

Supplementary Material

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Supplementary Table 1: Demographic and pathological data by TDP-43 stages.

	TDP-43 Negative (N=252)	TDP-43 Stage 1 (N=34)	TDP-43 Stage 2 (N=32)	TDP-43 Stage 3 (N=14)	TDP-43 Stage 4+ (N=75)	p value	Post hoc test
Gender (Female/Male)	105/147	17/17	22/10	9/5	39/36	0.021	<i>ns</i>
Education (years)	14.5±3.1	15.0±3.2	14.5±3.3	15.3±2.5	14.3±3.1	0.749	<i>ns</i>
Age at MRI (years)	78.4±10.6	82.4±7.7	80.1±8.1	84.7±9.6	83.5±7.3	<0.001	TDP 0 < TDP 4
Age at death (years)	81.8±10.8	84.8±7.7	85.3±9.1	88.2±9.9	87.4±7.5	<0.001	TDP 0 < TDP 4
Time MRI to death (years)	3.4±2.3	2.4±2.0	5.2±2.6	3.5±2.6	3.8±2.3	<0.001	(TDP 0, TDP 1, TDP 4) < TDP 2; TDP 1 < TDP 4
Clinical Status (CUI/CI)	85/166	9/25	6/26	2/12	8/67	0.001	TDP 0 versus TDP 4
APOE ε4 carrier	101 (40.2%)	23 (67.6%)	17 (53.1%)	10 (71.4%)	39 (52.0%)	0.005	TDP 0 versus TDP 1
Braak Stage						<0.001 ^a	TDP 0 versus (TDP 2, TDP 4)
0-II	58 (23.0%)	6 (17.6%)	0 (0.0%)	1 (7.1%)	6 (8.0%)		
III	33 (13.1%)	1 (2.9%)	1 (3.1%)	2 (14.3%)	6 (8.0%)		
VI	43 (17.1%)	3 (8.8%)	2 (6.2%)	1 (7.1%)	9 (12.0%)		
V	36 (14.3%)	12 (35.3%)	15 (46.9%)	4 (28.6%)	19 (25.3%)		
VI	82 (32.5%)	12 (35.3%)	14 (43.8%)	6 (42.9%)	35 (46.7%)		
Neuritic Plaques						0.001 ^a	TDP 2 versus (TDP 0, TDP 1, TDP 3, TDP 4)
0	45 (17.9%)	7 (20.6%)	2 (6.2%)	1 (7.1%)	11 (14.7%)		
1	47 (18.7%)	3 (8.8%)	3 (9.4%)	0 (0.0%)	5 (6.7%)		
2	53 (21.0%)	10 (29.4%)	2 (6.2%)	6 (42.9%)	22 (29.3%)		
3	107 (42.5%)	14 (41.2%)	25 (78.1%)	7 (50.0%)	37 (49.3%)		
Diffuse Plaques						0.124 ^a	<i>ns</i>
0	18 (7.1%)	2 (5.9%)	1 (3.1%)	1 (7.1%)	6 (8.0%)		
1	17 (6.7%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	6 (8.0%)		
2	42 (16.7%)	5 (14.7%)	1 (3.1%)	4 (28.6%)	4 (5.3%)		
3	175 (69.4%)	24 (70.6%)	30 (93.8%)	9 (64.3%)	59 (78.7%)		
Lewy Body Stage						0.013 ^a	<i>ns</i>
0	165 (65.5%)	25 (73.5%)	14 (43.8%)	5 (35.7%)	44 (58.7%)		
1	12 (4.8%)	0 (0.0%)	3 (9.4%)	0 (0.0%)	2 (2.7%)		
2	24 (9.5%)	3 (8.8%)	8 (25.0%)	1 (7.1%)	9 (12.0%)		
3	36 (14.3%)	5 (14.7%)	7 (21.9%)	4 (28.6%)	14 (18.7%)		
4	15 (6.0%)	1 (2.9%)	0 (0.0%)	4 (28.6%)	6 (8.0%)		
Argyrophilic grain disease						0.485	<i>ns</i>
0	215 (85.3%)	28 (82.4%)	30 (93.8%)	13 (92.9%)	68 (90.7%)		
1	37 (14.7%)	6 (17.6%)	2 (6.2%)	1 (7.1%)	7 (9.3%)		

Vascular pathology						0.422 ^a	ns
0	144 (57.1%)	14 (41.2%)	18 (56.2%)	10 (71.4%)	39 (52.0%)		
1	85 (33.7%)	16 (47.1%)	13 (40.6%)	3 (21.4%)	32 (42.7%)		
2	23 (9.1%)	4 (11.8%)	1 (3.1%)	1 (7.1%)	4 (5.3%)		

Unless otherwise indicated, values are mean \pm standard deviation. *P* values refer to analyses of chi-squared (or exact Fisher if appropriate) and ANOVA (followed by Tukey post-hoc tests) for categorical and continuous variables respectively. Refer to Methods for further details about the Braak, TDP-43 and Lewy body stages. ^a *p*-value estimated using a permutation chi-squared test, with 2000 permutations.

Supplementary Table 2: R-squared and adjusted r-squared from the robust regressions assessing the effect of pathological variables on gray matter volume.

	r-squared	Adjusted r-squared
Amygdala L	0.49	0.46
Amygdala R	0.46	0.43
Entorhinal Cortex L	0.56	0.54
Entorhinal Cortex R	0.52	0.49
Hippocampus L	0.57	0.55
Hippocampus R	0.5	0.47
Fusiform L	0.56	0.53
Fusiform R	0.52	0.49
Insula L	0.52	0.49
Insula R	0.54	0.51
Temporal Inferior L	0.58	0.56
Temporal Inferior R	0.53	0.5
Frontal Middle L	0.36	0.32
Frontal Middle R	0.36	0.33

Supplementary Table 3: Between TDP-43 stages differences in gray matter volume.

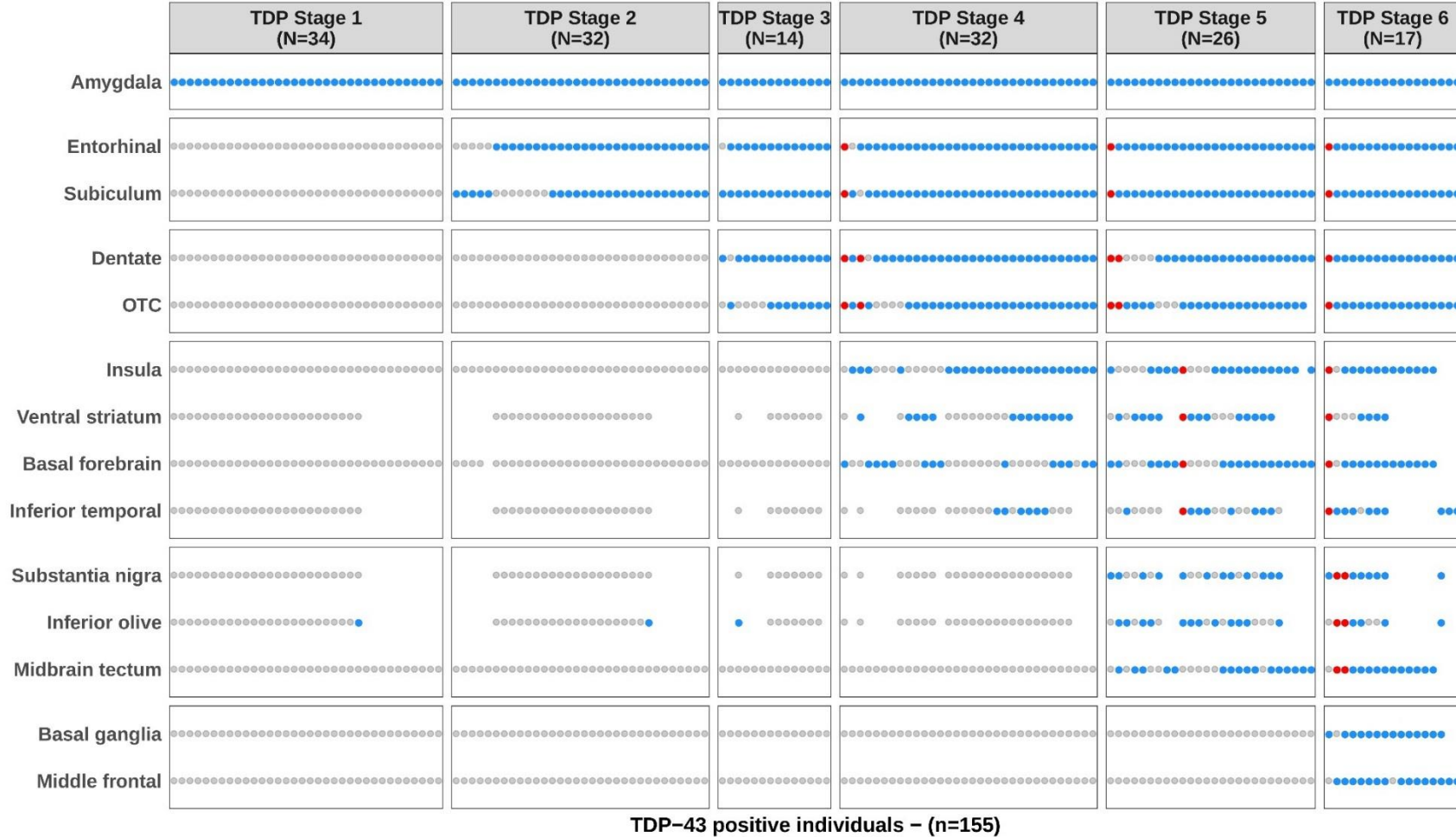
	TDP Stage 1 versus Stage 2	TDP Stage 1 versus Stage 3	TDP Stage 1 versus Stage 4+	TDP Stage 2 versus Stage 3	TDP Stage 2 versus Stage 4+	TDP Stage 3 versus Stage 4+
Amygdala L	2 [-4.9, 9.4], p=0.58	5.6 [-3.2, 15.3], p=0.22	1.8 [-4, 7.8], p=0.55	3.6 [-5.2, 13.2], p=0.44	-0.2 [-5.9, 5.9], p=0.94	-3.6 [-11, 4.3], p=0.36
Amygdala R	5.1 [-2.3, 13.1], p=0.18	0.6 [-8.2, 10.3], p=0.89	1.9 [-4.1, 8.2], p=0.55	-4.3 [-12.8, 5.2], p=0.36	-3.1 [-9, 3.2], p=0.33	1.2 [-6.9, 10.1], p=0.77
Entorhinal Cortex L	-3.9 [-12.8, 5.8], p=0.42	-1.9 [-13, 10.6], p=0.75	-4.3 [-11.5, 3.5], p=0.27	2.1 [-9.8, 15.5], p=0.74	-0.4 [-8.3, 8.2], p=0.92	-2.4 [-12.6, 8.8], p=0.66
Entorhinal Cortex R	-1 [-9.5, 8.3], p=0.83	-6.9 [-16.7, 4.1], p=0.21	-4.5 [-11.2, 2.8], p=0.22	-6 [-16.2, 5.5], p=0.29	-3.5 [-10.7, 4.3], p=0.37	2.6 [-7.3, 13.6], p=0.62
Hippocampus L	-4 [-10.3, 2.7], p=0.23	-8.2 [-15.5, -0.1], p=0.05	-9.6 [-14.5, -4.5], p<0.001	-4.3 [-12.2, 4.2], p=0.31	-5.8 [-11.1, -0.2], p=0.04	-1.6 [-8.8, 6.2], p=0.68
Hippocampus R	-2.2 [-9.2, 5.5], p=0.57	-12.2 [-20, -3.6], p=0.007	-9.2 [-14.6, -3.4], p=0.002	-10.2 [-18.4, -1.2], p=0.03	-7.2 [-13, -1], p=0.02	3.4 [-5, 12.5], p=0.44
Fusiform L	-2.9 [-9.4, 4], p=0.40	-5.8 [-13.6, 2.7], p=0.18	-3.2 [-8.4, 2.4], p=0.26	-2.9 [-11.2, 6.1], p=0.51	-0.2 [-6, 5.8], p=0.94	2.8 [-5, 11.1], p=0.49
Fusiform R	-2.8 [-9.3, 4.1], p=0.42	-6.1 [-13.8, 2.3], p=0.15	0.4 [-5.1, 6.2], p=0.89	-3.4 [-11.5, 5.5], p=0.44	3.3 [-2.6, 9.5], p=0.27	6.9 [-1, 15.6], p=0.09
Insula L	-3.3 [-8.4, 2], p=0.22	-5.2 [-11.4, 1.4], p=0.12	-4.4 [-8.5, -0.1], p=0.04	-1.9 [-8.5, 5.1], p=0.58	-1.1 [-5.6, 3.5], p=0.63	0.8 [-5.2, 7.2], p=0.79
Insula R	-4.3 [-9.1, 0.8], p=0.10	-6.2 [-12, 0.1], p=0.05	-4 [-8, 0.1], p=0.05	-2 [-8.2, 4.7], p=0.55	0.3 [-4, 4.8], p=0.90	2.3 [-3.5, 8.4], p=0.45
Temporal Inf L	-5.8 [-12.1, 1], p=0.09	-3 [-11.1, 5.9], p=0.50	-4.9 [-10.2, 0.7], p=0.09	3 [-5.8, 12.6], p=0.52	0.9 [-4.8, 7.1], p=0.75	-2 [-9.4, 6.1], p=0.62
Temporal Inf R	-2.6 [-9.3, 4.6], p=0.47	-3.3 [-11.5, 5.7], p=0.46	-0.2 [-5.8, 5.7], p=0.94	-0.7 [-9.3, 8.8], p=0.88	2.4 [-3.6, 8.9], p=0.44	3.2 [-4.8, 11.7], p=0.45
Frontal Mid L	-4.5 [-13.2, 5.1], p=0.35	-4.5 [-15.3, 7.6], p=0.45	-2.5 [-9.8, 5.5], p=0.53	-0.1 [-11.6, 13], p=0.99	2.1 [-5.9, 10.8], p=0.61	2.2 [-8.3, 13.9], p=0.70
Frontal Mid R	-6.5 [-14.5, 2.4], p=0.15	-7.8 [-17.8, 3.3], p=0.16	-2.8 [-9.8, 4.7], p=0.45	-1.5 [-12.3, 10.6], p=0.80	3.9 [-3.8, 12.1], p=0.33	5.4 [-4.9, 16.9], p=0.31

Results of the robust regressions showing the effect of TDP-43 stages on gray matter volume. Values represent the percentage of volume change [95% CIs] associated with the different TDP-43 stages compare to TDP-43 stage 1 (columns 1-3), TDP-43 stage 2 (columns 4-5) and TDP-43 stage 3 (columns 6). Results in bold survived Bonferroni correction for multiple comparisons (red, $\alpha=0.05$, $p<0.004$, 14 models considered). L: left; R: right.

Supplementary Table 4: Effect of diffuse and neuritic β -amyloid plaques, argyrophilic grain disease and vascular pathology on gray matter volume.

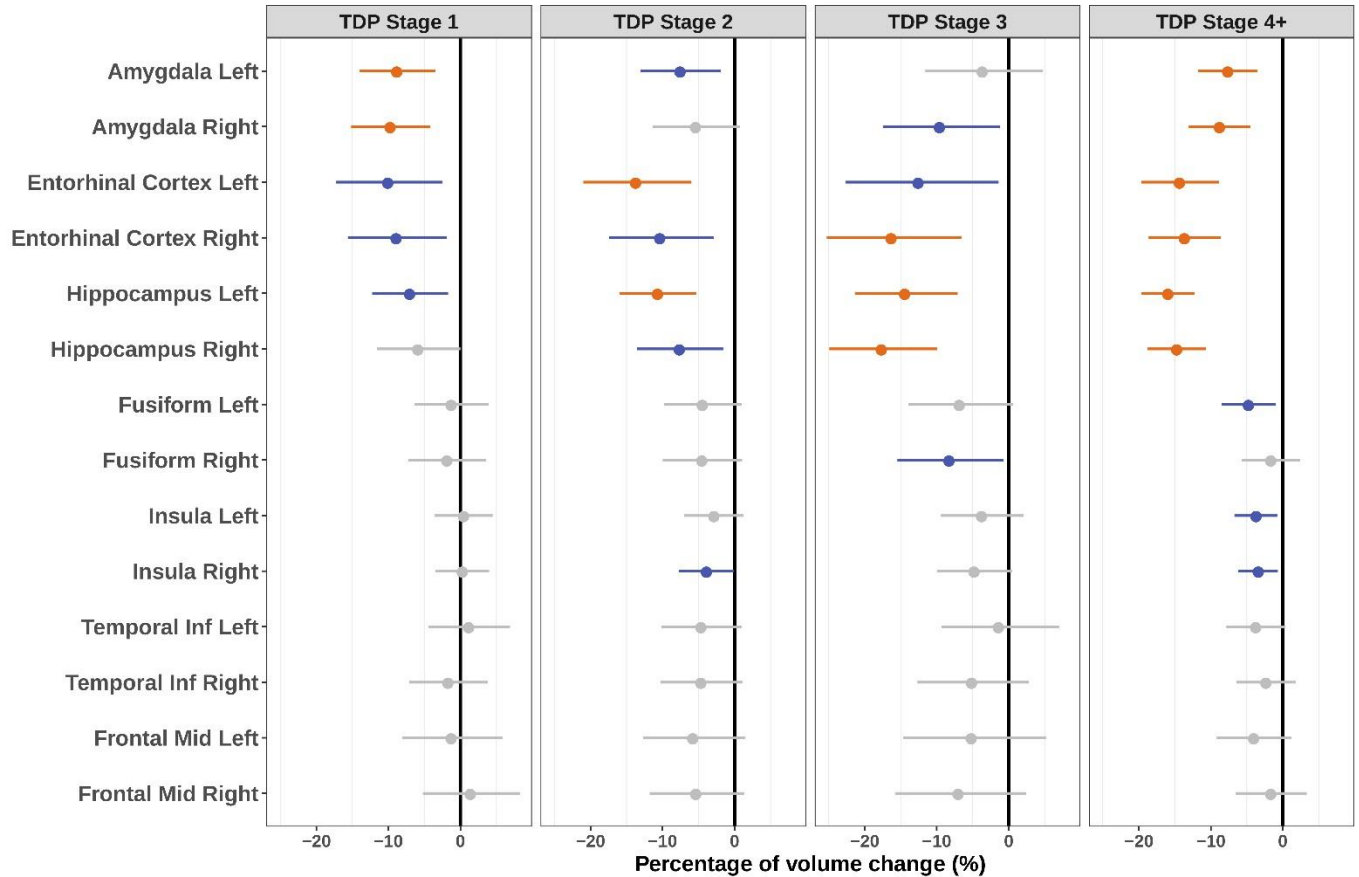
	Diffuse β -amyloid plaques	Neuritic β -amyloid plaques	Argyrophilic grain disease	Vascular pathology
Amygdala L	0.1 [-1.9, 2.2], $p=0.90$	-1.5 [-3.6, 0.7], $p=0.18$	-6.9 [-11, -2.6], $p=0.002$	1.4 [-0.8, 3.7], $p=0.21$
Amygdala R	0 [-2.1, 2.2], $p=1.00$	-1.7 [-3.9, 0.6], $p=0.16$	-2.6 [-7.1, 2.1], $p=0.27$	1.9 [-0.5, 4.4], $p=0.11$
Entorhinal Cortex L	3.1 [0.2, 6], $p=0.03$	-3 [-5.9, 0], $p=0.05$	-7.2 [-12.8, -1.1], $p=0.02$	2.4 [-0.7, 5.6], $p=0.13$
Entorhinal Cortex R	-0.4 [-3, 2.2], $p=0.76$	-1.7 [-4.4, 1.2], $p=0.24$	-4.4 [-9.8, 1.3], $p=0.13$	0.9 [-2, 3.8], $p=0.55$
Hippocampus L	0.8 [-1.2, 2.8], $p=0.42$	-0.3 [-2.4, 1.9], $p=0.79$	-4.3 [-8.4, 0], $p=0.05$	0.9 [-1.3, 3.1], $p=0.42$
Hippocampus R	-0.3 [-2.4, 1.9], $p=0.81$	-0.5 [-2.8, 1.9], $p=0.71$	-2.3 [-6.9, 2.5], $p=0.34$	0.7 [-1.7, 3.2], $p=0.57$
Fusiform L	-0.8 [-2.7, 1.3], $p=0.46$	-1 [-3.1, 1.2], $p=0.37$	-1.4 [-5.6, 3.1], $p=0.54$	2 [-0.2, 4.3], $p=0.07$
Fusiform R	-1 [-3, 1], $p=0.31$	0.2 [-1.9, 2.4], $p=0.85$	-1.9 [-6.2, 2.5], $p=0.39$	1.7 [-0.5, 4], $p=0.12$
Insula L	-0.3 [-1.9, 1.3], $p=0.73$	-0.4 [-2.1, 1.3], $p=0.63$	-3.3 [-6.6, 0.2], $p=0.07$	0.1 [-1.6, 1.9], $p=0.92$
Insula R	-0.4 [-1.9, 1.1], $p=0.62$	-0.5 [-2.1, 1.1], $p=0.54$	-3.9 [-7.2, -0.6], $p=0.02$	0.6 [-1.1, 2.3], $p=0.49$
Temporal Inferior L	0.6 [-1.4, 2.7], $p=0.56$	-2.6 [-4.7, -0.5], $p=0.02$	-5.7 [-9.8, -1.4], $p=0.01$	1.2 [-1, 3.5], $p=0.28$
Temporal Inferior R	0.3 [-1.8, 2.4], $p=0.79$	-1.3 [-3.5, 0.9], $p=0.24$	-4.4 [-8.7, 0.1], $p=0.06$	2.7 [0.4, 5.1], $p=0.02$
Frontal Middle L	-1.1 [-3.9, 1.7], $p=0.44$	-1.1 [-4.1, 1.9], $p=0.47$	1.3 [-4.8, 7.9], $p=0.68$	-0.8 [-3.8, 2.4], $p=0.63$
Frontal Middle R	-1 [-3.6, 1.6], $p=0.45$	-0.8 [-3.6, 2.1], $p=0.58$	-1.4 [-7.1, 4.7], $p=0.65$	0.7 [-2.2, 3.7], $p=0.63$

Results of the robust regressions showing the effect of diffuse and neuritic β -amyloid plaques, argyrophilic grain disease and vascular pathology on gray matter volume. Values represent the percentage of volume change [95% CIs] associated with each of these continuous variables (apart Argyrophilic grain disease coded in present/absent). Results in bold survived Bonferroni correction for multiple comparisons (red, $\alpha=0.05$, $p<0.004$, 14 models considered). L: left; R: right.



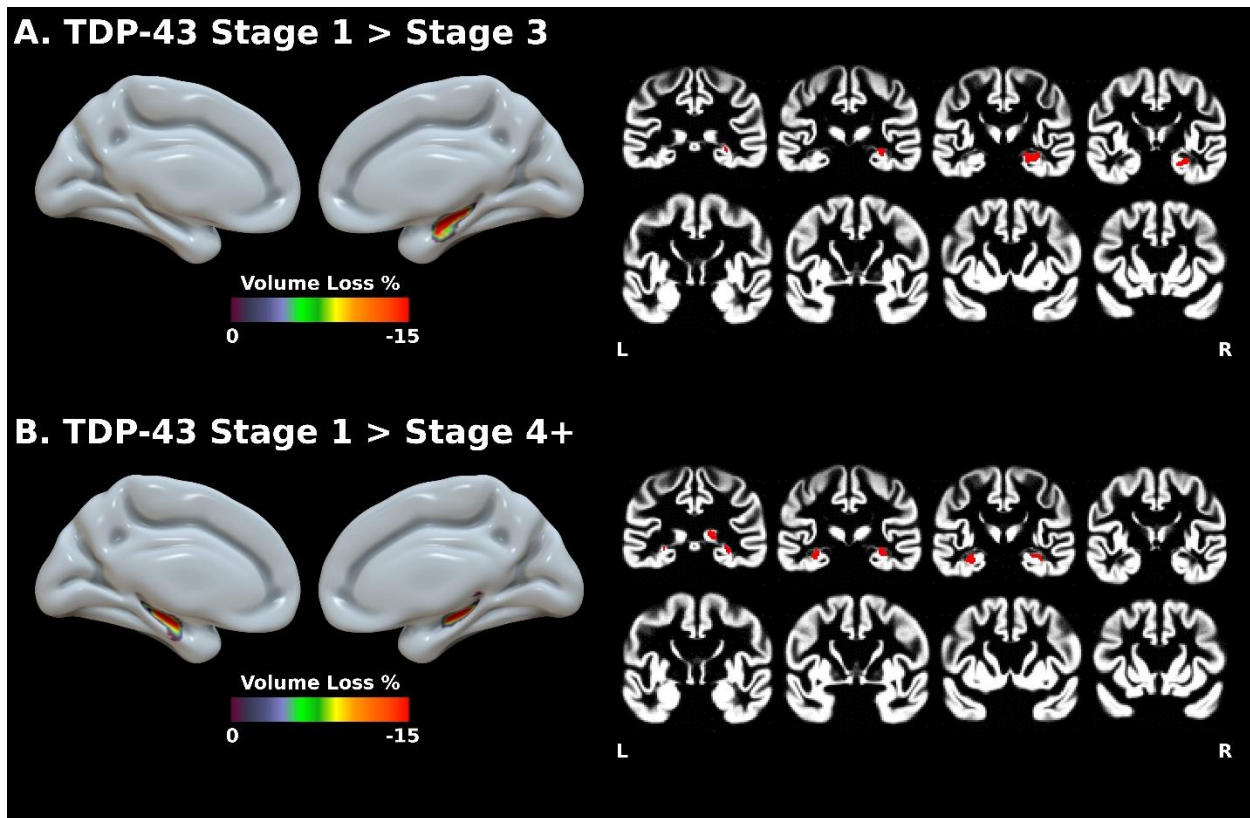
Supplementary Figure 1: Pathological TDP-43 staging in cases with TDP-43 inclusions.

Patterns of TDP-43 positivity across 14 regions for the 155 TDP-43 positive cases. Subjects are grouped by TDP-43 stages. Rows represent the brain regions, and columns the subjects (one column per subject). Blue dots indicate the presence of TDP-43 in the region, and gray dot the absence of TDP-43. Red dots indicate skipped regions, i.e. regions negative for TDP-43 but that would have been expected to be positive given subject stage (subjects with at least one stage skipped n=8/155). OTC = occipitotemporal cortex.



Supplementary Figure 2: Effect of pathological TDP-43 stages on gray matter volume using a match sample of TDP-43 negative group.

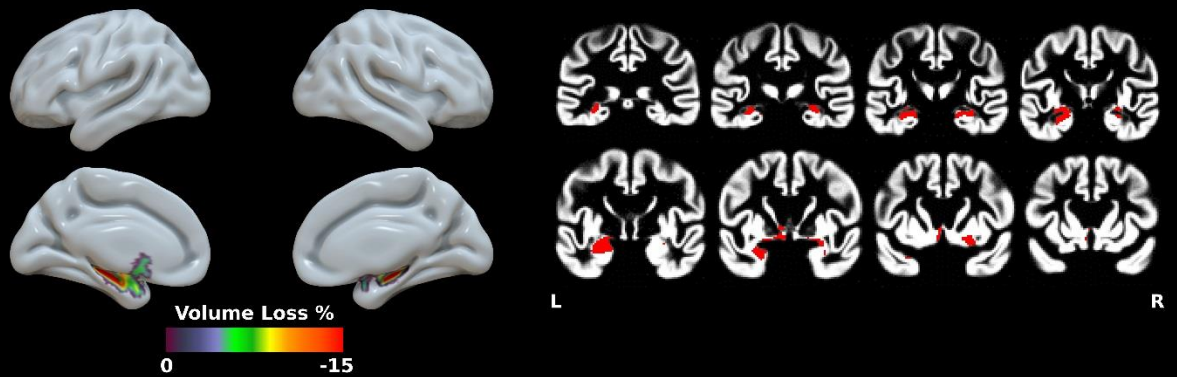
Values represent the percentage of volume change, with 95% CIs, associated with TDP-43 stages compare to the TDP-43 negative group matched for pathological and nuisance variables (see Results). Colors indicate results that survived Bonferroni correction for multiple comparisons (orange, $\alpha=0.05$, $p<0.004$, 14 models considered) or an uncorrected threshold of $p<0.05$ (blue). Columns indicate the pathological staging and rows the brain regions (i.e., dependent variables) ordered according to their progressive involvement with TDP-43 pathology. Note that the main difference with Figure 1 is that the left ($p=0.01$) and right ($p=0.01$) entorhinal cortex at Stage 1, and the right ($p=0.008$) entorhinal cortex at Stage 2 did not survived Bonferroni correction.



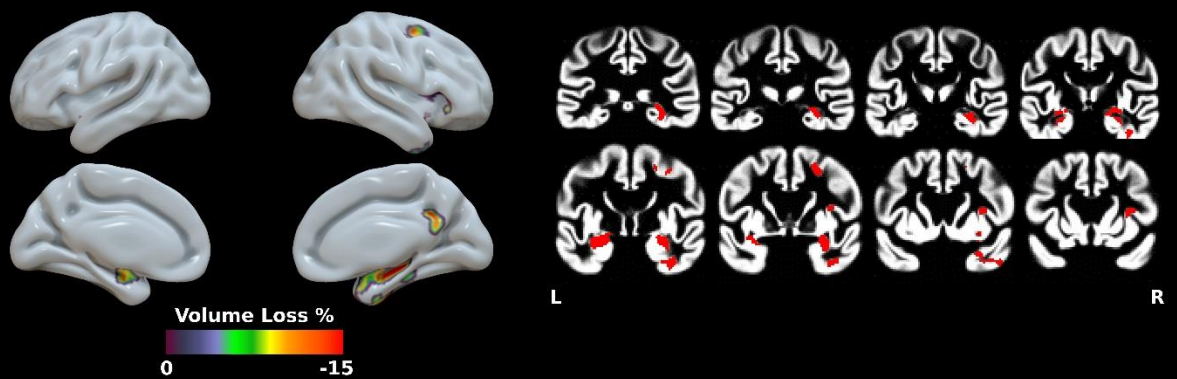
Supplementary Figure 3: Results of voxel-wise robust regressions showing the significant differences of gray matter volume between TDP-43 stages.

Values represent the percentage of volume change associated with TDP-43 stage 3 (A.) and 4+ (B.) compared to TDP-43 Stage 1 ($p < 0.001$ uncorrected, $k > 500 \text{ mm}^3$). Note that no results survived at a threshold of $p < 0.001$ FDR-corrected, $k > 500 \text{ mm}^3$. Results are presented in neurological convention. L: left; R: right.

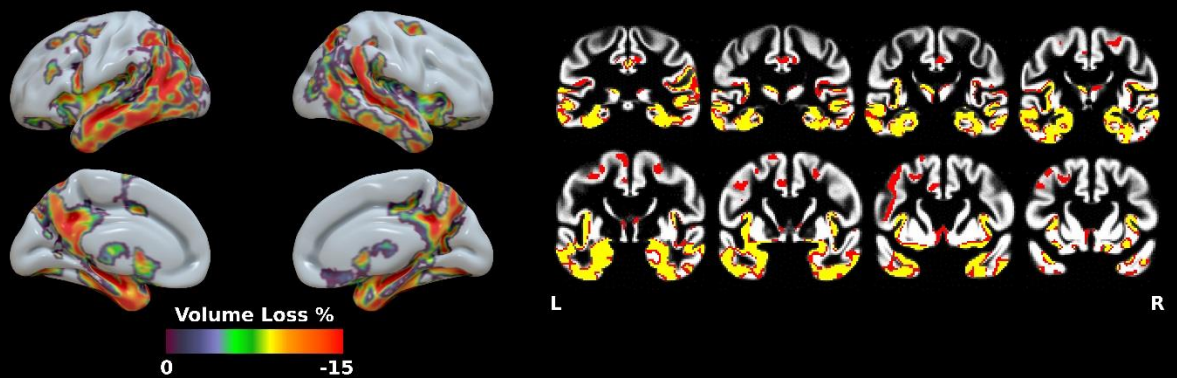
A. Braak Stage IV



B. Braak Stage V



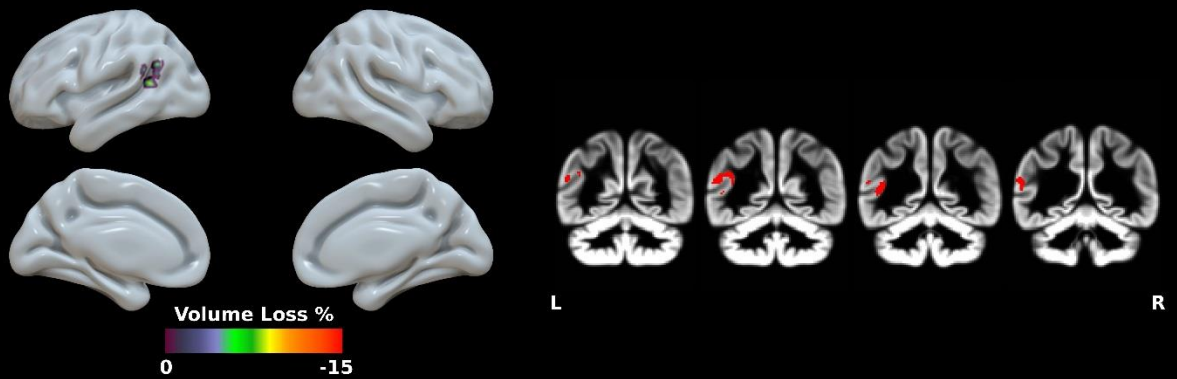
C. Braak Stage VI



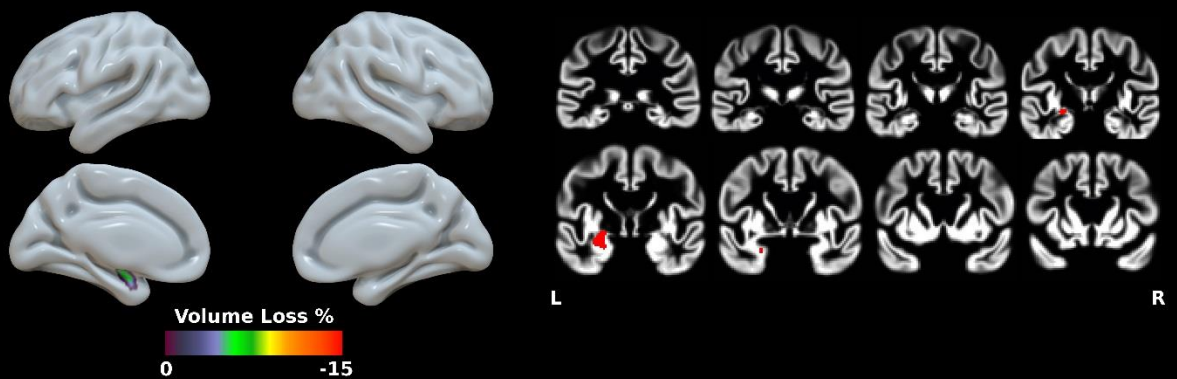
Supplementary Figure 4: Results of voxel-wise robust regressions showing the effect of Braak stages on gray matter volume.

Values represent the percentage of volume change associated with Braak stages IV (A.), V (B.) and VI (C.) compared to Braak Stage 0-II. Coronal slices show both $p < 0.001$ FDR-corrected (yellow) and $p < 0.001$ uncorrected (red) results ($k > 500 \text{ mm}^3$). Results are presented in neurological convention. L: left; R: right.

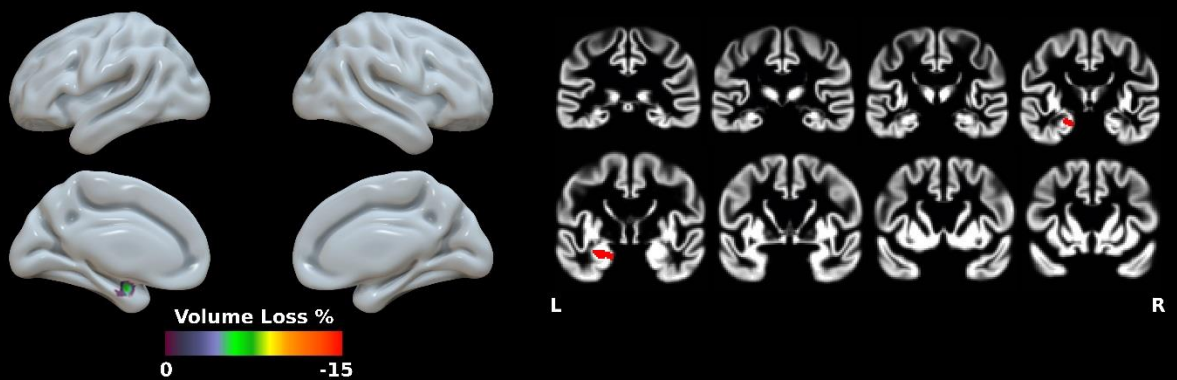
A. Lewy Body Stage 2



B. Lewy Body Stage 3



C. Argyrophilic grain disease



Supplementary Figure 5: Results of voxel-wise robust regressions showing the effect of Lewy Body stages and argyrophilic grain disease on gray matter volume.

Values represent the percentage of volume change associated with Lewy Body stages 2 (A.) and 3 (B.) compared to Lewy Body negative individuals, and with argyrophilic grain disease (C.) ($p < 0.001$ uncorrected, $k > 500 \text{ mm}^3$). Note that no results survived at a threshold of $p < 0.001$ FDR-corrected, $k > 500 \text{ mm}^3$. Results are presented in neurological convention. L: left; R: right.