

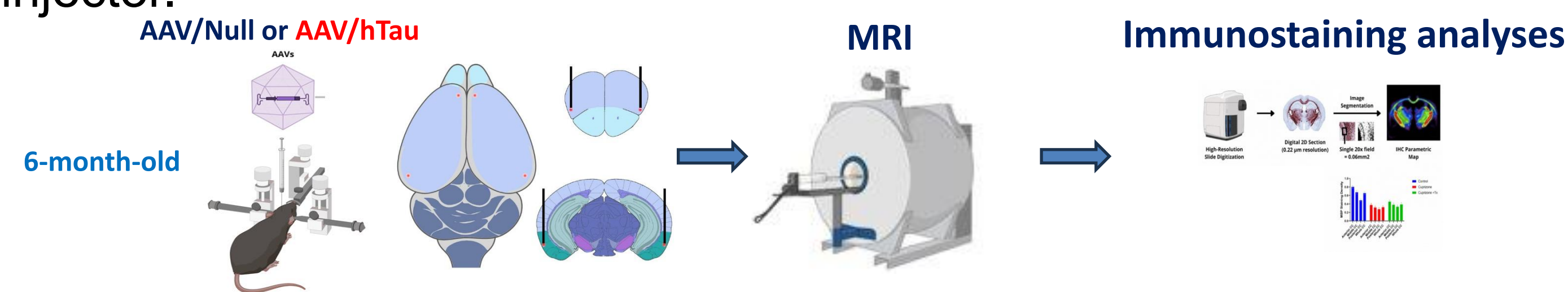


Introduction

Measurement of hippocampal atrophy on MRI scans is routinely performed in clinical trials of investigational disease-modifying therapeutic agents for Alzheimer's disease (AD). In order to facilitate the clinical translatability of preclinical studies to clinical trials, it is necessary to use animal models that accurately reflect human disease, as well as biomarkers that can span the different phases of drug development. The objective of this work was to evaluate atrophy of the hippocampus using *in vivo* MRI scans from a novel amyloid-beta/tau co-pathology mouse model using a new subcortical shape analysis approach.

Methods

Animal Model: Double transgenic APP/PS1 or wild-type (WT) animals injected with either an AAV-hTau vector (expressing human, wild-type, 2N4R tau) or an AAV-Null (control) vector bilaterally into the anterior cortex and the entorhinal cortex at 6 months-of-age using a digital stereotaxic device with an automated microinjector.



Data: High-resolution, *in vivo* anatomical MRI scans were acquired with a 7T Bruker BioSpec 70/30 animal MRI scanner. All MRI images (N=65) were analyzed using Biospective's fully-automated NIGHTWING™ MRI processing platform. Biospective's PERMITS™ platform was utilized for quantification of multiplex immunofluorescence (IF) staining of Iba-1 and GFAP as markers of microgliosis and astrogliosis, respectively.

Image Analysis:

- Automatic extraction of the boundary surface of the segmented hippocampus was performed 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 general linear model to assess the statistical significance of the between-groups and between-strains effects on the resulting surface deformation maps.

Results

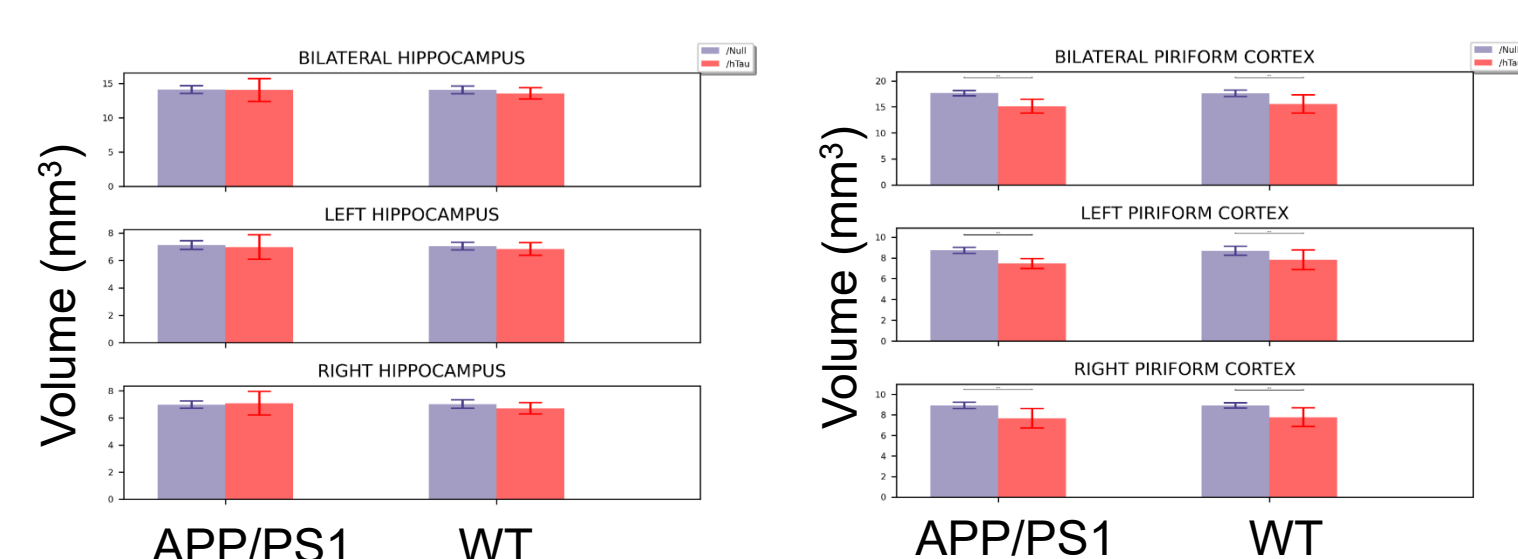


Figure 1. In contrast to the hTau-related atrophy detected in brain regions, such as the piriform cortex, no **regional volume changes** were identified between the hTau and Null conditions in the hippocampus.

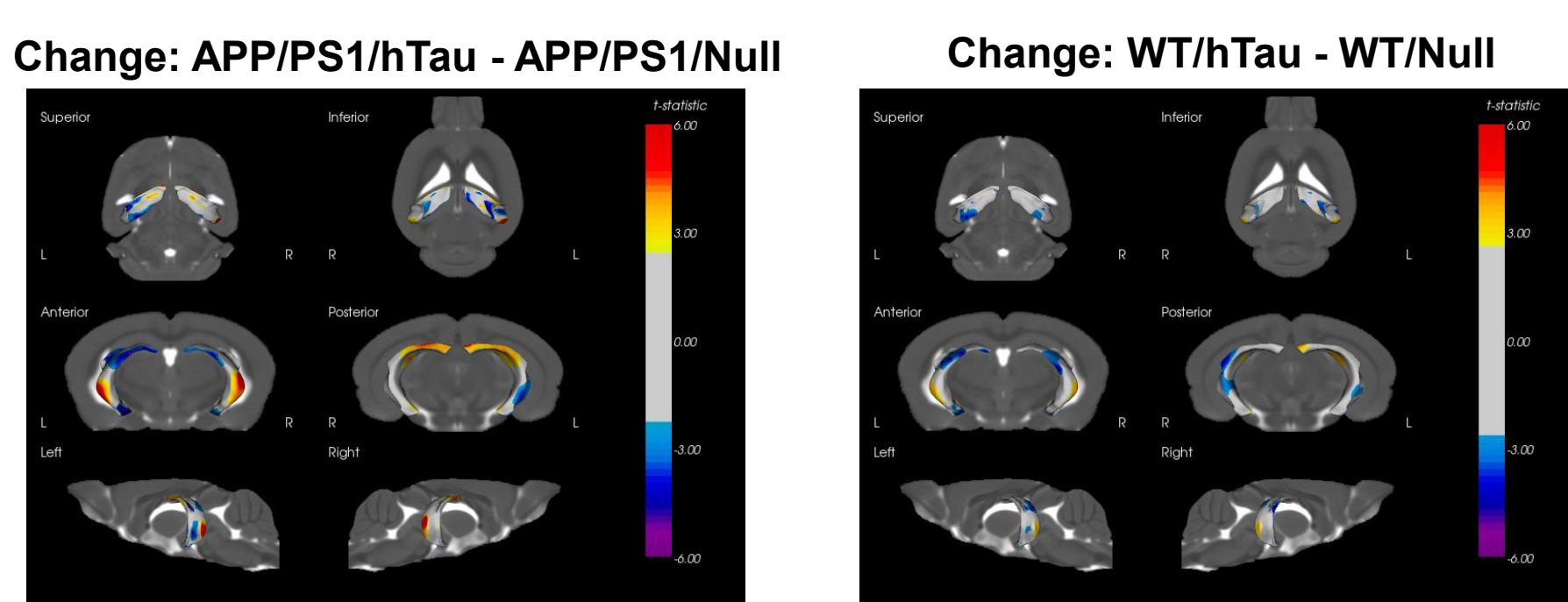
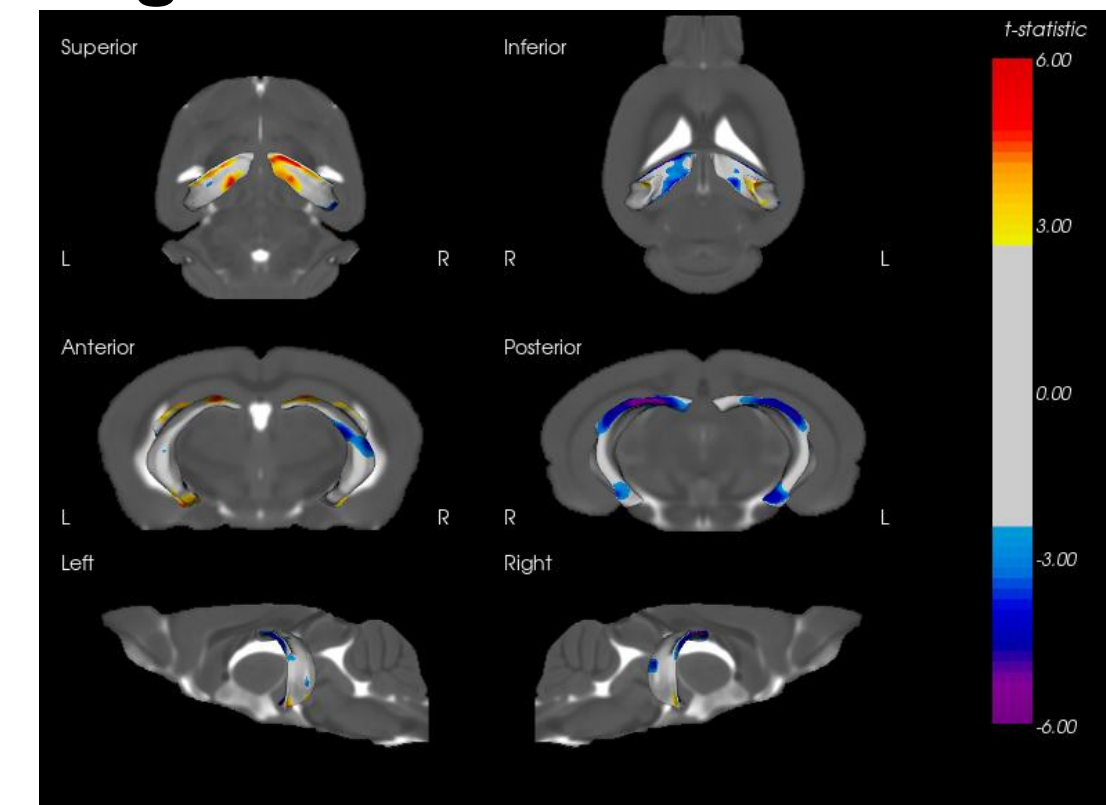


Figure 2. Statistically significant changes in **local deformations** between hTau and Null mice were detected in hippocampus bilaterally, which appeared to be stronger and more spatially extensive in APP/PS1 than in WT mice.

Change: WT/hTau - APP/PS1/hTau



Change: WT/Null - APP/PS1/Null

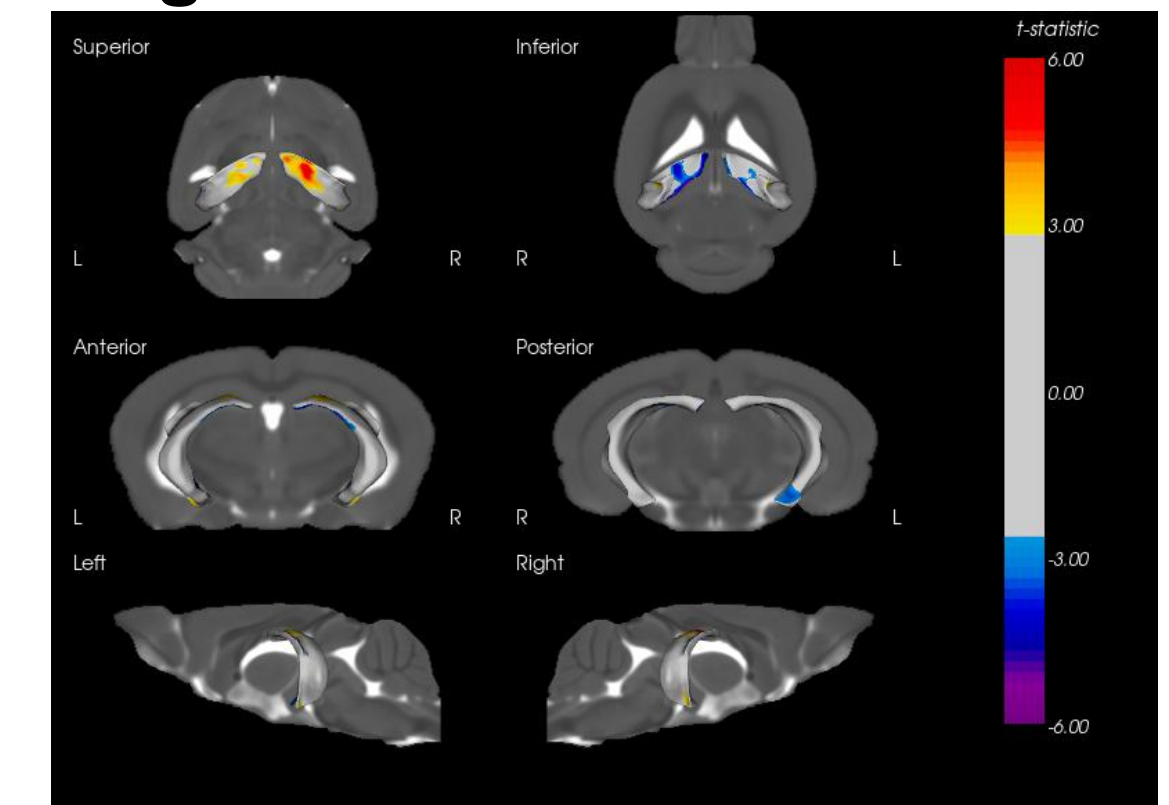


Figure 3. The strongest statistically significant effect of mouse model (*i.e.* APP/PS1 vs. WT) on the local deformations of the hippocampus surface corresponded to the AAV/hTau injected mice.

Iba-1 and GFAP Staining in Piriform Cortex

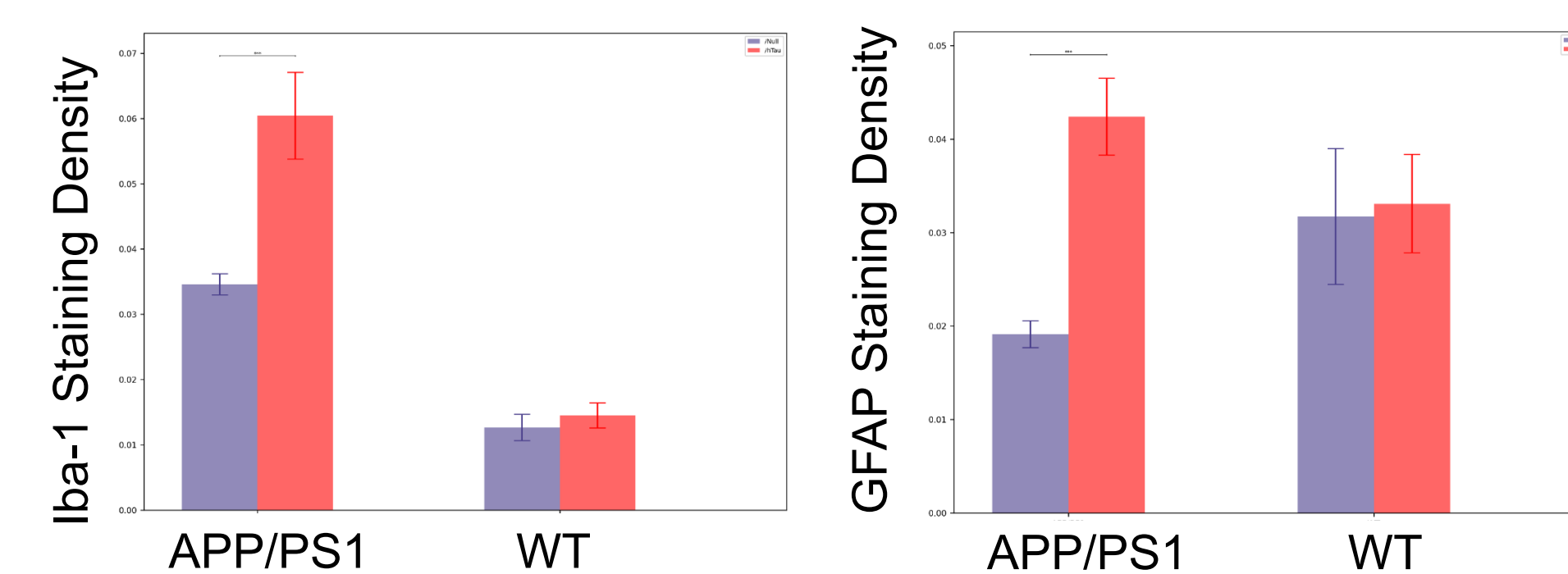
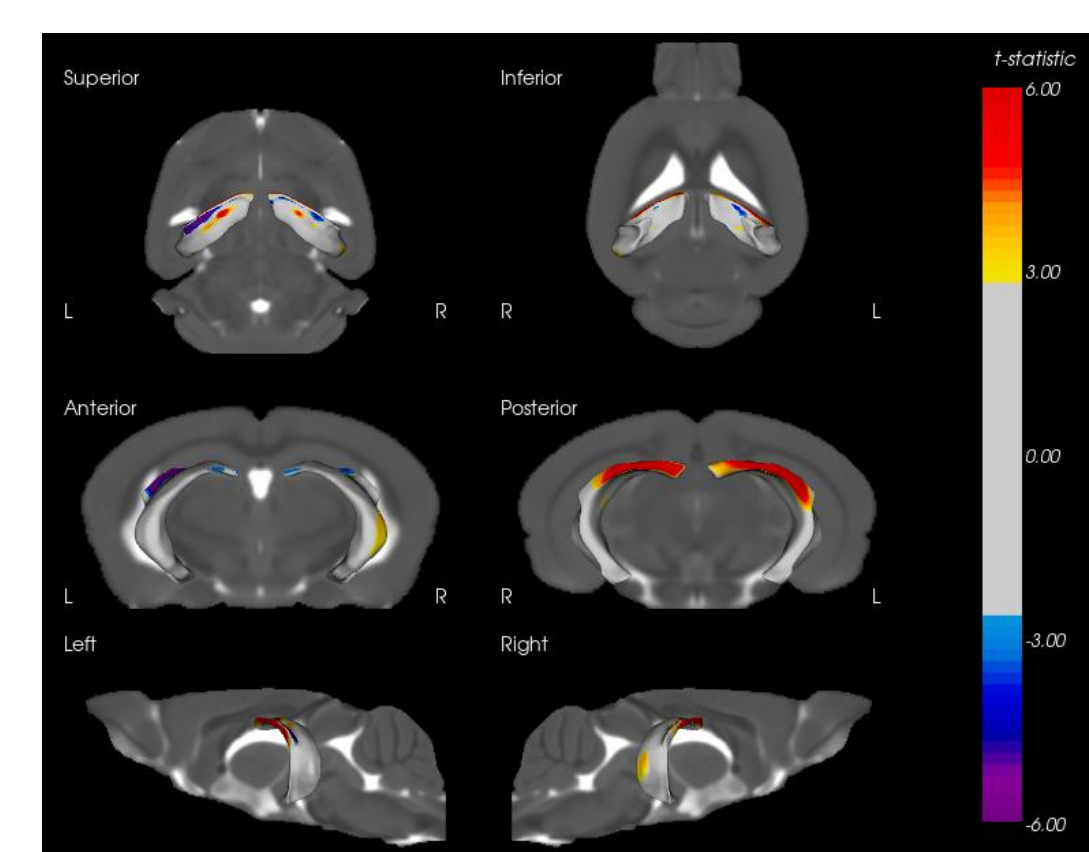


Figure 4. Iba-1 and GFAP staining within the piriform cortex showed statistically significant differences between Null and hTau in the APP/PS1 group only.

Correlation with Iba-1: APP/PS1



Correlation with GFAP: APP/PS1

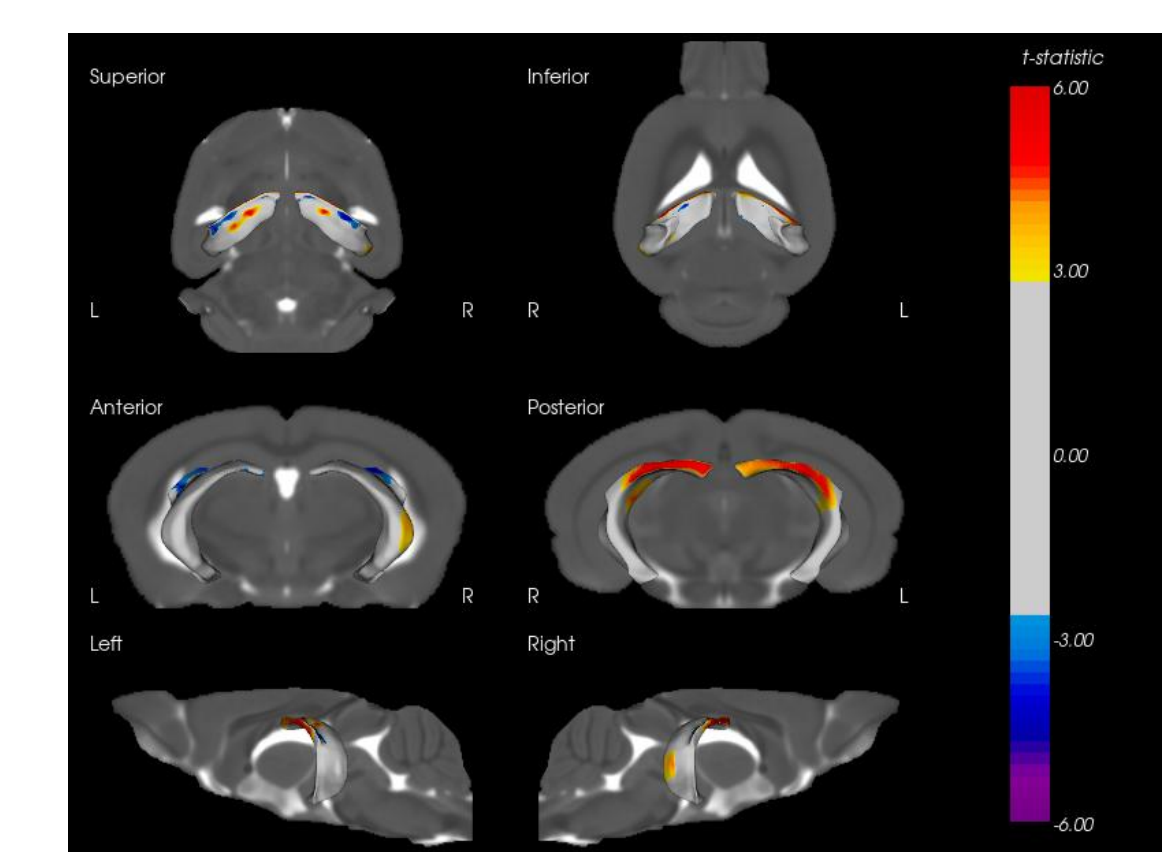


Figure 5. Statistically significant associations between the local surface deformations of the hippocampus and the Iba-1 and GFAP markers in the piriform cortex. The deformation changes between the hTau and Null conditions for the APP/PS1 mice (see **Figure 2**) are associated with the increase of microgliosis and astrogliosis within the piriform cortex.

Conclusions

We determined that local deformations in the shape of subcortical structures, such as the hippocampus, is a sensitive imaging biomarker for detecting the progression of hippocampal atrophy in an AD mouse model with amyloid-beta and tau co-pathologies. This novel amyloid-beta and tau co-pathology (APP/PS1/hTau) mouse model can serve as a useful tool for preclinical evaluation and tracking of disease-modifying therapeutics for Alzheimer's disease