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Age and Alzheimer's pathology disrupt default mode network functioning via alterations in white matter microstructure but not hyperintensities

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Abstract

The default mode network (DMN) comprises defined brain regions contributing to internally-directed thought processes. Reductions in task-induced deactivation in the DMN have been associated with increasing age and poorer executive task performance, but factors underlying these functional changes remain unclear. We investigated contributions of white matter (WM) microstructure, WM hyperintensities (WMH) and Alzheimer's pathology to age-related alterations in DMN function. Thirty-five cognitively normal older adults and 29 younger adults underwent working memory task fMRI and diffusion tensor imaging. In the older adults, we measured cerebrospinal fluid tau and A β_{42} (markers of AD pathology), and WMH on FLAIR imaging (marker of cerebrovascular disease). We identified a set of regions showing DMN deactivation and a set of inter-connecting WM tracts (DMN-WM) common to both age groups. There were negative associations between DMN deactivation and task performance in older adults, consistent with previous studies. Decreased DMN deactivation was associated with AD pathology and WM microstructure but not with WMH volume. Mediation analyses showed that WM microstructure mediated declines in DMN deactivation associated with both aging and AD pathology. Together these results suggest that AD pathology may exert a “second-hit” on WM microstructure, over-and-above the effects of age, both contributing to diminished DMN deactivation in older adults.

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Keywords

fMRI; DTI; Alzheimer's disease; executive function; cerebrovascular disease

1. Introduction

The default mode network (DMN) comprises brain regions that are highly active during in the brain's homeostatic baseline state and contribute to internally-focused thought processes, including autobiographical memory and planning, maintenance of the self, and mind wandering (Andrews-Hanna, Smallwood, & Spreng, 2014; Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard & Raichle, 2001). The regions making up the DMN show strong functional connectivity during resting-state fMRI, and greater activity during baseline conditions than during externally-directed cognitive tasks (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001; Shulman et al., 1997). This latter phenomenon is termed deactivation, which is thought to reflect an active mechanism to prevent continuously active DMN processes from interfering with attention-demanding, externally-oriented environmental demands (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). However, capacity for deactivation is reduced in aging (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007), which in turn is associated with poorer performance on executive function tasks (C. a. Brown, Hakun, Zhu, Johnson, & Gold, 2015; Persson et al., 2007; Prakash, Heo, Voss, Patterson, & Kramer, 2012).

Mechanisms contributing to age-related reduction in capacity for deactivation within the DMN remain unclear. These mechanisms are likely to include processes related to normal aging and/or clinically silent pathologies in cognitively normal older adults (Jagust, 2013). Two pathologies harbored by a significant number of cognitively normal older adults are AD pathology, present in 20-30% of cognitively normal older adults, and cerebrovascular disease pathology, present in up to 90% of cognitively normal older adults (de Leeuw, 2001; J. C. Morris et al., 1996; Shaw et al., 2009). Several studies have found that increasing AD pathology is associated with less deactivation in portions of the DMN in cognitively normal older adults (Elman et al., 2014; Huijbers et al., 2015; Sperling et al., 2009), while the two studies examining the effects of cerebrovascular pathology on DMN deactivation have been equivocal (Hedden et al., 2012b; Mayda, Westphal, Carter, & Decarli, 2011). Alterations in DMN deactivation may also be the result of subtler, age-related microstructural changes in white matter (WM), which can be assessed with diffusion tensor imaging (DTI). Age-related declines in the WM microstructural metric of fractional anisotropy (FA) are well-documented (Sullivan & Pfefferbaum, 2006), and have been associated with alterations in functional neuroimaging networks, including the DMN (C. a. Brown et al., 2015; Damoiseaux & Greicius, 2009; Daselaar et al., 2013; Zhu, Johnson, Kim, & Gold, 2015).

To summarize, separate previous studies have reported links between diminished DMN deactivation and increasing age, increasing AD pathology, higher cerebrovascular disease burden, and poorer WM microstructure. However, these age-related neurobiological factors are often themselves related, making it difficult to disentangle their relative contributions to

DMN deactivation in older adults. For example, several studies have reported associations between greater AD pathology and both greater cerebrovascular pathology (Marnane et al., 2016; Scott et al., 2015) and lower DTI-based FA values (C. A. Brown et al., 2017; Gold et al., 2014; Molinuevo et al., 2014) in cognitively normal older adults. Further, greater cerebrovascular pathology, as measured by white matter hyperintensities (WMH), is associated with lower WM microstructural properties within the tracts affected in cognitively normal older adults (Taylor et al., 2007). Therefore, a major question is whether age, AD pathology, cerebrovascular pathology, and WM microstructure are associated with DMN deactivation through shared or independent pathways.

The present study provided a novel test between these different possibilities. Younger and older adults performed a working memory fMRI experiment, a task paradigm selected based on previous links between executive task performance and DMN deactivation (C. a. Brown et al., 2015; Persson et al., 2007; Prakash et al., 2012). Participants also underwent DTI in order to identify and measure microstructure within DMN-WM pathways. Older adults further underwent FLAIR imaging for assessment WMHs, a measure of cerebrovascular pathology, and a lumbar draw for assessment of cerebrospinal fluid (CSF) markers of AD pathology, including β -amyloid ($A\beta$) and tau. Following initial bivariate analyses, mediation analyses utilizing competing path models were used to understand how these inter-related measures predicted alterations in DMN deactivation (see Salthouse, 2011; Bennett and Madden, 2014 for theoretical reviews of competing path models).

2. Methods

2.1. Participants

A total of 69 individuals (39 older adults and 30 younger adults) were recruited to participate in the present study. Written informed consent was obtained from each participant under an approved University of Kentucky Institutional Review Board protocol. Older adults were recruited from an existing longitudinal cohort at the Sanders-Brown Center on Aging who are followed annually for demographic, health, and neuropsychological data (Schmitt et al., 2012). Cognitive normality was determined through consensus conference per the procedures outlined in the Uniform Data Set (UDS, Morris et al., 2006). Younger adults were recruited from the University of Kentucky and the surrounding area through advertisements.

Exclusion criteria for all participants were significant head injury (operationally defined as loss of consciousness for greater than five minutes), heart disease, psychiatric or neurological disorder, claustrophobia, pacemakers, or presence of metal fragments and/or metallic implants contraindicated for MRI. Quality control measures (described below) led to the exclusion of 4 older adults (one due to excessive motion and three due to task performance or response rate > 3 SDs above/below the group mean) and one younger adult (due to an artefact on MR images). Characteristics of the final cohort of 35 older adults and 29 younger adults are shown in Table 1.

2.2. Cerebrospinal fluid sampling (CSF) and analysis

Older adults underwent a lumbar sampling of CSF in the morning following overnight fast, as previously described (Gold et al., 2014). Samples were shipped on dry ice to the Biomarker Research Laboratory at the University of Pennsylvania Medical Center. The multiplex xMAP Luminex Platform (Luminex Corp, Austin TX) with Innogenetics (INNO-BIA, AlzBio3; Ghent, Belgium) immunoassay kit was used for analysis as previously described (Shaw et al., 2009). CSF concentrations of $A\beta_{42}$ and total tau (t-tau) were measured and $A\beta_{42}$ and the tau/ $A\beta_{42}$ ratio were used as statistical predictors due to their relative sensitivity and specificity for AD (Shaw et al., 2009). These CSF values were log-transformed before statistical analyses due to their skewed distribution.

2.3. fMRI paradigm and behavioral analysis

Participants performed a visual working memory paradigm during fMRI scanning. The paradigm was a modified delayed-match-to-sample task (Figure 1) with multiple targets and repeating intervening distractors, which increases demands on executive processes (Jiang, 2000; Kane & Engle, 2002). The task stimuli were two-dimensional pictures of common objects selected from Snodgrass and Vanderwart (Snodgrass & Vanderwart, 1980). During task blocks, participants were asked to 'hold in mind' the two target images and indicate (via button press) whether or not each of 12 serially presented single samples represented a match with either target image. Sample images were either one of the two target (match) images presented at the beginning of the task block or distractor (non-match) images, which were repeated between 2-4 times in a block. The ratio of targets to distractors in each block ranged from 5:7 to 7:5. During baseline blocks, participants viewed scrambled versions of object images (created by Fast Fourier transform algorithms).

There were two fMRI runs, each consisting of 8 working memory task blocks (28s each) and 9 visual baseline blocks (10s each), which occurred between each task block as well as at the start and end of each run. E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) was used for stimulus presentation and response recording. Task accuracy was analyzed using corrected recognition (CR), which is the hit rate (# of targets correctly identified as targets) minus the false alarm rate (# of distractors incorrectly identified as targets). Mean response time (RT) was also calculated for each individual by averaging RT on all trials.

2.4. Imaging protocol

Neuroimaging was performed using a Siemens Trio TIM 3 Tesla scanner with a 32-channel head coil at the University of Kentucky Magnetic Resonance Imaging and Spectroscopy Center (MRISC). The core protocol consisted of the following sequences collected in the order they are listed: 1) High resolution T1-weighted anatomical image, 2) Two task-fMRI blood-oxygen-level dependent (BOLD) T2*-weighted functional imaging runs, 3) one resting state (rs)-fMRI BOLD T2*-weighted functional imaging run, and 4) diffusion tensor imaging (DTI). In addition to the core protocol, older adults also underwent fluid-attenuated inversion recovery (FLAIR) imaging, which was collected at the end of the scanning session.

The high resolution T1-weighted image was acquired using a magnetization-prepared rapid echo gradient-echo (MPRAGE) sequence [Repetition time (TR) = 2530ms, Echo time (TE) = 2.26ms, inversion time (TI) = 1100ms, Flip angle (FA) = 7°, acquisition matrix = $256 \times 256 \times 176$, field of view (FOV) = 256mm^2 , 1mm isotropic voxels]. Task- and rs-fMRI were acquired using gradient-echo echo-planar imaging (EPI) [TR = 2000ms, TE = 27ms, FA = 83°, acquisition matrix = 64×64 , FOV = 224mm^2 , 3.8mm isotropic voxels, 36 interleaved slices]. DTI was acquired using a double-spin echo EPI sequence [TR = 8000ms, TE = 96ms, FA = 90°, FOV = 224mm^2 , 2mm isotropic voxels, 52 contiguous slices] with 60 non-collinear encoding directions ($b = 1000\text{s/mm}^2$) plus 8 images without diffusion weighting (b_0). FLAIR images were collected using a fat saturated, turbo-spin echo (TSE) sequence [TR = 9000ms, TE = 89ms, TI = 2500ms, FA = 130°, acquisition matrix = $256 \times 174 \times 34$, $1 \times 1 \times 4\text{mm}$ voxels].

2.5. Image pre-processing and quality control

The FMRIB Software Library [FSL, (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; S. M. Smith et al., 2004) v.5.0.9] was used for all image processing and analysis unless otherwise stated. The T1-weighted structural image was bias-field corrected using FAST and brain extracted using BET (S. M. Smith, 2002; Y. Zhang, Brady, & Smith, 2001). Each participant's structural image was registered to the MNI152 T1 2mm template using FLIRT to generate an initial linear affine transformation (Jenkinson, Bannister, Brady, & Smith, 2002), followed by non-linear warping using FNIRT with 20mm warp resolution (J. Andersson, Jenkinson, & Smith, 2010).

fMRI data were motion corrected using MCFLIRT, smoothed with an 8mm Gaussian filter, and high-pass filtered at 90s using FEAT v.6.0.0 (S. M. Smith et al., 2004). Participants with $> 1.5\text{mm}$ root mean square absolute motion were excluded (one older adult). Within participants, frame-wise displacement was calculated using the FSL motion outlier utility, and volumes with frame-wise displacement $> 0.5\text{mm}$ were considered motion outliers (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). A threshold of no more than 20% of volumes being identified as outliers was applied but did not lead to the exclusion of any functional runs. Each functional run was registered to the individual's high-resolution T1-weighted structural image using boundary-based registration (Greve & Fischl, 2009), and then transformed into MNI152 T1 2mm space by applying the non-linear warp for the structural image (described above).

6mm Gaussian spheres were created in the lateral ventricles and frontal, temporal, parietal, and occipital WM to generate a CSF region-of-interest (ROI) and WM ROI. Time-series were extracted from both the CSF and WM ROIs for each of the functional runs. Regression was performed on each functional run using the `fsl_glm` utility with the following parameters: 1) Six motion parameters generated from MCLFIRT, 2) one “dummy” parameter for each volume classified as a motion outlier, 3) Time-series from the CSF ROI, and 4) Time-series from the WM ROI. The residuals of the regression analysis were saved as the cleaned functional data for further analyses.

2.6. Identifying regions showing DMN deactivation

The goal of the independent component analyses was to identify deactivations within core DMN regions. Independent component analysis was performed separately for the task-fMRI data and for the rs-fMRI data with FSL MELODIC using the concatenation approach with dimensionality set to 20 components (Beckmann, DeLuca, Devlin, & Smith, 2005). Dimensionality of 20 was selected based on previous studies demonstrating that this identifies the major large-scale brain networks without splitting, which occurs more frequently with higher dimensionalities (Laird et al., 2011; S. M. Smith et al., 2009). For the task-fMRI data, in each run, a component including DMN regions was visually identified based on a template from the BrainMap studies (Laird et al., 2011; S. M. Smith et al., 2009). The FSL independent component cross-correlation utility was then used to confirm high correlation between the time series of the selected components from the two task-fMRI runs. The components from the two task-fMRI runs were then averaged together and thresholded at $p < .005$ (which met an FDR-corrected threshold of $p < .05$ using FSL's *fdr* utility).

The resulting component included both DMN and non-DMN regions. In order to confine analyses to traditional DMN regions, the task-ICA results were then masked by the DMN component identified from rs-fMRI (which was also thresholded at $p < .005$). This served to identify a set of DMN regions showing deactivation during the working memory task. Surviving clusters (reflecting DMN deactivation) were then identified using a threshold of $Z > 0$ (as all voxels remaining had already been determined to reach significance) in order to locate peak voxels (Table 2). The resulting clusters (DMN deactivation ROIs) were used for time-series analyses and probabilistic tractography.

2.7. DMN deactivation Magnitude

Time-series were extracted across all DMN deactivation ROIs for each participant/run/block. BOLD signal during baseline was computed by averaging the middle 6s of all baseline blocks (in order to avoid the upshoot and downshoot associated with the onset/offset of blocks). BOLD signal during the task was computed by averaging the middle 6s of all working memory blocks (to parallel sampling of the baseline blocks). Deactivation was then computed as percent signal change by subtracting the BOLD signal during the baseline from the BOLD signal during the task, dividing by the BOLD signal during baseline and multiplying by 100. The sign of % signal change (i.e. magnitude) was then inverted for ease of interpretation of findings (i.e. more negative % signal change during the task is represented as more positive deactivation magnitude).

2.8. DTI analysis

FMRIB's Diffusion Toolbox (FDT) v.3.0 was used for pre-processing and analyses. FSL's EDDY tool v. 5.0.8 was used for motion and eddy-current correction with automatic replacement of outlier volumes (J. L. R. Andersson, Graham, Zsoldos, & Sotiropoulos, 2016; J. L. R. Andersson & Sotiropoulos, 2016). The b0 images were averaged to form a single b0 image, which was then brain extracted using BET in order to form a brain mask for DTI data. DTIFIT was used to fit a voxel-wise tensor model, and each participant's FA image was registered to the FMRIB58 1mm template using the tract-based spatial statistics (TBSS) pipeline (S. M. Smith et al., 2006). Data were projected onto a group skeleton with a

threshold of FA > 0.2mm to minimize partial volume effects and correct for residual misalignments.

In order to identify WM pathways connecting DMN cortical regions that showed deactivation, probabilistic tractography was performed. BEDPOSTX was used to fit a probabilistic diffusion model with 3 fibers in each voxel (Behrens et al., 2003; Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). PROBTRACKX2 was run in network mode using modified Euler streamlining with parameters described previously (C. a. Brown et al., 2015). Before use as seeds for tractography, the functionally-defined DMN deactivation ROIs (described above) were transformed to the FMRIB FA 1mm template using the resultant parameters from registering the MNI152 T1 2mm template to the FMRIB FA 1mm template using FLIRT. The DMN ROIs were then transformed to each participant's native diffusion space using the inverse of the non-linear warp generated in TBSS (described above). Additionally, a mask of the brain stem from the Harvard-Oxford Structural Atlas, which was used as an exclusion mask to avoid descending tracts, was transformed from FMRIB FA 1mm space to each participant's native diffusion space.

Successful streamlines were those originating in one DMN cortical seed and passing through another DMN cortical seed without passing through the brainstem exclusion mask or violating any of the other tractography parameters. A group template of DMN-WM pathways was formed in FMRIB FA 1mm space using a series of steps described in our previous work (C. A. Brown et al., 2017). The resulting DMN-WM group template was then masked by the mean FA skeleton generated in TBSS to minimize partial volume effects, resulting in a skeletonized DMN-WM group template. Mean FA was then extracted from the skeletonized DMN-WM group template in all participants.

2.9. FLAIR analysis

A semi-automated process was used to identify WMHs on older adult FLAIR images based on a previously described framework (C. D. Smith et al., 2016). Briefly, FreeSurfer (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002) segmentation was performed on each participants' T1-image to create a WM template. Following registration to the 3D-FLAIR brain using FLIRT, the T1-WM template was dilated using MIPAV and a 1mm Gaussian blur was applied using FSL's SUSAN. This WM template was then used to mask the 3D-FLAIR image. A two-Gaussian model was used to fit the voxel intensity histogram of the resulting FLAIR-WM image in order to identify the mean and standard deviation of the dominant fit. The FLAIR-WM image was then thresholded to include only voxels > 2.33 SD above this mean to form a WMH mask. The WMH mask was manually edited to remove artefactual voxels in regions between the lateral ventricles and in inferior slices (C. D. Smith et al., 2016). FLAIR images were then used to compute estimates of WMHs related to WM within the DMN of older adults (described below).

2.10. Computing WMH volume in the DMN-WM of Older Adults

This analysis sought to estimate the percentage of voxels within the DMN-WM of older adults affected by WMHs. DMN-WMH volume was calculated for older adults by masking each individual's FLAIR image by the unskeletonized DMN-WM mask. The volumes of

non-zero voxels were computed using `fsldstats` and divided by the volume of the DMN-WM mask in order to calculate the % of DMN WM identified as WMH.

2.11. Computing FA in Normal Appearing WM in Older Adults

This analysis sought to estimate FA in the DMN-WM of older adults within regions free from WMH, that is, areas of normal appearing WM (naWM). All WM was considered naWM in younger adults, in whom WMHs are rare (Putaala et al., 2009). The first step was to generate a DMN-naWM mask by registering older adult's WMH masks to their DTI space using the following steps: The FLAIR image of each older adult was registered to their b0 image using FLIRT, and the resultant parameters were used to transform each participant's WMH mask to native DTI space. The TBSS non-FA pipeline was then used to register each participant's WMH mask to the mean group skeleton in FMRIB FA 1mm space. A DMN-naWM mask was then generated for each older adult by subtracting their WMH-mask from the group skeletonized DMN mask. FA was then extracted from the DMN-naWM skeletonized mask in each older adult.

2.12. Computing Gray Matter Volume in DMN Regions

In order to determine if alterations in gray matter (GM) volume influenced our results, FreeSurfer was used to calculate gray matter volume within DMN regions. The standard FreeSurfer pipeline was used in order to calculate volume in the posterior cingulate, medial prefrontal cortex, dorsomedial prefrontal cortex, lateral parietal cortex, lateral temporal cortex, and hippocampi bilaterally using the high-resolution T1-weighted images for each participant (Dale et al., 1999; Fischl et al., 2002). The sum of these cortical volumes was calculated and then divided by the total intracranial volume to determine the percent of total intracranial volume belonging to DMN regions in each participant (DMN-GM volume).

2.13. Experimental Design & Statistical analysis

SPSS 23 (IBM, Chicago, IL) was used for all statistical analyses. Paired t-tests were performed to determine the difference between FA in DMN-WM and FA in DMN-naWM within older adults. FA in DMN-naWM was used in all further analyses. Linear regression was used to examine the relationship between DMN deactivation and performance on the working memory task (corrected recognition and RT separately). For each analysis sex and education were used as predictors of no-interest, while DMN deactivation, age group, and age group $\times$ DMN deactivation interaction were predictors of interest. Significant interactions were explored by performing partial correlations (controlling for age and sex) between DMN deactivation and task performance within each age group separately.

To determine which variables contributed to individual differences in DMN deactivation, initial bivariate relationships between all variables were explored using partial correlations controlling for sex and education when testing age effects across all participants (age, DMN deactivation, and FA in DMN-naWM) and controlling for age, sex, and education when testing effects of pathology within older adults (DMN deactivation, FA in DMN-naWM, DMN-WMH volume, CSF A β ₄₂, and CSF tau/A β ₄₂). Supplemental analyses were performed to determine if functional measures were correlated with DMN-GM volume. Further, partial correlations were repeated controlling for DMN-GM volume as well as age,

sex, and education. Bivariate relationships were explored in order to determine which variables should be entered into mediation analyses. Therefore, a liberal significance threshold of $p < .05$ without correction for multiple comparisons was used. Due to this threshold, limited inference was made from these bivariate results, and instead inferences were made primarily from the results of mediation analyses described below.

Multivariate relationships were explored using Preacher and Hayes mediation analyses using the PROCESS macro for SPSS (Hayes, 2013). Preacher and Hayes mediation uses multiple linear regression methods to simultaneously test direct and indirect effects and uses Monte-Carlo confidence intervals (CI) to assess significance. Effects that had 95% CIs that did not cross 0 were considered significant. In order to test whether the effects of age and pathology on DMN deactivation were mediated by DMN-naWM, separate mediation analyses were performed to test whether DMN-naWM mediated the effects of age and pathology on DMN deactivation. Importantly, in Preacher and Hayes mediation analysis, the finding that DMN-naWM mediates the effect of age or pathology on DMN deactivation does not necessitate that age and pathology cannot themselves also mediate the relationship between DMN-naWM and deactivation (Hayes, 2013; Salthouse, 2009). Therefore, alternative models were also tested in order to determine if DMN-naWM had a direct effect on DMN deactivation or if it was mediated by either age or pathology.

3. Results

Younger and older adults did not differ in male:female ratio ($\chi^2 = 0.03$, $p = 0.87$) or years of education ($t = 0.26$, $df = 62$, $p = 0.80$). Demographic and mean outcome measures are shown in Table 1. Older adults had significantly lower corrected recognition ($t = -4.29$, $df = 62$, $p < .001$) and higher RT ($t = 9.59$, $df = 62$, $p < .001$) than younger adults. Further, corrected recognition was inversely correlated with RT after controlling for age, sex, and education ($r = -0.31$, $df = 59$, $p = .017$).

3.1. Independent Component Analysis results

In each task-fMRI run, the time course of the component containing DMN regions had a strong inverse relationship with the working memory component of the task convolved with the double-gamma hemodynamic response function ($r = -0.71$, -0.72 , $p < .001$), thus indicating that these components reflected deactivation-related components. Further, cross-correlation between the deactivation-related component from each task-fMRI run was high ($r = 0.95$). After averaging across task-fMRI runs, and thresholding at an FDR-corrected level of $p < .005$, the task-component included core DMN regions and other non-DMN (task-specific) regions such as the thalamus and primary visual cortex (Figure 2a).

After masking the task-component by the rs-fMRI DMN component (Figure 2b), the final set of DMN deactivation regions (Figure 2c) consisted of: the midline posterior cingulate cortex/precuneus (PCC/pC) and ventromedial prefrontal cortex (vmPFC), as well as bilateral dorsal medial prefrontal cortex (dMPFC), lateral occipital/parietal cortices (LOC/LPC), and lateral temporal cortices (LTC). In addition, the DMN included the right hippocampus (HC) and left parahippocampal gyrus (PHG). Peak coordinates for each of these regions are shown in Table 2. A repeated-measures ANOVA controlling for sex and education found that

there was no significant effect of region on deactivation magnitude ($F_{9,53} = 0.96$, $MSE = .009$, $p = 0.47$). These results further supported the use of an overall network-level measure of DMN deactivation rather than looking at regional differences within the DMN. One-way t-tests found that both younger and older adults showed significant DMN deactivation ($t = 8.93, 4.41$; $df = 28, 34$; $p < .001$).

3.2. Association between DMN deactivation and Working Memory Performance

The linear regression model for corrected recognition ($F_{5,58} = 3.77$, $MSE = .007$, $p = .005$) found a main effect of age group ($\beta = 0.48$, $t = 4.03$, $p < .001$) but no main effect of DMN deactivation ($p = 0.99$) nor a DMN deactivation $\times$ age group interaction ($p = 0.47$). In contrast, the linear regression model for RT ($F_{5,58} = 27.35$, $MSE = 4519$, $p < .001$) found a significant DMN deactivation $\times$ age group interaction ($\beta = 0.42$, $t = 3.05$, $p = .003$). To examine this interaction, partial correlations between DMN deactivation and RT were performed separately in each group while controlling for age, sex, and education. Partial correlations (Figure 3) demonstrated that lower DMN deactivation magnitude was significantly associated with slower task RT within older adults ($r = -0.59$, $df = 30$, $p < .001$), but not in younger adults ($p = .424$).

3.3. Probabilistic tractography results

A common set of DMN-WM pathways (tracts connecting DMN cortical regions) was identified across younger and older adults (Figure 4a-c). The common DMN-WM pathways included midline association tracts (cingulum and fornix), lateral association tracts (inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus) and commissural tracts (genu and splenium of the corpus callosum).

3.4. WMHs in the DMN-WM of Older Adults

On average, $3.6 \pm 3.1\%$ of all DMN-WM voxels (median = 2.4%, range = 0.4-13%) were affected by WMHs. For visualization purposes, a mean WMH mask thresholded to show voxels in which at least 2 participants (Figure 4d) had WMHs was created and overlaid on the DMN-WM template. Within older adults, FA in all DMN-WM was significantly lower than FA in DMN-naWM ($t = -5.29$, $df = 34$, $p < .001$). Further, DMN-WMH volume was correlated with FA in all DMN-WM ($r = -0.48$, $df = 30$, $p = .005$) but not with FA in DMN-naWM ($r = -0.29$, $df = 30$, $p = .11$) after controlling for age, sex, and education within older adults.

3.5. Associations between DMN deactivation, age and WM microstructure

Increasing age was associated with less DMN deactivation (Figure 5a, $r = -0.26$, $df = 60$, $p = .043$) and lower FA in DMN-naWM (Figure 5b, $r = -0.76$, $df = 60$, $p < .001$). Further, lower FA in DMN-naWM was associated with less DMN deactivation (Figure 5c, $r = 0.38$, $df = 60$, $p = .002$). Further, DMN-GM volume was not correlated with DMN deactivation ($p = .747$). Repeating partial correlations with DMN-GM volume as a covariate did not alter the relationships between FA in DMN-naWM, age, or DMN deactivation (all p -values $< .045$). The first model tested using Preacher and Hayes mediation tested whether FA in DMN-naWM mediates the relationship between age and DMN deactivation magnitude. The

overall total effect model (direct effect and covariates only) was non-significant ($F_{3,60} = 1.77$, $R^2 = 0.08$, $p = 0.16$; total effect of age: $\beta = -0.26$, $p = .043$). In contrast, the mediation model (Figure 6a) was significant ($F_{4,59} = 2.78$, $R^2 = 0.16$, $p = .035$) and revealed that FA in DMN-naWM mediated the effect of age on DMN deactivation magnitude ($ab = -0.32$ [-0.62, -0.07], $c' = 0.06$ [-0.30, 0.43]). The alternative model tested whether age mediates the relationship between FA in DMN-naWM and DMN deactivation magnitude. The overall total effect model was significant ($F_{4,60} = 3.71$, $R^2 = 0.16$, $p = .016$; total effect of FA in DMN-naWM: $\beta = 0.38$, $p = .002$). The mediation model (Figure 6b) was also significant ($F_{4,59} = 2.78$, $R^2 = 0.16$, $p = .035$) and revealed that DMN-naWM had a direct effect on DMN deactivation that was not mediated by age ($c' = 0.44$ [0.06, 0.82], $ab = -0.05$ [-0.32, 0.24]).

All analyses using age as a continuous variable were repeated using age group as a dichotomous variable due to the gap between younger and older adults. Results of these analyses demonstrated the same qualitative pattern (point estimates changed but the same effects were found to be significant/non-significant).

3.6. Associations between DMN deactivation, AD pathology, and WM microstructure in older adults

Results of bivariate relationships are shown in Table 3. It should be noted that lower CSF A β_{42} reflects greater AD pathology, while higher CSF tau reflects greater AD pathology. Thus, higher tau/A β_{42} ratios also reflect greater AD pathology. Significant relationships were observed between AD markers (CSF A β_{42} and tau/A β_{42}), DMN deactivation, and FA in DMN-naWM (Figure 7a-e). DMN-WMH volume was not correlated with AD pathology or DMN deactivation (Figures 7f). Again, DMN-GM volume was not related to DMN deactivation ($p = .567$) and including it as a covariate did not alter the significance of any relationships shown in Table 3 (all p -values < .046).

The first mediation model tested whether the FA in DMN-naWM mediates the relationship between A β_{42} and DMN deactivation. The total effect model was non-significant ($F_{4,30} = 1.32$, $R^2 = 0.15$, $p = .28$; total effect of A β_{42} : $\beta = 0.37$, $p = .04$). The mediation model (Figure 6c) was non-significant overall ($F_{5,29} = 1.91$, $R^2 = 0.25$, $p = 0.12$) but revealed that the relationship between A β_{42} and DMN deactivation magnitude was mediated by FA in DMN-naWM ($ab = 0.15$ [0.02, 0.47], $c' = 0.21$ [-0.16, 0.59]). The alternative model tested whether A β_{42} mediates the relationship between FA in DMN-naWM and DMN deactivation magnitude. The total effect model was not significant ($F_{4,30} = 2.02$, $R^2 = 0.21$, $p = .12$; total effect of FA in DMN-naWM: $\beta = 0.54$, $p = .01$). The mediation model (Figure 6d) was non-significant ($F_{5,29} = 1.91$, $R^2 = 0.25$, $p = 0.12$) and found that A β_{42} did not mediate the relationship between FA in DMN-naWM and DMN deactivation magnitude ($ab = -0.11$ [-0.06, 0.35]). Similar models using the tau/A β_{42} ratio instead of A β_{42} (Figure 6e-f) found that FA in DMN-naWM mediated the relationship between tau/A β_{42} and DMN deactivation magnitude (Total effect model: $F_{4,30} = 1.30$, $R^2 = 0.15$, $p = .29$; total effect tau/A $\beta_{42} = -0.36$, $p = .045$; mediation model: $F_{5,29} = 1.92$, $R^2 = 0.25$, $p = .12$; $ab = -0.15$ [-0.49, -0.003], $c' = -0.21$ [-0.58, 0.15]), while the tau/A β_{42} ratio (mediation model: $F_{5,29} = 1.92$, $R^2 = 0.25$, $p = .12$; $ab = 0.11$ [-0.03, 0.41]) did not mediate the relationship between FA in DMN-naWM

and DMN deactivation magnitude (total effect model: $F_{4,30} = 2.02$, $R^2 = 0.21$, $p = .12$; total effect of FA in DMN-naWM: $\beta = 0.54$, $p = .01$).

4. Discussion

We explored associations between DMN deactivation, age, Alzheimer's pathology, WMH and WM microstructure. Consistent with previous results, lower DMN deactivation was uniquely associated with poorer task performance in cognitively normal (cognitively normal) older adults. Within older adults, lower deactivation was linked with higher AD pathology and lower FA in DMN-WM, but not WMH burden. Further, WM microstructure mediated the effects of age and AD pathology on DMN deactivation. Together these findings provide novel evidence suggesting that disruptive effects of AD pathology on DMN function may operate in part via a “second-hit” on WM microstructure subject to separate age-related effects.

4.1. DMN deactivation Magnitude, Age and Working Memory Performance

A common set of regions showing DMN deactivation was identified across younger and older adults to minimize bias in subsequent age-group comparisons. DMN deactivation was observed in the midline PCC and vMPFC, bilateral LOC/LPC, LTC, and dMPFC, as well as right HC and left PHG during the working memory task, which make up a central portion of DMN regions identified in resting-state studies and deactivation studies across younger and older adults (Grady et al., 2010; Raichle et al., 2001; Spreng et al., 2010). As expected, increasing age was associated with lower DMN deactivation. Further, lower deactivation was associated with slower working memory performance exclusively in older adults. Notably, slower performance on our working memory task reflected poorer performance, rather than a speed-accuracy trade-off, as faster performers were more accurate. These results are consistent with a view that diminished capacity to reduce DMN activity, and its associated internally-generated thought processes, interferes with executive task performance (Brown et al., 2015; Persson et al., 2007; Prakash et al., 2012) and fluid intelligence (Rieck, Rodrigue, Boylan, & Kennedy, 2017).

4.2. DMN deactivation Magnitude and DMN-WM Microstructure

Probabilistic tractography used functionally-defined seed regions to identify WM pathways connecting DMN regions in each individual, which were then combined to form a group template of DMN-WM using a previously established method shown to minimize bias towards one age group (C. A. Brown et al., 2017). This approach identified a common set of WM tracts interconnecting DMN regions (DMN-WM) prominently involving association paths connecting limbic structures (cingulum and fornix), long cortico-cortical association pathways (SLF, ILF, IFOF), and cross-hemispheric pathways (CC-genu and CC-splenium).

Within DMN-WM, there was a relationship between poorer WM microstructure (lower FA) and less DMN deactivation during an executive (working memory) task, a finding consistent with our previous work (C. a. Brown et al., 2015). WM is responsible for electrochemical signaling across large-scale brain networks, and decline in WM microstructural properties through decreased axonal, myelin, and/or synaptic density is thought to contribute to a

noisier signaling environment (Barnes & McNaughton, 1980; Bartzokis, 2011; Daselaar et al., 2013). One possibility would be that a noisier signaling environment may negatively impact the efficiency of network communication, which would be expected to reduce the capacity to dampen DMN activity during a demanding executive task (C. a. Brown et al., 2015). For example, a noisier signaling environment could decrease the capacity for inhibitory signaling, which could lead to greater DMN activity during task performance.

4.3. WMH Burden and DMN deactivation in cognitively normal Older Adults

WMH distribution was heterogeneous across individuals but common in periventricular regions (continuous anterior-posterior band in Figure 4c). Results indicated that WMH volume did not correlate with DMN deactivation. A previous study reported less deactivation within anterior portions of the DMN in older adults with severe compared to mild WMH burden (Mayda et al., 2011). In contrast, our study and a previous study failing to find an association between greater WMH burden and lower DMN deactivation (Hedden et al., 2012a) both utilized a network-wide approach, rather than focusing on a specific frontal ROI. WMHs are known to preferentially affect the frontal lobe, and, therefore, may impact frontal portions of the DMN to a greater extent in cognitively normal older adults (Breteler et al., 1994; de Leeuw, 2001; Mayda et al., 2011). However, if a local effect exists in frontal regions, it fails to result in observable effects at the network level.

This lack of relationship between WMH and DMN deactivation fits with our result that only 3.5% of all DMN-WM was impacted by WMHs. These areas of overlap were primarily confined to posterior periventricular regions and failed to have a significant effect on FA in DMN-naWM (which represented nearly 97% of all DMN-WM). While these findings suggest that early-stage cerebrovascular pathology in cognitively normal older adults does not significantly affect network-level DMN function, future work should explore the effects of WMHs on DMN function in later disease stages as pathology becomes more advanced and widespread (Sachdev, Wen, Chen, & Brodaty, 2007; Wen & Sachdev, 2004).

4.4. DMN-WM Microstructure Mediates Relationships of Age and AD Pathology with DMN deactivation

The most important finding of the present study is that both age and AD pathology were associated with less DMN deactivation through a common pathway of altered WM microstructure (Figure 8). These novel results suggest that negative effects of AD pathology on DMN deactivation may in part operate via a “second-hit” on DMN-WM that is separate from an “age-related hit.” Further, our results indicate that this “age-related hit” does not appear to occur via vascular alterations associated with WMH burden, due to the fairly circumscribed topology of these lesions in cognitively normal older adults. Future research will be required to explore the effects of WMHs on DMN function in older adults with more advanced pathology, such as groups with mild cognitive impairment or clinical dementia (D T Jones et al., 2011; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). In the meantime, however, the current results provide evidence suggesting that declines in WM microstructure appear sufficient to disrupt DMN deactivation in cognitively normal older adults.

Aging could negatively affect WM microstructure via a variety of neurobiological insults. Loss of axonal and myelin content is associated with aging, and the small-diameter, lightly-myelinated axons that make up much of the DMN-WM are particularly vulnerable to aging (Glasser, Goyal, Preuss, Raichle, & Van Essen, 2014; Peters, 2002; Tang et al., 1990). Further, WM microstructure may be negatively impacted via direct damage to oligodendrocytes and axons due to age-related increases in toxins and reactive oxygen species (ROS), axonal retraction secondary to age-related synaptic loss, and/or the increased prevalence of thinner, less-compact myelin sheaths due to increases in myelin breakdown and repair processes in aging (Bartzokis, 2011; Husain & Juurlink, 1995; JUURLINK, 1997; Masliah, Mallory, Hansen, DeTeresa, & Terry, 1993). Similarly, increasing AD pathology may also negatively affect WM microstructure through various mechanisms. A β ₄₂ could independently impact WM microstructure through oligodendrocyte toxicity and/or inhibition of myelin sheet formation (Horiuchi et al., 2012; Lee et al., 2004; Xu et al., 2001). In addition, A β ₄₂ and tau may act via a synergistic pathway in order to disrupt fast-axonal transport, which could interfere with repair processes, axonal integrity, and synaptic viability (Bartzokis, 2011; Vossel et al., 2010, 2015).

It should be noted that statistical mediation (whether based on cross-sectional or longitudinal data) does not indicate causation or temporal ordering of events. Instead, mediation analyses test for the possibility that a mediator variable (e.g., DMN-WM) accounts for a significant proportion of variance in the relationship between a predictor variable (e.g., AD pathology) and an outcome variable (DMN deactivation) (Hayes, 2013). It seems likely that WM degeneration, AD pathology, and functional brain alterations may synergistically influence one-another over time. For example, initial age-related declines in WM microstructural properties may lead to increased synaptic activity, which itself may contribute to greater AD pathology (Bero et al., 2011; Cirrito et al., 2005).

4.5. Considerations for Future Studies: Extension to Resting-State and DMN Sub-Networks

The present study focused on network-level changes in dynamic functioning of the DMN (i.e. network deactivation), as extensive previous work has already reported alterations in DMN resting-state functions, including resting-state connectivity, amplitude of task-independent fluctuations, and power of these task-independent fluctuations (Andrews-Hanna et al., 2007; Ding et al., 2018; Sheline et al., 2010). Changes in functional connectivity at rest may be more sensitive than structural connectivity measures in individuals with MCI (H. Zhang et al., 2016). Future work will be necessary to assess correspondence and diverge of relationships reported here and DMN resting state functions. In addition, there is growing appreciation that large-scale brain networks can be broken down into sub-networks/ components. Of particular interest is work demonstrating that these sub-systems may be affected at different points of the AD pathological process (David T Jones et al., 2016). Future work should examine whether the network-level effects demonstrated here can be replicated in various sub-networks of the DMN.

4.6. Limitations

This study is cross-sectional, and future longitudinal work should determine if similar results are obtained when using change-rate measures of DMN deactivation, WM microstructure,

AD pathology, and cerebrovascular pathology. Further, this study recruited groups of younger and older adults but not middle-aged adults. Future studies should look to recruit middle-aged adults in order to test these findings across the lifespan. It also should be noted that initial bivariate correlations did not correct for multiple comparisons and these results should be viewed as exploratory and intended to determine which variables to enter into mediation analyses. In addition, only cognitively normal older adults were included in the present study, which might underestimate the association between pathology and DMN function because only early changes were studied. Moreover, APOE4 status was not assessed in the present study. Recent evidence suggests that APOE4+ individuals show reduced DMN deactivation in aging (Foster, Kennedy, & Rodrigue, 2017). Future work should assess whether APOE4 status modulates the relationships observed in the present study. Finally, AD and cerebrovascular pathology were treated as a continuous variable in the present study. It is unclear whether the effects of pathology are better assessed through group comparisons or by treating pathology as a continuous variable. Future work should recruit individuals across the disease spectrum and assess pathology through group comparisons and through treatment as a continuous variable across and within groups.

4.7. Conclusions

The present study provides evidence that microstructural declines in WM represent a shared pathway by which increasing age and AD pathology are associated with DMN function. Further, subtle WM microstructural alterations appear sufficient to disrupt DMN function in cognitively normal older adults in the absence of more advanced cerebrovascular pathology. Future work will be needed to assess the biological underpinnings of our disconnection findings, such as potential alterations in axonal and myelin structure.

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Figure 1. Working memory paradigm

A schematic of the working memory paradigm (adopted from Jiang et al., 2016). Task blocks involved presentation of two target images surrounded by a green border followed by 12 single ‘test’ images (match or non-match). Participants were asked to hold ‘in mind’ the target images and decide whether each single test image represented a match, or a non-match, with either of the target images. Blank screens between images represent temporal jittering. The control condition involved viewing 5 sequentially-presented scrambled images. Analyses compared BOLD signal during a portion of the maintenance/decision epoch with BOLD signal during a portion of the control condition (baseline block).

Figure 2. Identification of DMN

A: ICA was used to identify the DMN component in rs-fMRI data. **B-C:** ICA was performed for run 1 (**B**) and run 2 (**C**) of the task-based fMRI separately. The task components were averaged together and masked by the rs-fMRI component to form a final mask of DMN regions (**C**). The clusters in this final mask were used for all functional analyses and as seeds for probabilistic tractography. **A-D:** The DMN regions overlaid on top of the MNI151 T1 2mm³ standard brain. Color scale is shown to the right, with values representing the minimum and maximum Z-values shown.

Figure 3. Relationship between DMN deactivation and working memory performance
 Scatter plots of RT against DMN deactivation show no relationship within younger adults (A) and a significant inverse relationship within older adults (B). Values are standardized residuals after regressing out the effects of age, sex, and education. The r - and p -values are for the linear best fit (thick dashed line). Thin dashed lines indicate the 95% confidence interval for the predicted response.

Figure 4. Results of probabilistic tractography and WMH analyses

The group template formed from combining individual tractography results is shown. **A-B:** Seeds used for tractography (red) and WM pathways connecting these seeds (blue). **C:** DMN-WM pathways include portions of the cingulum, fornix, corpus callosum splenium and genu, superior and inferior longitudinal fasciculi, and other unnamed association tracts. **D:** Voxels classified as WMH in at least 2 participants that overlapped (identified by black arrows and yellow-green shading) or did not overlap (red) with DMN-WM (blue) are presented, indicating that DMN-WM pathways are relatively spared from WMH. Areas shown in blue are portions of DMN-WM where < 2 older adults had WMHs. PCC: posterior cingulate cortex, MPFC: medial prefrontal cortex, dMPFC: dorsal medial prefrontal cortex, LTC: lateral temporal cortex, LOC/LPC: lateral occipital/parietal cortex, HC: hippocampus, CC: corpus callosum, SLF: superior longitudinal fasciculus, ILF: inferior longitudinal fasciculus.

Figure 5. Relationships between Age, FA in DMN-naWM, and DMN deactivation
A-B: DMN deactivation magnitude (**A**) and FA in DMN-naWM (**B**) plotted against age across all participants. **C:** DMN deactivation magnitude plotted against FA in DMN-naWM. **A-C:** All values are standardized residuals after controlling for age, sex, and education. The thick dashed line in the linear best-fit, and thin-dashed lines are the 95% confidence interval for the predicted response. R- and p-values are for the line of best-fit.

Figure 6. Results of age mediation analyses

A-B: Results of mediation analyses show that FA in DMN-naWM mediates the relationship between age and DMN deactivation magnitude across all participants, but age does not mediate the relationship between FA in DMN-naWM and DMN deactivation magnitude. **C-F:** Results of mediation analyses show that the FA in DMN-naWM mediates the relationship between CSF A β_{42} and DMN deactivation (**C**) and between CSF tau/A β_{42} and DMN deactivation (**E**). The alternative models found that neither CSF A β_{42} (**D**) or CSF tau/A β_{42} (**F**) mediated the relationship between FA in DMN-naWM and DMN deactivation. Instead, there was a direct effect of DMN-naWM on DMN deactivation and AD pathology, but AD pathology was not related to DMN deactivation in the presence of DMN-naWM. **A-F:** Values are standardized β -coefficients, with significant paths shown as solid lines with bold β -values, while non-significant paths are shown as dashed lines with β -values in italics. Values above the horizontal arrow are the total effect (c) and values below the arrow are the direct effect (c'). Significant mediation effects (**A,C,E**) are shown by solid lines along the indirect pathway and a dashed line along the direct pathway. Non-significant mediation effects (**B,D,F**) are indicated by a dashed line at some point in the indirect pathway and a solid line along the direct pathway.

Figure 7. Relationships of AD pathology, cerebrovascular pathology, FA in DMN-naWM, and DMN deactivation magnitude in older adults

A-B: DMN deactivation magnitude plotted against CSF A β_{42} (A) and CSF Tau/A β_{42} ratio (B). **C-D:** FA in DMN-naWM plotted against CSF A β_{42} (C) and CSF Tau/A β_{42} ratio (D). **E-F:** DMN deactivation magnitude plotted against FA in DMN-naWM (E) and DMN-WMH volume (F). **A-F:** All values are standardized residuals after controlling for age, sex, and education. Thick dashed lines are the linear best-fit, and thin dashed lines are the 95% confidence interval for the predicted response. R- and p-values are for the line of best-fit.

Figure 8. DMN-WM microstructure as common pathway contributing to diminished DMN deactivation

Schematic of the proposed role of DMN-WM microstructure as a common pathway by which age and AD pathology contribute to diminished DMN deactivation. Decline in WM microstructural properties creates a noisier signaling environment, which leads to less suspension of DMN activity (and default-mode processes) during the working memory task. This results in greater interference from the DMN that impairs performance. Reduced DMN deactivation may only become severe enough to impact working memory once WM microstructure is significantly impacted by both age and AD pathology.

Table 1
Group demographics and mean outcome measures

	Younger adults (n = 29)	Older adults (n = 35)	Group comparison (<i>p</i>)
Age (Years)	24.1 ± 3.9	76.7 ± 7.2	< .001
M:F	12:17	15:20	0.87
Education (Years)	16.6 ± 2.1	16.66 ± 2.4	0.80
Corrected Recognition	0.95 ± 0.055	0.86 ± 0.10	< .001
Reaction Time (ms)	543 ± 62	725 ± 85	< .001
DMN deactivation (% signal change)	-0.15 ± 0.09	-0.09 ± 0.12	.038
FA in all DMN-WM	0.62 ± 0.01	0.57 ± 0.03	< .001
FA in DMN naWM	0.62 ± 0.01	0.58 ± 0.03	< .001
Total WMH Volume (%ICV)	--	0.44 ± 0.24	--
DMN-WMH Volume (% DMN WM)	--	3.63 ± 3.15	--
CSF A β ₄₂ (pg/mL)	--	271 ± 81	--
CSF t-tau/A β ₄₂ ratio	--	0.23 ± 0.14	--
MMSE	--	29.5 (0.80)	--
CDR-Global	--	0 (0)	--
CDR-Sum Boxes	--	0 (0)	--

Mean ± standard deviation is shown in the younger and older adult columns. The p-value for a two-tailed, independent samples *t*-test is shown in the Group comparison column (M:F ratio was compared using χ^2 instead of *t*-test). MMSE: Mini-Mental State Exam, CDR: Clinical Dementia Rating Scale

Table 2

Peak coordinates of DMN deactivation ROIs

	Peak Z	# Voxels	MNI X	MNI Y	MNI Z
Posterior cingulate cortex	33.7	9050	-6	-52	26
Ventral medial prefrontal cortex	24.8	5481	-2	56	-2
L lateral occipital/parietal cortex	24.2	2965	-44	-68	36
R lateral occipital/parietal cortex	17.1	2322	52	-60	34
L dorsal medial prefrontal cortex	20.4	1042	-18	34	44
R dorsal medial prefrontal cortex	14.4	790	22	36	42
R lateral temporal cortex	12.4	696	60	-6	-16
L lateral temporal cortex	14.4	557	-60	-10	-14
L parahippocampal gyrus	7.12	218	-24	-36	-10
R hippocampus	5.16	78	30	-20	-16

Peak coordinates for ROIs are the peak Z-value from the average task-DMN component after masking with the rs-DMN (i.e. DMN deactivation; Figure 2c). The number of voxels is the total number of voxel belonging to the cluster (size of each ROI). All clusters were used in the subsequent time-series and tractography analyses.

Table 3

Bivariate relationships within older adults

	$L_g(A\beta_{42})$	$L_g(Tau/A\beta_{42})$	DMN-WMH Volume	FA in DMN-naWM	DMN deactivation
$L_g(A\beta_{42})$	--	-0.77 (<.001)	<i>-0.18 (.333)</i>	0.43 (.014)	0.36 (.043)
$L_g(Tau/A\beta_{42})$		--	<i>-0.11 (.566)</i>	-0.41 (.020)	-0.36 (.045)
DMN-WMH Volume			--	<i>-0.29 (.105)</i>	<i>-0.09 (.611)</i>
FA in DMN-naWM				--	0.44 (.012)

Values are partial correlation coefficients while controlling for age, sex, and education. P-values are shown in parentheses, with significant relationships in bold and non-significant relationships italicized. All tests had $df = 30$.