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- Structural connectivity approaches can advance understanding of white matter contributions to brain aging.
- We previously developed an antemortem R_2 structural connectome integrity matrix (R_2 -SCIM) from which five profiles were derived and demonstrated their differential associations with cognitive and motor function in older adults.
 - *R_2 is sensitive to multiple biological processes involved in brain aging*
 - *Postmortem studies suggest that white matter R_2 captures brain alterations beyond common age-related cerebrovascular disease (CVD) and neurodegenerative neuropathologies.*
- Whether neuropathologies exhibit distinct patterns of association with antemortem R_2 structural connectome integrity remains unclear.

- Examine associations of CVD and neurodegenerative neuropathologies with antemortem R₂-SCIM profiles in older adults.

- 245 decedents from five Rush Alzheimer's Disease Center cohort studies
- Inclusion criteria: antemortem 3T MRI, detailed postmortem neuropathologic evaluation, and last available MRI within 5 years of death

Table 1. Common age-related cerebrovascular and neurodegenerative neuropathologies.

Category	Neuropathologies
CVD	• Arteriolosclerosis^a • Atherosclerosis^a • Cerebral amyloid angiopathy (CAA)^a • Gross infarcts^b • Microinfarcts^b
Neurodegenerative	• Global AD burden^c • LATE-NC^d • Lewy bodies^b

Note. ^aModerate-to-severe vs. none/mild. ^bPresent vs. absent.
^cNeurofibrillary tangles and neuritic plaques counts, continuous. ^dStage 2-3 vs. Stage 0-1.

Dependent variables: Five R_2 -SCIM profiles (One global R_2 -SCIM metric & four R_2 -SCIM sub-network metrics).

- From the previously developed R_2 -SCIM containing 308 atlas-defined unique white matter nodal-pair connections, we derived:
 - Global R_2 -SCIM profile (average of the 308 median R_2 -SCIM values)
 - Four Principal Component Analysis (PCA)-derived weighted scores for sub-network (SN) profiles (**Figure 1**)

- Higher scores across all R₂-SCIM profiles indicate higher R₂ values

SN-1: Frontal, parietal, & basal ganglia nodes

SN-2: Frontal, temporal, & limbic nodes

SN-3: Parietal, temporal, & occipital nodes

SN-4: Cerebellar, basal ganglia, & limbic nodes

Factor loadings

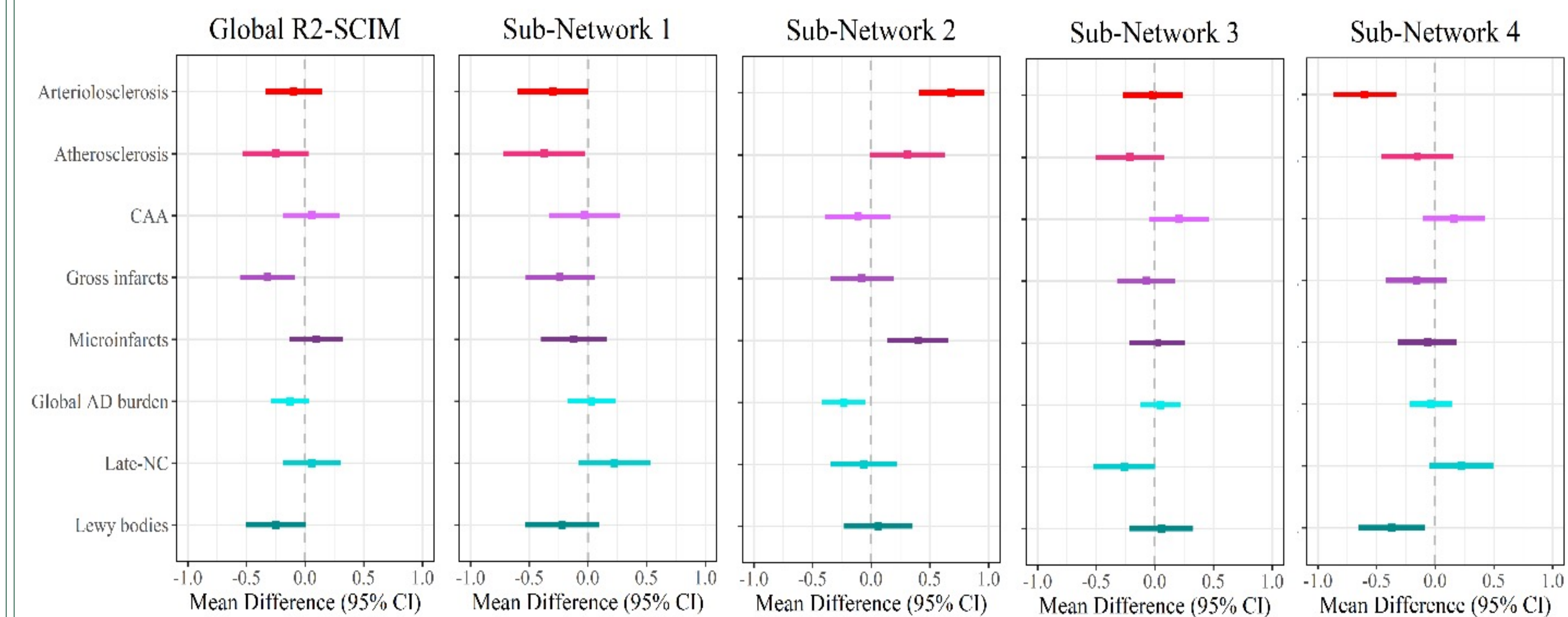
0.6 0.85

Note. Glass brain visualizations of atlas defined R_2 -SCIM connections with positive PCA loadings ≥ 0.60 for each of the four principal components (i.e., sub-networks).

- Linear regression models were employed to examine associations of all neuropathologies (simultaneously) with each R₂-SCIM profile (separately)
- Covariates: Age at last in-vivo MRI, sex, education, scanner, and antemortem interval (AMI) between last eligible MRI and death (**Table 3**)

Characteristic	
Age at last in-vivo MRI, mean (SD), years	87 (7)
Women, No. (%)	189 (77)
Education, mean (SD), years	16 (3)
<i>MRI Scanner, No. (%)</i>	
3T Philips Achieva	57 (23)
3T Siemens Trio	188 (77)
Antemortem interval (AMI), median (IQR), years	3 (2;4)

Figure 2. Associations of cerebrovascular and neurodegenerative neuropathologies with global R_2 -SCIM and PCA-derived sub-network R_2 -SCIM metrics at the last eligible MRI, adjusted for age at last MRI (continuous, years), sex, education (continuous, years), scanner, and antemortem interval (continuous, years) (N=245).



Note. Estimates are derived from five separate linear regression models; all neuropathologies were entered simultaneously.

- ✓ Only gross infarcts were associated with lower global R₂-SCIM.

- ✓ Large vessel disease (atherosclerosis) was associated with lower R_2 -SCIM in SN-1 (*predominantly fronto-parietal-basal ganglia connections*).
- ✓ Small vessel disease (arteriolosclerosis) was associated with higher R_2 -SCIM in SN-2 (*fronto-temporal-limbic connections*) and lower R_2 -SCIM in SN-4 (*cerebellar/subcortical connections*).
- ✓ Microinfarcts were associated with higher R_2 -SCIM in SN-2, whereas greater global AD burden was associated with lower R_2 -SCIM in SN-2.
- ✓ Lewy bodies were associated with lower R_2 -SCIM in SN-4.
- ✓ No neuropathology was associated with the predominantly parieto-temporal-occipital connections of SN-3.

- Common age-related cerebrovascular and neurodegenerative neuropathologies differentially associated with antemortem global and sub-network R_2 -SCIM profiles.
- R_2 -SCIM sub-networks may capture regional biological processes not evident using a global measure alone.
- Findings improve our understanding of how common age-related neuropathologies relate to structural connectome integrity in late life.