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Background



White matter hyperintensities (WMH) prevalent across diagnoses, reflect small vessel disease (SVD), associated with executive dysfunction and apathy



Apathy and executive dysfunction common across neurocognitive disorders (NCD), arise from disruptions in frontal-subcortical networks affected by white matter injury



Executive dysfunction may represent a pathway through which SVD contributes to apathy across NCD

Primary Hypothesis

Executive dysfunction will significantly mediate the indirect association between frontal WMH volume and apathy severity across NCD.

Secondary Hypothesis

Executive dysfunction will significantly mediate the indirect association between global WMH volume and apathy severity across NCD.

Methods



Participants from COMPASS-ND cohort across multiple diagnoses with WMH volumetrics (n=774)



Apathy severity derived from NPI-Q apathy item (0-3). Executive dysfunction operationalized as TMT B-A score, log-transformed (higher = worse)



Diagnostic groups: AD, MD, FTD, LBD, PD, MCI, vaMCI, SCI, CU controls



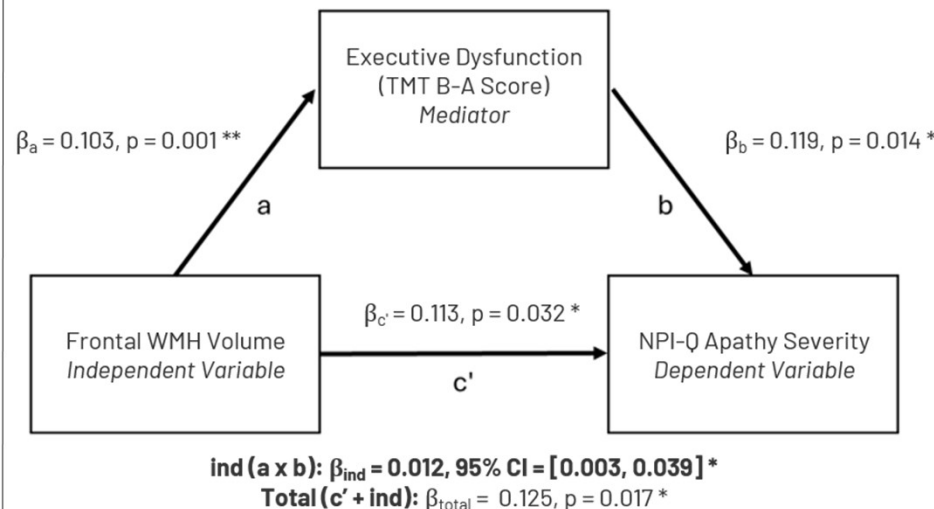
WMH segmentation performed within CCNA imaging pipeline (T1 + FLAIR MRI images). Frontal and global WMH volumes used (log-transformed and adjusted for head size)



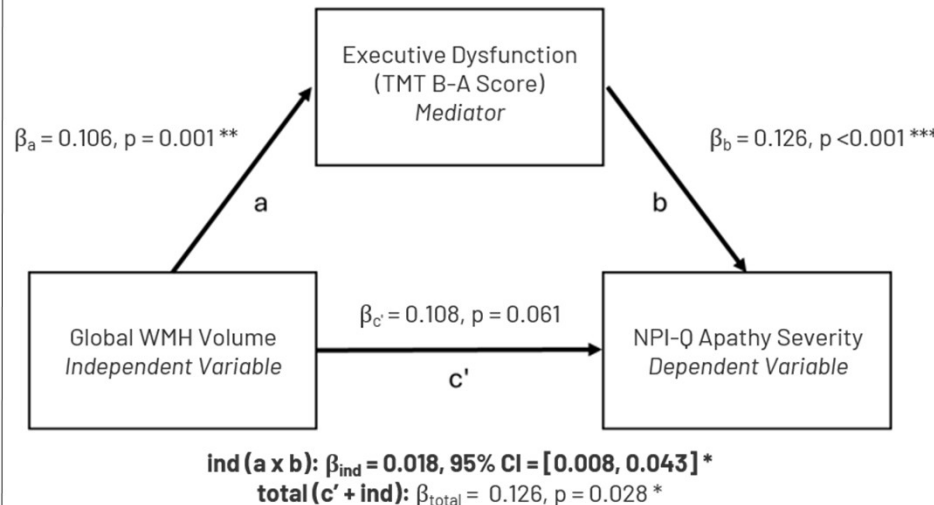
Structural equation modeling (mediation models). Covariates: age, sex, years of education, MoCA, depressive symptoms (GDS), diagnostic group, vascular risk factors

Results

Primary Model



Secondary Model



Discussion

- Results support a link between cerebrovascular injury, cognitive control deficits, and motivational impairment
- Frontal WMH demonstrated both direct and indirect associations with apathy, damage to frontal-subcortical circuits may influence motivation through executive dysfunction and additional pathways
- Association between global WMH burden and apathy largely explained by executive dysfunction, diffuse SVD may contribute to apathy primarily through its impact on cognitive control processes
- Regardless of diagnostic group, apathy and executive dysfunction appear to share common underlying disease processes, consistent with a transdiagnostic frontal-subcortical circuit mechanism
- Highlight importance of reducing vascular risk factors to prevent cognitive and behavioral decline

Future Directions

- Cross-sectional analysis cannot establish temporal ordering or causality, "mediation" should be interpreted statistically rather than mechanistically
- Longitudinal studies incorporating repeated assessments of WMH progression, executive functioning, and apathy are needed to determine whether executive dysfunction prospectively explains the emergence of apathy in individuals with increasing SVD burden

Acknowledgements

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