

FreeSurfer Morphometry is Sensitive to T2-Weighted Inputs and Manual Editing: A Multi-Cohort Assessment

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INTRODUCTION

- FreeSurfer** [1] is a widely used semi-automated brain MRI segmentation tool for quantifying cortical morphometrics, such as cortical thickness, frequently used in studies of aging and neurodegeneration [2,3]
- Variability in processing procedures** such as input MRI contrast(s) and presence of manual editing may systematically bias morphometric estimates and biological associations
- Establishing how processing choices shift morphometric estimates is critical for accurately interpreting **longitudinal and cross-study changes in biomarkers**.
- We assessed the effects of input contrast and manual editing on morphometric outcomes in two independent cohorts: the Carotids and Minds (CAM) and Alzheimer's Disease Neuroimaging Initiative (ADNI)**

METHODS

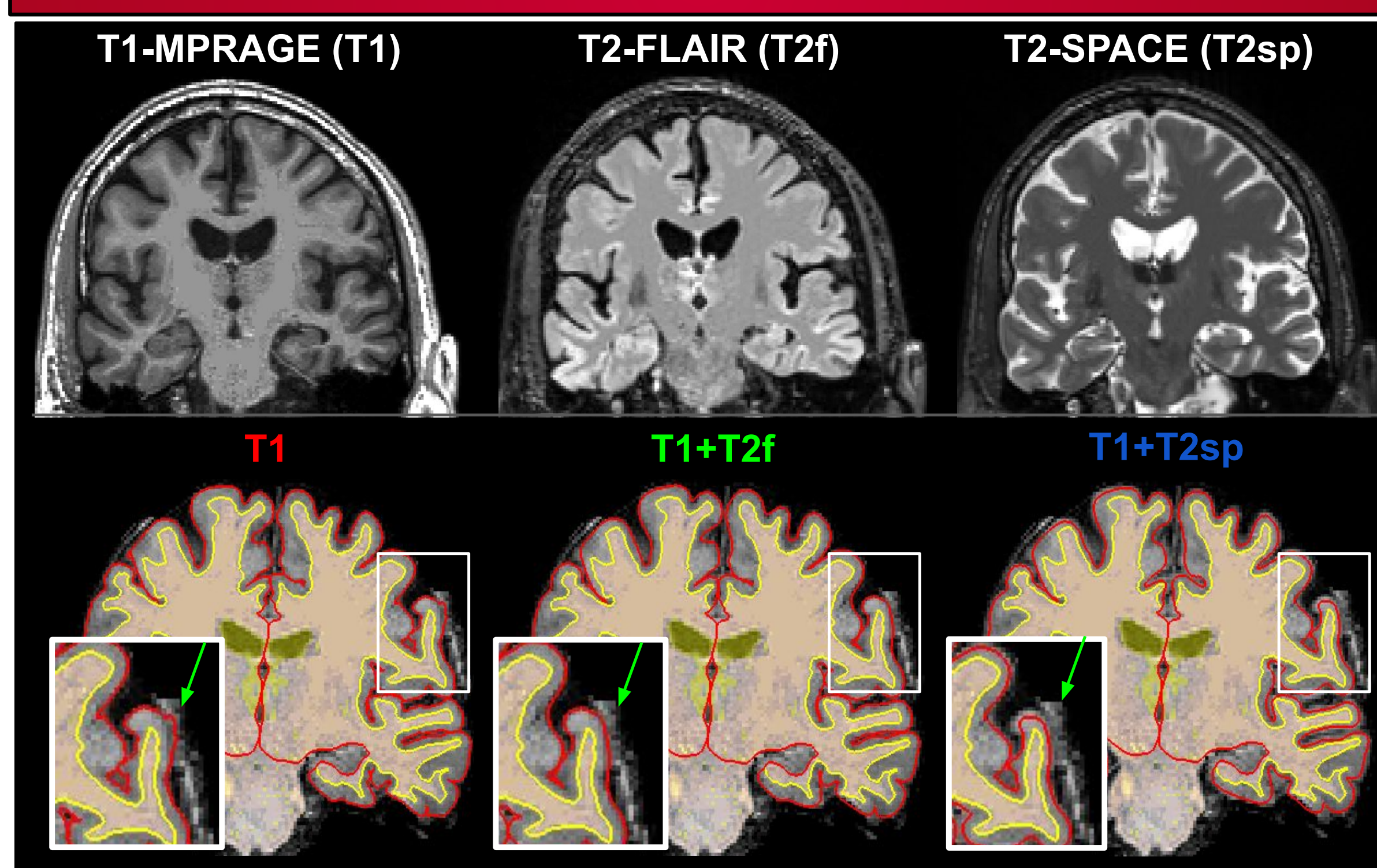


Figure 1. Representative subject input contrasts and FreeSurfer segmentations. Top: Three MRI contrasts of interest (T1-MPRAGE, T2-FLAIR, T2-SPACE). Bottom: FreeSurfer segmentation outputs from the three experimental run configurations (T1-MPRAGE [T1], T1 + T2-FLAIR [T1+T2f], T1 + T2-SPACE [T1+T2sp]).

Figure 2. Procedural workflow. MRI data (3T, Siemens Skyra) was gathered from the CAM study which recruits participants with varying degrees of vascular disease.

A primary cohort (N = 123) underwent **FreeSurfer** segmentation of the three run configurations (red). A secondary cohort underwent **manual editing and blinded expert grading** for each run configuration (blue). **Cognitively normal ADNI participant data (n=143) was assessed in parallel.**

Morphometrics were compared across run configurations and between pre/post editing.

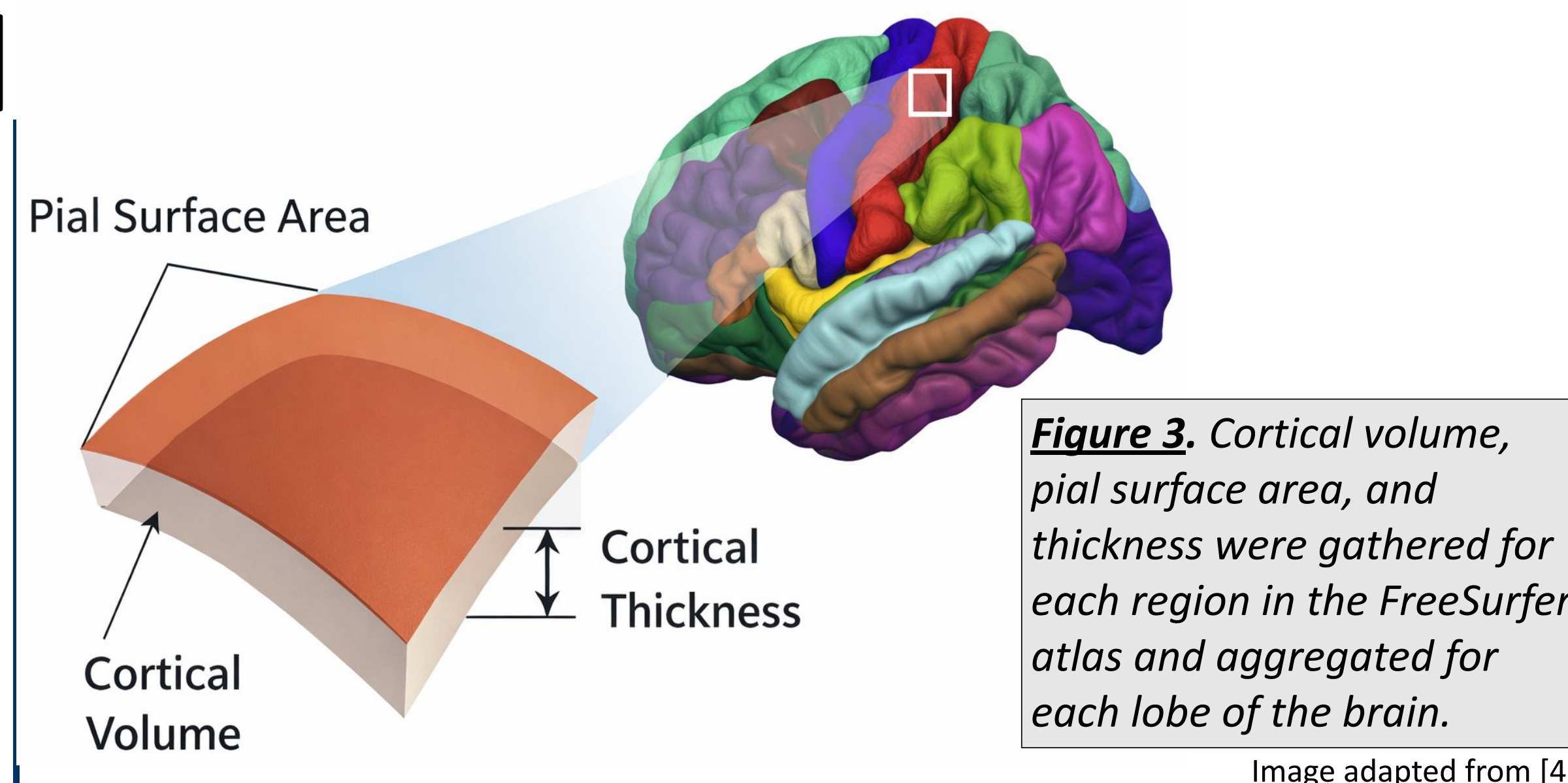
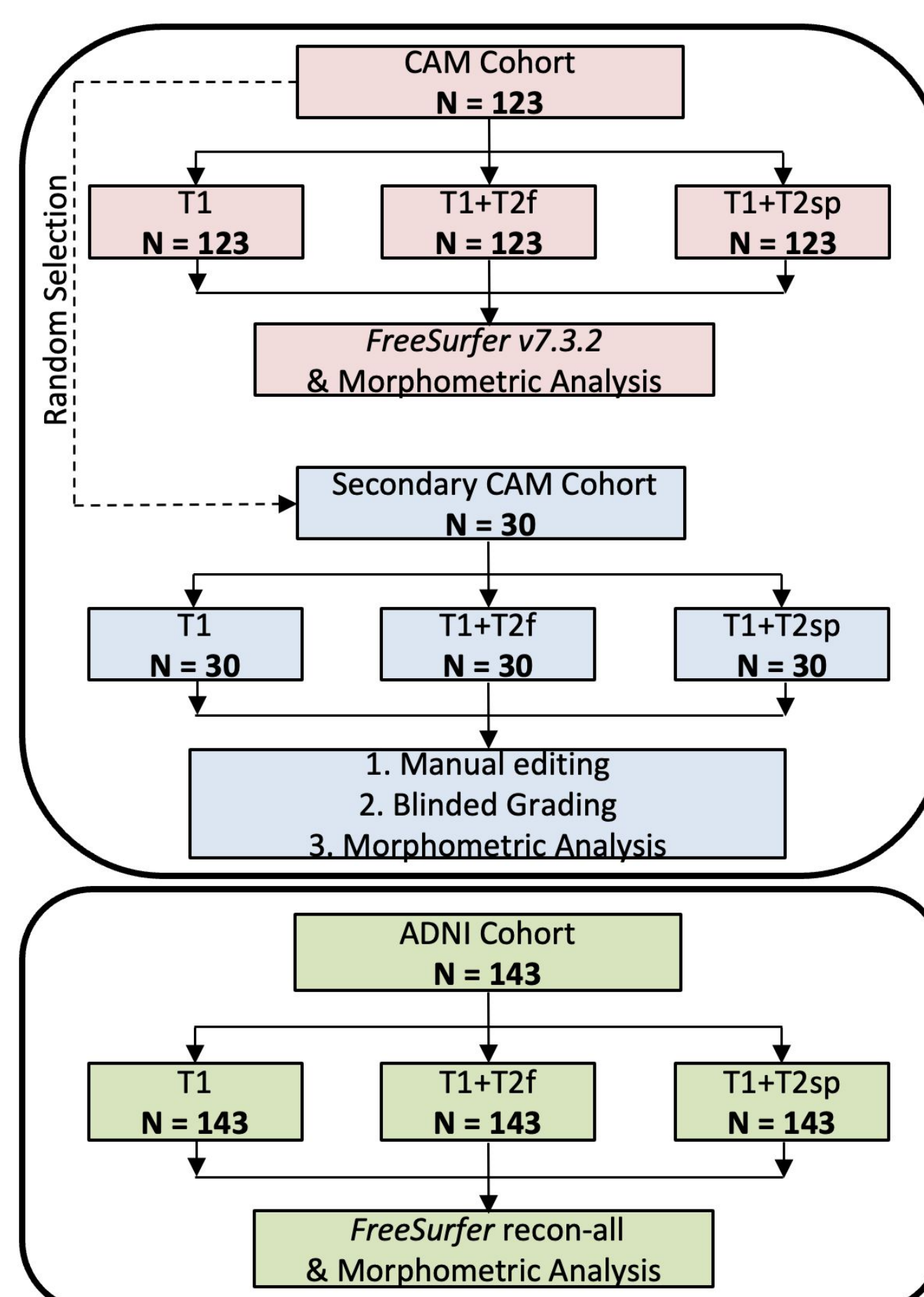


Image adapted from [4]

RESULTS

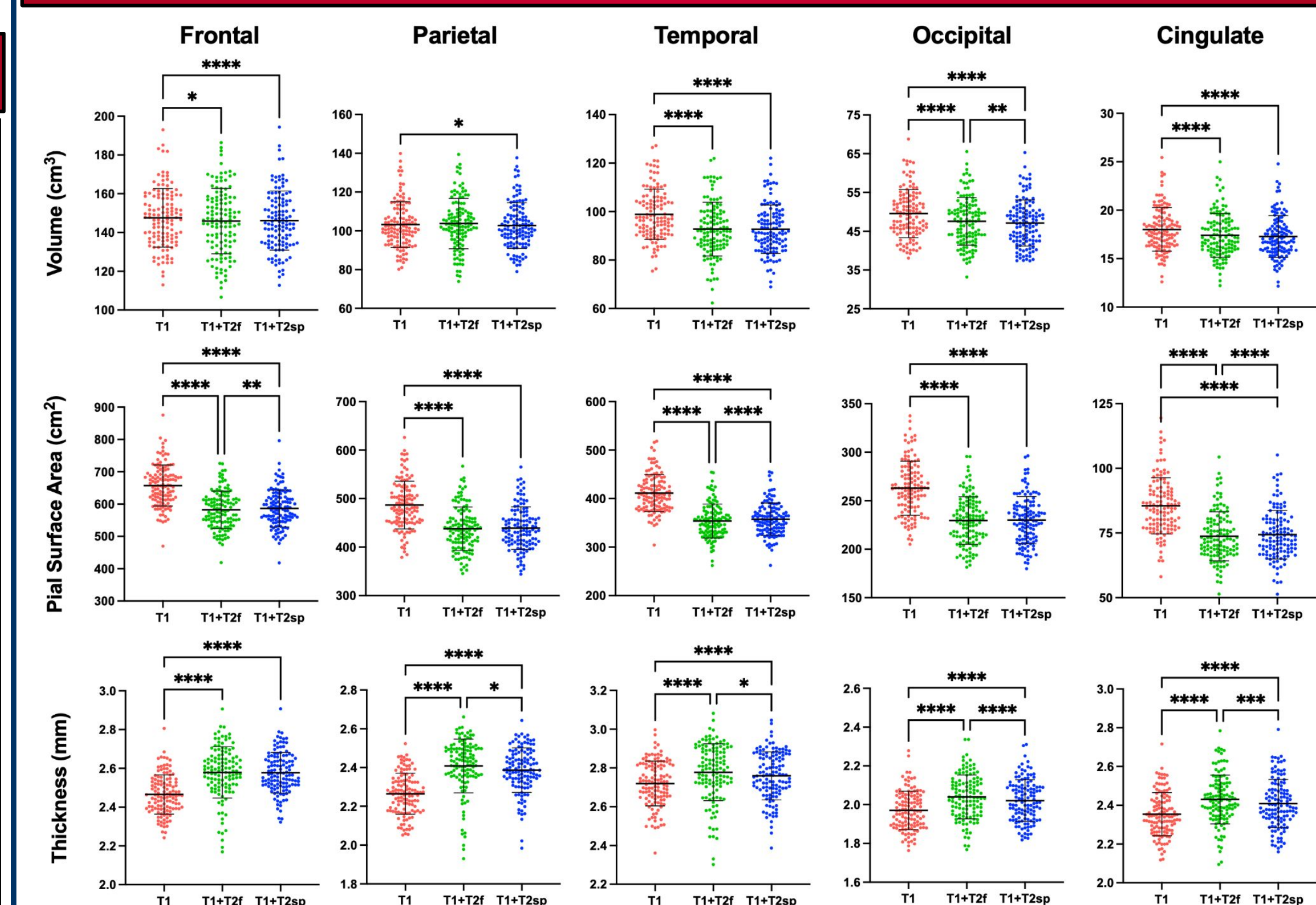


Figure 4. Cortical morphometrics by input contrast configuration. Morphometrics were statistically different across run configurations. T2-dependent pipelines produced lower volume and surface area, and higher thickness. Percent change relative to T1-only reached -14% for pial surface area of the temporal lobe. Findings were replicated in ADNI (data not shown).

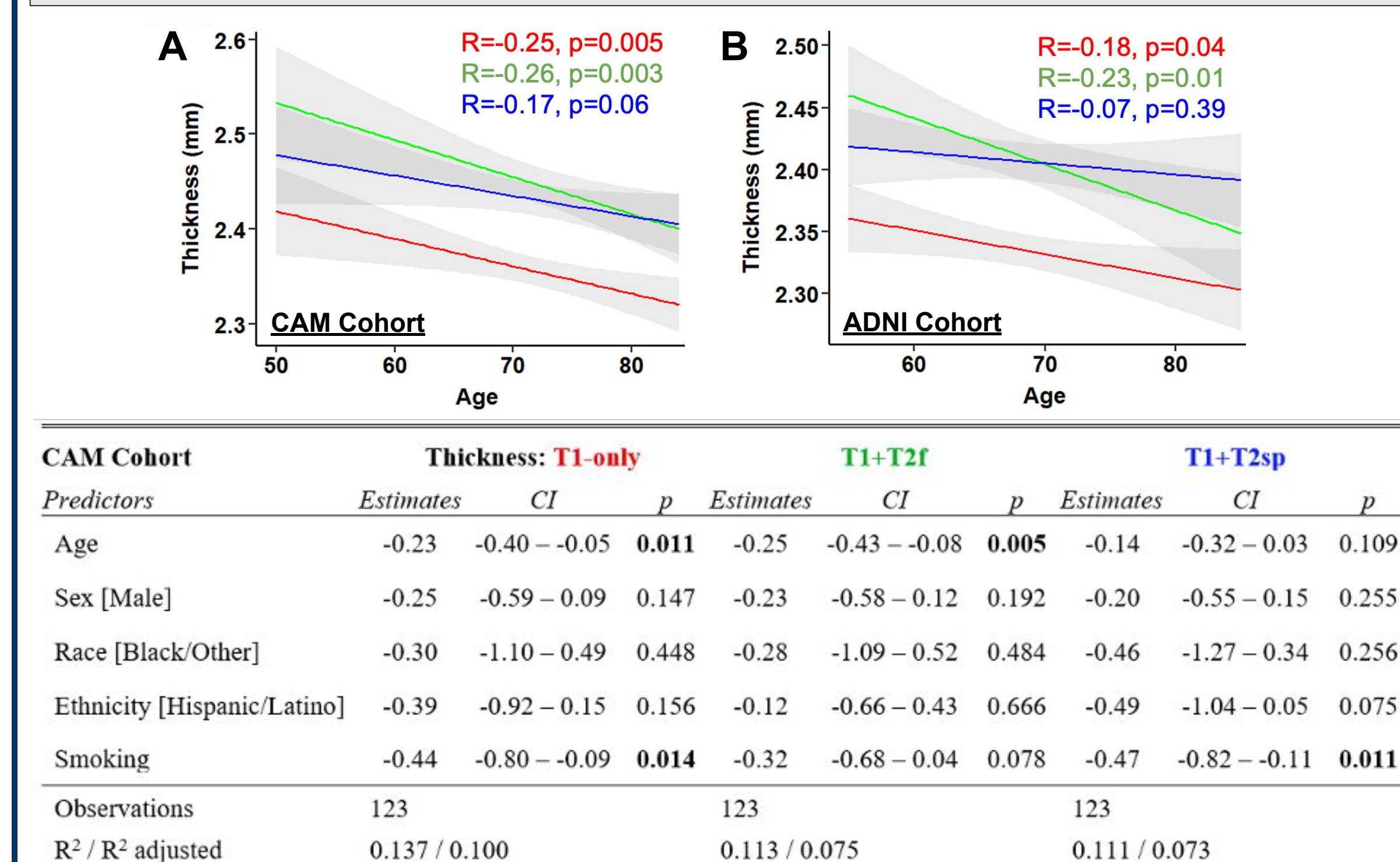


Figure 5. Age-thickness associations varied by input configuration in (A) CAM and (B) ADNI cohorts. Multivariable regression analyses show that established associations of age and smoking to cortical thickness are attenuated with the addition of a T2-weighted contrast.

RESULTS

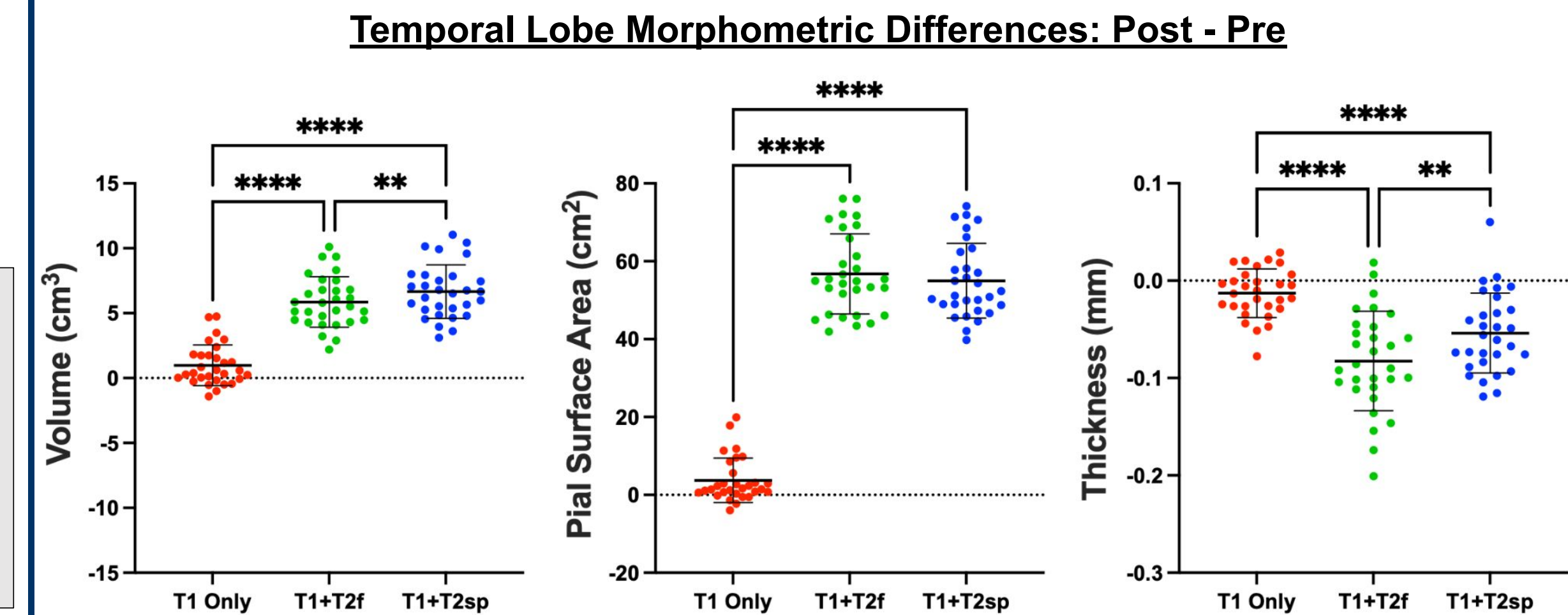
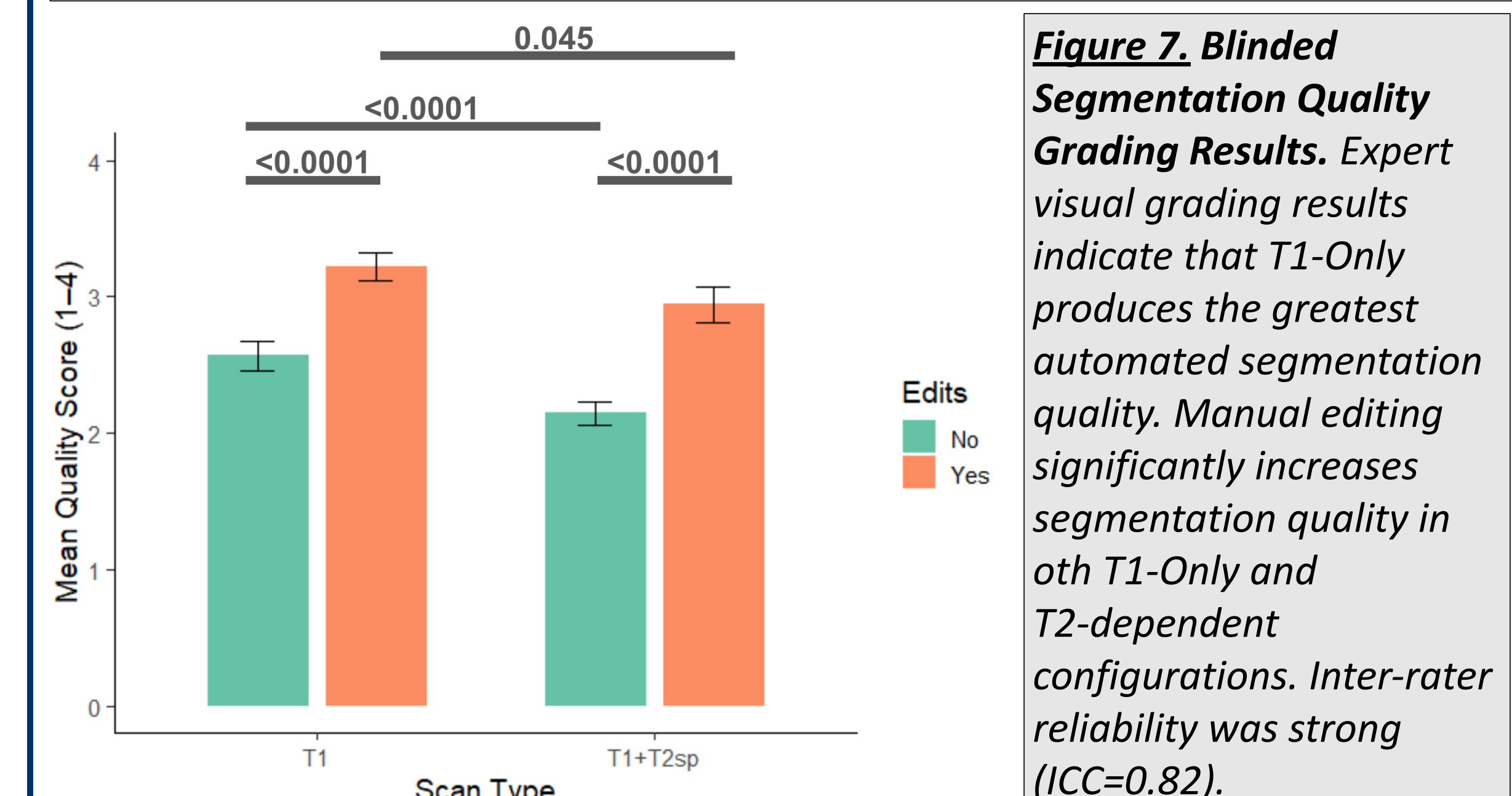


Figure 6. Secondary CAM cohort differences between pre- and post-edit morphometrics of the temporal lobe, calculated as post minus pre estimates. Across all lobar regions, percent change from baseline reached a maximum of +16% for pial surface area and +7% for volume of the temporal lobe in T2-dependent inputs but <1% in T1 despite similar grading effort across run configurations.



CONCLUSIONS

- The addition of T2-weighted contrasts, opposed to the default T1-only, **significantly altered cortical volume, surface area, and thickness estimates**.
- T2-related biases were large (up to 14%) and **obscured known biological associations**, though **manual edits corrected these deviations and improved segmentation quality**.
- The highest quality reconstructions are likely to be achieved with **manually edited, T1-only pipelines**.
- Findings highlight that methodological variations can meaningfully alter biological interpretations and should be carefully considered.**

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