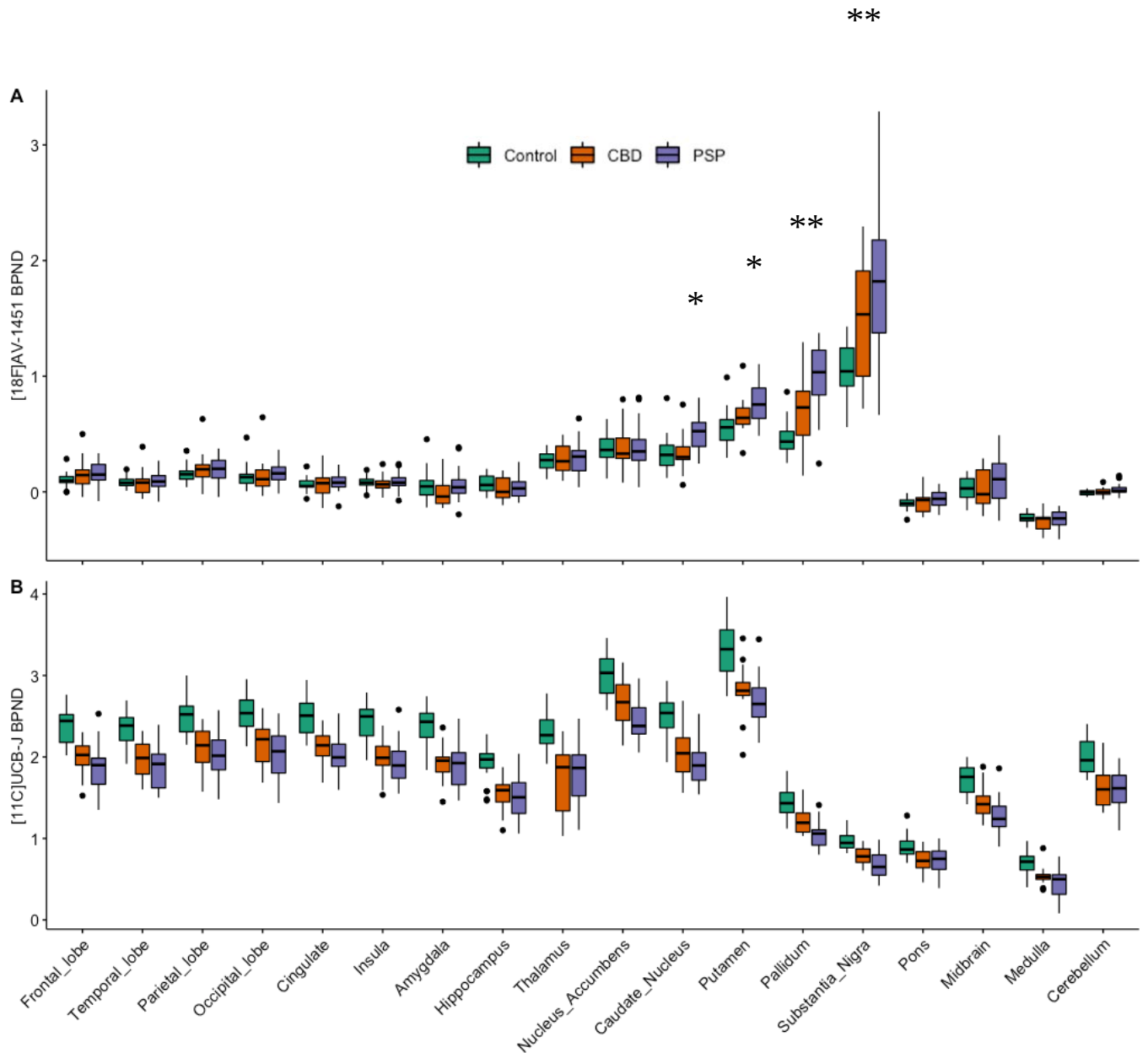


Molecular pathology and synaptic loss in primary tauopathies: A [¹⁸F]AV-1451 and [¹¹C]UCB-J PET study

Supplementary Figures = 5

Supplementary Tables = 4



Supplementary Figure 1. Boxplots of regional [¹⁸F]AV-1451 (A) and [¹¹C]UCB-J (B) non-displaceable binding potentials (BP_{ND}) across 18 regions of interest formed by aggregating Hammersmith atlas regions. Significantly higher [¹⁸F]AV-1451 binding potentials are seen in patients within the basal ganglia, and substantia nigra compared to controls (depicted with a black star). Patients with PSP and amyloid-negative CBS (CBD) have lower synaptic density in all the 18 regions illustrated in B, $p < 0.05$ (FDR corrected).

	Control (N = 19)	CBD (N = 12)	PSP (N = 23)
Frontal Lobe			
min	0	-0.045	-0.08
max	0.285	0.5	0.335
median (IQR)	0.10 (0.08, 0.13)	0.16 (0.10, 0.19)	0.15 (0.09, 0.25)
Parietal Lobe			
min	0.01	-0.06	-0.085
max	0.195	0.39	0.27
median (IQR)	0.08 (0.04, 0.11)	0.08 (-0.01, 0.12)	0.09 (0.05, 0.14)
Temporal Lobe			
min	0.04	-0.02	-0.045
max	0.355	0.63	0.375
median (IQR)	0.15 (0.09, 0.18)	0.20 (0.15, 0.25)	0.20 (0.11, 0.28)
Occipital Lobe			
min	0.005	-0.035	-0.015
max	0.47	0.645	0.365
median (IQR)	0.12 (0.07, 0.15)	0.12 (0.05, 0.20)	0.18 (0.09, 0.22)
Cingulate			
min	-0.06	-0.14	-0.125
max	0.22	0.315	0.235
median (IQR)	0.05 (0.03, 0.09)	0.08 (0.02, 0.13)	0.08 (0.04, 0.14)
Insula			
min	-0.03	-0.02	-0.075
max	0.19	0.24	0.24
median (IQR)	0.08 (0.05, 0.11)	0.07 (0.04, 0.11)	0.07 (0.06, 0.13)
Amygdala			
min	-0.135	-0.12	-0.195
max	0.455	0.285	0.385
median (IQR)	0.05 (-0.03, 0.12)	-0.03 (-0.09, 0.07)	0.04 (-0.03, 0.11)
Hippocampus			
min	-0.055	-0.115	-0.095
max	0.2	0.185	0.26
median (IQR)	0.03 (0.00, 0.15)	0.04 (-0.05, 0.12)	0.02 (-0.04, 0.11)
Thalamus			
min	0.11	0.095	0.04
max	0.405	0.495	0.635
median (IQR)	0.27 (0.21, 0.33)	0.28 (0.18, 0.40)	0.31 (0.18, 0.38)
Nucleus Accumbens			
min	0.115	0.08	0.04
max	0.63	0.8	0.815
median (IQR)	0.34 (0.30, 0.43)	0.35 (0.30, 0.47)	0.36 (0.26, 0.45)
Caudate Nucleus			

min	0.12	0.06	0.255
max	0.81	0.755	0.815
median (IQR)	0.30 (0.21, 0.38)	0.33 (0.28, 0.39)	0.53 (0.42, 0.62)
Pallidum			
min	0.25	0.38	0.245
max	0.865	1.295	1.375
median (IQR)	0.42 (0.37, 0.52)	0.76 (0.56, 0.92)	1.07 (0.86, 1.23)
Putamen			
min	0.295	0.55	0.485
max	0.99	1.09	1.105
median (IQR)	0.52 (0.43, 0.61)	0.65 (0.60, 0.73)	0.76 (0.65, 0.91)
Substantia Nigra			
min	0.56	0.8	0.665
max	1.43	2.295	3.29
median (IQR)	1.00 (0.91, 1.24)	1.57 (1.26, 1.96)	1.85 (1.38, 2.24)
Midbrain			
min	-0.16	-0.21	-0.25
max	0.18	0.29	0.49
median (IQR)	0.03 (-0.04, 0.10)	0.03 (-0.12, 0.20)	0.12 (-0.06, 0.26)
Pons			
min	-0.24	-0.22	-0.2
max	-0.04	0.13	0.07
median (IQR)	-0.10 (-0.12, -0.07)	-0.07 (-0.15, -0.04)	-0.06 (-0.11, -0.01)
Medulla			
min	-0.31	-0.4	-0.4
max	-0.14	-0.1	-0.12
median (IQR)	-0.23 (-0.26, -0.20)	-0.25 (-0.33, -0.22)	-0.23 (-0.28, -0.17)
Cerebellum			
min	-0.045	-0.065	-0.055
max	0.02	0.085	0.14
median (IQR)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.02)	0.01 (-0.00, 0.04)

Supplementary Table 1. Summary statistics for regional [^{18}F]AV-1451 non-displaceable binding potentials in controls, PSP, and amyloid negative CBS (CBD). min = minimum, max = maximum, IQR = interquartile range.

Contrast	Region	Estimate	SE	t-ratio	p-value	Adjusted p-value (FDR)
Control - PSP	Caudate Nucleus	-0.188889	0.05028779	-3.75616	0.00056	0.00378
Control - PSP	Pallidum	-0.5344782	0.05028779	-10.628389	0.00000	0.00000
Control - PSP	Putamen	-0.2039648	0.05028779	-4.05595	0.00017	0.00152
Control - PSP	Substantia Nigra	-0.7293099	0.05028779	-14.502722	0.00000	0.00000
Control – CBD	Pallidum	-0.2392405	0.06114926	-3.912402	0.00030	0.00234
Control - CBD	Substantia Nigra	-0.4502545	0.06114926	-7.363204	0.00000	0.00000
CBD - PSP	Caudate Nucleus	-0.1805226	0.05911996	-3.053497	0.00670	0.04020
CBSD- PSP	Pallidum	-0.2952377	0.05911996	-4.993875	0.00000	0.00003
CBD - PSP	Substantia Nigra	-0.2790554	0.05911996	-4.720155	0.00001	0.00010

Supplementary Table 2. Significant regional differences in [^{18}F]AV-1451 non-displaceable binding potential between patients with PSP and amyloid-negative CBS (CBD) compared to controls (corrected for multiple comparison across 18 regions of interest - including combined left and right cortical and subcortical areas of the modified Hammersmith Atlas).

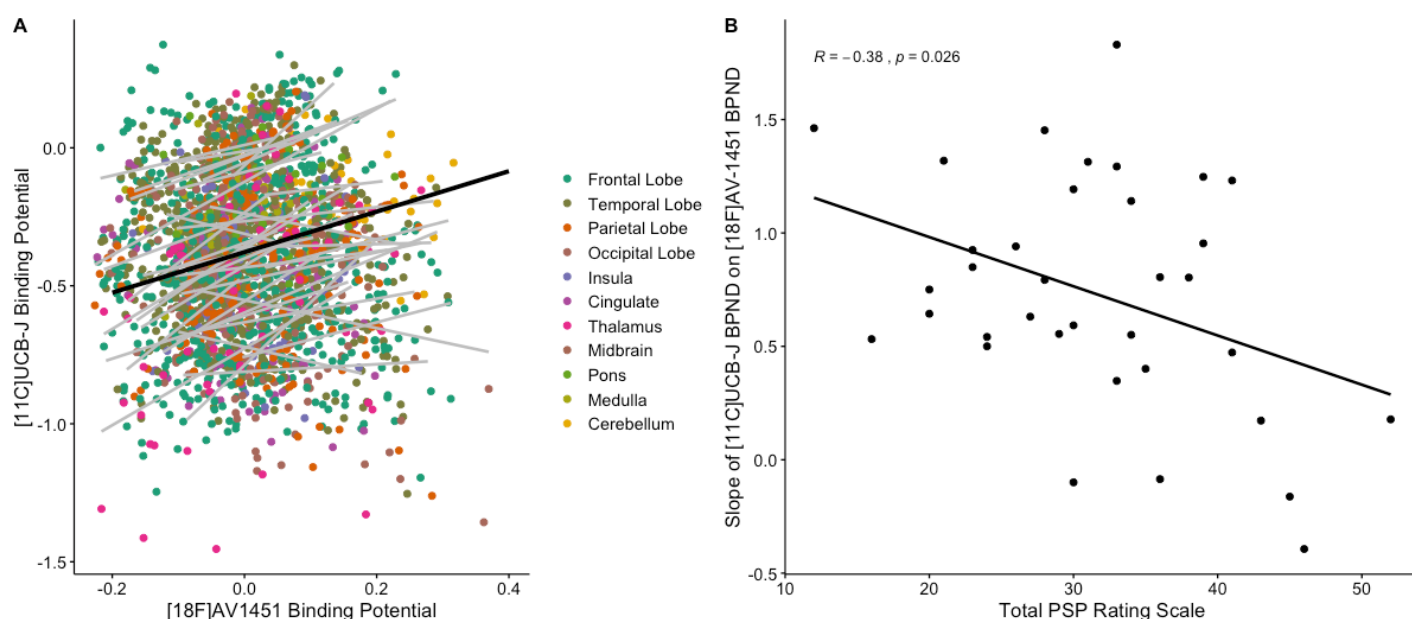
	Control (N = 19)	CBD (N = 12)	PSP (N = 23)
Frontal Lobe			
min	2.52	2.025	2.06
max	3.245	2.885	3.325
median (IQR)	2.96 (2.70, 3.06)	2.59 (2.50, 2.80)	2.37 (2.23, 2.58)
Temporal Lobe			
min	2.135	1.96	1.755
max	2.96	2.6	2.675
median (IQR)	2.67 (2.45, 2.77)	2.25 (2.09, 2.40)	2.17 (1.92, 2.34)
Parietal Lobe			
min	2.61	2.255	2.135
max	3.465	3.18	3.425
median (IQR)	3.12 (2.87, 3.19)	2.63 (2.52, 2.83)	2.52 (2.38, 2.81)
Occipital Lobe			
min	2.455	2.25	1.82
max	3.46	3.005	3.22
median (IQR)	2.91 (2.69, 3.09)	2.62 (2.43, 2.71)	2.48 (2.20, 2.73)
Cingulate			
min	2.52	2.085	2.03
max	3.425	2.995	3.02
median (IQR)	3.01 (2.81, 3.11)	2.57 (2.54, 2.78)	2.38 (2.25, 2.62)
Insula			
min	2.11	1.765	1.78
max	3.03	2.7	2.82
median (IQR)	2.75 (2.49, 2.83)	2.19 (2.09, 2.35)	2.06 (1.89, 2.33)
Amygdala			
min	1.875	1.565	1.5
max	3.035	2.535	2.74
median (IQR)	2.60 (2.36, 2.78)	2.11 (1.96, 2.18)	2.06 (1.85, 2.31)
Hippocampus			
min	1.265	1.05	1.025
max	2.335	1.805	2.15
median (IQR)	1.86 (1.78, 2.06)	1.58 (1.44, 1.68)	1.44 (1.31, 1.74)
Thalamus			
min	2.21	1.005	1.22
max	3.375	2.915	2.96
median (IQR)	2.77 (2.58, 2.96)	2.19 (1.55, 2.45)	2.29 (1.85, 2.40)
Nucleus Accumbens			
min	3.315	2.9	2.61
max	4.565	4.39	4
median (IQR)	3.90 (3.65, 4.10)	3.65 (3.47, 3.88)	3.16 (3.07, 3.52)
Caudate Nucleus			

min	2.235	1.92	1.82
max	3.515	3.305	3.11
median (IQR)	3.06 (2.82, 3.26)	2.50 (2.23, 2.75)	2.41 (2.16, 2.50)
Pallidum			
min	1.415	1.325	0.815
max	2.425	2.125	1.8
median (IQR)	1.80 (1.70, 1.94)	1.62 (1.40, 1.72)	1.24 (1.04, 1.35)
Putamen			
min	3.195	2.33	2.61
max	4.72	4.075	4.055
median (IQR)	3.88 (3.66, 4.18)	3.36 (3.31, 3.53)	3.17 (2.93, 3.35)
Substantia Nigra			
min	1.71	1.125	0.52
max	2.67	2.175	2.335
median (IQR)	2.07 (1.92, 2.37)	1.78 (1.48, 2.00)	1.53 (0.92, 1.84)
Midbrain			
min	1.66	1.25	0.69
max	2.83	2.41	2.55
median (IQR)	2.29 (2.10, 2.45)	1.61 (1.45, 2.10)	1.35 (0.99, 1.61)
Pons			
min	0.75	0.45	0.39
max	1.36	1.01	1.06
median (IQR)	0.94 (0.84, 1.02)	0.74 (0.65, 0.88)	0.76 (0.62, 0.90)
Medulla			
min	0.33	0.25	-0.05
max	0.95	0.83	0.74
median (IQR)	0.67 (0.58, 0.72)	0.46 (0.39, 0.48)	0.41 (0.21, 0.53)
Cerebellum			
min	1.805	1.36	1.19
max	2.535	2.3	2.115
median (IQR)	2.07 (1.93, 2.30)	1.71 (1.53, 1.87)	1.74 (1.54, 1.89)

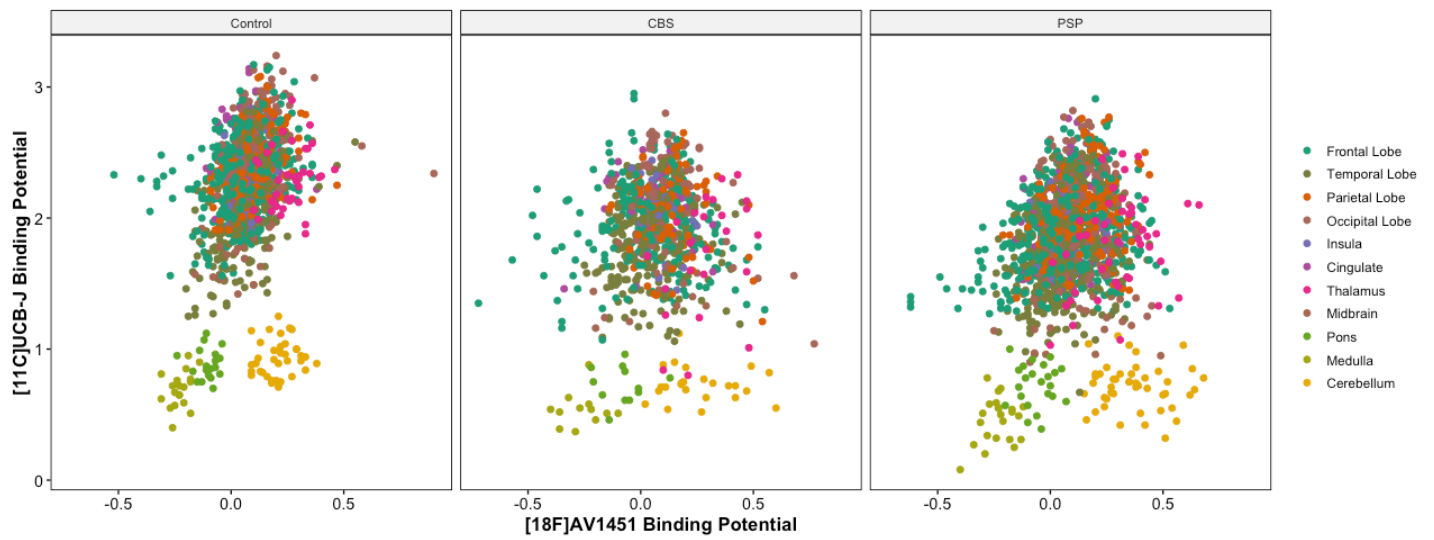
Supplementary Table 3. Summary statistics for regional [^{11}C]UCB-J non-displaceable binding potentials in controls, PSP, and amyloid negative CBS (CBD). min = minimum, max = maximum, IQR = interquartile range.

Contrast	Region	Estimate	SE	t-ratio	p-value	Adjusted p-value (FDR)
Control - PSP	Amygdala	0.43	0.10	4.42	0.0001	0.0002
Control - PSP	Caudate Nucleus	0.65	0.10	6.64	0.0000	0.0000
Control - PSP	Cerebellum	0.41	0.10	4.21	0.0001	0.0004
Control - PSP	Cingulate	0.52	0.10	5.29	0.0000	0.0000
Control - PSP	Frontal lobe	0.44	0.10	4.54	0.0000	0.0001
Control - PSP	Hippocampus	0.35	0.10	3.55	0.0014	0.0034
Control - PSP	Insula	0.50	0.10	5.11	0.0000	0.0000
Control - PSP	Medulla	0.30	0.10	3.08	0.0068	0.0125
Control - PSP	Midbrain	0.90	0.10	9.24	0.0000	0.0000
Control - PSP	Nucleus Accumbens	0.62	0.10	6.34	0.0000	0.0000
Control - PSP	Occipital lobe	0.44	0.10	4.54	0.0000	0.0001
Control - PSP	Pallidum	0.62	0.10	6.35	0.0000	0.0000
Control - PSP	Parietal lobe	0.42	0.10	4.27	0.0001	0.0003
Control - PSP	Putamen	0.71	0.10	7.30	0.0000	0.0000
Control - PSP	Substantia Nigra	0.73	0.10	7.49	0.0000	0.0000
Control - PSP	Temporal lobe	0.44	0.10	4.49	0.0000	0.0001
Control - PSP	Thalamus	0.59	0.10	6.02	0.0000	0.0000
Control – CBD	Amygdala	0.44	0.12	3.77	0.0007	0.0018
Control – CBD	Caudate Nucleus	0.48	0.12	4.11	0.0002	0.0005
Control – CBD	Cerebellum	0.40	0.12	3.49	0.0018	0.0040
Control – CBD	Cingulate	0.37	0.12	3.19	0.0048	0.0092
Control – CBD	Frontal lobe	0.31	0.12	2.69	0.0215	0.0332
Control – CBD	Hippocampus	0.34	0.12	2.92	0.0111	0.0187
Control – CBD	Insula	0.43	0.12	3.72	0.0008	0.0020
Control – CBD	Midbrain	0.53	0.12	4.53	0.0000	0.0001
Control – CBD	Occipital lobe	0.32	0.12	2.74	0.0186	0.0296
Control – CBD	Parietal lobe	0.36	0.12	3.07	0.0069	0.0125
Control – CBD	Putamen	0.54	0.12	4.61	0.0000	0.0001
Control – CBD	Substantia Nigra	0.42	0.12	3.60	0.0012	0.0030
Control – CBD	Temporal lobe	0.34	0.12	2.92	0.0110	0.0187
Control – CBD	Thalamus	0.72	0.12	6.19	0.0000	0.0000
CBD - PSP	Midbrain	0.38	0.11	3.32	0.0032	0.0066
CBD - PSP	Nucleus Accumbens	0.38	0.11	3.34	0.0029	0.0064
CBD - PSP	Pallidum	0.37	0.11	3.24	0.0041	0.0083
CBD - PSP	Substantia Nigra	0.31	0.11	2.76	0.0174	0.0285

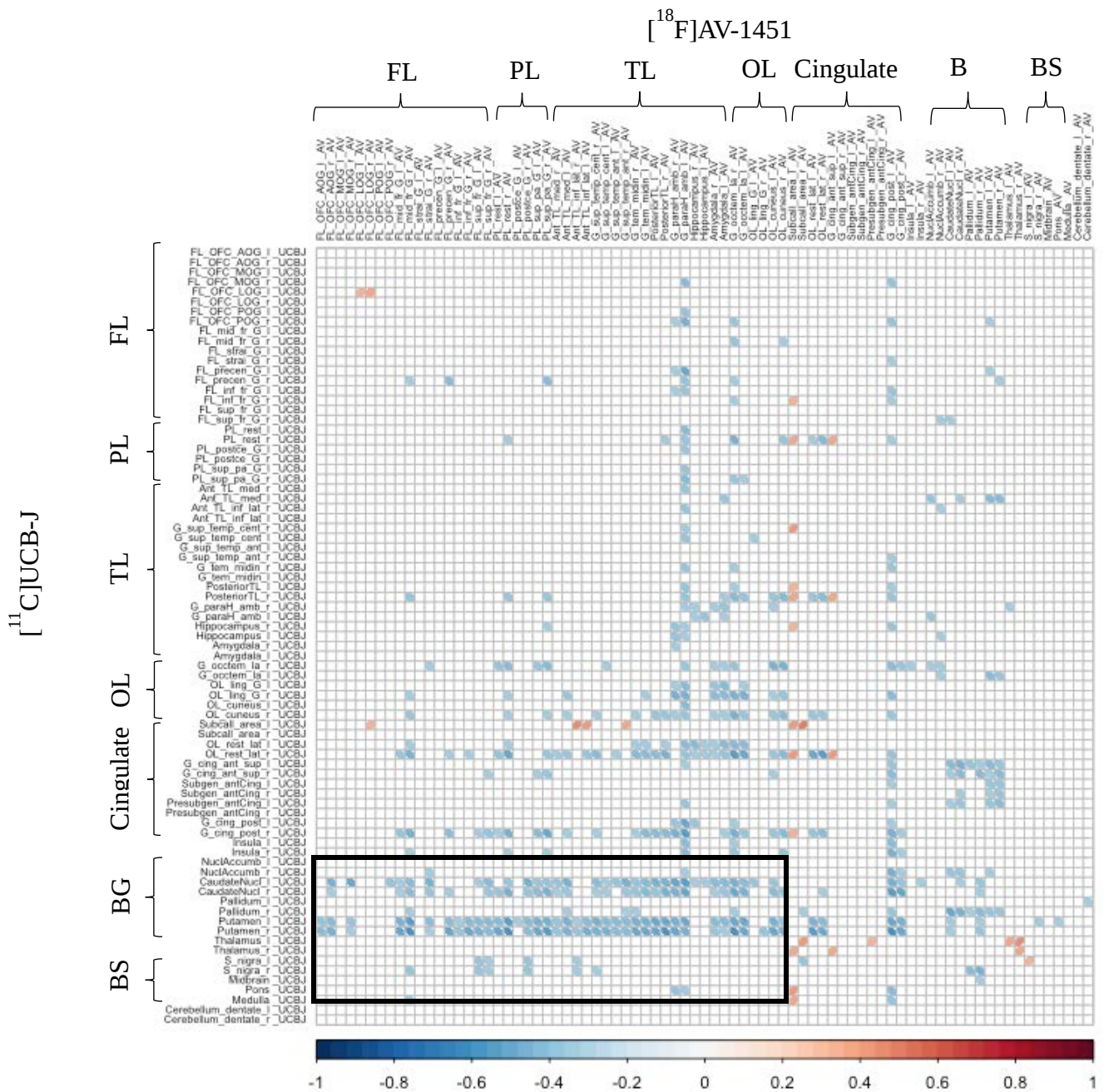
Supplementary Table 4. Significant regional differences in [^{11}C]UCB-J non-displaceable binding potential between patients with PSP and amyloid-negative CBS (CBD) compared to controls, with all surviving correction for multiple comparison across 18 combined regions of interest (aggregated areas of the modified Hammersmith atlas).



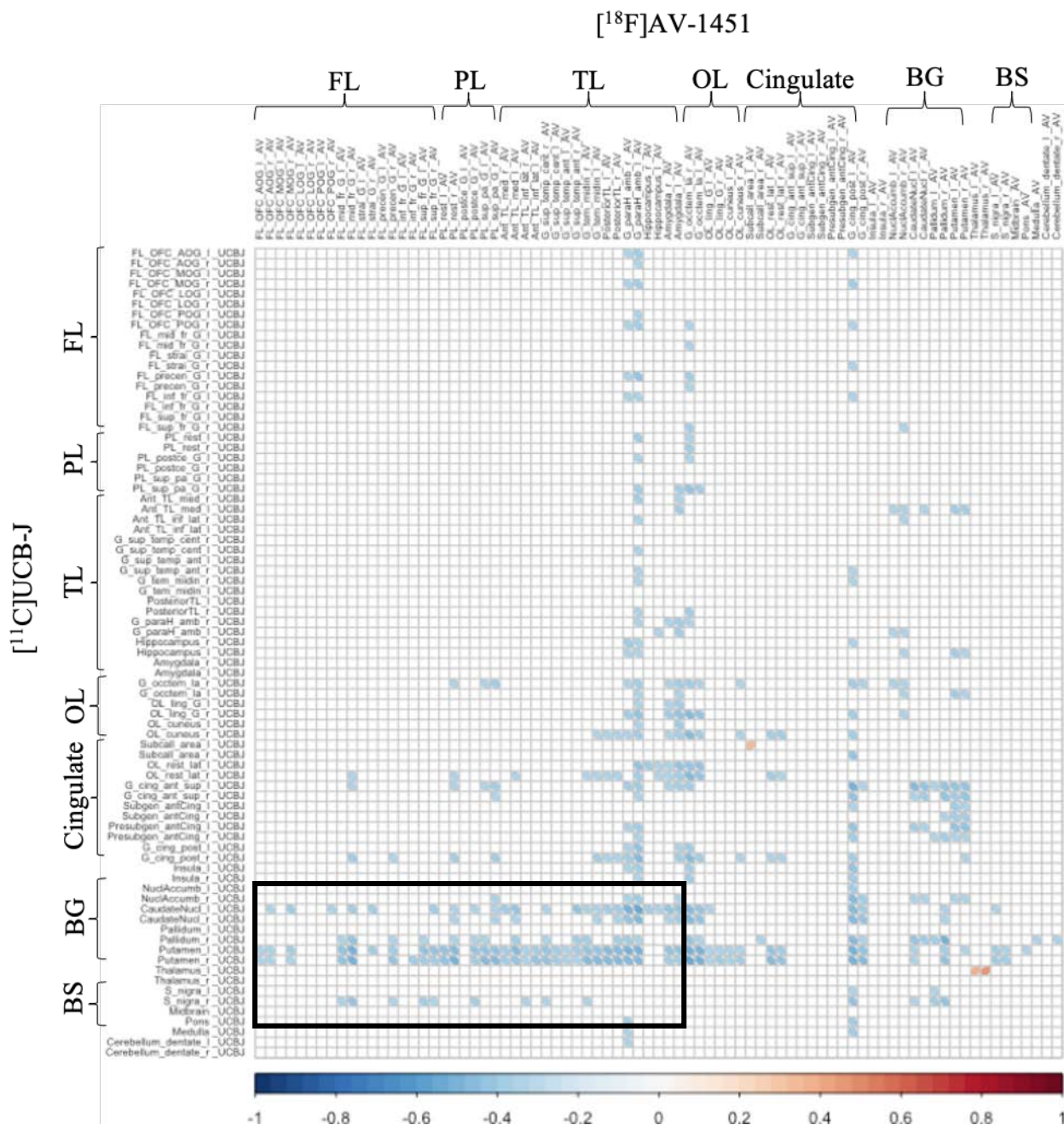
Supplementary Figure 2. The association between synaptic density ($[^{11}\text{C}]\text{UCB-J}$) and molecular pathology ($[^{18}\text{F}]\text{AV-1451}$) is a function of disease severity. A) Scatter plot of $[^{11}\text{C}]\text{UCB-J}$ and $[^{18}\text{F}]\text{AV-1451}$ non-displaceable binding potential (BP_{ND}) without partial volume correction from 23 patients with PSP and 12 patients with amyloid-negative corticobasal syndrome. Each grey line in A represents data from an individual patient across 73 regions of interest (excluding those with previously reported off-target binding, i.e. basal ganglia and substantia nigra); the black line illustrates the overall model. B) The slope for each individual (i.e. each grey line in A) is negatively correlated with disease severity (as measured with the PSP rating scale); $R = -0.38, p = 0.03$.



Supplementary Figure 3. Scatterplots of raw $[^{18}\text{F}]\text{AV-1451 BP}_{\text{ND}}$ against $[^{11}\text{C}]\text{UCB-J BP}_{\text{ND}}$, in controls, and patients with PSP and amyloid negative CBS, for all cortical and subcortical regions except those where there is known off-target binding of $[^{18}\text{F}]\text{AV-1451}$.



Supplementary Figure 4. Cortical molecular pathology is negatively correlated with subcortical synaptic density (data with partial volume correction). Correlation between $[^{18}\text{F}]\text{AV-1451}$ BP_{ND} in a source region (horizontal axis) and $[^{11}\text{C}]\text{UCB-J}$ BP_{ND} in a target region (vertical axis), across 79 regions of interest in patients, using non-displaceable binding potential (BP_{ND}) determined from data with partial volume correction. The black box in the lower left quadrant focuses on cortical $[^{18}\text{F}]\text{AV-1451}$ BP_{ND} and subcortical $[^{11}\text{C}]\text{UCB-J}$ BP_{ND}. Abbreviations: l: left, r: right, FL: Frontal Lobe, OFC: Orbitofrontal Cortex, AOG: Anterior Orbital Gyrus, MOG: Middle Orbital Gyrus, LOG: Lateral Orbital Gyrus, POG: Posterior Orbital Gyrus, mid_fr_G: Middle Frontal Gyrus, strai_G: Straight Gyrus, precen_G: Precentral Gyrus, inf_fr_G: Inferior Frontal Gyrus, sup_fr_G: Superior Frontal Gyrus; PL: Parietal Lobe, postce_G: Postcentral Gyrus, sup_pa_G: Superior Parietal Gyrus; TL: Temporal Lobe, Ant_med: Anterior Medial, Ant_inf_lat: Anterior Inferior lateral, "G_sup_temp_cent: Superior Temporal Gyrus – superior part, G_sup_temp_ant: Superior Temporal Gyrus- Anterior part, G_tem_midin_r: Middle and Inferior Temporal Gyrus, G_paraH_amb: Parahippocampal and ambient gyri, G_occtem_la: Occipitotemporal Gyrus – Lateral Part (Fusiform Gyrus), OL: Occipital Lobe, OL_ling_G_l: Lingual Gyrus, Subcall_area: Subcallosal Area, OL_rest_lat: Lateral Remainder of Occipital Lobe, G_cing_ant_sup: Cingulate Gyrus Anterior Part, Subgen_antCing: Subgenual Frontal Lobe, Presubgen_antCing: Presubgenual Frontal Lobe, G_cing_post: Cingulate Gyrus – posterior part; BG: Basal Ganglia; BS: Brainstem. Significant correlations at $p < 0.05$ (FDR uncorrected) are shown in the matrix above.



Supplementary Figure 5. Cortical molecular pathology is negatively correlated with subcortical synaptic density (data without partial volume correction). Correlation between $[^{18}\text{F}]\text{AV-1451}$ BP_{ND} in a source region (horizontal axis) and $[^{11}\text{C}]\text{UCB-J}$ BP_{ND} in a target region (vertical axis), across 79 regions of interest in patients, using non-displaceable binding potential (BP_{ND}) determined from data without partial volume correction. The black box in the lower left quadrant focuses on cortical $[^{18}\text{F}]\text{AV-1451}$ BP_{ND} and subcortical $[^{11}\text{C}]\text{UCB-J}$ BP_{ND}. Abbreviations: l: left, r: right, FL: Frontal Lobe, OFC: Orbitofrontal Cortex, AOG: Anterior Orbital Gyrus, MOG: Middle Orbital Gyrus, LOG: Lateral Orbital Gyrus, POG: Posterior Orbital Gyrus, mid_fr_G: Middle Frontal Gyrus, strai_G: Straight Gyrus, precen_G: Precentral Gyrus, inf_fr_G: Inferior Frontal Gyrus, sup_fr_G: Superior Frontal Gyrus; PL: Parietal Lobe, postce_G: Postcentral Gyrus, sup_pa_G: Superior Parietal Gyrus; TL: Temporal Lobe, Ant_med: Anterior Medial, Ant_inf_lat: Anterior Inferiolateral, G_sup_temp_cent: Superior Temporal Gyrus – superior part, G_sup_temp_ant: Superior Temporal Gyrus - Anterior part, G_tem_midin_r: Middle and Inferior Temporal Gyrus, G_paraH_amb: Parahippocampal and ambient gyri, G_occtem_la: Occipitotemporal Gyrus – Lateral Part (Fusiform Gyrus), OL: Occipital Lobe, OL_ling_G_l: Lingual Gyrus, Subcall_area: Subcallosal Area, OL_rest_lat: Lateral Remainder of Occipital Lobe, G_cing_ant_sup: Cingulate Gyrus Anterior Part, Subgen_antCing: Subgenual Frontal Lobe, Presubgen_antCing: Presubgenual Frontal Lobe, G_cing_post: Cingulate Gyrus – posterior part; BG: Basal Ganglia; BS: Brainstem. Significant correlations at $p < 0.05$ (FDR uncorrected) are shown in the matrix above.