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Hippocampal connectivity with retrosplenial cortex drives neocortical tau accumulation and memory function

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Abstract: The mechanisms underlying accumulation of Alzheimer's disease (AD)-related tau pathology outside of the medial temporal lobe (MTL) in older adults are unknown but crucial to understanding cognitive decline. Neural connectivity has recently been implicated in the propagation of tau in humans, consistent with data from animal studies. Using resting state functional connectivity and tau PET imaging, we examined MTL structures involved in medial parietal tau deposition in cognitively normal older adults. Functional connectivity between retrosplenial cortex and hippocampus, but not entorhinal cortex, correlated with tau in medial parietal lobe. Further, hippocampal-retrosplenial connectivity strength modulated the correlation between MTL and medial parietal lobe tau, as well as between medial parietal tau and episodic memory. Medial parietal tau spread thus reflects patterns of neural connectivity that represent a critical step in the evolution of cognitive dysfunction in aging and AD.

Introduction

The microtubule-associated protein tau forms neurofibrillary tangles (NFTs) in its hyperphosphorylated state, which together with amyloid- β (A β) plaques are the hallmark neuropathologies of Alzheimer's disease (AD). Early histopathology studies of these NFTs described tau pathology as first appearing in medial temporal lobe (MTL) structures such as the entorhinal cortex and hippocampus before later accumulating in limbic areas and association cortex ¹. In recent years, the use of positron emission tomography (PET) imaging has allowed the *in vivo* characterization of the distribution and extent of pathological tau burden in patients with AD as well as cognitively healthy older adults ^{2,3}. A developing body of work has used other neuroimaging modalities in concert with PET to investigate what factors and characteristics of the aging brain lead to stereotypical patterns of tau pathology.

Though the mechanisms underlying patterns of tau spread are not yet fully understood, there is converging evidence of transsynaptic propagation of tau through coactive neurons. Studies *in vitro* and in animal models suggest that tau pathology can be transferred between synaptic connections, and that enhanced neuronal activity stimulates the release of pathological tau and increases downstream accumulation⁴⁻⁶. In humans, transneuronal tau spread has been investigated by comparing the topography of tau accumulation with measures of structural and functional connectivity⁷⁻¹³. Graph theoretic measures of resting state functional magnetic resonance imaging (fMRI) indicate that connected nodes in the brain tend to exhibit greater tau accumulation⁷, and computational modeling of tau spread based on both structural and functional connectivity is highly predictive of the observed pattern of tau accumulation⁸. Further, the degree of between-region functional connectivity is associated with the covariance of change in tau PET signal over time⁹. Given that the degree of connectivity across the cortex has been shown to relate to the pattern of tau accumulation, connectivity measures in brain regions that first exhibit tau pathology may provide insights into the structures and processes involved in the spread of tau in aging and AD.

NFTs are thought to originate in the transentorhinal region, an area spanning the lateral entorhinal cortex and medial perirhinal cortex in humans^{14,15}. Tau pathology is in fact observed in MTL structures such as the entorhinal cortex and hippocampus in virtually all older adults¹⁶. However, its accumulation in cortical areas outside of the MTL, perhaps facilitated by A β ¹⁷, is often a feature of the earliest stages of AD, with medial parietal cortex being a particularly common area of deposition^{18,19}. A recent study from our group found that functional connectivity of the anterolateral entorhinal cortex (alEC), the entorhinal area most proximal to the transentorhinal region, showed the strongest association with neocortical tau PET signal in

cognitively normal older adults ¹¹. Tau may thus initially propagate directly to some neocortical areas via connectivity with the aIEC. However, cortical regions such as the medial parietal area that have not been reported to have strong structural connectivity to aIEC ^{20,21} also develop tau pathology as AD progresses. For these regions, it is plausible that connections with other MTL structures that show later tau deposition, including the posteromedial entorhinal cortex (pmEC) and hippocampus, underly tau spread from MTL to neocortex.

The medial parietal lobe is notable for its characteristic glucose hypometabolism in early AD ²², and exhibits greater tau accumulation relative to surrounding cortical areas both in patients with AD and cognitively healthy older individuals ^{19,23}. This region also comprises a large part of the posterior medial (PM) memory network, which together with the anterior temporal (AT) memory network represents a framework of two distinct large-scale neocortical memory networks with separable anatomical and functional connectivity with the MTL and support of different aspects of memory and cognitive function ^{24,25}. Though greater tau accumulation in regions of the AT network compared to PM regions is typically observed in cognitively normal older adults, there is a substantial increase in PM tau in mild cognitive impairment (MCI) and AD individuals ¹⁸. Tau accumulation in medial parietal lobe thus represents spread into the PM network, which may be a key condition under which memory performance begins to worsen prior to the clinical presentation of disease. Examining the role of connectivity in tau's pathway to the medial parietal lobe may help explain why this area is such a specific target of AD pathology and what effect the spread of tau has on memory processing.

In the present study, we use functional connectivity from resting state fMRI to investigate how tau spreads from the MTL to the medial parietal lobe. In a sample of cognitively normal older adults, we measured functional connectivity between key MTL subregions (aIEC, pmEC

and hippocampus) and medial parietal lobe, and tested whether this connectivity was related to tau deposition in medial parietal lobe. Given that hippocampus is known to develop tau pathology after entorhinal cortex and exhibits strong structural connectivity with medial parietal lobe regions²⁶, we hypothesized that the degree of functional connectivity with hippocampus would better predict tau burden in medial parietal lobe than functional connectivity with either entorhinal subregion. In addition, because pmEC also demonstrates some connectivity with medial parietal areas²¹ and aLEC is the earliest region of tau accumulation, we tested whether these regions would also contribute to medial parietal tau. Further, we were interested in examining how connectivity between the MTL and medial parietal lobe was related to both the correspondence of tau between the two regions and to cognitive function. We hypothesized that MTL and medial parietal tau would be more correlated as functional connectivity between these regions increased, and that greater tau burden and functional connectivity together would be associated with worse memory performance.

Results

Participants

We analyzed data from 97 cognitively unimpaired older adults from the Berkeley Aging Cohort Study (BACS) with structural and resting state functional 3T MRI scans. These individuals were also administered concurrent tau PET scans with ¹⁸F-Flortaucipir (FTP) and A β PET scans with ¹¹C-Pittsburgh Compound B (PiB), as well as a standard cognitive assessment. Demographic information for all participants is shown in Table 1.

Table 1. Participant characteristics. Demographic information for sample of 97 cognitively normal older adults including age, years of education, mini mental state examination (MMSE) score, global beta amyloid positron emission tomography (A β PET) signal, sex, beta amyloid positivity status (A β +), and apolipoprotein E positivity status (ϵ 4+).

	Mean (SD) or n (%)	Range
<i>Age (years)</i>	76.4 (6.1)	60 – 93
<i>Education (years)</i>	16.8 (1.9)	12 – 20
<i>MMSE</i>	28.6 (1.3)	25 – 30
<i>Global Aβ PET</i>	1.17 (0.25)	0.92 – 1.89
<i>Sex (female)</i>	58 (59.8)	
<i>Aβ+</i>	43 (45.7)	
<i>APOE ϵ4+</i>	28 (29.8)	

1 *Hippocampus exhibits strong resting state functional connectivity with retrosplenial cortex*

2 We first investigated resting state functional connectivity between MTL and medial
3 parietal lobe in our sample. We selected three regions of interest within MTL: the anterolateral
4 (alEC) and posteromedial (pmEC) entorhinal cortices as well as the hippocampus (Figure 1a).
5 Within the medial parietal lobe, we identified the retrosplenial cortex as a region where tau is
6 thought to spread to the neocortex via the MTL ¹⁵ and with known structural and functional
7 connectivity with MTL ^{21,24,26}. Hippocampus and retrosplenial cortex (“isthmus cingulate”, see
8 Methods) regions of interest were derived using the FreeSurfer segmentation of each
9 participant’s native space MRI, and template space alEC and pmEC were defined from a
10 previous high-resolution MRI study ²⁷. We performed bilateral region-to-region functional
11 connectivity analyses with semipartial correlations adjusting for age and sex.

12 Next, we carried out one-sample t-tests using β -weights from region-to-region semipartial
13 correlations to see if functional connectivity between each region was significantly different
14 from 0 (Figure 1b). We found significant connectivity between hippocampus and retrosplenial
15 cortex ($\beta = 0.45$, $p < 0.001$), as well as between pmEC and retrosplenial cortex ($\beta = 0.07$, $p =$
16 0.007). We further compared the connectivity of these two pathways using a paired samples t-
17 test and found that hippocampal-retrosplenial (HC-RsC) connectivity was significantly greater

than pmEC-RsC connectivity ($t(96) = 15.74, p < 0.001$). By contrast, no significant connectivity was observed between alEC and retrosplenial cortex ($\beta = 0.00, p = 0.891$). Thus, hippocampus and to a lesser extent pmEC, but not alEC, exhibited resting state functional connectivity with retrosplenial cortex in our sample of cognitively normal older adults.

Figure 1. Hippocampus exhibits strong resting state functional connectivity with retrosplenial cortex. (A) Regions of interest for functional connectivity analysis ($n=97$). Anterolateral entorhinal cortex (alEC), posteromedial entorhinal cortex (pmEC), and hippocampus (HC) were included from the medial temporal lobe, as well as retrosplenial cortex (RsC). (B) Retrosplenial cortex exhibits functional connectivity with hippocampus ($\beta=0.45, p<0.001$) and posteromedial entorhinal cortex ($\beta=0.07, p=0.007$), but not anterolateral entorhinal cortex ($\beta=0.00, p=0.89$). Line color and thickness correspond to the T-statistic of semipartial correlations of resting state activity between regions.

Hippocampal-retrosplenial connectivity strength is related to medial parietal tau pathology

Having observed strongest functional connectivity between hippocampus and retrosplenial cortex, we next sought to investigate the extent to which this connectivity is associated with tau accumulation in medial parietal lobe. We operationalized connectivity strength by again extracting the β -weights from region-to-region semipartial correlations for each participant. Tau pathology was quantified as the proportion of voxels above an *a priori* threshold

for tau PET ($\text{SUVR} > 1.4$), following previous work that demonstrated this to be a reliable marker of AD-related tau pathology²³. We computed this suprathreshold tau in a medial parietal lobe composite region comprising the retrosplenial cortex, precuneus, and posterior cingulate cortex such that for each participant, the number of voxels above threshold was divided by the total number of voxels in this region. To visualize this tau signal, we also computed the proportion of participants above threshold in each voxel of the composite region. (Figure 2a).

Using multivariate linear regression, we then examined the association of suprathreshold medial parietal lobe tau with connectivity strength between each MTL subregion and retrosplenial cortex. Adjusting for age, sex, and global $\text{A}\beta$ PET signal, we found that HC-RsC connectivity strength was associated with suprathreshold tau in the medial parietal lobe ($\beta = 0.145, p = 0.004$; Figure 2b). The global $\text{A}\beta$ term from this model was also associated with suprathreshold medial parietal tau ($\beta = 0.113, p = 0.014$). In contrast with HC-RsC, linear regression models adjusting for age, sex, and global $\text{A}\beta$ revealed that neither alEC-RsC ($\beta = 0.120, p = 0.145$) nor pmEC-RsC connectivity strength ($\beta = 0.015, p = 0.842$) were associated with medial parietal lobe tau (Figure 2c-d). In a separate model, we further examined whether individuals with more global $\text{A}\beta$ exhibited a stronger relationship between HC-RsC and medial parietal tau. Adjusting for age and sex, we did not observe a significant interaction between HC RsC connectivity and global $\text{A}\beta$ ($\beta = 0.442, p = 0.141$).

Figure 2. Hippocampal-retrosplenial connectivity strength is related to medial parietal tau pathology. (A) Percent of participants above tau threshold (FTP SUVR > 1.4) for each voxel in medial parietal lobe (MPL) region comprising retrosplenial cortex, precuneus, and posterior cingulate cortex. (B) Adjusting for age, sex, and global beta amyloid ($A\beta$), hippocampal-retrosplenial (HC-RsC) resting state functional connectivity strength is associated with mean suprathreshold tau within MPL. MPL suprathreshold tau defined as proportion of voxels above threshold (FTP SUVR > 1.4) within composite region. (C) Anterolateral entorhinal cortex-retrosplenial (alEC-RsC) and (D) posteromedial entorhinal cortex-retrosplenial (pmEC-RsC) connectivity strength are not associated with MPL tau. Significance value for each plot corresponds to effect of each term from linear regression model. Functional connectivity (FC) strength quantified as β -values extracted from semipartial correlations between regions.

To confirm that the relationship between HC-RsC connectivity and medial parietal tau was specific to retrosplenial cortex and not a general effect of strong resting state functional connectivity, we identified a control region within the superior frontal gyrus (SFG) analogous to

the medial portion of Brodmann area 10 from the Brainnetome Atlas ²⁸. Like retrosplenial cortex, this region is known to be part of the default mode network but does not have extensive structural connections with hippocampus and exhibited low signal dropout in our sample. Similar to retrosplenial cortex, we observed significant resting state functional connectivity between hippocampus and SFG ($\beta = 0.40, p < 0.001$), though not between SFG and aLEC ($\beta = 0.02, p = 0.439$) or pmEC ($\beta = -0.02, p = 0.379$; Supplementary Figure 1a). However, in contrast with retrosplenial cortex, we did not observe an association between the strength of hippocampus-SFG connectivity and medial parietal lobe tau ($\beta = 0.006, p = 0.907$; Supplementary Figure 1b).

We further wanted to verify that connectivity between hippocampus and retrosplenial cortex was associated specifically with tau in medial parietal lobe and not also in other early tau-accumulating regions. To this end, we examined tau within entorhinal cortex and inferior temporal cortex, a region often used as a marker for early tau accumulation in aging ^{29,30}. Again using linear regression adjusting for age, sex, and global A β , we found that HC-RsC connectivity was not associated with suprathreshold tau in the entorhinal cortex ($\beta = -0.017, p = 0.843$; Supplementary Figure 2a). Notably, though suprathreshold tau signal in medial parietal lobe and inferior temporal cortex were highly correlated ($r = 0.796, p < 0.001$), HC-RsC was only associated at trend level with inferior temporal tau ($\beta = 0.150, p = 0.082$; Supplementary Figure 2b). Finally, to confirm that the relationship between connectivity and pathology was specific to tau, we examined the association between HC-RsC and A β burden in the medial parietal lobe. Adjusting for age and sex, HC-RsC connectivity was not associated with medial parietal lobe A β PET signal ($\beta = 0.172, p = 0.193$; Supplementary Figure 2c). Taken together, these results demonstrate the specificity of tau pathology accumulation in medial parietal lobe via direct connectivity with hippocampus in cognitively unimpaired older adults.

Hippocampal-retrosplenial connectivity modulates the relationship between medial temporal and medial parietal tau

To further examine the role of functional connectivity in the spread of tau pathology from MTL, we tested whether HC-RsC connectivity strength modulated how closely MTL tau corresponded with medial parietal lobe tau. Measuring tau in MTL, particularly in hippocampus, is challenging given the confound of signal contamination from off-target FTP binding in choroid plexus. To address this, we quantified MTL tau pathology with hippocampal FTP SUVR using Rousset geometric transfer matrix partial volume correction, which minimizes choroid plexus spillover³¹. As an additional precaution, we adjusted for choroid plexus FTP signal in our linear regression model, in addition to age, sex, and global A β (Table 2).

As expected, there was a significant main effect of hippocampal tau ($\beta = 0.222, p = 0.003$) as well as a main effect of HC-RsC ($\beta = 0.120, p = 0.007$) on medial parietal lobe suprathreshold tau. Critically, we also observed an interaction between hippocampal tau and HC-RsC connectivity ($\beta = 0.635, p = 0.006$; Figure 3) such that there was a stronger association between MTL and medial parietal lobe tau with greater functional connectivity between these regions. To further verify that choroid plexus spillover into hippocampus was not driving these results, we replicated this analysis using partial volume corrected entorhinal tau PET, and found a trend-level interaction between entorhinal tau and HC-RsC in predicting medial parietal tau ($\beta = 0.265, p = 0.069$; Supplementary Figure 3). These findings implicate functional connectivity as a crucial factor in the spread of tau from hippocampus to medial parietal lobe.

Table 2. Model results. Examined variables from linear regression model examining the relationship between medial parietal lobe (MPL) suprathreshold tau and age, sex, global beta amyloid (A β), choroid plexus signal (partial volume corrected FTP SUVR), hippocampus mean tau (partial volume corrected FTP SUVR), hippocampal-retrosplenial (HC-RsC) functional connectivity (FC) strength, and hippocampus mean tau x HC-RsC FC strength interaction. Bolded term indicates interaction effect visualized in Figure 3.

Independent variables:	Dependent variable: MPL suprathreshold tau
age	$\beta = -0.001$ $p = 0.375$
sex	$\beta = 0.013$ $p = 0.508$
global A β	$\beta = 0.052$ $p = 0.229$
choroid plexus signal	$\beta = 0.016$ $p = 0.746$
hippocampus mean tau	$\beta = 0.222$ $p = 0.003$
HC-RsC FC strength	$\beta = 0.120$ $p = 0.007$
hippocampus mean tau x HC-RsC FC strength	$\beta = 0.635$ $p = 0.006$
Constant	$\beta = -0.009$ $p = 0.917$

Figure 3. Hippocampal-retrosplenial connectivity modulates the relationship between medial temporal and medial parietal tau.

Visualization of interaction between hippocampus mean tau (partial volume corrected FTP SUVR) and hippocampal-retrosplenial functional connectivity strength (HC-RsC) from linear regression model (see Table 2). Medial parietal lobe (MPL) suprathreshold tau is associated with a hippocampal tau x HC-RsC interaction. Plot displays the relationship predicted by linear regression at low (10th percentile), median, and high (90th percentile) HC-RsC.

Hippocampal-retrosplenial connectivity modulates the relationship between medial temporal and medial parietal tau

Having observed that increased functional connectivity between hippocampus and retrosplenial cortex modulates tau pathology burden in medial parietal lobe, we sought to test if connectivity and tau in these areas might also interact to predict cognitive function. We

constructed a composite episodic memory measure consisting of the mean z-score of four episodic memory tasks: the California Verbal Learning Test (CVLT) immediate free recall, CVLT long-delay free recall, Visual Reproduction (VR) immediate recall, and VR delay recall³². Adjusting for age, years of education, practice effects, and global A β , we did not observe a significant main effect of either medial parietal lobe tau ($\beta = 1.111$, $p = 0.318$) or HC-RsC connectivity ($\beta = 0.073$, $p = 0.861$) on episodic memory. However, we did find a significant interaction between medial parietal tau and hippocampal-retrosplenial connectivity ($\beta = -9.482$, $p = 0.018$), such that episodic memory performance was poorest when both medial parietal lobe tau and hippocampal-retrosplenial connectivity were greatest (Table 3). To further examine which subdomain of episodic memory might drive this finding, we broke down the episodic memory composite score into a verbal memory component consisting of the two CVLT tasks, and a visuospatial memory component consisting of the two visual reproduction tasks. The interaction between medial parietal lobe tau and hippocampal-retrosplenial connectivity was associated with visuospatial memory performance ($\beta = -12.016$, $p = 0.006$; Figure 4a), but not verbal memory performance ($\beta = -6.933$, $p = 0.145$; Figure 4b). Taken together, these findings indicate that the combination of greater tau in medial parietal lobe and greater connectivity between hippocampus and retrosplenial cortex is associated with poorer episodic memory, an effect that is perhaps driven by a relationship with visuospatial memory in particular.

Table 3. Model results. Examined variables from linear regression model examining the relationship between episodic memory performance (California Verbal Learning Test immediate and long-delay free recall, Visual Reproduction immediate and delay recall) and age, years of education, practice effects (see Methods), global beta amyloid (A β), medial parietal lobe (MPL) suprathreshold tau, hippocampal-retrosplenial (HC-RsC) functional connectivity (FC) strength, and MPL suprathreshold tau x HC-RsC FC strength interaction. Bolded term indicates interaction effect visualized in Figure 4.

Independent variables:	Dependent variable: Episodic memory composite
age	$\beta = -0.046$ $p = 0.006$
years education	$\beta = 0.013$ $p = 0.508$
practice effects	$\beta = 0.234$ $p = 0.029$
global A β	$\beta = -0.256$ $p = 0.475$
MPL suprathreshold tau	$\beta = 1.113$ $p = 0.288$
HC-RsC FC strength	$\beta = 0.071$ $p = 0.857$
MPL suprathreshold tau x HC-RsC FC strength	$\beta = -9.482$ $p = 0.018$
Constant	$\beta = 0.048$ $p = 0.917$

1

2

Figure 4. Episodic memory performance is associated with the interaction of hippocampal-retrosplenial connectivity and medial parietal tau. Visualization of interaction between hippocampal-retrosplenial (HC-RsC) functional connectivity (FC) strength (beta value) and medial parietal lobe (MPL) suprathreshold tau in relation to visuospatial and verbal memory, adjusting for age, sex, years of education, practice effects, and global A β . (A) Visuospatial memory (Visual Reproduction immediate and delay recall) is associated with the interaction of MPL tau and HC-RsC FC strength. (B) Verbal memory (CVLT immediate and long delay free recall) does not exhibit a significant interaction. Plots display the relationship predicted by linear regression at low (10th percentile), median, and high (90th percentile) MPL suprathreshold tau.

Discussion

In this study of cognitively unimpaired older adults, we measured functional connectivity between the MTL and medial parietal lobe using resting state fMRI, and measured tau pathology burden using tau PET imaging. Retrosplenial cortex exhibited strong functional connectivity with hippocampus, weaker yet significant connectivity with pmEC, and no connectivity with alEC. We found that the strength of HC-RsC connectivity was associated with the degree of tau accumulation in the medial parietal lobe, whereas neither alEC-RsC nor pmEC-RsC connectivity correlated with medial parietal lobe tau. Control analyses demonstrated that this result was specific to HC-RsC connectivity and to tau pathology in the downstream medial parietal lobe. We further observed that the correspondence between tau in hippocampus and medial parietal lobe was greater with stronger HC-RsC connectivity. Finally, we demonstrated that greater medial parietal lobe tau in combination with stronger HC-RsC connectivity was associated with poorer episodic memory performance, particularly in the visuospatial domain. Together, these findings provide strong evidence that AD-related tau pathology disrupts memory processing by spreading first from entorhinal cortex to hippocampus before later accumulating in medial parietal lobe. The combination of high MTL and medial parietal tau and high functional connectivity between these regions in cognitively normal individuals may thus represent the conditions under which the earliest stages of cognitive decline occur.

Tau accumulates in medial parietal lobe via connectivity with hippocampus

These results add to a growing literature linking patterns of resting state functional connectivity to the spread of AD-related tau pathology. In the aging brain, greater functional connectivity between regions is related to greater tau accumulation and correspondence of tau between these regions ^{11,12}. Further, models predicting the spread of tau using functional connectivity closely resemble the observed pattern of tau deposition in the brain ^{7,8}, and functional connectivity may even be a better predictor of tau propagation than traditional Braak staging ¹³. Our finding that connectivity between retrosplenial cortex and hippocampus, but not alEC or pmEC, was associated with medial parietal tau suggests that tau originating in MTL accumulates in hippocampus before later spreading directly to medial parietal lobe via connectivity with retrosplenial cortex. In addition, the finding that pmEC-RsC connectivity was weaker than HC-RsC connectivity indicates that although pmEC is functionally connected with several posterior medial areas ^{11,33}, it is not likely to be the primary structure involved in the propagation of tau to the medial parietal lobe. Instead, tau likely spreads to alEC-connected neocortex and hippocampus at a comparable rate, and later accumulates in posterior medial areas with connections to the hippocampus. This is consistent with cross-sectional histopathological data indicating that although the earliest cortical region to exhibit tau pathology is the alEC/transentorhinal area ^{14,34}, tau is typically observed in hippocampus prior to limbic areas such as the retrosplenial region ¹⁵. These findings also corroborate recent work that found that structural connectivity between hippocampus and posterior cingulate cortex (PCC) was associated with tau pathology in PCC ¹⁰.

The specificity of this key finding in our study is striking. The lack of association between HC-RsC connectivity and tau in entorhinal cortex suggests this connectivity is specifically related to tau in the downstream medial parietal region of this pathway. In addition to the medial parietal lobe, the inferior temporal cortex is one of the first areas outside of the MTL where tau pathology begins to accumulate, and tau burden in this region is often used as a marker of AD disease progression^{29,30}. That the strength of HC-RsC connectivity was only associated at trend level with tau in this region suggests that this connectivity is specific to tau pathology in the medial parietal lobe and not in other early-accumulating neocortical areas. In addition, though hippocampus showed strong functional connectivity with the medial portion of Brodmann area 10, a region of the default mode network in the superior frontal gyrus, there was no association between the strength of this connectivity and medial parietal tau. Thus, it appears that connectivity specifically between hippocampus and retrosplenial cortex is associated with medial parietal tau, not simply connectivity between hippocampus and other highly-connected cortical area. Finally, we failed to find an association between HC-RsC and A β burden within medial parietal lobe. This is not surprising given that A β does not originate in the MTL and is not thought to spread in the same transneuronal manner as tau, lending further support to the notion that functional connectivity is uniquely useful in predicting tau accumulation. Taken together, these results support a narrative of tau pathology in hippocampus spreading to medial parietal lobe in cognitively unimpaired older adults, reflected by resting state functional connectivity between these regions.

Functional connectivity may modulate tau propagation at different time scales

1 In addition to the association between functional connectivity and tau pathology, our
2 finding of greater correspondence between hippocampal and medial parietal tau with greater HC-
3 RsC connectivity strength lends further support to the notion that neural connectivity may
4 influence tau to spread from early-accumulating regions to connected downstream areas. In
5 particular, individuals with greater connectivity strength in our sample were more likely to have
6 tau pathology burden in hippocampus align with medial parietal lobe tau than individuals with
7 weaker connectivity. It is notable that although replicating this analysis using entorhinal tau PET
8 demonstrated this same relationship at trend level, the strongest relationship was evident with
9 hippocampal tau. Because tau in entorhinal cortex and hippocampus tend to be highly correlated
10 with one another, it is not surprising that using entorhinal tau yielded a similar result, and further
11 suggests that contamination of hippocampal signal from non-specific choroid plexus FTP
12 binding is not likely to be driving this finding.

13 An alternative explanation for these findings is that tau accumulation influences the
14 degree of functional connectivity between these regions. Indeed, some studies have found a
15 negative association between tau pathology and functional connectivity across the cortex^{29,35,36},
16 though these tended to use global measures of tau or focused on A β -positive individuals.
17 However, our findings together with previous work help illustrate how tau and functional
18 connectivity may produce distinct effects at different time scales. Initially, greater connectivity
19 within an individual circuit may facilitate the spread of tau from regions of early accumulation to
20 downstream cortical areas, perhaps enhanced by the presence of A β . Over time, however, the
21 influence of tau throughout this pathway leads to neurodegeneration and disruption of neuronal
22 signaling, and tau pathology may in fact show an inverse correlation with functional
23 connectivity. These distinct short- and long-term effects may help explain regional differences in

the tau-connectivity relationship such that pathways of early tau propagation are first to show local degeneration, whereas later pathways, such as the MTL-medial parietal lobe, may concurrently demonstrate increased connectivity leading to further tau spread. In the context of a cascading network failure model of AD³⁷, functional connectivity has proven to be a powerful tool in examining the effect of tau accumulation on functional isolation of brain regions³² and in predicting inter-individual variability in the pattern of tau spread and disease progression¹³.

Greater connectivity and tau together lead to worse episodic memory

In this study, functional connectivity and tau were also found to have consequences for cognitive function. Episodic memory performance, particularly visuospatial memory, was related to the combination of greater medial parietal lobe tau accumulation and greater HC-RsC strength. Though neither connectivity strength nor medial parietal tau alone predicted memory performance in our sample, it is notable that the interaction between them was associated with poorer episodic memory in individuals without clinical cognitive impairment, even after controlling for global A β burden. Existing work has yet to establish a clear relationship between memory performance and connectivity changes in aging. Greater functional connectivity between MTL and posterior medial areas is related to poorer memory performance both cross-sectionally and over time³⁶. By contrast, a positive association has been reported between MTL-medial parietal connectivity and memory performance^{38,39}, though these studies did not measure tau pathology with PET imaging. Abnormal diffusivity of the hippocampal cingulum bundle has also been shown to be related to greater decline in memory performance in older individuals with high PCC tau and high A β ¹⁰. It may be that propagation of tau, not tau burden per se, is associated with the earliest deficits in cognitive function, representing a state of mild circuit

1 disruption that has not yet reached the stage of widespread neurodegeneration and cascading
2 network failure. This view comports with a model of AD stemming from peptide-dependent
3 circuit dysfunction, as tau propagation leads to changes in circuit excitability associated with the
4 earliest-detectable cognitive changes ⁴⁰. Indeed, the correlation between tau spread to the medial
5 parietal lobe and worse episodic memory performance may be an indicator of consequences for
6 the PM memory system, which while not affected by tau as early as the AT system may begin to
7 be disrupted in MCI and AD ¹⁸.

8 It is also striking that our cognitive findings are driven by an association with visuospatial
9 memory in particular. Medial parietal areas have long been implicated in processing of spatial
10 information ^{41–43}, and the representation of visuospatial context is thought to be a key function of
11 the PM memory system ²⁴. Spatial information processing may also be one of the earliest-
12 affected domains in cognitive aging and Alzheimer’s disease ⁴⁴, but the relationship between
13 functional connectivity and spatial memory performance has not been extensively studied in
14 humans. In rodents, RsC-PCC resting state functional connectivity has been shown to be
15 associated with impaired spatial memory performance ⁴⁵. Inferring a causal link between
16 propagation of tau to the medial parietal lobe and domain-specific cognitive decline is beyond
17 the scope of this study, but these processes may underlie the beginnings of cognitive decline in
18 healthy older adults.

20 *Limitations*

21 It should be noted that the cross-sectional nature of these data means that we can only
22 infer the spread of tau rather than directly observing it. Longitudinal studies of tau accumulation
23 are needed to fully validate the notion of tau propagating to different regions over time via

connectivity. In addition, though we adjusted for A β PET signal throughout this study, we did not find that the relationships described here were stronger in individuals with greater global A β burden. Though A β was associated with medial parietal lobe tau independent of HC-RsC connectivity, there was no significant interaction with A β in any of our analyses. This was a somewhat surprising finding given a number of studies that have found a stronger association between tau and connectivity for those with greater A β pathology^{9–11}. It is possible that our sample did not provide us with enough statistical power to observe this interaction, though it was enriched to include nearly half A β -positive individuals. Another explanation is the processes examined here represent features of normal aging independent of AD-specific pathologies. Further study is needed to assess the role of A β in the association between medial parietal lobe tau and functional connectivity in cognitively normal older adults.

Conclusions

The findings described here support the view that tau pathology spreads from its origin in the entorhinal cortex to the hippocampus in cognitively normal older individuals, before later depositing in medial parietal lobe via direct connectivity between hippocampus and retrosplenial cortex. Though the accumulation of tau pathology in MTL and even some areas of the AT network has been observed in older adults without cognitive impairment, tau spread into the PM network and subsequent domain-specific memory decline may reflect a significant transition between normal aging and the processes involved in Alzheimer's disease. Future work with longitudinal data can help establish tau propagation into the medial parietal lobe as a crucial marker of the beginnings of Alzheimer's disease.

Materials and Methods

Study Design

The main objective of this study was to determine what medial temporal lobe structure is primarily involved in the propagation of tau into the medial parietal lobe in cognitively normal older adults. We hypothesized that hippocampus would show the strongest functional connectivity with medial parietal lobe, and that the strength of this connectivity would be associated with the degree of medial parietal tau. After initial analysis, we further hypothesized that the strength of this connectivity would modulate the correlation between medial temporal and medial parietal tau, as well as between tau and episodic memory performance. To test these hypotheses, we included data from 97 cognitively normal older adults from the Berkeley Aging Cohort Study. All participants underwent 3T structural and resting state functional MRI, 3T structural MRI, and a standard neuropsychological assessment. These participants also received tau PET imaging using ^{18}F -Flortaucipir (FTP) and $\text{A}\beta$ PET imaging using ^{11}C -Pittsburgh Compound B (PiB). There were 3 individuals who did not have PiB PET data available for analysis, and so were excluded from all analyses that adjusted for global $\text{A}\beta$ signal. We included only participants whose resting state fMRI data was collected within 146 days of their corresponding tau PET scan ($M = 42.5$, $SD = 37.9$).

Additional inclusion criteria for this study were 60+ years of age, cognitively normal status (Mini Mental State Examination score ≥ 25 and normal neuropsychological examination, defined as within 1.5 SDs of age, education, and sex adjusted norms), no serious neurological, psychiatric, or medical illness, no major contraindications found on MRI or PET, and independent community living status. This study was approved by the Institutional Review

Boards of the University of California, Berkeley, and the Lawrence Berkeley National Laboratory (LBNL). All participants provided written informed consent.

3T MRI acquisition

Structural and functional MRI data were acquired on a 3T TIM/Trio scanner (Siemens Medical System, software version B17A) using a 32-channel head coil. A T1-weighted whole brain magnetization prepared rapid gradient echo (MPRAGE) image was acquired for each subject (voxel size = 1mm isotropic, TR = 2300ms, TE = 2.98ms, matrix = 256×240×160, FOV = 256×240×160mm³, sagittal plane, 160 slices, 5 min acquisition time). Resting state functional MRI was then acquired using T2*-weighted echo planar imaging (EPI, voxel size = 2.6mm isotropic, TR = 1.067ms, TE = 31.2ms, FA = 45, matrix 80×80, FOV = 210mm, sagittal plane, 300 volumes, anterior to posterior phase encoding, ascending acquisition, 5 min acquisition time). During resting state acquisition, participants were told to remain awake with eyes open and focused on a white asterisk displayed on a black background.

Structural MRI preprocessing

Structural T1-weighted images were processed using Statistical Parametric Mapping (SPM12). Images were first segmented into gray matter, white matter, and CSF components in native space. DARTEL-imported tissue segments for all individuals in the sample were used to create a study-specific template, which was then used to warp native space T1 images and tissue segments to MNI space at 2mm isotropic resolution. Finally, native space T1 images were segmented with Freesurfer v.5.3.0 using the Desikan-Killany atlas parcellation.

Resting state fMRI preprocessing

Resting state fMRI images were preprocessed using a standard SPM12 pipeline. Slice time correction was first applied to adjust for differences in acquisition time for each brain volume. Then, all EPIs were realigned to the first acquired EPI, and translation and rotation realignment parameters were output. Each EPI was next coregistered to each individual's native space T1 image. Next all resting state EPIs and structural images were warped to the study-specific DARTEL template in 2mm isotropic MNI space from structural preprocessing. Unsmoothed fMRI data in MNI space was used to extract the time series correlation of all ROI seeds used in these analyses.

Functional connectivity analyses for these preprocessed resting states images were carried out using the CONN functional connectivity toolbox (version 17e) ⁴⁶ implemented in MATLAB version 2019b (The Mathworks Inc., Natick, MA). ART motion detection was first performed to identify volumes of high motion, using a movement threshold of $>0.5\text{mm/TR}$ and a global intensity z-score of 3. Outlier volumes were flagged and included as spike regressors during denoising. No individuals were excluded from these analyses due to excess motion, as all participants had $<20\%$ of outlier volumes ($M = 5.0\%$, $SD = 3.4\%$). Denoising was then performed with translation and rotation realignment parameters and their first-order derivatives, as well as anatomical CompCor (first five components of time series signal from white matter and CSF). A band pass filter of 0.008-0.1Hz and linear detrending were then applied to the residual time-series.

Regions of interest for functional connectivity analyses

A number of regions of interest (ROI) were defined for these analyses to examine the association of functional connectivity between these areas and tau burden. Many of these were obtained from the FreeSurfer segmentation of each participant's native space 3T structural image⁴⁷. The regions defined in this way included the hippocampus (HC), retrosplenial cortex (RsC), posterior cingulate cortex (PCC), precuneus (PrC), whole entorhinal cortex (EC), and inferior temporal cortex (IT). In the case of RsC, we used the FreeSurfer region analog labeled as "isthmus cingulate." The composite medial parietal lobe ROI used throughout this study consisted of the RsC, PCC, and PrC regions. To test connectivity between HC and a region outside of the medial parietal lobe, we also identified a region in the superior frontal gyrus (SFG) analogous to the medial portion of Brodman Area 10, labeled as A10m in the Brainnetome atlas parcellation²⁸.

Anterolateral entorhinal cortex (alEC) and posteromedial entorhinal cortex (pmEC) were defined in a previous study with high-resolution 7T MRI²⁷. In brief, anatomical borders of the entire entorhinal cortex were manually defined on a high-resolution T1-group template. Multivariate classification in a group of young adults was used to then identify clusters of voxels within this mask that showed preferential functional connectivity with perirhinal cortex, comprising the alEC ROI, or with the parahippocampal gyrus, comprising the pmEC ROI. These alEC and pmEC ROIs were then warped to a 2mm isotropic MNI template and made publicly available. In this study, we used these bilateral MNI space ROIs in our functional connectivity analyses. Because these regions are in close spatial proximity to one another, we extracted time series from the unsmoothed, denoised MNI space resting state data to avoid smoothing signal from each seed into each other.

To address signal dropout in these and every ROI in these analyses, we derived an explicit mask to remove regions of low signal across the whole brain. This mask was defined by calculating the mean functional MNI space image across all individuals, restricted to a group level grey matter mask. We then excluded voxels with less than 40% of the mean signal intensity of the image. Using this mean signal intensity threshold mask, a mean of 15.8% of voxels (SD = 11.9%) were removed across all ROIs with the highest proportion of voxels being removed from the A10m region (34.8%).

Functional connectivity analysis

Seed-to-seed functional connectivity analysis was carried out with the CONN toolbox⁴⁶ using the MNI space resting state fMRI data. We used semipartial correlations for all first-level analyses to compute the time series correlation between each seed, controlling for the variance of all other seed regions entered into the same model. We first constructed a model of functional connectivity between aIEC, pmEC, HC, and RsC using bilateral ROIs. Semipartial correlations and unsmoothed data were used to minimize spillover of signal between adjacent MTL regions. Statistical significance of functional connectivity was determined using one-sample t-tests of β -weights from region-to-region semipartial correlations to see if connectivity was significantly different from 0. All analyses were performed using an explicit mask to remove areas of high signal dropout across the whole brain, as described above.

PET acquisition and processing

PET was acquired for all participants at LBNL. Tau accumulation was assessed with ¹⁸F-Flortaucipir (FTP) synthesized at the Biomedical Isotope Facility at LBNL as previously

described³. Data were collected on a Biograph TruePoint 6 scanner (Siemens, Inc) 75-115 min post-injection in listmode. Data were then binned into 4 x 5 min frames from 80-100 min post-injection. CT scans were performed before the start of each emission acquisition. A β burden was assessed using ¹¹C-Pittsburgh Compound B (PiB), also synthesized at the Biomedical Isotope Facility at LBNL⁴⁸. Data were collected on the Biograph scanner across 35 dynamic frames for 90 min post-injection and subsequently binned into 35 frames (4 x 15, 8 x 30, 9 x 60, 2 x 180, 10 x 300, and 2 x 600s), and a CT scan was performed. All PET images were reconstructed using an ordered subset expectation maximization algorithm, with attenuation correction, scatter correction, and smoothing with a 4mm Gaussian kernel.

Processing of FTP images was carried out in SPM12. Images were realigned, averaged, and coregistered to 3T structural MRIs. Standardized uptake value ratio (SUVR) images were calculated by averaging mean tracer uptake over the 80-100 min data and normalized with an inferior cerebellar gray reference region³¹. The mean SUVR of each ROI (structural MRI FreeSurfer segmentation) was extracted from the native space images. This ROI data was partial volume corrected using a modified Geometric Transfer Matrix approach⁴⁹ as previously described³¹. SUVR images were then warped to 2mm MNI space for voxelwise analyses using the study-specific DARTEL template produced from structural data (see above). No additional spatial smoothing was applied.

Using SPM12, PiB images were realigned. An average of frames within the first 20 min was used to calculate the transformation matrix to coregister the PiB images to the participants' 3T structural MRI; this transformation matrix was then applied to all PiB frames. Distribution volume ratio (DVR) images were calculated with Logan graphical analysis over 35-90 min data and normalized to a whole cerebellar gray reference region^{50,51}. Global PiB was calculated

across cortical FreeSurfer ROIs as previously described⁵², and a threshold of DVR > 1.065 was used to categorize participants as A β -positive or A β -negative. In addition, mean DVR within each FreeSurfer ROI was extracted from coregistered, MNI space PiB images.

Suprathreshold tau quantification

To quantify tau deposition, we used the proportion of voxels above an *a priori* threshold of SUVR > 1.4 for FTP PET signal. This suprathreshold tau measure has previously been shown to be a reliable marker of AD-related tau pathology²³, and has been used in previous studies investigating functional connectivity and tau¹¹. One distinct advantage of using suprathreshold FTP over mean SUVR is that it is not confounded by different number of voxels within ROIs. For each individual, we computed the number of suprathreshold FTP voxels within each ROI and divided by the total number of voxels in the region.

Statistical analysis

All statistical analysis was carried out in R version 3.6.3, with a two-sided significance level of $\alpha=0.05$ throughout. We assessed the relationship between tau, resting state functional connectivity, and cognitive function in our sample using linear regression models carried out with the *lm()* function in the {stats} package. All analyses were adjusted for age at time of tau scan, sex, and mean global A β burden. Analyses involving cognitive test performance were additionally adjusted for years of education as well as practice effects quantified as the square root of the number of prior testing occasions⁵³.

Cognitive measures

To assess episodic memory in our sample of cognitively normal older adults, we used neuropsychological assessment data from closest in time to each individual's tau scan. There was a mean of 84.2 days (SD = 56.9) between each individual's cognitive assessment and tau PET scan. We computed an episodic memory composite measure by averaging the z-transformed individual test scores using mean and SD from the sample^{32,54} for four different tasks. These tasks were the California Verbal Learning Test (CVLT) immediate free recall, CVLT long-delay free recall, Visual Reproduction I (immediate recall), and Visual Reproduction II (delay recall). We analyzed distinct verbal and visuospatial episodic memory performance by considering performance in CVLT and Visual Reproduction tasks separately.

Supplementary Materials

Supplementary Figure 1. Hippocampal-retrosplenial resting state functional connectivity is associated with medial parietal lobe tau accumulation. (A) Superior frontal gyrus (SFG; medial portion of Brodmann Area 10) exhibits resting state functional connectivity with hippocampus ($\beta = 0.40, p < 0.001$), but not with posteromedial entorhinal cortex ($\beta = -0.02, p = 0.379$) or anterolateral entorhinal cortex ($\beta = 0.02, p = 0.439$). Line color and thickness correspond to the T-statistic of semipartial correlations of resting state activity between regions. (B) Adjusting for age, sex, and global A β , HC-SFG functional connectivity strength is not associated with proportion of voxels above threshold (SUVR > 1.4) within medial parietal lobe. Connectivity strength measured by extracting β -values of semipartial correlations between hippocampus and SFG.

Supplementary Figure 2. Hippocampal-retrosplenial resting state functional connectivity is specifically associated with medial parietal lobe tau accumulation. (A) HC-RsC is not associated with entorhinal cortex (EC) suprathreshold tau. (B) HC-RsC shows a trend-level association with inferior temporal (IT) suprathreshold tau. (C) HC-RsC is not associated with MPL A β measured by PiB PET DVR. Plots show residualized values from linear regression models adjusting for age, sex, and global A β . Connectivity strength measured by extracting β - values of semipartial correlations between HC and RsC. Suprathreshold tau defined as proportion of voxels above threshold (SUVR > 1.4) within each region of interest.

Supplementary Table 1. Model results. Examined variables from linear regression model examining the relationship between medial parietal lobe (MPL) suprathreshold tau and age, sex, global beta amyloid (A β), choroid plexus signal (partial volume corrected FTP SUVR), entorhinal mean tau (partial volume corrected FTP SUVR), hippocampal-retrosplenial (HC-RsC) functional connectivity (FC) strength, and entorhinal mean tau x HC-RsC FC strength interaction. Bolded term indicates interaction effect visualized in Supplementary Figure 3.

<i>Independent variables:</i>	<i>Dependent variable:</i>
	<i>MPL suprathreshold tau</i>

age	$\beta = -0.002$ $p = 0.373$
sex	$\beta = 0.011$ $p = 0.614$
global A β	$\beta = 0.033$ $p = 0.523$
choroid plexus signal	$\beta = 0.098$ $p = 0.026$
entorhinal mean tau	$\beta = 0.116$ $p = 0.027$
HC-RsC FC strength	$\beta = 0.130$ $p = 0.005$
entorhinal mean tau x HC-RsC FC strength	$\beta = 0.265$ $p = 0.069$
Constant	$\beta = -0.106$ $p = 0.209$

Supplementary Figure 3. Entorhinal tau pathology exhibits greatest association with medial parietal lobe tau when hippocampal-retrosplenial connectivity is greatest.

Visualization of interaction between entorhinal cortex (EC) mean tau (partial volume corrected FTP SUVR) and hippocampal-retrosplenial functional connectivity strength (HC-RsC) from linear regression model (see Supplementary Table 1). Medial parietal lobe (MPL) suprathreshold tau is associated with an entorhinal tau x HC-RsC interaction at trend level. Plot displays the relationship predicted by linear regression at low (10th percentile), median, and high (90th percentile) HC-RsC.

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Competing Interests: W.J.J. consults for Genentech, Biogen, and Bioclinica.

Materials and Correspondence: All communications and request for materials should be directed to the corresponding author (J.Z., jacob_ziontz@berkeley.edu). Suprathreshold medial parietal tau image is available for viewing at the following NeuroVault repository: <https://neurovault.org/collections/9317>. The code supporting the current study has not been deposited in a public repository because it contains participants' identifying information but is available on request.

Figures

Figure 1

Hippocampus exhibits strong resting state functional connectivity with retrosplenial cortex. (A) Regions of interest for functional connectivity analysis ($n=97$). Anterolateral entorhinal cortex (alEC), posteromedial entorhinal cortex (pmEC), and hippocampus (HC) were included from the medial temporal lobe, as well as retrosplenial cortex (RsC). (B) Retrosplenial cortex exhibits functional connectivity with hippocampus ($\beta=0.45$, $p<0.001$) and posteromedial entorhinal cortex ($b=0.07$, $p=0.007$), but not anterolateral entorhinal cortex ($\beta=0.00$, $p=0.89$). Line color and thickness correspond to the T-statistic of semipartial correlations of resting state activity between regions.

Figure 2

Hippocampal-retrosplenial connectivity strength is related to medial parietal tau pathology. (A) Percent of participants above tau threshold (FTP SUVR > 1.4) for each voxel in medial parietal lobe (MPL) region comprising retrosplenial cortex, precuneus, and posterior cingulate cortex. (B) Adjusting for age, sex, and global beta amyloid ($A\beta$), hippocampal-retrosplenial (HC-RsC) resting state functional connectivity strength is associated with mean suprathreshold tau within MPL. MPL suprathreshold tau defined as proportion of voxels above threshold (FTP SUVR > 1.4) within composite region. (C) Anterolateral entorhinal cortex-retrosplenial (aIEC-RsC) and (D) posteromedial entorhinal cortex-retrosplenial (pmEC-RsC) connectivity strength are not associated with MPL tau. Significance value for each plot corresponds to effect of each term from linear regression model. Functional connectivity (FC) strength quantified as b-values extracted from semipartial correlations between regions.

Figure 3

Hippocampal-retrosplenial connectivity modulates the relationship between medial temporal and medial parietal tau. Visualization of interaction between hippocampus mean tau (partial volume corrected FTP SUVR) and hippocampal-retrosplenial functional connectivity strength (HC-RsC) from linear regression model (see Table 2). Medial parietal lobe (MPL) suprathreshold tau is associated with a hippocampal tau $\times$ HC-RsC interaction. Plot displays the relationship predicted by linear regression at low (10th percentile), median, and high (90th percentile) HC-RsC.

Figure 4

Episodic memory performance is associated with the interaction of hippocampal-retrosplenial connectivity and medial parietal tau. Visualization of interaction between hippocampal-retrosplenial (HC-RsC) functional connectivity (FC) strength (beta value) and medial parietal lobe (MPL) suprathreshold tau in relation to visuospatial and verbal memory, adjusting for age, sex, years of education, practice effects, and global A β . (A) Visuospatial memory (Visual Reproduction immediate and delay recall) is associated with the interaction of MPL tau and HC-RsC FC strength. (B) Verbal memory (CVLT immediate and long delay free recall) does not exhibit a significant interaction. Plots display the relationship predicted by linear regression at low (10th percentile), median, and high (90th percentile) MPL suprathreshold tau.