Declines in default-mode network structure and function mediate the negative effects of Alzheimer's pathology on executive function in older adults

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Background: Executive function declines in older age negatively impact quality of life. Recent evidence suggests that the default mode network (DMN) may play an important role in maintaining executive function in older adults. DMN functional declines, as measured by lower resting-state connectivity (rsC) and task-induced deactivation (TID), are often observed in older adults, but it is unclear whether these declines are the result of mechanisms of normal aging or Alzheimer's disease (AD) pathology.

Purpose: To determine how white matter (WM) microstructure declines, associated with normal aging, and accumulation of tau and beta-amyloid (Aβ42), associated with AD, independently and synergistically contribute to early declines in DMN function and executive performance seen in cognitively normal (CN) older adults.

Methods: Participant were 35 CN older adults (ages 65-93) and 29 younger adults (ages 18-34) who underwent resting-state (rs-) and task-based (tb-) fMRI and diffusion tensor imaging. Older adults also had a lumbar draw of cerebrospinal fluid, from which concentrations of tau and Aβ42 were measured. Participants performed a working memory task during the tb-fMRI, and measures of accuracy and reaction time were obtained. Independent component analysis was used to identify a common set of DMN regions from rs- and tb-fMRI, from which DMN rsC and TID were measured. The same regions were then used for probabilistic tractography in order to identify WM pathways connecting DMN regions, from which WM microstructure was measured.

Results: Group comparisons confirmed significant age-related declines in DMN rsC, TID, WM microstructure, and working memory performance. Within older adults, partial correlation analyses (controlling for age and sex) found that lower DMN TID was associated with poorer WM microstructure ($r = 0.39$, $p = .03$) and increasing AD pathology ($r = -0.36$, $p = .04$). However, poorer WM microstructure was also associated with greater AD pathology ($r = -0.37$, $p = .04$), thus mediation analysis was used to test the independent and synergistic effects of these measures on DMN function. Results indicated that the effect of AD pathology on DMN function was mediated by declining WM microstructure. In addition, poorer working memory performance in older adults was associated with less DMN TID, poorer WM microstructure, and increasing AD pathology ($r = 0.59, 0.58, -0.40$; $p \leq .02$). Mediation analyses indicated that the effects of AD pathology on working memory performance were mediated by poorer WM microstructure and DMN function.

Conclusions: These findings show that higher levels of DMN TID are important for maintaining executive function in older age. Further, we provide the first evidence that the negative effect on AD pathology on DMN function is driven by declines in WM microstructure. Therefore, interventions aimed at protecting WM microstructure may preserve DMN function and, in turn, executive function in older adults.