



Introduction

Accumulation of tau neurofibrillary tangles measured by PET imaging is a well-established biomarker to detect early pathological signs of Alzheimer's disease (AD). Novel, quantitative, local surface-based measures of subcortical structures may potentially serve as a useful biomarker for tracking atrophy progression in several neurodegenerative diseases. We hypothesize that significant morphological changes in the shape of the hippocampus can predict both local and distant accumulation of aggregated tau protein in Cognitively Normal (CN) and Mild Cognitive Impairment (MCI) subjects.

Methods

- 3D T1-weighted MRI and [18F]Flortaucipir PET images (N=479) from cognitively normal (CN) and MCI subjects from the ADNI study were processed with the PIANO™ software package (Biospective Inc., Montreal, Canada)
- The hippocampus was segmented using a proprietary, fully-automated algorithm.
- Automatic extraction of the boundary surface of the segmented hippocampus was performed by using a Marching Cubes algorithm.
- A vertexwise deformation metric was defined as the projection of the individual nonlinear 3D spatial deformations onto the normal vector to the template surface.
- A Partial Least Squares (PLS) Regression model was trained between the local deformations from the hippocampus surface (predictors) and the Tau PET SUVR measurements from the hippocampus and from the entorhinal cortex (response variables).
- A leave-one-out (LOO) cross-validation technique was used to select the optimal number of PLS components based on the maximum value of the cross-validated R2 metric (Q2).
- Orthogonal PLS technique to remove components with nonsignificant predictive power.
- The resulting PLSR model was finally used to predict (also with a LOO technique) SUVR values from each individual deformation map.

Results

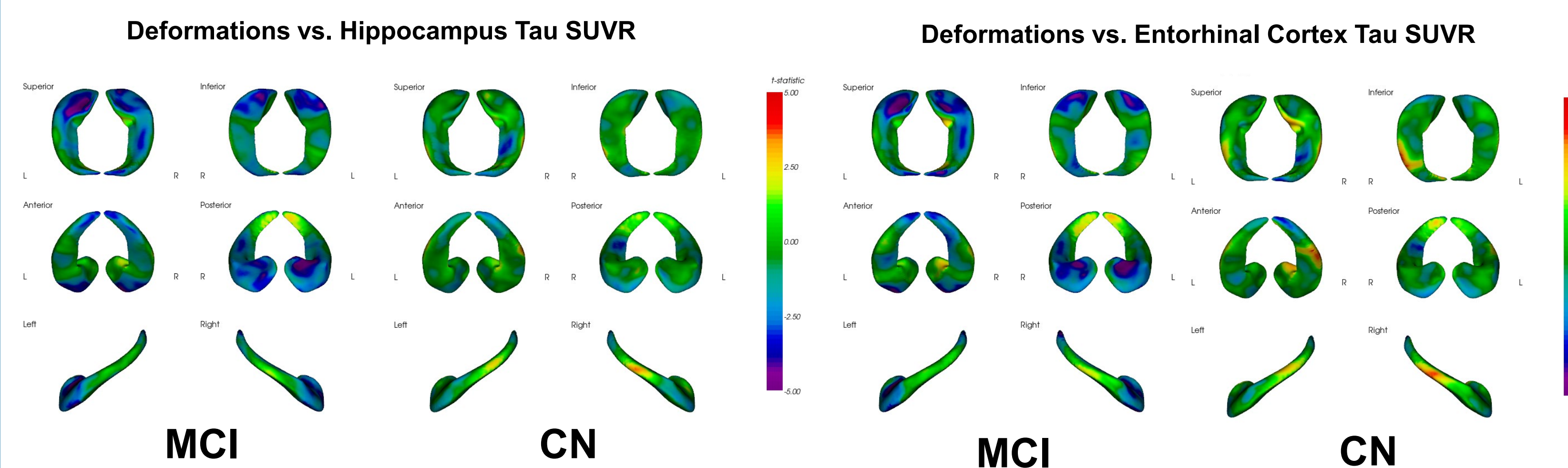


Figure 1. Local shape deformations in several regions of the hippocampus had statistically significant associations with the accumulation of tau in the hippocampus itself and in the entorhinal cortex for MCI subjects.

Association between Hippocampus Volume and Tau PET SUVR

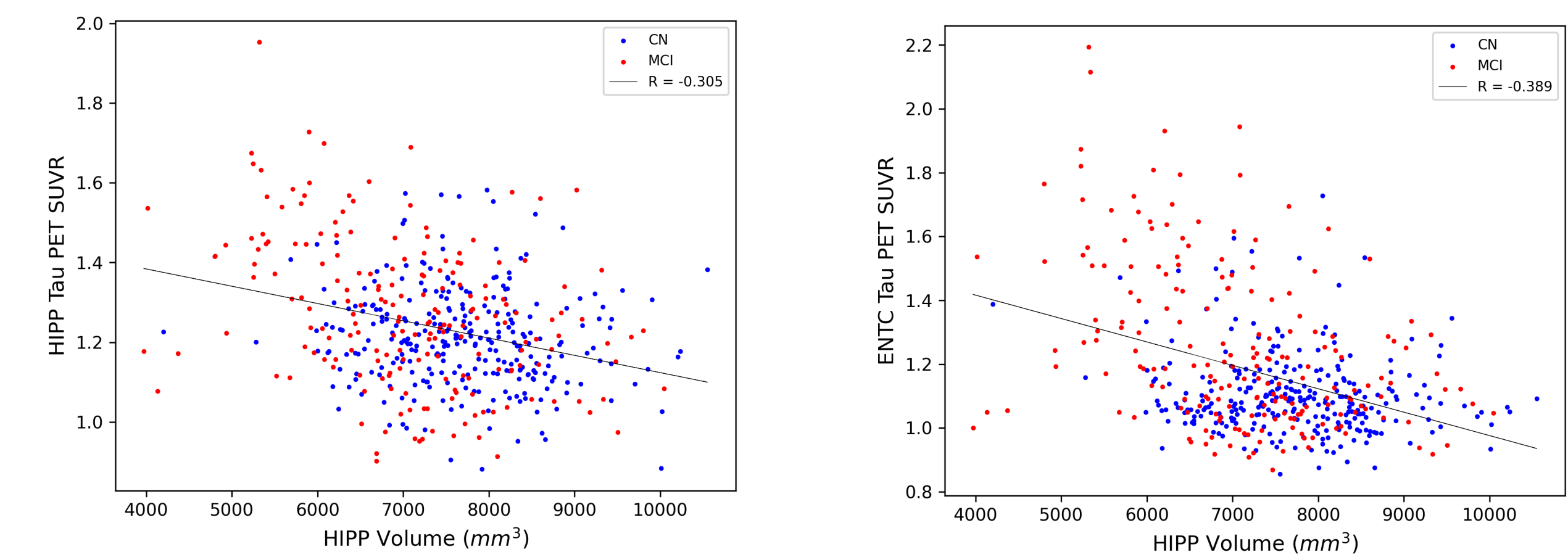


Figure 2. The hippocampus **volume** was only weakly correlated with the tau SUVR in both the hippocampus and the entorhinal cortex.

Observed vs. predicted Tau PET

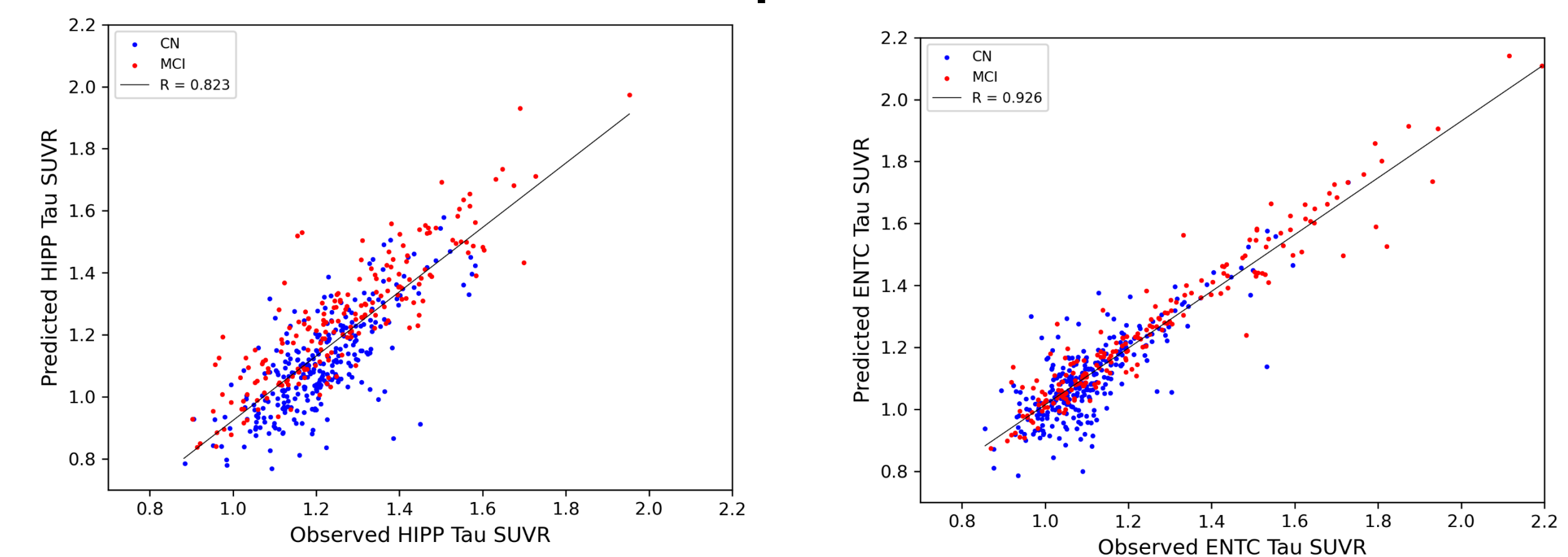


Figure 3. A LOO cross-validation analysis produced cross-validated R2 (Q2) values of 0.74 and 0.81 for the prediction of tau in the hippocampus and the entorhinal cortex, respectively.

Association between Hippocampus Deformations and fluid biomarkers in MCI

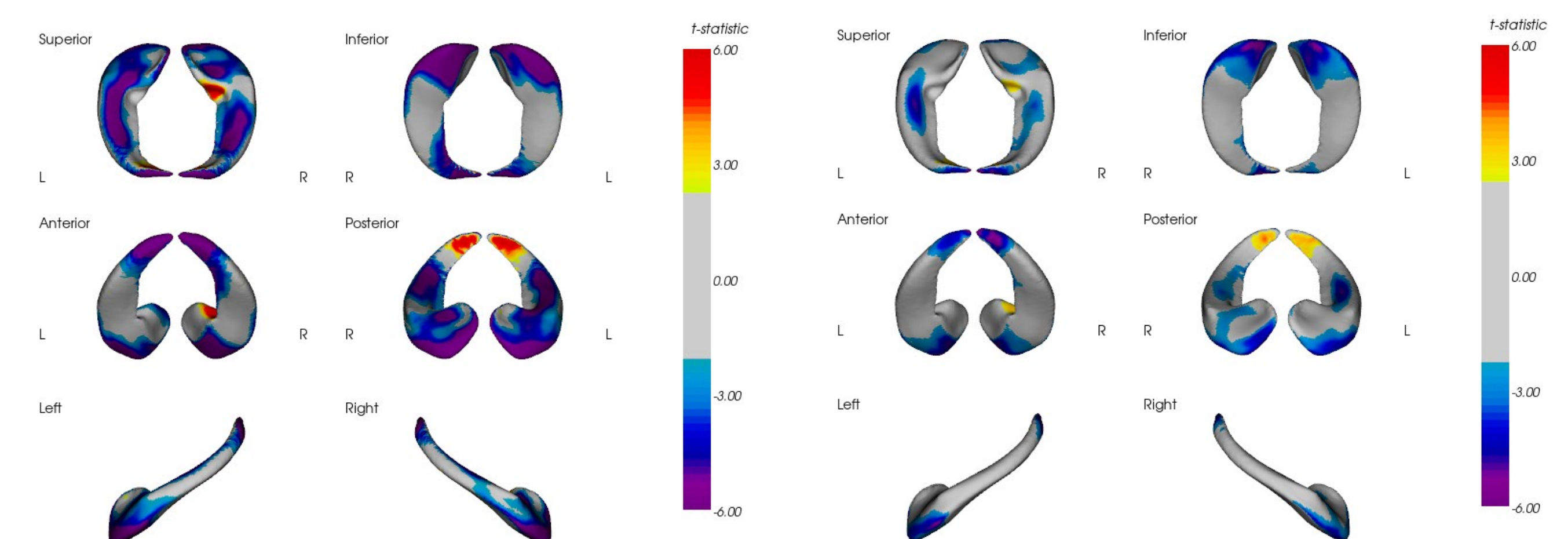


Figure 4. Statistically significant association between the hippocampus deformations and both CSF pTau181 and plasma GFAP.

Conclusions

We have determined that local deformations in the shape of the hippocampus is a sensitive MRI-based biomarker able to predict Tau PET accumulation not only in the hippocampus itself, but also in the entorhinal cortex. Our approach suggests the ability to use anatomical T1-weighted MRI data as a surrogate for Tau PET for eligibility screening for clinical trials of disease-modifying therapeutics.

Acknowledgements

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