DOI: 10.1002/alz70856_104871

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

BIOMARKERS

PODIUM PRESENTATION

NEUROIMAGING

Heterogeneous tau patterns in atypical AD are explained by connectivity-associated tau progression

Hannah de Bruin[1,2,3] | Colin Groot[1] | Alzheimer's Disease Neuroimaging Initiative (ADNI)[4] | Henryk Barthel[5] | Gérard N Bischof[6] | Ganna Blazhenets[7] | Ronald Boellaard[8] | Baayla D.C. Boon[9] | Matthias Brendel[10] | David M Cash[11] | William Coath[12] | Gregory S Day[13] | Brad C. Dickerson[14] | Elena Doering[15] | Alexander Drzezga[15] | Christopher H van Dyck[16] | Thilo van Eimeren[17] | Wiesje M. van der Flier[1] | Carolyn A Fredericks[18] | Tim D Fryer[19] | Elsmarieke van de Giessen[20] | Brian A. Gordon[21] | Jonathan Graff Radford[22] | Lea T. Grinberg[23] | Oskar Hansson[24] | Diana A Hobbs[25] | Günter U Höglinger[26] | Merle C Hönig[15] | David J. Irwin[27] | P Simon Jones[19] | Keith A. Josephs[28] | Yuta Katsumi[14] | Renaud La Joie[7] | Eddie B. Lee[29] | Johannes Levin[30] | Maura Malpetti[19] | Scott M McGinnis[31] | Adam P Mecca[32] | Rosaleena Mohanty[33] | Ilya M. Nasrallah[27] | John T O'Brien[34] | Ryan S O'Dell[32] | Carla Palleis[35] | Robert Perneczky[36] | Jeffrey S Phillips[37] | Deepti Putcha[38] | Gil D. Rabinovici[7] | Nesrine Rahmouni[39] | Pedro Rosa-Neto[39] | James B Rowe[40] | Michael Rullmann[41] | Osama Sabri[41] | Dorothee Saur[42] | Andreas Schildan[41] | Jonathan M Schott[43] | Matthias L Schroeter[44] | William W. Seeley[45] | Stijn Servaes[46] | Irene Sintini[47] | Ruben Smith[48] | Salvatore Spina[23] | Jenna Stevenson[39] | Erik Stomrud[48] | Olof Strandberg[48] | Joseph Therriault[39] | Pontus Tideman[48] | Alexandra Touroutoglou[14] | Anne E Trainer[49] | Denise Visser[50] | Fattin Wekselman[51] | Philip SJ Weston[52] | Jennifer L. Whitwell[47] | David A. Wolk[53] | Keir X X Yong[12] | Yolande A.L. Pijnenburg[54] | Nicolai Franzmeier[2] | Rik Ossenkoppele[1]

[1]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, Netherlands

[2]Institute for Stroke and Dementia Research, Klinikum der Ludwig-Maximilians Universität München, Munich, Germany

[3]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, Netherlands

[4]Laboratory of Neuro Imaging (LONI), University of Southern California, Los Angeles, CA, USA

[5]Leipzig University Medical Center, Leipzig, Germany

[6]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Nuclear Medicine, Cologne, Germany

[7]Memory and Aging Center, Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

[8]Amsterdam University Medical Center, Amsterdam, Netherlands

[9]Mayo Clinic, Jacksonville, FL, USA

[10]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU, Munich, Bavaria, Germany

[11]UK Dementia Research Institute at UCL, London, United Kingdom

[12]Dementia Research Centre, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom

[13]Mayo Clinic in Florida, Jacksonville, FL, USA

[14]Frontotemporal Disorders Unit and Massachusetts Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[15]Research Center Jülich, Institute for Neuroscience and Medicine II, Molecular Organization of the Brain, Jülich, Germany

[16]Alzheimer's Disease Research Unit, Yale School of Medicine, New Haven, CT, USA

[17]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany

[18]Yale School of Medicine, New Haven, CT, USA

[19]University of Cambridge, Cambridge, United Kingdom

[20]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, Netherlands

[21]Department of Radiology, Washington University School of Medicine, Saint Louis, MO, USA

[22]Mayo Clinic, Rochester, MN, USA

[23]Memory and Aging Center, UCSF Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA

[24]Clinical Memory Research Unit, Lund University, Malmö, Skåne, Sweden

[25]Department of Radiology, Washington University in St. Louis, St. Louis, MO, USA

[26]Munich Cluster for Systems Neurology (SyNergy), Munich, Bavaria, Germany

[27]University of Pennsylvania, Philadelphia, PA, USA

[28]Department of Neurology, Mayo Clinic, Rochester, MN, USA

[29]Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[30]Department of Neurology, LMU University Hospital, LMU Munich, Munich, Munich, Germany

[31]Frontotemporal Disorders Unit and Massachusetts Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[32]Alzheimer's Disease Research Unit, Yale University School of Medicine, Department of Psychiatry, New Haven, CT, USA

[33]Division of Clinical Geriatrics, Centre for Alzheimer Research, Karolinska Institutet, Stockholm, Sweden

[34]Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

[35]University Hospital, LMU Munich, Munich, Germany

[36]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

[37]Penn Frontotemporal Degeneration Center, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[38]Frontotemporal Disorders Unit, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[39]McGill University, Montreal, QC, Canada

[40]Department of Clinical Neurosciences and Cambridge University Hospitals NHS Trust and Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, United Kingdom

[41]Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany

[42]Department of Neurology, University of Leipzig, Leipzig, Germany

[43]University College London, London, England, United Kingdom

[44]Clinic for Cognitive Neurology, University of Leipzig, Leipzig, Germany

[45]Department of Pathology, University of California, San Francisco, San Francisco, CA, USA

[46]McGill Centre for Studies in Aging, Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

[47]Department of Radiology, Mayo Clinic, Rochester, MN, USA

[48]Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Faculty of Medicine, Lund University, Lund, Sweden

[49]Clinical Neurosciences Imaging Center, Yale University School of Medicine, New Haven, CT, USA

[50]Radiology & Nuclear Medicine, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, Netherlands

[51]Memory and Aging Center, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

[52]Dementia Research Centre, UCL Queen Square Institute of Neurology, London, United Kingdom

[53]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[54]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam UMC, location VUmc, Amsterdam, Netherlands

Correspondence
Hannah de Bruin, Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, Netherlands.
Email: h.debruin1@amsterdamumc.nl

Abstract

Background: The link between regional tau load and clinical manifestation of Alzheimer's disease (AD) highlights the importance of characterizing spatial tau distribution. In typical (memory-predominant) AD, the spatial progression of tau pathology mirrors the functional connections from temporal lobe epicenters. However, atypical (non-amnestic-predominant) AD variants with heterogeneous tau patterns provide a key opportunity to assess the universality of connectivity as a scaffold for tau progression.

Method: We included tau-PET data from 320 subjects with atypical AD, characterized by highly heterogeneous tau patterns (n = 139 posterior cortical atrophy/PCA-AD; n = 103 logopenic variant primary progressive aphasia/lvPPA-AD; n = 35 behavioural variant AD/bvAD; n = 43 corticobasal syndrome/CBS-AD) from 14 sites, with a subset of patients (n = 78) having longitudinal tau-PET data. As an independent sample, we further included regional post-mortem tau stainings from 93 atypical AD patients from two sites (n = 19 PCA-AD, n = 32 lvPPA-AD, n = 23 bvAD, n = 19 CBS-AD). Gaussian mixture modeling was used to harmonize different tau-PET tracers by transforming tau-PET standardized uptake value ratios to tau positivity probabilities (a uniform scale ranging from 0% to 100%). Using linear regression, we assessed whether 1) brain regions with stronger functional connectivity showed greater covariance in cross-sectional and longitudinal tau-PET and post-mortem tau pathology, and 2) functional connectivity of tau-PET epicenters and tau-PET accumulation epicenters was associated with cross-sectional and longitudinal tau patterns.

Result: Tau-PET epicenters—defined as the 5% brain regions with the highest tau load—aligned with clinical variants, e.g. a posterior pattern in PCA-AD ("visual AD") and left-hemispheric temporal predominance in lvPPA-AD ("language AD") (Figure 1). More strongly functionally connected regions showed correlated concurrent tau-PET levels, which was confirmed with post-mortem data (Figure 2). Moreover, the connectivity profile of tau-PET epicenters and accumulation epicenters corresponded to tau-PET progression patterns (Figure 3).

Conclusion: Our data are consistent with the hypothesis that tau propagation occurs along functional connections originating from local epicenters, across all AD clinical variants. Since tau proteinopathy is a key driver of neurodegeneration and cognitive decline, this finding may advance personalized medicine and participant-specific endpoints in clinical trials.

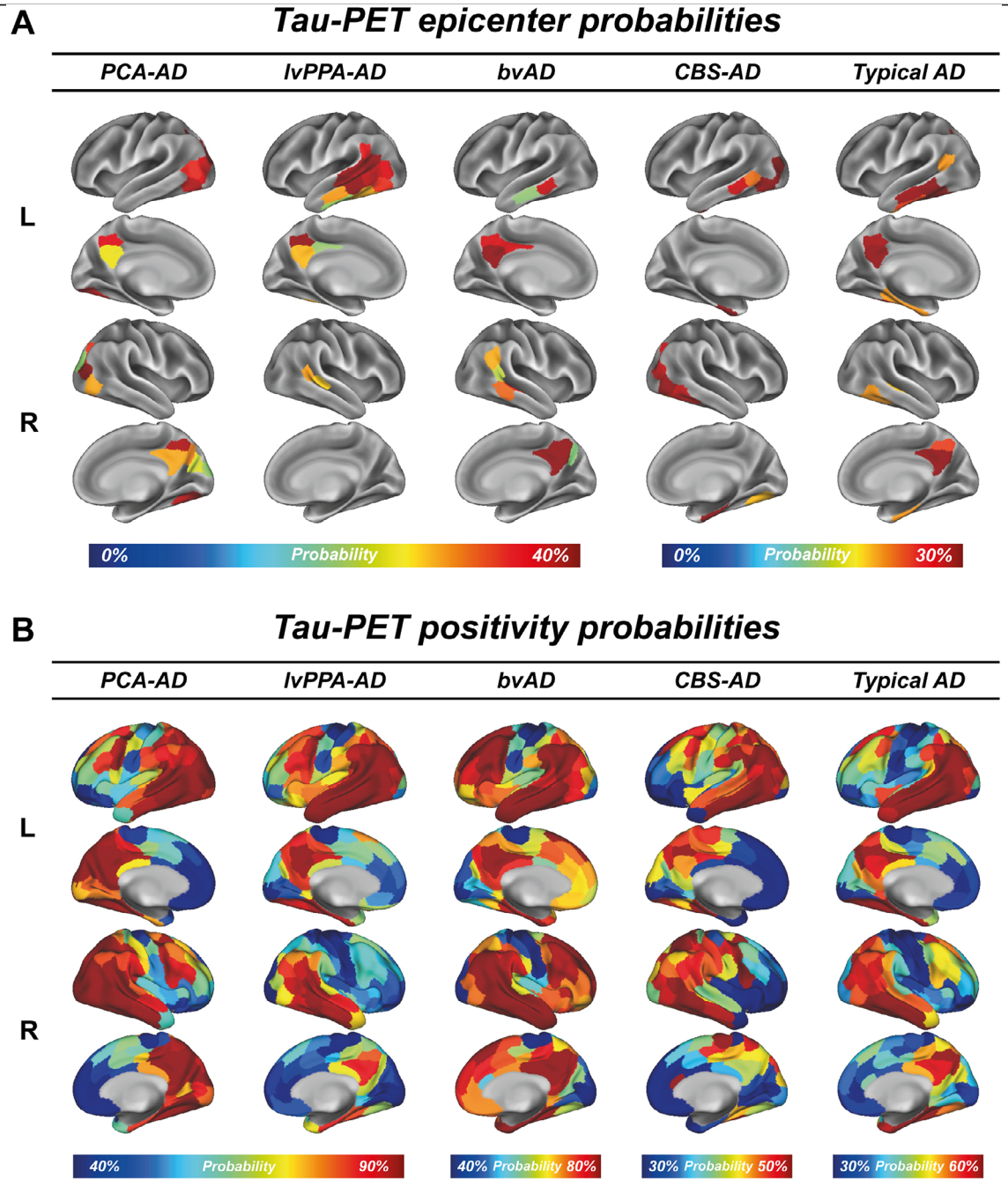

Figure 1: Tau-PET epicenters and positivity across AD variants. Tau epicenters (i.e., the regions with the assumed earliest and greatest tau burden) were defined at the subject level as the 5% regions with the highest tau-PET SUVRs. Group-average epicenter probabilities (**A**) indicate the likelihood of a region being part of the epicenter, with only epicenter probabilities ≥20% shown. Group-average tau-PET positivity probabilities (a uniform tau-PET scale ranging from 0% to 100%) across AD variants are shown in (**B**). AD = Alzheimer's disease; bvAD = behavioural variant Alzheimer's disease; CBS = corticobasal syndrome; L = left; lvPPA = logopenic variant primary progressive aphasia; PCA = posterior cortical atrophy; PET = positron emission tomography; R = right; SUVR = standardized uptake value ratio.

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

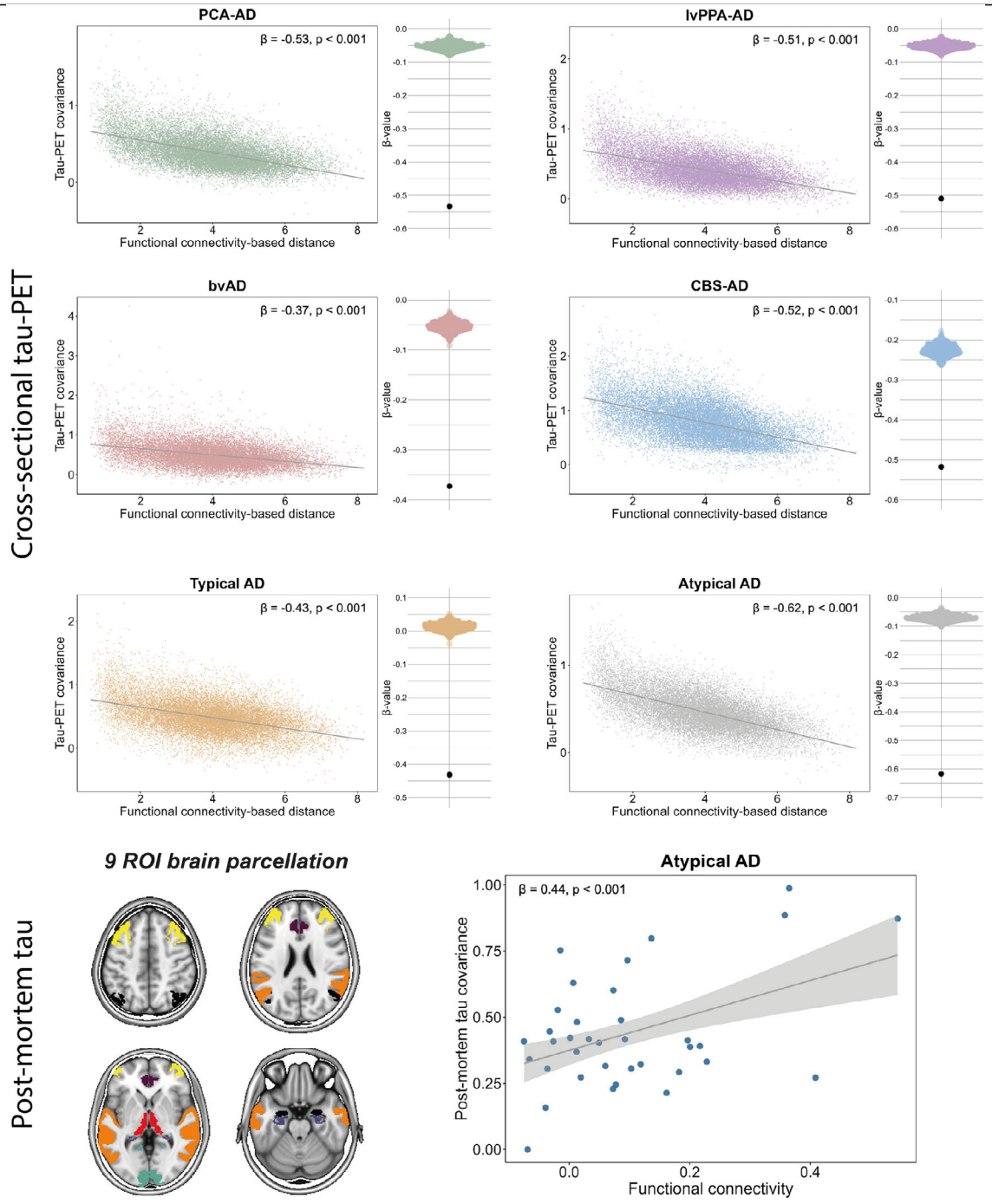

Figure 2: Association between functional connectivity and covariance in tau across variants of AD. Functional connectivity was derived from 42 CN Aβ-negative individuals from ADNI. Functional connectivity-based distance was used for tau-PET analyses, and functional connectivity for post-mortem analyses. Tau covariance was defined as average Fisher *z*-transformed partial correlations between tau positivity probabilities (tau-PET) or semi-quantitative tau pathology ratings (post-mortem tau) of all possible ROI pairs (200 Schaefer atlas for tau-PET, concatenated 9 ROI brain parcellation for post-mortem tau), while adjusting for age, sex, and site. Aβ = amyloid-β; AD = Alzheimer's disease; ADNI = Alzheimer's disease neuroimaging initiative; bvAD = behavioural variant Alzheimer's disease; CBS = corticobasal syndrome; CN = cognitively normal; lvPPA = logopenic variant primary progressive aphasia; PCA = posterior cortical atrophy; PET = positron emission tomography; ROI = region of interest.

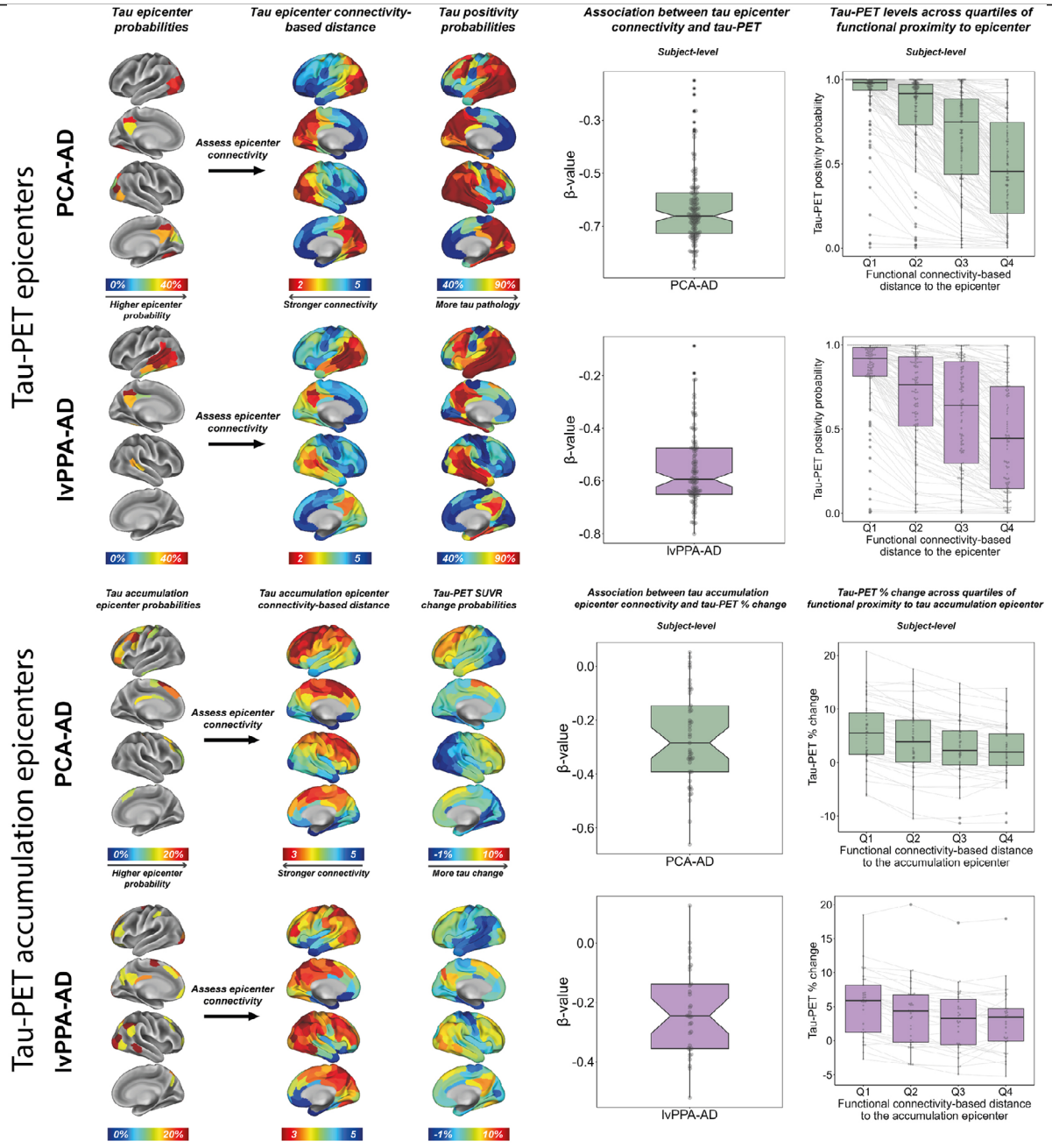

Figure 3: Association between tau (accumulation) epicenter connectivity and tau-PET (change) in PCA-AD and lvPPA-AD. Tau epicenters were defined as the top 5% of ROIs with the highest tau-PET SUVRs, and tau accumulation epicenters as the top 5% of ROIs with the highest rates of percentage change in tau-PET SUVR, both at the subject level. Tau (accumulation) epicenter connectivity was determined by taking the functional connectivity-based distance of each non-(accumulation-)epicenter ROI (n=190) to the (accumulation) epicenter (n=10). For each individual, linear regression was used to assess the association between functional connectivity-based distance to the tau (accumulation) epicenter and tau-PET SUVR/annual percentage change. Subject-level β-values are visualized per AD variant in the notched boxplots. Additionally, all non-(accumulation-)epicenter regions were grouped into quartiles based on their functional proximity to the (accumulation) epicenter (quartile 1 = close, quartile 4 = distant), and tau positivity probabilities/tau-PET SUVR percentage change rates across quartiles were significantly different by paired Wilcoxon signed-rank tests. AD = Alzheimer's disease; lvPPA = logopenic variant primary progressive aphasia; PCA = posterior cortical atrophy; PET = positron emission tomography; Q = quartile; ROI = region of interest; SUVR = standardized uptake value ratio.