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Synergism between fornix microstructure and beta amyloid accelerates memory decline in clinically normal older adults

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ABSTRACT

The fornix is the primary efferent white matter tract of the hippocampus and is implicated in episodic memory. In this study, we investigated whether baseline measures of altered fornix microstructure and elevated beta amyloid (Aβ) burden influence prospective cognitive decline. A secondary goal examined whether Aβ burden is negatively associated with fornix microstructure. 253 clinically normal older adults underwent diffusion-weighted imaging and Pittsburgh Compound B positron emission tomography at baseline. We applied a novel streamline tractography protocol to reconstruct a fornix bundle in native space. Cognition was measured annually in domains of episodic memory, executive function, and processing speed (median follow-up = 4.0 ± 1.4 years). After controlling for covariates, linear mixed-effects models demonstrated an interaction of fornix microstructure with Aβ burden on episodic memory, such that combined lower fornix microstructure and higher Aβ burden was associated with accelerated decline. By contrast, associations with executive function and processing speed were not significant. There was no cross-sectional association between Aβ burden and fornix microstructure. In conclusion, altered fornix microstructure may accelerate memory decline in preclinical Alzheimer's disease.

1. Introduction

The medial temporal lobe is an early site of Alzheimer's disease (AD) pathology (Braak and Braak, 1991), and dysfunction in this region is associated with episodic memory difficulties. The fornix provides the main efferent projections from the hippocampus to the mammillary bodies, anterior thalamic nuclei, and prefrontal cortex and also contains afferent cholinergic tracts from the septal nuclei in the basal forebrain (Aggleton and Brown, 1999; Aggleton et al., 2016). Lesions to the fornix produce severe memory deficits in studies of experimental animal models and human patients (Aggleton, 2008; Aggleton et al., 2010; Gaffan, 1994; Gilboa et al., 2006; Rosenbaum et al., 2014; Tsivilis et al., 2008).

Several diffusion imaging studies have observed microstructural alterations of the fornix in mild cognitive impairment (MCI) and AD dementia (Bozoki et al., 2012; Lee et al., 2012; Mielke et al., 2009; Nowrangi et al., 2013; Perea et al., 2018; Zhuang et al., 2012b). In addition, there are reports of white matter disruptions of the fornix in apolipoprotein E ε4 carriers who are at increased risk of AD (Gold et al., 2010), presymptomatic carriers of familial AD mutations (Ringman et al., 2007), and clinically normal older adults with elevated beta amyloid (Aβ) burden (Brown et al., 2017; Chao et al., 2013; Gold et al., 2014; Molinuevo et al., 2014; Song et al., 2018). However, there are also findings to the contrary. For example, one study failed to find altered fornix microstructure in individuals with

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presymptomatic familial AD (Sánchez-Valle et al., 2016), and another study paradoxically observed a positive association between heightened Aβ deposition and fornix white matter microstructure in clinically normal older adults (Racine et al., 2014).

Diffusion imaging studies have also reported associations between fornix microstructure and cognitive performance in individuals with symptomatic AD (Kantarci et al., 2014; Lee et al., 2012; Mielke et al., 2009, 2012; Zhuang et al., 2012b). Altered fornix microstructure has been shown to predict progression from normal to MCI (Fletcher et al., 2013; Zhuang et al., 2012a) and from MCI to AD dementia (Mielke et al., 2012). The findings in healthy older adults and individuals with preclinical AD have been mixed, with some studies observing an association between fornix microstructure and cognition (Bennett et al., 2015; Kantarci et al., 2014; Ly et al., 2016; Metzler-Baddeley et al., 2011) and others finding no relationship (Lancaster et al., 2016; Racine et al., 2014; Song et al., 2018). Most of the studies reporting significant relationships have focused exclusively on memory (Bennett et al., 2015; Ly et al., 2016; Metzler-Baddeley et al., 2011) or on global cognition (Kantarci et al., 2014). As such, the specificity or generality of these associations across different cognitive domains remains unclear.

Previous studies examining the relationship between fornix microstructure and cognition in clinically normal older adults have generally used cross-sectional designs (Bennett et al., 2015; Kantarci et al., 2014; Ly et al., 2016; Metzler-Baddeley et al., 2011), which only capture between-subject variance. Longitudinal studies have the advantage of capturing change over time within individuals. The few longitudinal studies that have been carried out in clinically normal older adults found no significant relationships between fornix microstructure and cognitive decline; however, these studies had only one follow-up visit (Lancaster et al., 2016; Racine et al., 2014; Song et al., 2018). Longitudinal studies with longer and more frequent cognitive follow-up visits may have greater predictive power for detecting associations of fornix microstructure with cognitive decline.

Most studies examining fornix microstructure have used templates, region of interest masks, or atlas-based approaches (Brown et al., 2017; Gold et al., 2014; Kantarci et al., 2014; Racine et al., 2014; Song et al., 2018). Although such approaches are useful for direct comparison of results across studies, one limitation is that they are more likely to include voxels outside of the tract of interest. This is particularly concerning for the fornix, a small fiber bundle in close proximity to the cerebrospinal fluid. Consequently, even minor misalignments of the template/atlas can result in substantial partial volume contamination and bias the results (Jones and Cercignani, 2010; Oishi and Lyketsos, 2014). An additional drawback of the commonly used Johns Hopkins White Matter Atlas (Mori et al., 2008) is that the template only captures segments of the fornix and does not differentiate the fornix from the stria terminalis. Studies that more accurately capture the fornix anatomy in native space are needed to examine questions relating to fornix microstructure and its association with cognitive decline and Aβ burden.

In the present study, we addressed the question: Are altered fornix microstructure and elevated Aβ burden measured at baseline independently or synergistically associated with prospective longitudinal cognitive decline? A synergistic interaction would suggest that the combination of altered fornix microstructure and elevated Aβ burden is associated with steeper declines in cognition than would be predicted by their additive contributions. A secondary question examined whether baseline Aβ burden is negatively associated with baseline microstructural characteristics of the fornix. We sought to answer these questions by leveraging diffusion and molecular neuroimaging data in a well-characterized sample of clinically normal older adults participating in the Harvard Aging Brain Study. We aimed to overcome some potential limitations by adapting a recently developed streamline tractography protocol to reconstruct a continuous fornix bundle in each participant's native diffusion space (Perea et al., 2018). We then examined diffusion characteristics of this reconstructed fornix bundle in relation to longitudinal cognitive decline in domains of episodic memory, executive function, and processing speed, as well as to baseline measures of Aβ burden. Because any of the observed effects related to this measurement of the fornix may represent a proxy of global white matter microstructure (Bennett and Madden, 2014; Penke et al., 2010; Rabin et al., 2018), we controlled for global white matter in statistical models. This allowed us to examine whether the observed associations attributed to the fornix were tract-specific, occurring over and above those related to global white matter microstructure.

2. Materials and methods

2.1. Participants

Participants were 266 clinically normal older adults from the Harvard Aging Brain Study (Dagley et al., 2017). Participants provided written informed consent before study procedures. Study protocols were approved by the Partners HealthCare Institutional Review Board. At study entry, all participants had a global Clinical Dementia Rating = 0 (Morris, 1993), Mini-Mental State Examination $\geq$ 27 with educational adjustment (Folstein et al., 1975), Geriatric Depression Scale <11 (Yesavage et al., 1983), and performed within education-adjusted norms on Logical Memory delayed recall (Wechsler, 1987). All participants were screened for major neurological, psychiatric, or unstable medical illnesses (see details in Supplemental material).

Participants included in the present analyses were required to have both diffusion-weighted imaging and Pittsburgh Compound B (PiB) positron emission tomography (PET) imaging at baseline. A continuous fornix bundle could not be reconstructed bilaterally in 13 participants and therefore these participants were excluded from all analyses. The excluded participants were significantly older than the main sample ($t = 3.6$; $p = 0.003$); however, they did not differ from the main sample in terms of Aβ burden ($t = 0.89$; $p = 0.39$), sex ($\chi^2 = 0.46$; $p = 0.50$), or a measure of global white matter microstructure ($t = 0.77$; $p = 0.45$). Thus, 253 participants were available for the final analyses. The demographic and clinical characteristics of the sample are summarized in Table 1.

2.2. Brain imaging sequences and processing

2.2.1. Magnetic resonance imaging scanning

Magnetic resonance imaging scanning was completed at baseline at the Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging on a Siemens TIM Trio 3T System with a 12-channel head coil. High-resolution 3D T1-weighted multiecho magnetization prepared rapid acquisition gradient-echo anatomical images were collected with the following parameters: repetition time (TR) = 2200 ms, echo times (TEs) = 1.54, 3.36, 5.18, and 7.01 ms, flip angle =7°, 4× acceleration, 1.2 × 1.2 × 1.2 mm voxels. T2-weighted SPACE images were collected with the following parameters: TR = 2800 ms, TE = 327 ms, 2 × acceleration, and 1.2 × 1.2 × 1.2 mm voxels.

Diffusion-weighted images were acquired at baseline with 30 diffusion encoding gradient directions (TR = 8040 ms, TE = 84 ms, inversion time = 2100 ms, 2 × 2 × 2 mm voxels, 64 transverse slices, b-value, 700 s/mm^2). Processing of diffusion-weighted data was performed in FSL v5.0.9 (The Oxford Centre for Functional MRI of the Brain Software Library). Diffusion images were corrected for eddy current and head motion. Head motion was calculated as the

Table 1
Baseline demographic characteristics

Characteristic	All participants (n = 253)	Aβ+ participants (n = 61)	Aβ− participant (n = 192)	*p* value
Age in years, mean (SD)	73.7 (6.0)	75.3 (5.9)	73.2 (6.0)	0.02
Education in years, mean (SD)	15.8 (3.1)	16.1 (2.8)	15.7 (3.1)	0.40
Females, n (%)	151 (59.7)	38 (62)	113 (59)	0.74
Core fornix FA, mean (SD)	0.35 (0.07)	0.33 (0.07)	0.35 (0.06)	0.02[a]
Global FA, mean (SD)	0.56 (0.02)	0.56 (0.03)	0.56 (0.02)	0.77
Aβ PET FLR DVR, mean (SD)	1.15 (0.19)	1.45 (0.18)	1.06 (0.05)	<0.001

Key: Aβ, beta amyloid; DVR, distribution volume ratio; FLR, frontal, lateral temporal and parietal, and retrosplenial regions; PET, positron emission tomography.
[a] Note that core fornix FA does not differ between Aβ+ and Aβ− groups after adjusting for age and sex.

absolute motion based on the translation parameter for each dimension (x, y, z) extracted from the FSL tool eddy (FMRIB Software Library; Andersson and Sotiropoulos, 2016).

2.2.2. Fornix reconstruction

We adapted a published protocol for fornix reconstruction (Perea et al., 2018). Briefly, the fornix template from that protocol was co-registered to each participant's mean b0 native diffusion image and was used as the seed region for each participant (i.e., where the tractography algorithm initializes). The fornix template used for seeding was slightly oversized so that it was large enough to encompass the fornix bundle in all participants. A region of avoidance (ROA) mask was created by dilating the fornix template and then zeroing out all voxels in the template to make it hollow. The ROA mask permitted adequate streamline reconstruction and was used to filter out streamlines not consistent with the fornix morphology. We placed 10,000 seeds in the co-registered fornix template, set the angular threshold to 40, and restricted the length of streamlines to range between 80 and 250 mm. We performed streamline tractography using the generalized q-imaging model in DSI Studio (Yeh et al., 2010).

This streamline tractography protocol was used to reconstruct a continuous fornix bundle in native space for each participant. We then implemented a number of postprocessing steps to standardize the anatomical definition of the fornix across participants. The T1 and T2 images (and the accompanying thalamic and hippocampal volumetric FreeSurfer segmentations) were coregistered and resampled to each participant's diffusion space using FLIRT in the FSL package (www.fmrib.ox.ac.uk/fsl); note that this results in dilation of structures owing to registration from higher to lower resolution image space. Using these coregistered images as a reference, we required that streamlines extend from the hippocampus to the thalamus (as defined by FreeSurfer); streamlines that did not reach these 2 anatomical landmarks were removed. Next, a modified Hausdorff distance (Dubuisson and Jain, 1994) metric was used to remove outliers (primarily streamlines likely to be part of the adjacent stria terminalis) and to select the most medial population of streamlines (streamlines most likely to be part of the fornix bundle). For statistical analyses and to minimize susceptibility to partial volume effects, diffusion metrics were extracted from the most robust streamline in the left and right fornices in each participant. The most robust streamline was defined as the streamline with the highest mean fractional anisotropy (FA); we refer to this operationalized measurement as the "core fornix." Each step underwent manual quality assessment, including checking accuracy of co-registration and the location of streamlines in each hemisphere. A schematic overview of the processing steps is depicted in Fig. 1. Thirteen participants failed core fornix reconstruction on the right side and 11 participants failed core fornix reconstruction on the left side. We ran a series of analyses to investigate possible reasons as to why the algorithm may have failed in these participants. When we compared the participants with unilateral core fornix reconstructions to those with bilateral core fornix reconstructions, we found that there was no difference in terms of head motion or Aβ burden ($p > 0.5$). However, participants with unilateral core fornix reconstructions were older ($t = -2.56$, $p = 0.02$), had larger ventricles (indicative of greater atrophy; $t = -2.7$, $p = 0.01$), and lower core fornix FA on the reconstructed side ($t = 3.3$, $p = 0.003$). As a result, the fornix was likely more difficult to track in these participants.

As in prior studies from our group (Hedden et al., 2016; Rabin et al., 2018; Rieckmann et al., 2016), we used FA as the primary measure of white matter microstructure. For completeness, we report analyses using other diffusivity metrics (mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AxD]) in Supplementary Tables S2–S3. We had no a priori hypotheses regarding laterality; therefore, mean FA from the most robust left and right streamlines were averaged together to reduce the number of comparisons. In participants where the algorithm failed on one side, we used mean FA from the most robust streamline in the successfully reconstructed hemisphere. In our analyses, we included a dummy covariate coding for whether participants contributed a unilateral or bilateral core fornix reconstruction. We additionally reran all analyses excluding participants with unilateral core fornix reconstructions (n = 24), and the results were nearly identical to those reported below.

2.2.3. Global measure of white matter microstructure

To ensure that any of the observed effects were specific to the core fornix and not to global white matter changes occurring

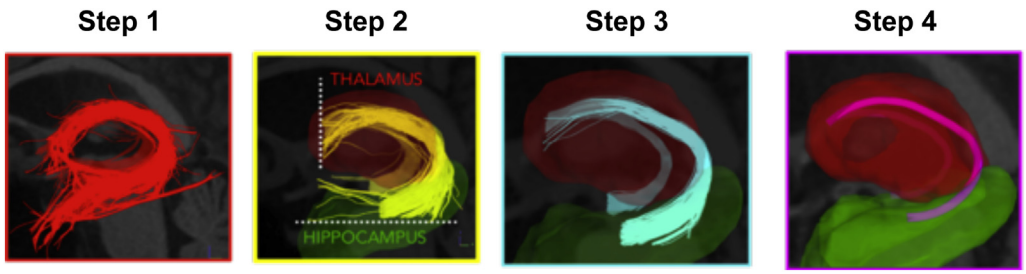

Fig. 1. Method for fornix bundle reconstruction. Step 1: We applied streamline tractography in native diffusion space using the coregistered fornix template as the seed region. The subject-specific region of avoidance (not shown here) filtered out streamlines not consistent with the fornix morphology. We then implemented a number of postprocessing steps to homogenize the anatomical definition of the fornix across participants. Step 2: Streamlines were required to extend from the hippocampus to the thalamus (as defined by FreeSurfer; structures are dilated due to registration to diffusion space resolution); streamlines that did not reach these 2 anatomical landmarks were removed. Step 3: A modified Hausdorff distance metric was used to remove outliers and to select the most medial population of streamlines. Step 4: For statistical analyses and to minimize partial volume effects, diffusion metrics were extracted from the most robust (i.e., highest mean fractional anisotropy) streamlines in the left and right fornices for each participant (the depicted streamline is dilated for visualization purposes).

globally, we controlled for global white matter microstructure in statistical models. This allowed us to conservatively examine the tract-specific association of core fornix microstructure with cognitive decline and Aβ burden over and above global white matter microstructural changes (Bennett and Madden, 2014; Penke et al., 2010; Rabin et al., 2018). We used a previously described method to compute a measure of global white matter microstructure for each participant (Rabin et al., 2018). Briefly, after tract-based spatial statistics procedures (Smith et al., 2006), we created a subject-specific template in Montreal Neurological Institute space (Montreal, Canada). This was then skeletonized and thresholded at 0.3 to exclude predominantly non–white matter voxels. Each participant's FA image was nonlinearly registered to the template (Avants et al., 2011), and the voxel with the highest FA value perpendicular to the skeleton was projected onto the mean skeleton. Nine major white matter tracts (anterior thalamic radiation, corticospinal tract, cingulum bundle, parahippocampal cingulum, forceps major, forceps minor, inferior-frontal-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus) as defined by the Johns Hopkins University probabilistic white matter atlas (Hua et al., 2008) were combined to form a single mask (see Rabin et al., 2018 for details). Mean FA from the skeleton was extracted from this aggregate mask and represented the measure of global FA.

2.2.4. Hippocampal volume

Measures of hippocampal volume were obtained using the FreeSurfer 6.0 default processing stream (Fischl et al., 2002) to use in statistical analyses. Estimates of hippocampal volume were averaged across left and right hemispheres and corrected for estimated total intracranial volume via regression before entry into statistical models.

2.2.5. Pittsburgh compound B positron emission tomography

Participants underwent baseline Aβ imaging with PiB-PET. The acquisition protocol has been described in detail previously (e.g., Hedden et al., 2012). Briefly, PiB-PET images were acquired with an 8.5–15.0 mCi bolus injection and immediately followed by a 60-minute dynamic acquisition. PET data preprocessing was performed using SPM12 (Wellcome Trust Centre for Neuroimaging). A summary distribution volume ratio was calculated for each participant by averaging the median PiB uptake value across voxels in frontal, lateral parietal and temporal, and retrosplenial cortices (the FLR region). Cerebellar gray matter served as the reference region. Aβ burden was used as a continuous variable in all analyses. However, for visualization purposes and for post hoc group analyses, a previously described Gaussian mixture modeling approach was used to classify participants as Aβ positive or Aβ negative (distribution volume ratio cutoff value = 1.2; Mormino et al., 2014b).

2.3. Cognitive measures

Participants were evaluated annually with a battery of cognitive tests. Because the Harvard Aging Brain Study is an ongoing study and enrollment is staggered, not all participants had the same number of cognitive follow-up visits. At the time of the present analyses, cognitive data were available for 253 participants at baseline, 250 at the first follow-up, 238 at the second follow-up, 230 at the third follow-up, 209 at the fourth follow-up, 124 at the fifth follow-up, and 84 at the sixth follow-up. The median neuropsychological follow-up period was 4.0 years (SD = 1.4). We measured cognitive change with a battery of neuropsychological and behavioral tasks selected primarily to represent domains of episodic memory, executive function, and processing speed. Episodic memory was assessed using the delayed recall score from the Wechsler Memory Scale-Revised Logical Memory subtest (Wechsler, 1987), the free recall score from the Free and Cued Selective Reminding Test (Grober et al., 2000), and the delayed recall score from Six-Trial Selective Reminding test (Masur et al., 1990). Executive function was assessed by Letter-Number Sequencing from the Wechsler Adult Intelligence Scale-III (the number of trials correctly completed; Wechsler, 1997), phonemic fluency (the sum of the words produced in response to the letters F, A, S, each over 60 seconds; Spreen and Benton, 1977), and the Trail Making Test (time to complete Form B minus Form A; Reitan, 1958). Processing speed was assessed by the Wechsler Adult Intelligence Scale-Revised Digit-Symbol Coding test (number of items completed; Wechsler, 1981) and the Trail Making Test (time to complete Form A; Reitan, 1958). As previously described, confirmatory factor analyses were conducted to construct longitudinal factor scores for cognitive domains of episodic memory, executive function, and processing speed (Orlovsky et al., 2017; Rabin et al., 2018).

2.4. Statistical analyses

Statistical analyses were performed using R, version 3.2.4. We used linear mixed-effects models to examine the first question of interest regarding whether core fornix FA and Aβ burden independently or synergistically predict prospective cognitive decline in domains of episodic memory, executive function, and processing speed. A random intercept and slope were included for each participant. Time was operationalized as years from baseline for each participant. All models included the following covariates: age at baseline, sex, education, global FA, head motion, and dummy-coded unilateral or bilateral core fornix reconstruction, and their interactions with time. To facilitate comparisons across predictor variables, we z-transformed continuous predictor variables before model entry. To correct for multiple comparisons, we applied a Bonferroni correction to account for testing of 3 different cognitive domains (i.e., episodic memory, executive function, and processing speed; $p < 0.05/3 = 0.017$). This same threshold was used to determine the significance of covariates. All tests were 2-tailed.

First, we used linear mixed-effects models to investigate the associations of core fornix FA and continuous levels of Aβ burden with cognitive decline (model 1); these models were repeated for each of the 3 cognitive domains: episodic memory, executive function, and processing speed. These analyses allowed us to test the hypothesis that fornix FA and continuous levels of Aβ burden are each associated with cognitive decline. Next, we investigated whether core fornix FA and continuous levels of Aβ burden are synergistically associated with cognitive decline. Synergistic effects were tested in models that included a three-way interaction term for core fornix FA, Aβ burden, and time (model 2); this allowed us to assess whether the impact of core fornix FA on cognitive decline is moderated by Aβ burden. These models were repeated for each of the 3 cognitive domains.

To ensure that any significant effects obtained were specific to the core fornix and not to white matter changes occurring globally (Bennett and Madden, 2014; Penke et al., 2010; Rabin et al., 2018), we controlled for the interaction of global FA with time in all models that included core fornix FA. We opted to report the results adjusting for the interaction of global FA with time rather than the three-way interaction of global FA, Aβ, and time, given that we previously found that this three-way interaction was not associated with cognitive decline in any of the 3 cognitive domains we examined (Rabin et al., 2018). It should be noted that the results did not depend on having the interaction of global FA with time in statistical models, as the results remained similar when this interaction term was removed.

Model 1: Cognition ~ Core fornix FA × time + Aβ × time + covariates × time.

Model 2: Cognition ~ Core fornix FA × Aβ × time + covariates × time.

Note that all models include lower order terms.

Cognition = Factor scores of episodic memory, executive function, or processing speed; separate models were run for each of the 3 cognitive domains.

Covariates = age, sex, years of education, global FA, head motion, and dummy-coded unilateral or bilateral core fornix reconstruction.

Algebraic descriptions of the models are included in Supplemental material.

With regard to the second question of interest, linear regression was used to examine the cross-sectional baseline relationship between core fornix FA and continuous levels of Aβ burden. Partial correlations were used to examine cross-sectional associations of core fornix FA with age, hippocampal volume, and global FA. Where appropriate, we adjusted for age, sex, head motion, global FA, and unilateral or bilateral core fornix reconstruction. Partial correlations were also used to examine cross-sectional associations of continuous levels of Aβ burden with age, hippocampal volume, and global FA, adjusting for age and sex where appropriate.

3. Results

3.1. Associations of core fornix FA and Aβ burden on longitudinal cognitive decline

We first investigated the associations of cognitive decline with core fornix FA and continuous levels of Aβ burden in the same model (model 1). Lower core fornix FA was associated with greater decline only in episodic memory ($\beta = 0.027$; SE = 0.010; t = 2.60; $p = 0.009$); associations with executive function ($\beta = 0.007$; SE = 0.007; t = 1.07; $p = 0.29$) and processing speed ($\beta = -0.001$; SE = 0.008; t = −0.16; $p = 0.87$) did not reach statistical significance. Consistent with our previous findings (Rabin et al., 2018), continuous levels of Aβ were associated with greater decline in episodic memory ($\beta = -0.066$; SE = 0.009; t = −7.33; $p < 0.001$), executive function ($\beta = -0.023$; SE = 0.006; t = −4.11; $p < 0.001$), and processing speed ($\beta = -0.023$; SE = 0.007; t = −3.35; $p < 0.001$). With respect to covariates, in these models, lower education was significantly associated with lower performance in all 3 cognitive domains; being male was associated with lower performance in episodic memory; global FA was associated with worse performance in executive function; and older age and unilateral core fornix reconstruction were each associated with greater declines in processing speed over time (all p values <0.017).

Next, we investigated whether core fornix FA and continuous levels of Aβ burden were synergistically associated with prospective cognitive decline (model 2). Analyses revealed a synergism between core fornix FA and Aβ burden on cognitive decline selectively in the domain of episodic memory ($\beta = 0.028$; SE = 0.009; t = 3.27; $p = 0.001$), such that the combination of lower core fornix FA and higher Aβ burden was associated with greater decline over time than would be predicted by their additive contributions (see Fig. 2 and Supplementary Table S1 for estimates from the full model). This interaction remained significant when applying either a log or square root transformation to the Aβ measure. By contrast, the interaction of core fornix FA with Aβ burden was not significantly associated with decline in executive function ($\beta = 0.009$; SE = 0.005; t = 1.63; $p = 0.10$) or processing speed ($\beta = -0.001$; SE = 0.007; t = −0.22; $p = 0.83$). With respect to covariates, we found the same pattern of results as reported above for model 1.

To further explore the synergism of core fornix FA and continuous levels of Aβ burden on episodic memory decline, post hoc analyses examined whether lower core fornix FA was associated with episodic memory decline in both Aβ-positive (n = 61) and Aβ-negative groups (n = 192; dichotomized based on a previously defined cutoff from our group Mormino et al., 2014b). Specifically, in each group, we examined the interaction of core fornix FA with time on episodic memory decline, adjusting for covariates, including the interaction of Aβ burden with time. Results suggested that lower core fornix FA was significantly associated with episodic memory decline in the Aβ-positive group ($\beta = 0.079$; SE = 0.030; t = 2.67; $p = 0.008$), but not the Aβ-negative group ($\beta = 0.014$; SE = 0.010; t = 1.47; $p = 0.14$). These findings further suggest that Aβ burden moderates the association of core fornix FA on episodic memory decline.

3.2. Associations of core fornix FA and Aβ burden with longitudinal memory decline over and above hippocampal volume

Given the close relationship between fornix microstructure and hippocampal volume (Fletcher et al., 2013; Mielke et al., 2012) along with previous findings demonstrating a synergism between hippocampal volume and Aβ burden on cognitive decline (Bilgel et al., 2018; Mormino et al., 2014a; Wirth et al., 2013), secondary analyses explored whether the synergism of core fornix FA and Aβ burden on episodic memory decline remained significant after adjusting for the interaction of hippocampal volume, Aβ burden, and time. As in previous studies, we found a significant three-way interaction between hippocampal volume, Aβ burden, and time on episodic memory decline ($\beta = 0.023$; SE = 0.009; t = 2.63; $p = 0.009$), after adjusting for covariates. Notably, when the three-way interaction of core fornix FA, Aβ burden, and time, and related covariates were added to this model, the three-way interaction of core fornix FA, Aβ burden, and time was significant ($\beta = 0.02$; SE = 0.01; t = 2.16; $p = 0.03$), whereas the three-way interaction of hippocampal volume, Aβ burden, and time no longer significantly predicted episodic memory decline ($\beta = 0.009$; SE = 0.011; t = 0.84; $p = 0.40$).

3.3. Associations of core fornix MD/RD/AxD and Aβ burden with longitudinal cognitive decline

In post hoc, exploratory analyses, we repeated the models examining the three-way interaction of core fornix FA, Aβ burden,

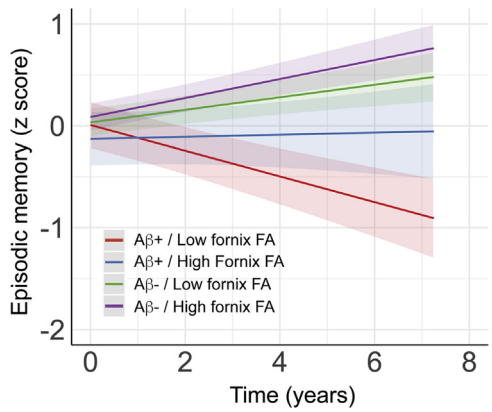

Fig. 2. Episodic memory decline as a function of the synergism between fornix fractional anisotropy and beta amyloid burden. For visualization purposes, estimates are from a linear mixed-effects model predicting change in episodic memory for groups based on a binary assessment of beta amyloid burden (Aβ+ or Aβ−) based on a previously published cutoff of a distribution volume ratio of 1.2 and high or low fornix fractional anisotropy (FA) (based on a median split at a score of 0.35). The Aβ+/low fornix FA group declined at the fastest rate over time. Shaded regions show 95% CIs.

and time on cognitive decline, and replaced FA with MD, RD, and AxD metrics (Supplementary Table S2). Contrary to expectation, the three-way interactions of core fornix MD/RD/AxD, Aβ burden, and time did not significantly predict decline in episodic memory nor did it predict decline in executive function or processing speed, after correcting for multiple comparisons. It is possible that these null findings were observed because we isolated the most robust FA streamlines and then extracted MD/RD/AxD diffusivity metrics from these streamlines. To address this possibility, we subsequently isolated the most robust MD streamline in each hemisphere and then extracted diffusion metrics (i.e., FA/MD/RD/AxD) from these streamlines (Supplemental Table S3). In this set of analyses, we again found a significant three-way interaction of core fornix FA, Aβ burden, and time on decline in episodic memory but not executive function or processing speed. When core fornix FA was replaced with the other diffusivity metrics (i.e., MD/RD/AxD), the results did not reach statistical significance for any of the cognitive domains. Of note, the diffusivity metrics (i.e., MD, RD, AxD) were highly correlated with one another and somewhat less so with FA (Supplemental Table S4).

3.4. Cross-sectional associations of core fornix FA with Aβ burden and other imaging biomarkers

In contrast to some prior studies (Brown et al., 2017; Chao et al., 2013; Gold et al., 2014; Molinuevo et al., 2014), we did not find a significant negative association between cross-sectional measures of core fornix FA and continuous levels of Aβ burden ($\beta = -0.085$; SE = 0.055; t = −1.55; $p = 0.12$). There were also no significant associations between core fornix and Aβ burden when FA was replaced with MD/RD/AxD. Next, we examined the correlations of core fornix FA with Aβ burden within each of the 4 groups shown in Fig. 2 (i.e., Aβ−/high fornix; Aβ−/low fornix; Aβ+/high fornix; and Aβ+/low fornix groups) and found that none of these correlations reached statistical significance ($p > 0.13$). As expected, core fornix FA was negatively associated with age (r = −0.37; $p < 0.001$), positively associated with global FA (r = 0.16, $p = 0.01$), and positively associated with hippocampal volume (r = 0.31; $p < 0.001$), after adjusting for covariates. Similar results were found when core fornix FA was replaced with MD/RD/AxD. With respect to Aβ burden, Aβ burden was not associated with age (r = 0.10; $p = 0.11$) or global FA (r = 0.03; $p = 0.65$), and there was a negative relationship with hippocampal volume (r = −0.17; $p = 0.006$), after adjusting for covariates.

4. Discussion

The primary goal of the present study was to investigate whether lower fornix FA and elevated Aβ burden are independently or synergistically associated with prospective cognitive decline in a cohort of clinically normal older adults. To accomplish this, we adapted a recently developed streamline tractography protocol to reconstruct a continuous core fornix bundle in each participant's native diffusion space (Perea et al., 2018). Results indicated a synergism between core fornix FA and Aβ burden in preferentially accelerating longitudinal decline in episodic memory, such that the combination of lower core fornix FA and elevated Aβ burden was associated with the fastest decline over time. This relationship held up after adjusting for hippocampal volume, age, sex, education, head motion, and global white matter FA. In addition, this effect appeared to be specific to the fornix, as interactions between other white matter tracts and Aβ burden were not associated with cognitive decline (Rabin et al., 2018). With regard to our second objective, elevated Aβ burden was not associated with lower core fornix FA at baseline.

The present findings suggest that alterations to white matter pathways directly connected to the hippocampus may interact with elevated Aβ burden to hasten cognitive decline in clinically normal older individuals. Notably, the synergism between core fornix FA and Aβ burden was specific to decline in episodic memory, as we did not observe significant relationships with changes in executive function or processing speed. This finding is consistent with previous reports suggesting that the fornix plays a specialized role in memory (Aggleton, 2008; Aggleton et al., 2000; Aggleton and Brown, 1999; D'Esposito et al., 1995; Gaffan and Gaffan, 1991; Rosenbaum et al., 2014). The fornix forms the predominant outflow pathway of the hippocampus (Aggleton and Brown, 1999; Aggleton et al., 2016), and disruptions to the fornix may "disconnect" the hippocampus from other regions within the network that support memory (Bartzokis et al., 2004; O'Sullivan et al., 2001).

The finding that combined lower core fornix FA and elevated Aβ burden was associated with accelerated decline in episodic memory is consistent with previous reports demonstrating cross-sectional associations of disrupted fornix microstructure with worse memory performance in healthy adults (Bennett et al., 2015; Rudebeck et al., 2009) as well as in older adults with MCI and AD dementia (Kantarci et al., 2014; Mielke et al., 2009, 2012; Zhuang et al., 2012b). Our results are also in line with studies suggesting that fornix degradation predicts progression from normal to MCI (Fletcher et al., 2013; Zhuang et al., 2012a) and from MCI to AD dementia (Mielke et al., 2012). However, several recent longitudinal studies with only one follow-up visit did not observe significant relationships between fornix microstructure and episodic memory decline in clinically normal individuals, possibly because of the limited longitudinal follow-up (Lancaster et al., 2016; Racine et al., 2014; Song et al., 2018). Future longitudinal studies are needed to confirm the present findings and to further investigate whether microstructural alterations of the fornix are in fact preferentially associated with decline in episodic memory.

The present findings should be interpreted within the context of prior findings in this same cohort. In a recent study, we investigated whether FA of 9 major white matter tracts interacts with Aβ burden to predict decline in episodic memory, executive function, and processing speed (Rabin et al., 2018). In that study, we focused on the following tracts: anterior thalamic radiation, corticospinal tract, cingulum bundle, parahippocampal cingulum, forceps major, forceps minor, inferior-frontal-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus. Interestingly, none of those tracts interacted with Aβ burden to predict cognitive decline; instead, we found that global white matter diffusion metrics had an association with cognitive decline that was independent from that of Aβ burden. Those results taken together with the present findings suggest a specialized role for the fornix and its interaction with Aβ burden to preferentially accelerate decline in episodic memory.

Post hoc exploratory analyses demonstrated that the synergism between core fornix microstructure and Aβ burden on memory decline was specific to FA, as we did not observe significant relationships when FA was replaced with RD, MD, and AxD. It is not entirely clear why this was the case; however, several other studies have also shown that fornix FA may be selectively associated with memory performance. For instance, Mielke et al., 2012 observed that fornix FA, but not RD or MD, significantly predicted longitudinal memory decline in MCI participants. Similarly, Metzler-Baddeley et al., 2011 reported a cross-sectional association of memory performance with fornix FA, but not MD, in a sample of older adults. In addition, there are reports from other studies showing significant relationships of fornix FA with memory performance (Kantarci et al., 2014; Ly et al., 2016; Zhuang et al., 2012a); however, those studies did not include other diffusivity metrics.

Together, these findings suggest that FA measures of the core fornix may preferentially capture associations with memory performance, although additional research is required to better understand this finding.

Consistent with other studies, we observed a significant relationship between lower core fornix FA and smaller hippocampal volume (Fletcher et al., 2013; Mielke et al., 2012), such that hippocampal volume was associated with ~10% of the variance in core fornix FA. This finding suggests that fornix FA and hippocampal volume are related but do not reflect redundant sources of information. Most notably, the three-way interaction of core fornix FA, Aβ burden, and time on episodic memory decline remained significant after controlling for the three-way interaction of hippocampal volume, Aβ burden, and time. An open question is whether hippocampal atrophy precedes fornix degradation. Because the white matter fibers that form the fornix arise from the hippocampus, it may be that hippocampal volume loss has negative downstream effects on the fornix (i.e., Wallerian degeneration). Another possibility is that degradation of the hippocampus and fornix occur in parallel and result from a common upstream pathological process (Amlien and Fjell, 2014). Longitudinal studies with serial imaging will be critical to provide insight into the temporal relationships between microstructural alterations of the fornix, hippocampal atrophy, and decline in episodic memory.

The association between Aβ burden and fornix microstructure has been inconsistently observed in clinically normal older adults, with some cross-sectional studies suggesting that heightened Aβ burden disrupts microstructural characteristics of the fornix (Brown et al., 2017; Chao et al., 2013; Gold et al., 2014; Molinuevo et al., 2014) and others showing no association (Kantarci et al., 2014; Sánchez-Valle et al., 2016). Our results are consistent with the latter. The lack of association between Aβ burden and core fornix microstructure in our study raises the possibility that our measure of fornix degeneration was not sensitive enough to detect Aβ-related changes. However, unlike previous studies (Brown et al., 2017; Chao et al., 2013; Gold et al., 2014), we did not directly extract diffusion metrics from a template, region of interest mask, or atlas. Our robust streamline approach may be preferable because it is carried out in native space and minimizes the likelihood of capturing voxels outside of the fornix. This null finding along with previous results from the same cohort (Rabin et al., 2018) suggest that elevated Aβ burden is not associated with alterations in cross-sectional measures of white matter microstructure in clinically normal adults. It may be that an association of Aβ burden with fornix microstructure is more likely to be observed when there is co-occurring gray matter neurodegeneration (Kantarci et al., 2014), in later stages of the disease, or when following individuals over time (Rieckmann et al., 2016; Song et al., 2018). Large cohorts of clinically normal adults with known Aβ status and improved markers of fornix microstructure at multiple imaging time points will be essential to clarify this association.

Strengths of the present study include the large, well-characterized sample of clinically normal older adults, the prospective longitudinal study design with up to 7 years of annual cognitive data (median follow-up = 4.0 years), and the application of a novel tractography method to examine fornix microstructure in native diffusion space. There were also some limitations. First, while we aimed to mitigate partial volume effects by reconstructing fornix bundles in native space and extracting diffusion metrics from the most robust streamlines (which are least likely to be contaminated by cerebrospinal fluid), partial volume effects may still occur given the resolution of our diffusion acquisition. Partial volume effects in the fornix are likely present in nearly all human diffusion imaging studies where the diffusion resolution is $\geq$1 mm^3, and analyses are not restricted to the fornix body. Second, although the diffusion metrics were extracted from native space, we did use co-registration tools to warp the fornix template into every participant's native diffusion space. This is unlikely to introduce error because the tractography algorithm was initiated in native space and only the most robust streamline was extracted from each hemisphere. Third, we used automatically parcellated hippocampal and thalamic regions and the accompanying volume estimates from the FreeSurfer software, which are necessarily limited by the accuracy of this parcellation scheme. Fourth, there is some flexibility in terms of the decisions that were made to define the fornix bundle (i.e., selecting the hippocampus and thalamus as landmarks, the size of the ROA mask, and so forth). Importantly, all of these decisions were made a priori; however, we cannot rule out that they had some influence on the results. Fifth, our current diffusion parameters limited our ability to examine smaller tracts, such as the perforant pathway, which may also interact with Aβ burden and show specific relationships with episodic memory decline in older adults (Yassa et al., 2010). Similarly, we were unable to differentiate between medial and lateral portions of the fornix, which have been shown to innervate anterior and posterior portions of the hippocampus, respectively (Christiansen et al., 2017). Future work should investigate whether the long-axis specialization of the hippocampus (i.e., different functions served by the anterior vs. posterior portions) (Poppenk et al., 2013) extends to medial and lateral fibers of the fornix. Sixth, we did not include measures of tau pathology in the present study, as tau was collected several years after study entry. However, work from our group suggests a relationship between disruption of the hippocampal cingulum bundle, another tract directly connected to the hippocampus, and tau accumulation in the neocortex in preclinical AD (Jacobs et al., 2018). Future work will need to explore this issue further. Last, participants in the Harvard Aging Brain Study are generally highly educated and predominately Caucasian, which may limit the generalizability of our findings.

5. Conclusion

To conclude, altered core fornix FA in the setting of co-occurring Aβ pathology was associated with longitudinal decline in episodic memory, despite no significant cross-sectional relationship between elevated Aβ pathology and fornix microstructure. The observed synergy suggests that disruption of a major white matter pathway directly connected to the hippocampus is sufficient to disrupt future memory performance in clinically normal individuals with elevated Aβ burden. These findings are consistent with disconnection processes as a pathological mechanism for accelerating memory decline early in the course of AD, and suggest that assessment of fornix microstructure may be an important tool for predicting later memory difficulties in individuals with elevated Aβ burden.

Disclosure

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Appendix A. Supplementary data

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References

Aggleton, J.P., 2008. Understanding anterograde amnesia: disconnections and hidden lesions. Q. J. Exp. Psychol. 61, 1441–1471.
Aggleton, J.P., Brown, M.W., 1999. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav. Brain Sci. 22, 425–444.
Aggleton, J.P., McMackin, D., Carpenter, K., Hornak, J., Kapur, N., Halpin, S., Wiles, C.M., Kamel, H., Brennan, P., Carton, S., Gaffan, D., 2000. Differential cognitive effects of colloid cysts in the third ventricle that spare or compromise the fornix. Brain 123, 800–815.
Aggleton, J.P., O'Mara, S.M., Vann, S.D., Wright, N.F., Tsanov, M., Erichsen, J.T., 2010. Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. Eur. J. Neurosci. 31, 2292–2307.
Aggleton, J.P., Pralus, A., Nelson, A.J.D., Hornberger, M., 2016. Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit. Brain 139, 1877–1890.
Amlien, I.K., Fjell, A.M., 2014. Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. Neuroscience 276, 206–215.
Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 125, 1063–1078.
Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 54, 2033–2044.
Bartzokis, G., Sultzer, D., Lu, P.H., Nuechterlein, K.H., Mintz, J., Cummings, J.L., 2004. Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "disconnection" in aging and Alzheimer's disease. Neurobiol. Aging 25, 843–851.
Bennett, I.J., Huffman, D.J., Stark, C.E., 2015. Limbic tract integrity contributes to pattern separation performance across the lifespan. Cereb. Cortex 25, 2988–2999.
Bennett, I.J., Madden, D.J., 2014. Disconnected aging: cerebral white matter integrity and age-related differences in cognition. Neuroscience 276, 187–205.
Bilgel, M., An, Y., Helphrey, J., Elkins, W., Gomez, G., Wong, D.F., Davatzikos, C., Ferrucci, L., Resnick, S.M., 2018. Effects of amyloid pathology and neurodegeneration on cognitive change in cognitively normal adults. Brain 141, 2475–2485.
Bozoki, A.C., Korolev, I.O., Davis, N.C., Hoisington, L.A., Berger, K.L., 2012. Disruption of limbic white matter pathways in mild cognitive impairment and Alzheimer's disease: a DTI/FDG-PET Study. Hum. Brain Mapp. 33, 1792–1802.
Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.
Brown, C.A., Johnson, N.F., Anderson-mooney, A.J., Jicha, G.A., Shaw, L.M., Trojanowski, J.Q., Van Eldik, L.J., Schmitt, F.A., Smith, C.D., Gold, B.T., 2017. Development, validation and application of a new fornix template for studies of aging and preclinical Alzheimer's disease. Neuroimage Clin. 13, 106–115.
Chao, L.L., DeCarli, C., Kriger, S., Truran, D., Zhang, Y., Laxamana, J., Villeneuve, S., Jagust, W.J., Sanossian, N., Mack, W.J., Chui, H.C., Weiner, M.W., 2013. Associations between white matter hyperintensities and β amyloid on integrity of projection, association, and limbic fiber tracts measured with diffusion tensor MRI. PLoS One 8, e65175.
Christiansen, K., Metzler-Baddeley, C., Parker, G.D., Muhlert, N., Jones, D.K., Aggleton, J.P., Vann, S.D., 2017. Topographic separation of fornical fibers associated with the anterior and posterior hippocampus in the human brain: an MRI-diffusion study. Brain Behav. 7, 1–8.
D'Esposito, M., Verfaellie, M., Alexander, M.P., Katz, D.I., 1995. Amnesia following traumatic bilateral fornix transection. Neurology 45, 1546–1550.
Dagley, A., LaPoint, M., Huijbers, W., Hedden, T., McLaren, D.G., Chatwal, J.P., Papp, K.V., Amariglio, R.E., Blacker, D., Rentz, D.M., Johnson, K.A., Sperling, R.A., Schultz, A.P., 2017. Harvard aging brain study: dataset and accessibility. Neuroimage 144, 255–258.
Dubuisson, M.-P., Jain, A.K., 1994. A modified Hausdorff distance for object matching. In: Proceedinds of 12th International Conference on Pattern Recognition, 1, pp. 566–568.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.
Fletcher, E., Raman, M., Huebner, P., Liu, A., Mungas, D., Carmichael, O., DeCarli, C., 2013. Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals. JAMA Neurol. 70, 1389–1395.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Gaffan, D., 1994. Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. J. Cogn. Neurosci. 6, 305–320.
Gaffan, D., Gaffan, E.A., 1991. Amnesia in man following transsection of the fornix. Brain 114, 2611–2618.
Gilboa, A., Winocur, G., Rosenbaum, R.S., Poreh, A., Gao, F., Black, S.E., Westmacott, R., Moscovitch, M., 2006. Hippocampal contributions to recollection in retrograde and anterograde amnesia. Hippocampus 16, 966–980.
Gold, B.T., Powell, D.K., Andersen, A.H., Smith, C.D., 2010. Alterations in multiple measures of white matter integrity in normal women at high risk for Alzheimer's disease. Neuroimage 52, 1487–1494.
Gold, B.T., Zhu, Z., Brown, C.A., Andersen, A.H., LaDu, M.J., Tai, L., Jicha, G.A., Kryscio, R.J., Estus, S., Nelson, P.T., Scheff, S.W., Abner, E., Schmitt, F.A., Van Eldik, L.J., Smith, C.D., 2014. White matter integrity is associated with cerebrospinal fluid markers of Alzheimer's disease in normal adults. Neurobiol. Aging 35, 2263–2271.
Grober, E., Lipton, R.B., Hall, C., Crystal, H., 2000. Memory impairment on free and cued selective reminding predicts dementia. Neurology 54, 827–832.
Hedden, T., Mormino, E.C., Amariglio, R.E., Younger, A.P., Schultz, A.P., Becker, J.A., Buckner, R.L., Johnson, K.A., Sperling, R.A., Rentz, D.M., 2012. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. J. Neurosci. 32, 16233–16242.
Hedden, T., Schultz, A.P., Rieckmann, A., Mormino, E.C., Johnson, K.A., Sperling, R.A., Buckner, R.L., 2016. Multiple brain markers are linked to age-related variation in cognition. Cereb. Cortex 26, 1388–1400.
Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D.S., Calabresi, P.A., Pekar, J.J., van Zijl, P.C., Mori, S., 2008. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 39, 336–347.
Jacobs, H.I.L., Hedden, T., Schultz, A.P., Sepulcre, J., Perea, R.D., Amariglio, R.E., Papp, K.V., Rentz, D.M., Sperling, R.A., Johnson, K.A., 2018. Structural tract alterations predict downstream tau accumulation in amyloid-positive older individuals. Nat. Neurosci. 21, 424–431.
Jones, D.K., Cercignani, M., 2010. Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed. 23, 803–820.
Kantarci, K., Schwarz, C.G., Reid, R.I., Przybelski, S.A., Lesnick, T.G., Zuk, S.M., Senjem, M.L., Gunter, J.L., Lowe, V., Machulda, M.M., Knopman, D.S., Petersen, R.C., Jack, C.R., 2014. White matter integrity determined with diffusion tensor imaging in older adults without dementia: influence of amyloid load and neurodegeneration. JAMA Neurol. 71, 1547–1554.
Lancaster, M.A., Seidenberg, M., Smith, J.C., Nielson, K.A., Woodard, J.L., Durgerian, S., Rao, S.M., 2016. Diffusion tensor imaging predictors of episodic memory decline in healthy elders at genetic risk for Alzheimer's disease. J. Int. Neuropsychol. Soc. 22, 1005–1015.
Lee, D.Y., Fletcher, E., Carmichael, O.T., Singh, B., Mungas, D., Reed, B., Martinez, O., Buonocore, M.H., Persianinova, M., DeCarli, C., 2012. Sub-regional hippocampal injury is associated with fornix degeneration in Alzheimer's disease. Front. Aging Neurosci. 4, 1–10.
Ly, M., Adluru, N., Destiche, D.J., Lu, S.Y., Oh, J.M., Hoscheidt, S.M., Alexander, A.L., Okonkwo, O.C., Rowley, H.A., Sager, M.A., Johnson, S.C., Bendlin, B.B., 2016. Fornix microstructure and memory performance is associated with altered

neural connectivity during episodic recognition. J. Int. Neuropsychol. Soc. 22, 191–204.
Masur, D.M., Fuld, P.A., Blau, A.D., Crystal, H., Aronson, M.K., 1990. Predicting development of dementia in the elderly with the Selective Reminding Test. J. Clin. Exp. Neuropsychol 12, 529–538.
Metzler-Baddeley, C., Jones, D.K., Belaroussi, B., Aggleton, J.P., O'Sullivan, M.J., 2011. Frontotemporal connections in episodic memory and aging: a diffusion MRI tractography study. J. Neurosci. 31, 13236–13245.
Mielke, M., Kozauer, N.A., Chan, K.C., George, M., Toroney, J., Zerrate, M., Bandeen-Roche, K., Wang, M.C., VanZijl, P., Pekar, J.J., Mori, S., Lyketsos, C.G., Albert, M., 2009. Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neuroimage 46, 47–55.
Mielke, M., Okonkwo, O.C., Oishi, K., Mori, S., Tighe, S., Miller, M.I., Ceritoglu, C., Brown, T., Albert, M., Lyketsos, C.G., 2012. Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease. Alzheimers Dement. 8, 105–113.
Molinuevo, J.L., Ripolles, P., Simó, M., Lladó, A., Olives, J., Balasa, M., Antonell, A., Rodriguez-Fornells, A., Rami, L., 2014. White matter changes in preclinical Alzheimer's disease: a magnetic resonance imaging-diffusion tensor imaging study on cognitively normal older people with positive amyloid β protein 42 levels. Neurobiol. Aging 35, 2671–2680.
Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A.V., Mahmood, A., Woods, R., Toga, A.W., Pike, G.B., Neto, P.R., Evans, A., Zhang, J., Huang, H., Miller, M.I., van Zijl, P., Mazziotta, J., 2008. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage 40, 570–582.
Mormino, E.C., Betensky, R.A., Hedden, T., Schultz, A.P., Amariglio, R.E., Rentz, D.M., Johnson, K.A., Sperling, R.A., 2014a. Synergistic effect of β-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. JAMA Neurol. 71, 1379–1385.
Mormino, E.C., Betensky, R.A., Hedden, T., Schultz, A.P., Ward, A., Huijbers, W., Rentz, D.M., Johnson, K.A., Sperling, R.A., 2014b. Amyloid and APOE ε4 interact to influence short-term decline in preclinical Alzheimer disease. Neurology 82, 1760–1767.
Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412–2414.
Nowrangi, M.A., Lyketsos, C.G., Leoutsakos, J.M., Oishi, K., Albert, M., Mori, S., Mielke, M.M., 2013. Longitudinal, region-specific course of diffusion tensor imaging measures in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 9, 519–528.
O'Sullivan, M., Jones, D.K., Summers, P.E., Morris, R.G., Williams, S.C., Markus, H.S., 2001. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 57, 632–638.
Oishi, K., Lyketsos, C.G., 2014. Alzheimer's disease and the fornix. Front. Aging Neurosci. 6, 241.
Orlovsky, I., Huijbers, W., Hanseeuw, B.J., Mormino, E.C., Hedden, T., Buckley, R.F., LaPoint, M., Rabin, J.S., Rentz, D.M., Johnson, K.A., Sperling, R.A., Papp, K.V., 2017. The relationship between recall of recently versus remotely encoded famous faces and amyloidosis in clinically normal older adults. Alzheimers Dement 10, 121–129.
Penke, L., Maniega, S.M., Murray, C., Gow, A.J., Valdes Hernandez, M.C., Clayden, J.D., Starr, J.M., Wardlaw, J.M., Bastin, M.E., Deary, I.J., 2010. A general factor of brain white matter integrity predicts information processing speed in healthy older people. J. Neurosci. 30, 7569–7574.
Perea, R.D., Rabin, J.S., Fujiyoshi, M.G., Neal, T.E., Smith, E.E., Van Dijk, K.R.A., Hedden, T., 2018. Connectome-derived diffusion characteristics of the fornix in Alzheimer's disease. Neuroimage Clin. 19, 331–342.
Poppenk, J., Evensmoen, H.R., Moscovitch, M., Nadel, L., 2013. Long-axis specialization of the human hippocampus. Trends Cogn. Sci. 17, 230–240.
Rabin, J.S., Perea, R., Buckley, R., Neal, T., Buckner, R.L., Johnson, K.A., Sperling, R.A., Hedden, T., 2018. Global white matter diffusion characteristics predict longitudinal cognitive change independently of amyloid status in clinically normal older adults. Cereb. Cortex 29, 1251–1262.
Racine, A.M., Adluru, N., Alexander, A.L., Christian, B.T., Okonkwo, O.C., Oh, J., Cleary, C.A., Birdsill, A., Hillmer, A.T., Murali, D., Barnhart, T.E., Gallagher, C.L., Carlsson, C.M., Rowley, H.A., Dowling, N.M., Asthana, S., Sager, M.A., Bendlin, B.B., Johnson, S.C., 2014. Associations between white matter microstructure and amyloid burden in preclinical Alzheimer's disease: a multimodal imaging investigation. Neuroimage Clin. 4, 604–614.
Reitan, R.M., 1958. Validity of the Trail Making Test as an indicator of organic brain damage. Percept. Mot. Skills. 8, 271–276.
Rieckmann, A., Van Dijk, K.R., Sperling, R.A., Johnson, K.A., Buckner, R.L., Hedden, T., 2016. Accelerated decline in white matter integrity in clinically normal individuals at risk for Alzheimer's disease. Neurobiol. Aging 42, 177–188.
Ringman, J.M., O'Neill, J., Geschwind, D., Medina, L., Apostolova, L.G., Rodriguez, Y., Schaffer, B., Varpetian, A., Tseng, B., Ortiz, F., Fitten, J., Cummings, J.L., Bartzokis, G., 2007. Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations. Brain 130, 1767–1776.
Rosenbaum, R.S., Gilboa, A., Moscovitch, M., 2014. Case studies continue to illuminate the cognitive neuroscience of memory. Ann. N. Y. Acad. Sci. 1316, 105–133.
Rudebeck, S.R., Scholz, J., Millington, R., Rohenkohl, G., Johansen-Berg, H., Lee, A.C., 2009. Fornix microstructure correlates with recollection but not familiarity memory. J. Neurosci. 29, 14987–14992.
Sánchez-Valle, R., Monté, G.C., Sala-Llonch, R., Bosch, B., Fortea, J., Lladó, A., Antonell, A., Balasa, M., Bargallób, N., Molinuevo, J.L., 2016. White matter abnormalities track disease progression in PSEN1 autosomal dominant Alzheimer's disease. J. Alzheimers Dis. 51, 827–835.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505.
Song, Z., Farrell, M.E., Chen, X., Park, D.C., 2018. Longitudinal accrual of neocortical amyloid burden is associated with microstructural changes of the fornix in cognitively normal adults. Neurobiol. Aging 68, 114–122.
Spreen, O., Benton, A.L., 1977. Neurosensory center comprehensive examination for aphasia. Neuropsychology Laboratory, Department of Psychology, University of Victoria.
Tsivilis, D., Vann, S.D., Denby, C., Roberts, N., Mayes, A.R., Montaldi, D., Aggleton, J.P., 2008. A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. Nat. Neurosci. 11, 834–842.
Wechsler, D., 1981. WAIS-R manual: Wechsler adult intelligence scale- revised. The Psychological Corporation, Harcourt Brace Jovanovich.
Wechsler, D., 1987. WMS-R: Wechsler Memory Scale-Revised. Psychological Corporation, San Antonio, TX.
Wechsler, D., 1997. Wechsler adult intelligence scale III: Administration and scoring manual. The Psychological Corporation, New York.
Wirth, M., Oh, H., Mormino, E.C., Markley, C., Landau, S.M., Jagust, W.J., 2013. The effect of amyloid β on cognitive decline is modulated by neural integrity in cognitively normal elderly. Alzheimers Dement. 9, 687–698.
Yassa, M.A., Muftuler, L.T., Stark, C.E., 2010. Ultrahigh-resolution microstructural diffusion tensor imaging reveals perforant path degradation in aged humans in vivo. Proc. Natl. Acad. Sci. U. S. A. 107, 12687–12691.
Yeh, F., Wedeen, V.J., Tseng, W.Y.I., 2010. Generalized q-sampling imaging. IEEE Trans. Med. Imaging 29, 1626–1635.
Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1983. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. 17, 37–49.
Zhuang, L., Sachdev, P.S., Trollor, J.N., Kochan, N.A., Reppermund, S., Brodaty, H., Wen, W., 2012a. Microstructural white matter changes in cognitively normal individuals at risk of amnestic MCI. Neurology 79, 748–754.
Zhuang, L., Wen, W., Trollor, J.N., Kochan, N.A., Reppermund, S., Brodaty, H., Sachdev, P., 2012b. Abnormalities of the fornix in mild cognitive impairment are related to episodic memory loss. J. Alzheimers Dis. 29, 629–639.