Preliminary autopsy findings from the Harvard Aging Brain Study

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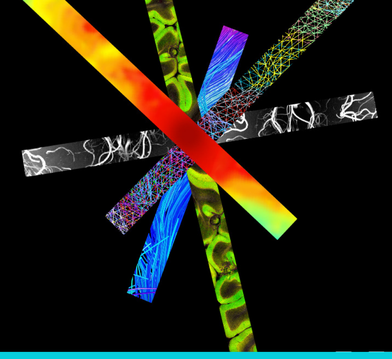

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Introduction

- Alzheimer disease (AD) biomarkers are evaluated on how well they detect AD-related pathoprogression *in vivo*, but conclusive evidence of AD neuropathologic change (ADNC) is only available at autopsy.
- We evaluate which biomarker and neuropathological assessments correlate with neuropathology in the Harvard Aging Brain Study (HABS).

Methods

- A subset of HABS participants with autopsy underwent Aβ PET (radioligand=PiB, n=15/16) and tau PET (radioligand=FTP, n=12/16)
- A subset of participants with autopsy (n=13/16) donated plasma samples, quantified by C2N Diagnostics (St. Louis, MO) using LC-MS/MS for p-tau217 and %p-tau217, and by the MIND Biomarker Core using MSD S-PLEX assay kits (Rockville, MD) for p-tau217, GFAP, and NfL.
- All participants were assessed using the CDR®, MMSE, and PACC5. A subset of participants with autopsy (n=10/16) were assessed using a dCDT (DCTclock, Digital Cognition Technologies Inc., Waltham, MA)
- Neuropathologic assessments of Aβ plaques (Thal phase), tau neurofibrillary tangles (Braak NFT stage), and neuritic plaques (CERAD NP score) were converted to A, B, and C scores following NIA-AA guidelines for the neuropathologic assessment of AD.
- Correlations are reported as partial Spearman's ϱ, controlling for age, sex, and time interval between assessment and death. Correlations involving neuropsychological assessments are also adjusted for education.

Results I

Table 1: Participant demographics.

Case	AAD	Sex	Yrs. Ed.	*APOE*	Final CDR	Neuropathologic diagnosis
1	93	F	18	34	0	LBD, ADNC (A2, B2, C0), CVD, TDP-43, HI injury
2	94	M	16	23	0.5	CVD, ADNC (A2, B1, C0), ARTAG
3	89	M	14	33	0	CVD, PART (A0, B1, C0), ARTAG
4	76	F	14	NA	0	HI injury, CAA, ADNC (A1, B1, C1)
5	93	F	12	33	0	LBD, ADNC (A2, B1, C1), Arteriolosclerosis
6	96	M	12	23	0.5	ADNC (A3, B3, C2), CVD, TDP-43, ARTAG
7	86	M	14	33	0	ADNC (A2, B1, C0), CVD, HI injury
8	84	F	13	44	0.5	ADNC (A3, B3, C2), CVD, HS, TDP-43, HI injury
9	92	M	12	33	0	ADNC (A3, B2, C1), CVD
10	89	M	16	23	0	CVD, ADNC (A1, B1, C0)
11	90	M	16	33	0.5	CVD, ADNC (A3, B1, C1), ARTAG
12	88	F	18	34	0	ADNC (A3, B3, C3), HS, TDP-43, CVD
13	92	F	16	33	0.5	Corticobasal degeneration, CVD
14	92	M	18	23	0	LBD, PART (A1, B2, C0), CVD, ARTAG
15	80	F	18	34	0.5	ADNC (A3, B3, C2), LATE, CVD
16	85	M	16	33	0	ADNC (A3, B3, C2), CVD, ARTAG

Abbreviations: AAD (age at death), ARTAG (aging-related tau astrogliopathy), CAA (cerebral amyloid angiopathy), CVD (cerebrovascular disease), HI (hypoxic-ischemic), HS (hippocampal sclerosis), LATE (limbic-predominant age-related TDP-43 encephalopathy), LBD (Lewy body disease).

Results II

Table 2: Visit-autopsy intervals (years)

Case	Neuropsych.	PiB	FTP	Plasma	dCDT
1	4	7	7	7	4
2	1	8	8	12	NA
3	0.6	3	3	NA	0.6
4	0.1	0.6	NA	NA	NA
5	1	5	4	4	1
6	0.8	4	4	12	0.8
7	0.8	NA	NA	NA	0.8
8	4	5	5	13	4
9	6	7	NA	7	NA
10	3	3	3	4	NA
11	0.4	5	5	8, 5*	0.4
12	5	6	NA	7	NA
13	2	0.9	1	2	3
14	1	1	1	1	1
15	4	5	5	5	4
16	4	5	5	5	NA
Mean	2	4	4	7, 6*	2

Abbreviations: dCDT (digital clock drawing test), FTP (flortaucipir), PiB (Pittsburgh Compound-B). Notes: *The plasma sample collected from Case #11 at their last visit was analyzed with the MSD, but not C2N, assay, due to a logistical failure.

Table 3: PET-neuropathologic correlations

	A score		B score		C score	
	ϱ	p	ϱ	p	ϱ	p
PiB FLR DVR (no PVC)	0.78	0.0025			0.73	0.0066
PiB FLR DVR (GTM PVC)	0.68	0.016			0.63	0.029
PiB FLR SUVR (no PVC)	0.77	0.0036			0.77	0.0036
FTP temporal SUVR (no PVC, cerebellar cortex RR)			0.38	0.36		
FTP temporal SUVR (GTM PVC, cerebellar cortex RR)			0.72	0.043		
FTP temporal SUVR (GTM PVC, composite* RR)			0.83	0.011		

Abbreviations: DVR (distribution volume ratio), FLR (frontal, lateral temporal, parietal, and retrosplenial), GTM (geometric transfer matrix), PVC (partial volume correction), RR (reference region), SUVR (standardized uptake value ratio). Notes: cerebral white, pons, cerebellum

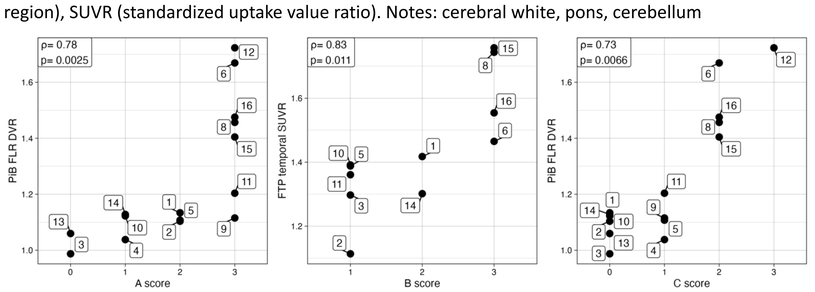

Figure 1: PET-neuropathologic correlations.

Results III

Table 4: Plasma-neuropathologic correlations.

	A score		B score		C score	
	ϱ	p	ϱ	p	ϱ	p
P-tau217 (C2N)	0.59	0.070	0.74	0.022	0.70	0.024
%p-tau-217 (C2N)	0.53	0.12	0.65	0.056	0.59	0.071
P-tau217 (MSD)	0.48	0.16	0.72	0.028	0.61	0.062
GFAP (MSD)	0.38	0.28	0.41	0.28	0.51	0.13
NfL (MSD)	0.064	0.86	0.25	0.51	0.38	0.28

Abbreviations: GFAP (glial fibrillary acidic protein), NfL (neurofilament light chain), p-tau217 (tau phosphorylated at threonine 217), %p-tau217 (tau phosphorylation occupancy at threonine 217).

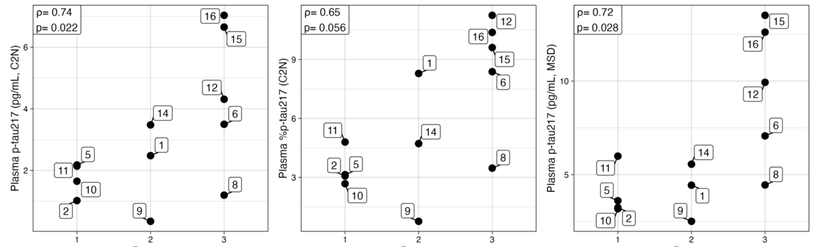

Figure 2: Plasma-neuropathologic correlations.

Standard scores on neuropsychological assessments

- CDR, CDR-SB, MMSE, and PACC5 do not correlate with A, B, or C scores.
- DCTclock summary score does not correlate with A, B, or C scores.
- DCTclock subscores do not correlate with A, B, or C scores.

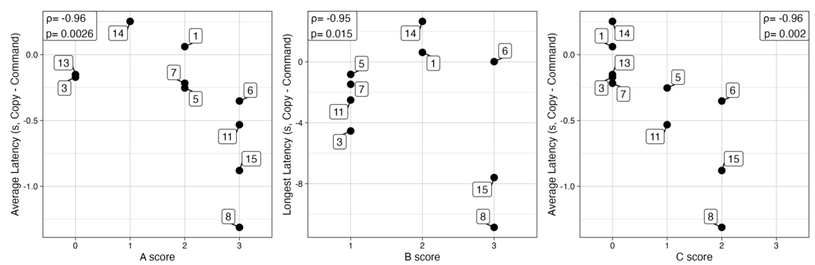

Figure 3: DCTclock-neuropathologic correlations. Average Latency and Longest Latency correlate with A, B, and C scores. Additionally, Drawing Process Efficiency correlates with A score (ϱ=0.82, p=0.044); Termination Speed (ϱ=-0.92, p=0.025) and Latency Variability (ϱ=-0.88, p=0.046) correlate with B score; and Percent Ink Time (ϱ=0.82, p=0.045) and Percent Think Time (ϱ=-0.82, p=0.045) correlate with C score.

Discussion

- Aβ PET, PVC-corrected tau PET, plasma p-tau217, and latency-related dCDT features appear to be powerful tools for *in vivo* diagnosis of ADNC even in the presence of co-pathologies.
- Non-Aβ and non-tau biomarkers (plasma GFAP and NfL) and standard scores on neuropsychological assessments (CDR, CDR-SB, MMSE, PACC5, dCDT summary score and subscores) did not correlate with ADNC.