

# Longitudinal rates of hypometabolism and tau accumulation in posterior cortical atrophy

Irene Sintini; Jonathan Graff-Radford; Christopher G. Schwarz; Matthew L. Senjem; Nick Corriveau-Lecavalier; Mary M. Machulda; David T. Jones; Bradley F. Boeve; Ronald C. Petersen; Clifford R. Jack Jr; Val J. Lowe; Keith A. Josephs; Jennifer L. Whitwell

Mayo Clinic, Rochester, MN

## Background

- Posterior cortical atrophy (PCA) is a neurodegenerative syndrome characterized by the early onset of visuospatial and visuoperceptual deficits, most often caused by Alzheimer's disease.<sup>1</sup>
- Metabolic dysfunction can be imaged with [<sup>18</sup>F]Fluorodeoxyglucose PET (FDG)-PET, which co-localizes with tau deposition in occipital, posterior temporal and parietal regions in PCA.<sup>2</sup>
- Tau precedes atrophy in the spreading toward anterior regions of the brain over time in PCA.<sup>3</sup>

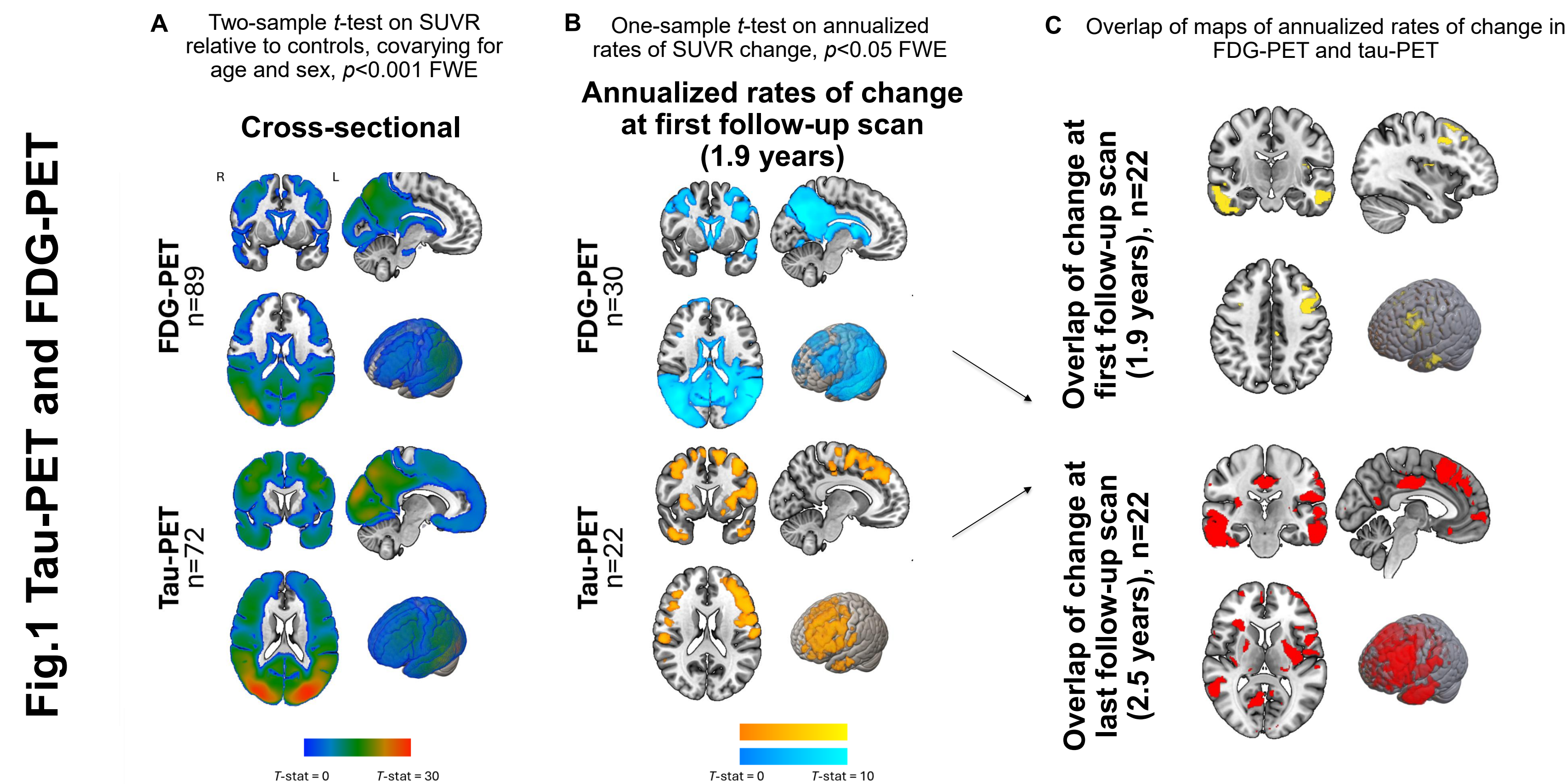
## Objective

To investigate the spatiotemporal trajectories of tau-PET and FDG-PET uptake and their associations with age and baseline clinical performance in participants with a clinical diagnosis of PCA.

## Methods

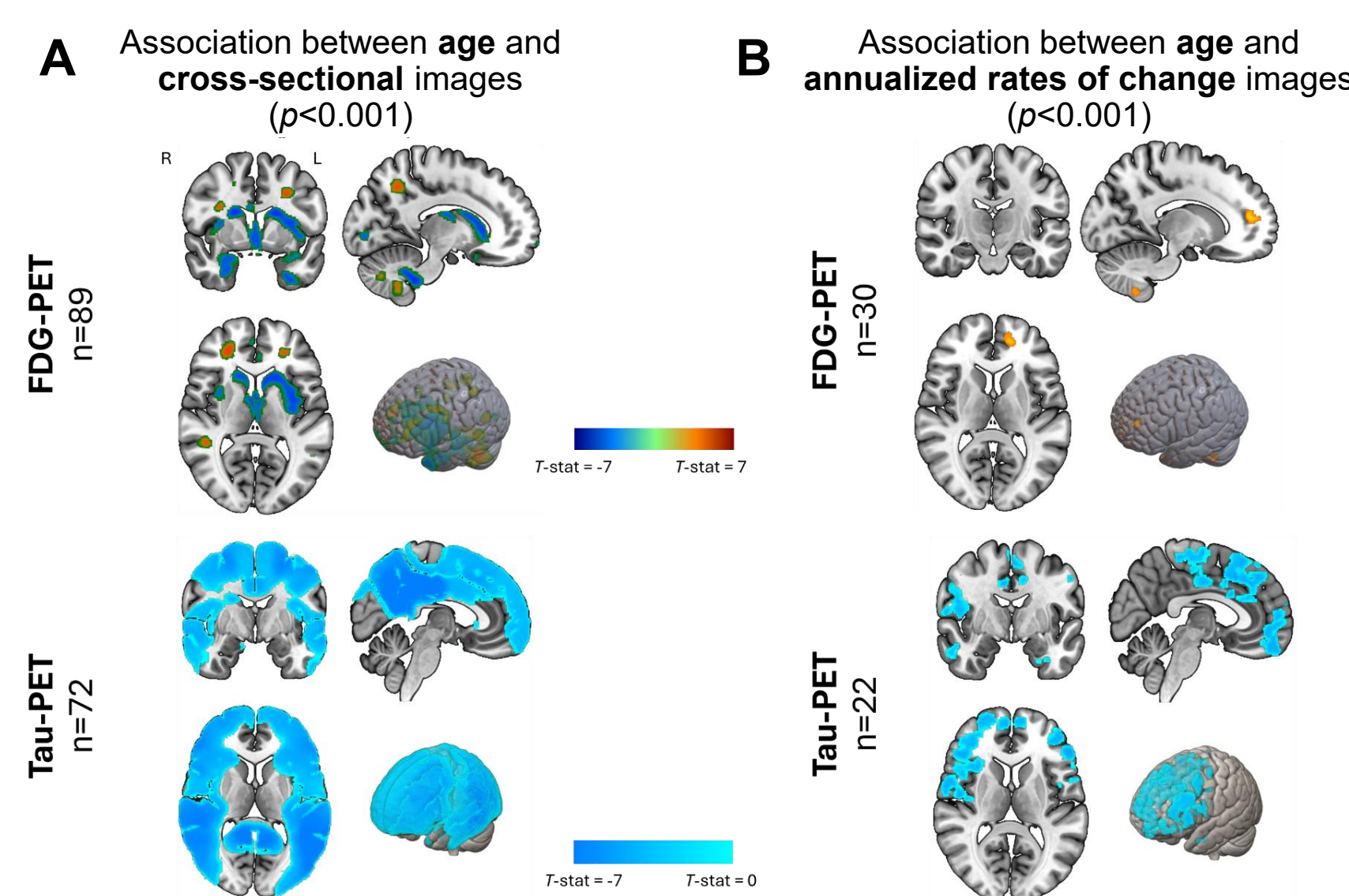
- 89 Aβ-positive PCA participants were recruited by the Neurodegenerative Research Group (NRG) and Alzheimer's Disease Research Center (ADRC) and underwent structural MRI and FDG-PET: 30 of them had ≥2 serial FDG-PET, 72 underwent tau-PET, and 22 had ≥2 tau-PET (**Table 1**).
- SUVr were calculated in each lobe and in a meta-ROI designed for atypical Alzheimer's disease.
- SUVr annualized rates of change and their association with age and baseline clinical scores were evaluated with voxel-based and linear mixed-effects models.

## Results



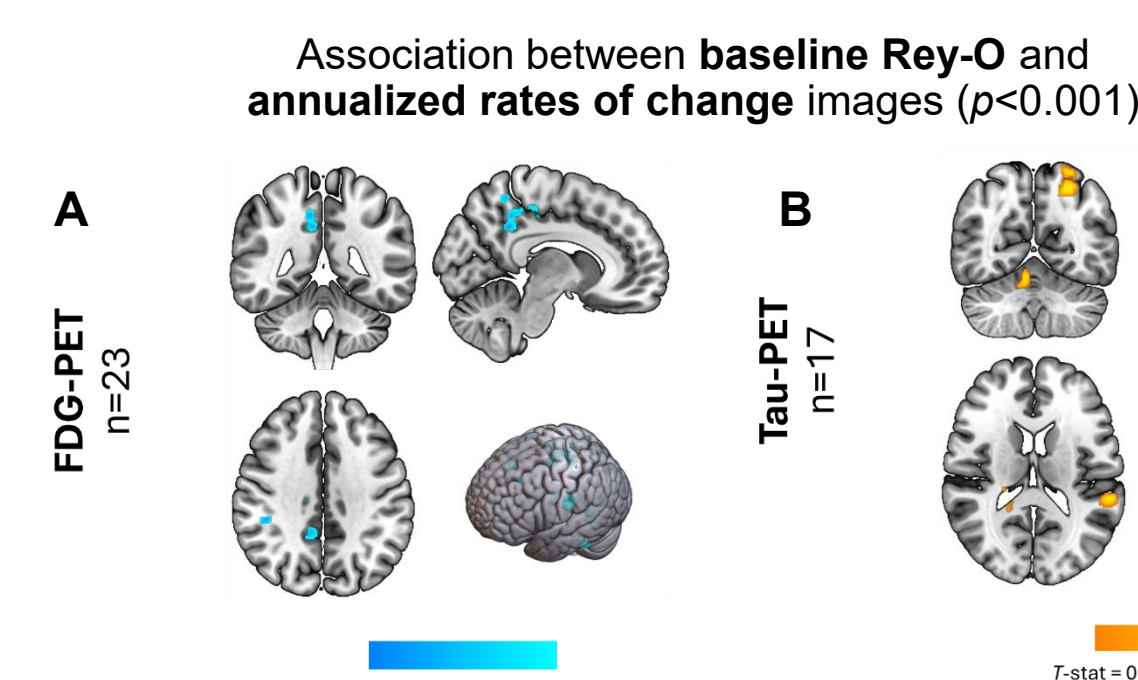
- At baseline, PCA participants had both higher tau-PET and lower FDG-PET uptake relative to controls in the bilateral occipitoparietal lobes, with maximum uptake in the middle and inferior occipital and angular gyri (**Fig. 1A**).
- Longitudinally, annualized rates of decline in metabolism from baseline scan to first follow-up scan were observed in posterior regions, particularly the left precuneus and middle temporal regions, while tau-PET uptake spread more frontally, with peak change in the left superior frontal gyrus (**Fig. 1B**).
- The overlap between declining hypometabolism and increasing tau was largely circumscribed to the temporal regions at the first follow-up (1.9 years), expanding to frontoparietal regions at the last follow-up (2.5 years) (**Fig. 1C**).

## Fig. 2 Age effect



- Age had a weak association with FDG-PET uptake in PCA:
  - Younger patients had lower FDG-PET SUVr in the bilateral precuneus and cerebellum, consistently with a more aggressive disease at younger age, and higher FDG-PET SUVr in the bilateral temporal lobe, including the hippocampus, and subcortically (**Fig. 2A**).
  - Older patients experienced a faster decline in metabolism in the left superior middle frontal gyrus (**Fig. 2B**).
- On the contrary, age had a strong and widespread negative association with tau-PET uptake in PCA:
  - Younger patients experienced more severe tau burden at baseline (**Fig. 2A**) and faster rates of tau accumulation over time in the frontal lobe (**Fig. 2B**).

## Fig. 3 Visuospatial abilities



Better Rey-Osterrieth (Rey-O) Complex Figure correlated with slower rates of decline in metabolism in the right precuneus (**Fig. 3A**) and faster rates of tau accumulation in left superior parietal and superior temporal region (**Fig. 3B**).

## Bivariate-outcome mixed-effects model

|             | Age and time                                         |                                                     |
|-------------|------------------------------------------------------|-----------------------------------------------------|
|             | Differential time effect between tau-PET and FDG-PET | Differential age effect between tau-PET and FDG-PET |
| Meta-ROI    | -0.27%, (-1.63%, 1.09%)                              | -1.59%, (-2.54%, -0.63%)                            |
| Frontal L   | 4.1%, (3.06%, 5.16%)                                 | -1.15%, (-1.71%, -0.57%)                            |
| Frontal R   | 4.17%, (3.14%, 5.22%)                                | -1.05%, (-1.69%, -0.41%)                            |
| Parietal L  | 1.4%, (0.04%, 2.75%)                                 | -1.49%, (-2.34%, -0.62%)                            |
| Parietal R  | -1.2%, (-2.8%, 0.44%)                                | -1.7%, (-2.69%, -0.7%)                              |
| Temporal L  | 2.45%, (1.36%, 3.54%)                                | -1.23%, (-1.97%, -0.49%)                            |
| Temporal R  | 0.39%, (-0.84%, 1.62%)                               | -1.42%, (-2.33%, -0.52%)                            |
| Occipital L | 0.85%, (-0.6%, 2.33%)                                | -1.1%, (-1.87%, -0.32%)                             |
| Occipital R | -1.35%, (-2.79%, 0.09%)                              | -1.04%, (-2.03%, -0.03%)                            |

- In PCA, **age** had a significantly more **negative** effect on **tau** than on hypometabolism across the brain.
- In PCA, **tau** accumulated **faster** than metabolism declined in the bilateral **frontal** lobe and **left temporal** lobe.

## Conclusion

In PCA, tau-PET and FDG-PET capture two aspects of the disease that follow similar but distinct patterns over time, with tau spreading from the posterior to the anterior parts of the brain faster than hypometabolism. Tau and hypometabolism rates of change related differently to age and visuospatial abilities in PCA.

## Acknowledgement

NIH R01-AG50603, P50 AG016574, U01 AG006786. AVID Radiopharmaceutical for supplying AV1451.

## References

- Chapleau et al. *The Lancet Neurology* 23.2 (2024): 168-177.
- Ossenkoppele et al. *Brain* 139.5 (2016): 1551-1567.
- Sintini et al. *Alzheimer's & Dementia* 19.10 (2023): 4396-4406.

| Table 1                  | Full cohort (n=89) | Sub-cohort with long. FDG-PET (n=30) | Sub-cohort with tau-PET (n=72) | Sub-cohort with long. tau-PET (n=22) |
|--------------------------|--------------------|--------------------------------------|--------------------------------|--------------------------------------|
| Age (years)              | 63 (59, 70)        | 62 (58, 68)                          | 63 (60, 70)                    | 61 (58, 69)                          |
| Male sex (n, %)          | 28, 31%            | 6, 20%                               | 20, 28%                        | 5, 23%                               |
| APOE ε4 carriers (n, %)  | 49, 37%            | 23, 29%                              | 49, 37%                        | 18, 33%                              |
| Disease duration (years) | 4 (2.6, 5.5)       | 3.2 (1.7, 4.5)                       | 4.2 (2.4, 5.5)                 | 3.2 (1.7, 4.4)                       |