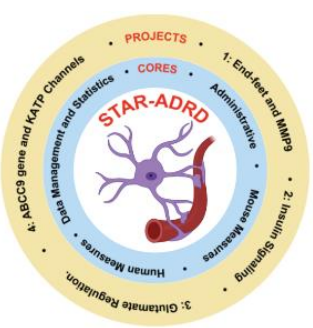




Predicting Brain Arteriolosclerosis Progression patterns Using Multi-Region Pathology by machine learning approaches in the UK-ADRC Autopsy Cohort

Khine Zin Aung ^{1,2}, Peter T. Nelson ^{2,3}, Aye Nandar Hlaing ⁴, Xian Wu ^{1,2}, Inori Tsuchiya ^{1,2}, Erin L. Abner ^{2,5}, David W. Fardo ^{2,6}, Yuriko Katsumata ^{1,2}

¹ Division of Biomedical Informatics, Department of Internal Medicine, University of Kentucky, Lexington, KY, USA, 2. Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA, 3. Department of Pathology, University of Kentucky, Lexington, KY, USA, 4. Department of Computer Science, Myanmar, 5. Department of Epidemiology and Environmental Health, University of Kentucky, Lexington, KY, USA 6. Department of Biostatistics, University of Kentucky, Lexington, KY, USA

Background & Motivation

- Brain arteriolosclerosis (B-ASC), a form of cerebral small vessel disease, affects more than 50% of individuals aged 80 years or older and is associated with cognitive, motor, and sleep disturbances.
- The University of Kentucky Alzheimer's Disease Research Center (UK-ADRC) systematically evaluates B-ASC presence or absence across 21 brain regions at autopsy
- This study aims to characterize the anatomical distribution of B-ASC and progression based on multi-region pathologies and their association with other neuropathologies.

Materials & Methods

- We applied the SusStaln machine learning algorithm to 21 region-specific B-ASC data from the UK-ADRC autopsy cohort to identify distinct spatial-temporal progression patterns of arteriolosclerosis in an unsupervised data-driven pseudotemporal axis [1].
- Individuals with extremely low or high B-ASC burden (0, 1, 20, or 21 affected regions) were excluded prior to model fitting.
- Regional binary scores (0 = absence and 1 = presence) were converted to probability distributions using a Gaussian kernel (SD = 0.5).
- Models with varying numbers of subtypes K were evaluated using 10-fold cross-validation and the Cross-Validation Information Criterion (CVIC) (Figure 1).
- The optimal four-subtype (i.e., K = 4) was selected according to the lowest CVIC and highest log-likelihood and then participants were assigned to the most probable subtype and disease stage, with stage representing progression severity.
- Sequence uncertainty was quantified using 100,000 MCMC iterations and 25 random start points.

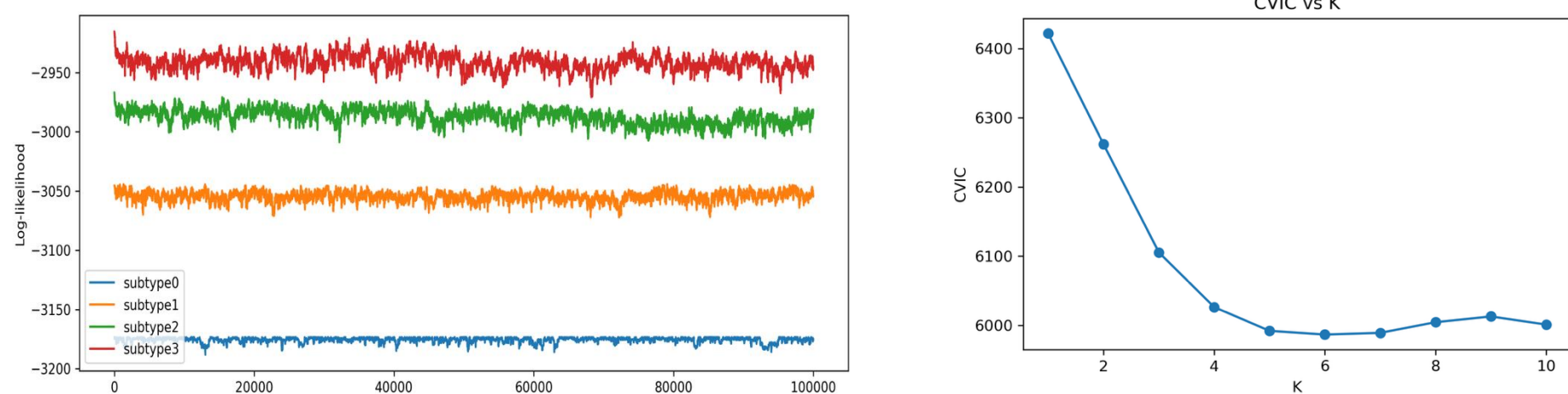


Figure1. MCMC log-likelihood trace and cross-validation plots for the four-subtypes from Ordinal SuStaln.

- Clinical and neuropathological variables are obtained from National Alzheimer's Coordinating Center (NACC) linking with UK-ADRC IDs.
- We then tested associations of hypertension, diabetes, and other neuropathologies with subtypes of B-ASC.
- Details of the hypertension classification and its relationship with B-ASC subtypes are presented in the Results section.

Results

Following exclusion of individuals assigned a most probable stage of 0, 281 participants remained for downstream analyses (Table 1).

Table 1. Clinical and neuropathological characteristics across SuStaln-defined B-ASC subtypes.

Characteristic	Overall N = 281 ¹	Subtype 1 N = 121 ¹	Subtype 2 N = 57 ¹	Subtype 3 N = 61 ¹	Subtype 4 N = 42 ¹
Age at death, years	86.3 ± 8.3	85.8 ± 8.6	85.8 ± 8.3	86.7 ± 7.8	88.2 ± 8.3
Female	156 (56%)	65 (54%)	36 (63%)	27 (44%)	28 (67%)
APOE ε4 carrier	100 (38%)	45 (40%)	21 (38%)	21 (36%)	13 (33%)
Hypertension	224 (88%)	95 (88%)	44 (85%)	50 (89%)	35 (90%)
Diabetes	49 (19%)	19 (18%)	9 (17%)	13 (23%)	8 (21%)
Braak stage B3	135 (50%)	63 (54%)	24 (42%)	24 (42%)	24 (57%)
Thal phase A3	123 (66%)	53 (64%)	19 (63%)	26 (63%)	25 (76%)
CERAD frequent plaques	108 (42%)	50 (46%)	24 (46%)	19 (34%)	15 (38%)
High ADNC	88 (48%)	41 (51%)	13 (43%)	15 (38%)	19 (58%)
LATE-NC ≥2	67 (54%)	28 (53%)	8 (50%)	16 (64%)	15 (50%)
CAA	69 (25%)	32 (26%)	6 (11%)	22 (36%)	9 (21%)*
moderate/severe					
Lewy body pathology	102 (38%)	45 (39%)	15 (28%)	26 (45%)	16 (41%)
Microinfarcts present	73 (28%)	35 (31%)	17 (31%)	15 (26%)	6 (15%)
Hippocampal sclerosis	99 (36%)	41 (34%)	20 (36%)	22 (37%)	16 (39%)
Vascular Dementia	54 (19%)	27 (22%)	10 (18%)	4 (6.6%)	13 (31%)*

¹Mean ± SD; n (%)

LATE-NC: Limbic Predominant TDP-43 Encephalopathy Neuropathologic Changes
ADNC: Alzheimer Disease Neuropathologic Changes
CAA: Cerebral Amyloid Angiopathy

*: p value < 0.05 using analysis of deviance (likelihood ratio test).

Results and Discussion

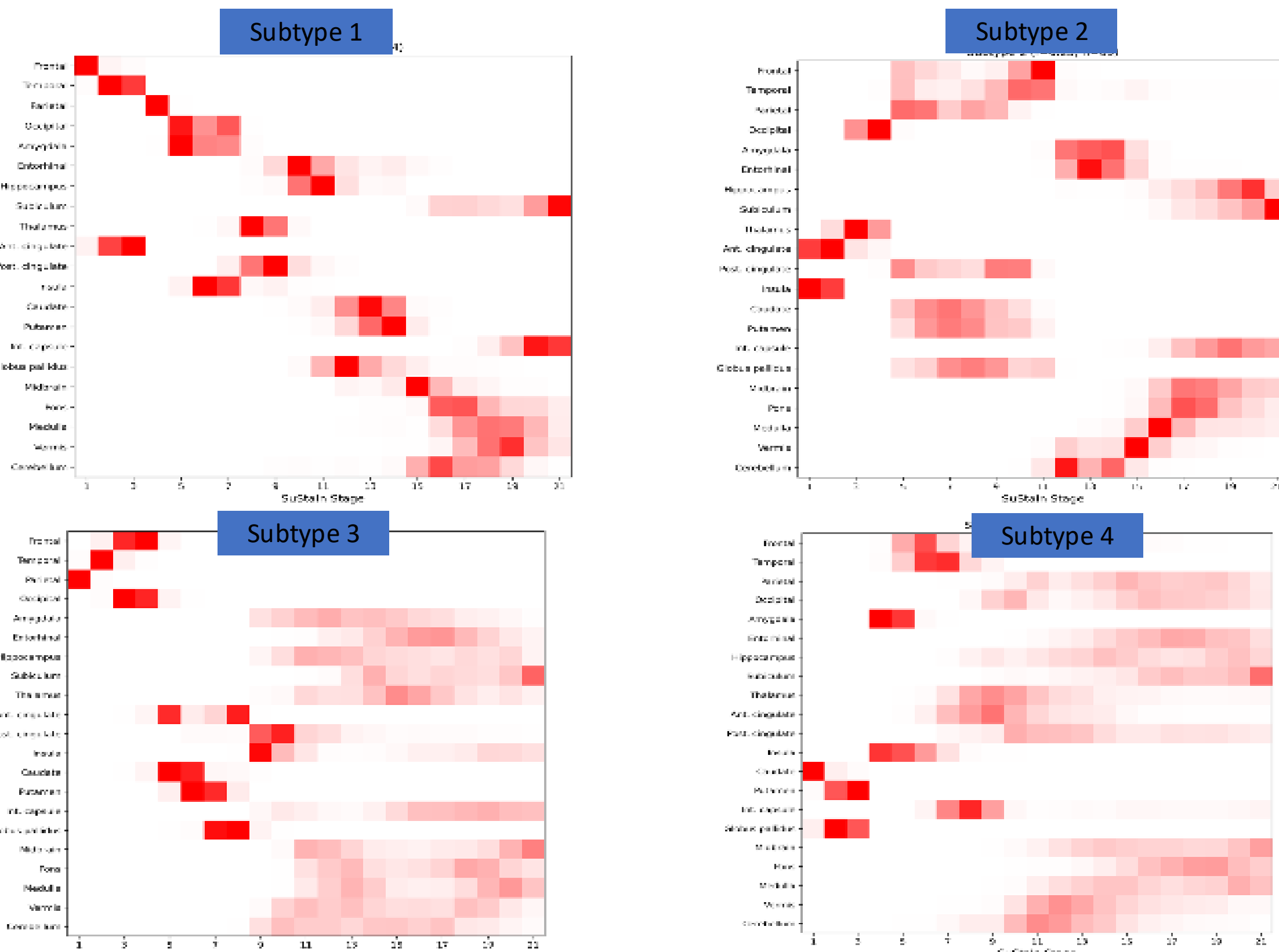


Figure 2. Positional variance diagrams of four spatiotemporal trajectories of B-ASC pathology

As shown in Figure 2,

- Subtype 1 demonstrated predominantly cortical-first progression.
- Subtype 2 showed early involvement of occipital, cingulate, and insular regions.
- Subtype 3 was characterized by concurrent early cortical and basal ganglia involvement.
- Subtype 4 exhibited the earliest involvement of basal ganglia structures, including the caudate, putamen, and globus pallidus, preceding spread to cortical, limbic, and brainstem regions.
- Positional variance diagrams indicated high certainty for early disease events, with increasing uncertainty at later stages as progression trajectories converged.

Table 2. Blood pressure and antihypertensive treatment characteristics across SuStaln-defined B-ASC subtypes.

Characteristic	Overall N = 281 ¹	Subtype 1 N = 121 ¹	Subtype 2 N = 57 ¹	Subtype 3 N = 61 ¹	Subtype 4 N = 42 ¹
SBP, mmHg	132.5 ± 20.9	129.4 ± 19.4	133.9 ± 21.9	131.1 ± 19.0	140.9 ± 24.0
DBP, mmHg	72.3 ± 11.0	71.7 ± 11.8	72.6 ± 9.7	72.0 ± 9.9	74.2 ± 12.2
On antihypertensive medication	168 (72%)	68 (70%)	33 (70%)	40 (78%)	27 (71%)
SBP ≥140 mmHg *	68 (34%)	20 (25%)	15 (38%)	16 (33%)	17 (53%)
DBP ≥90 mmHg	12 (6.0%)	6 (7.4%)	1 (2.5%)	3 (6.3%)	2 (6.3%)
Medication with <140 or DBP <90	87 (43%)	41 (51%)	16 (40%)	22 (46%)	8 (25%)
Medication with SBP ≥140 or DBP ≥90 *	56 (28%)	15 (19%)	12 (30%)	15 (31%)	14 (44%)

- Table 2 summarizes blood pressure characteristics across B-ASC subtypes using last-visit SBP, DBP, and antihypertensive medication status and history of hypertension at any visit. Continuous Blood pressure cut-off categories in our study were based on the 2024 European Society of Cardiology (ESC) Guidelines for the Management of Elevated Blood Pressure and Hypertension, which define office hypertension as SBP ≥140 mmHg and/or DBP ≥90 mmHg[2].
- This threshold also corresponds to Stage 2 hypertension in the 2017 ACC/AHA Guideline and is consistent with treatment targets of SBP <140 mmHg in functionally robust adults aged >80 years [3]. Significant differences across subtypes were observed for SBP ≥140 mmHg and antihypertensive medication users with SBP ≥140 mmHg or DBP ≥90 mmHg (Pearson's χ^2 test).

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Table 3. Relationship with neuropathological findings and B-ASC subtype (n = 281).

Outcome	Significant pairwise comparison	OR (95% CI)	P value
Vascular dementia pathology	Subtype 4 vs. Subtype 3	6.67 (1.18–33.33)	0.021
Moderate/severe CAA	Subtype 3 vs. Subtype 2	4.35 (1.03–20.00)	0.040

Adjusted for age at death and sex

- Overall differences among SuStaln-defined B-ASC subtypes were evaluated using analysis of deviance (likelihood ratio test), followed by Bonferroni-adjusted pairwise comparisons for significant outcomes. Only vascular dementia pathology and moderate-to-severe cerebral amyloid angiopathy (CAA) differed significantly among subtypes, with higher odds of vascular dementia pathology in Subtype 4 than Subtype 3 (OR 6.67, 95% CI 1.18–33.33; P = 0.021) and higher odds of moderate-to-severe CAA in Subtype 3 than Subtype 2 (OR 4.35, 95% CI 1.03–20.00; P = 0.040) (Table 3).
- As a sensitivity analysis, participants without B-ASC (n = 161) were included as the reference group, revealing additional significant associations with AD neuropathologic change, Braak stage, Thal phase, hippocampal sclerosis of aging, and microinfarcts (data not shown).
- Future studies will validate these findings in larger independent cohorts and further investigate subtype-specific neuropathological profiles using additional sensitivity analyses and longitudinal clinicopathological datasets.

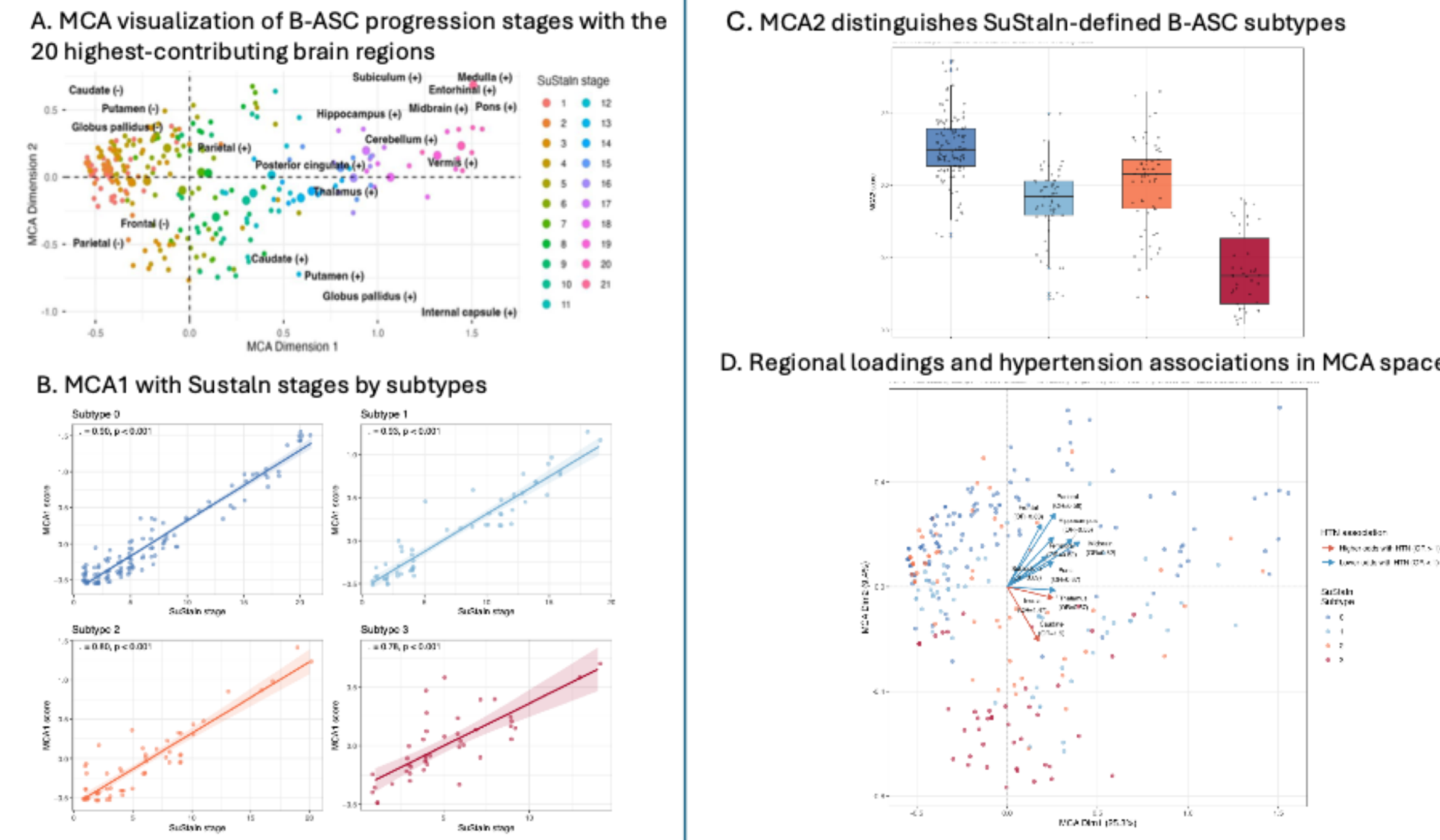


Figure 3. Multiple correspondence analysis (MCA) of regional B-ASC patterns

- To facilitate visualization of regional B-ASC patterns, we applied multiple correspondence analysis (MCA) to the 21 ROIs.
- MCA1 was strongly associated with SuStaln stages across all subtypes and represented overall B-ASC burden, with higher MCA1 values corresponding to more advanced pathology (Figure 3A,B).
- In contrast, MCA2 differentiated SuStaln-defined subtypes (Kruskal–Wallis p < 0.001) and represented a cortical-to-subcortical distribution axis, with lower values indicating greater basal ganglia and thalamic involvement (Figure 3C).
- Subtype 4 exhibited the lowest MCA2 scores and the highest prevalence of elevated blood pressure. Regional loadings demonstrated that basal ganglia and thalamic regions were associated with higher odds of hypertension, whereas cortical regions were associated with lower odds, suggesting that the spatial distribution of B-ASC, rather than overall burden alone, may underlie hypertension-related subtype differences (Figure 3D).

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