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Relationships between default-mode network connectivity, medial temporal lobe structure, and age-related memory deficits

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Abstract

Advanced aging negatively impacts memory performance. Brain aging has been associated with shrinkage in medial temporal lobe structures essential for memory---including hippocampus and entorhinal cortex---and with deficits in default-mode network connectivity. Yet, whether and how these imaging markers are relevant to age-related memory deficits remains a topic of debate. Using a sample of 182 older (age 74.6±6.2) and 66 young (age 22.2±3.6) participants, this study examined relationships between memory performance, hippocampus volume, entorhinal cortex thickness, and default-mode network connectivity across aging. Significant differences in all imaging markers and memory were found between young and older groups. Each imaging marker significantly mediated the relationship between age and memory performance and collectively accounted for the majority of variance in age-related memory performance. Within older participants, default-mode connectivity and hippocampus volume were independently associated with memory. Structural equation modeling of cross-sectional data within older participants suggest that entorhinal thinning may occur prior to reduced default-mode connectivity and hippocampal volume loss, which in turn lead to deficits in memory performance.

Keywords

Magnetic resonance imaging; memory; structural equation modeling; aging; cognitive aging

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1. Introduction

Memory performance declines with age (Park, et al., 2002, Small, 2001, Verhaeghen, et al., 1993). The structures in the medial temporal lobe---including hippocampus and entorhinal cortex---are essential for successful memory performance (Scoville and Milner, 1957, Sperling, et al., 2003, Zola-Morgan, et al., 1989). Further, loss of medial temporal lobe volume has been associated with age-related performance deficits (Hackert, et al., 2002, Head, et al., 2008, O'Brien, et al., 1997, Wolf, et al., 2001, see also Van Petten, 2004). Similarly, the structures of the default-mode network---including posterior cingulate and medial prefrontal cortex---are essential for supporting memory processes (Berryhill, et al., 2007, Janowsky, et al., 1989, Shapira-Lichter, et al., 2013, Spreng, et al., 2009, Sutherland, et al., 1988). Disruptions in the default-mode network have also been associated with age-related memory performance deficits (Hampson, et al., 2006, Ranganath, et al., 2005, Sala-Lluch, et al., 2012, Wang, et al., 2010). Several models propose that age-related memory deficits are mediated by declines in hippocampus (Chen, et al., 2010, Head, et al., 2008, Tisserand, et al., 2000, Walhovd, et al., 2004), entorhinal cortex (Tisserand, et al., 2000), and the default-mode network (Miller, et al., 2008, Sambataro, et al., 2010, Wang, et al., 2010).

Although hippocampus volume, entorhinal cortex thickness, and default network connectivity have each individually been linked to age-related memory deficits, the shared and independent contributions of these imaging markers are less clear (Salthouse, 2011). Establishing proximal the relationships between decline in grey matter structures, connections that support memory, and memory performance may help disambiguate “normal” and pathological processes that underlie age-related alterations in memory performance (Hedden and Gabrieli, 2004, Jagust, 2013).

The shared contribution of the hippocampus, entorhinal cortex, and default-mode network to age-related alteration in memory might be driven by connectivity between these structures. The entorhinal cortex links the hippocampus to default-mode regions of the neocortex (Kahn, et al., 2008, Lacy and Stark, 2012, Libby, et al., 2012, Ward, et al., 2013) and mediates the input and output streams of the hippocampus to default-mode neocortical regions (Burwell and Amaral, 1998, Witter, et al., 2000). Finally, the hippocampus can be dynamically coupled and uncoupled from the default-mode network (Huijbers, et al., 2011, Vannini, et al., 2010, Young and McNaughton, 2009), a phenomenon likely mediated by the entorhinal cortex (Lipton and Eichenbaum, 2008, Ward, et al., 2013). Thus, it is likely that age-related declines in the entorhinal cortex may impact communication between hippocampus and neocortical regions of the default-network, contributing to age-related memory deficits.

The unique involvement of the hippocampus, entorhinal cortex, and default-mode network in age-related alteration of memory performance might be driven by selective susceptibilities to different age-related pathologies. Neurofibrillary tangle pathology is thought to accumulate in the medial temporal lobe relatively early in mid-life (Braak and Del Tredici, 2011, Nelson, et al., 2012) whereas amyloid begins to accumulate in default-

mode network regions later in life (Braak and Braak, 1991, Buckner, et al., 2009). Although the first locus of deposition and the trajectories of accumulation for these pathologies differ (Nelson, et al., 2012), accumulation of tau and amyloid tend to co-occur in late life (Fagan, et al., 2009). These pathological processes, along with a host of other age-related changes, likely have spatially specific and therefore dissociable effects on brain structure and function, which in turn lead to downstream memory deficits.

Here, we explored the relationships between age, memory performance, medial temporal lobe structure, and default-mode connectivity. First, we determined the shared and unique contribution of each imaging marker to age-related memory deficits across young and older groups. Second, we postulated that hippocampal volume would demonstrate the most proximal relationship to memory performance, owing to the close association between hippocampal integrity and memory function (Corkin, et al., 1997, Erickson, et al., 2010, Petersen, et al., 2000, Squire, 1992). Finally, we examined relationships between these imaging markers and their hypothesized influences on memory within the older group. We focus on three hypotheses, which vary in the proximal ordering of entorhinal cortex thickness, hippocampal volume, and default-mode connectivity as influences on memory performance motivated by the differing loci and timing of pathological processes in aging.

2. Methods

2.1 Participants

One hundred eighty-two clinically normal older participants and sixty-six healthy young adults participated in the study (Table 1). All participants were native English speakers; had normal or corrected-to normal vision; had no history of psychiatric or neurological disorders; and had no history of head trauma. Older participant inclusion criteria included Mini Mental Status Exam (MMSE) scores of ≥ 26 , a Clinical Dementia Rating of 0, and scores within one standard deviation of education-adjusted norms for Logical Memory IIa. Older participants are Harvard Aging Brain Study participants who have data available for the examined metrics. Young participants were recruited from the community via online advertisements and include students and young working professionals from the greater Boston area, and were screened for history of neurologic illness or any MRI abnormalities. Informed consent was obtained in accordance with the guidelines and procedures governed by the institutional review board of the Massachusetts General Hospital (Boston, MA).

2.2 Neuropsychological measures

All participants underwent a neuropsychological testing battery. Older participants underwent this testing battery on average 51.3 ± 12.9 days from their MRI scan. Young participants underwent these tests on average 13.8 ± 9.9 days from their MRI scan. The neuropsychological tests were used in a confirmatory factor analysis described in a previous publication (Hedden, et al., 2012). Using the factor weights from this prior analysis, a factor score for memory was derived for each participant. The tests included in this factor score are: number of errors produced on the Self-Ordered Pointing task (95% of older participants completed; adapted from Petrides and Milner, 1982, Shimamura and Jurica, 1994), cued recall names and cued recall occupations scores from the Face-Name Associative Memory

Exam (99% of older completed; Amariglio, et al., 2012, Rentz, et al., 2011), delayed recall from the Six-Trial Selective Reminding Test (99% of older completed; Masur, et al., 1990), and List 2 free recall from the memory Capacity Test (99% of older completed; Rentz, et al., 2010). Missing data on individual tests were imputed using a linear regression approach. Six percent of older participants and no young had missing data on at least one neuropsychological test. This factor weighting was z-transformed across the entire group for all analyses.

2.3 Magnetic Resonance Imaging protocols

All participants underwent MRI exams on a Siemens Trio Tim 3.0 Tesla scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a 12-channel phased-array head coil. Head motion was restrained with extendable foam-padded clamps and a memory-foam head coil insert. The exam included an accelerated T1-weighted anatomical scan and two back-to-back blood oxygen level-dependent resting-state functional MRI scans.

2.4 Resting-state Acquisition and Processing

Resting-state fMRI scans were acquired using gradient-echo echo-planar imaging (Kwong, et al., 1992, Ogawa, et al., 1992). Participants were instructed to keep their eyes open. Forty-seven interleaved axial slices aligned parallel to the anterior-/posterior-commissure plane provided whole brain coverage with the following parameters: repetition time (TR) = 3000ms, echo time (TE) = 30ms, flip angle = 85°, field-of-view (FOV) = 216×216mm, matrix = 72×72, and 3×3×3mm voxels. 124 volumes were acquired in each scan.

Resting-state functional data were pre-processed using SPM8 using a standard, previously published procedure (Fox, et al., 2005, Hedden, et al., 2009, Ward, et al., 2013). The first four volumes of each run were discarded. Each run was slice-time corrected for interleaved acquisitions and realigned to the first volume of the run using a rigid-body rotation. These volumes were then normalized to the Montreal Neurological Institute echo-planar imaging template using a nonlinear warping technique, and were smoothed with a 6mm full width at half maximum Gaussian kernel. After preprocessing the following regressors were removed to suppress physiological noise (Fox et al., 2005): (1) estimated motion parameters, (2) average signal from deep white matter, ventricle, and whole brain masks, and (3) the first derivative of each regressor. The residuals were linearly detrended and low-pass filtered with a second order Butterworth filter with a frequency cutoff of 0.08 Hz. Analyses were conducted by concatenating the resting-state scans and included scan-specific regressors.

Three *a priori* regions of interest (ROIs) representing major nodal regions within the default-mode network (DMN) were chosen for examination using previously defined coordinates in the posterior cingulate cortex (PCC) MNI [0, -53, 26], medial prefrontal cortex (mPFC) MNI [0, 52, -6], and inferior parietal lobule (IPL) MNI [-48, -62, 36; 46, -62, 32] (Hedden, et al., 2009, Ward, et al., 2013). Pairwise correlations between individual cortical nodes were calculated and averaged to create a summary metric of default-mode network connectivity.

2.5 Anatomical acquisition and processing

T1-weighted anatomical images were acquired with a multi-echo magnetization-prepared rapid gradient echo sagittal-oriented sequence (van der Kouwe, et al., 2008) with the following parameters: TR = 2200ms; inversion time (TI) = 1100ms; TE = 1.54ms, 3.36ms, 5.18ms, and 7ms; flip angle = 7°; FOV = 230×230mm; matrix size = 192×192; NEX = 1; GRAPPA = 4; and 1.2×1.2×1.2mm voxels

Structural images were processed with FreeSurfer v5.1 (<http://surfer.nmr.mgh.harvard.edu>) using the default processing stream. Dural/pial boundaries were additionally estimated using the inherent T2* information contained in the multi-echo sequence (van der Kouwe, et al., 2008) which improves surface reconstruction (Fujimoto, et al., 2014). No reconstructions were manually edited, but all passed brief visual quality assurance. Entorhinal cortical (EC) thickness and hippocampal (HC) volume were extracted. HC was normalized by estimated total intracranial volume (eTIV; Buckner, et al., 2004) using a covariance approach where corrected HC = HC – [(β of HC~eTIV) * (subject eTIV - mean eTIV)]. Young and older participants were normalized separately. Spatial specificity of the relationships with default-mode connectivity and memory performance was tested at the vertex level (see Supplementary Figure 1 and Supplemental Materials for details).

2.6 Statistical Models

All statistics were computed using R (version 3.0.0; cran.r-project.org).

First, to determine the interrelationships of the imaging markers, age, and memory performance, we assessed age group differences with Mann-Whitney U tests. R values were computed to address statistical power: $r = 0.1$ is a small effect, $r = 0.3$ a medium effect, and $r = 0.5$ a large effect. Pair-wise relationships between HC volume, EC thickness, DMN connectivity, and memory were computed using linear regression in each age group separately. We also tested differences in slope between young and older participants by examining the age group by marker interaction.

Furthering this aim, we determined if each imaging marker contributed to age-related declines in memory using a mediation approach similar to Head et al. (2008). In these models, memory is the dependent variable (y), age group is the independent variable (x), and the imaging marker is the mediator variable (m). A separate mediation analysis was conducted for each imaging marker. The conditions for mediation are met if: (1) all of the pairwise correlations are significantly greater than zero, (2) the correlation of y (memory) and m (imaging marker) while controlling for x (age group) is significant, and (3) the correlation of x and y decreases in significance when controlling for m (Baron and Kenny, 1986, MacKinnon, et al., 2007, Preacher and Hayes, 2008). Significance of mediation was tested using a nonparametric bootstrap method (10,000 iterations) of the indirect effect (Preacher and Hayes, 2008) using the “mediation” R package as well as by the Sobel test. Significance using the nonparametric method is met when the confidence interval of the indirect effect does not include zero.

Second, to assess the proximity of hippocampus volume to memory performance, we estimated the relative contributions of each imaging marker to age-related memory deficits

using a series of multiple regression models to calculate the unique variance contributed. Results are presented as a percentage of the age-related sum of squares, calculated by sequentially removing one variable from a multiple regression model across all participants.

Finally, to assess the relationships of the imaging markers on memory in the elderly, we tested three hypothesized models of how the imaging markers relate to each other and memory performance within only the older group using structural equation modeling. These models were tested using the “lavaan” R package (v0.5–14; Rosseel, 2012). A model is considered well-fitting if the following criteria are met: a non-significant χ^2 test, Tucker-Lewis Index > 0.95 , a root mean square error of approximation (RMSEA) < 0.05 accompanied by a non-significant p of close fit (PCLOSE; Hu and Bentler, 1999). The Akaike information criterion (AIC) is used to quantify the relationship between goodness of fit and model complexity. AIC allows the comparison of non-nested models with identical degrees of freedom. In these cases, models with lower AIC are preferred.

3. Results

3.1 Interrelationships between markers in older, not in young participants

We found significant age group differences across all measures, such that older participants had worse memory ($U = 751$, $p < 0.0001$, $r = 0.67$), lower default-mode network (DMN) connectivity ($U = 2576.5$, $p < 0.0001$, $r = 0.43$), smaller hippocampus (HC) volume ($U = 852$, $p < 0.0001$, $r = 0.66$), and reduced entorhinal cortex (EC) thickness ($U = 3141$, $p < 0.0001$, $r = 0.36$) compared to young adults.

All imaging markers (DMN, HC, EC) were positively associated with memory performance in the older group (Table 2). Further, all imaging markers were interrelated in the older group (Table 2). These results are spatially specific, such that the EC thickness and HC volume were significantly correlated with memory performance, but thickness of other cortical regions was not (see Supplementary Figure 2 and Supplemental Materials for details). In contrast, none of the imaging measures predicted memory in the young group. HC volume and DMN connectivity were positively related in the young group, but neither was related to EC thickness (Table 2). Notably, the relationships between memory and HC ($F_{(1,279)} = 67.73$, $p < 0.001$), HC and EC ($F = 3.98_{(1,279)}$, $p = 0.05$), and DMN and EC ($F_{(1,279)} = 10.38$, $p = 0.001$) were significantly greater in the older group than the young.

3.2 Imaging markers mediate the relationship between age group and memory performance

HC volume (Figure 1A), EC thickness (Figure 1B), and DMN connectivity (Figure 1C) each significantly mediate the relationship between age group and memory (Table 3). However, these imaging markers do not completely mediate the age group/memory relationship. That is, age group remains a significant predictor of memory after accounting for each imaging marker, as noted by the significant c' pathways. To confirm these findings, we also tested a series of alternative models: (1) where age group mediates the relationship between each imaging marker and memory performance, and (2) where memory mediates the relationship between age group and each imaging marker (Salthouse, 2011). None of these models revealed significant mediation.

3.3 Hippocampus volume and default-network connectivity contribute significantly and independently to age-related memory deficits

The imaging markers were also simultaneously modeled and iteratively removed to examine their independent contributions to variance in memory across age group (50.9% of the total variance in memory was related to age group). This analysis revealed significant independent contributions of HC volume (29.2% of age group-related variance) and DMN connectivity (3.2% of age group-related variance), but not EC thickness (0.8% of age group-related variance). An additional 36.4% of age group-related variance in memory was shared among the three imaging markers.

When this analysis was conducted within the older group only (11.1% of the total variance in memory was related to age), greater HC volume (31.5% of age-related variance) and greater DMN connectivity (7.3% of age-related variance) again contribute significant independent variance to memory performance, while EC thickness (0.3% of age-related variance) does not. An additional 29.8% of the age-related variance was shared among imaging markers. Note that when modeled alone, EC thickness does significantly predict memory performance (Table 2), indicating that the predictive power of EC thickness is predominantly from variance shared with HC volume and DMN connectivity.

3.4 Entorhinal cortical thinning may occur upstream to other brain changes and memory deficits in the older group

We examined two theoretically motivated models (Figure 2A–B) and an atheoretical “null” model (Figure 2C). All models include age as the upstream driver of brain and memory deficits. Model A (Figure 2A) hypothesizes that early and parallel age-related pathology in EC and DMN regions contribute to HC decline that has the sole proximal relationship to memory. We include the correlation between EC thickness and DMN connectivity based on findings of functional connectivity between these regions (Ward et al., 2013) and associations between tau and amyloid pathology during normal aging (Fagan, et al., 2009). Model B (Figure 2B) hypothesizes that age-related deficits in EC thickness is related to alterations in both HC volume and DMN connectivity, while these two downstream changes have no direct relationship to one another (Ward et al., 2013) and each have an independent influence on memory. This model is motivated by the different trajectories of tau and amyloid accumulation during normal aging (Nelson, et al., 2012), and by cortical involvement of DMN regions in memory processing (Huijbers, et al., 2013, Shapira-Lichter, et al., 2013, Sperling, et al., 2009, Spreng, et al., 2009). Model C (the “null model”; Figure 2C) hypothesizes that each brain marker has independent age-related deficits, as well as independent direct influences on memory. The model also allows for associations between the markers, but with relationships between HC and DMN acting only through associations of each with EC.

Our data are most consistent with hypothesized model B (Model A: RMSEA=0.083; Model B: RMSEA=0.011; Model C: RMSEA=0.151; see Table 4 for additional fit statistics), in which hippocampal volume and default-mode connectivity have parallel proximal influences on memory, but are in turn influenced by entorhinal cortex thickness. All the paths of this model were significant. Importantly, we also tested this model with a direct age to memory

pathway. This path was not significant, and this model was not a better fit ($\chi^2 = 0.59$, $df = 1$, $p = 0.442$). This indicates that Model B accounts for the age/memory relationship, indicating both complete mediation and no confound of age (see Supplemental Materials for additional models and parameters).

4. Discussion

First, we found significant age group differences in hippocampus (HC) volume, entorhinal cortex (EC) thickness, default-mode network (DMN) connectivity, and memory performance. Within the older group, larger HC volume, thicker EC, and greater DMN connectivity were all associated with better memory performance. These imaging markers were not associated with memory in the young group. The paired EC/HC, EC/DMN, and HC/memory inter-relationships were significantly stronger in the older than the young. Further, all imaging markers significantly mediated age group-related memory differences. Second, when modeled simultaneously, HC volume and DMN connectivity contributed independent variance to memory performance both across age groups and within the older group. Finally, structural equation modeling of the cross-sectional relationships within the older group supports a model where reductions in EC thickness are upstream of reductions in HC volume and DMN connectivity, which each have direct influences on memory performance. Entorhinal cortex thinning is a distal marker of memory performance, indicating that pathology- or age-driven change in this region may either initiate or signal subsequent memory decline.

Overall, these results are consistent with previous work showing age group differences in medial temporal lobe structure, DMN connectivity, and memory performance (Damoiseaux, et al., 2008, Fjell, et al., 2013, Park, et al., 2002, Verhaeghen, et al., 1993, Walhovd, et al., 2011). Additionally, these results provide further imaging support for the central role of EC linking cortical components of the DMN and HC (Kahn, et al., 2008, Lacy and Stark, 2012, Libby, et al., 2012, Ward, et al., 2013). Further, our results suggest that DMN connectivity and HC volume are parallel proximal markers of memory performance within older participants, and declines in these regions may contribute more directly to memory processes. In contrast, structural changes in the EC may be an early initiating event or signal of this cascade. Our findings also suggest that these relationships are only evident in the aging brain. Importantly, these results are supported by findings that indicate that decreases in EC thickness may represent an early upstream marker of subsequent structural and memory decline (Dickerson, et al., 2001, Killiany, et al., 2002, Rodrigue and Raz, 2004).

From a mechanistic standpoint of early EC involvement, *tau* neurofibrillary tangle accumulation is observed in the EC in early- to mid-life (Braak and Braak, 1995, Braak and Del Tredici, 2011, Mitchell, et al., 2002, Nelson, et al., 2012) and is highly collinear with chronological age (Ball, 1977, Braak, et al., 1996, Ramsden, et al., 2005). Tangle deposition has been associated with decreased synaptic density and neural activity (Hatanpaa, et al., 1996). Changes in neural activity and synaptic loss may precede tangle deposition (Yoshiyama, et al., 2007). Further, recent evidence suggests that *tau* pathology and neurodegeneration may proceed along network lines (de Calignon, et al., 2012, Liu, et al.,

2012, Pievani, et al., 2011, Seeley, et al., 2009), linking EC thinning with DMN disconnection and HC volume reduction.

The independent downstream contributions of DMN connectivity and HC volume to memory performance raise the intriguing possibility of separate, but linked, cortical and subcortical components to age-related memory decline. First, the topography of amyloid deposition---which is prevalent in approximately one-third of clinically normal older participants (Knopman, et al., 2003, Morris, et al., 1996)---has significant spatial overlap with the DMN (Buckner, et al., 2009). Second, HC volume is reduced in the presence of amyloid (Jack, et al., 2008, Mormino, et al., 2009) and may mediate the relationship between amyloid and memory performance as memory declines (Mormino, et al., 2009). Thus, it is possible that amyloid may independently influence two systems that support memory processes. Alternatively, declines in DMN connectivity may reflect declines in white matter integrity (Greicius, et al., 2009), which is related to both aging (Bartzokis, et al., 2003, Bartzokis, et al., 2004, Guttmann, et al., 1998) and vascular pathology (Black, et al., 2009, Kennedy and Raz, 2009) and may be independent of amyloid and tau pathogenesis (Head, et al., 2004).

Importantly, it is very challenging to dissociate “normal” aging from preclinical stages of Alzheimer’s disease, Parkinson’s disease, or other neurodegenerative processes (Hedden and Gabrieli, 2004, Jagust, 2013). For example, previous studies have indicated that beta-amyloid burden and apolipoprotein E ϵ 4 affect HC volume and DMN connectivity in cognitively normal older participants (Hedden, et al., 2009, Mormino, et al., 2009, Sheline, et al., 2010). Conversely, the amyloid influence on memory in clinically normal individuals is modest cross-sectionally (Hedden, et al., 2013), and becomes more evident in longitudinal follow-up (Lim, et al., 2014, Mormino, et al., 2014). Regardless, EC has been shown to be vulnerable to “normal” aging in the absence of detectable amyloid accumulation (Fjell, et al., 2013, Jagust, 2013). Increased susceptibility to age-related pathologies, such as *tau* accumulation, may first impact EC due to the selective vulnerability of this region, which then lead to downstream effects on DMN connectivity and HC volume, which then result in cognitive decline.

Additionally, memory function is well described as a distributed process (Mesulam, 1990), and the brain substrates and modifiers of this process are highly variable, particularly in a cognitive aging context (Braskie, et al., 2010, Head, et al., 2008, Raz and Rodrigue, 2006, Verhaeghen, et al., 1993). Vascular risk factors, diabetes, and level of physical activity, sleep duration, and sleep quality have all been linked to brain structure and function necessary for supporting memory processes (den Heijer, et al., 2003, Goel, et al., 2009, Guzman, et al., 2013, Harrison and Horne, 2000, Honea, et al., 2009, Mander, et al., 2013, Raz and Rodrigue, 2006, Voss, et al., 2010, Zlokovic, 2011). Because of the variability inherent in age-related memory deficits, and the likely complex interactions of these factors, larger longitudinal datasets are necessary to begin to pull apart the potential overlapping contributions of Alzheimer’s and other neurodegenerative pathology, measures of white matter integrity, and other risk factors for cognitive decline. Future studies encompassing middle age may be better situated to detect these very early changes.

Finally, although this study finds statistical evidence for changes in EC being upstream of changes in HC and DMN, longitudinal data are necessary to assess these relationships independent of baseline effects and to appropriately model the temporal order of imaging marker changes. New PET ligands specific for the paired helical filament forms of tau found in neurofibrillary tangles (Chien, et al., 2013), and autopsy data (Dowling, et al., 2010), given sufficient power to detect the effects thereof, may help to disentangle the overlapping contributions of tau pathology to cognitive aging and preclinical Alzheimer's disease.

Although more work is necessary to determine pathological underpinnings of decline in the medial temporal lobe and cortical structure and function, the temporal ordering of these alterations will help to disambiguate the overlapping contributions of aging and AD pathology to age-related memory impairment. The identification of early markers that herald memory decline will be useful for diagnostic and therapeutic intervention purposes. Our finding that EC changes appear to be upstream of both hippocampal and DMN deficits emphasizes the essential role of medial temporal/cortical connectivity in memory processes (Hyman, et al., 1984, Wang, et al., 2010). Further, these results suggest that diagnostic and interventional approaches may be well served by focusing on preserving entorhinal integrity and preventing the pathologic processes underlying entorhinal damage in aging and early Alzheimer's disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Imaging markers mediate the relationship between age group and memory deficits
 Schematics of mediation between age group and memory (Mem; factor score) for three imaging markers: **(A)** hippocampus volume (HC; mm³), **(B)** entorhinal cortical thickness (EC; mm), and **(C)** default-mode network connectivity (DMN; z).

Figure 2. Models of imaging markers affecting memory in older participants

Schematics of three models of the brain substrates of age-related memory (Mem) deficits in older participants. The models are motivated by the age-related accumulation of amyloid in default-mode network (DMN) regions and *tau* tangles in entorhinal cortex (EC). Model A is specifically motivated by the proximal relationship of hippocampus (HC) volume to memory performance. Model B is motivated by the differing trajectories of amyloid and *tau* accumulation in older participants. Model C is an atheoretical model where each imaging marker acts separately on memory. Path parameters are presented as standardized betas.

** $p < 0.005$, * $p < 0.01$, [†] $p = \text{N.S.}$

Table 1

Demographics and variables of interest

	Older		Young	
	M ± SD	Range	M ± SD	Range
<i>n</i>	182	(80 male)	66	(37 male)
Age (yrs)	74.6 ± 6.2	65.3–90.5	22.2 ± 3.6	18.3–34.0
AMNART	121.7 ± 8.7	82 – 132	117.7 ± 5.9	103 – 129
Mem (z)	−0.41 ± 0.80	−2.46 – 1.21	1.11 ± 0.52	−0.47 – 2.12
DMN (z)	0.45 ± 0.15	0.06–0.85	0.59 ± 0.11	0.259–0.984
HC (mm ³)	7374 ± 872	5340–9698	8787 ± 773	7016–11441
EC (mm)	3.44 ± 0.31	2.45–4.22	3.67 ± 0.02	2.98–4.37

AMNART, American National Adult Reading Test (verbal IQ); Mem, memory factor score (z); DMN, default-mode network connectivity (z); HC, hippocampus volume (mm³); EC, entorhinal cortex thickness (mm)

Table 2

Relationships between variables of interest

P \ r	Older adults						Young adults					
	HC	EC	DMN	Mem	Age	HC	EC	DMN	Mem	Age	HC	Age
HC		0.361	0.298	0.359	-0.495		0.140	0.269	-0.025	-0.111		
EC	<0.0001		0.363	0.169	-0.173	0.678		0.140	0.040	0.002		
DMN	<0.0001	<0.0001		0.242	-0.273	0.027	0.872		0.064	-0.004		
Mem	<0.0001	0.023	0.001		-0.291	0.844	0.749	0.609		0.103		
Age	<0.0001	0.019	0.0002	<0.0001		0.373	0.984	0.974	0.409			

DMN, default-mode network connectivity (z); EC, entorhinal cortex thickness (mm); HC, hippocampus volume (mm²); Mem, memory factor score (z); Age (years)

Table 3

Mediation analysis statistics.

	c (CI)	a (CI)	b (CI)	c' (CI)	IE (CI)	P (mediation)
HC	-0.70 (-0.79, -0.61)	-0.70 (-0.75, -0.65)	0.57 (0.50, 0.66)	-0.58 (-0.70, -0.45)	-0.12 (-0.21, -0.03)	4.22*10 ⁻¹⁵
EC	-0.70 (-0.79, -0.61)	-0.38 (-0.47, -0.29)	0.34 (0.23, 0.45)	-0.62 (-0.71, -0.51)	-0.08 (-0.16, -0.01)	9.41*10 ⁻⁹
DMN	-0.70 (-0.79, -0.61)	-0.46 (-.54, -0.37)	0.41 (0.30, 0.52)	-0.60 (-0.70, -0.50)	-0.10 (-0.18, -0.03)	1.56*10 ⁻¹¹

Statistics for each path of mediation. Results presented are r values with nonparametric bootstrap 95% confidence intervals (CI; 10,000 iterations). Confidence intervals not including zero are significant. P of mediation is a reflection of the indirect effect (IE) and confidence interval. P values presented here are derived by the Sobel test.

Table 4

Path analysis model fits.

	χ^2 (df)	P	TLI	RMSEA	PCLOSE	AIC
Model A	6.464 (3)	0.091	0.907	0.083	0.229	2249.87
Model B	4.382 (3)	0.223	0.987	0.011	0.413	2449.23
Model C	10.307 (2)	0.006	0.684	0.151	0.024	2256.30

TLI, Tucker-Lewis Index; RMSEA, root mean square error of approximation; PCLOSE, *P* value of close fit; AIC, Akaike information criterion. Criteria for a well fitting model are: a non-significant χ^2 test, TLI > 0.95, and RMSEA < 0.05 accompanied by a non-significant PCLOSE. Models A and B have three degrees of freedom (df) and are not nested, so a statistical test cannot be used to directly compare them. However, Model A has poorer fit on every metric and does not meet the criteria for a well fitting model, whereas Model B meets all criteria. Model C is a poorly fitting model on all metrics.