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OBJECTIVE

- This exploratory study evaluated regional tau positron emission tomography (PET) extent to (1) estimate pathological tau volume, (2) capture tau heterogeneity across Alzheimer’s disease (AD) populations, and (3) detect treatment response in clinical trials.

CONCLUSIONS

- Regional tau PET extent is a novel, easily interpretable metric for estimating pathological tau volume.
- In this exploratory study, regional tau PET extent:
 - correlated with voxel-wise extent, providing an easily implementable approach by using atlas brain regions.
 - captured tau heterogeneity across AD populations, supporting its potential relevance in clinical trials.
 - showed similar signal-to-noise ratios to prespecified regional standardized uptake value ratios (SUVRs), complementing intensity-based metrics by quantifying the distribution of tau pathology.
 - was consistent with established SUVR measurements for evaluating treatment response in clinical trials, supporting its reliability and validity.
- Regional extent is more directly applicable to the entire spectrum of AD patients than population-specific regional SUVR measurements, as it samples the entire neocortex.

BACKGROUND

Tau PET

- Tau PET is a neuroimaging technique used to visualize and quantify tau neurofibrillary tangles, a key pathological hallmark of AD.^{1,2}

SUVR

- Tau PET is commonly quantified using SUVR, which compares radiotracer uptake in a target region of interest to a reference region.^{1,3}
- The SUVR reflects the intensity of tau PET signal within a specific region and might not capture the extent (i.e., volume or spread) of tau pathology.^{1,2}

Spatial extent

- Spatial extent reflects how widely tau is distributed across the brain and can serve as a valuable metric for diagnostic and prognostic purposes.¹ Compared to SUVR, it may be less affected by noise, more intuitive, and potentially more strongly associated with cognitive performance.^{1,2}

Voxel-wise approach:

- Spatial extent, quantified using a voxel-wise approach, estimates the percentage of gray matter voxels with pathological tau PET signal.¹
- However, this approach is computationally intensive, requires pre-specifying masks, and might not identify distinct regions, limiting interpretability.

Regional extent approach:

- Here, we propose regional extent as a novel approach to quantifying pathological tau PET volume using prespecified atlas brain regions.

METHODS

Data

- Tau PET images from three studies were included, representing individuals across the AD spectrum:
 - 18F-AV-1451-A05E (NCT02016560): Participants who were amyloid PET negative (healthy controls).⁴
 - Anti-Amyloid Treatment in Asymptomatic AD (A4; NCT02008357): Participants with cognitively unimpaired AD (amyloid PET positive).⁵
 - PROSPECT-ALZ (NCT05063539): Participants with early symptomatic AD (tau PET positive).⁶

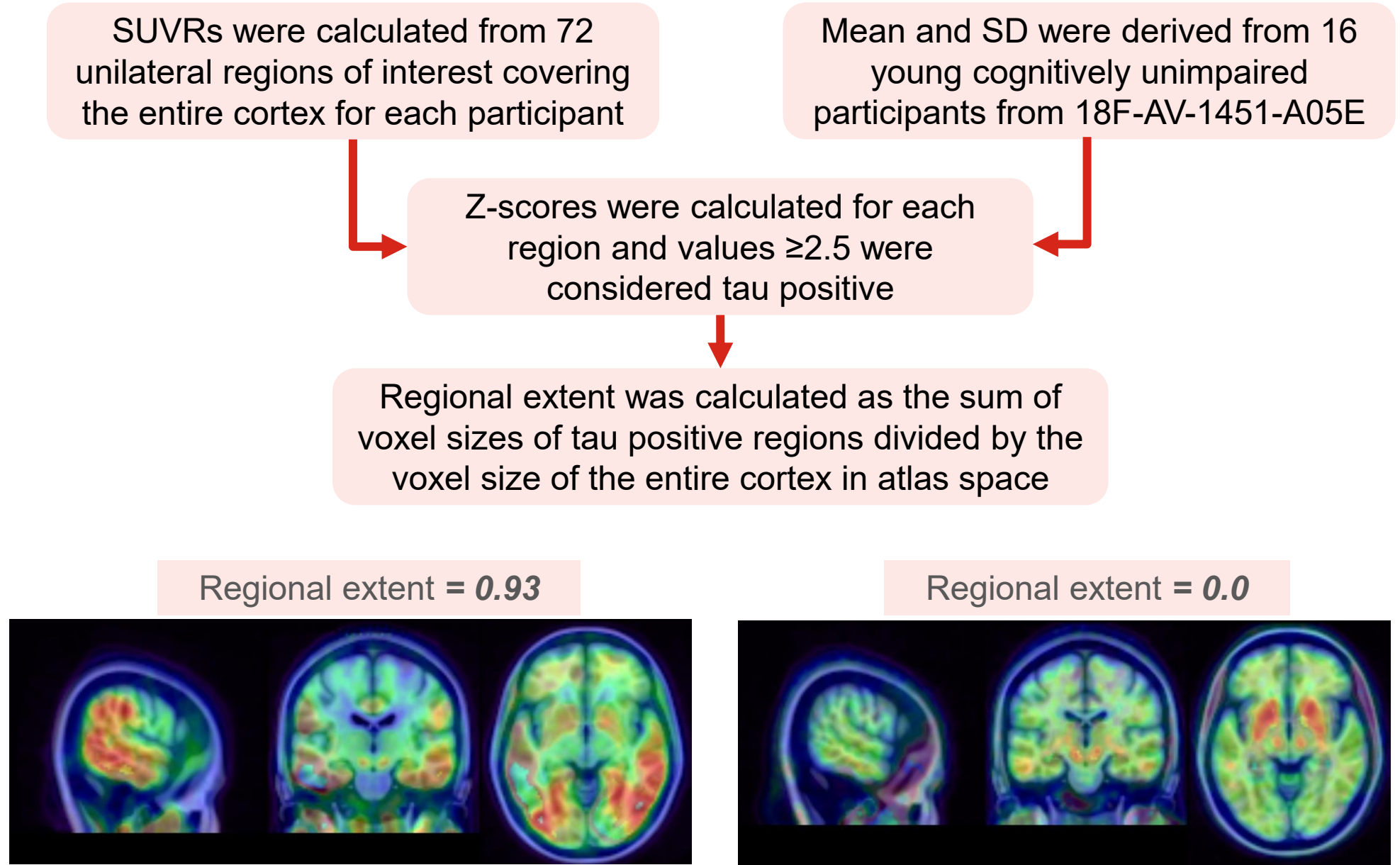
RESULTS

Table 1. Demographics from the three studies

Characteristic	18F-AV1451-A05E NCT02016560 Cognitively Unimpaired, Amyloid PET Negative	Anti-Amyloid Treatment in Asymptomatic AD (A4) NCT02008357 Cognitively Unimpaired AD		PROSPECT-ALZ NCT05063539 Early Symptomatic AD		
	Placebo	Solanezumab	Placebo	Ceperognastat (0.75mg)	Ceperognastat (3mg)	Placebo
Treatment group						
Sample size with FTP data	N=52	N=172	N=168	N=108	N=110	N=108
Mean age (SD)	67.6 (10.25)	72.4 (4.78)	71.6 (4.71)	73.3 (5.43)	73.4 (5.36)	73.4 (5.47)
Female sex (%)	46.2%	54.1%	58.9%	63.9%	58.2%	63.0%
APOE ε4 carrier (%)	19.2%	57.0%	57.7%	63.0%	66.4%	70.4%
Mean baseline global FTP SUVR (SD)	1.00 (0.04)	1.03 (0.07)	1.03 (0.14)	1.30 (0.21)	1.29 (0.22)	1.30 (0.24)
Tau PET assessments	Baseline, Week 76	Baseline, Week 84, Week 168, Week 240		Baseline, Week 76, Week 100		

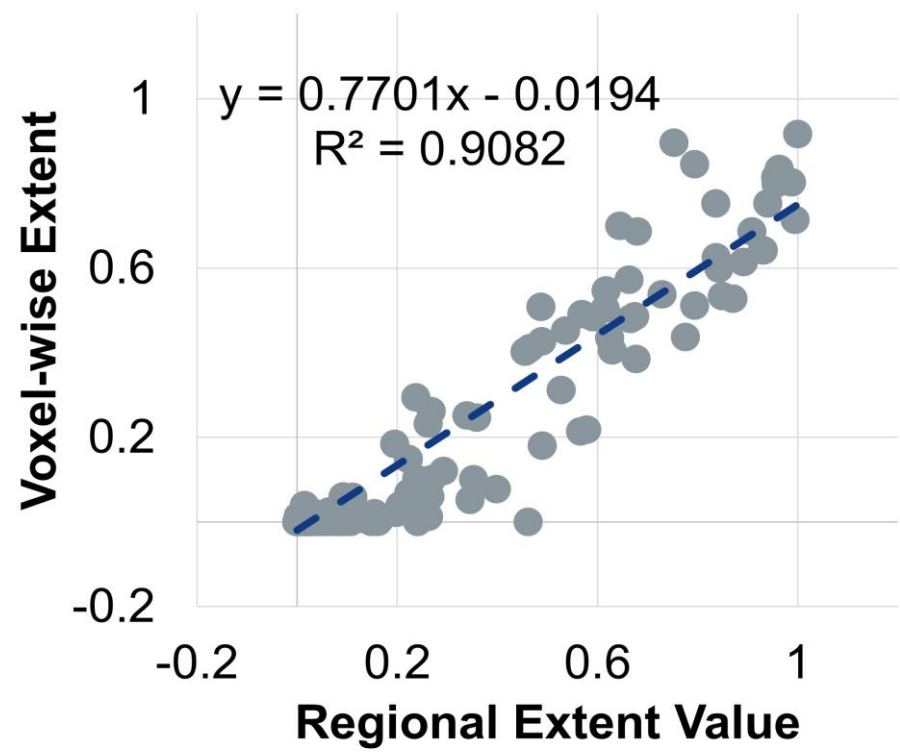
The table shows participants with at least one post-baseline scan.

Figure 1. How regional extent was calculated to estimate pathological tau PET volume



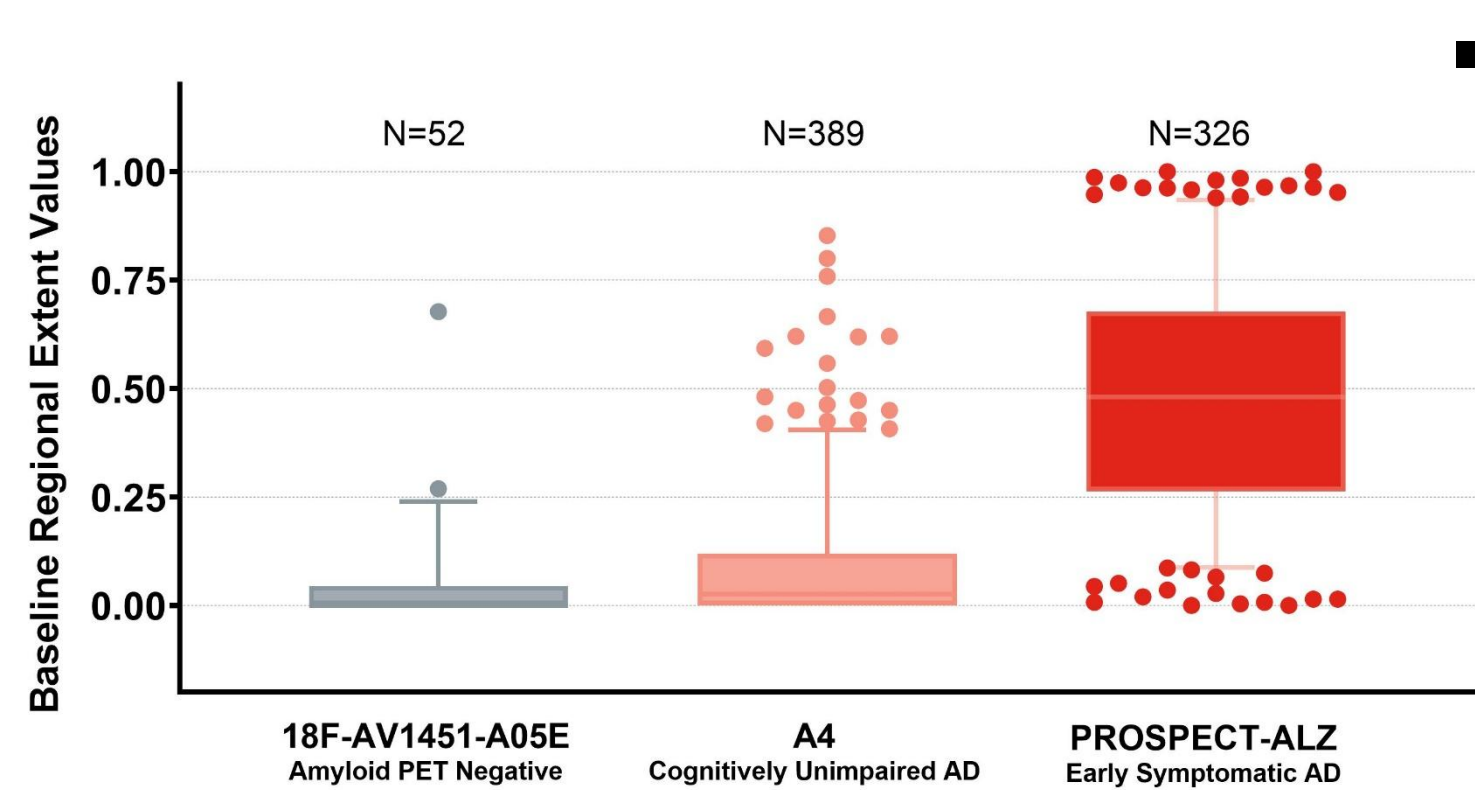
RESULTS AND DISCUSSION

Figure 2. Regional extent and voxel-wise extent



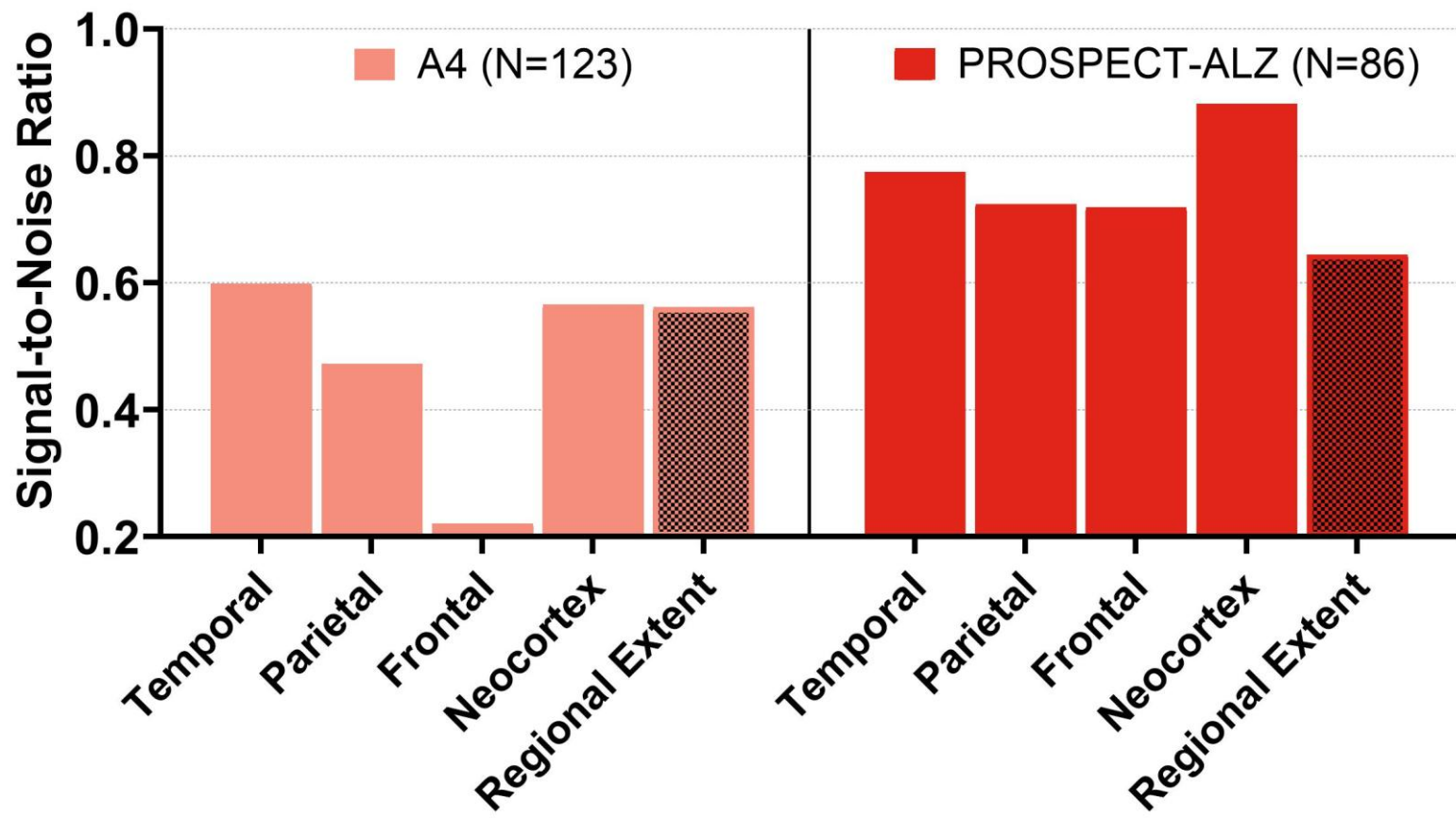
- In 18F-AV-1451-A05E, regional extent was strongly correlated with voxel-wise extent (R²=0.91; Figure 2).

Figure 3. Regional extent across AD populations at baseline



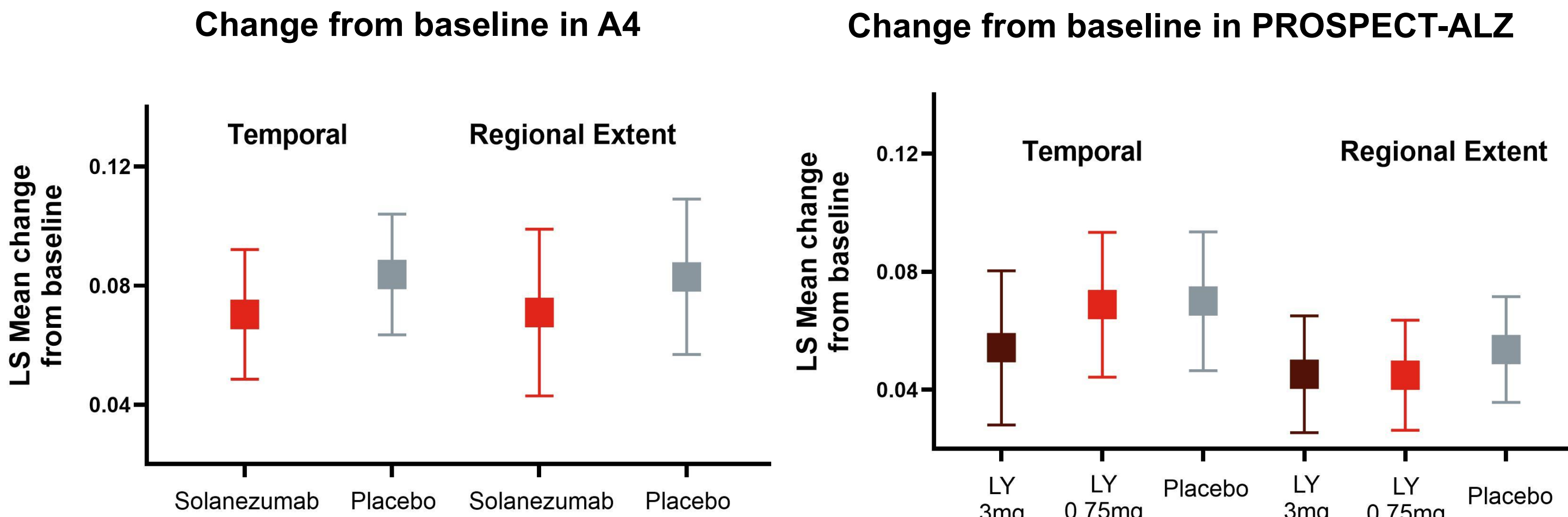
- Baseline regional extent was 4% in participants who were amyloid PET negative, 9% in participants with cognitively unimpaired AD, and 49% in participants with early symptomatic AD (Figure 3). Means (SDs) are reported.

Figure 4. Regional extent vs SUVR by region of interest



- Longitudinally, within the placebo populations, signal-to-noise ratios were similar for regional extent and prespecified regional SUVRs (Figure 4).
- Signal-to-noise ratio was defined as the mean change in SUVR divided by the standard deviation of change in SUVR.
- Longitudinal data were only available for a subset of participants.

Figure 5. Regional extent vs SUVR longitudinally (treatment response)



- Treatment response on regional extent to solanezumab (A4) and ceperognastat (PROSPECT-ALZ) was consistent with previously reported SUVR-based results (Figure 5).⁷ The drugs did not have an effect in these studies.

Abbreviations:

A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer’s disease; AD, Alzheimer’s disease; APOE, Apolipoprotein E; FTP, flortaucipir; LY, ceperognastat; PET, positron emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

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Disclosures:

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