# Voxel-based multiple regression of multimodal MRI: applications to physiological aging

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## Introduction

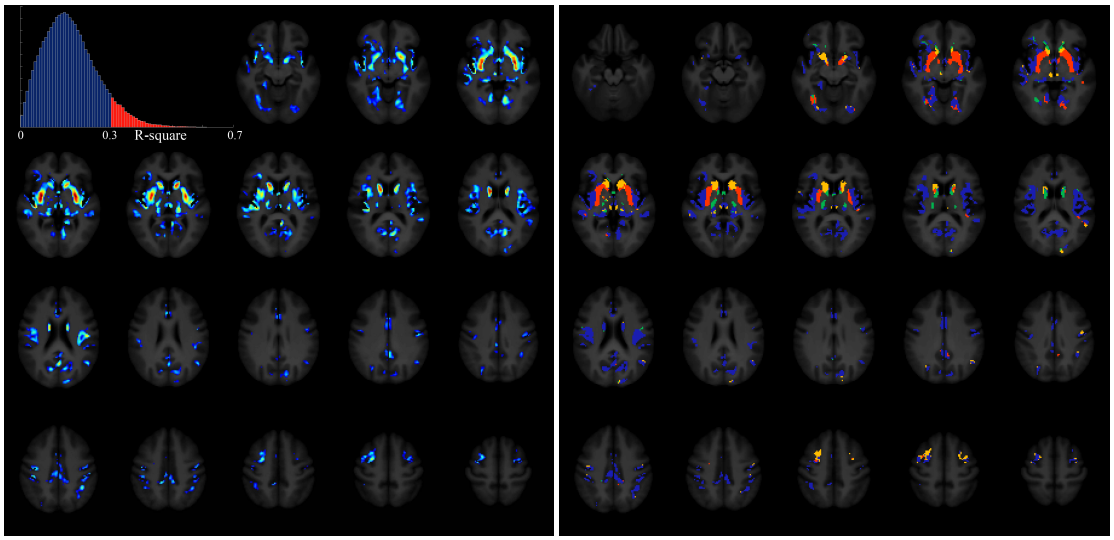
Different MRI methods have been applied with success to the investigation of structural changes induced by natural aging (Galluzzi 2008). However, when using a single methodology it might be difficult to disentangle the relative proportion of different types of alterations in different anatomical locations. In the present study, we measured simultaneously voxel-based morphometry (VBM), DTI scalars, and T2* relaxation rates in a large cohort of healthy subjects. These parameters were compared with a voxel-by-voxel methodology, transforming different image modalities to the same template. We used multiple linear regression analysis to evaluate the relevance, the relative contribution, and the rate of change of these parameters with age.

## Methods

A total of 140 healthy subjects (73 women, 67 men; age range 20-74 years; mean age ± standard deviation 44±16 years) were included in this study. The volunteers were examined using a 3 Tesla Siemens Allegra MR Imager. Participants underwent the same MR imaging protocol including whole-brain T2*-weighted, T1-weighted, DTI, T2-weighted and FLAIR scanning. Technical details of acquired sequences and image processing are described in prior publications (Cherubini 2009a,b). Briefly, an optimized VBM processing was applied to T1-weighted volumes. The nonlinear transformation calculated from the T1-weighted volume to standard space was combined with the affine transformation calculated for other image modalities to T1 space, thereby aligning all individual data to the standard space. As a result of the processing, for each voxel on each subject four quantitative parameters were available: T2*, MD, FA, and the value derived from VBM processing. Subsequently, we evaluated for each voxel the following linear model: age = beta × [predictors] + constants. Finally, we used a stepwise method to identify for each voxel the best predictor of age-related variation.

## Results

Figure 1 (left) shows the spatial distribution of voxels where the variance explained by the multiple regression linear model of aging was largest. We observed that 7.9% of brain voxels showed values above a threshold of R-square>0.3. Voxel belonging to this mask were identified as grey matter (65.1%) and white matter (34.9%). Structures most affected by age-related changes were the bilateral putamen, the bilateral caudate, the temporal-insular regions, and portions of the superior frontal gyrus. Subsequently, we identified for each voxel in the mask the unessential predictors. Figure 1 (right) shows the spatial distribution of the main predictors as identified by the multiple regression. MD (blu) resulted the main predictor for 62.4% of the voxels, followed by VBM (18.3%, yellow), T2* (14.2%, red), and FA (5.1%, green). Areas where MD was identified as the main contributor to the model were spread across the brain, mainly in the grey matter (70.8%). Clusters could be identified in the thalamus, and in the insular, temporal and frontal cortices. T2* resulted the best predictor mainly in the pallidum and putamen, with the rest of smaller clusters belonging to white matter (39.7%). VBM could be identified as the best predictor of linear aging in the caudate, with very large R-square values. Other smaller clusters were present in the thalamus, in the middle and superior frontal gyri, and in the cerebellum. Finally, voxels where FA resulted the main predictor were almost completely (93.7%) identified as white matter. The main clusters comprised the anterior and posterior limbs of internal capsule, the genu of the corpus callosum, and the fornix.




## Discussion

We explored for the first time with a voxel-based approach the simultaneous variation induced by physiological aging on four quantitative MR parameters sensitive to complementary tissue characteristics (VBM, T2* relaxometry, diffusion tensor imaging). This allowed us to compare the performance of different predictors and to identify without a priori information the best biomarker of age-induced structural variation for each voxel. Our results showed that brain areas most affected by age are evenly distributed between white matter and grey matter. Moreover, the best quantitative predictors in most brain areas resulted to be iron deposition and microstructural damage rather than macroscopic atrophy of tissues. These findings highlights the importance of quantitative evaluation of multimodal biomarkers for the study of normal aging and point to a number of novel application for the method described.

## References

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