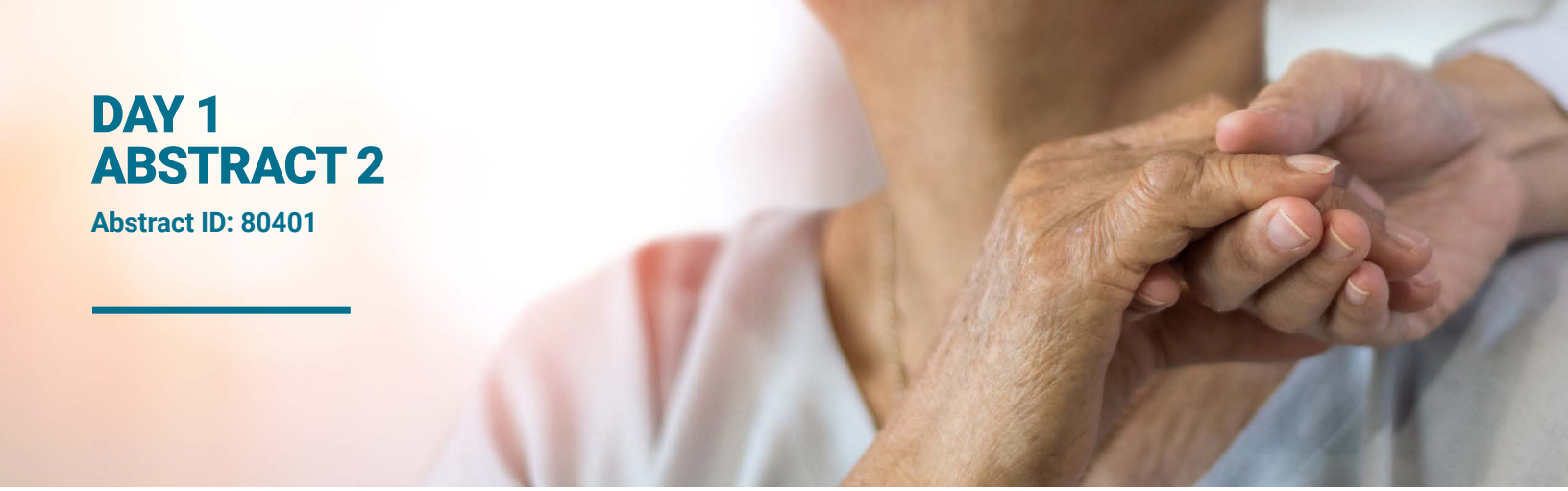

DAY 1
ABSTRACT 2

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A multi-site study of Alzheimer's disease neuroimaging and cognitive biomarkers in 2819 cognitively normal individuals

Abstract:

Long Xie, PhD[1]; Sandhitsu R. Das, PhD2,3; Laura EM Wisse, PhD4; Xueying Lyu, BA5; Emily McGrew, PhD5; Robin de Flores, PhD6; Eli Gibson, PhD7; Paul A. Yushkevich, PhD3; David A. Wolk, MD3,8 and Alzheimer's Disease Neuroimaging Initiative, (1)Siemens Healthineers, Princeton, NJ, USA, (2)Penn Image Computing and Science Laboratory (PICSL), University of Pennsylvania, Philadelphia, PA, USA, (3)Penn Alzheimer's Disease Research Center, University of Pennsylvania, Philadelphia, PA, USA, (4)Department of Diagnostic Radiology, Clinical Sciences, Lund University, Lund, Sweden, (5)University of Pennsylvania, Philadelphia, PA, USA, (6)Normandie Univ, UNICAEN, INSERM, U1237, PhIND 'Physiopathology and Imaging of Neurological Disorders', NeuroPresage Team, GIP Cyceron, Caen, France, (7)Siemens Heathineers, Princeton, NJ, USA, (8)Institute on Aging, University of Pennsylvania, Philadelphia, PA, USA

Background: Developing effective Alzheimer's disease (AD) biomarkers in cognitively normal (CN) individuals is crucial. Prior studies have identified neuroimaging and cognitive measures that are sensitive to preclinical AD. However, the generalizability of these biomarkers in large, multi-site cohorts and their power to predict disease progression remain unclear. Structural MRI, tau PET and standardized cognitive tests of 2819 CN adults were pooled from three studies to investigate the power of these measures in discriminating β-amyloid positivity (A+/-) and predicting disease progression.

Method:

T1-weighted MRI and cognitive data of 2819 CN (A-/A+: 1180/1540, Table 2) individuals from ADNI, HABS and A4 were included. Baseline medial temporal lobe structural measures were extracted from MRI (complete list in Table 1). For participants with prospective longitudinal MRI or cognitive measures (4.5 years), annualized change rate of each measurement was estimated. ANCOVA and receiver operating characteristic analyses were used to test biomarker differences between A+/A-. In 563 CN with cross-sectional tau PET available, stepwise linear mixed effect modeling was performed to identify the subset of baseline cross-sectional biomarkers (tau, MRI and cognition) that

yields the optimal model (smallest Akaike information criterion) in predicting longitudinal atrophy and cognitive decline. The area under the curve (AUC) of each model in discriminating the first (fast) and last (slow progressors) tertiles of each longitudinal measurement was reported.

RESULT:

Significant differences between A+/A- (Table 2) were observed in cross-sectional tau (most significant), cross-sectional and longitudinal cognitive, as well as longitudinal structural MRI measures. When predicting disease progression with baseline measures (Figure 1-a), tau (selected in all the models) and cognitive biomarkers were included in the most predictive models while MRI biomarkers did not provide additional information. The selected biomarkers can identify fast versus slow progressors with AUCs ranging from 0.63-0.78 (Figure 1-b).

CONCLUSION:

The results demonstrated that both cross-sectional (tau PET and cognition) and longitudinal biomarkers (MRI and cognition) are sensitive to amyloid status in CN. In addition, baseline tau PET and cognitive measures provide complementary information in predicting disease progression regardless of amyloid status. This indicates that these biomarkers may have important utility in preclinical AD clinical trials and normal aging studies.

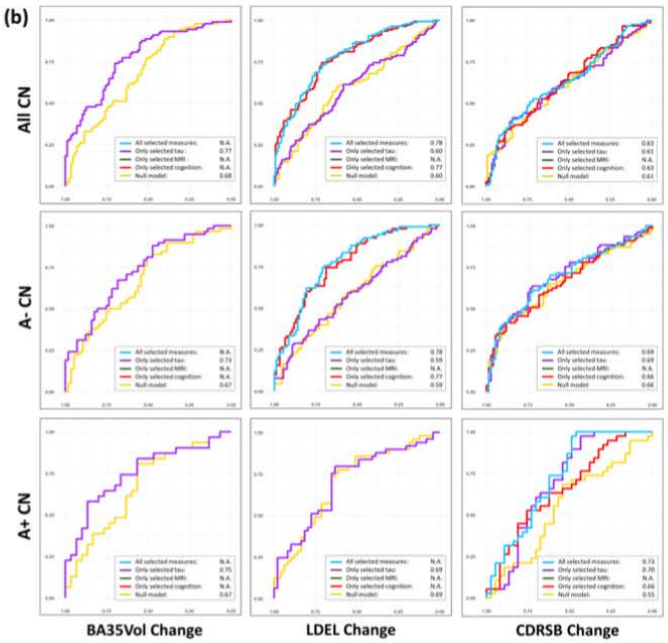
Figure 1. Results of the stepwise linear mixed effect model analyses (a, left) and receiver-operating characteristic (ROC) analyses for discriminating fast vs. slow progressors (b, right) in the all cognitively normal individuals (CN), together with A+ and A- subgroups for longitudinal atrophy (longitudinal BA35Vol) and cognitive decline (longitudinal LDEL, longitudinal CDRSB) measurements. Abbreviations: AIC = Akaike information criterion; AUC = area under the curve.

(a)

Dependent Variable	Group	Model statistics	Baseline measurements that are included in the model	
Longitudinal BA35Vol	All CN	N = 262 AIC = 471.7 R^2 = 0.99 AUC = 0.77	ERCBA35Tau	β = -0.02, p = $1.6x10^{-6}$
	A- CN	N = 171 AIC = 298.1 R^2 = 0.99 AUC = 0.73	ERCBA35Tau PHCTau	β = -0.03, p = $1.7x10^{-4}$ β = 0.02, p = 0.018
	A+ CN	N = 91 AIC = 191.3 R^2 = 0.98 AUC = 0.75	BA36Tau	β = -0.02, p = $4.4x10^{-3}$
Longitudinal LDEL	All CN	N = 416 AIC = 2445.9 R^2 = 0.58 AUC = 0.78	BA36Tau LDEL	β = -0.07, p = $4.0x10^{-8}$ β = 0.06, p = $8.9x10^{-7}$
	A- CN	N = 276 AIC = 1621.1 R^2 = 0.56 AUC = 0.78	BA36Tau LDEL	β = -0.05, p = $1.1x10^{-4}$ β = 0.10, p = $3.3x10^{-11}$
	A+ CN	N = 140 AIC = 834.9 R^2 = 0.63 AUC = 0.69	ERCBA35Tau	β = -0.07, p = $4.3x10^{-3}$
Longitudinal CDRSB	All CN	N = 429 AIC = 1587.8 R^2 = 0.79 AUC = 0.63	BA36Tau LDEL	β = 0.12, p = $3.5x10^{-9}$ β = -0.08, p = $1.2x10^{-5}$
	A- CN	N = 287 AIC = 1043.3 R^2 = 0.78 AUC = 0.69	BA36Tau LDEL ERCBA35Tau	β = 0.20, p = $2.0x10^{-6}$ β = -0.07, p = $1.4x10^{-3}$ β = -0.11, p = $6.6x10^{-3}$
	A+ CN	N = 142 AIC = 544.2 R^2 = 0.80 AUC = 0.73	ERCBA35Tau LDEL	β = 0.13, p = $3.0x10^{-4}$ β = -0.10, p = $3.4x10^{-3}$

Note: Variables fixed in the model: age, sex, APOE ε4 status and followup time. Baseline cross-sectional variables: MRI (green), tau PET (purple) and cognitive (red) biomarkers in Table 1. Tau PET and cognitive biomarkers provide complementary information in the prediction. None of the model selected MRI biomarkers.

(b)



Note: Curves include models using none (yellow, null model with age, sex, APOE ε4 status and followup time), only tau-based (purple), only MRI-based (green), only cognition-based (red) or all of the (light blue) selected baseline cross-sectional biomarkers in Table 3. Analyses were done in all cognitively normal individuals (CN, first row), A- (second row) and A+ (third row) separately. Tau and cognitive biomarkers provide complementary information in the prediction. None of the model selected MRI biomarkers. See Table 1 for biomarker abbreviations.

Table 2. Characteristics, cross-sectional and longitudinal biomarkers of the cognitively normal individuals (CN) together with β-amyloid negative (A-) and positive (A+) subgroups. See Table 1 for biomarker abbreviations. MRI and tau PET measures were harmonized to remove site effects using the neuroCombat package in R (Fortin et al., NeuroImage 2018).

		All (2819)	A- (1180)	A+ (1540)	*p*	Effect Size	AUC
	A4/HABS/ADNI	1787/278/754	541/202/437	1246/74/220	< 0.001		
	Age (years)	72.1 (5.7)	71.4 (5.8)	72.6 (5.4)	< 0.001		
	Education (years)	16.6 (2.7)	16.6 (2.6)	16.5 (2.8)			
	Sex (M/F)	1155/1664	494/686	629/911			
	APOE ε4 (C/NC)	1562/1143	898/253	638/880	< 0.001		
	CDRSB	0.06 (0.19)	0.07 (0.19)	0.06 (0.17)			
Cross-sectional	MRI Sample #	2819	1180	1540			
	AHVol	1722 (265)	1730 (220)	1725 (228)			0.52
	PHVol	1628 (187)	1640 (157)	1625 (162)			0.54
	ERCThk	2.07 (0.17)	2.07 (0.15)	2.07 (0.16)			0.51
	BA35Thk	2.33 (0.18)	2.35 (0.17)	2.33 (0.17)			0.54
	BA36Thk	2.39 (0.21)	2.40 (0.20)	2.39 (0.21)			0.52
	PHCThk	2.17 (0.15)	2.18 (0.14)	2.18 (0.15)			0.51
	LDEL Sample #	2805	1170	1536			
	LDEL	12.8 (3.5)	13.1 (3.6)	12.7 (3.5)	0.042	0.002	0.53
	MMSE Sample #	2809	1172	1539			
	MMSE	28.9 (1.2)	29.0 (1.2)	28.8 (1.3)	2.7×10^{-4}	0.005	0.55
	Tau Sample #	563	372	191			
	ERCBA35Tau	1.11 (0.14)	1.08 (0.11)	1.18 (0.17)	5.6×10^{-9}	0.061	0.67
	BA36Tau	1.17 (0.14)	1.15 (0.12)	1.22 (0.17)	6.0×10^{-6}	0.037	0.63
	PHCTau	1.12 (0.13)	1.10 (0.11)	1.16 (0.14)	4.0×10^{-6}	0.039	0.62
Longitudinal	MRI Sample #	657	445	201			
	Followup Year	3.09 (0.90)	3.13 (0.88)	3.02 (0.92)			
	AHVolChg	-0.30 (1.95)	-0.06 (1.69)	-0.80 (2.37)	2.7×10^{-4}	0.021	0.59
	PHVolChg	-0.31 (1.91)	-0.10 (1.67)	-0.76 (2.31)	3.3×10^{-3}	0.014	0.58
	ERCVolChg	-0.25 (2.17)	0.01 (2.08)	-0.80 (2.26)	1.7×10^{-4}	0.022	0.61
	BA35VolChg	-0.64 (2.17)	-0.32 (1.76)	-1.33 (2.77)	3.0×10^{-6}	0.034	0.62
	BA36VolChg	-0.42 (2.06)	-0.21 (1.67)	-0.88 (2.71)	3.0×10^{-4}	0.020	0.57
	PHCVolChg	-0.32 (1.95)	-0.13 (1.86)	-0.75 (2.10)	3.9×10^{-4}	0.020	0.58
	LDEL Sample #	778	528	236			
	Followup Year	3.36 (0.89)	3.38 (0.89)	3.31 (0.89)			
	LDELChg	9.98 (14.70)	10.77 (14.62)	8.21 (15.10)			0.54
	MMSE Sample #	779	529	236			
	Followup Year	3.37 (0.88)	3.38 (0.89)	3.33 (0.87)			
	MMSEChg	-0.01 (1.20)	0.09 (0.98)	-0.21 (1.59)	3.0×10^{-3}	0.012	0.55
	CDRSB Sample #	792	538	241			
	Followup Year	3.35 (0.89)	3.37 (0.90)	3.29 (0.89)			
	CDRSBChg	0.10 (0.61)	0.04 (0.51)	0.21 (0.78)	7.7×10^{-5}	0.020	0.61

Note: C = APOE ε4 carrier; NC = APOE ε4 non-carrier; M = male; FM = female; AUC = area under the curve. Covariates for all analyses: age, sex and APOE ε4 status. Additional covariates for cross-sectional volume analyses: intracranial volume. Additional covariates for longitudinal analyses: followup time. Maximum followup time is set to 4.5 years. Only subjects with at least 1.2 years of followup data were included in the longitudinal analysis.

Table 1. List of cross-sectional and longitudinal neuroimaging and cognitive biomarkers. Longitudinal tau biomarkers are not available due to limited longitudinal tau PET data.

	Biomarker	Abbreviation	Modality
Cross-sectional	Anterior hippocampal (AHippo) volume (mm^3)	AHVol	T1-weighted MRI
	Posterior hippocampal (PHippo) volume (mm^3)	PHVol	T1-weighted MRI
	Entorhinal cortex (ERC) thickness (mm)	ERCThk	T1-weighted MRI
	Brodmann area 35 (BA35) thickness (mm)	BA35Thk	T1-weighted MRI
	Brodmann area 36 (BA36) thickness (mm)	BA36Thk	T1-weighted MRI
	Parahippocampal cortex (PHC) thickness (mm)	PHCThk	T1-weighted MRI
	Logical memory delayed recall (second)	LDEL	Cognition
	Mini-mental state examination	MMSE	Cognition
	Tau burden in ERC and BA35	ERCBA35Tau	Tau PET
	Tau burden in BA36	BA36Tau	Tau PET
	Tau burden in PHC	PHCTau	Tau PET
Longitudinal	AHippo volume change rate (%/year)	AHVolChg	T1-weighted MRI
	PHippo volume change rate (%/year)	PHVolChg	T1-weighted MRI
	ERC volume change rate (%/year)	ERCVolChg	T1-weighted MRI
	BA35 volume change rate(%/year)	BA35VolChg	T1-weighted MRI
	BA36 volume change rate (%/year)	BA36VolChg	T1-weighted MRI
	PHC volume change rate (%/year)	PHCVolChg	T1-weighted MRI
	LDEL change rate (/year)	LDELChg	Cognition
	MMSE change rate (/year)	MMSEChg	Cognition
	Clinical dementia rating scale sum of boxes (CDRSB) change rate (/year)	CDRSBChg	Cognition