

SUPPLEMENTARY MATERIAL

Alzheimer's Disease neuropathologic changes outside the cerebrum are related to a higher odds of dementia

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Supplementary Table 1. Frequencies of regional tau-tangles and A β positivity

Region	*Binary Tau-tangles	**Fraction Tau-tangles	Binary Aβ	Fraction Aβ
Neocortical	94.7%	52.4%	88.7%	78.7%
Limbic/subcortical	99.7%	89.8%	79.7%	72.6%
Brainstem	86.0%	55.1%	45.3%	26.6%
Olfactory bulb	69.3%	69.3%	51.0%	51.0%
Spinal cord	34.3%	12.7%	NA	NA

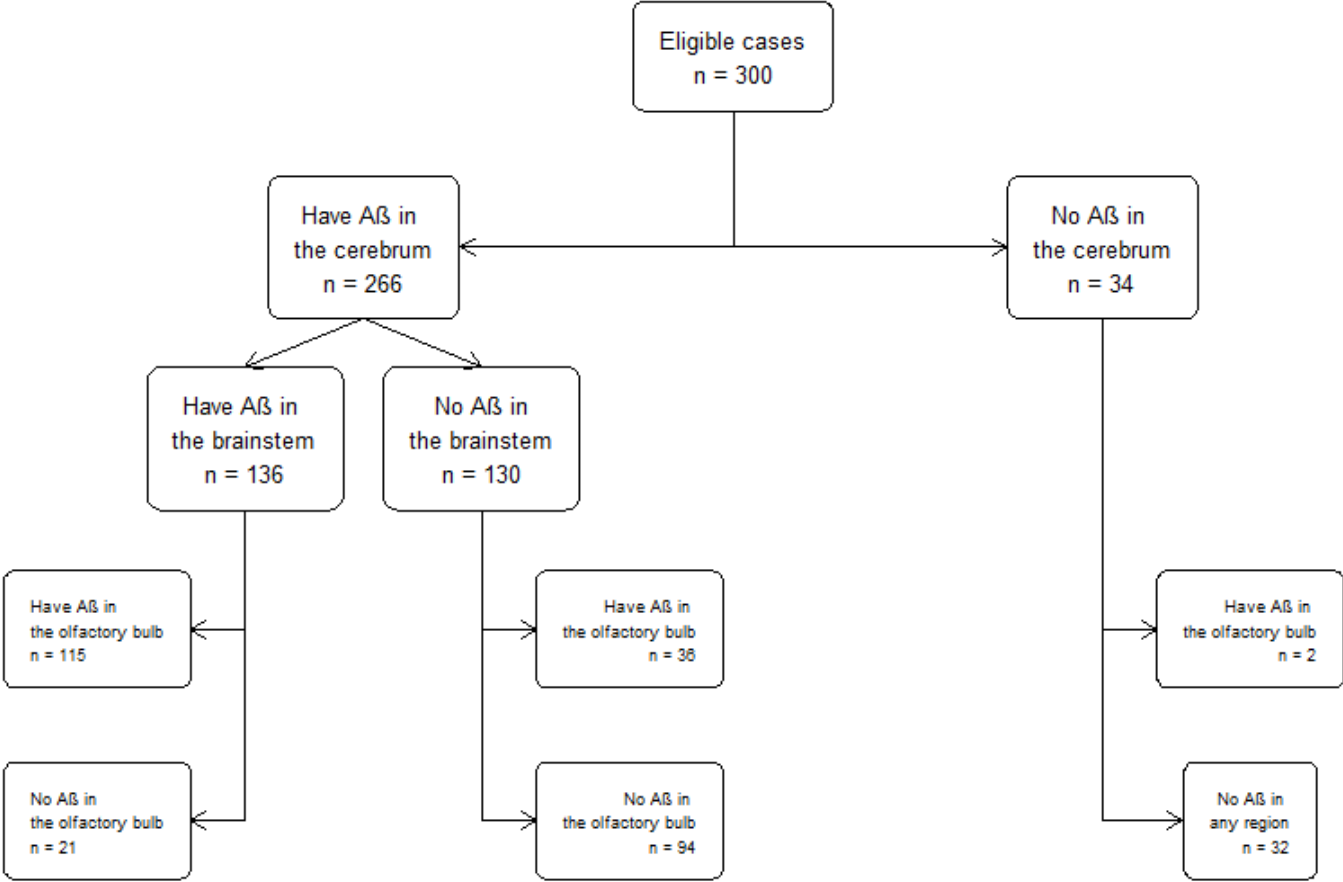
*Frequency of the regional positivity for binary tau-tangles or A β .

** Percentage of sites in each region showing binary positivity of tau-tangles or A β .

Supplementary Table 2. Distribution of tau-tangles in spinal cord

Spinal Level	# Missing	# tau-tangles	%	# tau-tangles Upper level	# tau-tangles Lower level	p-Value
Cervical (Cerv)	0	81	79 %	78		
Thoracic (Thor)	4	26	26%	25	26	
Lumbar (Lum)	2	24	24%	21	23	
Sacral (Sac)	14	13	15%		13	
ANY	0	103	100%			
Cerv vs Thor				78 vs 26 of 99		<0.001
Thor vs Lum				25 vs 23 of 97		0.715
Lum vs Sac				21 vs 13 of 87		0.103

Supplementary Figure 1. Flow char of the distribution of A β in cerebrum and brainstem



Supplementary Table 3. Regional tau-tangles and A β positivity in adults with and without APOE4 allele

Tau-tangles positivity	No APOE4	Yes APOE4	Chi-Square	Aβ positivity	No APOE4	Yes APOE4	Chi-Square
Tau-tangles Neocortical	202 (94%)	72 (97%)	1.51 p=0.219	Aβ Neocortical	184 (85%)	72 (97%)	7.81 p=0.005
Tau-tangles Limbic/subcortical	215 (99.5%)	74 (100%)	0.558 p=0.558	Aβ Limbic/subcortical	160 (74%)	70 (95%)	14.14 p<0.001
Tau-tangles Brainstem	184 (85%)	67 (91%)	1.358 p=0.244	Aβ Brainstem	79 (37%)	52 (70%)	25.27 p<0.001
Tau-tangles Olfactory	145 (67%)	57 (77%)	2.55 p=0.110	Aβ Olfactory	97 (45%)	50 (68%)	11.28 p<0.001
Tau-tangles Spinal cord	70 (32%)	31 (42%)	2.18 p=0.139				

Supplementary Table 4. Demographics and multistage analysis of location of A β and tau-tangles with odds of a final diagnosis of dementia

	Stage 1 A β regions alone				Stage 2 All A β regions	Stage 3 A β & tau-tangles
Region	Model A Odds Ratio (95th CI) p-Value	Model B Odds Ratio (95th CI) p-Value	Model C Odds Ratio (95th CI) p-Value	Model D Odds Ratio (95th CI) p-Value	Model I Odds Ratio (95th CI) p-Value	Model K Odds Ratio (95th CI) p-Value
Age	1.01(0.98,1.05) p=0.449	1.01(0.97,1.05) p=0.486	1.01(0.97,1.05) p=0.645	1.00(0.96,1.04) p=0.954	1.0 (0.96,1.04) p=0.922	0.98(0.94,1.03) p=0.423
Sex	1.04(0.62,1.78) p=0.922	1.04(0.62,1.77) p=0.871	0.98(0.58,1.67) p=0.945	0.96(0.56,1.63) p=0.875	0.98(0.57,1.68) p=0.928	1.06(0.61,1.86) p=0.831
Education	0.96 (0.89,1.04) p=0.267	0.97(0.89,1.05) p=0.282	0.96(0.89,1.04) p=0.348	0.98 (0.90,1.06) p=0.540	0.98(0.57,1.68) p=0.543	0.98(0.90,1.06) p=0.578
A β Neocortical	2.11 (0.94, 4.75) p=0.070				0.63 (0.18, 2.20) p= 0.470	
A β Limbic/subcortical		2.83 (1.47, 5.44) p=0.002			1.94 (0.66, 5.68) p= 0.228	
A β Brainstem			2.76 (1.71,4.44) p <0.001		1.75 (0.96, 3.19) p=0.068	
A β Olfactory				2.91 (1.79,4.74) p <0.001	1.80 (0.96, 3.38) p=0.065	
Any A β						1.44 (0.61,3.39) p<0.406
	Stage 1 Tau-tangle regions alone				Stage 2 All tau-tangle regions	
Region	Model E Odds Ratio (95th CI) p-Value	Model F Odds Ratio (95th CI) p-Value	Model G Odds Ratio (95th CI) p-Value	Model H Odds Ratio (95th CI) p-Value	Model J Odds Ratio (95th CI) p-Value	
Age	1.01(0.97,1.05) p=0.582	1.00(0.96,1.04) p=0.993	1.01(0.97,1.05) p=0.683	1.01(0.97,1.05) p=0.582	0.99(0.95,1.03) p=0.685	
Sex	1.00 (0.59,1.69) p=0.994	0.93(0.55,1.58) p=0.794	0.99(0.59,1.68) p=0.978	1.08(0.64,1.83) p=0.781	1.04(0.60,1.80) p=0.881	
Education	0.96 (0.88,1.03) p=0.267	0.97(0.90,1.05) p=0.449	0.954(0.88,1.03) p=0.242	0.96(0.88,1.03) p=0.262	0.96(0.89,1.04) p=0.342	
Tau-tangles Neocortical	5.21 (1.16, 23.48) p=0.032				2.56 (0.52,12.68) p=0.249	2.41 (0.48, 12.00) p=0.282
Tau-tangles Brainstem		5.03 (2.02,12.51) p<0.001			4.02 (1.58,10.25) p=0.004	4.00 (1.57,10.21) p=0.004
Tau-tangles Olfactory			2.13 (1.26,3.63) p= 0.005		1.78 (1.02,3.10) p=0.041	1.74 (1.00,3.05) p=0.051
Tau-tangles Spinal cord				2.07 (1.27, 3.39) p= 0.004	1.90 (1.14,3.15) p=0.014	1.87 (1.21,3.11) p=0.017

This table summarizes the three stages of our primary analysis. All cells refer to logistic regression models in which dementia is the outcome. Each column represents a single model with the terms shown on the left. Each cell contains an estimated odds ratio for the presence of **A β** or **tau-tangles** in each of the regions (Left column) and the corresponding 95% confidence interval, as well as the fitted coefficient (logit) and the p-value. **Stage 1: Models A-D** and **E-H** provide results from a separate model for **A β** or **tau-tangles** in each region group shown in the left column and illustrated in Figure 1. **Stage 2: Models I & J** show the associations of either **A β** or **tau-tangles** for all the region groups in a single model, **Stage 3: Model K** shows the results for the probability of dementia when we included the single dominant **A β** factor and the four region groups for **tau-tangles** together in a single model. Bolded cells identify regions that are significantly associated with a final diagnosis of dementia proximate to death.

Supplementary Table 5. Fraction of sites within different regions showing ADNC and risk of dementia

Region	Model A	Model B	Model C	Model D	Model E	
	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	
A β Neocortical	4.69(2.14,10.29) p<0.001				1.12 (0.16,7.61) p=0.911	
A β Limbic/subcortical		4.06(2.10,7.84) p<0.001			1.98 (0.37,10.78) p=0.427	
A β Brainstem			4.94(2.41,10.12) p<0.001		2.37 (0.99,5.66) p=0.052	
A β Olfactory				2.91(1.79,4.73) p<0.001	1.50 (0.80,2.84) p=0.209	
	Model F	Model G	Model H	Model I	Model J	Model K
	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value
Tau-tangles Neocortical	17.82 (7.77,40.85) p<0.001					4.95 (1.76,13.91) p=0.002
Tau-tangles Limbic/subcortical		130.89 (18.03,950.34) p <0.001				2.60 (0.26,26.41) p=0.420
Tau-tangles Brainstem			20.58 (8.63,49.07) p <0.001			7.04 (2.57,19.29) p=0.001
Tau-tangles Olfactory				2.13 (1.26,3.63) p=0.005		1.17 (0.63, 2.18) p=0.621
Tau-tangles Spinal Cord					2.07 (1.27,3.39) p=0.004	1.59 (0.91, 2.77) p=0.102

Supplementary Table 6. Head trauma and health conditions and brainstem A β and tau-tangles with odds of dementia

Region	Dementia YN	Dementia YN	Dementia YN	Dementia YN
	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value
Head trauma		0.81 (0.50,1.33) p=0.410		0.878(0.54,1.43) p=0.599
Health conditions	0.72(0.58,0.88) p=0.002		0.73(0.59,0.89) p=0.002	
A β Brainstem	2.64 (1.62,4.30) p<0.001	2.79 (1.73,4.51) p<0.001		
Tau-tangles Brainstem			4.31(1.71,10.82) p=0.002	4.84(1.94,12.04) p=<0.001

Supplementary Table 7. A β and tau-tangles positivity in regions outside of cerebrum and odds of higher conventional AD staging score

Region	ADNC	CERAD YN	B score (BRAAK score)
	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value	Odds Ratio (95 th CI) p-Value
Aβ Brainstem	7.30(2.90,18.37) p<0.001	8.60(2.73,27.12) p<0.001	8.30 (4.21,16.38) p<0.001
Aβ Olfactory	4.76(2.11,10.77) p<0.001	15.27(5.18 ,44.97) p<0.001	1.61 (0.85,3.07) P=0.147
Tau-tangles Brainstem	2.9010(1.20,7.04) p=0.019	4.00 (1.55 ,10.34) P=0.004	2.91(1.37 ,6.17) P=0.005
Tau-tangles Olfactory	3.06(1.55,6.05) p=0.001	2.2 9(1.11,4.72) P=0.025	2.97 (1.70,5.21) p<0.001
Tau-tangles Spinal cord	2.02 (1.00,4.09) p=0.050	1.26 (0.62,2.58) P=0.520	2.08(1.21,3.58) P=0.009