

BACKGROUND

Atypical clinical presentations of Alzheimer's disease (AD) are associated with heterogeneous patterns of cortical tau-PET uptake. However, little is known about the relationship between tau-PET positivity and SUVR burden in each region. Insight into this relationship will better our understanding of tau progression.

OBJECTIVES

To assess the relationship between the spatial extent and severity of tau-PET uptake across atypical AD variants.

METHODS

- ❖ 122 biomarker-confirmed AD (visual-AD=68, language-AD=39, motor-AD=15) patients were recruited by the Neurodegenerative Research Group, Mayo Clinic, Rochester, MN.
- ❖ A previously developed method using the 95th percentile of tau-PET SUVR was used to determine tau positivity for 65 regions.
- ❖ To measure tau burden in each region, the relative difference between the patient's standard uptake value ratio (SUVR) and the SUVR threshold for that region was calculated providing a regional tau score. These values are populated into the heatmap shown in figure 1.
- ❖ These tau scores were then averaged across all tau-positive regions for each patient, giving a global tau score.
- ❖ Tau score represents tau burden and tau spread represents the number of tau positive regions.
- ❖ Linear mixed effects models estimating tau burden and spread (number of tau+ regions), adjusting for age, sex, disease duration, diagnosis and Apolipoprotein E (*APOE*) $\epsilon 4$ status were fit to determine the relationship between tau burden and spread, and the influence of age, sex, disease duration, diagnosis and *APOE* $\epsilon 4$ status on tau burden and spread.

RESULTS & DISCUSSION

Figure 1

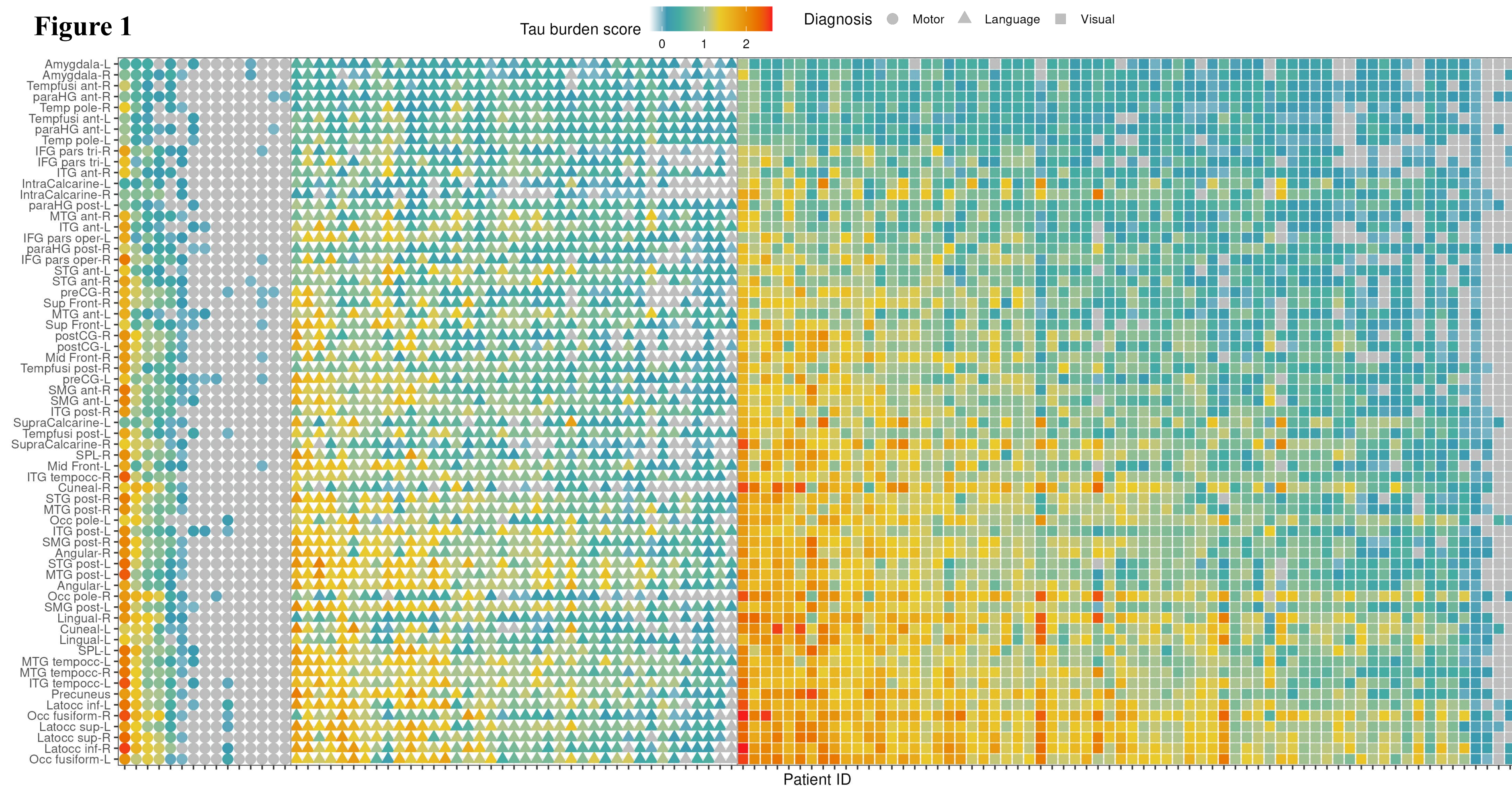


Figure 1 highlights the number of tau+ regions (tau spread) and tau-PET SUVR burden. Patients are grouped by diagnosis, with patients with most tau+ regions sorted to the left-side of the figure. Likewise, regions with the most tau+ patients and highest tau burden are sorted closer to the bottom of the figure. Regions in gray colour represent tau negative regions. Here a tau score=1 denotes a 100% difference from the tau-PET positivity threshold of that region, while a tau score=2 denotes a 200% differences. Yellow-Red numbers indicate higher tau burden, while blue-green numbers indicate lower tau burden

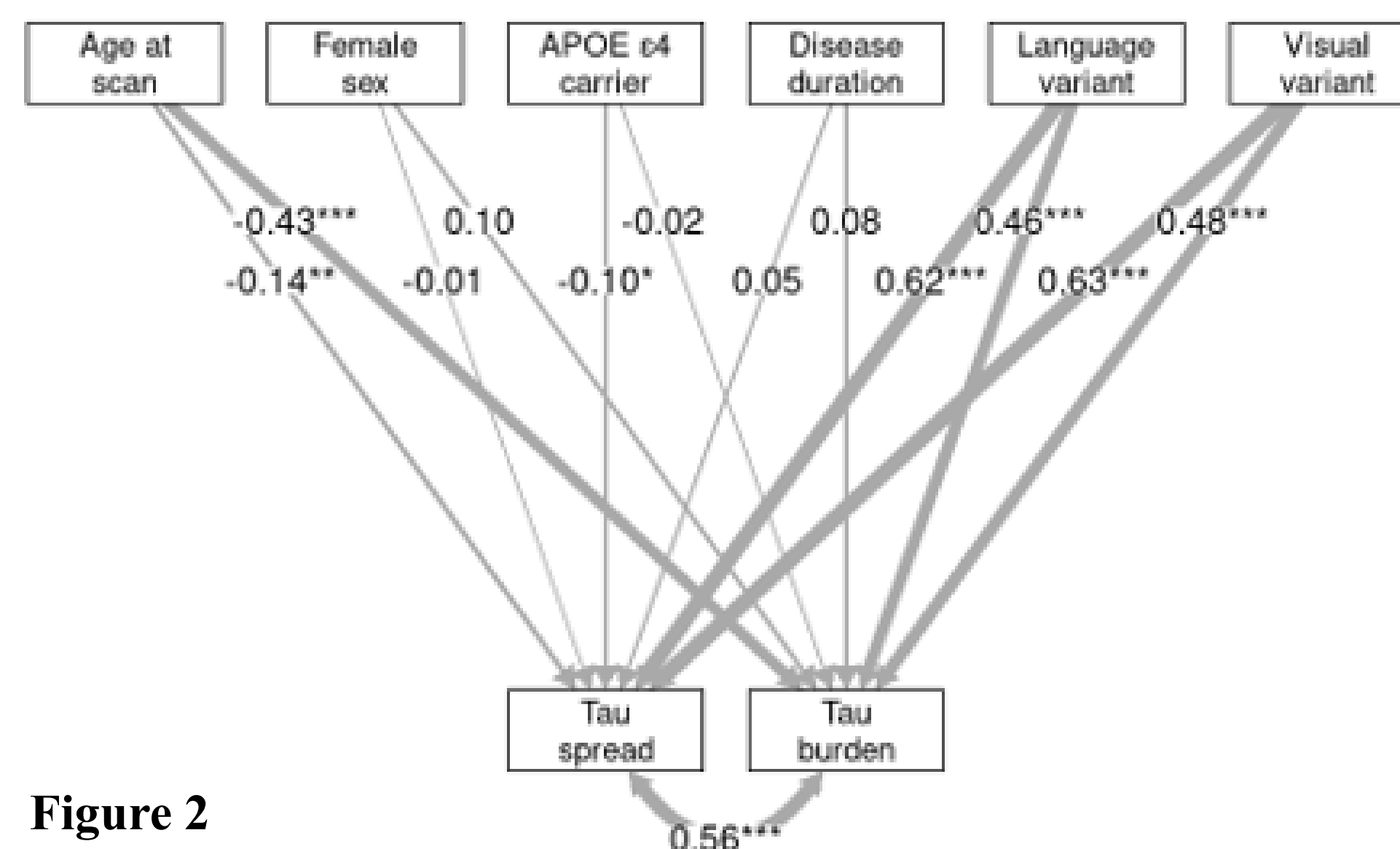


Figure 2

Figure 2 highlights the relationship between tau spread and tau burden, while adjusting for sex, age, disease duration, diagnosis and *APOE* $\epsilon 4$ status.

- ❖ Tau-PET uptake was typically widespread in both language-AD and visual-AD, while motor-AD mainly showed focal uptake (**Figure 1**).
- ❖ Severity of tau uptake was typically higher in the occipital, parietal and temporal lobes (**Figure 1**).
- ❖ Considerable heterogeneity in tau score existed among patients with a similar number of tau-positive regions (tau spread) (**Figure 1**).

- ❖ Tau spread and burden measures were moderately correlated (standardized $r=0.56$) (**Figure 2**). *Younger age* was associated with both tau spread and burden; however, this relationship was stronger with tau burden than spread (**Figure 2**). *APOE* $\epsilon 4$ carriers were associated with lower tau spread and not tau burden. Sex and disease duration did not influence either measure (**Figure 2**).
- ❖ Tau spread and burden were greater in language-AD (spread=59, burden=0.55) and visual-AD (spread=58, burden=0.55) compared to motor-AD (spread=26, burden=0.16). Diagnosis had a relationship with both tau spread and burden; however, this relationship was stronger with tau spread than burden (**Figure 2**).

CONCLUSIONS

We show that accounting for only tau spread is not sufficient to understand tau progression as there is considerable heterogeneity in tau burden among patients with similar tau spread. Hence, studies should consider both the spatial extent and severity of tau uptake in characterizing patient-level tau metrics in AD.

This work was supported by the **National Institutes of Health** (R01-AG50603)