

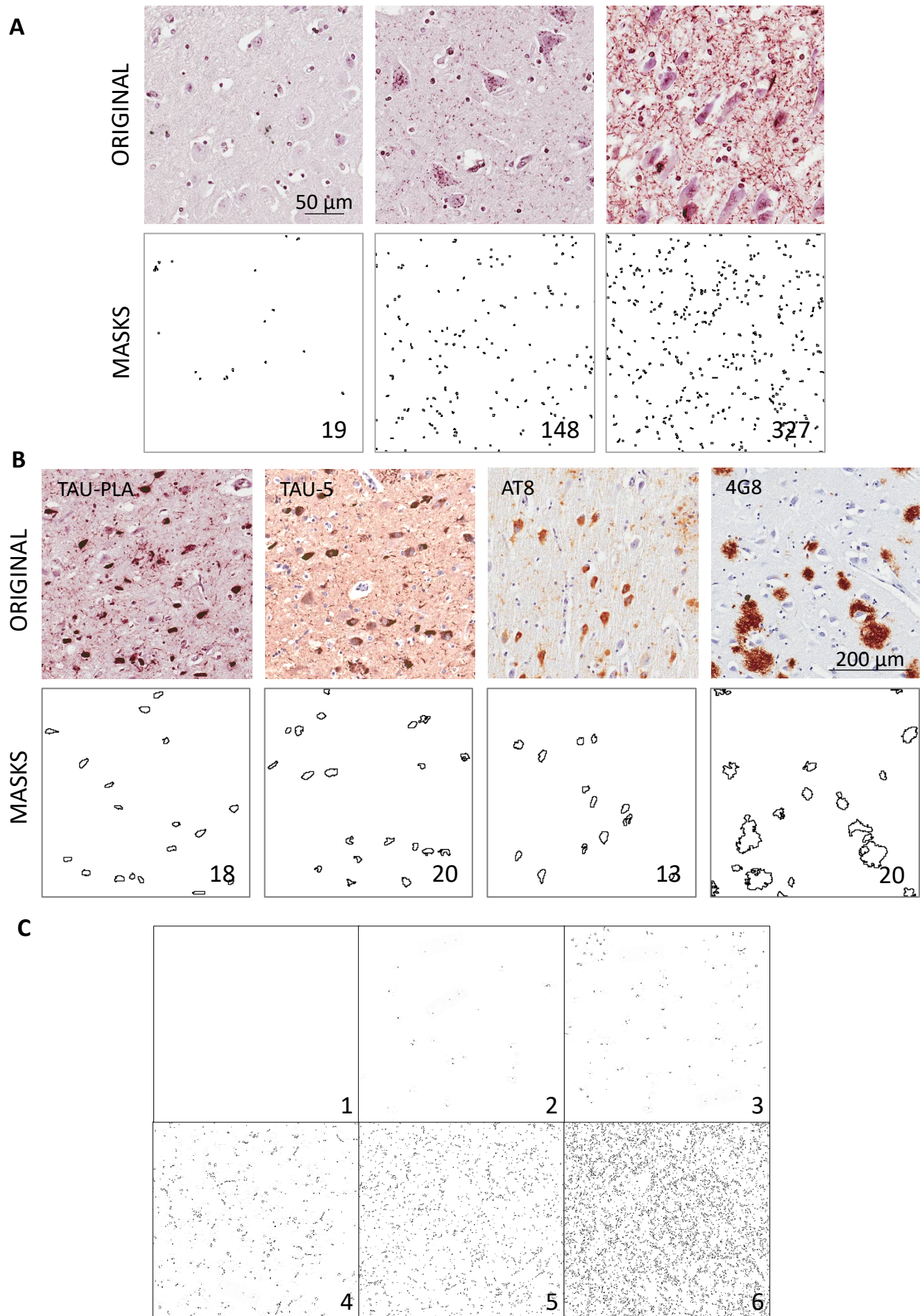
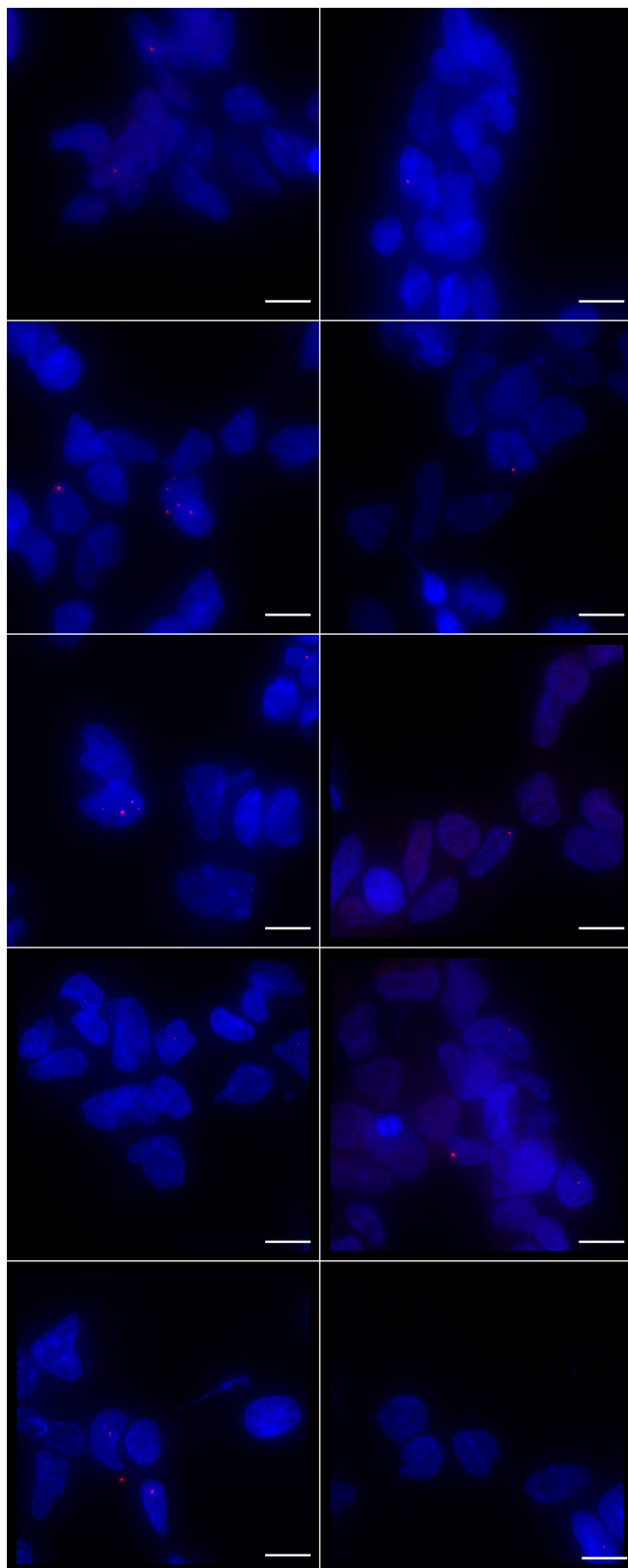


Figure S1. Automated analysis and semi-quantitative scales used for analysis.

- Rapamycin



+ Rapamycin

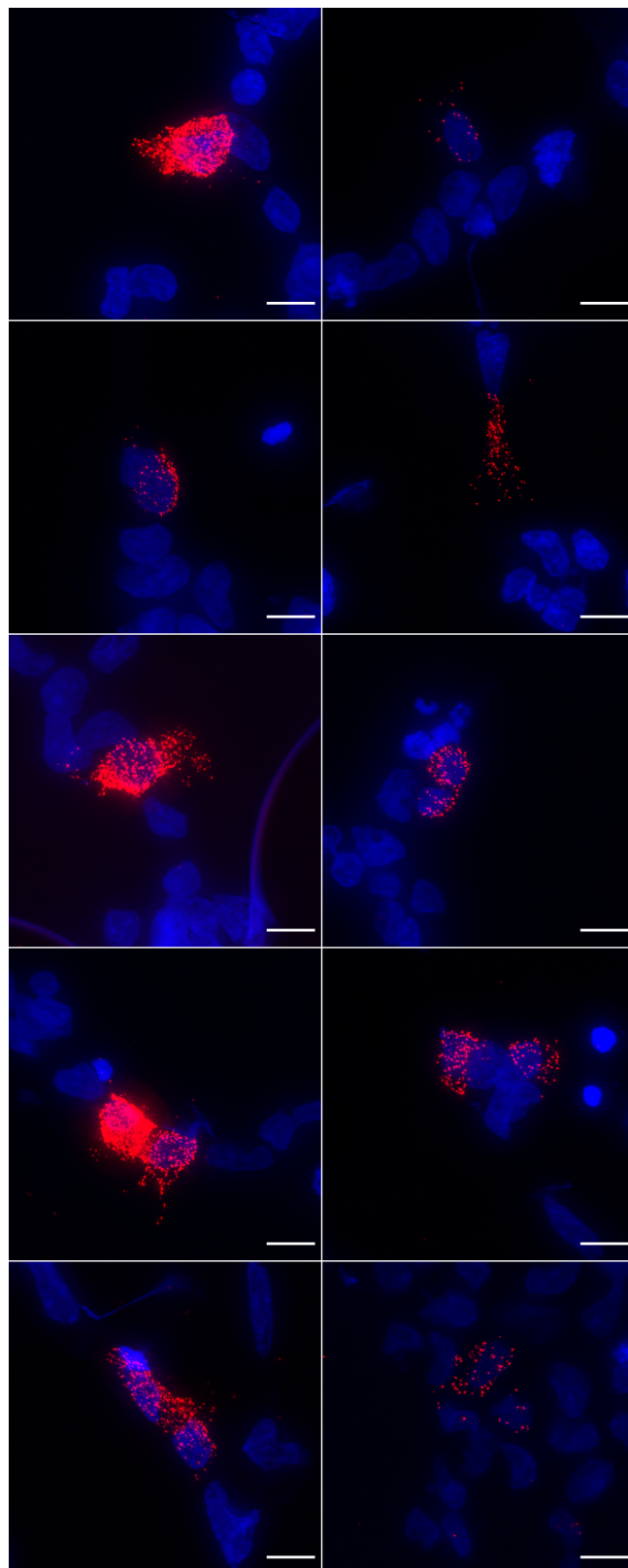


Figure S2. Detection of tau-tau interactions in HEK293 cells.

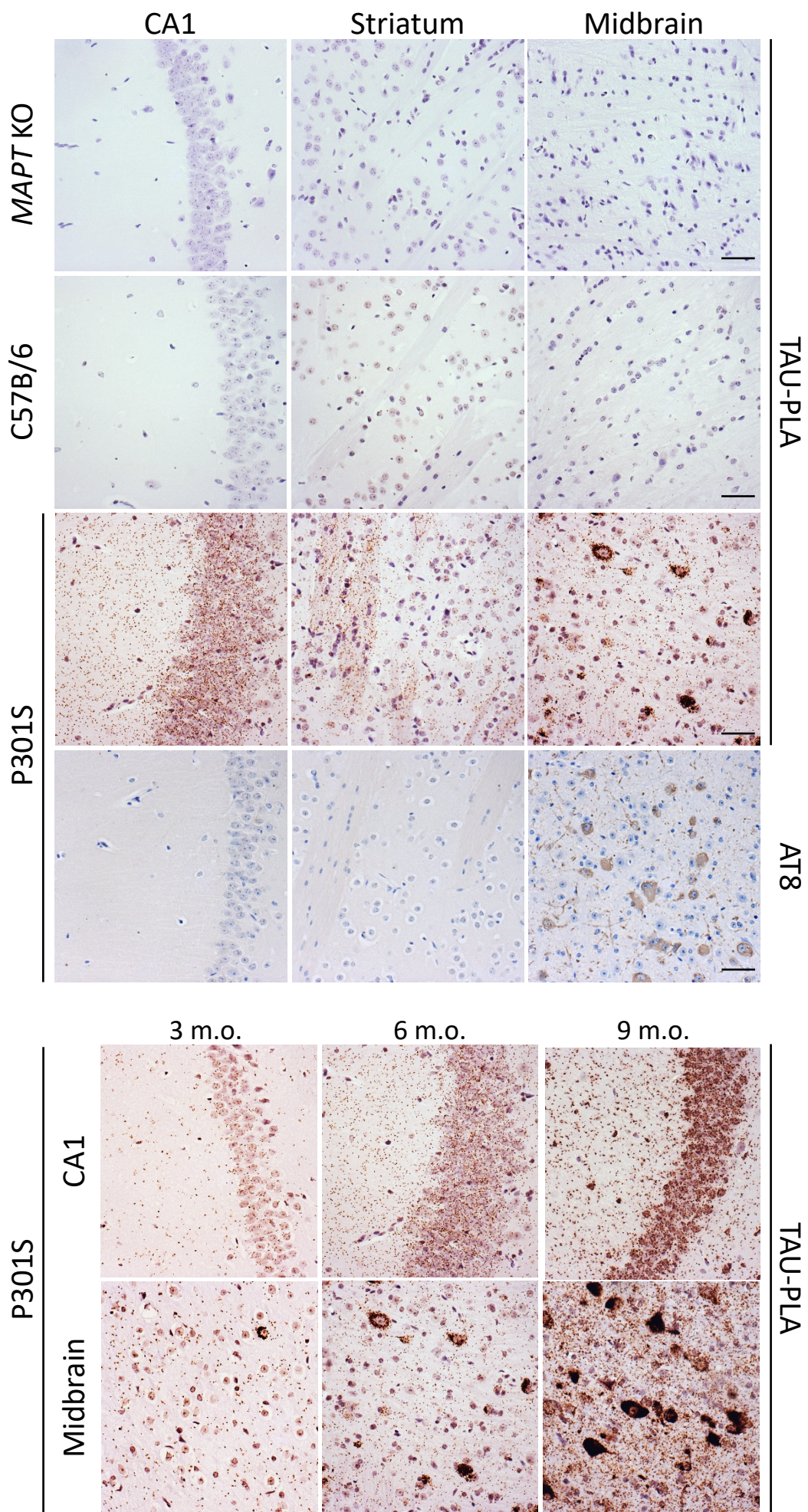


Figure S3. Demonstration of the *in situ* specificity of tau-PLA in mouse brain tissue.

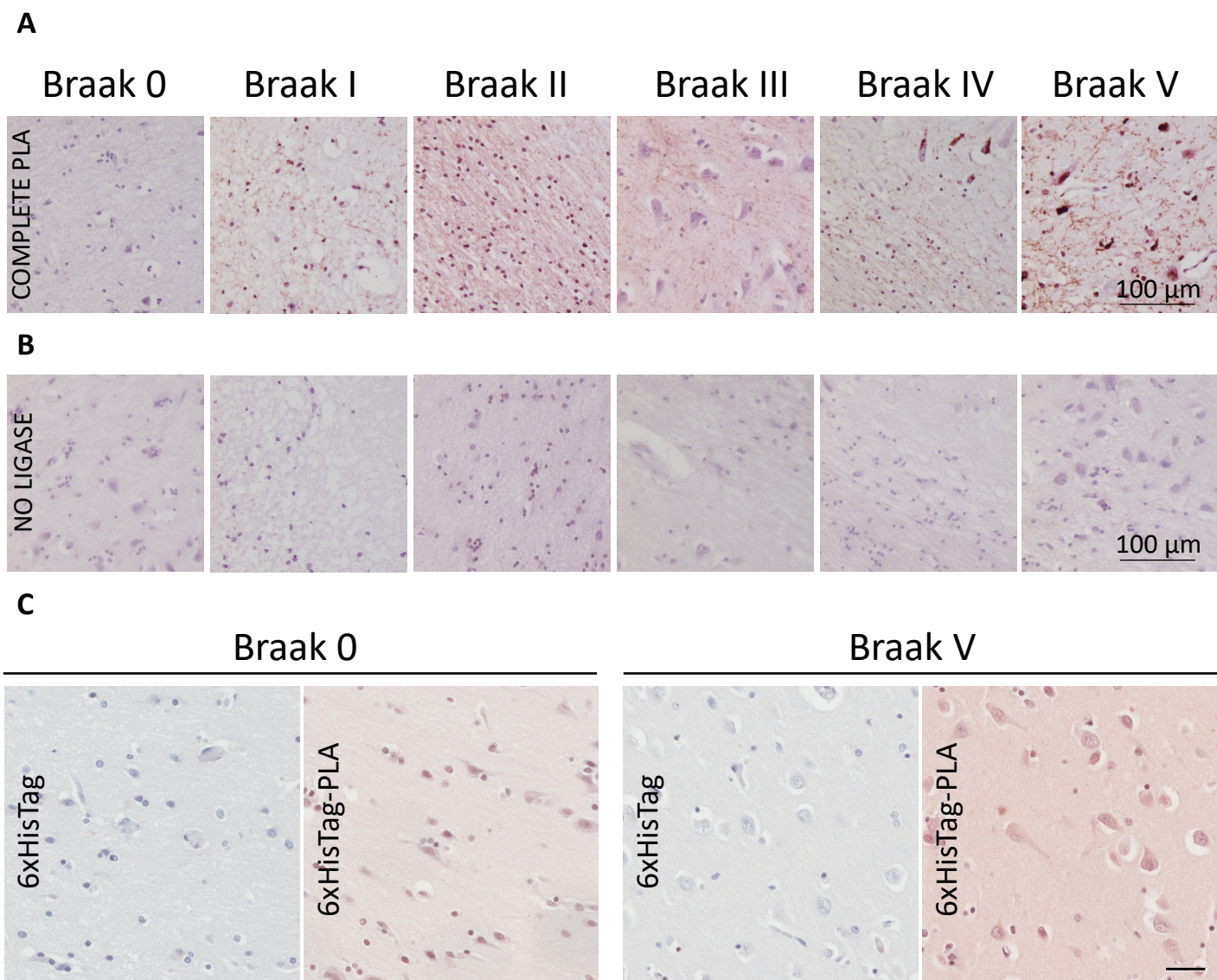


Figure S4. Tau-PLA detects endogenous human tau-tau interaction *in situ*.

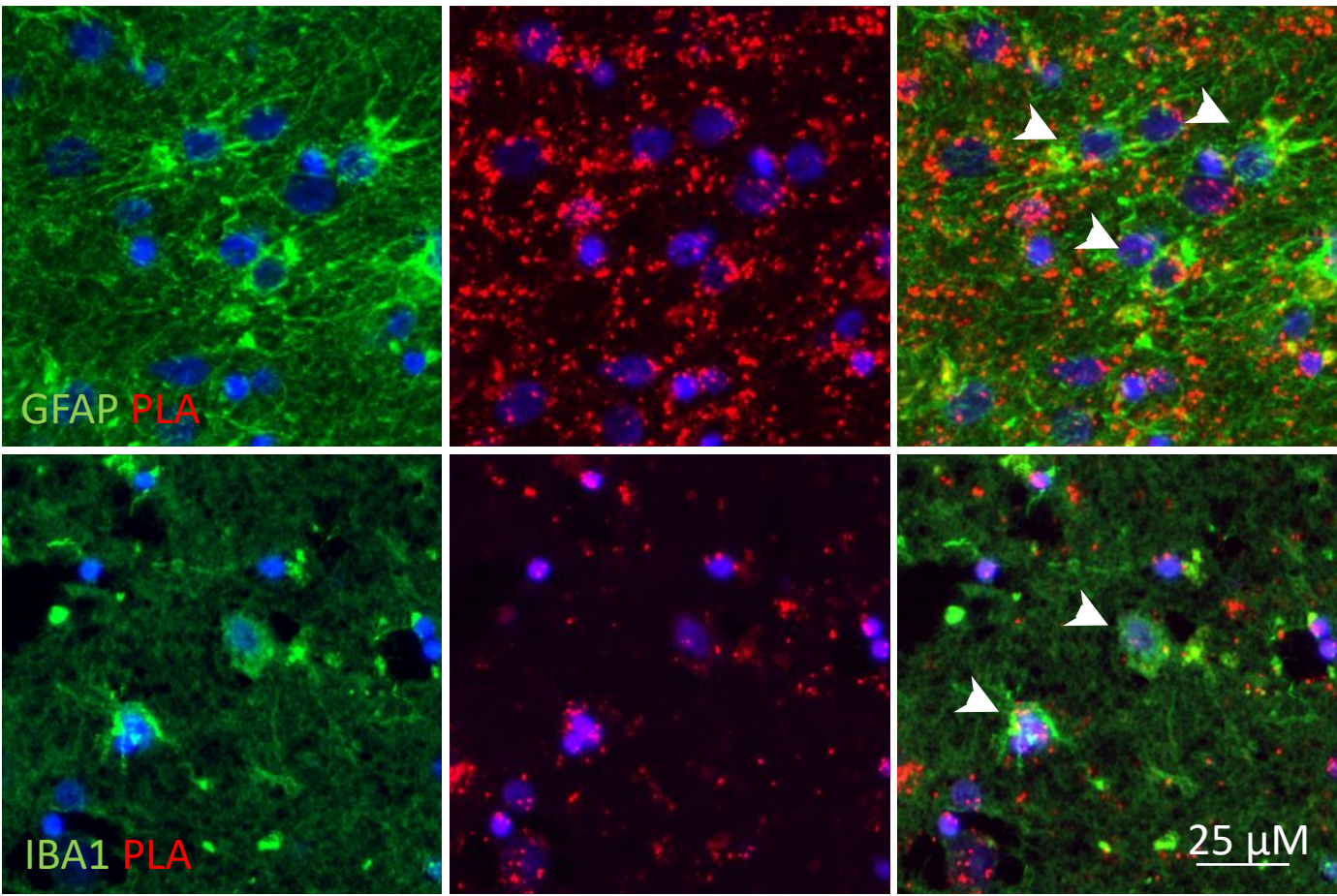


Figure S5. A proportion of diffuse tau complexes locates to astrocytes and microglia.

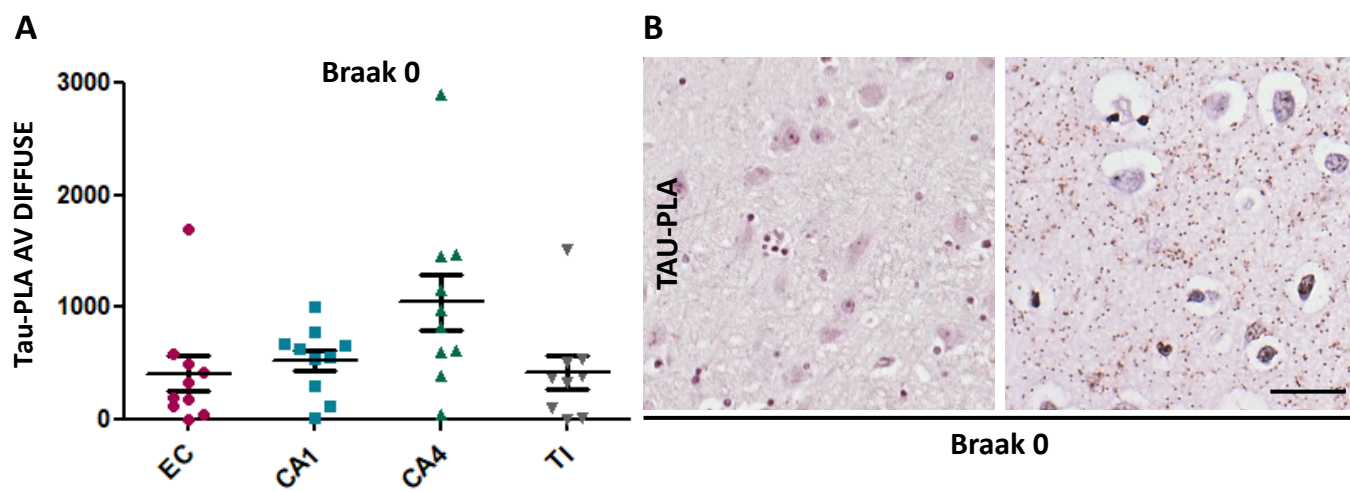


Figure S6. Tau-PLA revealed that cases in Braak 0 group presented heterogenicity.

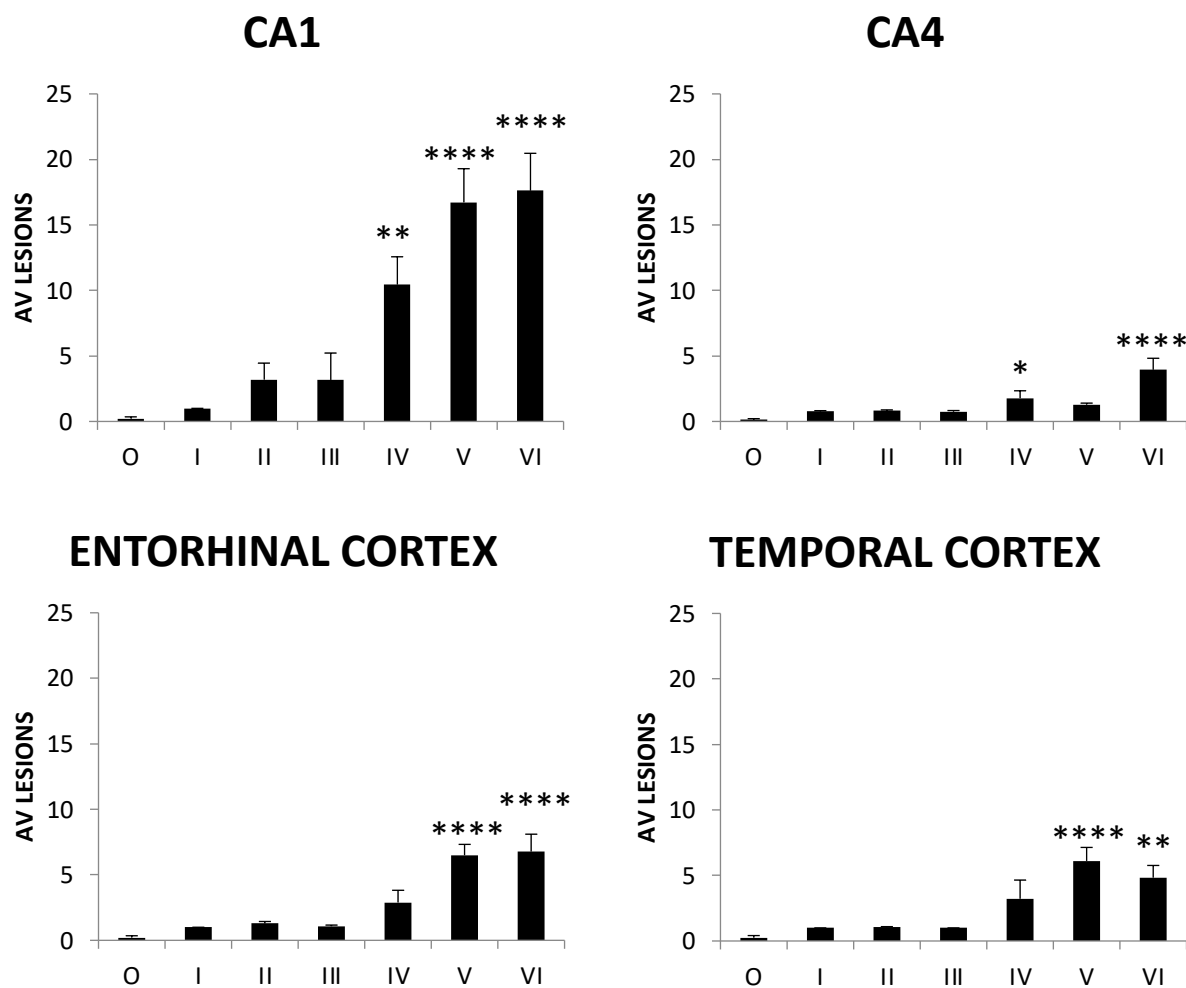


Figure S7. Quantification of lesions in samples labelled with tau5 IHC.

A CA4

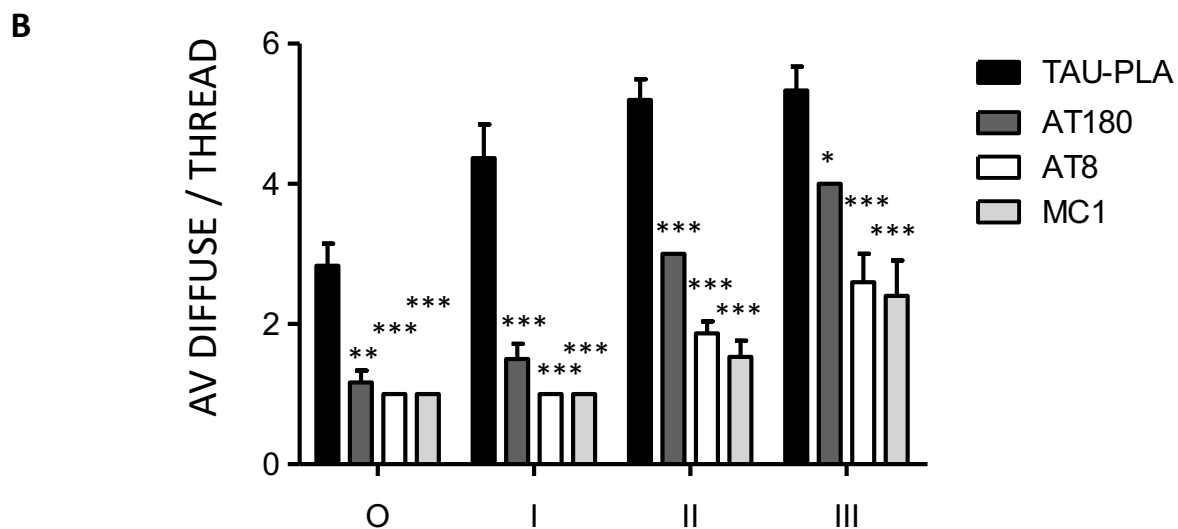
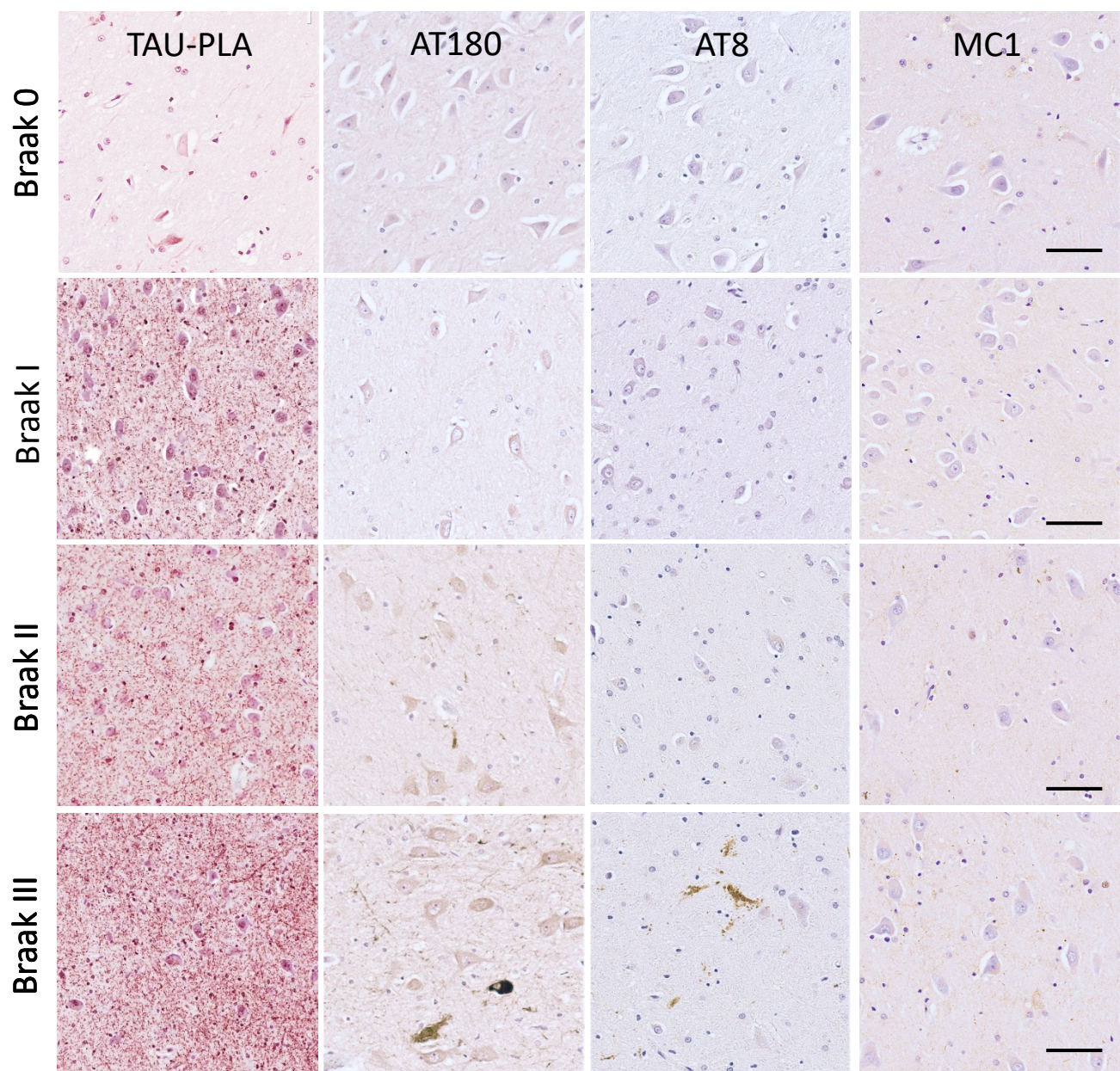
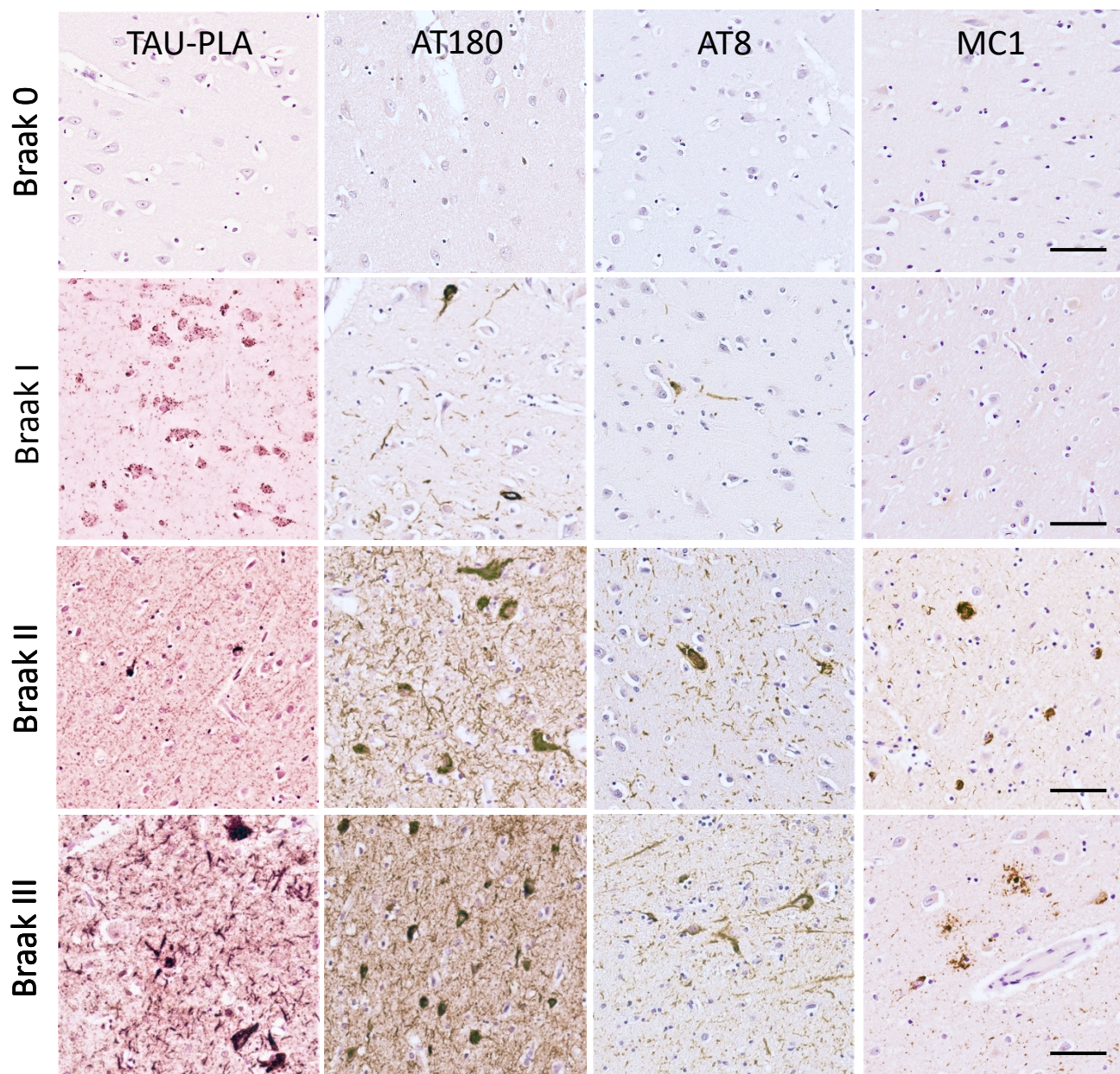


Figure S8. Early tau multimerization detection, prior to detection of tau hyperphosphorylation and misfolding across hippocampal regions and temporal isocortex– CA4.

A

ENTORRHINAL REGION



B

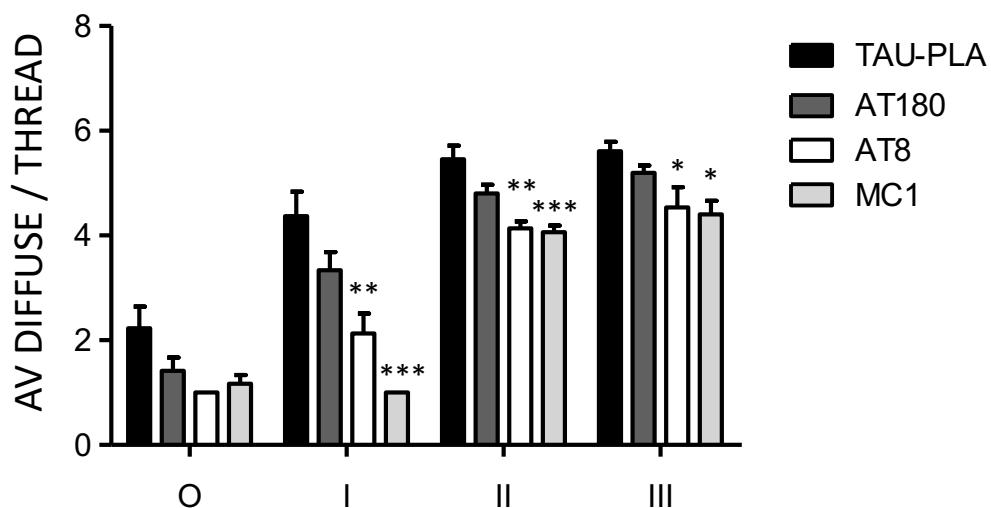


Figure S9. Early tau multimerization detection, prior to detection of tau hyperphosphorylation and misfolding across hippocampal regions and temporal isocortex– Entorhinal Cortex.

A CA1

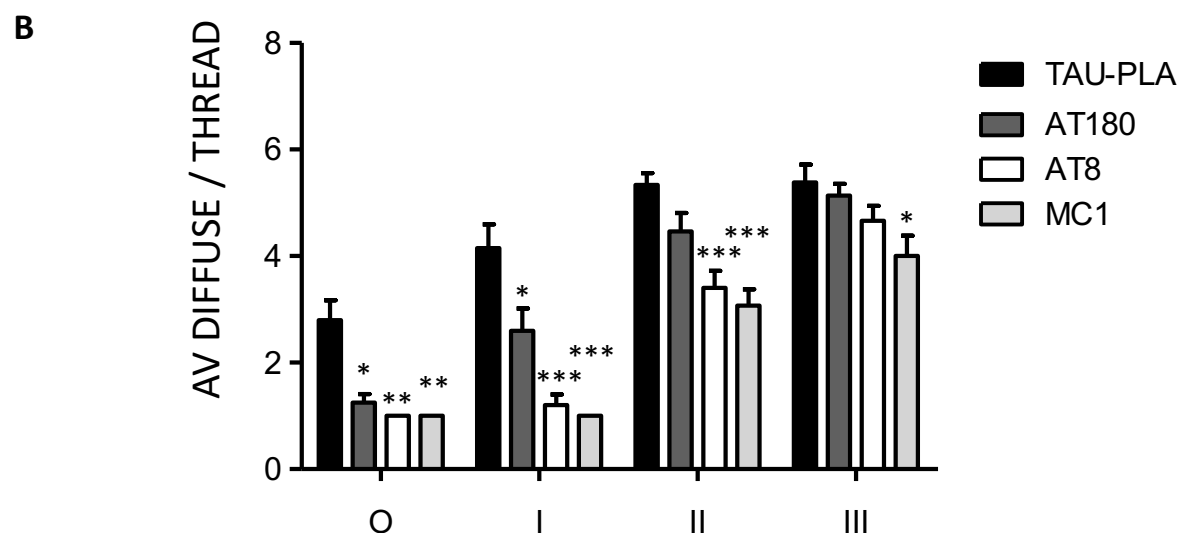
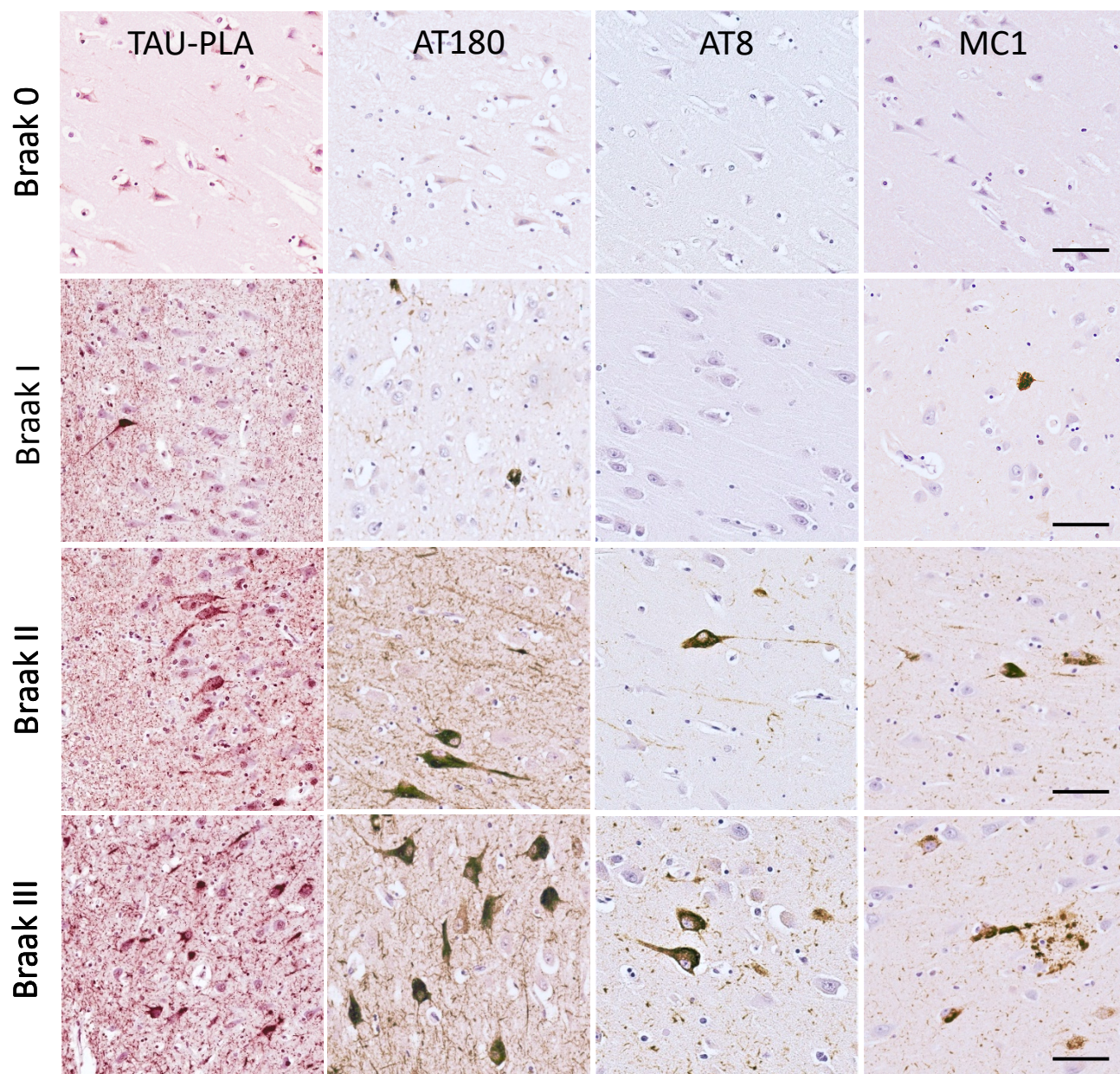
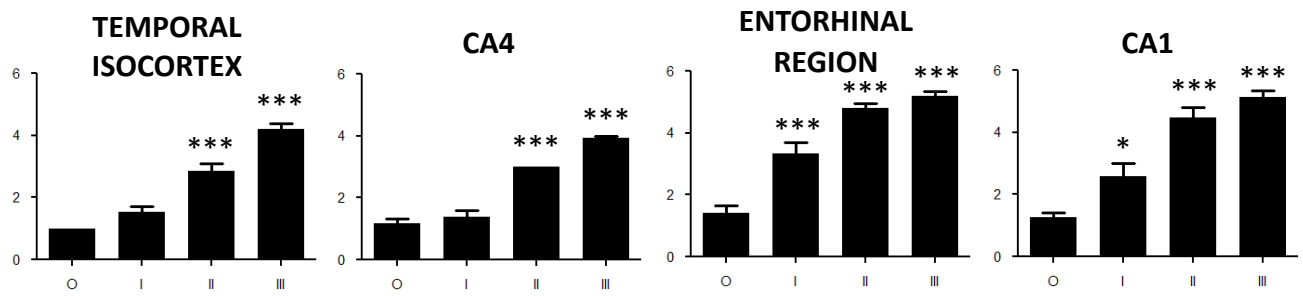
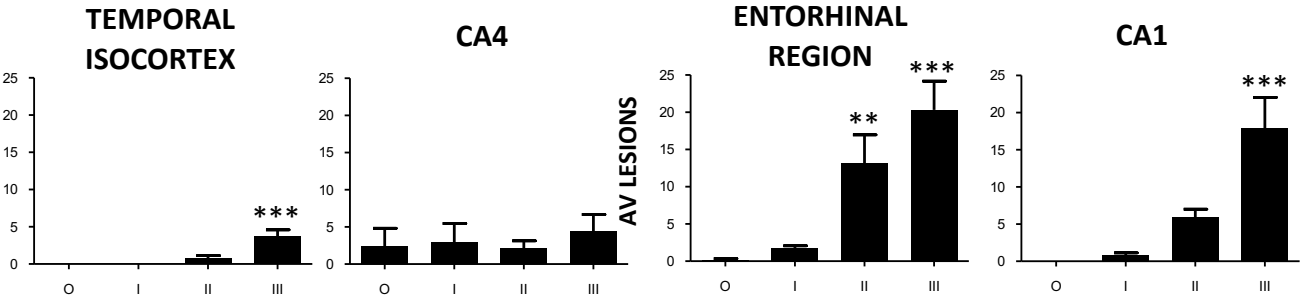


Figure S10. Early tau multimerization detection, prior to detection of tau hyperphosphorylation and misfolding across hippocampal regions and temporal isocortex– CA1.

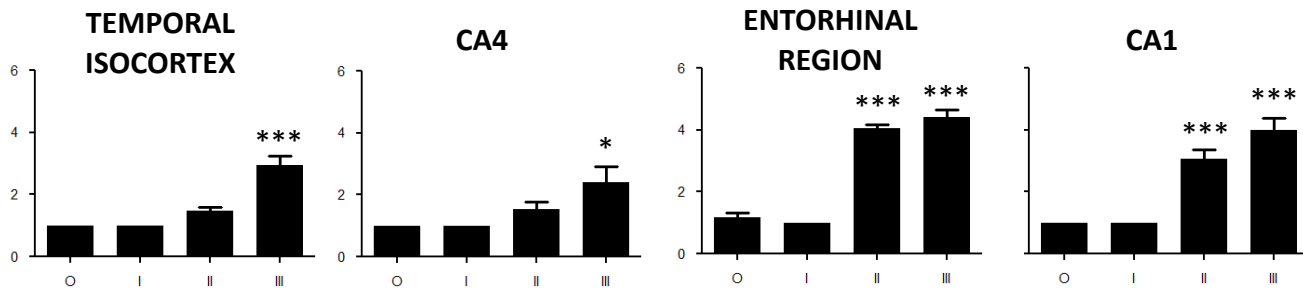
A. AT180 – diffuse/threads



B. AT180 IHC – lesions



C. MC1 IHC – diffuse/threads



D. MC1 IHC – lesions

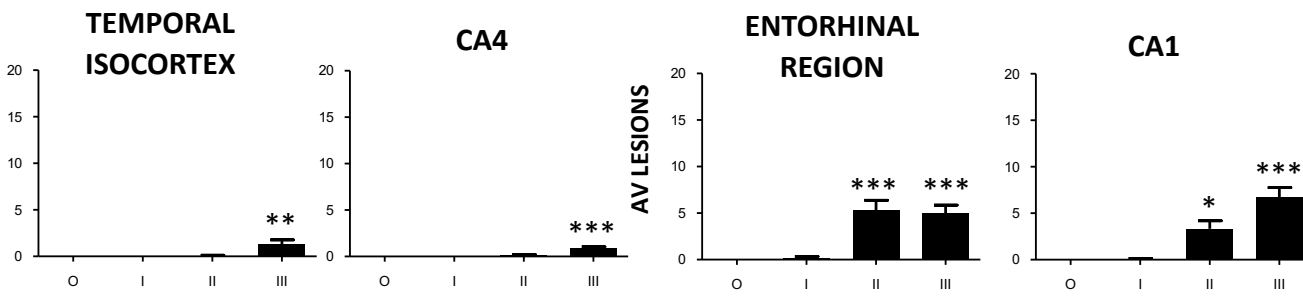


Figure S11. Quantification of diffuse pathology/threads and lesions labelled by AT180- and MC1- IHC in hippocampal regions and temporal isocortex.

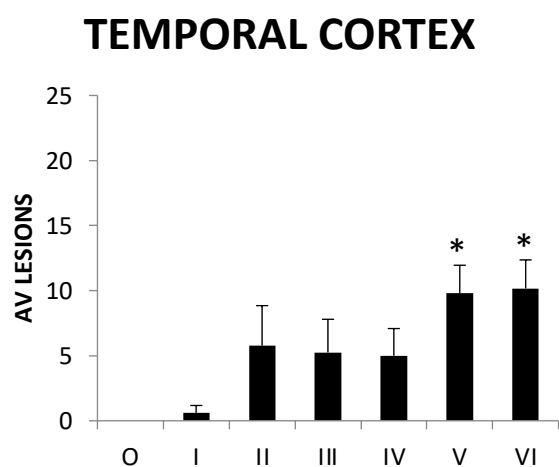
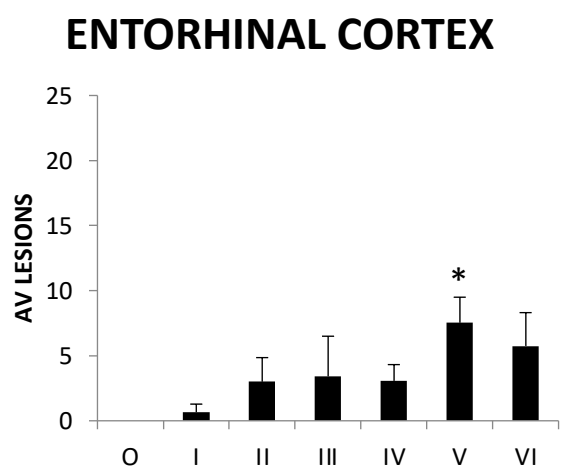
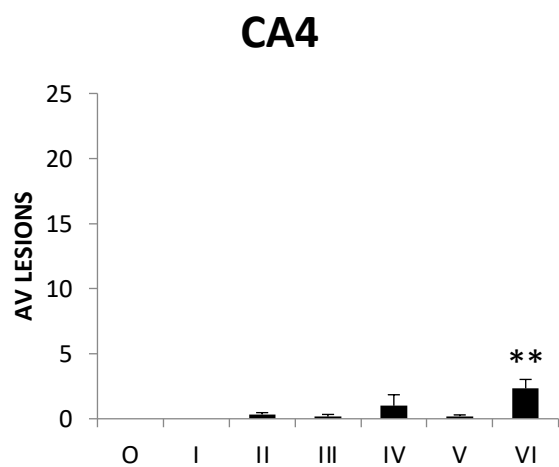
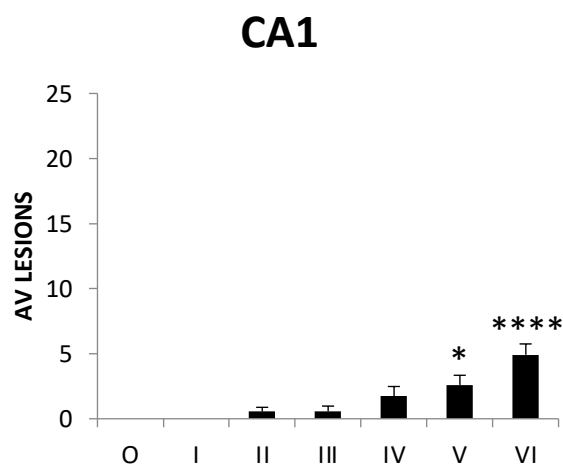


Figure S12. Quantification of lesions in samples labelled with 4G8 IHC.

Updated summary table (Oxford +Imperial cases)

	BRAAK 0	BRAAK I	BRAAK II	BRAAK III	BRAAK IV	BRAAK V	BRAAK VI
N=67	11	12	12	9	7	8	8
AV. AGE AT DEATH	54.6	68.7	82.6	89.1	87	85.7	76.5
% DEMENTED INDIVIDUALS	0%	0%	8.3%	11.1%	59.8%	100%	100%

Table S1. Summary of patient information

Updated table (Oxford +Imperial cases)

PMI	Dementia	Age at death	Gender	Amyloid burden (CERAD)	α-syn burden (Braak stage)	Neurofibrillary Braak stage
24	no	65	female	0, no neuritic plaques	0	0
48	no	42	female	0, no neuritic plaques	0	0
48	no	48	female	0, no neuritic plaques	0	0
72	no	51	male	0, no neuritic plaques	0	0
48	no	45	male	0, no neuritic plaques	0	0
48	no	41	female	0, no neuritic plaques	0	0
48	no	56	male	0, no neuritic plaques	0	0
19	no	74	male	0, no neuritic plaques	0	0
29	no	68	male	0, no neuritic plaques	0	0
20	no	52	female	0, no neuritic plaques	0	0
45	no	59	female	0, no neuritic plaques	0	0
48	no	56	male	0, no neuritic plaques	0	I
42	no	56	male	0, no neuritic plaques	0	I
65	no	92	female	0, no neuritic plaques	0	I
12	no	77	female	0, no neuritic plaques	0	I
100	no	88	female	0, no neuritic plaques	0	I
48	no	60	female	0, no neuritic plaques	0	I
48	no	51	male	0, no neuritic plaques	0	I
26	no	77	male	0, no neuritic plaques	0	I
19	no	91	female	1, sparse neuritic plaques	0	I
28	no	50	female	0, no neuritic plaques	0	I
15	no	61	female	0, no neuritic plaques	0	I
23	no	66	male	0, no neuritic plaques	0	I
54	no	92	female	0, no neuritic plaques	0	II
24	no	87	female	0, no neuritic plaques	0	II
48	no	57	female	0, no neuritic plaques	0	II
26	MCI	83	female	3, frequent neuritic plaques	1	II
24	no	89	female	1, sparse neuritic plaques	0	II
48	no	91	female	0, no neuritic plaques	0	II
96	no	79	male	0, no neuritic plaques	0	II
15	no	82	female	0, no neuritic plaques	0	II
26	no	83	male	2, moderate neuritic plaques	0	II
20	yes	82	female	2, moderate neuritic plaques	0	II
25	no	79	male	1, sparse neuritic plaques	0	II
15	no	87	female	2, moderate neuritic plaques	0	II
80	no	83	male	1, sparse neuritic plaques	0	III
86	MCI	90	female	0, no neuritic plaques	0	III
34	no	69	male	1, sparse neuritic plaques	0	III
72	no	92	male	1, sparse neuritic plaques	0	III
18	no	89	male	0, no neuritic plaques	0	III
24	no	92	female	3, frequent neuritic plaques	0	III
24	yes	98	female	3, frequent neuritic plaques	0	III
11	no	95	male	2, moderate neuritic plaques	0	III
40	MCI	94	female	3, frequent neuritic plaques	0	III
48	no	92	male	1, sparse neuritic plaques	0	IV
24	MCI	87	male	1, sparse neuritic plaques	0	IV
120	no	80	male	2, moderate neuritic plaques	0	IV
48	yes	89	male	3, frequent neuritic plaques	0	IV
12.75	yes	85	female	2, moderate neuritic plaques	0	IV
13	yes	89	female	3, frequent neuritic plaques	0	IV
28	no	95	female	2, moderate neuritic plaques	0	IV
31.25	yes	77	female	3, frequent neuritic plaques	0	V
46	yes	75	male	3, frequent neuritic plaques	Amygdala-only	V
66	yes	91	male	3, frequent neuritic plaques	0	V
34	yes	87	male	3, frequent neuritic plaques	0	V
24	yes	85	male	3, frequent neuritic plaques	0	V
45	yes	80	male	3, frequent neuritic plaques	0	V
34	yes	89	male	3, frequent neuritic plaques	0	V
21	yes	92	female	3, frequent neuritic plaques	0	V
7	yes	77	male	3, frequent neuritic plaques	0	VI
28	yes	64	female	3, frequent neuritic plaques	0	VI
13.67	yes	85	female	3, frequent neuritic plaques	0	VI
23	yes	61	female	3, frequent neuritic plaques	0	VI
69	yes	85	male	3, frequent neuritic plaques	0	VI
120	yes	83	male	3, frequent neuritic plaques	0	VI
7	yes	78	male	3, frequent neuritic plaques	0	VI
41	yes	79	male	2, moderate neuritic plaques	0	VI

Table S2. Additional information of brain samples.