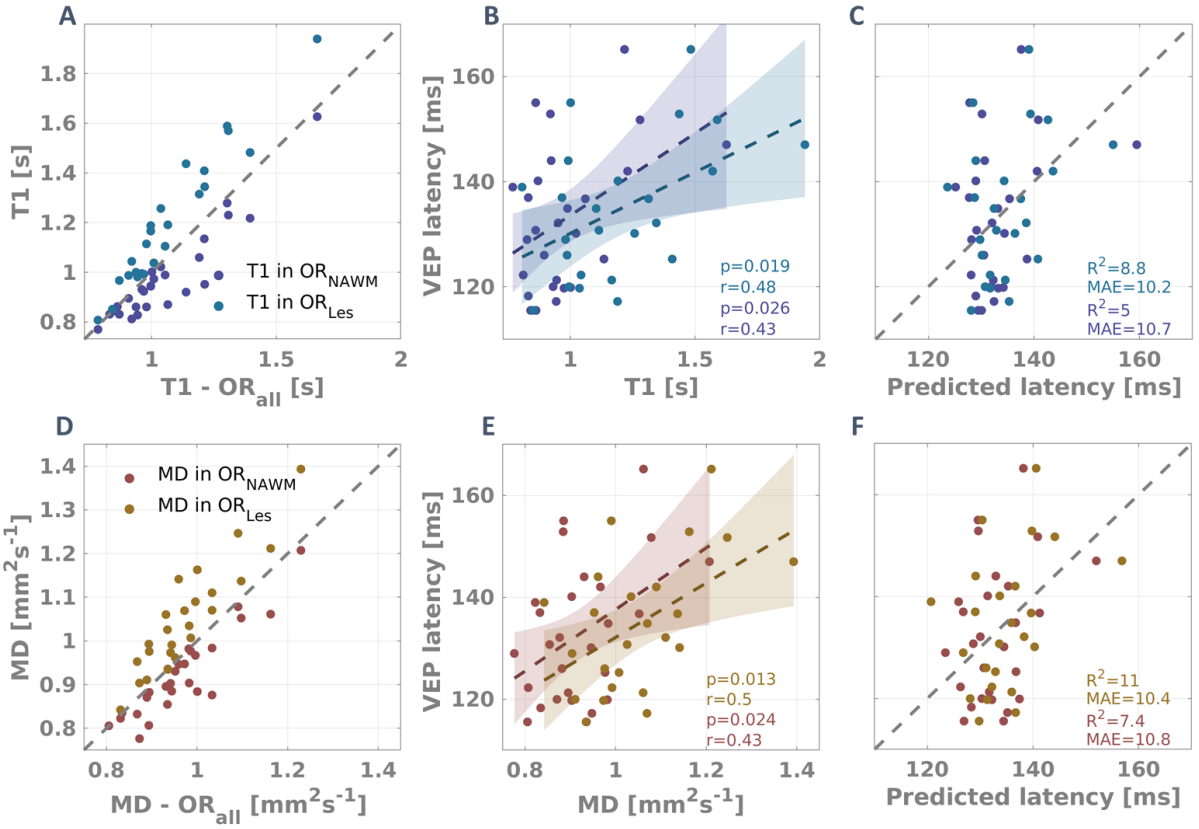
Supp. Figure 5: Lesion load estimates. The lesion load was estimated as its volume fraction in the white matter ($Lesion_{WM}$) and in the OR ($Lesion_{ORvol}$), and by sampling the lesion mask along the OR ($Lesion_{ORafq}$). $Lesion_{WM}$ (A) and $Lesion_{ORvol}$ (B) are both correlated with $Lesion_{ORafq}$. Furthermore, both measures show a small correlation with the VEP latency (C-D). Neither method is useful in predicting VEP latency on its own (E-F).



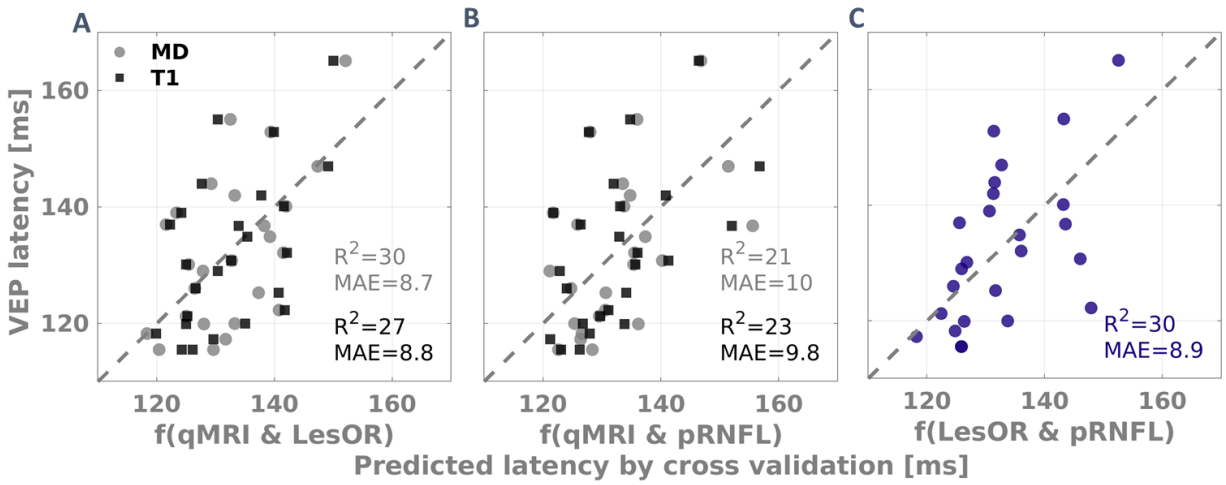
Supp. Figure 6: MTV, FA and RD estimates. The lipid and macromolecular tissue volume (TV) (A), and the FA (B) values along the OR are not significantly correlated with the VEP latency. C. the RD values along the OR, which are highly correlated with MD (inset, r =0.99), are positively correlated with the VEP latency. Cross validation analysis (not shown) shows RD explains slightly less of the variance (19%) in VEP latency, compared with MD (23%).



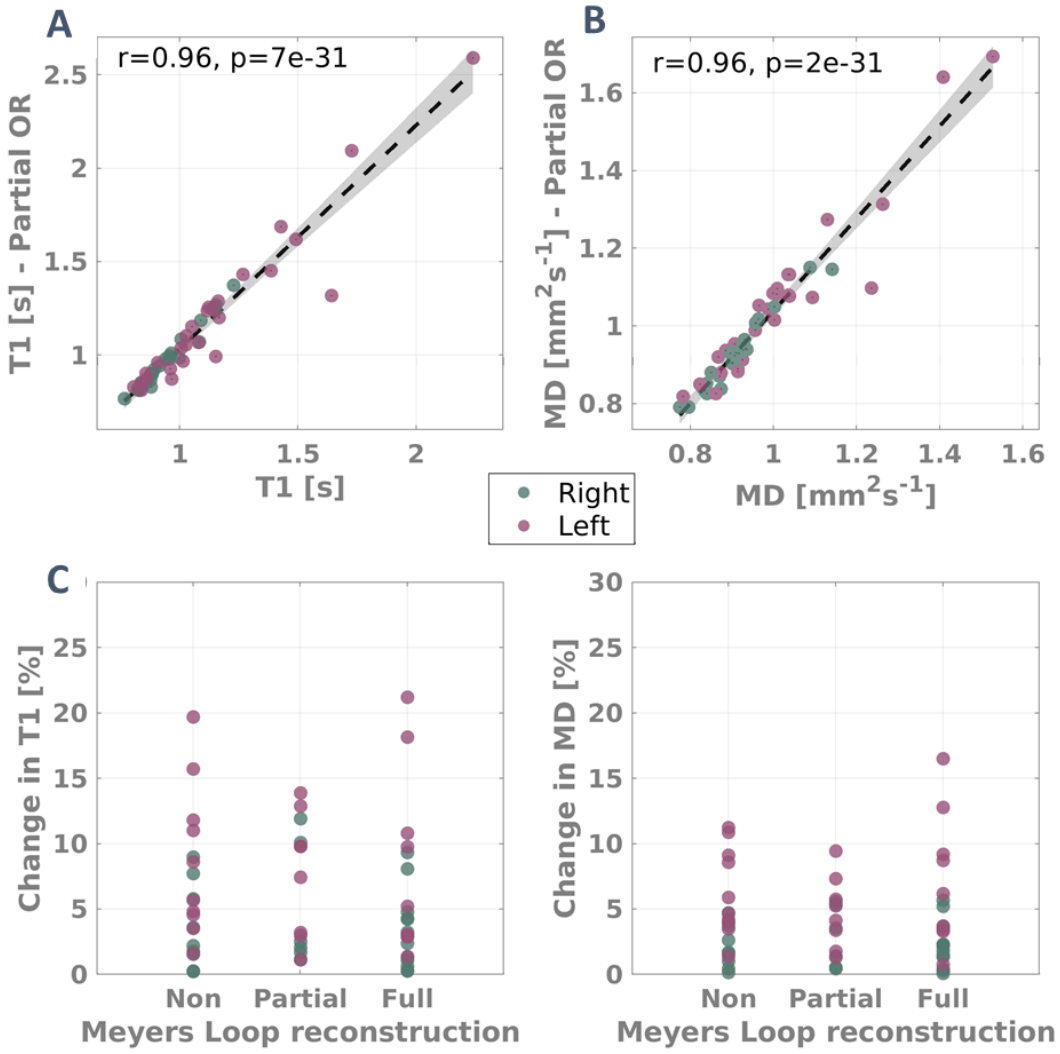
Supp. Figure 7: MD and T1 along the OR are positively correlated.



Supp. Figure 8: MD and T1 estimates. The qMRI maps along the OR were averaged in 3 ways. The average over the entire OR tract (OR_{all}), is used in the main analysis. It is compared for T1 (A) and MD (D) with the 2 other calculations: over areas in the OR that were classified as NAWM (OR_{NAWM}), or over regions that were classified as lesions (OR_{Les}). The two calculation are similarly correlated with the VEP latency, both for T1 (B) and for MD (E). Cross-validation analysis shows that both for T1 (C) and MD (F), taking the lesions into consideration leads to a better prediction of the VEP latency. Both methods are not as effective as calculating the mean over the entire tract (Figure 4).

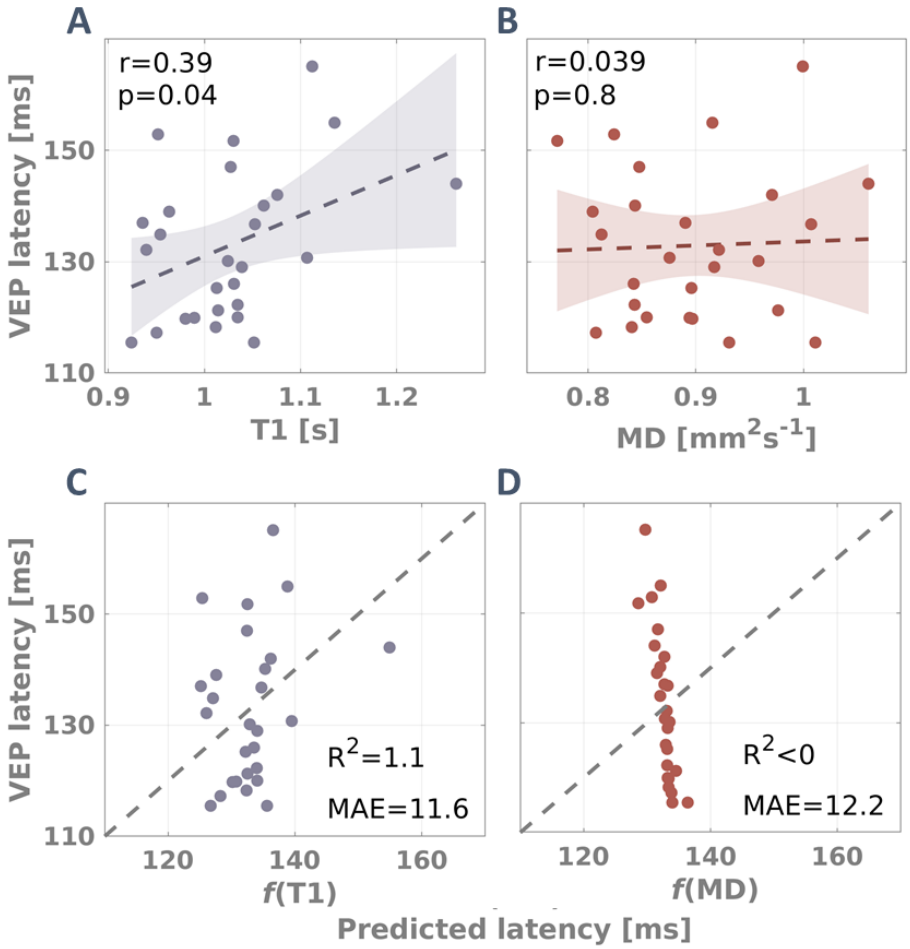


Supplementary Figure 9: combining parameter pairs to predict VEP latency. Cross-validation was used to test prediction with pairs of predictors. A. Using both the lesion load along the OR (LesOR) with either MD (gray circles, R^2=30, MAE=8.7) or T1 (black squares, R^2=27, MAE=8.8). B. Using the pRNFL thickness with either MD (R^2=21, MAE=10) or T1 (R^2=23, MAE=9.8) is not as informative as using the qMRi parameters on their own (Fig. 4). C. using LesOR with pRNFL thickness is comparable to using LesOR with either MD or T1.

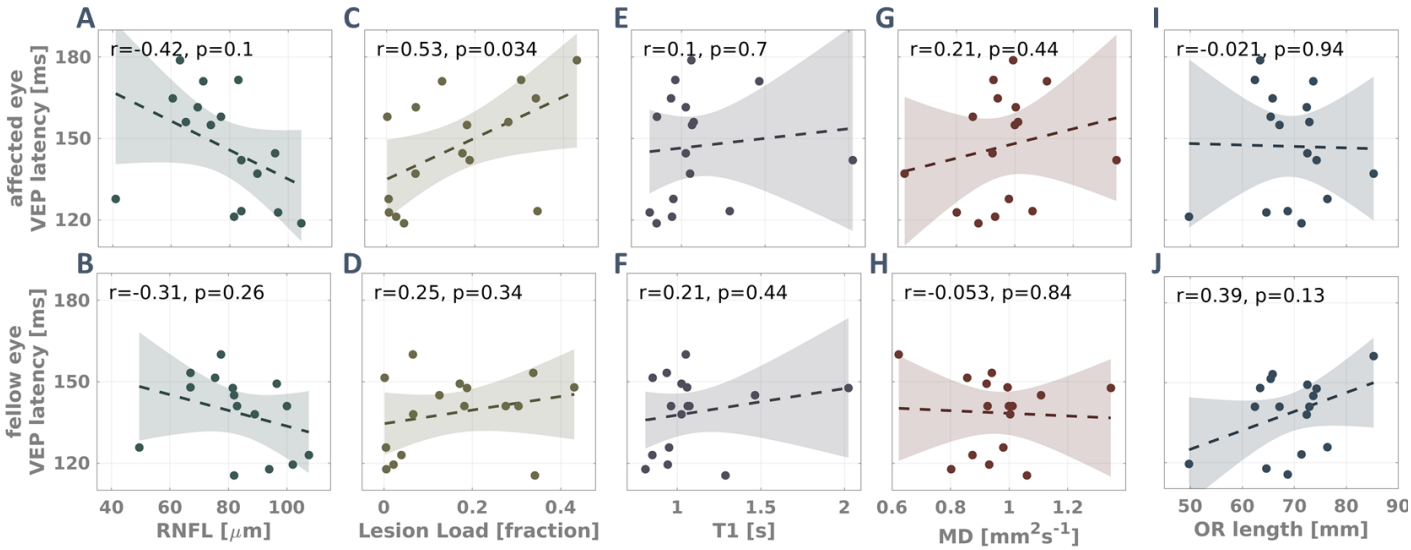


Supp. Figure 10: the effect of Meyer's loop on OR microstructure estimates. Estimates of T1 (A) and MD (B) are similar when averaged across the entire OR tract (excluding the edges, i.e. nodes 11:90) compared with the average across the tract portion excluding the Meyer's loop (i.e. nodes 35:90). The differences between the two estimates are shown for each OR, separated according to the quality of Meyer's loop reconstruction. Both for T1 (C) and MD (D) the results suggest that the difference in calculation does not depend on the Meyer's loop reconstruction.

.



Supp. Figure 11: MD and T1 along the optic tract (OT). The optic tracts were delineated using the probabilistic fiber-tracking algorithm, ConTrack, to identify the most likely pathway between two ROIs (Sherbondy et al., 2008). The optic chiasm and LGN were defined on T1 maps. A collection of 10,000 possible pathways was sampled and the most likely optic tracts were estimated as those pathways scoring at the top 10% (1,000). Since the optic tract is a direct continuation of the optic nerve, it should be highly informative on the VEP latency. However, no clear results were seen in this cohort using our methods to analyze it. The figure shows T1 and MD values along the optic tract in subjects with no history of ON. (A) T1 is positively correlated with the VEP latency, but (C) explains only 1% of the inter-subject variance. (B) the MD along the OT is not correlated with the VEP latency and (D) cannot be used to predict the variance in VEP latency.



Supplementary Figure 12: VEP correlations in ON-MS patients. The relationships between the VEP latency and the structural parameters are plotted separately for the subjects' affected eyes (top row) and the unaffected, fellow eyes (bottom row). The pRNFL thickness (A-B) is measured separately for the two eyes. The OR-dependent parameters - Lesion load (C-D), T1 (E-F), MD (G-H) and OR length (I-J) - are averaged across hemispheres and the same values are used in the relationship with the VEP latency. The only moderate correlation we found is between the lesion load and the VEP latency of the affected eyes.