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## BIOMARKERS

## POSTER PRESENTATION

## NEUROIMAGING

# Exploring Associations Between Longitudinal [<sup>18</sup>F]RO-948 Tau PET, Baseline Fluid tau Biomarkers, and memory in the Early Alzheimer's Disease continuum

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#### Abstract

**Background:** The relationship between longitudinal tau-PET trajectories and fluid tau biomarkers in early Braak stages is crucial for understanding Alzheimer's disease (AD) progression and identifying predictive biomarkers for early diagnosis and intervention. This study examines how baseline plasma and cerebrospinal fluid (CSF) tau biomarkers, amyloid plaques, and cognitive performance interact with longitudinal tau-PET trajectories in cognitively unimpaired (CU) individuals.

**Method:** Forty-six CU individuals from ALFA+ cohort were included, each with two [18F]RO-948 tau-PET scans ( $\Delta t = 2.31 \pm 0.34$  years), two T1-weighted MRIs, and baseline [18F]flutemetamol amyloid-PET (Figure 1). Baseline fluid tau biomarkers, measured using RocheNTK, RocheElecsys, Simoa, and Lilly assays, as well as memory, were also available. [18F]RO-948 uptake was measured in entorhinal (BraakI/II), limbic (BraakIII/IV), and neocortical (BraakV/VI) regions and normalized to the inferior cerebellum to render SUVR. Amyloid-PET was quantified using Centiloid. Tau-PET stage transitions from baseline to follow-up assessed using predefined positivity thresholds. Linear mixed-effects models evaluated associations between baseline biomarkers, Centiloid, memory, and tau-PET SUVR over time, adjusting for age, sex, APOE- $\epsilon 4$ , and time intervals.

**Result:** Three participants (6.52%) were positive for BraakI/II at both baseline and follow-up (Stable-Positive), two (4.34%) transitioned to positive (Progressors), while the majority (41, 89.13%) remained negative (Stable-Negative) (Figure 1). Interaction between baseline predictors and time was not statistically significant for any predictive variables (Table 2). However, higher plasma ptau181 and ptau217 levels were significantly associated with higher baseline BraakI/II SUVR, while only plasma ptau181 showed a significant association with baseline BraakIII/IV. For CSF, higher ptau217 and ptau181/A $\beta$ 42 ratio were significantly associated with higher baseline tau-PET SUVR in both BraakI/II and BraakIII/IV (Table 1 & Figure 2). Additionally,

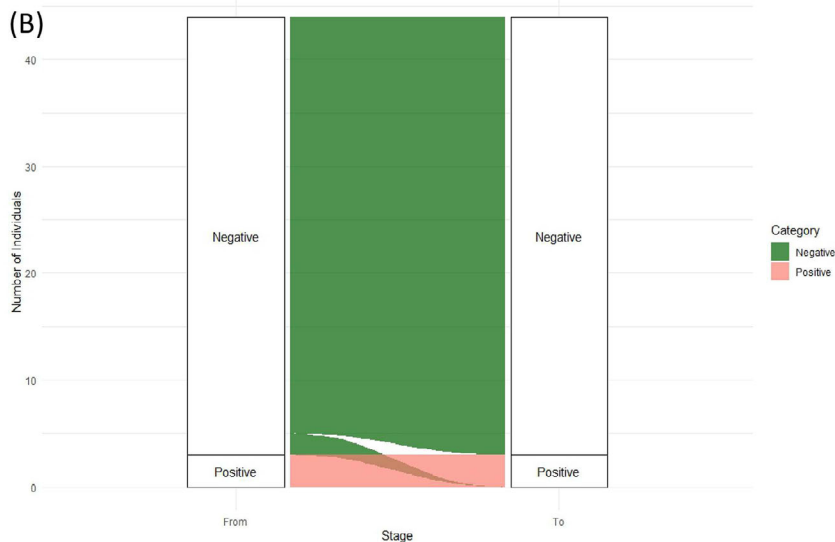
Centiloid was positively associated with tau-PET SUVR in BraakI/II but not in other regions. Lower baseline memory scores were significantly associated with higher tau-PET SUVR in BraakI/II and BraakIII/IV in baseline.

**Conclusion:** Our findings support the potential of plasma and CSF tau biomarkers as early indicators of Alzheimer's pathology in cognitively unimpaired individuals. The negative association between memory and tau-PET SUVR suggests subtle cognitive differences may reflect underlying tau accumulation. However, no significant longitudinal effects were observed, likely due to the limited sample size or short follow-up.

(A) Figure 1.

Demographic information	A-T-	A+T-	A+T+	P-values	Total
N	15	11	15	NA	47
Age	62.86±5.41	62.72±4.90	66.00±6.06	n.s	64.31±5.68
Sex (women %)	8 (17.02%)	7 (14.89%)	11 (23.40)	n.s	17 (36.17%)
APOE-ε4 carriership	10 (21.27%)	6 (12.76%)	10 (21.27%)	n.s	26 (55.31%)
Centiloid at baseline	-2.27±8.25	18.04±14.93	44.71±23.35	<b>&lt;0.001</b>	19.86±25.39
Braak I/II SUVr at baseline	1.01±0.15	1.10±0.14	1.20±0.28	n.s	1.20±0.21
Memory at baseline	0.07±0.70	0.29±0.73	-0.37±0.56	<b>0.05</b>	-0.02±0.73

A. Demographic information, Centiloid, Braak I/II SUVr and PACC scores of participants at baseline stratified by CSF-based AT status, defined by pre-established cut-offs based on CSF Aβ<sub>42</sub>/40<0.071 and ptau<sub>181</sub>>24(pg/ml) measured by the exploratory NeuroToolKit and Elecsys immunoassays (Milà-Alomà et al, 2020). B. Sankey graph showing the transition of tau PET scans status between baseline and follow up Sankey Diagram of Transitions



<i>Braak I/II</i>	<i>statistic</i>	<i>Effect size</i>	<i>L (95%CI)</i>	<i>U (95%CI)</i>	<i>p-value</i>	<i>Braak III/IV</i>	<i>statistic</i>	<i>Effect size</i>	<i>L (95%CI)</i>	<i>U (95%CI)</i>	<i>p-value</i>
(Intercept)	1.288	0.282	-0.158	0.721	0.204	(Intercept)	5.86	0.72	0.47	0.97	0.00
CSF ptau217 (Lilly)	2.915	0.013	0.004	0.021	0.005	CSF ptau217 (Lilly)	2.27	0.01	0.00	0.01	0.03
ΔTime (years)	0.328	0.009	-0.048	0.066	0.746	ΔTime (years)	0.16	0.00	-0.03	0.03	0.87
Age	3.082	0.011	0.004	0.018	0.003	Age	2.61	0.01	0.00	0.01	0.01
Sex	2.785	0.101	0.028	0.175	0.008	Sex	2.15	0.04	0.00	0.09	0.04
APOE-ε4 Carriership	-2.533	-0.096	-0.172	-0.020	0.015	APOE-ε4 Carriership	-1.37	-0.03	-0.07	0.01	0.18
ΔTime(CSF and tau PET)	-2.143	-0.065	-0.126	-0.004	0.037	ΔTime(CSF and tau PET)	-2.32	-0.04	-0.07	-0.01	0.02
CSF ptau217 (Lilly)*ΔTime (years)	-0.398	-0.001	-0.005	0.003	0.692	CSF ptau217 (Lilly)*ΔTime (years)	0.15	0.00	0.00	0.00	0.88
(Intercept)	1.208	0.269	-0.179	0.717	0.233	(Intercept)	5.67	0.71	0.46	0.96	0.00
CSF ptau181/AB42 (RocheNTK)	2.715	0.709	1.740	11.679	0.009	CSF ptau181/AB42 (RocheNTK)	2.20	3.10	0.27	5.93	0.03
ΔTime (years)	0.315	0.010	-0.054	0.073	0.755	ΔTime (years)	0.20	0.00	-0.03	0.04	0.85
Age	2.890	0.010	0.003	0.017	0.006	Age	2.46	0.00	0.00	0.01	0.02
Sex	3.188	0.118	0.043	0.192	0.003	Sex	2.60	0.05	0.01	0.10	0.01
APOE-ε4 Carriership	-1.963	-0.076	-0.154	0.002	0.055	APOE-ε4 Carriership	-0.84	-0.02	-0.06	0.03	0.41
ΔTime(CSF and tau PET)	-2.195	-0.068	-0.130	-0.006	0.033	ΔTime(CSF and tau PET)	-2.37	-0.04	-0.08	-0.01	0.02
CSF ptau181/AB42 (RocheNTK)*ΔTime (years)	-0.356	-0.374	-2.491	1.742	0.724	CSF ptau181/AB42 (RocheNTK)*ΔTime (years)	0.06	0.03	-1.14	1.21	0.95
(Intercept)	1.119	0.258	-0.206	0.723	0.269	(Intercept)	5.71	0.64	0.42	0.87	0.00
CSF ptau205 (Simoa)	2.421	0.065	0.011	0.119	0.019	Plasma ptau181 (Simoa)	2.29	0.01	0.00	0.01	0.03
ΔTime (years)	0.278	0.010	-0.065	0.085	0.784	ΔTime (years)	0.16	0.00	-0.05	0.05	0.87
Age	2.803	0.010	0.003	0.018	0.007	Age	3.01	0.01	0.00	0.01	0.00
Sex	3.043	0.121	0.041	0.201	0.004	Sex	1.68	0.03	-0.01	0.07	0.10
APOE-ε4 Carriership	-2.425	-0.096	-0.176	-0.016	0.019	APOE-ε4 Carriership	-1.23	-0.02	-0.06	0.01	0.23
ΔTime(CSF and tau PET)	-2.714	-0.087	-0.151	-0.022	0.009	ΔTime(Plasma and tau PET)	-4.65	-0.06	-0.09	-0.04	0.00
CSF ptau205 (Simoa)*ΔTime (years)	-0.261	-0.003	-0.027	0.021	0.795	Plasma ptau181 (Simoa)*ΔTime (years)	0.02	0.00	0.00	0.00	0.99
(Intercept)	0.723	0.175	-0.313	0.663	0.473	(Intercept)	5.71	0.67	0.43	0.90	0.00
CSF ptau235 (Simoa)	2.197	0.011	0.001	0.020	0.033	Plasma ptau217 (Lilly)	1.72	0.35	-0.06	0.75	0.09
ΔTime (years)	0.224	0.010	-0.084	0.104	0.824	ΔTime (years)	-0.07	0.00	-0.05	0.05	0.95
Age	2.770	0.011	0.003	0.018	0.008	Age	2.97	0.01	0.00	0.01	0.00
Sex	3.428	0.139	0.057	0.221	0.001	Sex	1.71	0.03	-0.01	0.07	0.09
APOE-ε4 Carriership	-2.291	-0.094	-0.177	-0.011	0.027	APOE-ε4 Carriership	-1.60	-0.03	-0.07	0.01	0.12
ΔTime(CSF and tau PET)	-2.908	-0.095	-0.161	-0.029	0.006	ΔTime(Plasma and tau PET)	-4.39	-0.06	-0.09	-0.03	0.00
CSF ptau235 (Simoa)*ΔTime (years)	-0.213	0.000	-0.005	0.004	0.832	Plasma ptau217 (Lilly)*ΔTime (years)	0.22	0.02	0.15	0.18	0.83
(Intercept)	0.319	0.076	-0.403	0.555	0.751	(Intercept)	5.55	0.65	0.42	0.89	0.00
CSF ttau (Lilly)	1.994	0.000	0.000	0.000	0.952	PACC-Memory	-2.69	-0.05	-0.10	-0.01	0.01
ΔTime (years)	0.528	0.021	-0.061	0.104	0.602	ΔTime (years)	0.00	0.00	-0.02	0.02	1.00
Age	3.565	0.013	0.006	0.020	0.001	Age	4.21	0.01	0.00	0.01	0.00
Sex	3.117	0.123	0.044	0.202	0.003	Sex	1.53	0.03	-0.01	0.07	0.13
APOE-ε4 Carriership	-2.536	-0.105	-0.188	-0.022	0.015	APOE-ε4 Carriership	-0.55	-0.01	-0.05	0.03	0.59
ΔTime(CSF and tau PET)	-2.618	-0.085	-0.150	-0.020	0.012	PACC-Memory*ΔTime (years)	0.72	0.01	-0.01	0.02	0.48
CSF ttau (Lilly)*ΔTime (years)	-0.517	0.000	0.000	0.000	0.607						
(Intercept)	0.695	0.168	-0.319	0.656	0.491						
CSF NTAtau (Simoa)	1.947	0.002	0.000	0.003	0.058						
ΔTime (years)	0.368	0.011	-0.053	0.076	0.716						
Age	3.267	0.013	0.005	0.020	0.002						
Sex	3.130	0.130	0.046	0.214	0.003						
APOE-ε4 Carriership	-2.385	-0.101	-0.187	-0.016	0.021						
ΔTime(CSF and tau PET)	-2.633	-0.089	-0.157	-0.021	0.011						
CSF NTAtau (Simoa)*ΔTime (years)	-0.423	0.000	-0.001	0.001	0.674						
(Intercept)	0.342	0.081	-0.397	0.560	0.734						
CSF ptau181 (RocheElevcsys)	1.944	0.006	0.000	0.013	0.058						
ΔTime (years)	0.464	0.018	-0.062	0.099	0.647						
Age	3.580	0.013	0.006	0.021	0.001						
Sex	3.068	0.121	0.042	0.200	0.004						
APOE-ε4 Carriership	-2.528	-0.104	-0.187	-0.021	0.015						
ΔTime(CSF and tau PET)	-2.801	-0.090	-0.155	-0.026	0.007						
CSF ptau181 (RocheElevcsys)*ΔTime (years)	-0.455	-0.001	-0.003	0.002	0.651						
(Intercept)	0.446	0.106	-0.372	0.584	0.658						
CSF ptau181 (RocheNTK)	1.857	0.006	0.000	0.013	0.069						
ΔTime (years)	0.420	0.016	-0.061	0.093	0.678						
Age	3.510	0.013	0.006	0.020	0.001						
Sex	3.095	0.122	0.043	0.202	0.003						
APOE-ε4 Carriership	-2.443	-0.101	-0.184	-0.018	0.018						
ΔTime(CSF and tau PET)	-2.773	-0.090	-0.155	-0.025	0.008						
CSF ptau181 (RocheNTK)*ΔTime (years)	-0.406	-0.001	-0.003	0.002	0.687						
(Intercept)	0.299	0.063	-0.359	0.486	0.766						
Plasma ptau181 (Simoa)	2.665	0.012	0.003	0.020	0.010						
ΔTime (years)	0.436	0.020	-0.073	0.112	0.666						
Age	3.744	0.012	0.005	0.018	0.000						
Sex	1.785	0.063	-0.008	0.134	0.080						
APOE-ε4 Carriership	-1.680	-0.058	-0.126	0.011	0.099						
ΔTime(Plasma and tau PET)	-3.369	-0.087	-0.139	-0.035	0.001						
Plasma ptau181 (Simoa)*ΔTime (years)	-0.458	-0.001	-0.004	0.003	0.649						
(Intercept)	0.471	0.101	-0.329	0.531	0.639						
Plasma ptau217 (Lilly)	2.387	0.864	0.138	1.590	0.021						
ΔTime (years)	0.273	0.012	-0.080	0.105	0.786						
Age	3.667	0.012	0.005	0.018	0.001						
Sex	1.786	0.064	-0.008	0.137	0.080						
APOE-ε4 Carriership	-2.057	-0.072	-0.142	-0.002	0.045						
ΔTime(Plasma and tau PET)	-3.139	-0.083	-0.136	-0.030	0.003						
Plasma ptau217 (Lilly)*ΔTime (years)	-0.299	-0.046	-0.351	0.260	0.766						
(Intercept)	0.057	0.101	-0.428	0.453	0.955						
Plasma ptau181 (RocheNTK)	2.156	0.864	0.021	0.583	0.036						
ΔTime (years)	0.359	0.012	0.083	0.119	0.722						
Age	4.017	0.012	0.006	0.019	0.000						
Sex	2.549	0.064	0.019	0.160	0.014						
APOE-ε4 Carriership	-1.775	-0.072	-0.133	0.008	0.082						
ΔTime(Plasma and tau PET)	-3.074	-0.083	-0.136	-0.029	0.003						
Plasma ptau181 (RocheNTK)*ΔTime (years)	-0.341	-0.046	-0.139	0.099	0.735						
(Intercept)	2.053	0.441	0.009	0.873	0.045						
Centiloid	2.243	0.172	0.018	0.327	0.029						
ΔTime (years)	0.089	0.002	-0.039	0.043	0.929						
Age	2.651	0.009	0.002	0.016	0.011						
Sex	3.237	0.117	0.044	0.190	0.002						
APOE-ε4 Carriership	-0.694	-0.024	-0.095	0.046	0.491						
ΔTime (Amyloid and tau PET)	-4.313	-0.109	-0.161	-0.058	-0.001						
Centiloid*ΔTime (years)	-0.077	-0.002	-0.067	0.062	0.939						
(Intercept)	0.653	0.135	-0.278	0.548	0.516						
PACC-Memory	-2.614	-0.092	-0.163	-0.021	0.012						
ΔTime (years)	-0.133	-0.003	-0.044	0.038	0.895						
Age	5.054	0.016	0.009	0.022	0.000						
Sex	1.687	0.061	-0.011	0.133	0.097						
APOE-ε4 Carriership	-1.318	-0.046	-0.116	0.024	0.193						
PACC-Memory*ΔTime (years)	0.310	0.005	-0.026	0.035	0.758						

Table 2. Linear mixed effect models results for Braak I/II and Braak III/IV, effect size and corresponding 95

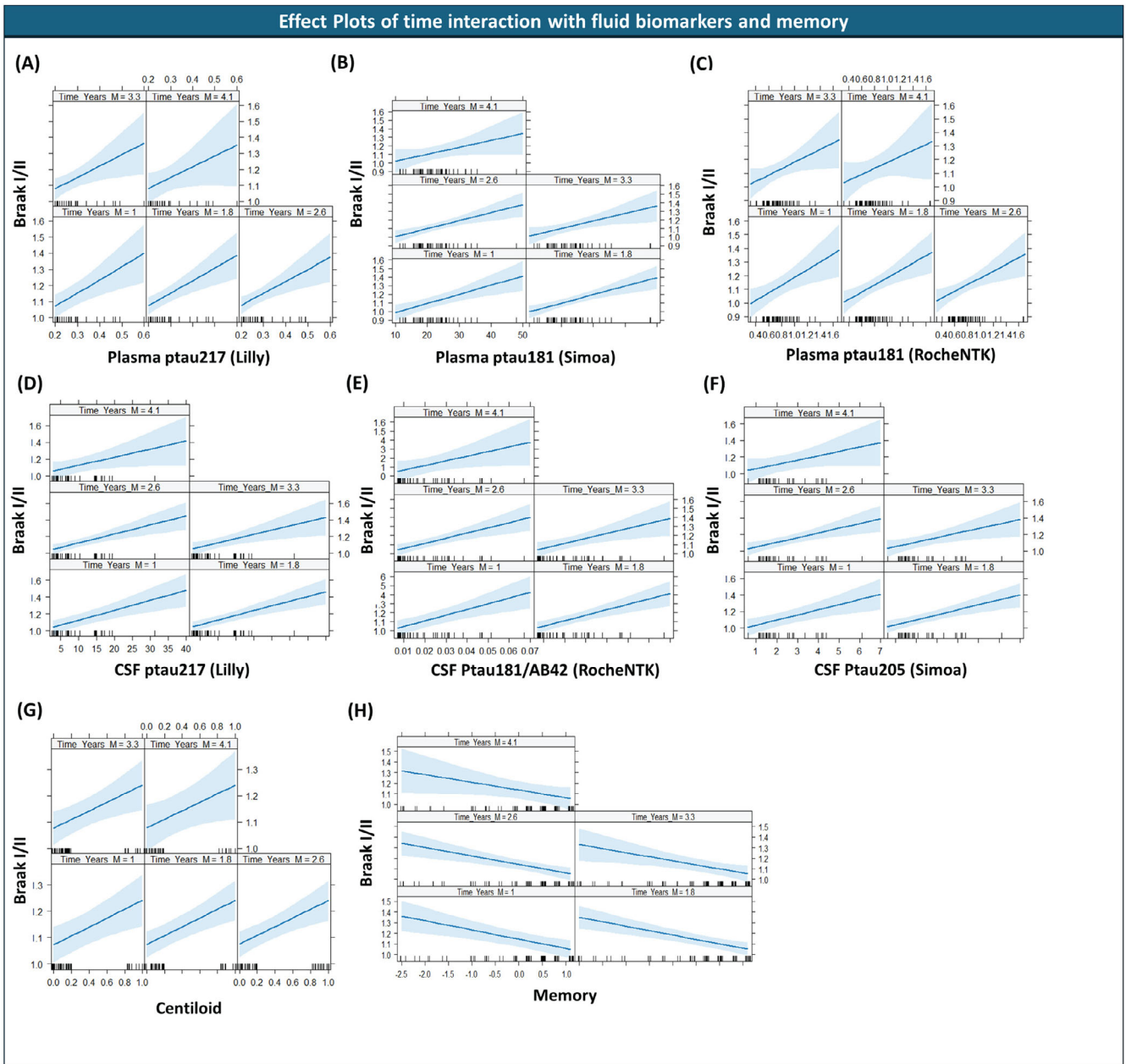


Figure 1. Effect plots and corresponding 95% CI for (A) plasma ptau217 (Lilly), (B) plasma ptau181 (Simoa), (C) Plasma ptau181 (RocheNTK), (D) CSF ptau217 (Lilly), (E) CSF ptau181/AB42 (RocheNTK), (F) CSF ptau205 (Simoa), (G) Centiloid, and (H) Memory.