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Biomarker Associations with Cognition: Results from the Autonomy Phase 2 Clinical Trial

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Disclosures

- **Gil D. Rabinovici** receives research support from NIH, Alzheimer's Association, American College of Radiology, Rainwater Charitable Foundation, Eli Lilly, GE Healthcare, Life Molecular Imaging, Genentech. Paid consultant for Bristol Myers Squibb, Danaher, Eli Lilly, Genentech, Johnson & Johnson, Merck, Novo Nordisk, Roche.

- **Reisa Sperling** has served as a consultant or on scientific advisory boards for AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Immunobrain, Janssen, Novo Nordisk, Oligomerix, Prothena, Roche, Ionis, Therini and Vaxxinity over the past 3 years, all under the NIH guidelines of $5k. She also has institutional consulting contracts with Eli Lilly and Roche. She has received research funding from Eisai and Eli Lilly for public-private partnership clinical trials and receives research grant funding from the National Institute on Aging/National Institutes of Health, GHR Foundation, and the Alzheimer's Association. Her spouse, K. Johnson, reports consulting fees from Bristol-Myers Squibb, Janssen, Merck, Novartis and Voyager Therapeutics over the past 3 years.

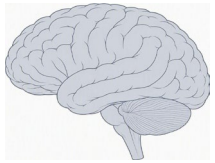
- **Henrik Zetterberg** has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alamar, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, Johnson & Johnson, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, New Amsterdam, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work).

- **Ziad S. Saad, Xingjian Zhang, Ritobrato Datta, Maggie Fedgchin, Tricia Thornton-Wells, Jaren Landen, Janice Wong, Gayle Wittenberg, Arthur Simen, and Fiona Elwood** are or were employees of Johnson & Johnson and may hold stock or stock options in Johnson & Johnson.

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Introduction: AUTONOMY findings raise questions about the relationship between Tau pathology and clinical decline

WHAT AUTONOMY SHOWED[1]



Tau PET

Slower accumulation of neurofibrillary tangles in some brain regions



Clinical outcome

No demonstrated slowing of clinical decline

UNDERSTANDING THE RELATIONSHIP



Tau pathology ---→  **Neurodegeneration** ---→  **Cognition**



Across brain regions



Over time

How do the timing and spatial distribution of Tau pathology relate to neurodegeneration and cognitive decline?



Objective: Evaluate biomarker correlations between tau pathology, neurodegeneration and cognition, cross-sectionally and longitudinally over 2 years.

1. Cohen et al. Results from the Phase 2b AUTONOMY Trial of Anti-p-tau Monoclonal Antibody Posdinemab for Early Alzheimer's Disease. AD/PD 2026, March 17-21 in Copenhagen, Denmark Alzheimer's disease; AD, Alzheimer's disease; PET, positron emission tomography.NFT, neurofibrillary tangles.

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Methods: Study population and assessments

Study population: 464 randomized participants from the Auτonomy trial



Tau pathology

^{18}F-MK-6240 Tau PET SUVR (cerebellar gray reference), assessed over FreeSurfer-defined cortical regions and voxel-wise analyses



Cognition

RBANS total score and five domain indices: immediate memory, delayed memory, language, attention and visuospatial ability



Neurodegeneration and fluid biomarkers

- MRI-derived regional gray-matter volumes were adjusted for intracranial volume and converted to region-specific z-scores using a reference dataset of 201 amyloid-negative, cognitively unimpaired ADNI participants.
- Plasma biomarkers: eMTBR243 (C2N), pTau217 (QTX), brain-derived pTau181 (NU) and brain-derived pTau217 (NU)

Analysis timeframe: Cross-sectional snapshots and longitudinal tracking over approximately 2 years

ADNI, Alzheimer's Disease Neuroimaging Initiative; ^{18}F-MK-6240, fluorine-18 labelled tau PET tracer; MRI, magnetic resonance imaging; NU, nucleic acid-linked immuno-sandwich assay (NULISA) ; PET, positron emission tomography; QTX, Quanterix; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SUVR, standardised uptake value ratio.
Only subjects with baseline MRI, baseline tau PET and RBANS at baseline, week 36 and week 88 are included in the modelling.

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Methods: Modeling cognition using regional imaging measures

Baseline imaging predictors (X)

Regional gray matter volume z-scores OR **Regional Tau PET SUVR**

68 FreeSurfer cortical ROIs
lh.bankssts
lh.caudalanteriorcinagulate
lh.caudalmiddlefrontal
…

Cognitive outcomes (Y)

RBANS total score and five domain indices

Immediate memory
Visuospatial
Language
Attention
Delayed memory

Baseline, Week 36 and Week 88

Model fitting and evaluation

- Generalized linear model with elastic net regularization (α = 0.3)

$$Y = \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_{68} X_{68}$$

- Elastic net regularization with combined L1 and L2 regularization.

$$\lambda(0.3 * \mathrm{L1} + 0.7 * \mathrm{L2})$$

λ selected to minimize cross-validation error

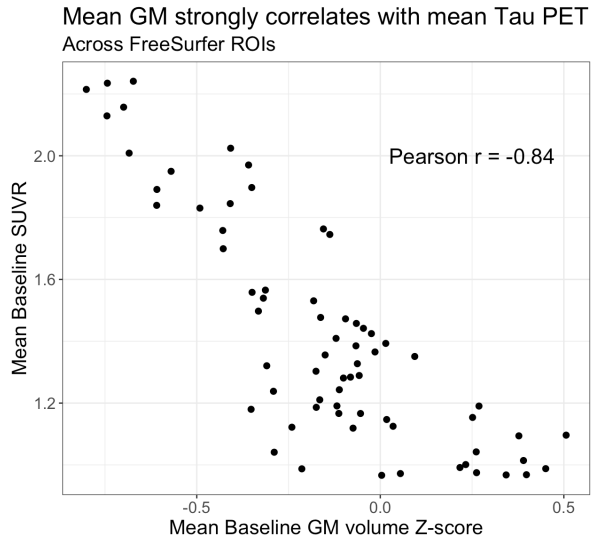
- 5-fold cross-validation, repeated 10 times

PET, positron emission tomography; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SUVR, standardised uptake value ratio.

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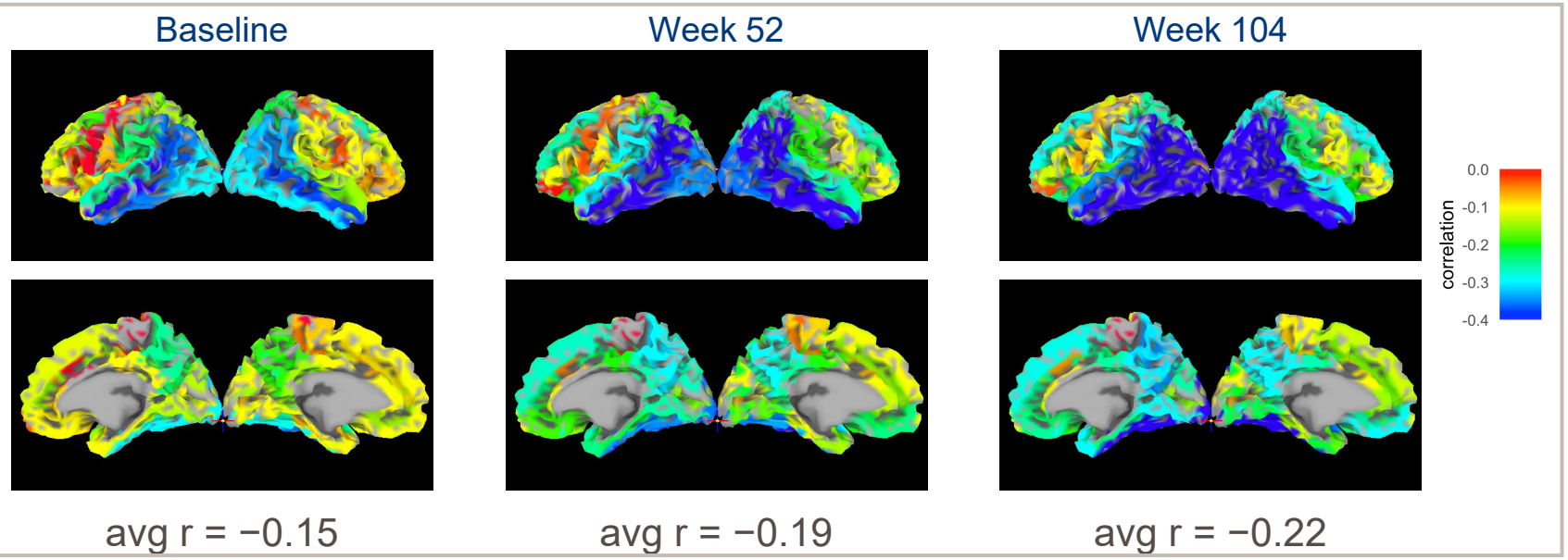
Results: Baseline levels of tau show stronger correlations with later than concurrent MRI measures of neurodegeneration

Across-region association at baseline



Within-region associations over time

Baseline Tau PET versus gray-matter volume at each timepoint



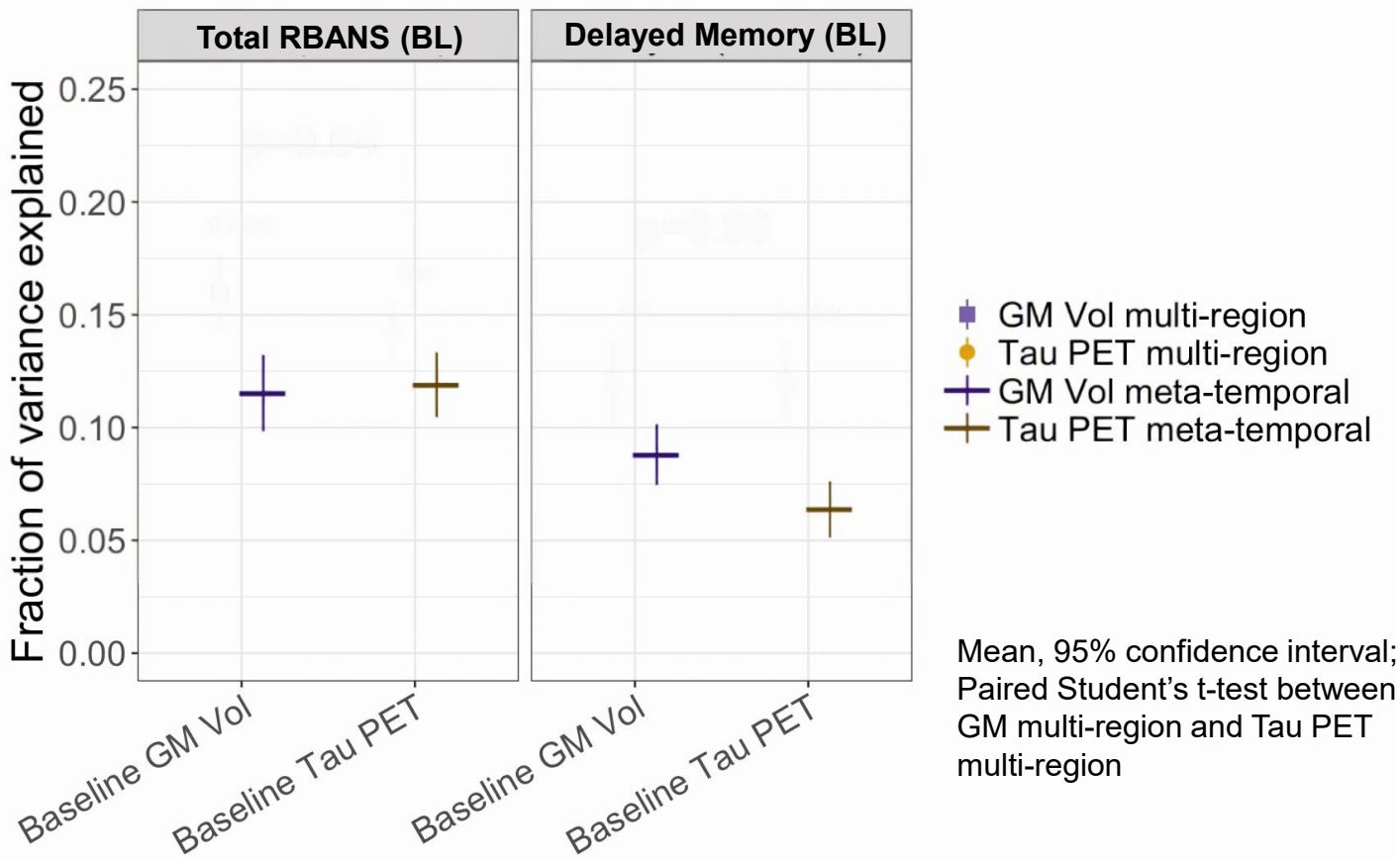
Across FreeSurfer cortical regions, average baseline Tau PET SUVR and gray-matter volume z-scores were strongly inversely correlated (r = −0.84)

- At baseline, negative within-region correlations were observed in 43 of 68 regions, with an average correlation coefficient (r) of −0.15 across all regions
- When substituting baseline neurodegeneration with Week 52 and Week 104 neurodegeneration, correlation with baseline Tau PET SUVR monotonically increased to -0.22 ($p<0.01$)

BL, baseline, ND, neurodegeneration

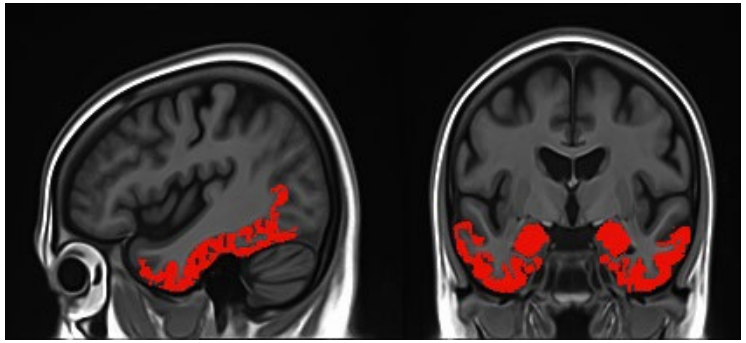
Results: Integrating measures of multiple brain regions better predicts cognitive domain performance compared to single region

Comparison of multi-regional models with meta-temporal region

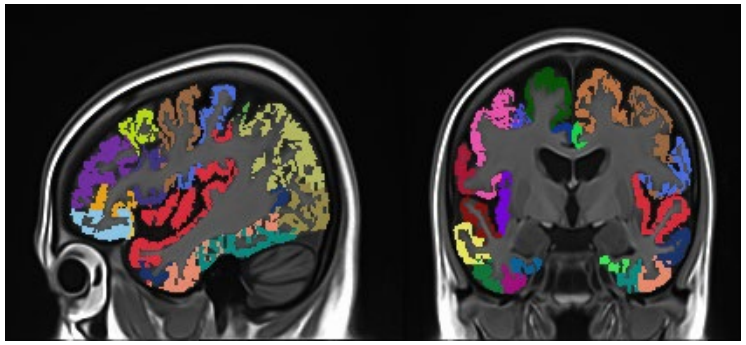


Mean, 95% confidence interval; Paired Student's t-test between GM multi-region and Tau PET multi-region

Meta-temporal region



FreeSurfer cortical regions



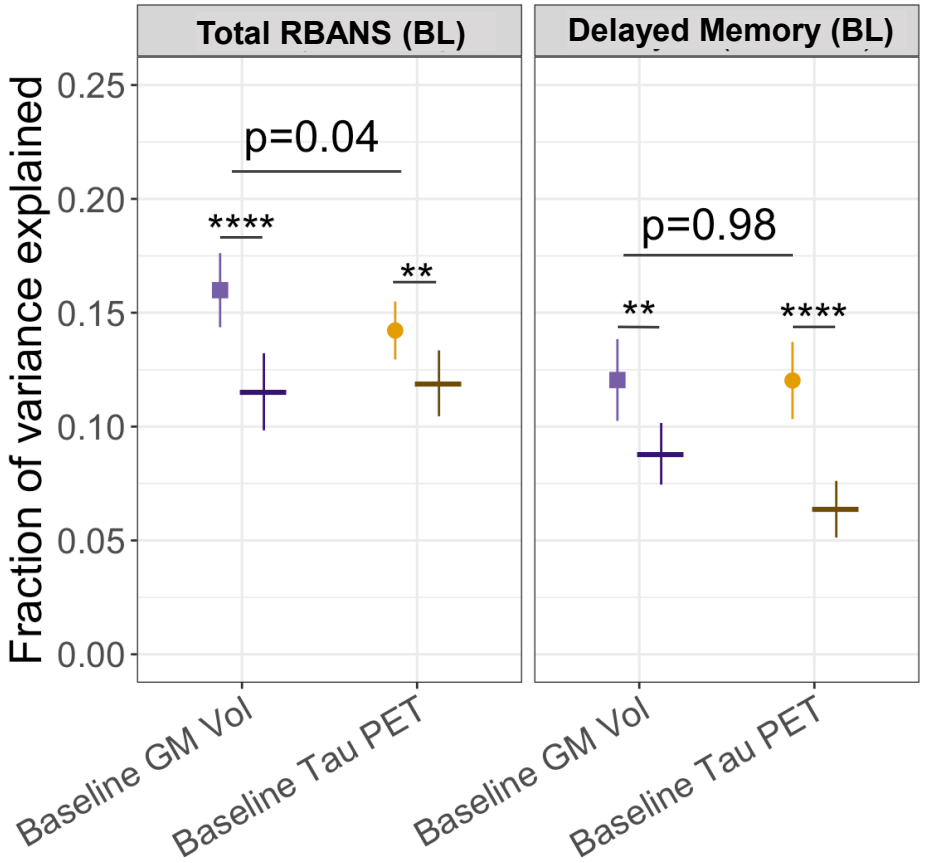
Multi-regional models better reflect cognitive performance than single-region models

Significance levels: P < 0.05, *; P < 0.01, **; P < 0.001, ***; P < 0.0001, ****; n.s. not significant.

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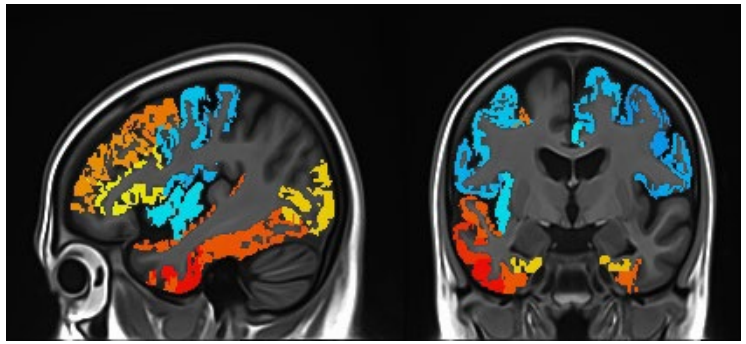


GM Vol multi-region
Tau PET multi-region
GM Vol meta-temporal
Tau PET meta-temporal

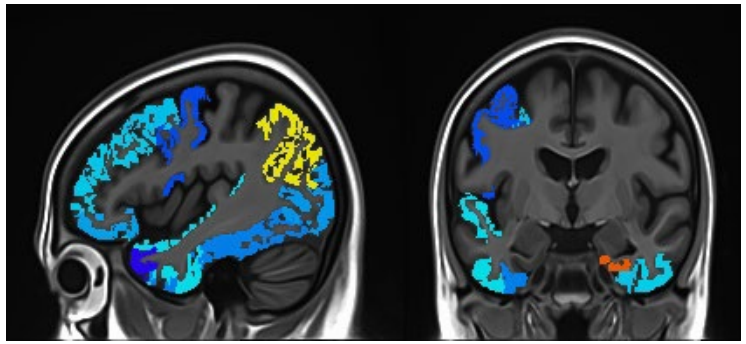
Mean, 95% confidence interval; Paired Student's t-test between GM multi-region and Tau PET multi-region

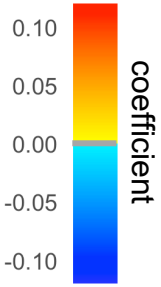
RBANS Total GLM coefficient maps

GM Vol Multi-region model



Tau PET Multi-region model





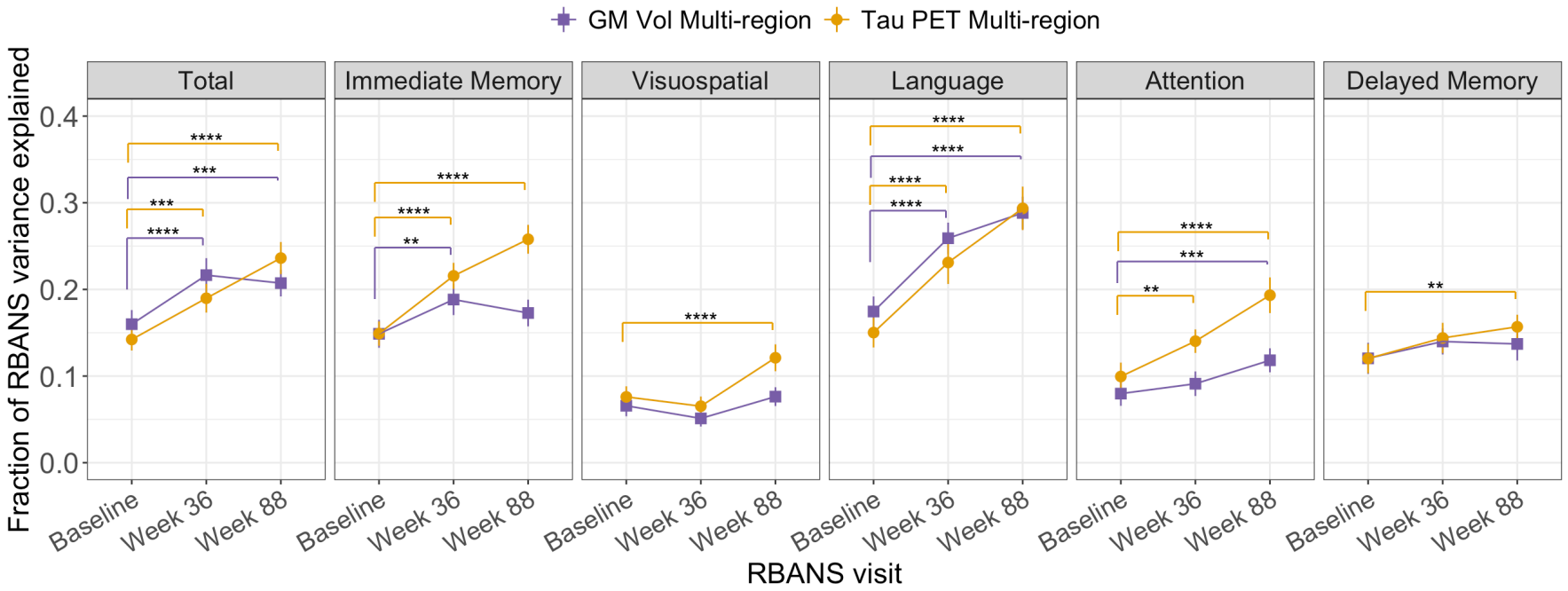
Multi-regional models better reflect cognitive performance than single-region models

Significance levels: P < 0.05, *; P < 0.01, **; P < 0.001, ***; P < 0.0001, ****; n.s. not significant.

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Results: Baseline tau PET shows stronger correlation with cognitive performance at later timepoints

Baseline imaging measures in relation to cognition at baseline, week 36 and week 88

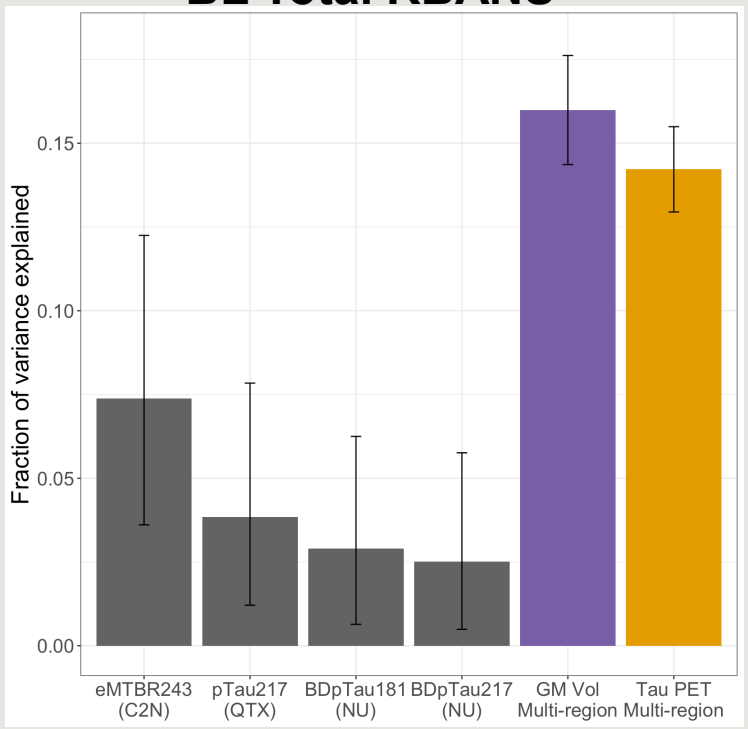


- Baseline Tau PET SUVR showed stronger correlations with cognition at later timepoints, while GM correlations were more variable
- Correlations with delayed memory were flat across time, possibly due to floor effects
- Tau PET often outperformed GM volume in predicting cognition, especially in later timepoints

Mean, 95% confidence interval; **Two-way ANOVA followed by Bonferroni-adjusted paired t-tests for between-group (GM multi-region vs Tau PET multi-region, shown in figure) and unpaired t-test for within-group (BL vs Week 36/Week 88 shown in table).**
Significance levels: P < 0.05, *; P < 0.01, **; P < 0.001, ***; P < 0.0001, ****; n.s. not significant.

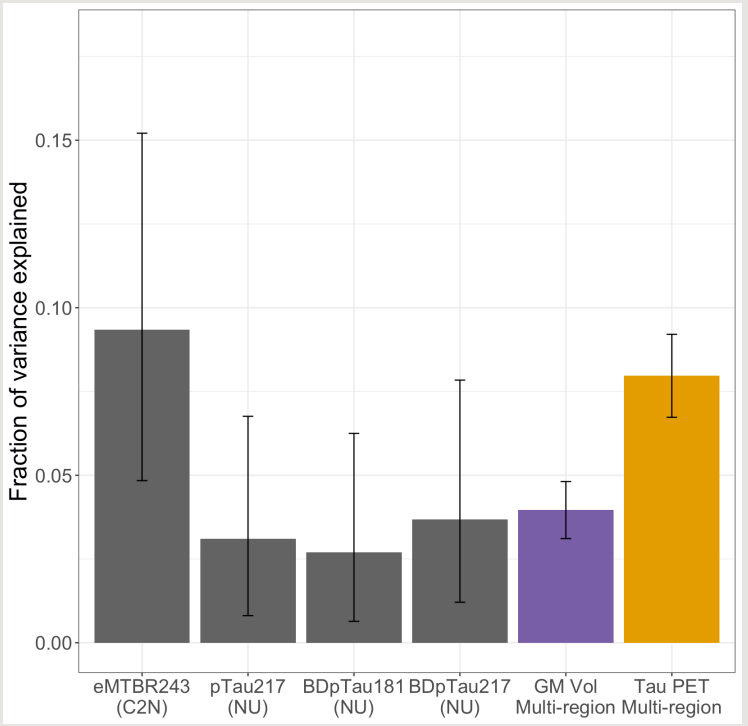
Results: Selected plasma Tau biomarkers show modest correlations with cognition

BL Biomarker Correlations with BL Total RBANS



eMTBR243 (R^2=0.07), pTau217 (R^2=0.04),
BD pTau181(R^2=0.03), BD pTau217(R^2=0.03),
GM Vol (R^2=0.16), Tau PET (R^2=0.14)

BL Biomarker Correlations with Week 88 change in Total RBANS



eMTBR243 (R^2=0.09), pTau217 (R^2=0.03),
BD pTau181 (R^2=0.03), BD pTau217 (R^2=0.04),
GM Vol (R^2=0.04), Tau PET (R^2=0.08)

* A total of 322 plasma biomarkers were examined, only those explaining more than 3% of the variance are shown (unadjusted p<0.001)

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Biomarker interpretation and clinical context



Timing

- Baseline Tau pathology showed stronger relationships with neurodegeneration and cognition assessed at later time points.

Spatial information

- Models incorporating multiple brain regions explained more variance in cognitive decline than single-region summary measures.

Comparison across biomarkers

- Baseline Tau PET explained more variance in future than concurrent cognition across RBANS domains.
- Baseline Tau PET generally outperformed baseline GM Vol in predicting cognition at later timepoints.
- Selected fluid tau biomarkers showed modest baseline correlations with cognition. However, eMTBR243 is as prognostic as multi-regional tau PET models and more so than GM vol models.

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When target engagement is not enough: Implications

- Posdinemab had a strong impact on soluble tau, but this was not a predictor of brain-wide effects on tangles or clinical efficacy
- Soluble CSF tau biomarkers may not be a good surrogate endpoint for aggregated tau as measured by tau PET
- This work raises questions about why reduction of the tau epitopes is not sufficient to affect tau seeding/spreading
- Brain regions with the highest tau load are likely also the areas of earliest tau pathology and the ability of extracellular tau antibodies to impact these regions warrants further investigation.

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