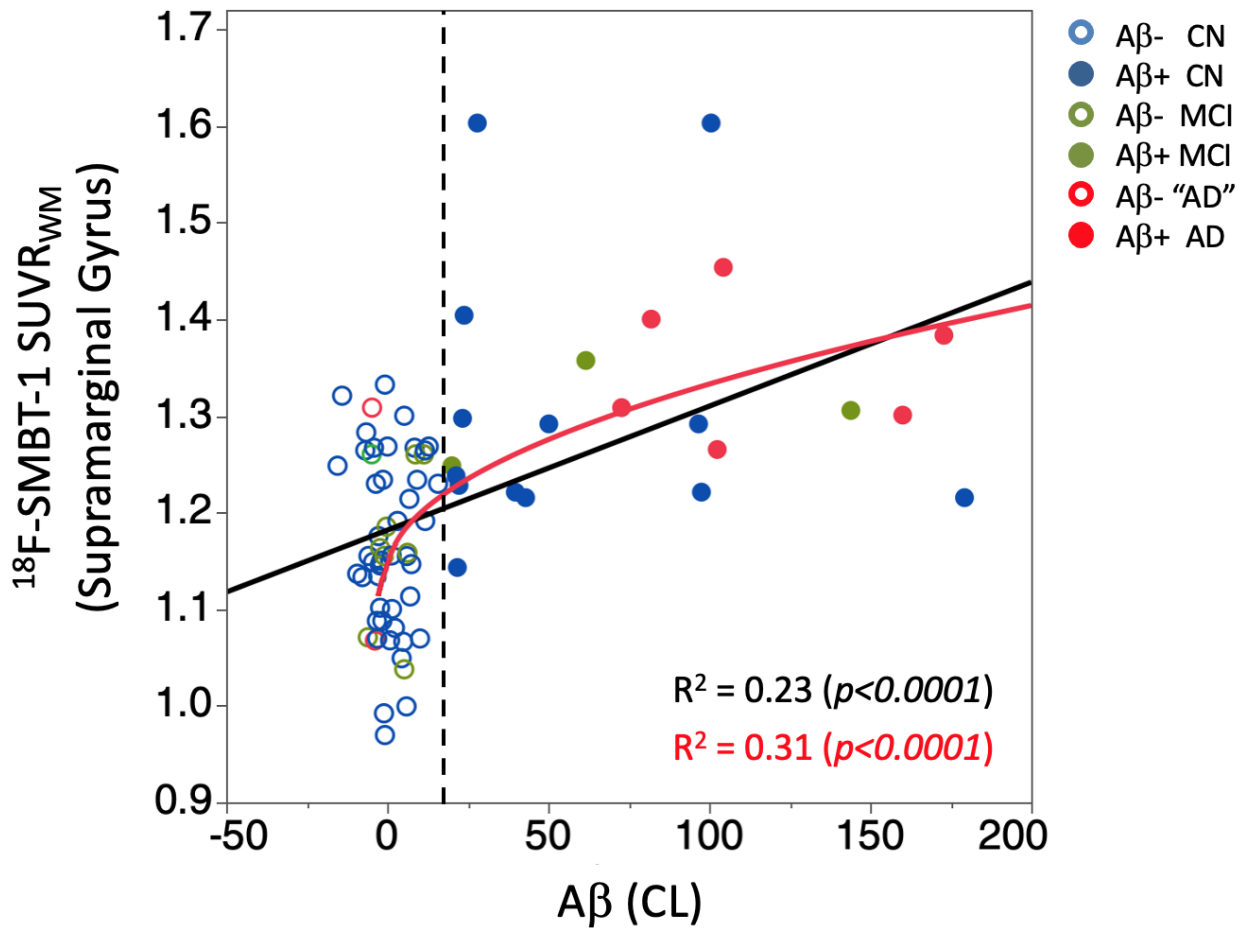


Neuropsychological evaluation

Participants were administered the Mini Mental State Examination (MMSE), the Clinical Dementia Rating (CDR), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and a battery of neuropsychological tests. The primary cognitive performance measures were the composite memory and non-memory scores, and the AIBL-PACC score that were calculated as previously described.(1,2) Briefly, we calculated a composite episodic memory score from the mean of the z-scores (means and standard deviation for creating the z-scores were generated using data from 65 cognitively normal controls with both low ¹¹C-PiB PET retention and normal MRI as the reference) for Rey complex figure test (RCFT, 30 min) long delay, the delayed recall from the California verbal learning test second edition (CVLT-II), and Logical Memory II. We calculated a composite non-memory score by taking the mean of the z scores for the Boston naming test, letter fluency, category fluency, digit span forwards and backwards, digit symbol-coding, and RCFT copy. (1) The AIBL-PACC score was calculated from the mean of the z-scores of the delayed recall from CVLT-II and Logical Memory II, the digit symbol substitution Test and the MMSE total score. (2)

Supplemental Figure 1. Correlation between ^{18}F -SMBT-1 binding and $\text{A}\beta$ burden



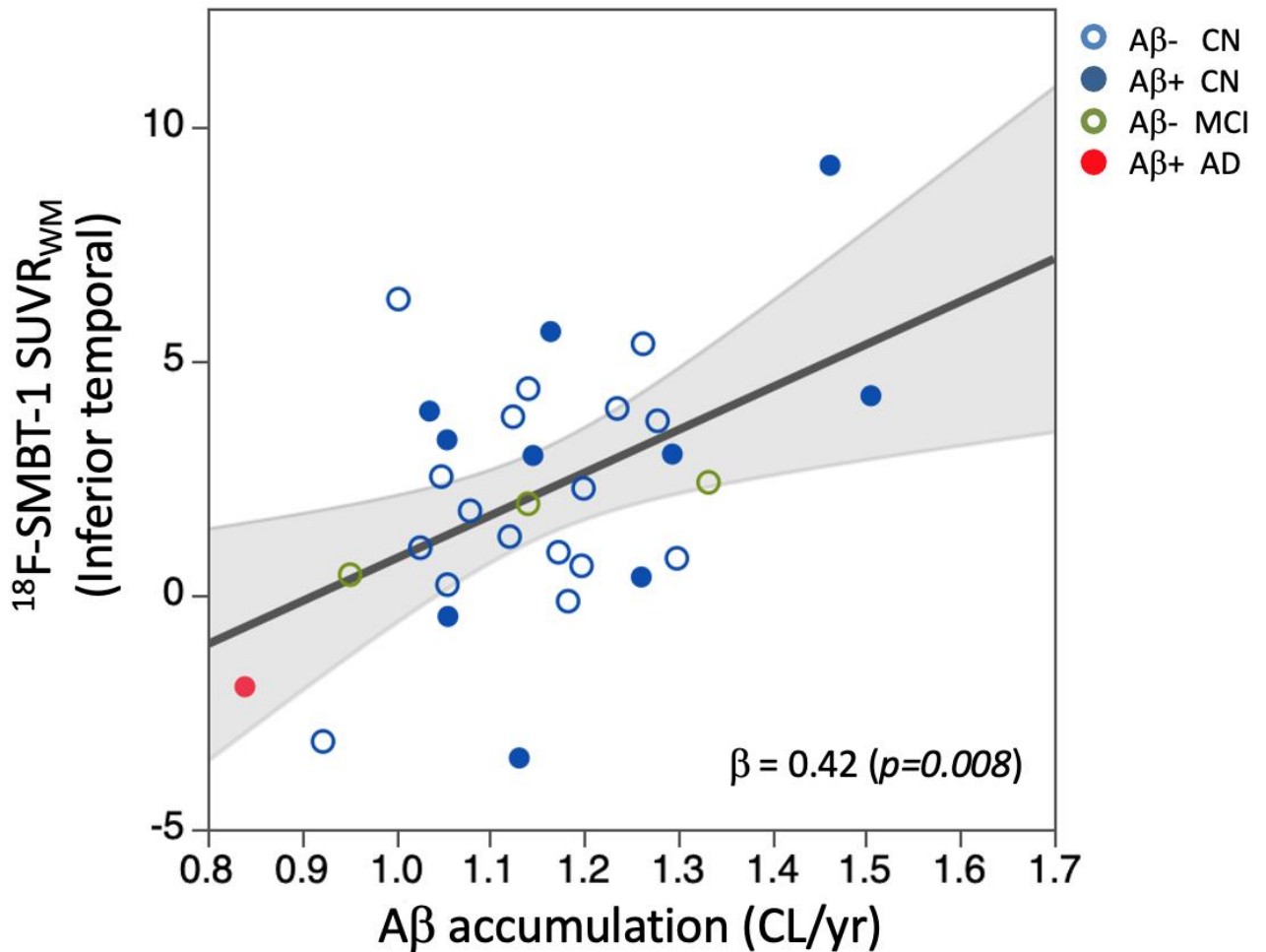
Linear and non-linear associations between ^{18}F -SMBT-1 binding in the supramarginal gyrus and global $\text{A}\beta$ burden. The non-linear fit better described the relationship between ^{18}F -SMBT-1 binding and $\text{A}\beta$ burden, suggesting that the ^{18}F -SMBT-1 signal starts increasing before $\text{A}\beta$ becomes abnormal.

The dotted line denotes the 20 CL use to separate high from low $\text{A}\beta$.

Linear fit: $y = a + b \cdot x$

Square root fit: $y = a + b \cdot \text{Sqrt}(x)$

Supplemental Figure 2. Correlation between ^{18}F -SMBT-1 binding and $\text{A}\beta$ accumulation



Linear association between ^{18}F -SMBT-1 binding in the inferior temporal and global rates of $\text{A}\beta$ accumulation in 31 participants (1 $\text{A}\beta$ + AD, 3 $\text{A}\beta$ - MCI, 17 $\text{A}\beta$ - and 10 $\text{A}\beta$ + CN) with available $\text{A}\beta$ imaging longitudinal data. The association suggests that the ^{18}F -SMBT-1 signal in the inferior temporal is higher on those participants with higher rates of $\text{A}\beta$ accumulation. Association was adjusted for age, sex and baseline $\text{A}\beta$ burden.

SUPPLEMENTAL TABLE 1. Demographics of cognitively unimpaired controls (CN) and Alzheimer's disease (AD) patients by amyloid status

	A β - CN	A β + CN	A β - MCI	A β + MCI	A β - AD	A β + AD
n	44	13	9	3	2	6
Age	76.0 \pm 4.8	78.9 \pm 5.5	72.8 \pm 6.6	75.1 \pm 2.8	66.5 \pm 3.5	79.7 \pm 4.8
Sex	25F/19M	7F/6M	4F/5M	0F/3M	1F/1M	4F/2M
Education (years)	14.8 \pm 2.7	14.7 \pm 3.2	10.0 \pm 1.7*	11.7 \pm 4.2	10.9 \pm 1.8	10.3 \pm 1.3*
%APOE4	30%	69%*	22%	33%	0%	80%*
MMSE	28.6 \pm 1.5	28.6 \pm 1.6	28.4 \pm 1.7	26.3 \pm 0.6*	26.0 \pm 1.4	23.5 \pm 4.6*
CDR	0.05 \pm 0.1	0.00 \pm 0.0	0.28 \pm 0.3*	0.50 \pm 0.0*	0.75 \pm 0.4	0.67 \pm 0.3*
CDR SoB	0.07 \pm 0.2	0.00 \pm 0.0	0.39 \pm 0.3*	0.67 \pm 0.3*	4.50 \pm 0.7	6.50 \pm 2.4*
Episodic Memory	0.12 \pm 0.9	0.28 \pm 0.6	-1.03 \pm 0.5*	-1.19 \pm 0.5*	-1.96 \pm 0.0*	-3.58 \pm 1.5*
Non-Memory	-0.07 \pm 0.6	-0.04 \pm 0.7	-0.90 \pm 0.6*	-0.76 \pm 0.2*	-0.90 \pm 0.1*	-2.90 \pm 1.8*
AIBL PACC	0.07 \pm 0.7	0.15 \pm 0.6*	-0.76 \pm 0.7*	-1.11 \pm 0.4*	-2.56 \pm 0.0*	-4.53 \pm 2.1*
Hippocampus (cc)	5.94 \pm 0.5	5.83 \pm 0.4	5.81 \pm 0.9	5.73 \pm 0.8	5.71 \pm 0.2	4.50 \pm 0.5*
Cortical GM (cc)	472 \pm 38	452 \pm 14	468 \pm 10	465 \pm 14	452 \pm 27	419 \pm 13*
WM (cc)	387 \pm 27	390 \pm 22	388 \pm 18	383 \pm 17	381 \pm 52	390 \pm 19
Ventricles (cc)	34.0 \pm 15	33.0 \pm 7	35.1 \pm 22	42.0 \pm 38	39.6 \pm 19	45.0 \pm 12
WMH (cc)	5.41 \pm 6.9	4.25 \pm 5.6	4.54 \pm 7.8	4.79 \pm 6.0	5.44 \pm 6	22.7 \pm 21*
A β burden (CL)	0.79 \pm 6.9	57.5 \pm 48*	1.96 \pm 6.2	75.3 \pm 63*	-4.25 \pm 0.6	116 \pm 41*
A β accumulation (CL/yr)	0.61 \pm 2.6	5.32 \pm 4.6*	-0.22 \pm 0.1	-	-	4.08
Tau Me (SUVR)	0.89 \pm 0.2	1.16 \pm 0.2*	1.00 \pm 0.1	1.58 \pm 0.4*	0.88 \pm 0.3	2.05 \pm 1.1*
Tau Te (SUVR)	1.02 \pm 0.2	1.13 \pm 0.1	1.13 \pm 0.1	1.42 \pm 0.2*	1.06 \pm 0.2	2.52 \pm 1.2*
Tau R (SUVR)	0.90 \pm 0.1	0.93 \pm 0.1	0.98 \pm 0.1	1.10 \pm 0.0*	0.97 \pm 0.3	1.84 \pm 0.8*
Tau MT (SUVR)	0.98 \pm 0.2	1.18 \pm 0.2	1.10 \pm 0.1	1.56 \pm 0.3	1.00 \pm 0.3	2.39 \pm 1.3*
%Tau+	9%	46%*	22%*	100%*	50%*	75%*

Abbreviations

CN: elderly controls; MCI: mild cognitive impairment; AD: Alzheimer's disease; APOE: Apolipoprotein E; MMSE: Mini mental State Examination; CDR: Clinical Dementia Rating; CDR SoB: Clinical Dementia Rating Sum of Boxes; AIBL PACC: the Australian Imaging Biomarkers and Lifestyle's Preclinical Alzheimer Cognitive Composite. GM: Grey matter; WM: White Matter; WMH: White Matter Hyperintensities; SUVR: Standard Uptake Value Ratio. CL: Centiloids; Me: Mesial Temporal; Te: Temporoparietal; MT: Meta temporal; R: Rest of neocortex.

* Significantly different from A β - controls ($p < 0.05$)

SUPPLEMENTAL TABLE 2. Regional ¹⁸F-SMBT-1 SUVR across clinical groups stratifies by Aβ status

	Aβ- CN SUVR _{WM} (n=44)	Aβ+ CN SUVR _{WM} (n=13)	<i>d</i>	Aβ- MCI SUVR _{WM} (n=9)	<i>d</i>	Aβ+ MCI SUVR _{WM} (n=3)	<i>d</i>	Aβ- "AD" SUVR _{WM} (n=2)	Aβ+ AD SUVR _{WM} (n=6)	<i>d</i>
Dorsolateral Prefrontal	1.05 ± 0.09	1.08 ± 0.17	0.22	1.07 ± 0.10	0.21	1.18 ± 0.07	1.61	1.10 ± 0.19	1.13 ± 0.14	0.68
Ventrolateral Prefrontal	1.20 ± 0.10	1.27 ± 0.14	0.58	1.21 ± 0.08	0.11	1.32 ± 0.06	1.46	1.26 ± 0.16	1.30 ± 0.11	0.95
Orbitofrontal	1.21 ± 0.10	1.31 ± 0.13	0.86	1.22 ± 0.08	0.11	1.29 ± 0.10	0.80	1.30 ± 0.13	1.30 ± 0.08	0.99
Anterior Cingulate	1.44 ± 0.12	1.43 ± 0.17	-0.07	1.49 ± 0.05	0.54	1.44 ± 0.05	0.00	1.46 ± 0.08	1.41 ± 0.10	-0.27
Posterior Cingulate	1.24 ± 0.12	1.36 ± 0.19	0.76	1.25 ± 0.06	0.11	1.36 ± 0.16	0.85	1.32 ± 0.20	1.42 ± 0.11	1.56
Superior Parietal	0.96 ± 0.12	1.06 ± 0.14	0.77	0.96 ± 0.12	0.00	1.05 ± 0.12	0.75	1.06 ± 0.17	1.10 ± 0.17	0.95
Supramarginal Gyrus	1.16 ± 0.09	1.31 ± 0.15	1.21	1.17 ± 0.08	0.12	1.30 ± 0.05	1.92	1.19 ± 0.17	1.35 ± 0.07	2.36
Lateral Occipital	0.97 ± 0.10	1.07 ± 0.12	0.91	0.94 ± 0.05	-0.38	1.06 ± 0.04	1.18	1.00 ± 0.16	1.21 ± 0.08	2.65
Primary Visual Cortex	0.96 ± 0.10	1.02 ± 0.12	0.54	0.96 ± 0.07	0.00	1.02 ± 0.02	0.83	0.97 ± 0.03	1.15 ± 0.14	1.56
Gyrus Angularis	1.18 ± 0.13	1.29 ± 0.13	0.85	1.16 ± 0.09	-0.18	1.33 ± 0.05	1.52	1.24 ± 0.23	1.36 ± 0.10	1.55
Temporooccipital	1.23 ± 0.12	1.32 ± 0.12	0.75	1.18 ± 0.08	-0.49	1.38 ± 0.09	1.41	1.23 ± 0.22	1.36 ± 0.08	1.27
Lateral Temporal	1.23 ± 0.12	1.35 ± 0.12	1.00	1.22 ± 0.09	-0.09	1.28 ± 0.03	0.57	1.31 ± 0.21	1.34 ± 0.07	1.12
Inferior Temporal	1.10 ± 0.15	1.26 ± 0.21	0.88	1.08 ± 0.15	-0.13	0.94 ± 0.07	-1.37	1.27 ± 0.37	1.21 ± 0.20	0.62
Amygdala	1.75 ± 0.16	1.80 ± 0.14	0.33	1.81 ± 0.12	0.42	1.86 ± 0.09	0.85	1.98 ± 0.09	1.66 ± 0.23	-0.45
Hippocampus	1.60 ± 0.11	1.61 ± 0.12	0.09	1.62 ± 0.11	0.18	1.64 ± 0.06	0.45	1.58 ± 0.20	1.44 ± 0.08	-1.66
Parahippocampus	1.36 ± 0.16	1.38 ± 0.17	0.12	1.37 ± 0.12	0.07	1.16 ± 0.15	-1.29	1.17 ± 0.44	1.17 ± 0.20	-1.05
Entorhinal Cortex	0.87 ± 0.25	0.78 ± 0.17	-0.42	0.77 ± 0.24	-0.41	0.72 ± 0.20	-0.66	1.00 ± 0.16	0.84 ± 0.29	-0.11
Caudate	2.44 ± 0.26	2.40 ± 0.27	-0.15	2.37 ± 0.32	-0.24	2.11 ± 0.31	-1.15	2.48 ± 0.28	2.15 ± 0.15	-1.37
Putamen	2.16 ± 0.22	2.10 ± 0.09	-0.36	2.19 ± 0.19	0.15	2.13 ± 0.10	-0.18	2.01 ± 0.15	1.99 ± 0.12	-0.96
Globus Pallidus	1.85 ± 0.09	1.74 ± 0.08	-1.29	1.86 ± 0.11	0.10	1.78 ± 0.04	-1.01	1.81 ± 0.05	1.69 ± 0.08	-1.88
Thalamus	2.26 ± 0.20	2.28 ± 0.14	0.12	2.28 ± 0.20	0.10	2.19 ± 0.14	-0.41	2.27 ± 0.04	2.15 ± 0.20	-0.55
Midbrain	1.27 ± 0.14	1.33 ± 0.14	0.43	1.26 ± 0.06	-0.09	1.45 ± 0.07	1.63	1.31 ± 0.15	1.39 ± 0.11	0.95
Pons	1.44 ± 0.12	1.49 ± 0.12	0.42	1.48 ± 0.11	0.35	1.36 ± 0.02	-0.93	1.56 ± 0.09	1.33 ± 0.14	-0.84

Abbreviations

CN: elderly controls; MCI: mild cognitive impairment; AD: Alzheimer's disease; SUVR: Standard Uptake Value Ratio; WM: white matter (reference region)

In red bold: Significantly higher than controls ($p < 0.05$)

In blue bold: Significantly lower than controls ($p < 0.05$)

In green bold: Cohen's effect size d against Aβ- CN

SUPPLEMENTAL TABLE 3. Association between regional ¹⁸F-SMBT-1 binding and brain volumetrics

SMBT-1 Region	Hippocampus (n=73)		Grey Matter (n=73)		White Matter (n=73)		Ventricles (n=73)		White Matter Hyperintensities (n=72)	
	r	p	r	p	r	p	r	p	r	p
Ventrolateral Prefrontal	-0.016	0.893	0.004	0.975	0.014	0.905	0.088	0.459	0.140	0.241
Orbitofrontal	0.033	0.781	0.010	0.933	0.083	0.483	0.077	0.516	0.056	0.638
Anterior Cingulate	0.212	0.072	0.104	0.383	-0.105	0.379	0.045	0.703	-0.041	0.734
Posterior Cingulate	-0.097	0.413	-0.187	0.110	0.084	0.482	0.146	0.219	0.098	0.412
Superior Parietal	-0.188	0.112	-0.192	0.104	0.134	0.260	0.198	0.094	0.206	0.083
Supramarginal Gyrus	-0.228	0.052	-0.280	0.017*	0.069	0.562	0.093	0.436	0.134	0.262
Lateral Occipital	-0.282	0.016*	-0.225	0.055	0.145	0.220	0.070	0.559	0.253	0.032*
Primary Visual Cortex	-0.198	0.093	-0.180	0.129	0.011	0.928	0.035	0.766	0.279	0.018*
Gyrus Angularis	-0.159	0.180	-0.170	0.150	0.149	0.209	0.045	0.705	0.151	0.206
Temporooccipital	-0.143	0.228	-0.084	0.479	0.166	0.161	0.011	0.930	0.042	0.728
Lat Temporal	-0.064	0.588	-0.021	0.861	0.210	0.074	0.007	0.954	-0.017	0.885
Inferior Temporal	-0.007	0.957	-0.042	0.722	0.323	0.005*	-0.169	0.153	0.022	0.855
Amygdala	0.118	0.322	0.166	0.160	0.427	0.000*	-0.073	0.542	0.037	0.761
Hippocampus	0.343	0.003*	0.337	0.004*	0.232	0.048*	-0.071	0.554	-0.231	0.051
Parahippocampus	0.338	0.004*	0.331	0.004*	0.080	0.499	-0.274	0.019*	-0.253	0.032
Entorhinal	0.031	0.792	0.034	0.775	0.052	0.662	-0.013	0.911	0.132	0.268
Caudate	0.201	0.089	0.303	0.009*	-0.063	0.594	-0.198	0.093	-0.170	0.155
Putamen	-0.018	0.883	0.197	0.129	-0.194	0.101	0.060	0.616	-0.058	0.630
Globus Pallidus	0.115	0.332	0.321	0.006*	0.130	0.273	-0.056	0.636	-0.056	0.639
Thalamus	0.235	0.046*	0.303	0.009*	0.062	0.604	-0.151	0.203	-0.074	0.539
Midbrain	0.069	0.560	0.163	0.171	0.347	0.003*	0.002	0.984	-0.007	0.951
Pons	0.163	0.169	0.250	0.033*	0.221	0.060	-0.050	0.678	-0.137	0.252
Aβ burden (CL)	-0.432	0.000*	-0.449	0.000*	-0.031	0.793	0.207	0.078	0.218	0.065
Tau burden (SUVR)	-0.358	0.003*	-0.410	0.001*	0.018	0.886	0.204	0.093	-0.184	0.129

*Significantly associated ($p < 0.05$)