help to bridge competing theories of dementia progression in preclinical AD studies.

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6 Posterior cerebral artery-defined white matter hyperintensities are associated with object domain memory and transentorhinal volume independently of global beta-amyloid burden

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**Objective:** White matter hyperintensities (WMH) are a radiological marker of small vessel cerebrovascular disease that are related to cognition and memory decline in aging and Alzheimer’s disease (AD). However, the mechanisms that link WMH to memory impairment and whether they interact with or act independently of AD pathophysiology are unclear. The transentorhinal cortex (BA35) is among the earliest anatomical regions to show tau deposition and subsequent atrophy, and baseline posterior WMH is related to longitudinal cortical thinning of the entorhinal cortex. However, it is unclear whether regional WMH are related to BA35 volume specifically, and whether this relationship is influenced by amyloid-β (Aβ) burden. We hypothesized that WMH in the vascular territory of the posterior cerebral artery (PCA), which perfuses both posterior and medial temporal lobe regions, would be associated with reduced BA35 volume and with lower memory in older adults independently of Aβ.

**Participants and Methods:** 114 older adults without dementia, aged 60 to 98 years (mean (SD) = 78.31 (11.02), 71 (62.8%) women), were included. Regional WMH volumes were derived from T2-FLAIR images using ANTs, a vascular territory atlas and manual editing. Global Aβ was assessed with 18F-florbetapir PET, using SUVR of a cortical composite region (FBP mean SUVR) with a cerebellar reference region. Total transentorhinal (BA35) volume was derived using T1 and T2-weighted images using ASHS. To assess hippocampal pattern separation ability, an index of episodic memory, participants completed both object (MDT-O) and spatial (MDT-S) versions of a mnemonic discrimination task, with the lure discrimination index as the outcome. Using linear regressions, we first tested for associations among PCA-defined WMH, Aβ, BA35 volume, and MDT-S and MDT-O scores. We then tested whether the relationship between PCA-defined WMH and MDT-O performance was mediated by BA35 volume and whether this mediation was moderated by Aβ. All models adjusted for age, sex, and education.

**Results:** PCA-defined WMH were related to higher FBP mean SUVR (b=-0.287, p=0.042) and lower BA35 volume (b=-0.222, p=0.038). PCA-defined WMH were also negatively related to MDT-O performance (b=-0.229, p=0.044), but not to MDT-S (b=-0.171, p=0.118). FBP mean SUVR was not related to BA35 volume (b=-0.131, p=0.344) or MDT performance (MDT-S: b=-0.138, p=0.348; MDT-O: b=0.059, p=0.690). Furthermore, FBP mean SUVR did not interact with PCA-defined WMH to predict memory performance (interaction b=-0.039, p=0.973), nor BA35 volume (interaction b=-0.140, p=0.894). The association of PCA-defined WMH to MDT-O was fully mediated by BA35 volume (indirect effect b=-0.0005, 95% CI (-0.0014, -0.0003)). This mediation was not moderated by FBP mean SUVR (indirect effect b=-0.00001, 95% CI (-0.001, 0.001)).

**Conclusions:** We found that PCA-defined WMH were related to memory performance in older adults, and this association is fully mediated by transentorhinal volume. While PCA-defined WMH are related to higher global Aβ burden, there is no interaction between PCA-defined WMH and Aβ on BA35 volume. These findings point to an amyloid-independent vascular pathway towards memory decline in aging and AD. Future work should examine whether the pathway linking PCA-defined WMH to transentorhinal cortex atrophy and subsequent memory decline is mediated by regional tau pathology.
Sluggish Cognitive Tempo in Children and Adolescents with Fetal Alcohol Spectrum Disorders: Associations with Executive Function and Subcortical Volumes

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Objective: Fetal alcohol spectrum disorder (FASD) is a common neurodevelopmental condition associated with deficits in cognitive functioning (executive functioning [EF], attention, working memory, etc.), behavioral impairments, and abnormalities in brain structure including cortical and subcortical volumes. Rates of comorbid attention-deficit/hyperactivity disorder (ADHD) are high in children with FASD and contribute to significant functional impairments. Sluggish cognitive tempo (SCT) includes a cluster of symptoms (e.g. underactive/slow-moving, confusion, foginess, daydreaming) found to be related to but distinct from ADHD, and previous research suggests that it may be common in FASD. We explored SCT by examining the relationship between SCT and both brain volumes (corpus callosum, caudate, and hippocampus) and objective EF measures in children with FASD vs. typically developing controls.

Participants and Methods: This is a secondary analysis of a larger longitudinal CIFASD study that consisted of 35 children with prenatal alcohol exposure (PAE) and 30 controls between the ages of 9 to 18 at follow-up. Children completed a set of cognitive assessments (WISC-IV, DKEFS, & NIH Toolbox) and an MRI scan, while parents completed the Child Behavior Checklist (CBCL), which includes a SCT scale. We examined group differences between PAE and controls in relation to SCT symptoms, EF scores, and subcortical volumes. Then, we performed within- and between-group comparisons with and without controlling for total intracranial volume, age, attention problems, and ADHD problems between SCT and subcortical brain volumes. Finally, we performed correlations between SCT and EF measures for both groups.

Results: Compared to controls, participants with PAE showed significantly more SCT symptoms on the CBCL ($t_{[57]} = 3.66, p = 0.0006$), more parent-rated attention problems and ADHD symptoms, lower scores across several EF measures (DKEFS Trail-Making and Verbal Fluency; WISC-IV Digit Span, Symbol Search, and Coding; effect sizes ranging from 0.44 to 1.16), and smaller regional volumes in the caudate, hippocampus, and posterior areas of the corpus callosum. In the PAE group, a smaller hippocampus was associated with more SCT symptoms (controlling for parent-rated attention problems and ADHD symptoms, age, and intracranial volume). However, in the control group, a larger mid posterior and posterior corpus callosum were significantly associated with more SCT symptoms (controlling for parent-rated attention problems, intracranial volume, and age; $r_{[24]} = 0.499, p = 0.009$; $r_{[24]} = 0.517, p = 0.007$). In terms of executive functioning, children in the PAE group with more SCT symptoms performed worse on letter sequencing of the Trail-Making subtest (controlling attention problems & ADHD symptoms). In comparison, those in the control group with more SCT symptoms performed better on letter sequencing and combined number letter sequencing of the Trail-Making subtest (controlling attention problems).

Conclusions: Findings suggest that children with FASD experience elevated SCT symptoms compared to typically developing controls, which may be associated with worse performance on EF tasks and smaller subcortical volumes (hippocampus) when taking attention difficulties and ADHD symptoms into account. Additional research into the underlying causes and correlates of SCT in FASD could result in...