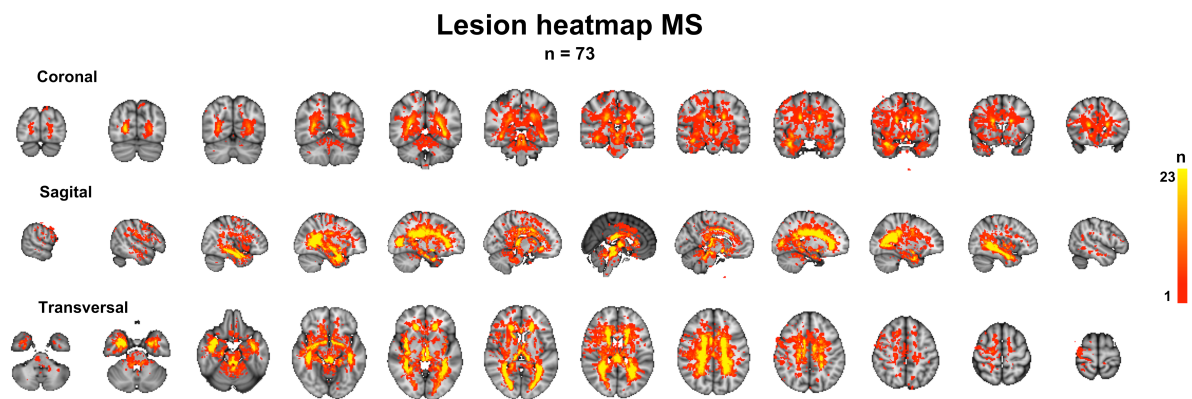


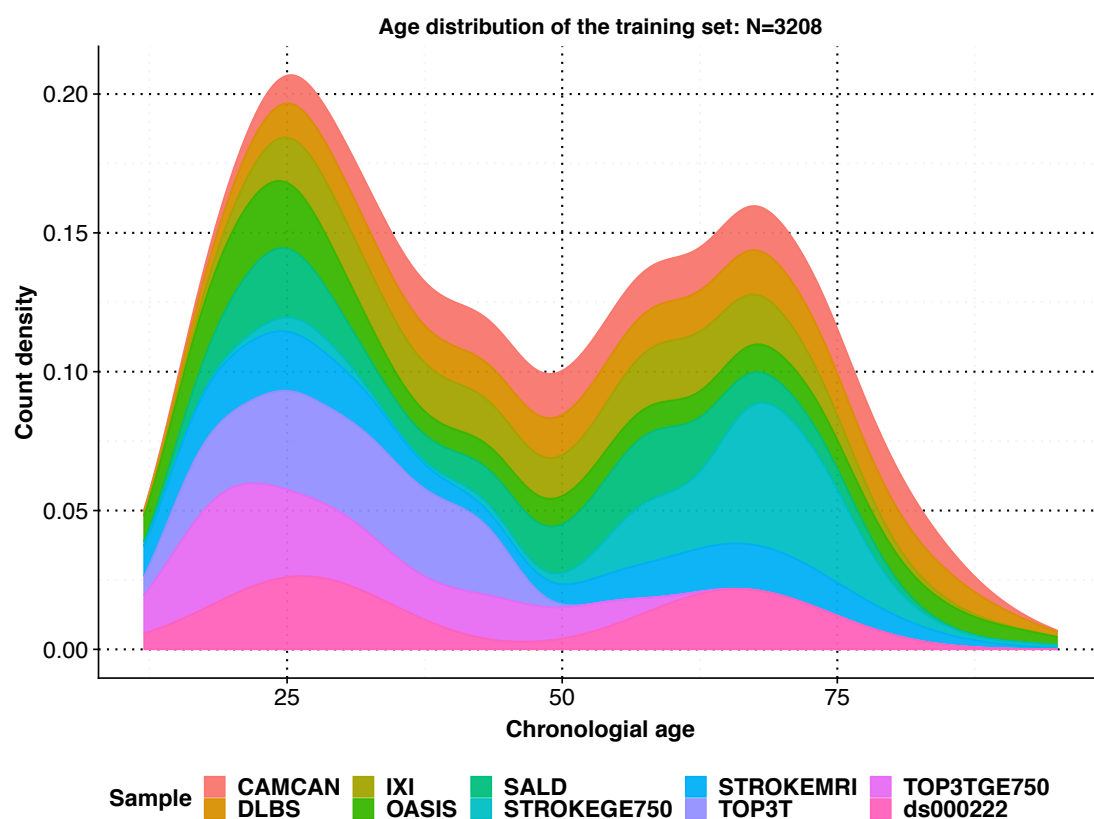
## SUPPLEMENTARY MATERIAL

Manual editing of the automatically acquired FreeSurfer segmentation was performed after standard quality control of all the MRI brain scans (Kaufmann *et al.*, 2018). We utilized the same MRI processing pipeline as described in detail in the preprint by Kaufmann *et al.* (Kaufmann *et al.*, 2018).



### **Supplementary figure 1. Heat map showing the distribution of MS lesions in the brain.**

Utilizing automatically generated lesion masks from Cascade (Damangir *et al.*, 2012), we plotted all normalized MS lesions from time point 1 on the standardized MNI-152–template to visualize the distribution of the MS lesions in the brain. Depicted are slices in the coronal, sagittal and transversal plane evenly distributed. Increasing yellow colour represents higher lesion count, as depicted in the colour bar.

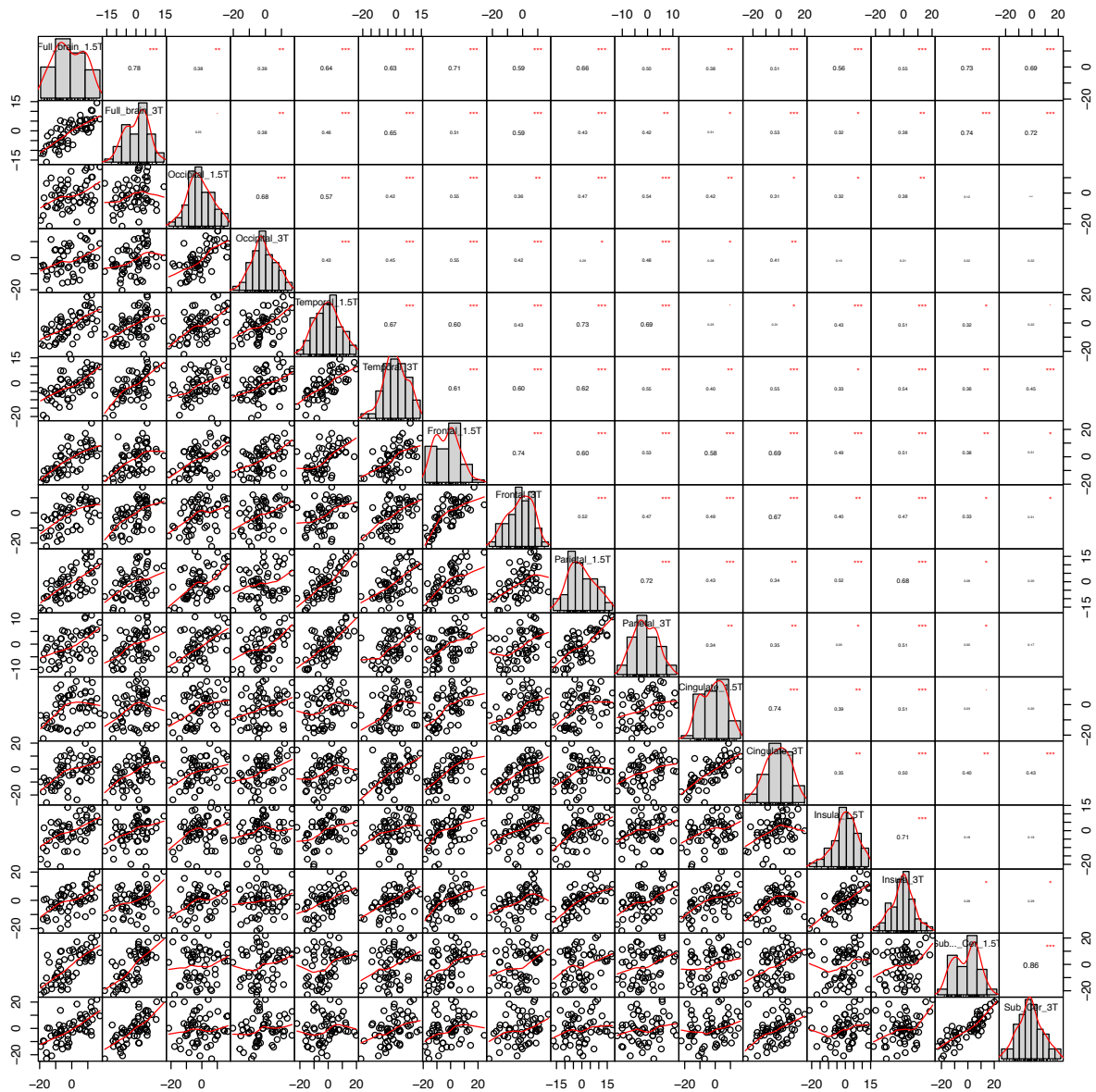


**Supplementary figure 2. Overview age distribution of the training set.** Histogram showing the age distribution of the training set, including the age distributions of the different cohorts using different colours. Information concerning the different sample cohorts (CAMCAN, DLBS, IXI, OASIS, SALD, STROKEGE750, STROKEMRI, TOP3T, TOP3TGE750 and ds000222) contributing to the training set are available in the article by Kaufman et al (Kaufmann *et al.*, 2018).

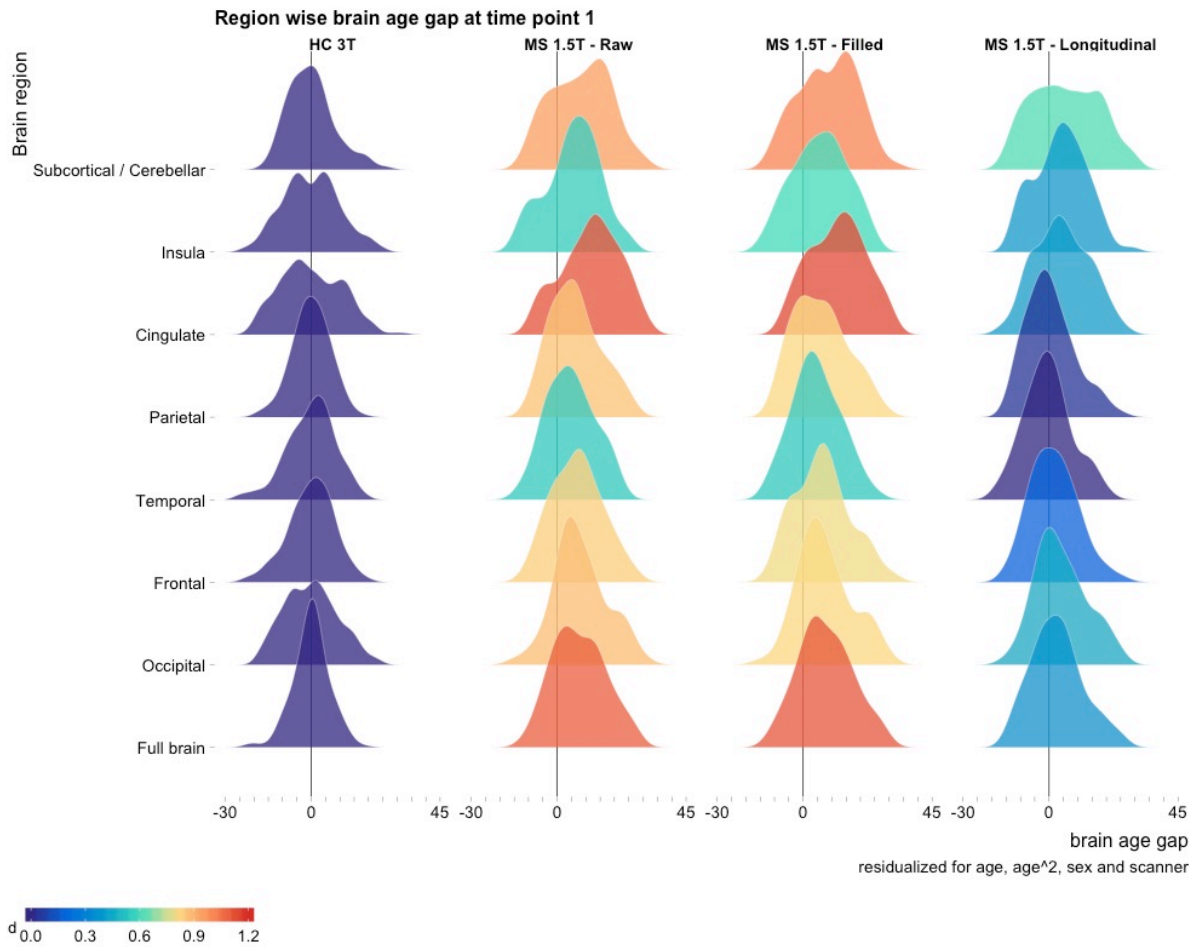


**Supplementary figure 3. Result of the brain age estimates from the training set.**

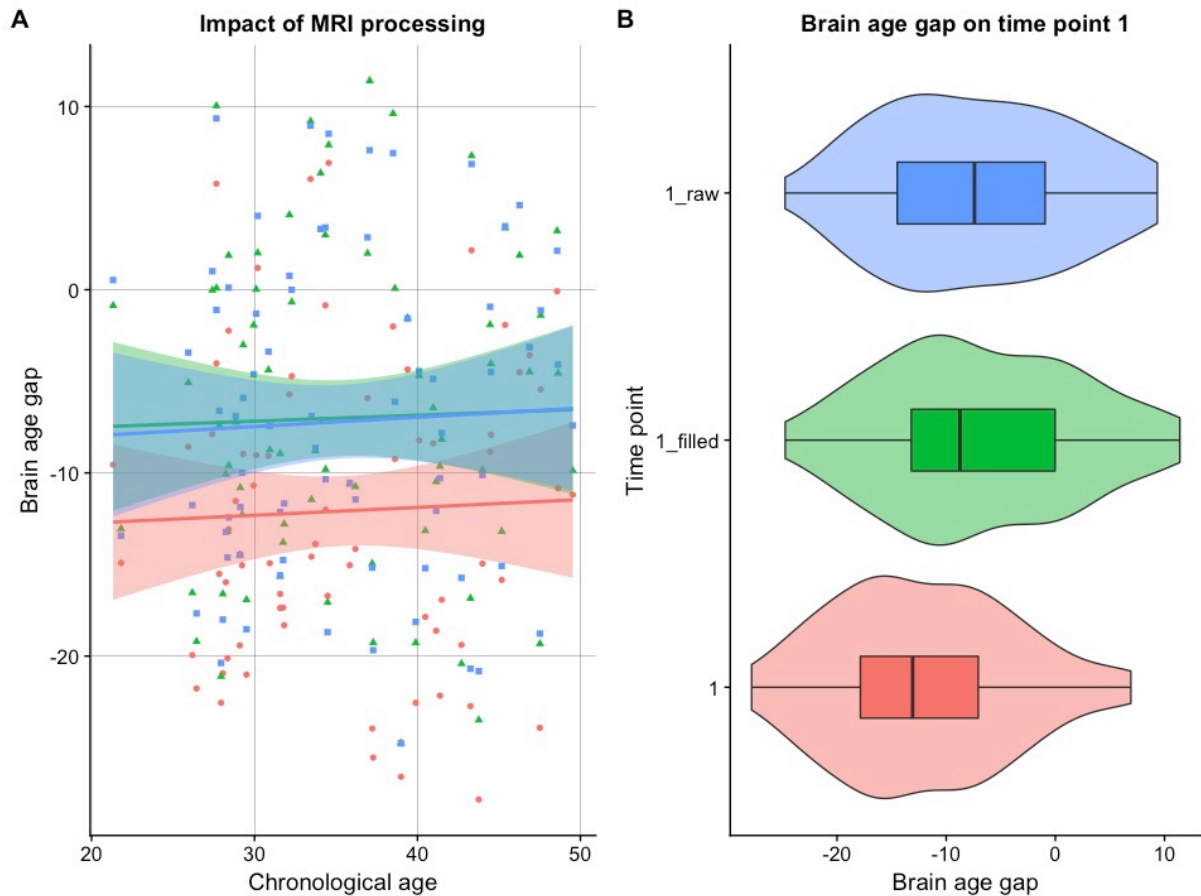
Correlations between brain age estimations and age after performing a 10-fold cross validation in the training set ( $r = 0.91$ ). We found a shift in the estimations  $<50$  and  $>50$  years of age, with increasing overestimation of age  $<50$  years and increasing underestimation of age  $>50$  years, which is a known effect when utilizing a machine learning model to estimate brain age (Cole and Franke, 2017; Kaufmann *et al.*, 2018).



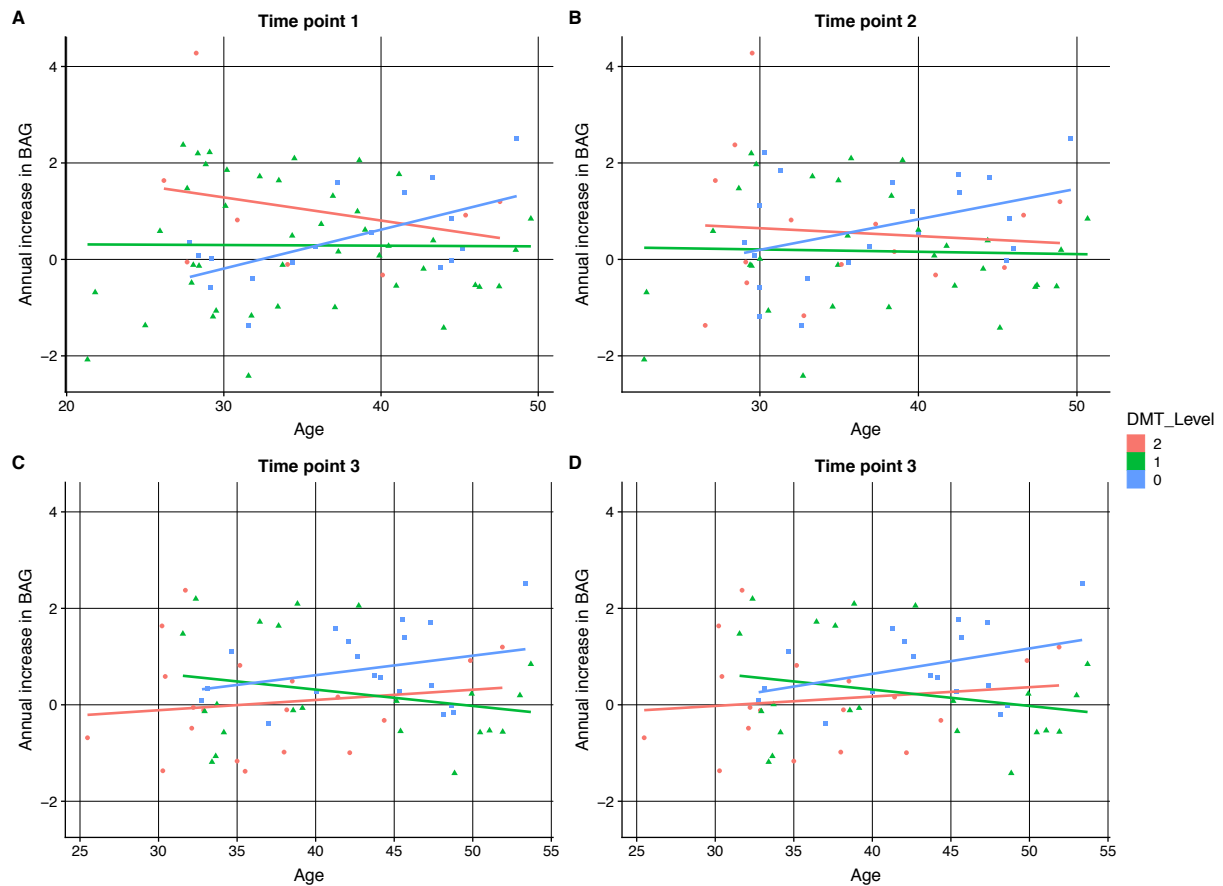
**Supplementary figure 4. Correlation matrix between the two MRI scanners.** A chart of the correlation matrix for the comparison of the BAG estimates for global and all brain regions from the 1.5 T and 3 T MRI scanner ( $n = 58$ ). The distribution of each variable is shown on the diagonal. On the bottom of the diagonal we see the bivariate scatter plots displayed with a fitted line. On the top of the diagonal we show the value of the correlation plus the significance level as stars and symbols (p-values; “\*\*\*” = 0-0.001, “\*\*” = 0.001-0.01, “\*” = 0.01-0.05, “.” = 0.05-0.1, “ ” = 0.1-1). The chart is made using the “PerformanceAnalytics” package in R.



**Supplementary figure 5. Overview of all brain age estimations from time point 1.** The distribution of brain age gaps across brain regions based on MRI data from time point 1 (raw, lesion filling and longitudinal stream). Resulting brain age gaps from the three different processing steps are compared with the HC sample after we controlled for age, age<sup>2</sup>, sex and scanner. Shown are the resulting brain age estimations from the raw images, raw images including lesion filling and images after being processed through the FreeSurfer longitudinal stream. All three processing steps were highly correlated when compared group wise using the resulting predicted brain age ( $r > 0.95$ ). Cohen's D effect sizes for the brain age gap between MS and HC are depicted using the colour bar.



**Supplementary figure 6. The effects on brain age gap before correcting for scanner effects by different processing steps of the MRI data from time point 1. A,** The associations between chronological age and brain age gap are plotted. Depicted in red are the resulting brain age estimations from the FreeSurfer longitudinal stream, in green the brain age estimations from the MRI scans after lesion filling and in blue are the brain age estimations from the raw images. **B,** Plots visualizing the same as in **A**, using box plots to show the distribution of the brain age estimates. Brain age gap for each of the groups are -2.4, 2.6 and 2.4 for the red, green and blue groups respectively. All three processing steps were highly correlated group wise using the resulting predicted brain age ( $r > 0.95$ ). Brain age gaps were residualized for age, age<sup>2</sup> and sex to minimize confounding effects of the variables.



**Supplementary figure 7. Associations between annualized brain aging rate and chronological age in the MS sample.** Subjects are marked as coloured symbols, depending on their DMT level, and grouped together to visualize possibly the trajectories for each group independently. All data are derived from global BAG estimates, residualized for age, age<sup>2</sup> and sex. Analyses showed no significant associations between DMT treatment and rate of brain aging. **A**, DMT level at time point 1. **B**, DMT level at time point 2. **C**, DMT level at time point 3. **D**, DMT level at time point 3, also taking into account retrospective DMT switches, defined into three groups.