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Comparison of Structural and Metabolic Biomarkers of Neurodegeneration for Brain Age Prediction

The Link Between Brain Age and Alzheimer's Disease Development Using Different Modalities

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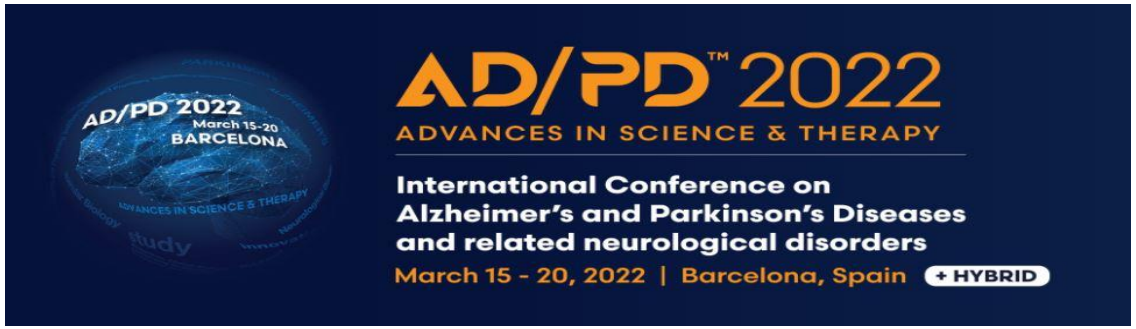
Jan 24, 2022 | virtual | Elena Doering, MSc.

AD/PD™ 2022
ADVANCES IN SCIENCE & THERAPY

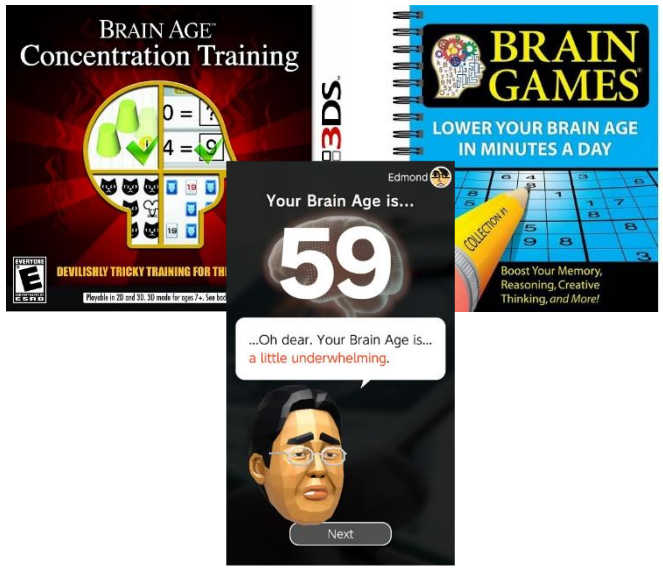
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders

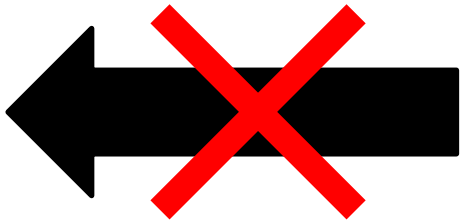
March 15 - 20, 2022 | Barcelona, Spain + HYBRID

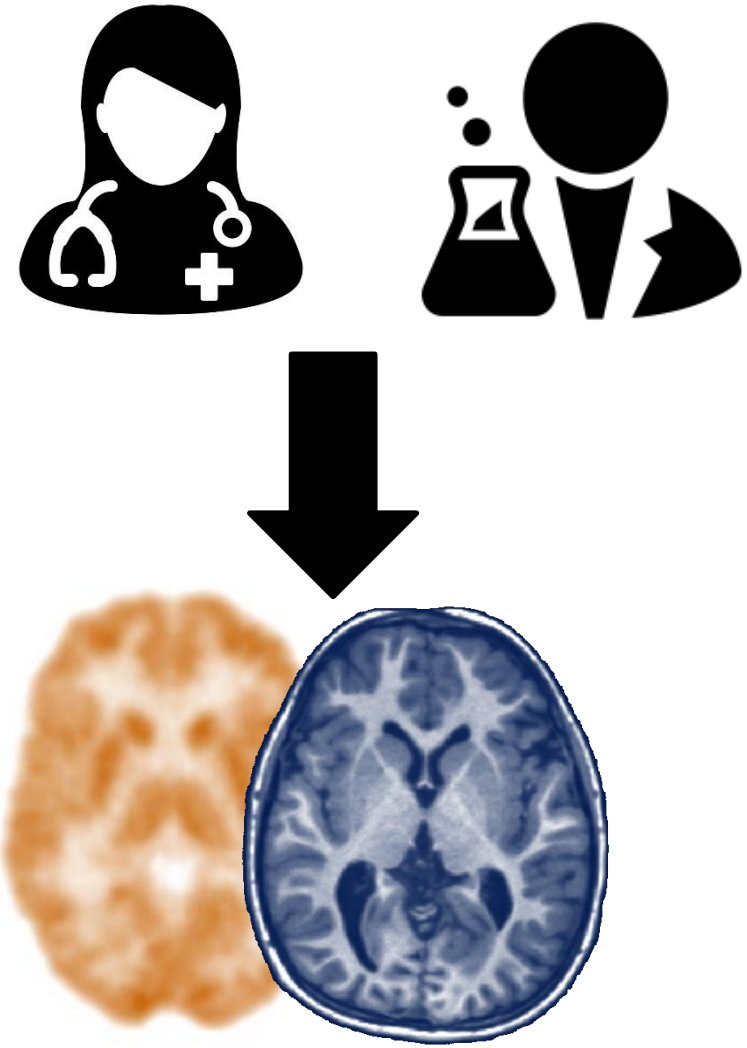


Nothing to disclose.

A biological definition of brain age







Brain-predicted age & BPAD

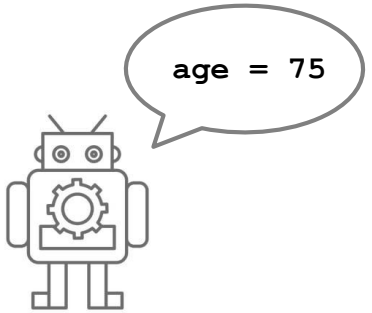
Brain-predicted age = machine learning algorithms learn to **predict chronological age** (CA) **from brain scans**

BPAD

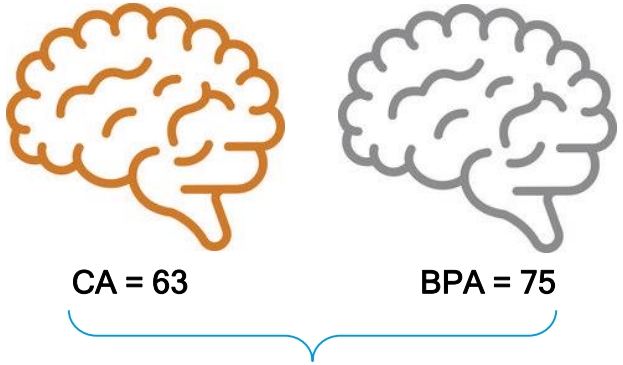
= Difference between chronological age and brain-predicted age

- deviation from "normal" aging in a single number.

Chronological Age = 63



Brain age Prediction



Brain-Predicted Age Difference = 12 years

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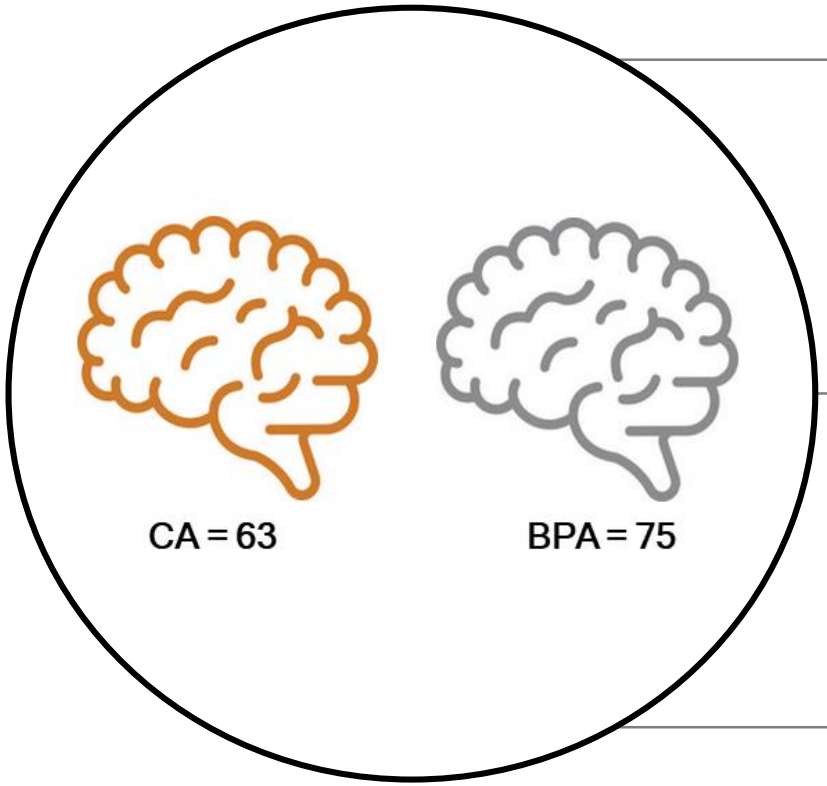
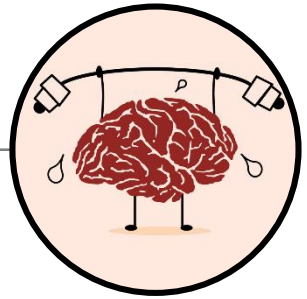
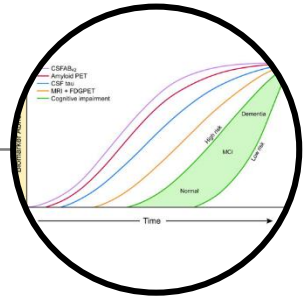
Brain age can have various clinical functions

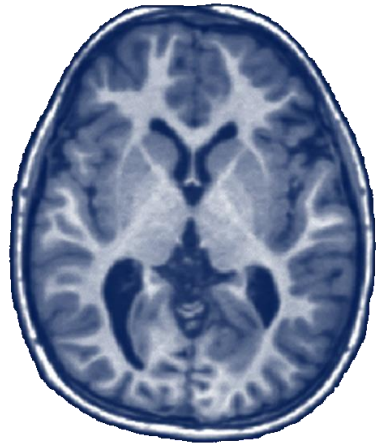


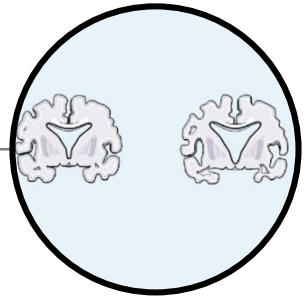


assess general brain health



detect disorders before symptom onset





support differential diagnosis

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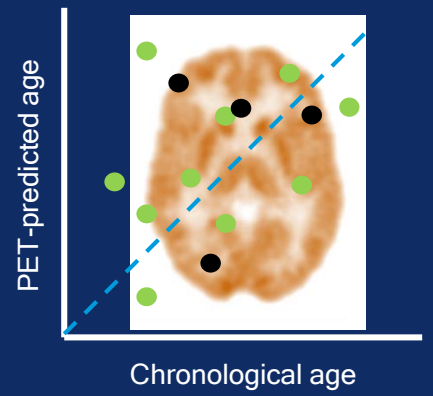
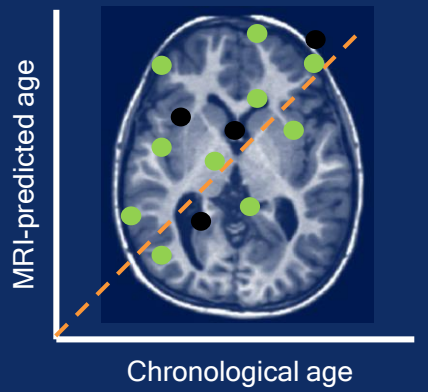
Research aims

1. Compare **precision of brain-predicted age using MRI and FDG-PET** in cognitively normal individuals (CN).





2. Compare association of MRI and FDG-PET-BPAD with **cognitive function, neuropathology and cognitive decline** in CN and individuals with mild cognitive impairment (MCI).

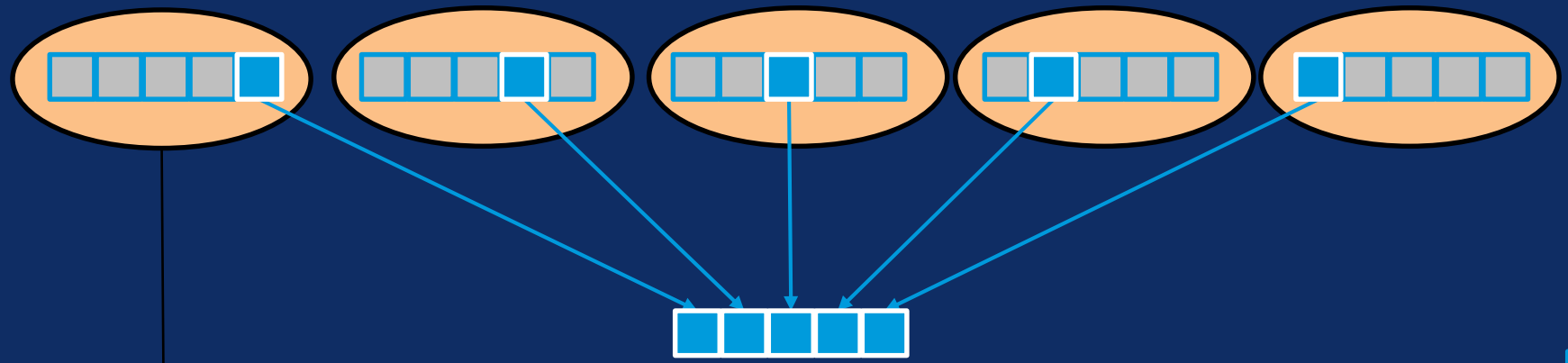
Compare precision of brain-predicted age in CN

- 379 FDG-PET and MRI scans from of CN from ADNI

frontal lobe left: 1.03 frontal lobe right: 1.25 … hippocampus left: 0.95 hippocampus right: 0.98

70 % training data (n = 256) → Trained model → 30% testing data (n = 123) (ADNI) + External validation sample (n = 59) (OASIS) + MCI sample (n = 621) (ADNI)

Five Models



One test prediction for each CN subject

Training Sample

Test Sample

Model 1: One test prediction for each subject in CN_validation and MCI sample

Participants

Table 1. Overview of samples

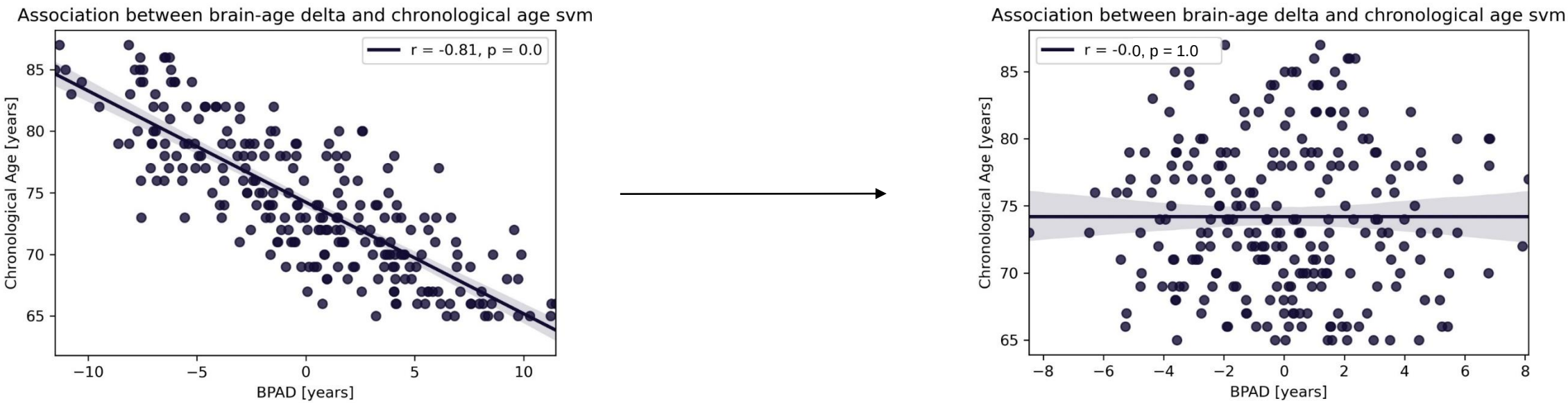
	CN	CN_validation	MCI
	ADNI	OASIS	ADNI
***n* total**	**379**	**59**	**621**
Age [avg. years]	74	72 (PET)/70 (MRI)	73
Sex (F/M)	196/183	35/24	264/355
MMSE [avg. score]	29	29	28
Education [avg. years]	16	16	16

Bias Correction

$$\boldsymbol{Predicted\ age_{corrected\ with\ CA} = Predicted\ age_{uncorrected} - (\alpha * CA + \beta)}$$

α = slope; β = intercept from linear model of CA X BPAD

PET



Precision in brain age prediction is comparable across FDG and MRI

Table 2. Precision of predicting chronological age from FDG-PET and MRI scans. For CN_validation and MCI, results of the first model and metrics over all five models are shown.

	CN (ADNI)		CN_validation (OASIS)		MCI (ADNI)	
	FDG	MRI	FDG	MRI	FDG	MRI
***n* total**	345⁺	345⁺	59⁺	59⁺	621	621
MAE	1.99	1.89	1.83	2.42	1.94	2.66
Mean (SD) over 5 models	-	-	2.04 (0.30)	2.45 (0.19)	2.17 (0.44)	2.57 (0.11)
Mean difference	-0.10	-0.05	-0.80	-0.80	0.78	1.15
Mean (SD) over 5 models	-	-	-0.66 (0.41)	-0.92 (0.16)	0.67 (0.21)	1.42 (0.16)

⁺After outlier exclusion using CN train set (IQR > 6)

Association of BPAD with Cognitive Function, Neuropathology, and Cognitive Decline

- Cognitive Function (CF): ADNI-MEM, ADNI-EF
- Neuropathology (NP):
  CSF Aβ, PET amyloid (global AV45),
  CSF Tau, CSF Ptau, PET tau (AV1451 meta-ROI)

Pearson/Spearman Correlations
between BPAD and CF/NP

Partial correlations
between BPAD and CF/NP controlling for age and sex

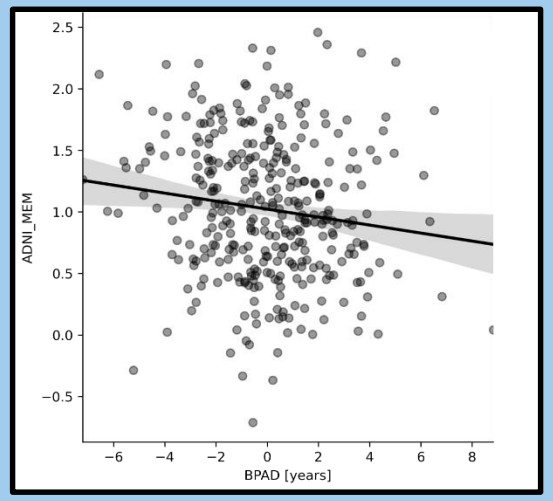
- Cognitive Decline (CD): Diagnosis after 24 months

Logistic Regression
to predict CD from BPAD, age and sex

BPAD in CN

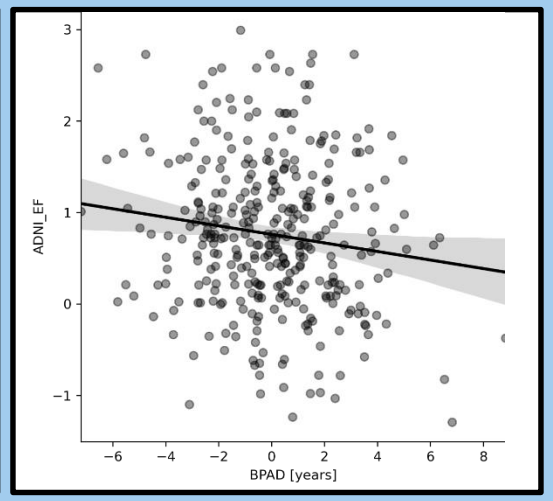
Higher MRI-BPAD is associated with worse cognitive performance in CN

Memory

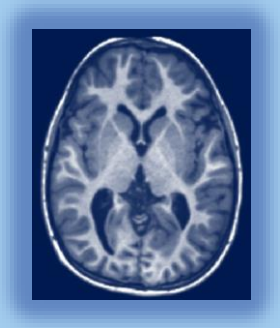


n = 345
r = -0.138**
Not correlated after correction for age and sex

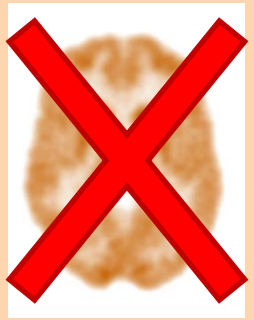
Executive Function



n = 345
r = -0.137**
$r_{partial}$ = -0.150**

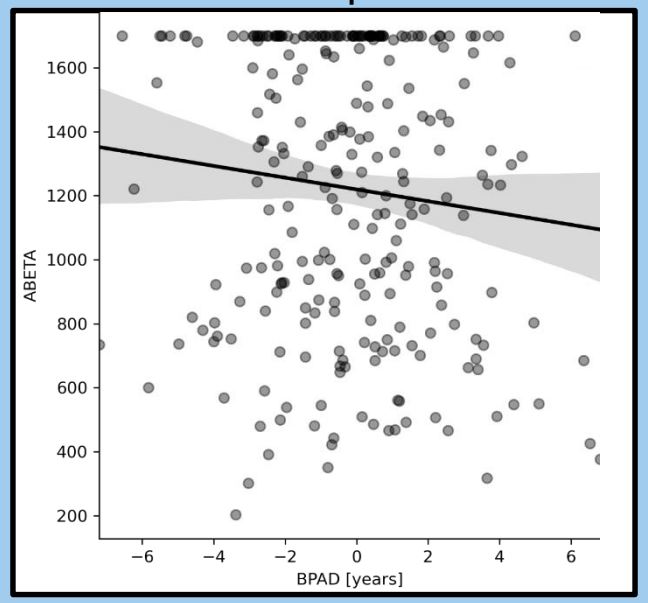


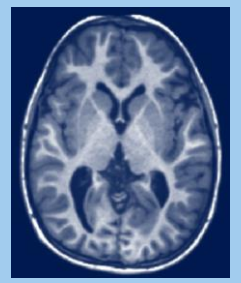
* Significant at p < 0.05, ** significant after Bonferroni correction



Higher BPAD (esp. FDG) is associated with lower CSF Aβ levels

CSF Aβ

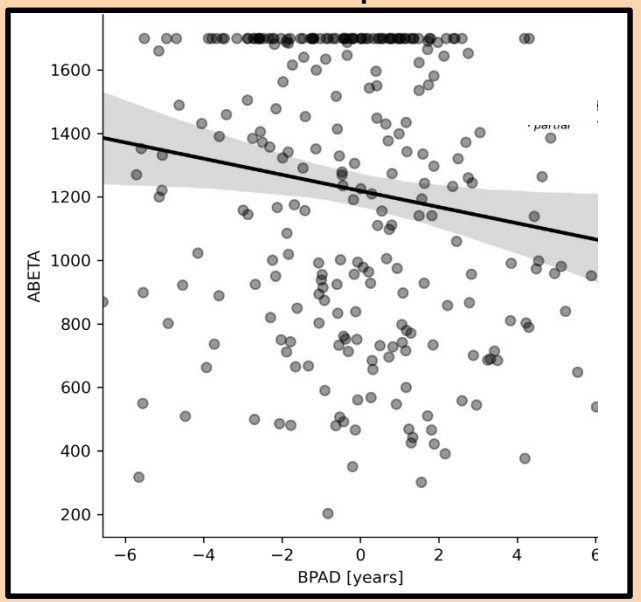




n = 266
Not significant without correction for age and sex
$\rho_{partial}$ = 0.126*

* Significant at p < 0.05, ** significant after Bonferroni correction

CSF Aβ

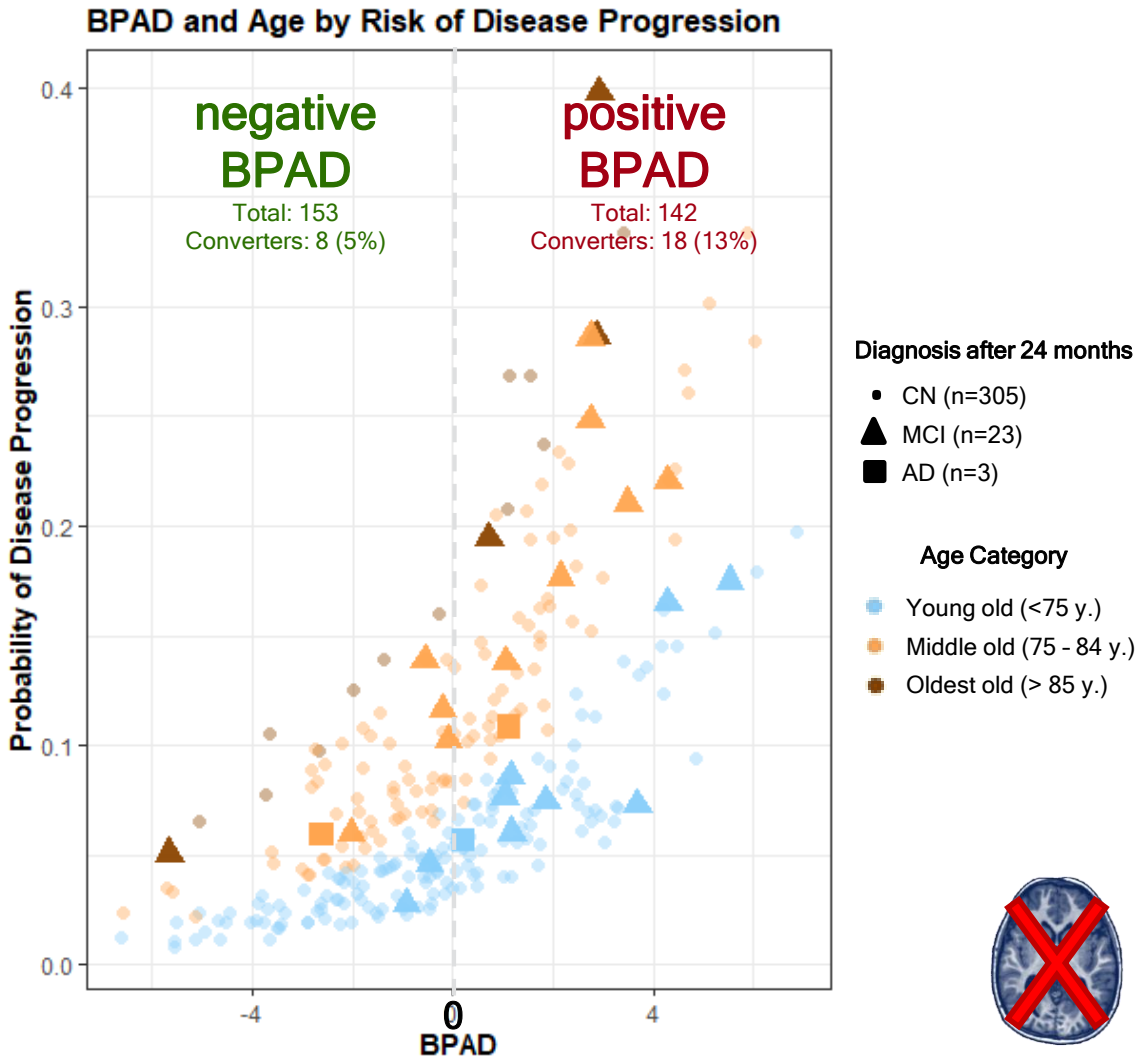


n = 266
ρ = -0.157*
$\rho_{partial}$ = 0.160**

FDG-BPAD predicts conversion to MCI/Alzheimer's disease in CN

27% increased odds to develop (mild) cognitive impairment within two years **per one year BPAD** (95%CI [7%, 51%])

age: OR = 10% (95%CI [3%, 19%])**, sex not significant in logistic regression

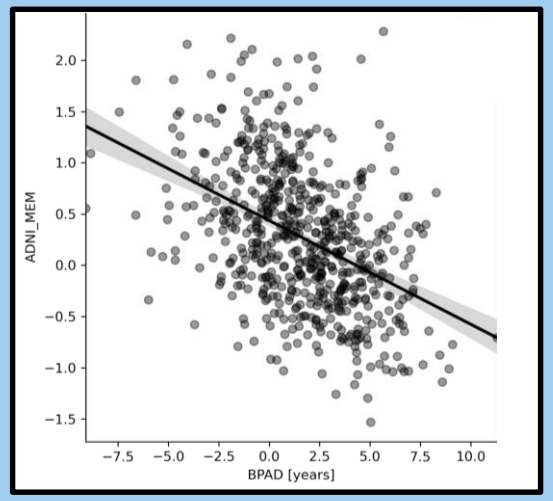


* Significant at p < 0.05, ** p < 0.01, *** p < 0.001

BPAD in MCI

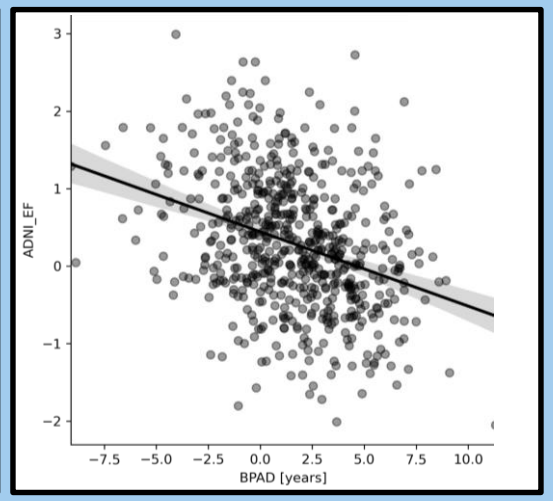
Higher BPAD (esp. MRI) is associated with worse cognitive performance in MCI

Memory

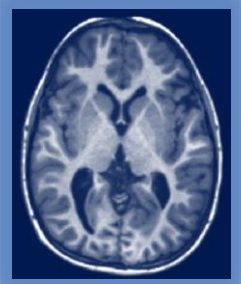


n = 618
ρ = -0.447**
$\rho_{partial}$ = -0.397**

Executive Function



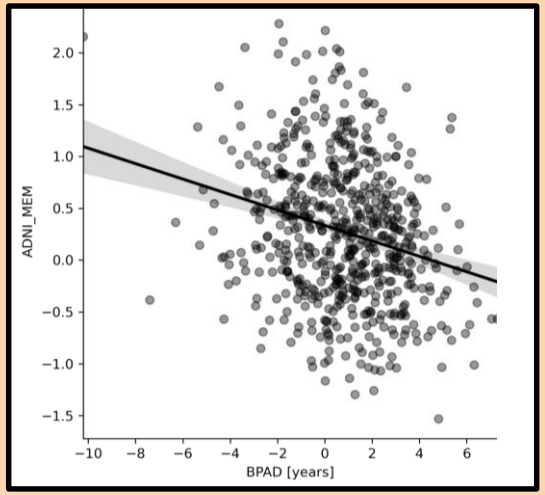
n = 618
r = -0.332**
$r_{partial}$ = -0.294**



* Significant at p < 0.05, ** significant after Bonferroni correction

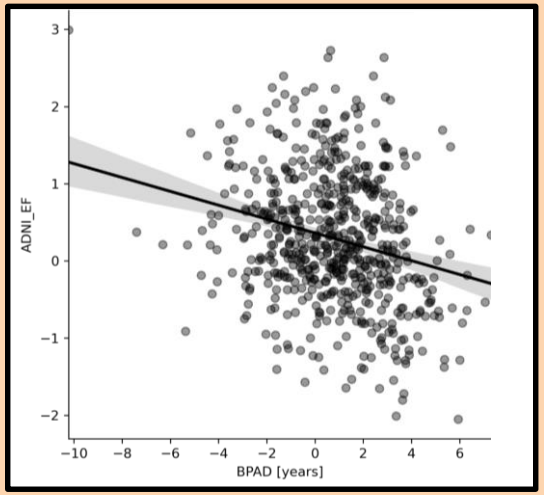
n = 618
ρ = -0.234**
$\rho_{partial}$ = -0.237**

Memory



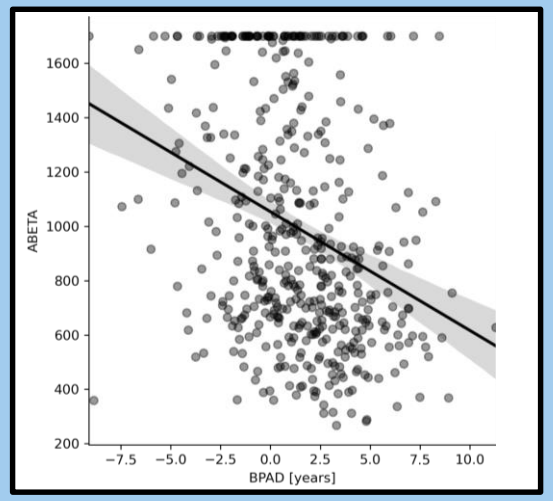
n = 618
r = -0.242**
$r_{partial}$ = -0.258**

Executive Function



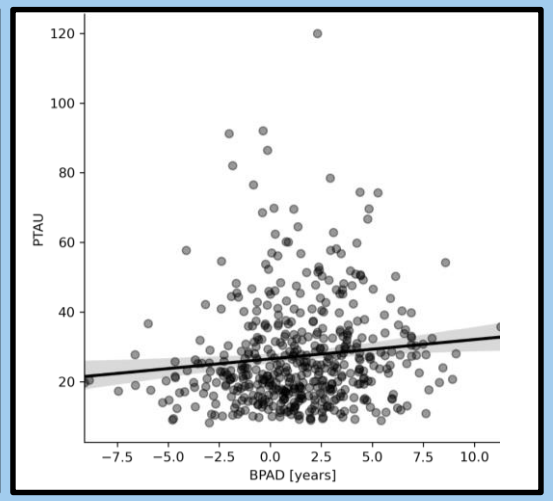
Higher BPAD (esp. MRI) is associated with more neuropathology in MCI

Amyloid

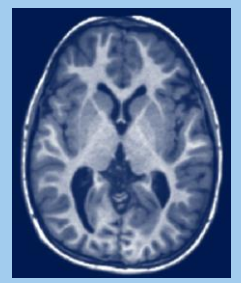


n = 479
ρ = -0.319**
$\rho_{partial}$ = -0.273**

PTau



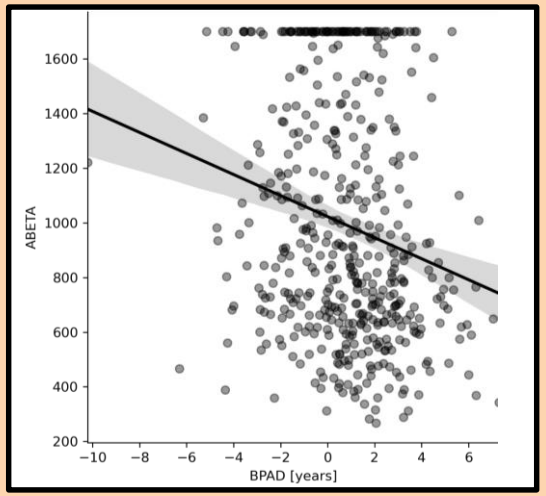
n = 479
ρ = 0.147**
$\rho_{partial}$ = 0.139**



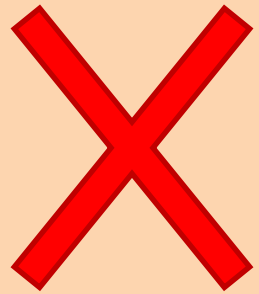
* Significant at p < 0.05, ** significant after Bonferroni correction

n = 479
ρ = -0.222**
$\rho_{partial}$ = -0.224**

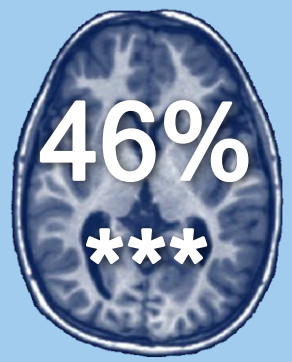
Amyloid



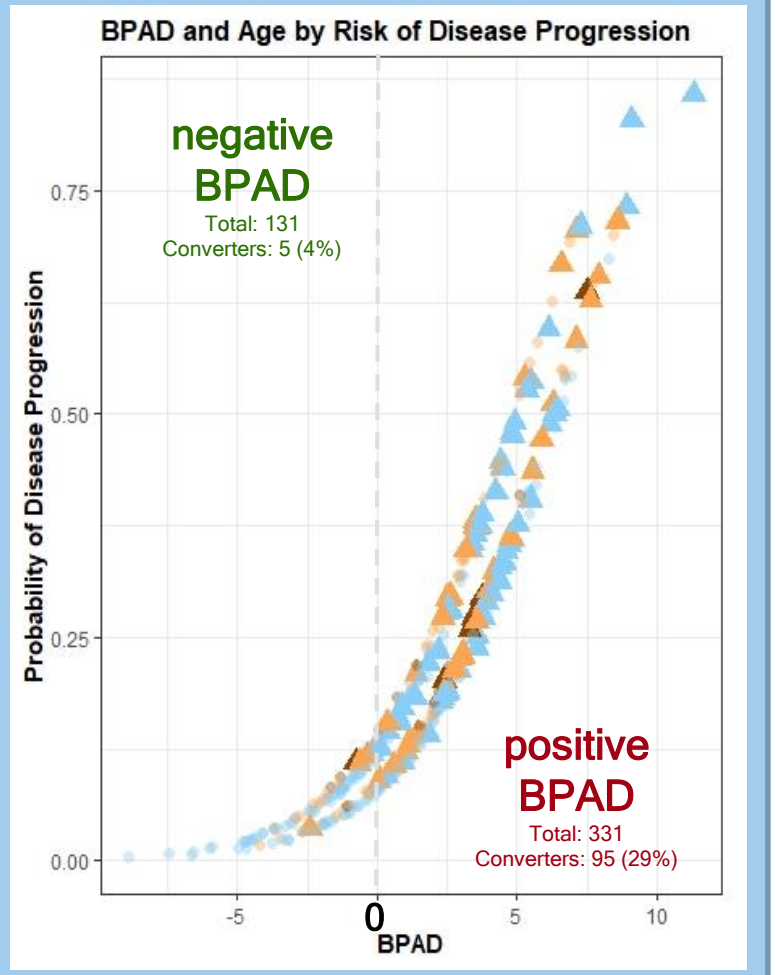
Tau



Higher BPAD (esp. MRI) predicts conversion to Alzheimer's disease in MCI

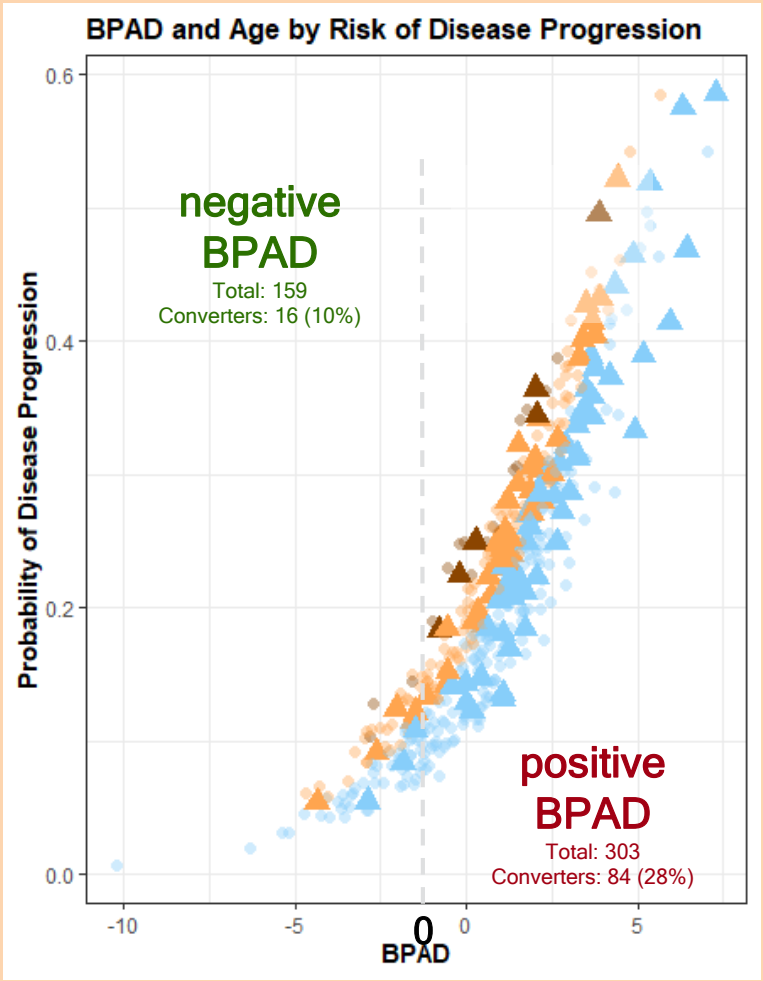


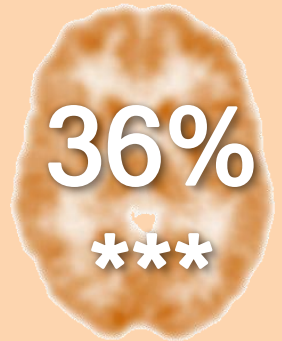
increased odds per 1 year BPAD to develop AD within 2 years



* Significant at p < 0.05, ** p < 0.01, *** p < 0.001

Diagnosis after 24 months • MCI (n=362) ▲ AD (n=100) Age Category ● <75 y. ● 75 - 84 y. ● > 85 y.

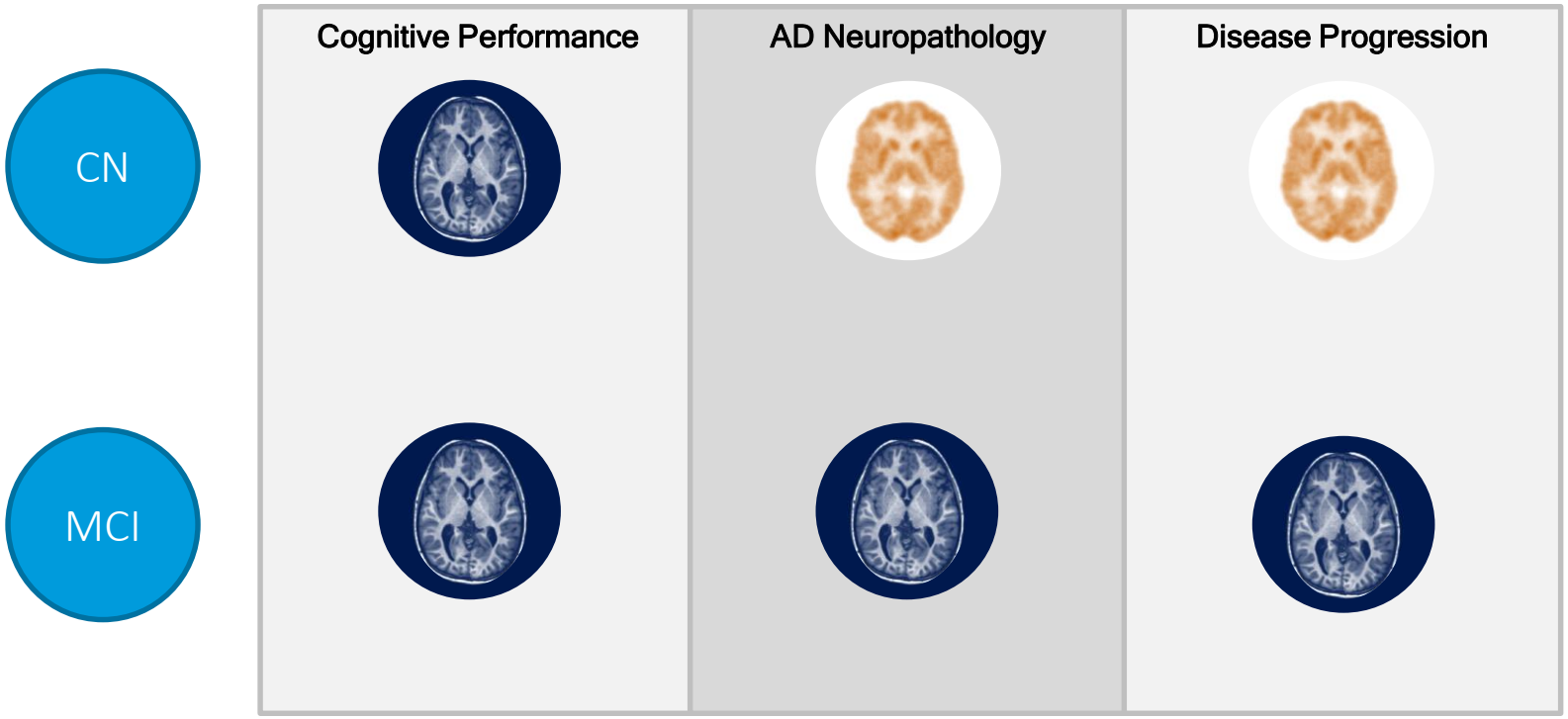




increased odds per 1 year BPAD to develop AD within 2 years

And the winner is…

Brain age can be predicted comparably well from FDG-PET or MRI, but…



FDG-PET-predicted age better captures early disease-related neuropathology and risk.

Onset of tau-related neurodegeneration and of objective cognitive decline is more strongly associated with signals of increasing brain age on **MRI**.

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Thank you for your attention!

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